Drug Class Review
on
Disease-modifying drugs for Multiple Sclerosis

Final Report
Evidence Tables

July 2007

The Agency for Healthcare Research and Quality has not yet seen or approved this report

A scan of the medical literature is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). Upon review of the last scan, the Drug Effectiveness Review Project governance group elected not to proceed with another full update of this report. Some portions of the report may not be up to date.

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Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of β interferons					
Author Year	**Aims**	**Time period covered**	**Eligibility criteria**	**Number of patients**	**Characteristics of identified articles: study designs**
Rice 2001 (Cochrane) Good	To assess the effects of recombinant interferons in adults with RRMS.	1966-2000	Double-blind, placebo-controlled RCTs of SC or IM interferons	919 pts	Seven trials: all placebo-controlled, double-blind RCTs
Namaka et al 2006 Fair-good Limited data provided on types of trials included	To determine the incidence and clinical importance of neutralizing antibodies in patients with RRMS	1983-2005	NR, however included studies had to meet American Academy of Neurology standard on reliability of trial data.	NR	Ten trials: 3 head-to-head trials; 5 placebo-controlled trials; 2 dose comparison trials

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of β interferons				
Author Year	**Characteristics of identified articles: populations**	**Characteristics of identified articles: interventions**	**Main results**	**Subgroups**
Rice 2001 (Cochrane) Good	RRMS pts only	Inf β 1a IM: 6.0 MIU/wk Inf β 1b SC: 1.6 MIU and 8.0 MIU every other day Placebo this systematic review also included inf α 2a studies, however these are outside the scope of this review	Exacerbation free: Pooled risk difference for interferons (inc. inf α 2a): RR -23% 95%CI -8% - -39% w/no differences among interferons Exacerbations: Pooled RR of exacerbations w/interferon use: 1.11 95% CI 0.73-1.68; p=0.6 Disease progression: WMD in EDSS change: -0.25 95% CI -0.05 - -0.46; p=0.001	NR
Namaka et al 2006 Fair-good Limited data provided on types of trials included	RRMS pts only	Inf β 1a IM 30 ug/wk Inf β 1a IM 60 ug/wk Inf β 1a SC 22 ug/wk Inf β 1a SC 22ug 3x/wk Inf β 1a SC 44 ug 3x/wk Inf β 1b SC 1.6 MIU every other day Inf β 1b SC 8.0 MIU every other day placebo	Presence of NABs varies from 2-45% in β interferon treated patients Odds of relapse during NAB+ period b/t 1.51 and 1.58 (p<0.03) Time to relapse also shortened with NAB+ status to 244 days Inf β 1a IM appeared to have lowest rates of antibody presence compared to other interferon products	NR

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of β interferons		
Author **Year**	**Adverse events**	**Comments**
Rice **2001** **(Cochrane)** Good	Pooled rates: interferons vs placebo Flu-like symptoms - p=0.001 Fever - p<0.0001 Myalgias/arthalgias - p<0.0001 Fatigue - p<0.05 Nausea/vomiting - p<0.2 Headache - p<0.02 Injection-site reactions - p=0.0001	
Namaka et al **2006** Fair-good Limited data provided on types of trials included	NR	

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of β interferons					
Author Year	**Aims**	**Time period covered**	**Eligibility criteria**	**Number of patients**	**Characteristics of identified articles: study designs**
Goodin et al 2007 Fair-good Methods of article selection not reported, very limited data on included studies	To assess the clinical impact of neutralizing antibodies to interferon beta; Report of the Therapeutics and Technology Assessment Csubcommittee of the American Academy of Neurology	1966-2005	Studies 'reporting clinical or radiographic outcomes in both antibody positive and antibody negative patients" - design criteria not stated	923	List of 13 studies includes trials and non-RCT designs

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of β interferons				
Author Year	**Characteristics of identified articles: populations**	**Characteristics of identified articles: interventions**	**Main results**	**Subgroups**
Goodin et al 2007 Fair-good Methods of article selection not reported, very limited data on included studies	any MS pateint	Inf β 1a IM 30 ug/wk Inf β 1a IM 60 ug/wk Inf β 1a SC 22 ug/wk Inf β 1a SC 22ug 3x/wk Inf β 1a SC 44 ug 3x/wk Inf β 1b SC 1.6 MIU every other day Inf β 1b SC 8.0 MIU every other day placebo	Class II and III evidence indicates all 3 ifns are associated with the production of NAbs (Level A). NAbs in the serum are probably associated with a reduction in the clinical effectiveness of Inf β treatment (Level B). The rate of NAb production is probably less with Inf β-1a treatment than with IInf β-1b treatment, although the magnitude and persistence of this difference is difficult to determine (Level B). It is probable that there is a difference in seroprevalence due to variability in the dose ofInf βor in the frequency or route of its administration (Level B). Inf β-1a IM is less immunogenic than Inf β-1a or IInf β-1b given >1 times per week SQ (Level A). Because NAbs disappear in some patients even with continued Inf β treatment (especially with low titers), the persistence of this difference is difficult to determine (Level B). Sustained **high**-titer NAbs (>100 to 200 NU/mL) is associated with a reduction in the therapeutic effects of Inf β on clinical measures of MS disease activity.	NR

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Systematic reviews of β interferons		
Author **Year**	**Adverse events**	**Comments**
Goodin et al **2007** Fair-good Methods of article selection not reported, very limited data on included studies	NR	

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of glatiramer acetate					
Author Year	**Aims**	**Time period covered**	**Eligibility criteria**	**Number of patients**	**Characteristics of identified articles: study designs**
Munari 2003 (Cochrane) Good	To determine efficacy and safety of glatiramer acetate in MS patients.	1966-2004	RCTs, either single or double blind, of GA vs placebo in MS pts	646 pts	4 RCTs, described in 17 papers (including 5 abstracts and one letter)
Martinelli Boneschi 2003 Fair no systematic search for included studies; no quality assessment or data validation methods reported	To assess the efficacy of GA in treating the following outcomes in RRMS pts: annualized relapse rate, on-trial # of relapses, time to first relapse and accumulated disability and to explore the role of individual clinical variables as predictors of relapse rate and treatment efficacy.	NR	Double-blind, placebo-controlled RCTs assesing efficacy of GA	540 pts	3 RCTs, described in 4 papers.

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of glatiramer acetate				
Author Year	**Characteristics of identified articles: populations**	**Characteristics of identified articles: interventions**	**Main results**	**Subgroups**
Munari 2003 (Cochrane) Good	Adults (range 18-60yrs) with RRMS (3 trials) and "chronic progressive" MS (Note: "Chronic progressive" refers to a combo of PP and SPMS) Concomitant meds included methylprednisolone and/or unspecified "standard steroids" as rescue therapy in all trials; "symptomatic" medication in 1 trial; "conventional" medication in 1 trial	GA: 20 mg/day self-administered subcutaneously (RRMS) 30 mg BID self-administered subcutaneously (CPMS) Placebo	Disease progression: 2 yrs - pooled RR of progression 0.77 (95% CI 0.51-1.14, p=0.19) in RRMS pts and 0.69 (95% CI 0.33-1.46, p=0.19 in CPMS. For all pts, regardless of MS type, RR 0.75 (95% CI 0.53-1.07. p=0.11) Mean change in EDSS: 2 yr mean difference -0.33 (95% CI -0.58 - -0.08, p=0.01) in favor of GA in RRMS pts 35 mo mean difference -0.45 (95% CI -0.74 - -0.16, p=0.002 in favor of GA in RRMS pts Exacerbations: RRs of at least 1 exacerbation were: 0.77 (0.61-0.99, p=0.04) within 1 yr of treatment 0.87 (0.74-1.02, p=0.08) at 2 yrs, and 0.89 (0.74-1.06, p=0.19) at 35 mos. Conclusion: No beneficial effect of GA use for main outcomes (disease progression and risk of relapse/exacerbations)	Disease severity: Relapse rate was higher for pts w/higher baseline EDSS regardless of treatment (GA or placebo.) Interpolated figures (from Figure 1 in text): EDSS 0-2: Relapse rate 0.7 GA vs 0.875 placebo EDSS >2-4: Relapse rate 0.8 GA vs 1.15 placebo EDSS >4: Relapse rate 0.9 GA vs 1.3 placebo
Martinelli Boneschi 2003 Fair no systematic search for included studies; no quality assessment or data validation methods reported	Adults (range 18-50 yrs) with RRMS with at least one (one study) or two (two studies) documented relapses within the previous 2 yrs with no clinical relapses in 30 days preceding study entry. EDSS between 0.0 and 5.0 (two studies) or 6.0 (one study.)	GA: 20 mg/day self-administered subcutaneously Placebo	Annualized relapse rate GA vs placebo: 0.82 vs 1.14 (p=0.004) Number of relapses: RR 0.64 (95 % CI 0.52-0.78; p<0.0001) Time to first relapse GA vs placebo: 322 days vs 219 days (ratio 1.59; 95% CI 1.16-2.19; p=0.005)	NR

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of glatiramer acetate		
Author **Year**	**Adverse events**	**Comments**
Munari **2003** **(Cochrane)** Good	Withdrawals due to AEs: 10/269 (3.7%) for GA; 3/269 (1.1%) for placebo Serious AEs: none were described in any of the 4 trials. Non-serious AEs: Patterned reactions consisting of flushing, chest tightness, sweating, palpitations and anxiety in GA pts (RR 3.40; 2.22-5.21, p=<0.00001) Dizziness in GA pts (RR 1.96, 1.38-2.78, p=0.0002) Palpitations in GA pts (RR 2.23, 1.16-4.28, p=0.02) No diff b/t GA and placebo for other non-serious AEs	
Martinelli Boneschi **2003** Fair no systematic search for included studies; no quality assessment or data validation methods reported	NR	

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of mitoxantrone					
Author Year	**Aims**	**Time period covered**	**Eligibility criteria**	**Number of patients**	**Characteristics of identified articles: study designs**
Martinelli Boneschi 2005 (Cochrane) Good	To assess efficacy and safety of mitoxantrone for RR, PR and SPMS.	1966-2005	Double-blind, placebo-controlled RCTs	270 pts	Four studies: all double-blind, placebo-controlled RCTs. One study, identified as placebo-controlled, was of mx + steriod vs steroid alone.

