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Long-term follow-up of a randomized study of combination interferon and glatiramer acetate in multiple sclerosis: efficacy and safety results up to 7 years

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Author Conflicts of Interest

Fred Lublin, MD, has received consulting fees/fees for non-CME/CE activities from Bayer HealthCare Pharmaceuticals, Biogen, EMD Serono, Novartis, Teva Neuroscience, Actelion, Sanofi/Genzyme, Acorda, Questcor/Mallinckrodt, Roche/Genentech, MedImmune, Osmotica, Xenoport, Receptos/Celgene, Forward Pharma, Akros, TG Therapeutics, AbbVie, Toyama, Amgen, Medday, Atara Biotherapeutics, Polypharma, Pfizer, Johnson & Johnson, Revallesio, Coronado Bioscience, and Bristol-Myers Squibb; has served on speakers' bureaus for Genentech/Roche and Genzyme/Sanofi; has performed contracted research for Acorda, Biogen, Novartis, Teva Neuroscience, Genzyme, Xenoport, and Receptos; is the co-chief editor of *Multiple Sclerosis and Related Disorders*; and has an ownership interest in Cognition Pharmaceuticals.

Stacey S. Cofield, PhD.

Gary Cutter, PhD, has participated on Data and Safety Monitoring Committees for AMO Pharma, Apotek, Gilead Pharmaceuticals, Horizon Pharmaceuticals, Modigenetech/Prolor, Merck, Merck/Pfizer, Opko Biologics, Neuren, Sanofi-Aventis, Reata Pharmaceuticals, Receptos/Celgene, Teva Pharmaceuticals, NHLBI (Protocol Review Committee), and NICHD (OPRU Oversight Committee); has received consulting fees from and/or served on speakers' bureaus and scientific advisory boards for Cerespir, Genzyme, Genentech, Innate Therapeutics, Janssen Pharmaceuticals, Klein-Buendel Incorporated, MedImmune, Medday, Nivalis, Novartis, Opexa Therapeutics, Roche, Savara, Somahlution, Teva Pharmaceuticals, Transparency Life Sciences, and TG Therapeutics; and is President of Pythagoras, Inc., a private consulting company located in Birmingham, AL.

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Abstract

Background—To report the long-term results of the blinded extension phase of the randomized, controlled study of the combined use of interferon beta-1a (IFN) 30ug IM weekly and glatiramer acetate (GA) 20mg daily compared to each agent alone in relapsing-remitting multiple sclerosis (RRMS).

Methods—1008 RRMS patients were followed on protocol until the last participant enrolled completed 3 years, allowing some subjects to be followed for up to 7 years. The primary endpoint was reduction in annualized relapse rate. Secondary outcomes included time to confirmed disability, Multiple Sclerosis Functional Composite (MSFC) score and MRI metrics.

Results—Similar to the core study, combination IFN + GA was not superior to the better of the single agents (GA) in risk of relapse. Both the combination therapy and GA were significantly better than IFN in reducing the risk of relapse. The combination was not better than either agent alone in lessening confirmed EDSS worsening or change in MSFC. Also similar to the core result, the combination was superior to either agent alone in reducing new lesion activity, but the 3 year MRI result did not presage a clinical benefit over the extended observation interval.

Conclusion—Combining GA & IFN did not produce a significant clinical benefit over the entire study duration. The earlier effect on reducing MRI activity did not result in a later clinical advantage. The combination showed a sustained advantage in reducing disease activity free status.

Keywords

RRMS; disease activity free status; clinical trial; interferon beta-1a; glatiramer acetate

1. Introduction

The CombiRx study was a double blind, placebo controlled, randomized clinical trial comparing the combination of interferon beta-1a (IFN) and glatiramer acetate (GA) to either agent alone in treating relapsing-remitting multiple sclerosis (RRMS). The study was planned to assess clinical and magnetic resonance imaging (MRI) activity over three years. Subjects were followed in the blinded protocol until the last subject completed the three

years. This provided an opportunity to follow the earlier recruited participants in blinded fashion through seven years and allowed longer per protocol follow-up than any MS clinical trial. We previously reported the baseline characteristics of the study population (Lindsey et al., 2012) and the primary and secondary outcomes for the cohort at three years (Lublin et al., 2013). The combination of these two agents, the most commonly prescribed MS therapies at the inception of the study, did not achieve the primary outcome of reducing the risk of relapse over that of the better of the two monotherapies, GA. Both the combination and GA were superior to IFN in relapse reduction. There were no significant differences between the groups in time to relapse, development of confirmed disability or MS functional composite (MSFC). The combination was superior to either agent alone in reducing new lesion activity and the accumulation of total lesion volumes on MRI.

