Evidence for Long-Term Use of Intramuscular Interferon Beta-1a: An Overview of Relapse, Disability, and MRI Data from Selected Clinical Trials

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ABSTRACT

The treatment options for multiple sclerosis are rapidly changing. With the increasing number of products available to treat this disease, treatment decisions are becoming more complex. Over the years, diagnosis and assessment of treatment efficacy in multiple sclerosis have evolved, but the primary endpoints used to evaluate patients have remained relatively consistent. Relapse rates, magnetic resonance imaging parameters, and disability progression are all key considerations when assessing efficacy for multiple sclerosis treatments. As selection of therapy becomes increasingly complex for both patients and physicians, risk-benefit considerations that incorporate long-term efficacy and safety on an individualized basis will be of greater importance. The information provided in this article will help to elucidate these considerations.

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Summary Points Presented in this Article

• Multiple sclerosis (MS) is a chronic, immune-mediated neurologic disease that is associated with progressive disability and diminished quality of life by interfering with a person’s ability to work, pursue leisure activities, and conduct typical life activities.

• Several approved disease-modifying therapies (DMTs) are available to treat MS. These DMTs have demonstrated efficacy in key traditional MS outcome measures, including relapses, disability progression, and magnetic resonance imaging (MRI) measures.

• This article provides an overview of the key traditional outcomes assessed in MS studies and critically evaluates phase 3 and long-term follow-up outcomes data for intramuscular interferon beta-1a (IM IFNβ-1a), one of the frequently prescribed treatments for patients with MS.

• IM IFNβ-1a administered once weekly has demonstrated efficacy in reducing relapse rates, disability progression, and disease activity visible on MRI in multiple MS studies.

• IM IFNβ-1a has been an effective first-line treatment option for patients with MS for more than 15 years. Its efficacy and safety profiles have been well established in the post-marketing setting, and no new safety considerations have emerged. The adverse reactions most commonly reported in patients associated with the use of IM IFNβ-1a are flu-like symptoms occurring within hours to days following an injection.

Several disease-modifying therapies (DMTs) are currently approved to treat multiple sclerosis (MS), with proven efficacy in reducing relapse rates, disability progression, and disease activity visible on magnetic resonance imaging (MRI). Positive outcomes for approved DMTs (subcutaneous [SC] interferon beta-1b [IFNβ-1b], intramuscular [IM] IFNβ-1a, glatiramer acetate, SC IFNβ-1a, natalizumab, fingolimod, and mitoxantrone) have been demonstrated in patients with MS for many of these endpoints. Over the next few years, the introduction of new agents to treat MS will result in significant changes in treatment. Fingolimod is the most recently approved DMT for treatment of relapsing forms of MS, and several other drugs are currently in late-stage development. The pivotal studies for these latest therapies, which include daclizumab, teriflunomide, dimethyl fumarate (BG-12), alemtuzumab, and PEGylated interferon beta-1a, have primary endpoints (relapse rates, disability progression, MRI activity) similar to those used in the registration trials of currently approved DMTs.

Because traditional measures of efficacy in MS do not capture other important aspects of the disease, additional measures, including the Multiple Sclerosis Functional Composite (MSFC), cognition, and quality of life (QoL), as well as newer imaging techniques, such as brain atrophy and magnetization transfer, are often included as endpoints in more recent clinical trials. The objective of this article is to provide an overview of the key traditional outcomes assessed in MS studies and to summarize and critically evaluate the published phase 3 studies and respective long-term follow-up outcomes data for IM IFNβ-1a, one of the more frequently prescribed treatments for patients with MS. This review provides an overview of traditional MS outcomes and is not a systematic review of all studies of the drug. The studies selected for this review examined patients who were naïve to treatment with IFNβ. Evidence supporting the use of relapses, disability progression, and MRI activity in clinical trials will be summarized. A brief overview of the key clinical trials and a long-term follow-up study for IM IFNβ-1a are provided, and the primary and secondary efficacy outcomes from these studies are described. Finally, important considerations for clinical trials in MS are reviewed.

Traditional MS Outcome Measures

Expanded Disability Status Scale

Measures of disability have often been used to assess efficacy in the clinical trials of the treatments that have received approval of the U.S. Food and Drug Administration (FDA) for MS. Measuring disability is clinically relevant because it is an evaluation of the long-term progressive course of the disease. The Kurtzke Expanded Disability Status Scale (EDSS) is the most commonly used measure of neurologic impairment in MS clinical trials. The EDSS scale ranges from 0.0 (indicating no clinical effects) to 10.0 (indicating death due to MS) in 0.5-unit increments. EDSS scores are based on the sum of 8 functional systems, including pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral function. Functional system scores have a greater bearing on total scores of <4.5, whereas higher scores are influenced more by the patient’s ambulation status. The EDSS scale is nonlinear. A 1.0-point change in EDSS at the low end of the scale is often...
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Relapses
Relapse rate is often the primary outcome measure in clinical trials evaluating therapies developed to treat relapsing-remitting MS (RRMS). In many MS studies, a relapse has been defined as the appearance of new or worsening neurological symptoms or the reappearance of old neurological symptoms preceded by a 30-day period of stability. However, a simplified definition of relapse, which does not include a 30-day period of stability, has also been used. Preventing relapses is critical to the patient’s functional status, daily living activities, and QoL. Relapses are also important to quantify because they can be associated with significant residual deficits, and relapse rate in the early stages of the disease can be a key determinant of later accumulation of disability. Relapse outcomes in most clinical trials are measured by (a) annualized relapse rate, (b) average number of relapses per patient, (c) proportion of patients who are relapse free, and (d) the cumulative probability of relapse. While annualized relapse rate, or the number of confirmed relapses per patient per year, is commonly used as the primary outcome measure in MS studies, it is difficult to compare annualized relapse rate with the relapse results of older trials of IM IFNβ-1a, SC IFNβ-1b, SC IFNβ-1a, and glatiramer acetate that used relapse counts per year as the primary outcome measure. Annualized relapse rate, calculated as the total number of relapses experienced by the patient cohort divided by the patient-years at risk, is currently the standard measure for assessing relapses. Because the measurement of annualized relapse rate is not consistent across studies, care should be taken when making cross-trial comparisons to ensure that a similar definition was utilized.