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of mitoxantrone				
Author Year	**Characteristics of identified articles: populations**	**Characteristics of identified articles: interventions**	**Main results**	**Subgroups**
Martinelli Boneschi 2005 (Cochrane) Good	Adults (range 18-65 yrs) with diagnosis or RR or SPMS and clear disease progression based on EDSS scores. Disease duration was <10 yrs in two studies and unspecified in two studies. One study included patients identified as PRMS, however the description of disability described more closely matches the definition of worsening RRMS.	Mitoxantrone Placebo	Disease progression: 1 yr results - data available from 51 pts 1 study: 8 pts had disease progression (2/27 mx pts (7.4%) and 6/24 placebo (25%.) Fixed effect model OR 0.24 (95% CI 0.04-1.33, p=0.1) 2 yr results - data available from 179 pts in 2 studies: 27 pts had disease progression (6/90 mx pts (6.6%) and 21/89 placebo pts (23.6%.) Fixed effects OR 0.23 (95% CI 0.09-0.59, p=0.0002) Mean change in EDSS: 1yr results - data available from small (n=25) subgroup found no SS difference between treatments (mean difference -0.35; 95% CI -0.86-0.16, p=0.18) 2 yr results - data from 175 pts found SS difference between treatments (mean difference -0.36; 95% CI -0.7- -0.02, p=0.04) Relapse rate: 6mo/1yr results - 45/93 (48.3%) of pts in 2 studies experienced no relapse at 6mo/1yr (68.7% mx pts; 28.8% placebo) OR 5.4 (95% CI 2.2-13.1, p=0.0002) 2 yr results - 79/179 (44.1%) of pts in 2 studies experienced no relapse at 2 yrs (56.6% mx pts; 31.4% placebo) OR 3.11 (1.68-5.72, p=0.0003)	NR

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Systematic reviews of mitoxantrone		
Author Year	**Adverse events**	**Comments**
Martinelli Boneschi 2005 (Cochrane) Good	Withdrawals: Due to major or minor AEs - 13/139 mx pts (9.4%); 3/131 placebo/control pts (2.3%) All (include lost to f/u) - 33/139 mx pts (23.7%); 30/131 placebo/control pts (22.9%) Specific AEs: Amenorrhea: OR 22.3 (4.0-123.0, p=0.0004) for mx vs placebo-treated female pts; OR 8.3 (1.0-67.2, p=0.05) for persistant amennorhea following end of therapy for mx vs placebo-treated pts. Cardiac: decrease of Left Ventricular Ejection Fraction (LVEF) below 50% in 5/138 pts (3.6%) of mx pts OR 5.7 (95% CI 0.7-48.4, p=0.11) No serious cardiac AEs reported in any mx or placebo pts. Nausea/vomiting: 86/138 mx pts (62.3%) vs 20/130 placebo pts (15.4%) Alopecia: 65/138 mx pts (47.1%) vs 25/130 placebo pts (19.2%) UTI: 35/138 mx pts (25.4%) vs 14/130 placebo pts (10.8%)	Some heterogenetity among studies regarding types of pts (diagnosis) and intervention schedules

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of immunomodulatory drugs for MS					
Author Year	**Aims**	**Time period covered**	**Eligibility criteria**	**Number of patients**	**Characteristics of identified articles: study designs**
Clegg et al 2000, 2001 Fair-Good Summary of total number of included patients with detailed summary of their baseline characteristics not included	To compare the clinical and cost effectiveness of various immunomodulatory treatments for MS	1980-2000	Previously conducted systematic reviews; comparative RCTs, including placebo-controlled trials; cost utility studies	NR	Seven placebo-controlled trials of relevant interventions - β interferons, glatiramer acetate and mitoxantrone (numerous other trials included relating to interventions outside the scope of this review)

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of immunomodulatory drugs for MS				
Author Year	**Characteristics of identified articles: populations**	**Characteristics of identified articles: interventions**	**Main results**	**Subgroups**
Clegg et al 2000, 2001 Fair-Good Summary of total number of included patients with detailed summary of their baseline characteristics not included	Not prespecified although patients from included studies were a mix of RRMS and SPMS	Interferon β 1a Interferon β 1b Glatiramer acetate Mitoxantrone	No comparative analysis of effectiveness; summary of trial results presented and discussed within this review	NR

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of immunomodulatory drugs for MS		
Author **Year**	**Adverse events**	**Comments**
Clegg et al **2000, 2001** Fair-Good Summary of total number of included patients with detailed summary of their baseline characteristics not included	No comparative analysis of adverse events; summary of trial results presented and discussed within this review	

Evidence Table 2. Head-to-head trials of beta-interferons

Study	Population Type	Design	Recruitment	Eligibility	Exclusion
Durelli 2002 Italy INCOMIN	RRMS	Open Parallel Multicenter Setting: NR	Screened:205 Eligible: 188 Enrolled:188 Withdrawn:24 Lost to F/U: 6 Analyzed: 188	Adults 18-50 years with clinically definite RRMS, baseline EDSS 1-3.5, two documented relapse in preceding 2 years with no relapse in 30 days prior to study.	Previous systemic beta interferon treatment, immunosuppressive or immunomodulatory drugs except corticosteroids; pregnant of lactating women and/or unwillingness to practice birth control; major depression or suicide attempt; clinically significant heart, liver, renal or bone marrow disease.
Etemadifar 2006 Iran	RRMS	Single Blind Parallel Multicenter Specialty Clinic	Screened:NR Eligible:90 Enrolled:90 Withdrawn:0 Lost to F/U:0 Analyzed:90	Men and women of 15-50 years with a clinical or laboratory supported diagnosis of relapsing MS and with >= 2 relapses within the 2 year period to treatment initiation documented by a neurologist and sould have a EDSS score of <=5.	Exclusion criteria included history of severe allergic or anaphylactic reaction to any interferon, or to other components of drug formulation, no evidence of neurologic, psychiatric, cardiac, endocrinologic, hematologic, hepatic, renal, active malignancy, auto immune diseases or other chronic diseases, history of an uncontrolled seizure or suicidal ideation or an episode of severe depression within 3 months before enrollment, lactation and pregnancy as determined by history, physical examination and screening blood tests.
Koch-Henriksen 2006 Denmark Danish Multiple Sclerosis Study Group	RRMS	Single Blind Parallel Multicenter Research Center	Screened:NR Eligible:421 Enrolled:301 Withdrawn:77 Lost to F/U:NR Analyzed:	RRMS by Poser criteria or laboratory supportive of definitive MS, at least 2 relapses within 2 years prior to enrollment, stable symptoms for 30 days, 18-55 years, EDSS 0-5.5.	Pregnanacy or risk of pregnanacy, breast feeding, serious epilepsy, liver disease, prior treament with IFN beta 1b, hypersensitivity to IFN beta, genatamycin or paracetamol.

Evidence Table 2. Head-to-head trials of beta-interferons

Study	Sample size, Age, Gender, Ethnicity
Durelli **2002** **Italy** **INCOMIN**	N=188 Mean age (SD): 36 (range: 18-50) 34.57% male 65.43% female
Etemadifar **2006** **Iran**	N=90 Mean age (SD): 28.5 (7.0) (range: 18-49) 24.44% male 75.56% female
Koch-Henriksen **2006** **Denmark** **Danish Multiple Sclerosis Study Group**	N=301 Mean age (SD): 37 (range: 18-55)

Evidence Table 2. Head-to-head trials of beta-interferons

Study	Population Type	Design	Recruitment	Eligibility	Exclusion
Panitch 2002 USA, Canada, Europe EVIDENCE	RRMS	SingleBlind Parallel Multicenter Research Center	Screened:767 Eligible:688 Enrolled:677 Withdrawn:46 Lost to F/u:1 Analyzed:677	IFN-naïve, definite RRMS, EDSS 0-5.5, >/= 2 exacerbations in past 2 years.	Prior IFN use, cladribine or lyphoid irradiation, glatiramer or cytokine therapy in past 3 months, IVIG in past 6 months, other immunomodulatory agents in past 12 months.

Evidence Table 2. Head-to-head trials of beta-interferons

Study	Sample size, Age, Gender, Ethnicity
Panitch 2002 USA, Canada, Europe EVIDENCE	N=677 Mean age (SD): 38 (range: 18-55) 25.26% male 74.74% female 91% white

Evidence Table 3. Effectiveness and adverse events in head-to-head trials of beta-interferons

Study	Dosage, Population	Outcomes	Withdrawals
Durelli 2002 Italy INCOMIN Efficacy Quality: Fair Adverse event quality: Poor	Interferon beta-1a (Avonex) 30 ug (6MIU) once a week for 24 months N=92 Male: 35 (38%) Female: 57 (62%) Mean age (SD): 35 (7.9)	EDSS increase of at least 1.0 or more or 0.5 or more: 28 (20%) Mean change in EDSS: -0.54 Mean EDSS scores: 2.5 (1.1) Annualized relapse rate: 0.7 (SD 0.9), p: 0.3 Mean rate of steroid use per relapse: 0.5 (0.8) Proportion of relapse-free patients: 33 (36%), p: 0.03	Total withdrawals: 19 (20.6%) AE withdrawals: 1 (1%)
Durelli 2002 Italy INCOMIN Efficacy Quality: Fair Adverse event quality: Poor	Interferon beta-1b (Betaseron) 250 ug (8MIU) every other day for 24 months N=96 Male: 30 (31%) Female: 66 (69%) Mean age (SD): 39 (7.1)	EDSS increase of at least 1.0 or more or 0.5 or more: 13 (13%) Mean change in EDSS: -0.13 Mean EDSS scores: 2.1 (1.0) Annualized relapse rate: 0.5 (SD 0.7), p: 0.03 Mean rate of steroid use per relapse: 0.38 (sd 0.62) Proportion of relapse-free patients: 49 (51%), p: 0.03	Total withdrawals: 11 (11.5%) AE withdrawals: 5 (5.2%)

Evidence Table 3. Effectiveness and adverse events in head-to-head trials of beta-interferons

Study	Adverse Events	Comments
Durelli 2002 Italy INCOMIN Efficacy Quality: Fair Adverse event quality: Poor	Abnormal liver function test: 23/88 (26.1%) Depression: 18/88 (20.5%) Fatigue/Tiredness: 52/88 (59.1%) Fever: 63/88 (71.6%) Flu-like illness: 68/88 (77.3%) Headache: 6/88 (6.8%) Injection site reactions (e.g. bleeding): 7/88 (8%) Total patients reporting any AE:1/88 (1.1%)	On Outcome:Time to sustained progression 1b > 1a, p<0.01 On Adverse event: AE analysis is based only on patients completing follow-up.
Durelli 2002 Italy INCOMIN Efficacy Quality: Fair Adverse event quality: Poor	Abnormal liver function test: 22/94 (23%) Depression: 18/94 (19.1%) Fatigue/Tiredness: 45/94 (47.9%) Fever: 69/94 (73.4%) Flu-like illness: 72/94 (76.6%) Headache: 15/94 (16%) Injection site reactions (e.g. pain): 35/94 (37.2%) Total patients reporting any AE: 5/94 (5.3%)	

Evidence Table 3. Effectiveness and adverse events in head-to-head trials of beta-interferons

Study	Dosage, Population	Outcomes	Withdrawals
Etemadifar 2006 Iran Efficacy quality: Fair Adverse event quality: Poor	Interferon beta-1a (Avonex) Injection 30 Ug once a week for 24 months N=30 Male: 6 (27%) Female: 24 (35%) Mean age (SD): 28 (1.2)	Mean change in EDSS: 0.1, CI: -0.2-0.5 Mean EDSS scores: 1.8 (1.4) Mean change in relapses per person-yr: 0.8, p: <0.001, CI: 0.5-1.2 Proportion of relapse-free patients: 6 (20)	Total withdrawals: NR AE withdrawals: NR
Etemadifar 2006 Iran Efficacy quality: Fair Adverse event quality: Poor	Interferon beta-1a (Rebif) injection 44 ug three times a week for 24 months N=30 Male: 7 (32%) Female: 23 (34%) Mean age (SD): 27 (1.4)	Mean change in EDSS: 0.3 at 24 months, p: <0.05, CI: 0.03-0.5 Mean EDSS scores: 1.8 (1.2) Mean change in relapses per person-yr: 1.8, p: <0.001, CI: 1.3-2.2 Proportion of relapse-free patients: 17 (57%)	Total withdrawals: NR AE withdrawals: NR