This report addresses whether the MRI benefits seen at three years translated into clinical differences in the longer studied cohort. The trial design allowed for the longest on protocol blinded assessment of study metrics, both clinical and MRI, and a composite measure of disease activity.

2. Materials and Methods

2.1 Study population and design

At the start of the 3-year core study, eligible participants with a confirmed diagnosis of RRMS (by Poser or McDonald criteria), aged 18–60 years, with an Expanded Disability Status Scale (EDSS) score of ≤ 6 , and with at least 2 relapses in the prior 3 years were randomized (2:1:1) to combination IFN+GA or each single agent plus matching placebo (Bhanushali et al., 2014). There was no dual placebo arm; all participants received at least one active agent. All participants administered 8 injections weekly: GA (Copaxone; Teva Pharmaceuticals, Petah Tikva, Israel) 20mg was given subcutaneously daily and IFN (Avonex; Biogen-Idec, Weston, MA) 30 μ g used intramuscularly weekly, with matched placebo preparations provided by the respective manufacturers. Those who completed the 3-year placebo-controlled core study were eligible for inclusion in the extension phase with up to 7 years of total follow up on blinded medication. Study design, randomization allocation, baseline characteristics, and core study results have been reported (Lindsey et al., 2012, Lublin et al., 2013). The results of the extension phase of the trial are provided here.

2.2 Protocol and Procedures

CombiRx enrolled 1008 participants from January 2005 through April 2009. The protocol and 4 amendments were approved by the 68 US and Canada center's applicable central or institutional review boards and the NIH appointed data and safety monitoring board (DSMB). Informed consent was obtained prior to screening and enrollment procedures.

Following enrollment, participants were followed every 12 weeks with neurological assessments by a treating clinician and examining clinician, both blinded to treatment assignment. Relapse assessments occurred every 12 weeks and as needed, EDSS examinations occurred every 12 weeks in the core study through Month 42 and every 6 months thereafter in the extension. MSFC was performed quarterly in the core study and

annually in the extension study. MRI was performed at study entry, months 6, 12, 24, 36, 48 and 60 and at the End of Study (EOS) visit in the extension if it had been more than 12 weeks since the prior MRI; the variable amount of data on MRI available, especially at years 5 and year 7, relate to when patients had EOS scans. (Figure 1).

2.3 Study Outcomes

2.3.1 Annualized Relapse Rate—The primary outcome of the core trial was the annualized relapse rate (ARR), with 3 exacerbation definitions determined centrally according to the relapse assessment and EDSS data provided by the center: protocol-defined exacerbations (PDE), non-protocol defined exacerbations (NPDE) and suspect exacerbations (SE), differing by the time of EDSS confirmation and amount of change in EDSS (Figure 2).

2.3.2 Confirmed Worsening—Confirmed worsening was defined as a minimum 1.0 increase in the EDSS from baseline if baseline EDSS ≥ 5.0 , or minimum increase of 0.5 for baseline ≤ 5.5 , confirmed at 2 successive quarterly visits through month 42 and 1 successive semi-annual visit in the extension phase. The time of confirmed worsening was taken as the onset of the first recorded change and only the first occurrence of worsening was used for the analyses.

2.3.3 MSFC—The MSFC score was determined centrally using the pooled baseline population of the core study as the reference standard in accordance with the protocol specified by the MSFC training manual ([http://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Multiple-Sclerosis-Functional-Composite-\(MSFC\)](http://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Multiple-Sclerosis-Functional-Composite-(MSFC))).