Early relapse activity that is evident while a patient is on treatment has been shown to be a contributing factor in predicting future disability. While it is generally understood that relapses in MS result in cumulative disability, the direct relationship between successive relapses and disability progression has been difficult to demonstrate in clinical trials. An observational study that examined the effect of relapses (defined as the appearance of a new neurological symptom [or a worsening in a previous symptom], lasting more than 48 hours, without fever) on disability progression found that having 1 or more relapses during the first 2 years of IFNβ treatment was associated with earlier progression of disability. Progression of disability was defined by the following change in EDSS: 1.5-point increase for patients with a baseline EDSS score from 0.0 to 2.0, 1 point for scores from 2.5 to 4.0, and 0.5 points for scores equal to or higher than 4.5, confirmed 3 months later. Because of the observational nature of this study, a more simplified definition of relapse, which did not include neurologic stability for the previous 30 days, was employed. For patients who had 1 relapse in the past 2 years, the probability of disability progression was 3-fold greater than for patients who had no relapses (hazard ratio: 3.4; P = 0.005). This increased to a 4-fold greater risk of disease progression in patients with 2 or more relapses during the first 2 years of treatment (hazard ratio: 4.3; P < 0.001). There was no difference in probability of disability progression between patients who had 1 relapse in the past 2 years versus patients who had 2 relapses. However, there were also patients in the study who experienced no relapses and yet had a sustained increase in disability over the 2-year period. Results from a separate study showed that the occurrence of clinical relapses in patients treated with IFNβ had a low specificity in predicting accumulation of disability. The inconsistent findings among these studies highlights the need for further trials examining the relationship between relapses and disability.

Magnetic Resonance Imaging Outcome Measures
MRI outcome measures play an important role in evaluating treatment efficacy in randomized controlled trials, as they provide objective, supportive evidence for clinical endpoints. Conventional MRI techniques, including T2-weighted and gadolinium-enhancing (Gd+) T1-weighted lesions, provide quantitative assessment of inflammatory activity and lesion load. A T2-weighted MRI scan shows the total number of hyperintense lesions, often referred to as the lesion load. A Gd+ MRI scan shows active lesions, signifying a breakdown of the blood-brain barrier and inflammation. Because T2-weighted and Gd+ T1-weighted lesions occur at a higher rate than relapses, these MRI measures are more sensitive indicators of disease activity. A meta-analysis demonstrated an association between lesion load measured early in the disease process and future relapse rate. However, lesion load was not a strong predictor of the development of cumulative impairment or disability. In addition, there is an apparent relationship between lesion load and the degree of accumulated disability over time. In a 15-year follow-up study assessing the predictive value of T2 lesions on the rate of progression of disability in MS, the number of T2 lesions had a small predictive value for progression of disability in RRMS but did not influence the rate of progression in progressive MS. MRI methods and endpoints have evolved to include such parameters as T1 hypointense lesions (so-called black holes) and brain atrophy. These newer methods allow for greater accuracy of lesion detection and the ability to detect unique lesion types, such as gray matter T2 lesions. Combining these newer techniques with conventional MRI-based measures may better predict clinical progression in MS. These MRI techniques and associated outcome measures will be reviewed in the following article of this supplement.
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Development of CDMS

The development of clinically definite MS (CDMS) is also a common outcome in clinical trials of clinically isolated syndrome (CIS). CIS is defined as a first neurologic episode that lasts at least 24 hours and is caused by inflammation/demyelination in 1 or more sites in the central nervous system. Several studies have shown that approximately 60% to 80% of patients with CIS and demyelinating lesions will ultimately experience a second demyelinating event, thus confirming a diagnosis of MS (CDMS by Poser criteria, e.g., 2 relapses and clinical evidence of 2 separate lesions, or 2 relapses and clinical evidence of 1 lesion, and paraclinical evidence of another separate lesion).43,57,63 Future clinical trials will likely include patients who have been diagnosed earlier in their disease course by the use of the more sensitive McDonald criteria.36,64 McDonald criteria include the use of MRI findings for the diagnosis of MS in lieu of the presence of a second relapse, where Poser criteria do not. This allows for the diagnosis of MS in patients with a variety of presentations, including monosymptomatic disease; disease with a typical relapsing-remitting course; and disease with gradual progression, without clear attacks and remissions.64 Results from multiple studies have demonstrated an advantage in early initiation of treatment in order to slow the progression from a CIS to CDMS.41,10,65,67 Patients with CIS have a high risk of developing CDMS, and treatment with IFNβ has shown to be effective in the early stages of MS.67