Evidence Table 3. Effectiveness and adverse events in head-to-head trials of beta-interferons

Study	Adverse Events	Comments
Etemadifar 2006 Iran Efficacy quality: Fair Adverse event quality: Poor	NR. See comments	On population: Mean age is for onset of MS, not at the time of study. Age at time of study NR. On outcome:ANOVA analysis of EDSS at end of trial indicaed all groups improved significantly ($p<0.001$), but significant differences were found between the drugs - favoring IFN beta 1b, but p value not reported. On AE: Interferon products were well tolerated and most of the adverse events reported were mild in severity.
Etemadifar 2006 Iran Efficacy quality: Fair Adverse event quality: Poor	NR	

Evidence Table 3. Effectiveness and adverse events in head-to-head trials of beta-interferons

Study	Dosage, Population	Outcomes	Withdrawals
Etemadifar 2006 **Iran** Efficacy quality: Fair Adverse event quality: Poor	Interferon beta-1b (Betaseron) Injection 250 ug every other day for 24 months N=30 Male: 9 (41%) Female: 21 (31%) Mean age (SD): 30 (1.4)	Mean change in EDSS: 0.7, p: <0.001, CI: 0.5-0.9 Mean EDSS scores: 1.2 (0.6) Mean change in relapses per person-yr: 1.5, p: <0.001, CI: 1.2-1.8 Proportion of relapse-free patients: 13 (43%)	Total withdrawals: NR AE withdrawals: NR

Evidence Table 3. Effectiveness and adverse events in head-to-head trials of beta-interferons

Study	Adverse Events	Comments
Etemadifar 2006 Iran Efficacy quality: Fair Adverse event quality: Poor	NR	

Evidence Table 3. Effectiveness and adverse events in head-to-head trials of beta-interferons

Study	Dosage, Population	Outcomes	Withdrawals
Koch-Henriksen 2006 Denmark Danish Multiple Sclerosis Study Group Efficacy quality: Fair Adverse event quality: Poor	Interferon beta-1a (Rebif) 22 mcg weekly N=143 Mean age (SD): 37 Ratio of female to male=1.83:1 Relapses in previous 2 years mean (range): IFN 1a 3.2 (2-15) EDSS at baseline mean (range) IFN 1A 2.98	EDSS increase of at least 1.0 or more or 0.5 or more: 36 (25.1%) at 2 years Time to confirmed progression: 651days Annual exacerbation rates (per patient-year): 0.66 at 2 yr, CI: 0.52-0.83 Annual exacerbation rates (per patient-year): 0.71 at 1+2 yrs, CI: 0.61-0.82 Annual exacerbation rates (per patient-year): 0.74 at 1 yrs, CI: 0.60-0.90 Exacerbation requiring hospitalization: 0.17 at 2, CI: 0.12-0.23 Mean rate of steroid use per relapse: 0.21 at 2, CI: 0.16-0.28 Median Time to first relapse (days): 450 days	Total withdrawals: 33 (23%) AE withdrawals: 18 (12.5%)

Evidence Table 3. Effectiveness and adverse events in head-to-head trials of beta-interferons

Study	Adverse Events	Comments
Koch-Henriksen 2006 Denmark Danish Multiple Sclerosis Study Group Efficacy quality: Fair Adverse event quality: Poor	Depression: 12/301 (4%) Fever: 14/301 (4.7%) Flu-like illness: 29/301 (9.6%) AE data reported only for combined groups, stated to be non-significant between groups.	On Design: Those who qualified but refused randomization were given IFN-beta and followed as well. On population: Ratio of female to male=1.83:1, Relapses in previous 2 years; mean (range): IFNBeta 1a 3.2 (2-15), IFNBeta 1B: 3.04 (2-8) EDSS at baseline mean (range) IFNBeta 1a 2.98 (0-5.5) ifN 1B 2.82 (0-5.5) On Outcome:Annualized relapse rate IFN beta1b va 1a: p=0.86 1yr, 2 yr = 0.97, Time to frist relapse: HR 0.98 (0.72-1.32) IFN beta1a vs 1b, Time to sustained proression HR 0.905 (0.56-1.45) IFNbeta1a vs 1b. Multivariate regression: age, gender, center not found SS

Evidence Table 3. Effectiveness and adverse events in head-to-head trials of beta-interferons

Study	Dosage, Population	Outcomes	Withdrawals
Koch-Henriksen 2006 Denmark Danish Multiple Sclerosis Study Group Efficacy quality: Fair Adverse event quality: Poor	Interferon beta-1b (Betaseron) 250 mcg every other day N=158 Mean age (SD): 38 Ratio of female to male=1.83:1 Relapses in previous 2 years mean (range): 3.04 (2-8) EDSS at baseline mean (range) 2.82 (0-5.5)	EDSS increase of at least 1.0 or more or 0.5 or mo: 33 (20.9%) at 2 yr time to confirmed progression: 645.6 days Annual exacerbation rates (per patient-year): 0.70 at 1+2 yr, CI: 0.60-0.81 Annual exacerbation rates (per patient-year): 0.76 at 1 yr, CI: 0.63-0.92 Annual exacerbation rates (per patient-year): 0.66 at 2 yr, CI: 0.52-0.82 Exacerbation requiring hospitalization: 0.19 at 2 yr, CI: 0.14-0.25 Mean rate of steroid use per relapse: 0.20 at 2yr, CI: 0.15-0.27 Median Time to first relapse (days): 431 days	Total withdrawals: 44 (28%) AE withdrawals: 24 (15.2%)

Evidence Table 3. Effectiveness and adverse events in head-to-head trials of beta-interferons

Study	Adverse Events	Comments
Koch-Henriksen 2006 Denmark Danish Multiple Sclerosis Study Group Efficacy quality: Fair Adverse event quality: Poor	Depression: 12/301 (4%) Fever: 14/301 (4.7%) Flu-like illness: 29/301 (9.6%) AE data reported only for combined groups, stated to be non-significant between groups.	

Evidence Table 3. Effectiveness and adverse events in head-to-head trials of beta-interferons

Study	Dosage, Population	Outcomes	Withdrawals
Panitch 2002 **USA, Canada, Europe** **EVIDENCE** **Efficacy quality: Fair** **Adverse event quality: Poor/Fair**	Interferon beta-1a (Avonex)30 mcg once weekly N=338 Mean age (SD): 37 Mean EDSS 2.0 Median (mean) duration of MS, y: 4 (6.6) Median (mean) # relapses in 2 years: 2.0 (2.6)	Prop. of patients with EDSS deterioration: 49 at 48 wks Prop. of patients with EDSS deterioration: 0.17 at 60 wks Neutralizing antibodies: 7/330 (2%) at 48 wks Annual rate of 1-point EDSS progressions: 0.28 at 60 wks Annualized relapse rate: 0.65 at 60 wks Mean rate of steroid use per relapse: 0.19 at 24 wks Mean relapse rate: 0.40 at 24 wks Mean relapse rate: 0.64 at 48 wks Median Time to first relapse (days): 6.7 at 60 wks Proportion of relapse-free patients: 63% (214/338) at 24 wks Proportion of relapse-free patients: 52% (177/338) at 48 wks Proportion of relapse-free patients: 48% at 60 wks	Total withdrawals: 21 (6.2%) AE withdrawals: 14 (4.1%)

Evidence Table 3. Effectiveness and adverse events in head-to-head trials of beta-interferons

Study	Adverse Events	Comments
Panitch 2002 **USA, Canada, Europe** **EVIDENCE** Efficacy quality: Fair Adverse event quality: Poor/Fair	Abnormal liver function test: 10/337 (3%) Depression: 18/337 (5.3%) Fatigue/Tiredness: 20/337 (5.9%) Fever: 8/337 (2.4%) Flu-like illness: 53/337 (15.7%) Injection site inflammation: 9/337 (2.7%) Injection site pain: 10/337 (3%) Injection site reactions (e.g.bleeding): 33/337 (9.8%) Lymphopenia: 5/337 (1.5%)	On outcome: Relapse Free at 24 weeks: OR adjusted for Center = 1.9 (1.3-2.6) Time to first relapse: HR 0.70 (0.55-0.98) 44mcg/30 mcg

Evidence Table 3. Effectiveness and adverse events in head-to-head trials of beta-interferons

Study	Dosage, Population	Outcomes	Withdrawals
Panitch 2002 **USA, Canada, Europe** **EVIDENCE** Efficacy quality: Fair Adverse event quality: Poor/Fair	Interferon beta-1a (Rebif) 44 mcg three times weekly N=339 Mean age (SD): 38	Prop. of patients with EDSS deterioration: 43 at 48 wks Prop. of patients with EDSS deterioration: 0.16 at 60 wks Neutralizing antibodies: 84/335 (25%) at 48 wks Annualized relapse rate: 0.54 at 60 wks Mean annual rate of steriod courses: 0.19 at 60 wks Mean rate of steroid use per relapse: 0.12 at 48 wks Mean relapse rate: 0.29 at 24 wks Mean relapse rate: 0.54 at 48 wks Median Time to first relapse (days): 13.4 at 60 wks Median Time to first relapse (days): HR 0.70 at 60 wks, p: 0.002, CI: 0.56-0.88 Proportion of relapse-free patients: 75% (254/339) at 24 Wks Proportion of relapse-free patients: 62% (209/339) at 48 wks Proportion of relapse-free patients: 56% at 60 wks Proportion of relapse-free patients: OR 1.5 at 60 wks, p: 0.023, CI: 1.1-2.0`	Total withdrawals: 25 (7.4%) AE withdrawals: 16 (4.7%)

Evidence Table 3. Effectiveness and adverse events in head-to-head trials of beta-interferons

Study	Adverse Events	Comments
Panitch 2002 **USA, Canada, Europe** **EVIDENCE** Efficacy quality: Fair Adverse event quality: Poor/Fair	abnormal liver function test: 18/339 (5.3%) Depression: 17/339 (5%) Fatigue/Tiredness: 18/339 (5.3%) fever: 6/339 (1.8%) Flu-like illness: 45/339 (13.3%) injection site inflammation: 35/339 (10.3%) injection site pain: 19/339 (5.6%) Injection site reactions (e.g.bleeding):85/339 (25.1%) Lymphopenia: 14/339 (4.1%)	