2.3.4 MRI Outcomes—MRI of the brain with and without contrast was acquired using a previously described standardized protocol and semiautomated processing and segmentation approach (Wolinsky, 2000, Lublin et al., 2013, Wolinsky et al., 2013). In this multimodal analysis system total lesion volume is defined as the sum of the T1-hypointense and T2-hyperintense lesion volume components. Combined unique lesion activity (CUA) was defined as the sum of the number of new enhanced lesions at a given imaging session and the number of new unenhanced T2 and substantially enlarged unenhanced T2 lesions with reference to the immediately prior scan session, where the unenhanced new or substantially enlarged images found were subjectively defined when compared to images from the prior imaging session and could not be explained by partial volume effects or errors in alignment in post-registered paired image sets. In the CUA assessment, lesions that enhanced on T1 weighted images were counted once and only once, and new lesions on T2-weighted images that also enhanced on T1-weighted images were not included in the CUA to avoid double counting. Atrophy was assessed as change in the normalized cerebrospinal fluid (nCSF) calculated as the percentage of the total intracranial contents that segmented as CSF over the total segmented intracranial contents; where the calvarium is not expected to change in size over the course of the clinical trial. Increasing nCSF is a reflection of reduction of the intracranial contents analogous to the inverse of the brain parenchymal fraction; the larger change the nCSF from baseline the greater the intracranial tissue loss.

2.3.5 Clinical and Disease Activity Free Status—Clinical activity free status (CAFS) was defined as participants without relapse and without confirmed worsening. Disease activity free status (DAFS, also sometimes referred to as NEDA-no evident disease activity) was defined as CAFS plus no new MRI activity (absence of CUA). DAFS was a post-hoc analysis.

2.3.6 Safety Outcomes—Safety was assessed quarterly and as necessary by recording all adverse events both serious and non-serious. Estimated glomerular filtration rate (eGFR) monitoring was added in 2008. Safety was monitored by an external safety monitor and the DSMB.

2.4 Statistical Analysis

Descriptive measures are presented as means, medians, standard deviations (SD) and minimum and maximum (range) values, as applicable. Comparisons at baseline among the treatment arms, as well as power and sample size estimations for the primary trial are described elsewhere (Lublin et al., 2013). A significant but slight difference in mean age occurred at the start of the core study. ARR was calculated for each treatment arm by dividing the total number of relapses by the total person years within each arm. Confidence intervals for ARR were calculated using a Poisson regression model. The risk of relapse (hazard rate) was evaluated using a covariate adjusted Cox proportional hazards model with the Anderson Gill modification to allow for multiple relapses within participants with its associated confidence interval (Therneau and Grambsch, 2000).

Covariate adjusted for age and baseline EDSS score logistic regression was used to evaluate confirmed worsening and CAFS, and adjusted for age, baseline EDSS, and presence of gadolinium enhanced (Gd⁺) lesions at baseline for DAFS. A repeated measure mixed model with unstructured covariance was used to assess T1-hypointense, T2-hyperintense, and nCSF differences on trial. Total lesion volume was analyzed as age adjusted, percent change from baseline volume using a repeated measures mixed-model with compound symmetric covariance. Cumulative Gd⁺ and CUA numbers and the number of Gd⁺ and CUA lesions were assessed using a negative binomial repeated measures model with a log-link and offset for time on study and adjusted for presence or absence of Gd⁺ lesions at baseline. All MRI analyses were adjusted for age and the associated baseline MRI measure, except percent change of total lesion volume was adjusted only for age.

In accordance with the hypotheses of the core study, all treatment arm comparisons were made by a two-sided comparison of the two single agent arms to determine the single agent winner; if there was not a statistically significant difference, the nominal winner was used as the single agent winner in a subsequent 1-sided test of the combination and single agent winner. Probability values <0.05 were considered meaningful for the primary comparisons, since success for the combination required statistical significance against each single-agent arm. For non-treatment, non-significant statistical tests, p-values > 0.05 are not shown. Analyses were performed using JMP v10–12 and SAS v9.3 (SAS Institute, Cary, NC).

2.4.1 Alignment of Study Time by Year

ARR: CombiRx clinic visits occurred quarterly on 12-week intervals with ± 7 day windows, resulting in 28-day months. Therefore, Year 1 target date was 336 days following enrollment (12 months * 28 days), Year 2 at 662 days, Year 3 at 1008 days, Year 4 at 1344 days, Year 5 at 1680 days, Year 6 at 2,016 days, and Year 7 at 2,352 days (Figure 1). Relapses were assigned to the applicable year based upon symptom start date as reported by the participant.

MRI: In the core study, MRI scans were acquired at Baseline, Months 6, 12, 24 and 36. In the extension phase scans were performed at 48 and 60 months and at end of study (EOS) when the most recent prior MRI was 12 or more weeks before EOS. For this analysis, Year 4 contains scans obtained at months 42–51, Year 5 at months 54–63, Year 6 at months 66–75, and Year 7 at months 78–87 (Figure 1).