**IM IFNβ-1a in the Long-Term Treatment of Multiple Sclerosis**

In 1996, IM IFNβ-1a was approved for use in the treatment of MS in the United States and in 1997 in Europe, and it is currently authorized for use in approximately 80 countries.68 As of April 2011, an estimated 402,250 patients with 1,492,407 years of cumulative exposure had been treated with IM IFNβ-1a (Biogen Idec Inc., unpublished data). IM IFNβ-1a is indicated for the treatment of patients with relapsing forms of MS to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations, including relapses.69 Patients with MS in whom efficacy has been demonstrated include those who have experienced a first relapse and have MRI features consistent with MS. The efficacy and safety of this DMT as a first-line treatment for MS is well established, and several clinical studies of IM IFNβ-1a have been published. Most patients who are treated with IM IFNβ-1a experience flu-like symptoms (fever, chills, sweating, muscle aches, and tiredness) early in the course of therapy, but for many patients, these symptoms decrease in frequency with continued treatment. The pivotal phase 3 trial for IM IFNβ-1a was published in 1996,68 followed by the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) in 2000;11 the 5-year CHAMPS extension study in 2006 (the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurologic Surveillance [CHAMPIONS]);65 the Assessment of Drug Utilization, Early Treatment, and Clinical Outcomes (ASSURANCE) long-term follow-up study of the Multiple Sclerosis Collaborative Research Group (MSCRG) in 2010;70 and the 10-year CHAMPS extension study (CHAMPIONS) in 2011.42 A flow chart of the pivotal and follow-up studies of IM IFNβ-1a can be found in Figure 1. A brief overview of the designs of these studies can be found in Table 1, and a summary of study results for IM IFNβ-1a can be found in Table 2. With regard to the review of outcomes from clinical trials, it is important to consider the time frame in which the studies were conducted. The availability of therapies to treat MS has changed substantially over the past 15 years, thereby resulting in differences in the patient populations between earlier and later studies. There are now several DMTs approved to treat MS that were not commercially available at the time of the early studies in this disease, resulting in its being more difficult now to recruit patients who are naive to treatment.71 Additionally, MS is now being detected in patients earlier in the stage of the disease, resulting in clinical trial patient populations with lower overall EDSS scores. Therefore, disease activity in placebo groups will be much lower in more recent trials than in trials from more than 10 years ago.

**Multiple Sclerosis Collaborative Research Group Study and Safety Extension Study**

MSCRG, the pivotal study for IM IFNβ-1a in relapsing MS, was a phase 3, multicenter, double-blinded, placebo-controlled, randomized trial that examined whether systemically administered IFNβ-1a (30 micrograms [μg] IM once per week for up to 104 weeks; n = 158) compared with placebo (n = 143) could slow the progression of irreversible neurological disability associated with relapsing forms of MS.8 Patients were between the ages of 18 and 55 years and had a diagnosis of MS for at least 1 year, a baseline EDSS score between 1.0 and 3.5, at least 2 documented relapses in the prior 3 years, and no relapses for at least 2 months prior to study entry. The primary outcome measure was time to onset of sustained worsening in disability, defined as an increase in EDSS score of at least 1.0 that persisted for at least 6 months. MS relapses were also assessed and were defined as the appearance of new, or worsening of pre-existing neurological, symptoms lasting at least 48 hours in a patient who had been neurologically stable or improving for the previous 30 days, accompanied by objective change on neurological examination (worsening of EDSS score by at least 0.5 point or worsening by at least 1.0 point on the EDSS pyramidal, cerebellar, brainstem, or visual functional system scores). The number and volume of Gd+ lesions were assessed by MRI on a yearly basis. At the time this study was conducted, monitoring of Gd+ lesions was a new imaging modality being used in the clinical setting for the first time. The study was initiated in November 1990, and by early 1993, the reported patient drop-out rate (3%) was considerably lower than the anticipated drop-out rate of 10%.8 This low drop-out rate allowed investigators to end the study approximately 1 year earlier than originally planned without affecting the statistical robustness of the analyses. Fifty-seven percent of the 301 patients (87 placebo patients, 85 IM IFNβ-1a patients) were enrolled early enough to accumulate 2 years of follow-up data.
Results from the MSCRG study demonstrated that time to sustained disability progression was significantly greater in patients treated with IM IFNβ-1a than in those receiving placebo ($P = 0.020$). In addition, the proportion of patients with disability progression at 2 years was significantly lower in the IM IFNβ-1a group than in the placebo group ($21.9\%$ vs. $34.9\%; P = 0.020$) according to Kaplan-Meier estimates. There was also a significant difference between IM IFNβ-1a and placebo in the unsustained mean change in EDSS scores ($0.25$ for IM IFNβ-1a vs. $0.74$ for placebo; $P = 0.020$) as well as in the mean sustained change in EDSS scores ($0.02$ for IM IFNβ-1a vs. $0.61$ for placebo; $P = 0.020$).
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### Table 1: Summary of Studies of Intramuscular Interferon Beta-1a

<table>
<thead>
<tr>
<th>Study Name (Date Published)</th>
<th>Patient Population</th>
<th>Study Type</th>
<th>Duration in Years</th>
<th>Number of Patients Exposed to IM IFNβ-1a 30 µg (Total Enrolled)</th>
<th>Enrollment Criteria</th>
<th>Endpoints Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSCRG (1996)(^8) RRMS</td>
<td>Multicenter, placebo-control, randomized, double-blind</td>
<td>Up to 2</td>
<td>158 (301)</td>
<td>18-55 years old, RRMS for at least 1 year</td>
<td>Participation in MSCRG</td>
<td>Time to sustained disability progression, ARR, Gd+ lesions, safety</td>
</tr>
<tr>
<td>ASSURANCE (2010)(^6) RRMS</td>
<td>Multicenter, observational, open-label, non-standardized treatment, single time point, follow-up</td>
<td>Up to 15</td>
<td>56 (122); 18 of 56 (32%) received placebo in MSCRG, of the 22 patients not on therapy at the 15-year follow-up, 5 never received a DMT and 1 received no DMT after completion of MSCRG, but did receive IM IFNβ-1a during MSCRG</td>
<td>Participation in MSCRG, alive</td>
<td>Change in EDSS and percentage of patients with EDSS scores of at least 4.0, 6.0, or 7.0; data was assessed by current treatment at the 15-year follow-up (on IM IFNβ-1a vs. not on IM IFNβ-1a)</td>
<td></td>
</tr>
<tr>
<td>CHAMPS (2000)(^11) CIS</td>
<td>Multicenter, placebo-control, randomized, double-blind</td>
<td>Up to 3, pre-treatment with corticosteroids</td>
<td>193 (383)</td>
<td>18-50 years old, first acute clinically demyelinating event (optic neuritis, incomplete transverse myelitis, or brainstem or cerebellar syndrome), and at least 2 clinically silent brain lesions (at least 1 ovoid or periventricular) No prior neurologic or visual events consistent with demyelination that lasted more than 48 hours</td>
<td>Participation in CHAMPS in either the placebo or IM IFNβ-1a group</td>
<td>Development of CDMS, Gd+ lesions, T2 lesions</td>
</tr>
<tr>
<td>CHAMPIONS (2006; 5-year study)(^6); (2012; 10-year study)(^4) CIS, CDMS</td>
<td>Observational, open-label, extension</td>
<td>Up to 5</td>
<td>203 (203) [53% (203/383) of CHAMPS patients enrolled in the 5-year CHAMPIONS study]; 155 (155) [76% (155/203) of CHAMPS 5-year study patients enrolled in the 10-year study]</td>
<td>Participation in CHAMPS in either the placebo or IM IFNβ-1a group</td>
<td>Rate of development of CDMS, ARR, EDSS, Gd+ lesions, T2 lesions</td>
<td></td>
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</table>