Evidence Table 4. Placebo-controlled trials of interferon beta 1a

Study	Population Type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
Andersen 2004 Multiple European Countries	SPMS	Double-blind Parallel Multicenter Setting: NR	Screened: NR Eligible: NR Enrolled: 371 Withdrawn: 63 LostToFU: NR Analyzed: 301	18-65 years of age, diagnosis of clinically definite MS for at least 1 year, classified as SPMS with an EDSS score below 7.0, prior history of RRMS and had experienced progressive deterioration of disability for at least 6 months, with an increase of at least 1.0 point on the EDSS in the previous 4 year (or 0.5 point if the entry EDSS score was 6.0 or 6.5), with or without superimposed exacerbations, stable neurological condition for the 4 weeks preceding study day 1.	Similar to those used in previous IFN beta trials (no further critera specified by authors)	N=371 Mean age (SD): 45.7 (range: 18-65) 40% male 60% female
Cohen 2002 US, Canada, Europe IMPACT	SPMS	Double-blind Parallel Multicenter Setting: Research Center	Screened: NR Eligible: NR Enrolled: 436 Withdrawn: 115 LostToFU: 5 Analyzed: 321	Clinically definite SPMS with or without recent relapses, disease progression over the previous year, cranial MRI demonstrating lesions consistent with MS, EDSS 3.5-6.5, age 18-60 years.	Primary progressive course, inability to perform the component tests of the MSFC at baseline, and prior treatment with IFNb.	N=436 Mean age (SD): NR (NR) (range: NR) NR% male NR% female

Evidence Table 4. Placebo-controlled trials of interferon beta 1a

Study	Population Type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
Comi; Fillipi 2001; 2004 Multiple European Countries	CIS	Double-blind Parallel Multicenter Setting: Specialty Clinic	Screened: 375 Eligible: NR Enrolled: 309 Withdrawn: 31 LostToFU: NR Analyzed: 308	Clinical syndromes indicating unifocal or multifocal involvement of the CNS; age 18-40 years; first neurological episode suggestive of MS in 3 mos prior to study entry; one or more abnormalites in neurological exam; positive MRI brain scan.	Previous immunosuppressive or immunomodulatory treatment; participation in an experimental procedure during year before study; other serious intercurrent systemic illness or psychiatris disorders; pregnancy; unwillingness to use reliable contraception.	N=309
Jacobs 2000	RRMS	Double-blind Multicenter Setting: Specialty Clinic	Screened: NR Eligible: NR Enrolled: 301 Withdrawn: NR LostToFU: NR Analyzed: 301	Defiinite MS for at least 1 year, baseline EDSS of 1.0-3.5 inclusive, at least two documented exacerbations in the prior 3 years, no exacerbatiosn for at least 2 months at study entry, and age 18-55 years	NR	N=301 Mean age (SD): NR (NR) (range: NR) NR% male NR% female

Evidence Table 4. Placebo-controlled trials of interferon beta 1a

Study	Population Type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
Jacobs et al 1996 USA	RRMS	Double-blind Parallel Multicenter Setting: Research Center	Enrolled: 301	Definite MS for at least 1 year, baseline EDSS of 1.0-3.5 inclusive, at least 2 documented exacerbations in the prior 3 years, no exacerbations for at least 2 months at study entry, and age 18-55 years.	Prior immunosuppressant or interferon therapy, adrenocorticotropic hormone or corticosteriod treatment within 2 months of study entry, pregnancy or nursing, an unwillingness to practice contraception, the presence of chronic-progressive MS, or any disease other than MS compromising organ function.	N=301 Mean age (SD): 36.8 (7.4) (range: 16-55) 26.58% male 73.42% female 92% white 7% black 0% Asian 0% Hispanic 2% other
Jacobs et al (CHAMPS Study; 3 publications) 2000, 2001 US and Canada CHAMPS	CIS	Double-blind Parallel Multicenter Setting: Specialty Clinic	Screened: NR Eligible: NR Enrolled: 383 Withdrawn: 57 LostToFU: 16 Analyzed: 383	Age 18-50; first isolated well-defined neurologic event consistent with demyelination and involving the optic nerve, spinal cord or brain stem/cerebellum; confirmed on opthalmologic or neurologic exam; >/= 2 lesions at least 3mm in diameter on MRI; onset of visual or neurologic symptoms no more than 14 days before corticosteriod therapy was begun.	Prior neurologic or visual event consistent with demyelination lasting longer than 48 hours	N=383 Mean age (SD): 33 (7) 24.54% male 75.46% female 86% white 8% black 1% Asian 3% Hispanic 3% other

Evidence Table 4. Placebo-controlled trials of interferon beta 1a

Study	Population Type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
Leary 2003 UK	PPMS	Double-blind Parallel Single Center Setting: Research Center	Screened: 57 Eligible: NR Enrolled: 50 Withdrawn: 7 LostToFU: 0 Analyzed: 49	1. PPMS of at least 2 years' duration 2. aged 18-60 years 3. EPSS score of 2 to 7 inclusive	Interferon, immunosuppressant, or chronic steroid therapy within the previous 3 months, pregnancy or lactation, seizure within the previous 3 months, history of severe depression	N=50 Mean age (SD): 45 (range: 25-59) 64% male 36% female
Liu 1999 PRISMS	RRMS	Double-blind Parallel Multicenter Setting: Research Center	Screened: Eligible: Enrolled: 560 Withdrawn: LostToFU: Analyzed: 533	Same as PRISMS(1) 1998	Same as PRISMS(1) 1998	Same as PRISMS(1) 1998
Liu (2) 2002 PRISMS (Re-analysis of PRISMS)	See PRISMS(1), 1998	See PRISMS (1), 1998	See PRISMS(1), 1998	See PRISMS(1), 1998	See PRISMS(1), 1998	N=560
Miller 2006 USA,Canada IMPACT	SPMS	Double-blind Parallel Multicenter Setting: Research Center	See Cohen, 2002	See Cohen, 2002	See Cohen, 2002	N=324

Evidence Table 4. Placebo-controlled trials of interferon beta 1a

Study	Population Type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
MS Collaborative Research Group (2) 1995 USA MSCRG	RRMS	Double-blind Parallel Multicenter Setting: Research Center	See Jacobs 1996	Males and females between the ages of 18-55, definite diagnosis of MS of at least 1 year duration, exacerbating-remitting MS, at least 2 exacerbations in the 3 years before study entry. patients with disease duration less than 3 years must have had at least 1 exacerbation per year prior to study entry, free of exacerbations for at least 2 months before study entry, Kurtzke EDSS greater than or equal to 1.0 but less than or equal to 3.5, capable of understanding and complying with protocol, prestudy exacerbation rates of at least 0.67 per year (in abstract).	Prior therapy with immunosuppressant drugs, e.g, cyclophosphamide, azathioprine, prior treatment with interferon, treatment with ACTH or corticosteroids within 2 months before study entry, concurrent infection, the presence of any serious disease, other than MS, requiring specific tx or compromising organ system function, chronic progressive MS, pregnant women or nursing mothers, unwilling to practice a form of contraception during the study that is acceptable to the investigator	N=301 Mean age (SD): 36.8 (7.4) (range: 16-55) 26.91% male 73.09% female 92% white
MS Collaborative Research Group (3) 1997 USA MSCRG (Post-hoc analysis)	RRMS	Double-blind Parallel Multicenter Setting: Research Center	Enrolled: 301	See Jacobs 1996	See Jacobs 1996	see Jacobs et al, 1995 & 1996

Evidence Table 4. Placebo-controlled trials of interferon beta 1a

Study	Population Type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
Oger 2005 PRISMS (Analysis of PRISMS data)	RRMS	Double-blind Crossover Multicenter Setting: Research Center	Screened: 187 Eligible: 177 Enrolled: 172 Withdrawn: 36 LostToFU: 1 Analyzed: 172	same as PRISMS 1998	same as PRISMS 1998	N=187
OWIMS Study Group 1999 OWIMS Study	RRMS	Double-blind Multicenter Setting: Research Center	Screened: NR Eligible: NR Enrolled: 293 Withdrawn: 22 LostToFU: 1 Analyzed: 293	Clinically definite or laboratory supported definite RRMS of at least 1 year's duration and Kuirtzke EDSS scores of 0-5.0.one relapse in the prior 24 months but not in the 8 weeks before entry; at least 3 lesions consistnet with MS were required on a screening MRI. No corticosteriods within 8 weeks of study start.	Prior IFN, cyclophosphamide, or lymphoid irradiation treatment; any immunosuppressive or experimental therapyies in the precedign 12 months. Pregnancy, lactation, and severe medical or psychiatric illness.	N=293 Mean age (SD): 35.2 (7.6) (range: 18-50) 27.3% male 72.7% female
Patten 2002 SPECTRIMS Trial	SPMS	Double-blind Parallel Multicenter Setting: NR	See SPECTRIMS, 2001	See SPECTRIMS, 2001	See SPECTRIMS, 2001	N=365 Mean age (SD): 42.6 (range: 19-55) 36.44% male 63.56% female

Evidence Table 4. Placebo-controlled trials of interferon beta 1a

Study	Population Type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
PRISMS (1) 1998 Multiple (Europe, North American & Australia)	RRMS	Double-blind Parallel Multicenter Setting: Research Center	Screened: NR Eligible: NR Enrolled: 560 Withdrawn: 31 LostToFU: 27 Analyzed: 502	Adults with relapsing/remitting MS were eligible if they had had at least 2 relapses in the preceding 2 years and had EDSS scores of 0-5.0. All patients had clinically definite or laboratory-supported definite MS of at least 1 year's duration.	Any previous systemic treatment with interferons, lymphoid irradiation, or cyclophospamide, or with other immunomodulatory or immunosuppressive treatments in the preceding 12 months.	N=560 Mean age (SD): 34.9 (range: 29.1-40.4) 31.07% male 68.93% female
SPECTRIMS 2001	SPMS	Double-blind Parallel Multicenter Setting: NR	Screened: NR Eligible: NR Enrolled: 618 Withdrawn: 112 LostToFU: 47 Analyzed: 506	clinically definite SPMS (secondary progressive MS) defined as progressive deterioration of disability for at least 6 months with an increase of at least 1 EDSS (Expanded Disability Status Scale) point over the last 2 years (or 0.5 point between EDSS scor	immunosuppressive or immunomodulatory treatments during the previous 3 to 12 months depending on the drug, prior treatment with interferon or total lymphoid irradiation, corticosteriod use or a disease exacerbation in the previous 8 weeks, severe concurre	N=506 Mean age (SD): 42.8 (7.1) (range: 18-55) 37% male 63% female

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Andersen 2004 Multiple European Countries Efficacy quality: Good Adverse event quality: Fair	Interferon beta-1a (Rebif) injection 22 ug weekly, over 3 years N=186 Male: 74 (40%) Female: 112 (60%) Mean age (SD): 45	Total withdrawals: 38 (20.4%) AE withdrawals: NR	Annualized relapse rate: 0.25 (RR 0.90) at 3 years, p-value: 0.55, CI: 0.64-1.27 Proportion of relapse-free patients: 61% (OR=1.03) at 3 years, p-value: 0.89, CI: 0.67-1.58 Proportion of relapse-free patients (men): 60%, (OR=0.68) at 3 years, p-value: 0.27, CI: 0.34-1.36 Proportion of relapse-free patients (women): 62% (OR=1.14) at 3 years, p-value: 0.65, CI: 0.65-1.98	Abnormal liver function test: 6/186 (3.2%) Depression: 37/186 (19.9%) Fatigue/Tiredness: 35/186 (18.8%) Fever: 19/186 (10.2%) Flu-like illness: 69/186 (37.1%) Headache: 67/186 (36%) Injection site inflammation: 58/186 (31.2%) Injection site reactions (e.g. bleeding): 50/186 (26.9%) Lymphopenia: 2/186 (1.1%) Weakness/muscle weakness: 28/186 (15.1%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
Andersen 2004 Multiple European Countries	On outcome: Time to progression based on change in EDSS, Inf 1-a vs placebo:HR 1.13; 0.82-1.57; p=0.45, Increase in RFSS Inf 1-a vs placebo:80/146 (43%) vs 79/178 (44%), Time to progression based on change in RFSS: HR=0.93, 0.68-1.28; p=0.67. Subgroup analysis of previous relapsers vs non-relapsers in 4 years preceding study found no SS difference in treatment effect between groups regardless of intervention On population: Demographic characteristic were similar between the 2 groups. Placebo patients had a longer duration of SPMS, and a larger BL EDSS and ambulation index. The difference for duration of SPMS was significant (p=0.03). However author report that the duration of SPMS did not significantly affect the primary outcome, nor the tx impact on primary outcome. On intervention: Mean baseline values, Inf 1-a; placebo, EDSS: 4.7; 5.0, Relapses 4 years preceding study: 1.7; 1.6. In case of toxicity, the dose could be reduced or treatment interrupted according to protocol. Steroids were to be given only for disabling acute exacerbations.