CAFS and DAFS: For comparison of CAFS and DAFS at Years 3, 4, and 6 only participants that were eligible for 6 month confirmed worsening and had an MRI at those years (N=740, 500, and 261; respectively) were included.

2.4.2 Analysis populations and missing values—All participants that continued into the extension were used for extension data analyses. The intent-to-treat cohort (ITT) was defined as all participants who were recruited and randomized into the study. The safety population was defined as all participants who received at least 1 dose of study drug and had at least 1 post-baseline assessment of the safety parameter being analyzed. The modified intent-to-treat (mITT) population included all randomized participants who had taken at least 1 dose of a study medication and had at least 1 valid post-baseline MRI.

2.5 Role of the Funding Source and Study Management

The study was funded by the NINDS of the NIH, with medications and matched placebos provided by Biogen Idec and Teva Pharmaceuticals to a central distribution site at the Veterans Administration Distribution Center at Perry Point, Maryland. Design, analysis, and decision to publish results were the responsibility of the study investigators with the oversight of the DSMB and NINDS. The trial is listed on www.clinicaltrials.gov as NCT00211887. (Lindsey et al., 2012, Lublin et al., 2013).

3. Results

3.1 Participant Characteristics and Cohort Disposition

A total of 1008 participants were randomized into the core study, with 194 (19.2%) terminating prior to year 3. Of the 814 participants who completed the core study, 687 (84.4%) entered the extension with 584 (85.0%) of the extension participants completing an EOS visit during the designated termination period between November 2011 and April 2012 (Figure 1). A significantly higher proportion of participants in the IFN group terminated the core study prior to month 36. However, in the extension phase there was no difference in time on study, reason for early termination or extension completion among the three treatment arms. The mean and median times on study, including both the core and extension phase, from baseline were 3.9 (SD 1.7) and 3.9 (range 0–6.9) years. Older participants at

baseline were more likely to continue into the extension phase but the mean age at baseline of those that continued into the extension was not different by treatment group (Table 1). In addition, those with fewer relapses in the 12 months prior to randomization and a lower EDSS score at baseline were more likely to continue into the extension at the end of the core study, with no differences by treatment group. There were no differences in baseline MRI metrics across treatment groups or between those in the core study only and those continuing into the extension (Table 2).

3.2 ARR

The ARR, including both the relapses occurring in the core and extension phase, was low for all three treatment arms, ranging from 0.09 to 0.39 dependent on the stringency of relapse definition and the treatment assignment at randomization (Figure 3). For the most stringent definition of a relapse (PDE), adjusted for age, both the combination of IFN+GA and GA alone had a significantly lower risk of relapse compared to IFN but the combination of IFN +GA was not better than GA alone (Table 3). The results were similar for all relapse definitions. After adjusting for age, there were no statistical differences across treatment groups in the proportion of participants ever experiencing a relapse for the PDE or PDE +NPDE relapse definitions (all $p > 0.05$, Table 3). The combination had a lower proportion of participants ever experiencing a relapse compared to IFN alone for the PDE+NPDE+SE definition but IFN+GA was not better than GA alone (Table 3).

3.3 Secondary Outcomes

3.3.1 Disease Worsening—While the proportion of participants ever experiencing confirmed worsening increased from the core study to the extension phase, there were no significant differences in the proportion of participants experiencing worsening by treatment group (Figure 4). The absolute percent increases in the extension were 5.5% for the combination, 6.6% for IFN and 6.9% for GA and as a percentage increase over the core phase, 23.9%, 21.6% and 24.8%, respectively.

3.3.2 MRI—The number of scans available for analysis diminished over the trial and varied considerably during the extension, in part due to EOS scans done at years 5 and 7 (Figure 1). All treatment differences noted are for specific time points or are averaged across time. Unless noted, there were no significant time by treatment differences, i.e. treatment differences were consistent across time (all $p > 0.05$).

Gd⁺: The combination of IFN+GA had a lower mean number of Gd⁺ lesions over the entire study compared to the nominal winner IFN (0.39 fewer enhancements at any given scan, $p < 0.003$); IFN and GA were not different ($p = 0.24$, supplemental Figure 1). The proportion of participants cumulatively Gd⁺ free at years 3, 4 and 6 was higher in the combination compared to the single agent winner ($p = 0.0002$, < 0.008 and < 0.02 , respectively by year; supplemental Figure 2).