\(^6\)Groups differed in disease type with 79% (n = 76) with relapsing stable disease and 19% (n = 18) with relapsing active disease in the IT group versus 66% (n = 61) and 32% (n = 30), respectively, in the DT group.

\(^8\)ARR = annualized relapse rate; ASSURANCE = Assessment of Drug Utilization, Early Treatment, and Clinical Outcomes; CDMS = clinically definite multiple sclerosis; CHAMPS = Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study; CHAMPIONS = Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurologic Surveillance; CIS = clinically isolated syndrome; DMT = disease-modifying therapies; DT = delayed treatment; EDSS = Expanded Disability Status Scale; Gd+ = gadolinium enhancing; IFNβ = interferon beta; IM = intramuscular; IT = immediate treatment; MRI = magnetic resonance imaging; MSCRG = Multiple Sclerosis Collaborative Research Group; RRMS = relapsing-remitting multiple sclerosis; μg = micrograms.

Patients receiving IM IFNβ-1a experienced significantly fewer relapses (62%; n = 53/85) than those receiving placebo (74%; n = 64/87; P = 0.030). In this study, the definition of a relapse was based on that of a typical MS trial (the appearance of new neurological symptoms lasting at least 48 hours in a patient who had been neurologically stable or improving for the previous 30 days) but was more stringent in that patients also had to have had an objective change on neurological examination (worsening of 0.5 point on EDSS or a worsening by ≥1.0 point on the pyramidal, cerebellar, brainstem, or visual function system scores). The annualized relapse rate for patients who had completed 104 weeks of treatment by the end of the study was 0.61 in the IM IFNβ-1a group and 0.90 in the placebo group (relative relapse rate reduction = 32%; P = 0.002). Despite the shortened study period, the robustness of this result was confirmed in a sensitivity analysis on all patients irrespective of duration of treatment, which gave annualized relapse rates of 0.67 and 0.82 in the IM IFNβ-1a and placebo groups, respectively (relative relapse rate reduction: 18%; P = 0.040). Additionally, patients receiving IM IFNβ-1a had a significantly lower mean number of Gd+ lesions at 1 year than placebo-treated patients (1.04, standard error [SE] = 0.28 vs. 1.59, SE = 0.31; P = 0.020). Similar results were seen for mean volume of Gd+ lesions in patients receiving IM IFNβ-1a (70.0 cubic millimeters [mm³], SE = 24.9) versus patients receiving placebo (96.5 mm³, SE = 21.2; P = 0.020). These differences between the groups were still evident at the end of the second year of the study.\(^8\)
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### TABLE 2 Summary of Outcomes of Phase 3 Studies of Intramuscular Interferon Beta-1a