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Andersen 2004 Multiple European Countries Efficacy quality: Good Adverse event quality: Fair	Placebo injection weekly, over 3 years N=178 Male: 71 (40%) Female: 107 (60%) Mean age (SD): 46	Total withdrawals: 25 (14%) AE withdrawals: NR	Annualized relapse rate: 0.27 at 3 years Proportion of relapse-free patients: 62% at 3 years Proportion of relapse-free patients (men): 67% at 3 years Proportion of relapse-free patients (women): 58% at 3 years	Abnormal liver function test: 0/178 (0%) Depression: 25/178 (14%) Fatigue/Tiredness: 23/178 (12.9%) Fever: 7/178 (3.9%) Flu-like illness: 39/178 (21.9%) Headache: 36/178 (20.2%) Injection site inflammation: 3/178 (1.7%) Injection site reactions (e.g. bleeding): 14/178 (7.9%) Lymphopenia: 4/178 (2.2%) Weakness/muscle weakness: 14/178 (7.9%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
Andersen 2004 Multiple European Countries	

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Cohen 2002 **US, Canada, Europe** **IMPACT** Efficacy quality: Good Adverse event quality: Fair	Interferon beta-1a (Avonex) injection 60ug weekly, over 24 months N=217 Male: 76 (36%) Female: 138 (64%) Mean age (SD): 47 (8.2)	Total withdrawals: 29 (13%) AE withdrawals: 5 (2.3%)	Mean change in EDSS: 0.258 at 24 months Mean change in MSFC: -0.362 at 24 months, p-value: 0.333 Annualized relapse rate: 0.20 at 24 months, p-value: 0.008 Mean annual rate of steriod courses: 0.19 at 1 year, p-value: 0.030	Total patients reporting any AE: 215/217 (99%) Flu-like illness: 151/217 (70%) Headache: 106/217 (49%) Myalgia: 65/217 (30%) Depression: 56/217 (26%) UTI: 54/217 (25%) Arthralgia (joint pain): 52/217 (24%) Fever: 38/217 (18%)
Cohen 2002 **US, Canada, Europe** **IMPACT** Efficacy quality: Good Adverse event quality: Fair	Placebo weekly, over 24 months N=219 Male: 78 (36%) Female: 141 (64%) Mean age (SD): 48 (7.7)	Total withdrawals: 23 (10.5%) AE withdrawals: 4 (1.8%)	Mean change in EDSS: 0.272 at 24 months Mean change in MSFC: -0.495 at 24 months Annualized relapse rate: 0.30 at 24 months Mean annual rate of steriod courses: 0.26 at 1 year	Total patients reporting any AE: 215/218 (99%) Flu-like illness: 72/218 (33%) Headache: 107/218 (49%) Myalgia: 67/218 (31%) Depression: 49/218 (22%) UTI: 45/218 (21%) Arthralgia (joint pain): 43/218 (20%) Fever: 16/218 (7%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
Cohen 2002 US, Canada, Europe IMPACT	On population:The authors state that the subjects in this trial were similar to those of the North American IFNB-1b study and SPECTIRMS On intervention: Mean baseline values Inf 1a vs placebo:EDSS: 5.2 for both groups, Relapses 3 years preceding study: 1.5; 1.3, Disease duration: 16.2; 16.7
Cohen 2002 US, Canada, Europe IMPACT Efficacy quality: Good Adverse event quality: Fair	

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Comi; Fillipi 2001; 2004 Multiple European Countries Efficacy quality: Good Adverse event quality: Fair	Interferon beta-1a (Rebif) N=154 Male: 60 (39%) Female: 94 (61%) Mean age (SD): 29 (6.0)	Total withdrawals: 13 (8%) AE withdrawals: NR	Number of patients converting to MS: 52 (34%) at 2 years, p-value: 0.047 Time to conversion for CIS to MS: 569 days, p-value: 0.034 Annualized relapse rate: 0.33 at 2 years, p-value: 0.045	Chills: 17/154 (11%) Fever: 43/154 (27.9%) Injection site reactions (e.g. bleeding): 92/154 (59.7%) Myalgia: 26/154 (16.9%)
Comi; Fillipi 2001; 2004 Multiple European Countries Efficacy quality: Good Adverse event quality: Fair	Placebo subcutaneous injection once a week, 2 years N=155 Male: 52 (34%) Female: 103 (66%) Mean age (SD): 28 (6.1)	Total withdrawals: 18 (11.6%) AE withdrawals: NR	Number of patients converting to MS: 69 (45%) at 2 years Time to conversion for CIS to MS: 252 days Annualized relapse rate: 0.43 at 2 years	Chills: 17/154 (11%) Fever: 18/154 (11.7%) Injection site reactions (e.g. bleeding): 18/154 (11.7%) Myalgia: 14/154 (9.1%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
Comi; Fillipi 2001; 2004 Multiple European Countries	Subgroup analysis based on brain-volume change on MRI scan: 41/131(31%) inf 1-a vs 62/132 (47%) placebo patients converted to MS at 24 months
Comi; Fillipi 2001; 2004 Multiple European Countries	

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Jacobs 2000 Efficacy quality: Fair Adverse event quality: Poor/Fair	Interferon beta-1a (Avonex) injection 30ug weekly, up to 104 weeks N=301	Total withdrawals: NR AE withdrawals: NR	Time to confirmed progression: 21.9% at wk 104, p-value: NR, CI: NR Mean change in EDSS: mean 0.02 at wk 104, p-value: 0.02, CI: SE 0.14 Annualized relapse rate: 0.67, p-value: 0.04, CI: NR	No data reported. See comments on AE.
Jacobs 2000 Efficacy quality: Fair Adverse event quality: Poor/Fair	Placebo injection weekly, up to 104 weeks	Total withdrawals: NR AE withdrawals: NR	Time to confirmed progression: 34.9% at wk 104, CI: NR Mean change in EDSS: 0.61 at wk 104, CI: SE 0.18 Annualized relapse rate: 0.82, CI: NR	NR

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
Jacobs 2000	On population: "There were no significant group differences in baseline demographic, clinical disease, or MRI characteristics (Jacob et al, 1995, 1996"). On intervention: Baseline EDSS and previous relapses NR On Adverse event: No data reported except narrative: " 93% of patients completed treatment as scheduled. Symptoms reported more frequently p<0.1 by IFNB1a recipients were restricted to flu-like symptoms, muscle aches, asthenia, chills and fever. Injection site reactions occurred rarely and with equal frequency in IFNB1a and placebo patients. "Flu-like symptoms were reported more frequently in IFNB1a recipients.
Jacobs 2000	

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Jacobs et al 1996 **USA** Efficacy quality: Good Adverse event quality: Poor/Fair	Interferon beta-1a (Avonex) 30 ug (6 million IU) weekly, up to 104 weeks N=158 Male: 40 (25%) Female: 118 (75%) Mean age (SD): 37	Total withdrawals: 14 (8.8%) AE withdrawals: 7 (4.4%)	Probability of Onset of Sustained Progression: 21.9% at 104 wks, p-value: 0.02 Probability of Onset of Sustained Progression: 12.5% at first 52 wks Probability of Onset of Sustained Progression: 10.8% at second 52 wks Proportion of patients with confirmed progression: 21.2% at wk 104 Mean change in EDSS (sustained changed): 0.02 at wk 104 Mean change in EDSS (unsustained change): 0.25 at wk 104 Annual exacerbation rates (per patient-year): 0.67 at wk 104, p-value: 0.04	Chills: 33/158 (20.9%) Fever: 37/158 (23.4%) Flu-like illness: 96/158 (60.8%) Headache: 106/158 (67.1%) Nausea/vomiting: 49/158 (31%) Weakness/muscle weakness: 53/158 (33.5%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
Jacobs et al 1996 USA	On population: Mean baseline values: EDSS: 2.3, Disease duration: 6.5 years (SD 5.8), Prestudy relapse rate: 1.2 (SD 0.6) On intervention:Mean baseline values Inf 1-a vs placebo: EDSS: 2.3 vs 2.4, Prestudy relapse rate: 1.2 for both groups, Disease duration: 6.4 vs 6.6

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Jacobs et al 1996 **USA** Efficacy quality: Good Adverse event quality: Poor/Fair	Placebo N=143 Male: 40 (28%) Female: 103 (72%) Mean age (SD): 37	Total withdrawals: 9 (6.2%) AE withdrawals: 2 (1.4%)	Probability of Onset of Sustained Progression: 16.5% at second 52 wks Probability of Onset of Sustained Progression: 34.9% at wk 104 Probability of Onset of Sustained Progression: 22.0% at first 52 wks Proportion of patients with confirmed progression: 33.3% at wk 104 Mean change in EDSS (sustained change): 0.61 at wk 104 Mean change in EDSS (unsustained change): 0.74 at wk 104 Annual exacerbation rates (per patient-year): 0.82 at wk 104	chills: 10/143 (7%) fever: 18/143 (12.6%) Flu-like illness: 57/143 (39.9%) Headache: 82/143 (57.3%) Nausea/vomiting: 32/143 (22.4%) Weakness/muscle weakness: 21/143 (14.7%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
Jacobs et al 1996 USA	

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Jacobs et al (CHAMPS Study; 3 publications) 2000, 2001 US and Canada CHAMPS Efficacy quality: Good Adverse event quality: Fair/Good Other CHAMPS publications (data included here): CHAMPS Study Group, 2001 Galetta, 2001	Interferon beta-1a (Avonex) IM 30 ug 1/wk, up to 3 years N=193 Male: 52 (27%) Female: 141 (73%) Mean age (SD): 33 (8)	Total withdrawals: 38 (7.3%) AE withdrawals: 1 (0.5%)	Cumulative probability of conversion to MS: Adjusted rate ratio 0.49 at 3 years p-value: <0.001 CI: 0.33-0.73	Depression: 39/193 (20.2%) Flu-like illness: 104/193 (53.9%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
Jacobs et al (CHAMPS Study; 3 publications) 2000, 2001 US and Canada CHAMPS Other CHAMPS publications (data included here): CHAMPS Study Group, 2001 Galetta, 2001	On outcome: Subgroup analysis of only patients presenting with optic neuritis (n=192): Conversion to clinically definite MS inf 1-a vs placebo: Adjusted rate ratio 0.58 (0.34-1.00; p=0.05) On intervention:Run-in: 1 g methylprednisolone qd via IV for 3 days followed by 1 mg/kg prednisone qd orally for 11 days and a 4-day tapering period according to the following schedule: 20mg day 1; 10 mg day 2; 0 mg day 3; 10 mg day 4.