Combined Unique Activity from Baseline: The combination had lower cumulative combined unique activity (CUA) lesion counts compared to the nominal single agent winner IFN, by 0.54 lesions ($p = 0.001$), when adjusted for baseline age (supplemental Figure 3). The

proportion remaining cumulative CUA free (no new activity) was higher in the combination compared to the single agent winner at years 3, 4, and 6 ($p<0.0001$, <0.0003 and $=0.008$, respectively by year, Figure 5). Considerable variability was seen due to the numbers of available scans at each time point.

Volumetric MRI Measures: When adjusted for baseline age, the combination had lower increase in percent change from baseline in total lesion volume compared to both IFN and GA alone ($p=0.03$, $=0.0006$, respectively, supplemental Figure 4). There were no significant differences in T1-hypointense lesion volume across treatment arms (supplemental Figure 5). GA alone had lower change in nCSF over the study compared to the combination IFN+GA when adjusted for age and baseline nCSF ($p<0.02$, but not IFN $p=0.1$, supplemental Figure 6).

Clinical and Disease Activity-Free Status: There were no differences in the proportion of participants who were clinical activity free (CAFS: no PDE and no worsening), up to years 3, 4, and 6 (all $p>0.15$, Figure 6A). When incorporating MRI activity, the combination had a higher proportion of participants DAFS (no PDE, no worsening, no CUA) compared to the single agent winner at years 3 and 4 ($p=0.001$, 0.014) but not at year 6 ($p=0.10$, Figure 6B).

3.3.3 Safety—No new safety issues arose during the extension. The safety profile was similar to that seen in the core study and there were no unique safety events noted for the combination. The safety profile followed the known patterns of each of the agents. There was 1 death in the extension phase (as previously reported (Lublin et al., 2013)); a participant in the GA arm died from anoxic brain injury following a drug overdose.

4. Discussion

The CombiRx trial has been the longest per protocol MS clinical trial to date. Its design without a full placebo control group allowed for longer term, blinded follow up and collection of considerable data on performance metrics. Patient retention was quite good, despite requiring 8 injections weekly. There were no unique combination related side effects or safety issues reported.

The extension results are similar to those seen in the core study with all groups experiencing relatively low event rates (Lublin et al., 2013). The combination of IFN+GA was not better than the better of the two single agents, GA, for the clinical outcomes of relapse (Figure 3) or IFN for worsening (Figure 4). The combination was superior to either single agent in reducing the number of gadolinium enhanced lesions and in lower CUA. The combination was superior to either agent in the percentage achieving DAFS, driven by the MRI effects. GA was superior to IFN in reducing the risk of exacerbation, but not in any of the other clinical measures.

In the 3-year core study, a beneficial effect of the combination was seen on several MRI metrics, including lesion volumes, but no effect on clinical outcomes was demonstrated. This raised the possibility that the MRI changes might presage a later clinical effect. Follow up through 7 years for some patients failed to demonstrate a significant clinical effect of the

combination over the better of the two agents. The absence of a clinical effect could relate to the relatively mild, early-in-disease course population enrolled in this trial. Perhaps, given more time, clinical differences might have emerged. Graded dropout over the course of the study might also mask an effect. Taken at face value, this result does not support a strong link between the specific MRI changes observed and subsequent development of clinically meaningful outcomes. The results do not distinguish between the possibility that MRI changes are too sensitive or that our clinical metrics are too insensitive. Nor can we speculate on how differences might have been masked by the failure to include a full placebo arm. While other study analyses using different statistical techniques have shown a link between MRI changes and clinical activity (Sormani et al., 2013), we were unable to show a linear progression from early MRI changes to clinical consequences (Wolinsky et al., 2013).

Relapse rates in this and several other recent clinical trials have been very low, limiting the power of ARR as a useful metric when comparing agents due to the small magnitude of the absolute differences. DAFS was achieved in less than 50% of treated subjects in studies of any of the currently marketed therapies for MS (Bevan and Cree 2014), thus providing considerable potential for gauging improvement of superior next generation agents. The continued therapeutic effect of the combination on DAFS, while driven primarily by the MRI changes, supports DAFS as a sensitive but harder to achieve indicator of therapeutic effect that could be useful in future clinical trials.

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Role of Funding Source

The study was funded by the NINDS of the NIH, with medications and matched placebos provided by Biogen Idec and Teva Pharmaceuticals to a central distribution site at the Veterans Administration Distribution Center at Perry Point, Maryland. Design, analysis, and decision to publish results were the responsibility of the study investigators with the oversight of the DSMB and NINDS. The trial is listed on www.clinicaltrials.gov as NCT00211887. (Lindsey et al., 2012, Lublin et al., 2013).