<table>
<thead>
<tr>
<th>Study</th>
<th>EDSS/Disability Progression</th>
<th>Relapse</th>
<th>MRI</th>
<th>Development of CDMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSCRG³⁹</td>
<td>Greater time to sustained disability progression in patients treated with IM IFNβ-1a than in those receiving placebo (P=0.020)</td>
<td>Lower ARR for patients treated with IM IFNβ-1a (0.61) versus patients treated with placebo (0.90); P=0.002</td>
<td>Lower mean number of Gd+ lesions at 1 year (IM IFNβ-1a, 1.04, SE=0.28 vs. placebo, 1.59, SE=0.31; P=0.020) and volume of Gd+ lesions at 1 year (IM IFNβ-1a, 70.0 mm³, SE=24.9 vs. placebo 96.5 mm³, SE=21.2; P=0.020) in IM IFNβ-1a-treated patients versus placebo-treated patients</td>
<td>-</td>
</tr>
<tr>
<td>ASSURANCE⁴⁰</td>
<td>Differences in mean EDSS scores for patients on IM IFNβ-1a versus patients not on IM IFNβ-1a (4.4 vs. 5.7; P=0.011)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CHAMPIONS⁵</td>
<td>Few patients developed significant neurologic disability as measured by EDSS score; 71% of patients had an EDSS score ≤1.5, 16% had EDSS scores from 2.0 to 2.5, 13% reached EDSS scores ≥3.0</td>
<td>Mean (SD) ARR was lower for the IT group 0.17 (0.24) than the DT group 0.32 (0.51), P=0.020</td>
<td>Median number of new or enlarging T₁ lesions was lower in the IT group versus the DT group (3.5 vs. 6.0; P=0.050)</td>
<td>Cumulative probability of developing CDMS was 35% in the IM IFNβ-1a treatment group versus 50% in the placebo group at 3 years (rate ratio=0.56, 95% CI=0.38-0.81; P=0.002)</td>
</tr>
<tr>
<td>CHAMPIONS 5-year extension⁶⁰</td>
<td>At 10 years, 81% had EDSS scores &lt;3.0, 9% of all patients and 16% of patients who had CDMS reached an EDSS score ≥4.0, 6% of all patients and 10% of CDMS patients reached an EDSS score ≥6.0</td>
<td>Between years 5 and 10, ARR in the IT group was 2 times that of the IT group (0.31 vs. 0.14; P=0.03)</td>
<td>No differences between IT and DT groups in median number of new or enlarging T₁ lesions (5.0 vs. 7.0, P=0.500) and number of Gd+ lesions (0 lesions: 81 vs. 80; 1 lesion: 11 vs. 15, at least 2 lesions: 4 vs. 3, P=0.870), median T₁ lesion volume (1,906 mm³ vs. 2,089 mm³, P=0.79), or median change in T₁ lesion volume from baseline to 10 years (+2,600 mm³ vs. +2,516 mm³, P=0.640)</td>
<td>Cumulative probability of developing CDMS lower in the IT than the DT group (58% ± 10% vs. 69% ± 9%; unadjusted HR 0.64, 95% CI=0.48-0.87, P=0.004)</td>
</tr>
<tr>
<td>CHAMPIONS 10-year extension⁶²</td>
<td>At 10 years, 81% had EDSS scores &lt;3.0, 9% of all patients and 16% of patients who had CDMS reached an EDSS score ≥4.0, 6% of all patients and 10% of CDMS patients reached an EDSS score ≥6.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Notes:** ARR = annualized relapse rate; ASSURANCE = Assessment of Drug Utilization, Early Treatment, and Clinical Outcomes; CDMS = clinically definite multiple sclerosis; CHAMPIONS = Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurologic Surveillance; CHAMPS = Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study; CI = confidence interval; DT = delayed treatment (defined as patients from the original CHAMPS placebo group who initiated IM IFNβ-1a at the time CDMS developed or after the CHAMPS closeout visit); EDSS = Expanded Disability Status Scale score; Gd+ = gadolinium enhancing; HR = hazard ratio; IFNβ = interferon beta; IM = intramuscular; IT = immediate treatment; mm³ = cubic millimeter; MRI = magnetic resonance imaging; MSCRG = Multiple Sclerosis Collaborative Research Group; SD = standard deviation; SE = standard error.

The majority of patients who enrolled early enough to accumulate 2 years of follow-up completed the MSCRG study (93%). One percent of patients (n = 2) in the placebo group and 4% of patients (n = 7) in the IM IFNβ-1a group discontinued therapy due to adverse events (AEs). AEs occurring more frequently in the IM IFNβ-1a group than in the placebo group included headache, flu-like symptoms, muscle aches, nausea, fever, asthenia, chills, and diarrhea. Injection-site reactions, depression, and menstrual disorders were evident in 10%-15% of patients in both treatment arms.

An open-label extension period of the MSCRG study was conducted to evaluate the safety and immunogenic properties of IM IFNβ-1a when administered to patients for over 6 years. The extension period was not restricted to patients who had participated in the main MSCRG study but was also open to new patients. All patients received once weekly IM IFNβ-1a 30 µg for 6 years (new patients) or up to 8 years (MSCRG patients). Of the 382 patients enrolled in the extension study, 218 had participated in MSCRG, 115 of whom had received IM IFNβ-1a, and 103 had received placebo. Of the 164 “new” patients enrolled into the extension study, 24 were naive to IFNβ treatment. Serum levels of IM IFNβ antibodies were assessed every 6 months. Although the primary focus of this study was immunogenicity and safety, for the purposes of this
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Long-Term Follow-Up of MSCRG: The ASSURANCE Study
Patients who completed the 2-year MSCRG study were eligible to enter the ASSURANCE 15-year multicenter follow-up study.20 Data were captured using a mailed survey. The study objective was to evaluate the long-term tolerability of IM IFNβ-1a and effects on disability and QoL. Patient-reported EDSS scores, which have been shown to highly correlate with physician-derived scores,73 were recorded at 15 years.70 Of the 172 patients who were eligible for inclusion in ASSURANCE, the status of 136 (79%) was ascertained; 14 (8%) patients were reported as deceased. Of the 122 living patients, 56 were receiving IM IFNβ-1a, and 66 patients were receiving either another MS therapy or no therapy at the start of the ASSURANCE follow-up study. The primary study endpoints were change in EDSS score from baseline (start of MSCRG study) and percentage of patients with EDSS scores of ≥ 4.0, ≥ 6.0, and ≥ 7.0. Patients with a change in EDSS of < 1.0 were considered "progression free.

Based on patients’ current treatment at the 15-year follow-up (on IM IFNβ-1a versus not on IM IFNβ-1a), significantly lower mean EDSS scores were seen in ASSURANCE patients who were receiving IM IFNβ-1a at MSCRG baseline (P = 0.034), 2 years (P = 0.031), 8 years (P = 0.0016), and 15 years (P = 0.011) compared with patients who were not.70 Patients who were on IM IFNβ-1a therapy also had a smaller mean change from baseline in EDSS score than patients not currently taking IM IFNβ-1a (2.3 vs. 3.3; P = 0.011). Fewer patients who were on IM IFNβ-1a had progressed to EDSS scores ≥ 4.0 (P = 0.062), ≥ 6.0 (P = 0.007), and ≥ 7.0 (P = 0.008). There was no statistically significant difference in the percentage of patients receiving IM IFNβ-1a who were "progression free" from the time of enrollment in the MSCRG study versus patients not currently on IM IFNβ-1a (26.8% vs. 16.7%; P = 0.326).