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Jacobs et al (CHAMPS Study; 3 publications) 2000, 2001 US and Canada CHAMPS Efficacy quality: Good Adverse event quality: Fair/Good Other CHAMPS publications (data included here): CHAMPS Study Group, 2001 Galetta, 2001	Placebo IM 1/wk N=190 Male: 42 (22%) Female: 148 (78%) Mean age (SD): 33 (7)	Total withdrawals: 35 (18.4%) AE withdrawals: 7 (3.7%)		Depression: 25/193 (13%) Flu-like illness: 49/190 (25.8%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
Jacobs et al (CHAMPS Study; 3 publications) 2000, 2001 US and Canada CHAMPS Other CHAMPS publications (data included here): CHAMPS Study Group, 2001 Galetta, 2001	

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Leary 2003 UK Efficacy quality: Good Adverse event quality: Good	Interferon beta-1a (Avonex) 30 ug weekly, 24 months N=15 Male: 10 (67%) Female: 5 (33%) Mean age (SD): 46	Total withdrawals: 1 AE withdrawals: 1	Probability of Onset of Sustained Progression: 0.8 at 12 months Probability of Onset of Sustained Progression: 0.45 at 24 months Nine-hole peg test (NHPT) - left: 27.2 secs at 24 months Nine-hole peg test (NHPT) - left: 27.1 secs at 12 months Nine-hole peg test (NHPT) - right: 23.8 secs at 24 months Nine-hole peg test (NHPT) - right: 23.6 secs at 12 months Timed ten-meter walk (TTMW): 19 secs at 24 months Timed ten-meter walk (TTMW): 12 secs at 12 months	Abnormal liver function test: 0/15 (0%) Anemia: 1/15 (6.7%) Depression: 7/15 (46.7%) Flu-like illness: 13/15 (86.7%) Injection site reactions (e.g. bleeding): 1/15 (6.7%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
Leary 2003 UK	On outcome: Outcomes were read off figure that had "survival distribution function on y axis although the legend states "survival cures for time to sustained disease progression- -see Figure 2-page 47. The primary clinical endpoint was reached in 48% of subjects. There was no significant difference in disease progression between the individual or combined treatment arms and placebo. On intervention: Mean baseline values:EDSS: 5.25, Disease duration: 8 years, TTMW: 11 secs, NHPT left - 28.7 secs, NHPT right - 28.9 secs. In the event of study drug intolerance there was an option to half the dose.

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Leary 2003 UK Efficacy quality: Good Adverse event quality: Good	Interferon beta-1a (Avonex) 60 ug weekly, 24 months N=15 Male: 7 (47%) Female: 8 (53%) Mean age (SD): 47	Total withdrawals: 4 AE withdrawals: 4	Probability of Onset of Sustained Progression: 0.66 at 12 months Probability of Onset of Sustained Progression: 0.55 at 24 months Nine-hole peg test (NHPT) - left: 27.9 secs at 12 months Nine-hole peg test (NHPT) - left: 30.9 secs at 24 months Nine-hole peg test (NHPT) - right: 28.6 secs at 12 months Nine-hole peg test (NHPT) - right: 29.0 secs at 24 months Timed ten-meter walk (TTMW): 13 secs at 12 months Timed ten-meter walk (TTMW): 13 secs at 24 months	abnormal liver function test: 5/15 (33%) Depression: 6/15 (40%) Fatigue/Tiredness: 3/15 (20%) Flu-like illness: 15/15 (100%) Injection site reactions (e.g. bleeding): 2/15 (13.3%) Lymphopenia: 3/15 (20%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
Leary 2003 UK	

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Leary 2003 UK Efficacy quality: Good Adverse event quality: Good	Placebo, weekly, 24 months N=20 Male: 15 (75%) Female: 5 (25%) Mean age (SD): 43	Total withdrawals: 2 (10%) AE withdrawals: 0 (0%)	Probability of Onset of Sustained Progression: 0.5 at 24 months Probability of Onset of Sustained Progression: 0.6 at 12 months Nine-hole peg test (NHPT) - left: 29.9 secs at 12 months Nine-hole peg test (NHPT) - left: 31.2 secs at 24 months Nine-hole peg test (NHPT) - right: 31.1 secs at 24 months Nine-hole peg test (NHPT) - right: 30.3 secs at 12 months Timed ten-meter walk (TTMW): 11 secs at 12 months Timed ten-meter walk (TTMW): 14 secs at 24 months	Abnormal liver function test: 0/20 (0%) Depression: 2/20 (10%) Fatigue/Tiredness: 5/20 (25%) Flu-like illness: 11/20 (55%) Injection site reactions (e.g. bleeding): 1/20 (5%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
Leary 2003 UK	

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Liu 1999 PRISMS (Re-analysis of PRISMS).	Interferon beta-1a (Rebif) injection 22 mcg (6 MIU) 3x/week, over 2 years (66 ug/wk)	NR	Mean change in EDSS: 0.23 at 2 year, p-value: 0.026, CI: 1.29 Mean change in ambulation index (AI): 0.46 at 2 year, CI: 1.25	NR
Liu 1999 PRISMS (Re-analysis of PRISMS).	Interferon beta-1a (Rebif) injection 44 mcg (12 MIU) 3x/week, over 2 years (132 ug/wk) N=533	NR	Mean change in EDSS: 0.24 at 2 year, p-value: 0.052, CI: 1.13 Mean change in ambulation index (AI): 0.24 at 2 year, CI: 0.96	NR
Liu 1999 PRISMS (Re-analysis of PRISMS).	Placebo injection 3x/week	NR	Mean change in EDSS: 0.48 at 2 year, CI: 1.27 Mean change in ambulation index (AI): 0.44 at 2 year, CI: 1.30	NR

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
Liu 1999 PRISMS (Re-analysis of PRISMS).	On outcome: Subgroup analysies: EDSS </= 3.5: 22 ug was better than placebo for both "2 year EDSS difference" (p=0.016) and AUC(sum) analyses (p=0.043). For AUC(Change), both treatment doses were favored compared with placebo (p-0.036 and 0.016 for 44 ug and 22 ug Interferon On population: PRISMS (1) 1998, n=466 for those with baseline EDSS less than or equal to 3.5, n=94 for those with baseline EDSS >3.5
Liu 1999 PRISMS (Re-analysis of PRISMS).	
Liu 1999 PRISMS (Re-analysis of PRISMS).	

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Liu (2) 2002 PRISMS (Re-analysis of PRISMS)	Interferon beta-1a (Rebif) 44 ug /22ug/Placebo	Data was not included in this post-hoc analysis	See comments	NR
Miller 2006 USA,Canada IMPACT (Subgroup analysis of IMPACT data)	Interferon beta-1a (Avonex) injection 60ug weekly, over 24 months N=162 Male: 57 (35%) Female: 105 (65%) Mean age (SD): 48 (7.8)	NR	NR	NR

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
Liu (2) **2002** **PRISMS** (Re-analysis of PRISMS)	On outcome: On total cohort: combined data (n=533), Treat effect: p=0.002), Total cohort: scheduled visits data (n=533), Treatment effect: p=0.018), Entry EDSS less than or = 3.5: combined data (n=444), Treat effect: p=0.010) Entry EDSS > 3.5; combined data (n=89), Treatment effect: p=0.018) On intervention: Results reflect the combined groups of IFNbeta-1a 22 ug and 44ug vs. placebo. The outcomes are not the typically outcomes so results were included as narrative under outcomes.
Miller **2006** **USA,Canada** **IMPACT** (Subgroup analysis of IMPACT data)	On outcome:The only demographic difference noted in baseline MSQLI scorews were that males reported worse satsifaction with sexual function (female=10.39 vs. male 12.29, p=0.02)(data not shown). The correlations between baseline MSQLI components and disease characteristcs were generally non-significant. On intervention: Mean baseline values IFNB 1A; placebo: EDSS: 5.2; 5.3, Relapses in 3 years preceding study: 1.6; 1.4, Disease duration: 17.0 for both groups General comments: Numerous tables included that reflects Pearson correlations between BL to month 234 change in the MSQLI, MSFC and its components, EDSS

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
MS Collaborative Research Group (2) 1995 USA	Interferon beta-1a (Avonex) 30 ug (6 M IU) weekly/ Placebo	NR	NR	NR

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
MS Collaborative Research Group (2) 1995 USA MSCRG Quality assessment - refer to Jacobs et al 1996.	On outcome: Other outcomes conducted but not reported in the main publication included visual function, upper and lower extremity function (nine-hole peg test (9HPT) and the box and block test (BBT), ambulation index (AI); emotional status etc On population:Prestudy exacerbation rates ranged form 0.67 to 3.7 exacerbations per year (mean 1.2 exacerbations per year). Mean and median prestudy duration of disease were 6.5 years and 4.5 years respectively. Of the reviewer: This article was a review of design and baseline characteristics of patients of the MSCRG trial.

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
MS Collaborative Research Group (3) 1997 USA MSCRG (Post-hoc analysis)	Interferon beta-1a (Avonex) 30 ug IU (million IU) weekly, up to 104weeks	See comments	Probability of patients progressing by 2 years: 21.9 at sustained 6 months, at least 1 point, p-value: 0.024 Probability of patients progressing by 2 years: 11.5 at sustained 1 year, at least 1 point, p-value: 0.002 Probability of patients progressing by 2 years: 6.1 at sustained 6 months, at least 2 points, p-value: 0.028 Mean EDSS scores: 2.4 at baseline, p-value: 0.576 Mean EDSS scores: 2.4 at week 26 Mean EDSS scores: 2.5 at week 52 Mean EDSS scores: 2.6 at week 78, p-value: 0.333 Mean EDSS scores: 2.5 at week 104, p-value: 0.013 Mean EDSS scores: 2.7 at week 130, p-value: 0.014	NR

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
MS Collaborative Research Group (3) 1997 USA MSCRG (Post-hoc analysis. Quality assessment - refer to Jacobs et al 1996.)	On outcome: Time to disability progression was calculated as the no. of days from randomization until the onset of sustained worsening from baseline EDSS. On Withdrawals: 5 patients, all IFNbeta-1a prematurely withdrew from the study while still at risk to progress (i.e.. At least 2 scheduled visits left in their treatment course). 8 patients (5 IFNbeta-1a and 3 placebo) failed on the primary endpoint or were beyond the date when they could have reached the primary endpoint (one scheduled visit left in their treatment course and the EDSS had not increased by at least 1.0 point from baseline.