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Highlights

- The CombiRx trial has been the longest per protocol MS clinical trial to date
- Up to 7 years of follow up on blinded active treatment: combination of interferon beta-1a (IFN) plus glatiramer acetate (GA) or each single agent with matching placebo
- No unique combination side effects or safety issues
- GA was superior to IFN in reducing the risk of exacerbation, but not in any of the other clinical measures
- The combination was not better than single agents clinically but was superior in reducing gadolinium enhanced lesions and in lower combined unique activity The combination was not better than single agents clinically but was superior in reducing gadolinium enhanced lesions and in lower combined unique activity
- The combination was superior to either agent in the percentage achieving DAFS, driven by the MRI effects.

Figure 1.
Cohort Disposition

Figure 2.
CombiRx Relapse Definitions

Figure 3.

Annualized relapse rate by treatment group (core study + extension)

Legend: PDE=Protocol Defined Exacerbation, NPDE=Non-protocol Defined Exacerbation, SE=Suspect Exacerbation (Figure 1).

Figure 4.
EDSS 6-Month Confirmed Worsening

Figure 5.
Proportion Cumulative CUA Free from Baseline at Years 3, 4, and 6

Figure 6.

A Clinical activity-free status at Year 3, Year 4, Year 6 (PDE). B. Disease Activity Free Status at Years 3, 4, and 6 (PDE)

Table 1
Demographics for the core study cohort and extension study cohort from baseline (Month 0)

Demographics	Core			Extension		
	IFN + GA (N=499)	IFN (N=250)	GA (N=259)	IFN + GA (N=340)	IFN (N=158)	GA (N=189)
Sex, Female, N (%)	372 (74.6)	173 (69.2)	185 (71.4)	260 (76.5)	102 (64.6)	132 (69.8)
Race, White, N (%)	440 (88.2)	212 (84.8)	234 (90.3)	302 (88.8)	137 (86.7)	173 (91.5)
Ethnicity, Non-Hispanic/Non-Latino, N (%)	446 (89.4)	225 (90.0)	237 (91.5)	315 (92.7)	150 (94.9)	176 (93.6)
Age (years)						
Mean (SD) ^a	37.1 (9.4)	37.6 (10.2)	39.0 (9.5)	37.7 (9.4)	38.5 (9.7)	39.7 (9.8)
Median (range) ^b	37 (18–61) ^c	37.5 (18–60)	38 (19–60)	38 (18–60)	39 (20–59)	39 (19–60)
Clinical characteristics						
Duration of disease (years), Mean (SD)	1.1 (3.1)	1.4 (4.0)	1.0 (2.9)	0.9 (2.5)	1.2 (2.9)	1.0 (3.0)
Relapses in prior 3 years, Mean (SD)	2.4 (0.8)	2.6 (1.2)	2.4 (0.9)	2.4 (0.8)	2.5 (0.9)	2.4 (0.9)
Relapses in prior 12 months, Mean (SD) ^d	1.7 (0.7)	1.7 (0.9)	1.6 (0.7)	1.7 (0.7)	1.7 (0.9)	1.6 (0.7)
EDSS Score, Mean (SD) ^e	1.9 (1.2)	2.0 (1.2)	1.9 (1.2)	1.8 (1.1)	1.9 (1.2)	2.0 (1.1)

^a mean age within Core: IFN+GA vs GA, $p = 0.025$

^b one participant 61 years old was admitted on protocol exception

^c mean age at baseline for those in Core only vs Extension: $p=0.0007$

^d median number relapses in prior 12 months at baseline for those in Core only vs Extension: $p=0.0414$

^e median EDSS at baseline for those in Core only vs Extension: $p=0.0007$

Table 2

MRI characteristics at baseline at the start of core study and on entry into the extension*