The overall results indicated that long-term treatment with IM IFNβ-1a was well tolerated, and no new safety concerns arose over the course of treatment.70 For the 14 deceased patients, the mean time to death since MSCRG enrollment was 9.4 years. Of the 6 patients originally randomized to receive IM IFNβ-1a, the mean time to death since MSCRG enrollment was 11.5 years (median, 12.4; range, 8.0-13.0), and for the 8 deceased patients randomized to placebo, the mean time to death was 7.8 years (median, 6.9; range, 2.6-16.6 years). There was no significant difference in time to death for the 2 groups (P = 0.058). With regard to the evaluation of the results from this study, it is, however, important to note the relatively small patient population. Additionally, 18 of the 56 patients in the ASSURANCE IM IFNβ-1a treatment group had originally received placebo in the MSCRG study.

Early Initiation of Therapy: Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study
CHAMPS was a randomized, placebo-controlled, double-blind trial of 383 patients who had a first CIS, defined as a first acute clinical demyelinating event, and evidence of prior subclinical demyelination on MRI of the brain.11 Patients were randomly assigned to receive weekly injections of IM IFNβ-1a 30 µg (n = 193) or placebo (n = 190). Patients were eligible for the study if they were between the ages of 18 and 50 years and were considered at a high risk for developing CDMS. Patients had a CIS involving the optic nerve, spinal cord, brain stem, or cerebellum that was confirmed on ophthalmologic or neurologic examination. Additionally, patients had to have had at least 2 asymptomatic brain lesions that were at least 3 mm in diameter, and at least 1 lesion had to be periventricular, or ovoid, in shape. The primary study endpoint was the development of CDMS, as defined by Poser criteria.91 Patients were also assessed using MRI for the number of new or enlarging T2 lesions, the volume of T2-weighted lesions, and the number of T1-weighted Gd+ lesions.

MRI outcomes showed significant differences in the median change in volume of T2 lesions between IM IFNβ-1a- and placebo-treated patients at 6 months (IM IFNβ-1a, -123 mm3; placebo, 40 mm3; P < 0.001), 12 months (IM IFNβ-1a, 102 mm3; placebo, 214 mm3; P = 0.004), and 18 months (IM IFNβ-1a, 28 mm3; placebo, 313 mm3; P < 0.001).11 At 18 months, the median increase in lesion volume was 1% in the IM IFNβ-1a group versus 16% in the placebo group (P < 0.001). At 6, 12, and 18 months, patients treated with IM IFNβ-1a had fewer new or enlarging T2 lesions (P < 0.001, P < 0.001, respectively) and fewer T1 Gd+ lesions (P < 0.030, P < 0.020, P < 0.001, respectively) than those treated with placebo. Patients treated with IM IFNβ-1a had 42% fewer Gd+ lesions at 6 months (mean [standard deviation (SD)] IM IFNβ-1a, 0.9 [2.3]; placebo, 1.5 [3.1]; P = 0.030), 55% fewer lesions at 12 months (IM IFNβ-1a, 0.7 [2.0]; placebo, 1.6 [3.8]; P = 0.020), and 67% fewer lesions at 18 months (IM IFNβ-1a, 0.4 [1.5]; placebo, 1.4 [3.6]; P < 0.001).

Immediate treatment initiation of IM IFNβ-1a after a CIS significantly reduced the development of CDMS in high-risk patients.11 The cumulative probability of the development of CDMS was significantly lower in the IM IFNβ-1a treatment group compared with the placebo group at 3 years (rate ratio = 0.56, 95% confidence interval [CI] = 0.38-0.81,
During CHAMPS, the cumulative probability of developing CDMS was 35% in the IFNβ-1a treatment group and 50% in the placebo group. Flu-like symptoms were the most common AE in patients treated with IM IFNβ-1a. Flu-like symptoms were reported in 54% of patients in the IFNβ-1a treatment group and in 26% of patients in the placebo group (P < 0.001).6 Serious AEs occurred in 12 patients receiving IM IFNβ-1a and in 19 patients receiving placebo. Treatment was discontinued due to an AE in <1% (n = 1) of patients in the IFNβ-1a group and in 4% (n = 7) of patients in the placebo group. Treatment was not discontinued in any patient due to an abnormal laboratory value.

5- and 10-Year Extension Studies of CHAMPS: Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurologic Surveillance

The CHAMPIONS study was an ongoing open-label extension study of CHAMPS. The CHAMPIONS study was designed to determine if the benefits of IM IFNβ-1a observed in CHAMPS were sustained over the long term. For the purposes of this article, the 5- and 10-year results were reviewed. Patients were eligible to enroll in the study if they had participated in CHAMPS and their study site elected to participate in CHAMPIONS. Patients were required to meet the following enrollment criteria: (a) completion of the 1-month follow-up visit in CHAMPS, (b) signed informed consent, (c) willingness to enroll in CHAMPIONS less than 5 years after CHAMPS enrollment, (d) no evidence of systemic disease with significant organ dysfunction or potential mortality within 3 years of CHAMPS enrollment, (e) no alternative neurologic diagnosis other than MS following enrollment in CHAMPS, and (f) no participation in another clinical trial of an investigational drug or device. At the end of the enrollment visit, the patient was provided with IM IFNβ-1a and instructions for use, if necessary.