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
MS Collaborative Research Group (3) 1997 USA (Post-hoc analysis)	Placebo	NR	Probability of patients progressing by 2 years: 18.3 at sustained 6 months, at least 2 points Probability of patients progressing by 2 years: 29.8 at sustained 1 year, at least 1 point Probability of patients progressing by 2 years: 34.9 at sustained 6 months, at least 1 pt Mean EDSS scores: 2.3 at baseline Mean EDSS scores: 2.5 at week 26 Mean EDSS score: 2.8 at week 52 Mean EDSS scores: 3.0 at week 78 Mean EDSS scores: 3.1 at week 104 Mean change in EDSS: 3.4 at week 130	NR

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
MS Collaborative Research Group (3) 1997 USA MSCRG (Post-hoc analysis. Quality assessment - refer to Jacobs et al 1996.)	

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Oger 2005 PRISMS (Analysis of PRISMS data)	Interferon beta-1a (Rebif) 22 ug 3x/week Total daily dose: over two years N=85 Male: 23 (27%) Female: 62 (73%) Mean age (SD): 36	Total withdrawals: 12 (14%) AE withdrawals: 3 (4%)	Percentage progression -free: 72% at years 3-4, p-value: 0.170 Annual rate of 1-point EDSS progressions: 0.3 at years 3-4, p-value: 0.001 AUC of the EDSS (EDSS step-years): 110 at years 3-4, p-value: 0.118 Annualized relapse rate: 0.6 at years 3-4 Proportion of relapse-free patients: 40% at years 3-4, p-value: <0.001 Total no. of relapses: 1.2 at years 3-4, p-value: <0.001	Fatigue/Tiredness: 29/85 (34.1%) Flu-like illness: 36/85 (42.4%) Injection site reactions (e.g. bleeding): 24/85 (28.2%) Lymphopenia: 44/85 (51.8%) Weakness/muscle weakness: 18/85 (21.2%)
Oger 2005 PRISMS (Analysis of PRISMS data)	Interferon beta-1a (Rebif) 44 ug 3x/week, over two years N=87 Male: 19 (22%) Female: 68 (78%) Mean age (SD): 37	Total withdrawals: 25 (29%) AE withdrawals: 13 (15%)	Percentage progression -free: 76% at years 3-4, p-value: 0.019 Annual rate of 1-point EDSS progressions: 0.2 at years 3-4, p-value: <0.001 AUC of the EDSS (EDSS step-years): 56 at years 3-4, p-value: 0.118 Annualized relapse rate: 0.7 at years 3-4 Proportion of relapse-free patients: 28% at years 3-4, p-value: 0.007 Total no. of relapses: 1.2 at years 3-4, p-value: <0.001	Fatigue/Tiredness: 32/87 (36.8%) Flu-like illness: 53/87 (60.9%) Injection site reactions (e.g. bleeding): 33/87 (37.9%) Lymphopenia: 49/87 (56.3%) Weakness/muscle weakness: 20/87 (23%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
Oger 2005 PRISMS (Analysis of PRISMS data)	On outcome: Relapse count in the 2 years prior to PRISMS was 3.0, while during the first 2 years the relapse count was 2.6 (13$ RR). Once IFN treatments was started, a 54% RR in relapses in years 3 and 4 for patients in both 22 and 44 ug groups compared with years on placebo (p<0.001) On intervention:Mean baseline values: Inf 1-a 22 mcg; Inf 1-a 44 mcg EDSS: 3.0; 2.6, Disease duration: 8.5 years; 7.6 years
Oger 2005 PRISMS (Analysis of PRISMS data)	

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
OWIMS Study Group 1999 Efficacy quality: Good Adverse event quality: Fair	Interferon beta-1a (Rebif) 22 ug every week, 48 weeks N=95 Male: 26 (27%) Female: 69 (73%)	Total withdrawals: 8 (8.42%) AE withdrawals: 1 (1.05%)	Use of rescue medication in relapsing patients: 0.58 (range 0-4) at 48 wk (1 yr) Mean relapse rate: 1.08 at 48 week, CI: 1.04 Median Time to first relapse (days): 152 at 48 week Percentage of patients with moderate/severe relapses: 36 at 48 week Proportion of relapse-free patients: 33% at 48 week	Abnormal liver function test: 4/95 (4.2%) Chills: 7/95 (7.4%) Depression: 4/95 (4.2%) Fever: 8/95 (8.4%) Flu-like illness: 39/95 (41.1%) Headache: 46/95 (48.4%) Injection site inflammation: 68/95 (71.6%) Injection site necrosis: 0/95 (0%) Injection site pain: 13/95 (13.7%) Weakness/muscle weakness: 17/95 (17.9%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
OWIMS Study Group 1999 OWIMS Study	On intervention: Dose adjustments were allowed for management of symptomatic or laboratory-identified AE. APAP was recommended for prophylactic use and to ameliorate constitutional symptoms as required throughout the study.

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
OWIMS Study Group 1999 Efficacy quality: Good Adverse event quality: Fair	Interferon beta-1a (Rebif) 44 ug every week, 48 weeks N=98 Male: 28 (29%) Female: 70 (71%)	Total withdrawals: 13 (13.26%) AE withdrawals: 5 (5.1%)	Use of rescue medication in relapsing patients: 0.38 (range 0-3) at 48 week (1 yr), p-value: 0.014 vs placebo Mean relapse rate: 0.87 at 48 wk, CI: 0.96 Median time to first relapse: 239 days at 48 week Percentage of patients with moderate/severe relapses: 32 at 48 week Proportion of relapse-free patients: 40% at 48 week	abnormal liver function test: 4/98 (4.1%) chills: 12/98 (12.2%) Depression: 8/98 (8.2%) fever: 24/98 (24.5%) Flu-like illness: 59/98 (60.2%) Headache: 49/98 (50%) injection site inflammation: 68/98 (69.4%) Injection site necrosis: 0/98 (0%) injection site pain: 17/98 (17.3%) Weakness/muscle weakness: 20/98 (20.4%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
OWIMS Study Group 1999 OWIMS Study	

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
OWIMS Study Group 1999 **OWIMS Study** Efficacy quality: Good Adverse event quality: Fair	Placebo every week 48 weeks N=100 Male: 26 (26%) Female: 74 (74%)	Total withdrawals: 3 (3%) AE withdrawals: 0 (0%)	Use of rescue medication in relapsing patients: 0.76 (range 0-7) at 48 week (1 yr) Mean relapse rate: 1.08 at 48 week, CI: 1.15 Median Time to first relapse (days): 189 days at 48 week Percentage of patients with moderate/severe relapses: 41 at 48 week Proportion of relapse-free patients: 36% at 48 week	abnormal liver function test: 1/100 (1%) chills: 3/100 (3%) Depression: 8/100 (8%) fever: 7/100 (7%) Flu-like illness: 33/100 (33%) Headache: 34/100 (34%) injection site inflammation: 12/100 (12%) Injection site necrosis: 0/100 (0%) injection site pain: 17/100 (17%) Weakness/muscle weakness: 11/100 (11%)
Patten 2002 SPECTRIMS Trial (Re-analysis of SPECTRIMS)	Interferon beta-1a (Rebif) injection 22 mcg 2x/week, over 3 years	NR	See SPECTRIMS, 2001	Depression, based on CES-D score: 8/46 (17.4%) Suicide risk, based on BHS ratings: 17/79 (21.5%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
OWIMS Study Group 1999 OWIMS Study	
Patten 2002 SPECTRIMS Trial (Re-analysis of SPECTRIMS)	On population: 365(sample size) represented 59.1% of the 618 SPECTRIMS particpants. Median date of onset of MS in this sample was 12.3 years prior to enrollment in the study. The median time since onset of the secondary progressive pharse was 3.1 years. Both time since onset of MS and mean time since onset of pregression were comparable between the 3 groups.

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Patten 2002 SPECTRIMS Trial (Re-analysis of SPECTRIMS)	Interferon beta-1a (Rebif) injection 44 mcg 3x/week, over 3 years N=98	NR	See SPECTRIMS, 2001	Depression, based on CES-D score: 17/57 (29.8%) Suicide risk, based on BHS ratings: 9/76 (11.8%)
Patten 2002 SPECTRIMS Trial (Re-analysis of SPECTRIMS)	Placebo injection 3x/week Total daily dose: over 3 years N=104	NR	See SPECTRIMS, 2001	Depression, based on CES-D score: 17/53 (32.1%) Suicide risk, based on BHS ratings: 16/78 (20.5%)
PRISMS (1) 1998 Multiple (Europe, North American & Australia) Efficacy quality: Good Adverse event quality: Good	Interferon beta-1a (Rebif) injection 22 ug (6 million IU) 3x/weekly, 6 ug/wk over 2 years N=189 Male: 62 (33%) Female: 127 (67%) Mean age (SD): 35	Total withdrawals: 22 (11.6%) AE withdrawals: 6 (3.2%)	Time to confirmed progression: RR=0.68 at 2 years, p-value: <0.05, CI: 0.48-0.98 Mean change in EDSS: 0.23 at 2 years, p-value: =<0.05, CI: 1.3 Use of rescue medication in relapsing patients: 0.97 at 2 years, p-value: =<0.05 Mean mod. & severe exacerb. per person-yr,n: 0.71 at 2 years, p-value: <0.005 Mean relapse rate per pt: 1.82 at 2 years, p-value: <0.005 Relapse requiring hospitalization: 0.38 at 2 years	Depression: 39/189 (20.6%) Fatigue/Tiredness: 27/189 (14.3%) Fever: 25/189 (13.2%) Flu-like illness: 47/189 (24.9%) Headache: 89/189 (47.1%) Injection site reactions (e.g. bleeding): 128/189 (67.7%) Lymphopenia: 9/189 (4.8%) Weakness/muscle weakness: 24/189 (12.7%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
Patten 2002 SPECTRIMS Trial (Re-analysis of SPECTRIMS)	
Patten 2002 SPECTRIMS Trial (Re-analysis of SPECTRIMS)	
PRISMS (1) 1998 Multiple (Europe, North American & Australia) PRISMS	On outcome: Disease progression: groups with high baseline EDSS (>3.5): First quartile time to progression 7.3 months (placebo); 7.5 months, RR (Risk Ratio) 0.75 (0.35-1.56) (22 ug group); 21.3 months, 0.42 (0.18-0.99) (44ug group, p <0.05) On population:Median baseline data:, Age: 34.9, History of MS: 5.3 years.Mean baseline data: Number of relapses in previous 2 years: 3. Mean EDSS: 2.5 On intervention:The age entered is median age. Relapses could be treated with a standard regimen of 1.0 g IV methylprednisolone for 3 consecutive days.