	Core			Extension ^a		
	IFN + GA (N=499)	IFN (N=250)	GA (N=259)	IFN + GA (N=297)	IFN (N=139)	GA (N=150)
Gadolinium enhanced lesions (Gd+)						
N (%) with lesion(s)	189 (37.9)	104 (41.6)	106 (40.9)	121 (40.7)	54 (38.9)	64 (42.7)
Mean (SD) ^b	4.4 (4.9)	4.1 (5.5)	4.6 (7.6)	4.2 (4.4)	3.6 (4.4)	5.1 (8.8)
Median (range)	3 (1–39)	3 (1–41)	2 (1–41)	3 (1–27)	3 (1–25)	2 (1–41)
Gd+ Volume, Mean (SD)	0.3 (0.4)	0.3 (0.5)	0.3 (0.7)	0.3 (0.3)	0.3 (0.6)	0.3 (0.3)
Gd+ Volume, Median (range)	0.1 (0.003–2.6)	0.1 (0.003–3.4)	0.1 (0.003–4.3)	0.1 (0.003–1.7)	0.1 (0.003–3.4)	0.1 (0.003–2.6)
Total lesion volume			0.			
Mean (SD)	12.1 (13.5)	11.7 (12.2)	12.9 (13.7)	12.6 (13.3)	10.4 (10.1)	12.4 (13.7)
Median (range)	7 (0.1–87.4)	7.6 (0.4–79.5)	7.8 (0.4–73.5)	7.3 (0.1–66.0)	7.3 (0.4–58.3)	6.8 (0.7–66.3)
T1-hypointense lesion component volume						
Mean (SD)	1.6 (2.1)	1.6 (2.0)	1.9 (2.5)	1.7 (2.1)	1.3 (1.5)	1.7 (2.3)
Median (range)	0.9 ^c (0–14.8)	0.8 (0.01–13.6)	0.9 (0.01–15.4)	0.9 (0–12.8) ^c	0.8 (0.03–8.5)	0.8 (0.04–15.2)
T2-hyperintense lesion component volume						
Mean (SD)	10.5 (11.8)	10.1 (10.7)	11.0 (11.6)	10.9 (11.7)	9.0 (9.1)	10.8 (11.9)
Median (range)	6.2 (0.1–76.2)	6.6 (0.4–69.8)	6.7 (0.3–60.9)	6.4 (0.1–62.8)	6.0 (0.4–55.9)	5.7 (0.6–60.9)
Normalized CSF, % mean (SD)	22.1 (2.2)	22.2 (2.2)	22.3 (2.4)	22.1 (2.3)	22.3 (2.3)	22.3 (2.4)

* volume in mL unless noted

^a 586/687 (85.3%) of participants entering into the extension phase had at least 1 additional MRI

^b number and volume of enhancements for those with an enhancement

^c one participant had no T1-hypointense lesions

Table 3

Exacerbation Summary and Relapse risk comparisons by exacerbation type and treatment group

No. Relapse by Type	IFN+GA	IFN	GA
PDEs	191	120	89
NPDEs	185	128	102
SEs	187	124	109
PDE+NPDEs	376	248	191
PDE+NPDE+SEs	563	372	300
Total Person Years	1906.6	952.0	1023.0
No. (%) participants relapse free			
PDEs	366 (73.4)	175 (70.0)	196 (75.7)
PDE+NPDEs	279 (55.9)	125 (50.0)	151 (58.3)
PDE+NPDE+SEs	226 (45.3)	97 (38.8)	119 (46.0)
Group Comparisons ^a	Hazard Ratio (95% CI)		p ^b
PDE treatment group			
IFN+GA vs GA	1.05 (0.81–1.36)		0.35
IFN+GA vs IFN	0.78 (0.61–0.99)		0.019 ^c
IFN vs GA	1.35 (1.02–1.79)		0.038 ^c
PDE+NPDE treatment groups			
IFN+GA vs GA	1.01 (0.85–1.22)		0.45
IFN+GA vs IFN	0.75 (0.63–0.88)		0.0004 ^c
IFN vs GA	1.33 (1.09–1.63)		0.006 ^c
PDE+NPDE+SE treatment groups			
IFN+GA vs GA	0.97 (0.83–1.13)		0.34
IFN+GA vs IFN	0.75 (0.65–0.86)		<0.0001 ^c
IFN vs GA	1.28 (1.08–1.52)		0.004 ^c

^aFor first listed treatment arm compared to second listed treatment arm: statistically significant hazard ratios (HR) greater than 1 indicate increased risk of relapse, HR lower than 1 indicate lower risk of relapse

^bAge-adjusted, Cox proportional hazards model with Anderson–Gill modification.

^cStatistically significant.

CI=confidence interval; GA=glatiramer acetate; IFN=interferon b-1a; NPDE=non-protocol-defined exacerbation; PDE=protocol-defined exacerbation; SE=suspect exacerbation