CHAMPIONS specifically examined whether immediate initiation of IM IFNβ-1a was more effective than delayed initiation of treatment. Treatment groups were determined based on the original randomization in CHAMPS; patients who received IM IFNβ-1a in CHAMPS were considered the immediate-treatment (IT) group, while patients receiving placebo were considered the delayed-treatment (DT) group. Patients in the CHAMPS study were given the opportunity to remain on or switch to IM IFNβ-1a 30 µg at the end of the study. Those who had originally received placebo could be treated with IM IFNβ-1a when they developed CDMS or at the completion of the study, whichever occurred first. Because placebo patients could start on IM IFNβ-1a at the onset of CMDS or at the end of the study, whichever came first, there was a range of time during which patients were without treatment. The median time to initiation of IM IFNβ-1a or the first DMT in the DT group was 29 months. Over the course of CHAMPIONS, patients could be on IM IFNβ-1a, on another treatment, or no treatment, according to the discretion of their treating physician. The primary outcome measure was the rate of development of CDMS. Additional outcomes included annualized relapse rate, EDSS score at 5 years, and MRI assessments at 5 years. Significance was predefined at P < 0.01 to take into account multiple assessments. In the CHAMPIONS 5-year study, 64% (32/50) of the CHAMPS study sites participated; 53% (203/383) of patients from CHAMPS were enrolled. An equal distribution of patients from the original CHAMPS IM IFNβ-1a group (n = 100) and the placebo group (n = 103) enrolled in the CHAMPIONS 5-year study. Not all of the CHAMPIONS study sites participated in CHAMPIONS, which is the main reason for patients not continuing in CHAMPIONS. Patient demographics and disease characteristics in the CHAMPIONS 5-year study were similar to those in the CHAMPS study. Ninety-six percent (195/203) of patients completed their 5-year visits, and 98% (198/203) completed the 5-year or subsequent yearly visits per protocol. (Three patients missed the 5-year visit; therefore, therapy at 5 years was reported retrospectively at a subsequent visit.)

Patients who participated in the CHAMPIONS 5-year study were eligible to continue in the 10-year extension if they had no alternative neurologic diagnosis other than MS following enrollment in CHAMPS, if they provided informed consent, and if the study site at which they were enrolled was willing to participate in the 10-year extension. A total of 155 patients enrolled in the 10-year extension. There was a slightly higher number of patients from the IT group (n = 81, 81% of the CHAMPIONS 5-year group) who enrolled in the 10-year study versus the DT group (n = 74, 72% of the CHAMPIONS 5-year group). Reasons given for not participating in the 10-year extension included the following: the patient was lost to follow-up (n = 13), had refused to participate (n = 5), was deceased (n = 1), was participating in another study (n = 1), or there was no reason given (n = 4). The patients who did not participate in the 10-year extension study were predominantly from the original CHAMPIONS DT group (68% [19 of 28]) and had a higher rate of conversion to CDMS at 5 years (57% [16 of 28]) than the 155 patients who did participate (45% [70 of 155]). In the DT group, the median time to initiation of IM IFNβ-1a was 30 months, similar to that seen at the at the start of the 5-year follow-up period.

In the CHAMPIONS 5-year study, very few patients developed significant neurologic disability, as measured by EDSS score. The majority (71%) of patients had an EDSS score ≤ 1.5, 16% had an EDSS score of 2.0 to 2.5, and 13% had an EDSS score ≥ 3.0. At 10 years, the majority of patients (81%, n = 103) had EDSS scores < 3.0, as seen in Table 3.92 Nine percent of all patients and 16% of patients with CDMS reached an EDSS score ≥ 4.0; 6% of all patients and 10% of CDMS patients reached an EDSS score ≥ 6.0. There was no significant difference between the IT and DT groups in the distribution of EDSS scores at both 5 and 10 years.

In the CHAMPIONS 5-year study, the annualized relapse rate for different treatment epochs was evaluated to determine if the reduction in relapses during CHAMPS was sustained once patients originally randomized to placebo were switched to IM IFNβ-1a.65 Mean (SD) annualized relapse rate between years 0 and 2 for the IT and DT populations was 0.15 (0.31) and 0.31 (0.45), respectively (P = 0.004), while at 5 years, mean (SD) annualized relapse rates were 0.17 (0.24) and 0.32 (0.51),
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respectively (P=0.020). Between years 3-5, the annualized relapse rate (SD) was lower in the IT group (0.18 [0.36]) than in the DT group (0.32 [0.71]), although the difference was not statistically significant (P=0.280). However, between years 5 and 10, the annualized relapse rate in the DT group was more than double that in the IT group (0.31 vs. 0.14; P=0.03) despite IM IFNβ-1a use being comparable between groups during that time.62

In the 5-year study, the median number of new or enlarging T2 lesions was lower in the IT group compared with the DT group (3.5 vs. 6.0; P=0.050) at 5 years.63 There was no significant difference between the IT and DT groups in the change in T2 lesion volume from CHAMPS baseline to CHAMPIONS at 5 years. No statistically significant difference was observed in the percentage of patients with Gd+ lesions between the IT (≥ 1, 29%; ≥ 2, 11%) and DT (≥ 1, 30%; ≥ 2, 13%) treatment groups. Additionally, at 10 years, there were no significant differences between the IT (n = 55) and DT (n = 55) groups in median number of new or enlarging T2 lesions (5.0 vs. 7.0, P = 0.500), number of Gd+ lesions (0 lesions: 81 vs. 80; 1 lesion: 11 vs. 15; ≥ 2 lesions: 4 vs. 3; P = 0.870), median T2 lesion volume (1,906 mm³ vs. 2,089 mm³, P = 0.79), or median change in T2 lesion volume from baseline to 10 years (+2,600 mm³ vs. +2,516 mm³, P = 0.640). A summary of MRI outcomes at 10 years is presented in Table 3.42

At 5 years, the cumulative probability of developing CDMS was significantly lower in the IT group compared with the DT group (5-year mean [SD] incidence: 36 [9%] vs. 49 [10%]; P = 0.030). Similarly, at year 10, the cumulative probability of developing CDMS was significantly lower in the IT group than in the DT group (58% ± 10% vs. 69% ± 9%; unadjusted hazard ratio [HR] 0.64, 95% CI = 0.48-0.87, P = 0.004); Figure 2.2 The treatment effect was comparable when adjusting for age, CHAMPS qualifying event, CHAMPS baseline brain MRI T2 lesions number, and baseline number of Gd+ lesions (adjusted HR = 0.61, 95% CI = 0.45-0.82, P = 0.001).

During the entire follow-up period (both 5- and 10-year extensions) of CHAMPIONS, 34 serious AEs occurred in 25 patients, including 2 deaths (metastatic breast cancer and an automobile accident).62,65 Unblinded investigators determined that all serious AEs were unlikely to be related or were unrelated to treatment.65 No new safety concerns arose with IM IFNβ-1a during either study.

Important Considerations for Clinical Trials in MS

With increasing numbers of approved MS drugs available, important considerations have emerged with regard to the design of newer MS trials.74,75 Considerable difficulty exists for initiating placebo-controlled trials for relapsing forms of MS, with patient populations limited to those who have failed therapy or perhaps those who refuse approved therapies because of their expense or mode of administration.74 Some MS trials are incorporating an active comparator, since placebo-controlled trials do not provide information on the comparative efficacy among available agents. As mentioned previously, MS trials are also evolving to include patient populations that are earlier in their disease course and have more advanced MRI methods. These and other shifts in MS trial design must be considered when making comparisons between older and newer studies of MS therapies.

There are several important limitations to consider when interpreting the results of the studies discussed in this article. It is important to note that while patients in the CHAMPIONS study had a diagnosis of CIS and were naive to therapy, patients in the MSCRG study had been diagnosed with CDMS for at least 1 year and may have received prior treatment for MS. Also, patients in the CHAMPIONS study had a significantly lower rate of CDMS during CHAMPS than in CHAMPIONS. Both the ASSURANCE16 and CHAMPIONS extension studies enrolled patient populations that were relatively small, based on select criteria for disease activity, potentially introducing selection bias in the continuing patients. As with all studies, caution should be taken when making cross-trial comparisons.

### TABLE 3 Disability and MRI Outcomes at 10 Years in CHAMPIONS

<table>
<thead>
<tr>
<th>MRI outcomes (n = 110)</th>
<th>Immediate-Treatment Group</th>
<th>Delayed-Treatment Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of new or enlarging T2 lesions, median (quartiles)</td>
<td>5 (1, 12)</td>
<td>7 (3, 17)</td>
<td>0.50d</td>
</tr>
<tr>
<td>Number of Gd+ lesions, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>44 (81)</td>
<td>43 (80)</td>
<td>0.87d</td>
</tr>
<tr>
<td>1</td>
<td>6 (11)</td>
<td>8 (15)</td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>4 (7)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>T2 lesion volume at 10 years, mm³, median (quartiles)</td>
<td>(1,906, 11,902)</td>
<td>(2,089, 11,611)</td>
<td>0.79f</td>
</tr>
<tr>
<td>Change in T2 volume, mm³, from baseline to 10 years, median (quartiles)</td>
<td>+2,600 (±398, +5,862)</td>
<td>+2,516 (±721, +6,682)</td>
<td>0.64f</td>
</tr>
<tr>
<td>EDSS score (n = 127,6 a n (%)</td>
<td>Immediate-Treatment Group</td>
<td>Delayed-Treatment Group</td>
<td>P Value</td>
</tr>
<tr>
<td>≤ 2.5</td>
<td>n = 68</td>
<td>n = 59</td>
<td>0.61d</td>
</tr>
<tr>
<td>3.0-3.5</td>
<td>56 (82)</td>
<td>47 (80)</td>
<td></td>
</tr>
<tr>
<td>4.0-5.5</td>
<td>2 (3)</td>
<td>3 (5)</td>
<td></td>
</tr>
<tr>
<td>≥ 6.0</td>
<td>5 (7)</td>
<td>2 (3)</td>
<td></td>
</tr>
</tbody>
</table>

fThe delayed-treatment group received placebo in the CHAMPS study.11

1Limited to 127 of 155 patients who completed the 10-year visit. Results were similar using last observation carried forward for the 28 subjects who did not complete the 10-year visit (data not shown).

2Fisher exact test. Because of multiple comparisons, P values ≥ 0.01 were considered not significant in the secondary analyses.

3Missing for 2 MRI scans.

4Wilcoxon rank-sum test.

aThe delayed-treatment group received placebo in the CHAMPS study.11

bThe delayed-treatment group received placebo in the CHAMPS study.11

cThe treatment group received placebo in the CHAMPS study.11

### Notes

- **CHAMPS** = Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study; **EDSS** = Expanded Disability Status Scale; **Gd+** = gadolinium enhancing; **mm³** = cubic millimeter; **MRI** = magnetic resonance imaging.
as selecting therapy for patients will become more complicated over the next few years with the introduction of new therapies, some of which have unique safety considerations, the information presented here should be useful when evaluating risk-benefit considerations.

## Conclusions

Disability (as determined by EDSS), annualized relapse rate, and standard MRI measures continue to be the mainstays of efficacy assessment in MS clinical trials. Although newer endpoints, such as MSFC, brain atrophy, and QoL, are becoming more common in MS studies, the traditional outcome measures should continue to be evaluated when considering any new treatment for MS. Both conventional and newly evolving outcome measures should be considered together when evaluating efficacy. For more than 15 years, IM IFNβ-1a has been an effective first-line treatment option and among the most commonly prescribed therapies for patients with MS. With approximately 402,250 patients having been treated with IM IFNβ-1a at the time of this publication, the efficacy and safety profile of IM IFNβ-1a has been well established in the post-marketing setting, and no new safety considerations have emerged. As selecting therapy for patients will become more complicated over the next few years with the introduction of new therapies, some of which have unique safety considerations, the information presented here should be useful when evaluating risk-benefit considerations.

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