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
PRISMS (1) 1998 Multiple (Europe, North American & Australia) Efficacy quality: Good Adverse event quality: Good	Interferon beta-1a (Rebif) injection 44 ug (12 million IU) 3x/weekly, 132 ug/wk over 2 years N=184 Male: 63 (34%) Female: 121 (66%) Mean age (SD): 36	Total withdrawals: 19 (10.3%) AE withdrawals: 9 (4.8%)	Time to confirmed progression: RR=0.62 at 2 years, p-value: <0.05, CI: 0.43-0.91 Mean change in EDSS: 0.24 at 2 years, p-value: <=0.05, CI: 1.1 Use of rescue medication in relapsing patients: 0.75 at 2 years, p-value: <0.005 Mean mod. & severe relapses per person-yr,n: 0.62 at 2 years, p-value: <0.005 Mean relapse rate per pt: 1.73 at 2 years, p-value: <0.005 Relapse requiring hospitalization: 0.25 at 2 years, p-value: <0.005	Depression: 44/184 (23.9%) Fatigue/Tiredness: 34/184 (18.5%) Fever: 22/184 (12%) Flu-like illness: 50/184 (27.2%) Headache: 83/184 (45.1%) Injection site reactions (e.g. bleeding): 114/184 (62%) Lymphopenia: 23/184 (12.5%) Weakness/muscle weakness: 25/184 (13.6%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
PRISMS (1) 1998 Multiple (Europe, North American & Australia) PRISMS	

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
PRISMS (1) 1998 Multiple (Europe, North American & Australia) Efficacy quality: Good Adverse event quality: Good	Placebo injection placebo 3x/weekly N=187 Male: 47 (25%) Female: 140 (75%) Mean age (SD): 35	Total withdrawals: 17 (9.1%) AE withdrawals: 2 (1.0%)	Time to confirmed progression: RR=1.00 at 2 years Mean change in EDSS: 0.48 at 2 years, CI: 1.3 Use of rescue medication in relapsing patients: 1.39 at 2 years Mean mod. & severe exacerb. per person-yr,n: 0.99 at 2 years Mean relapse rate per pt: 2.56 at 2 years Relapse requiring hospitalization: 0.48 at 2 years	Depression: 52/187 (27.8%) Fatigue/Tiredness: 29/187 (15.5%) fever: 12/187 (6.4%) Flu-like illness: 45/187 (24.1%) Headache: 82/187 (43.9%) Injection site reactions (e.g. bleeding): 41/187 (21.9%) Lymphopenia: 7/187 (3.7%) Weakness/muscle weakness: 15/187 (8%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
PRISMS (1) 1998 Multiple (Europe, North American & Australia) PRISMS	

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
SPECTRIMS 2001 Efficacy quality: Good Adverse event quality: Good	Interferon beta-1a (Rebif) injection 44 mcg 3x/week, for 3 years N=204 Male: 229 (37%) Female: 389 (63%) Mean age (SD): 43 (7.1)	Total withdrawals: 43 (21%) AE withdrawals: 18 (8.8%)	Time to confirmed progression at 3 years: HR=0.93 (patents without prestudy relapse, n=325), p-value: 0.688, CI: 0.65-1.33 HR=0.76 (patients with prestudy relapse, n=293), p-value: 0.142, CI: 0.53-1.10 HR=1.30 (male patients), p-value: 0.226, CI: 0.85-2.01 HR=0.63 (female patients), p-value: 0.006, CI: 0.45-0.87 (adjusted analysis): HR=0.78 (adjusted for center), p-value: 0.046, CI: 0.60-1.00 In disability: HR=0.83 at 3 years, p-value: 0.146, CI: 0.65-1.07 Exacerbation requiring hospitalization: 0.15 at 3 years (per person-year), CI: 0.12-0.18 Mean exacerbations per person-year: 0.50 at 3 years, CI: 0.45-0.56 Mean mod. & severe exacerb. per person-yr,n: 0.27 at 3 years,CI: 0.23-0.31 Mean steroid courses per person-yr: 0.34 at 3 years, CI: 0.30-0.39 Median time between first & second	Depression: 71/204 (34.8%) Flu-like illness: 102/204 (50%) Injection site necrosis: 18/204 (8.8%) Injection site reactions (e.g. bleeding): 177/204 (86.8%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
SPECTRIMS 2001 SPECTRIMS Trial	On population: 506 (82%) completed 3 years of treatment, and an additional 65 who stopped therapy were followed for the remainder of the 3 years, providing full data for 92.4% of pts. Baseline data: Mean EDSS - 5.4. Relapses 2 years preceding study entry: 0.9. Disease duration: 13.3 years, Ambulation index: 3.6 On intervention:therapy was administered over 3 years. 82% completed 3 years of treatment and an additional 65 who stopped therapy were followed for the remainder of the 3 years. Mean baseline values Inf 1a 22ug; Inf 1a 44ug; placebo:EDSS: 5.5; 5.3; 5.4

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
SPECTRIMS 2001 Efficacy quality: Good Adverse event quality: Good	Interferon beta-1a (Rebif) injection 22 mcg 3x/week, over 3 years N=209	Total withdrawals: 37 (17.7%) AE withdrawals: 15 (7.1%)	Exacerbation requiring hospitalization: 0.14 at 3 years, CI: 0.11-0.17 Mean exacerbations per person-year: 0.50 at 3 years, CI: 0.44-0.56 Mean mod. & severe exacerb. per person-yr,n: 0.26 at 3 years, CI: 0.22-0.31 Mean steroid courses per person-yr: 0.31 at 3 years, CI: 0.27-0.36 Median time between first & second exacerbation,d: 572 at 3 years, CI: 241-903 Median time to first exacerbation in days: 476 at 3 years, CI: 307-645	Depression: 67/209 (32.1%) Flu-like illness: 107/209 (51.2%) Injection site reactions (e.g. bleeding): 170/209 (81.3%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
SPECTRIMS 2001 SPECTRIMS Trial	

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
SPECTRIMS 2001 Efficacy quality: Good Adverse event quality: Good	Placebo injection 3x/week, over 3 years N=205	Total withdrawals: 32 (15.6%) AE withdrawals: 5 (2.4%)	Exacerbation requiring hospitalization: 0.22 at 3 years, CI: 0.18-0.26 Mean exacerbations per person-year: 0.71 at 3 years, CI: 0.65-0.78 Mean mod. & severe exacerb. per person-yr,n: 0.39 at 3 years, CI: 0.34-0.44 Mean steroid courses per person-yr: 0.52 at 3 years, CI: 0.46-0.58 Median time between first & second exacerbation,d: 279 at 3 years, CI: 181-377 Median time to first exacerbation in days: 281 at 3 years, CI: 167-395	Depression: 59/205 (28.8%) Flu-like illness: 107/205 (52.2%) Injection site reactions (e.g. bleeding): 84/205 (41%)

Evidence Table 5. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1a

Study	Comments
SPECTRIMS 2001 SPECTRIMS Trial	

Evidence Table 6. Placebo controlled trials of interferon beta 1b

Study	Population Type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
European Study Group on Interferon (ESG) 1998 Europe-Switzerland	SPMS	Double-blind Parallel Multicenter Setting: NR	Screened: 768 Eligible: NR Enrolled: 718 Withdrawn: 187 LostToFU: 57 Analyzed: 711	Clinically or laboratory supported definite diagnosis of MS, secondary progression defined as a period of deterioration, independent of relapses, sustatined for at least 6 months and that followed a period of relapsing-remitting MS, ages 18-55 years, baseline EDSS score of 3.0-6.5 recorded history of either two relapses or more or 1.0 point or more increase in EDSS in the previous two years.	Immunosuppressive treatment or other putative treatments for MS for defined periods before entry	N=718 38.86% male 61.14% female
Freeman 2001 Europe	Same as European Study Group, 1998	Double-blind Multicenter Setting: NR	Same as European Study Group, 1998	Same as European Study Group, 1998	Same as European Study Group, 1998	Same as European Study Group, 1998
IFNB MS Study Group 1993 USA and Canada	RRMS	Double-blind Parallel Multicenter Setting: Research Center	Screened: NR Eligible: NR Enrolled: 372 Withdrawn: 65 LostToFU: NR Analyzed: 338	Ages 18-50 years EDSS scores of 5.5 or less at least two acute exacerbations during the previous 2 years. Clinically stable for at least 30 days before study entry and received no steroids during this period.	Patients taking azathioprine or cyclophosphamide.	N=372 Mean age (SD): 35.5 (0.63) (range: NR) 30.38% male 69.62% female 93.5% white 6.5% other

Evidence Table 6. Placebo controlled trials of interferon beta 1b

Study	Population Type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
INFB MS Study Group (1) 1995	Same as IFNB 1993	Same as IFNB 1993	Same as IFNB 1993	Same as IFNB 1993	Same as IFNB 1993	Same as IFNB 1993
Kappos 2001 Europe-Switzerland	Same as European Study group, 1998	Double-blind Parallel Multicenter Setting: NR	Same as European Study group, 1998	Same as European Study group, 1998	Same as European Study group, 1998	Same as European Study group, 1998

Evidence Table 6. Placebo controlled trials of interferon beta 1b

Study	Population Type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
kappos 2006 Multiple European; Canada; Israel BENEFIT	CIS	Double-blind Parallel Multicenter Setting: NR	Screened: 603 Eligible:511 Enrolled:487 Withdrawn:62 LostTo FU:31 Analyzed:468	Patients with a CIS—defined as a first neurologic event suggestive of MS lasting for at least 24 hours and with symptoms and signs indicating either a single lesion (monofocal) or more than one lesion (multifocal) within the CNS; age 18 and 45 yrs; have presented with a first neurologic event suggestive of MS that lasted for at least 24 hours, and had to have at least two clinically silent lesions on their T2-weighted brain MRI scan with a size of at least 3 mm, at least one of which being ovoid, periventricular, or infratentorial. Baseline Expanded Disability Status Scale (EDSS) between 0 and 5.	Patients in whom any disease other than MS could explain their signs and symptoms; any previous episode that could possibly be attributed to an acute demyelinating event; patients with complete transverse myelitis or bilateral optic neuritis; patients who had received prior immunosuppressive therapy.	N=468 Mean age (SD): 30 (NR) Range: 24-37.5 29.27% male 70.73% female 98% white 2% other
Knobler 1990	RRMS	Double-blind, Parallel, Single Center, Research Center	Screened: NR Eligible: NR Enrolled: 31 Withdrawn: 1 LostToFU:NR Analyzed: NR	Ages 18-50 with clinically definite RRMS for not less than 1 year and not more than 15 years and had at least two exacerbations in the previous 2 years In clinical remission at the time of study entry Contraception for fomen of child-bearing potential EDS	NR	N=31 Others NR

Evidence Table 6. Placebo controlled trials of interferon beta 1b

Study	Population Type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
Montalban 2004 Europe	PPMS	Blinding not reported Setting: NR	Screened: NR Eligible: NR Enrolled: 73 Withdrawn: 5 LostToFU: NR Analyzed: NR	Age 18-65 EDSS score of 3.0-7.0	Previous immunosuppressive or immunomodulatory therapy	N=73 Mean age (SD): NR (range: NR) NR% male NR% female
North American Study Group on SPMS (1) 2004	SPMS	Double-blind, Parallel, Multicenter Setting: NR	Screened: NR, Eligible: NR, Enrolled: 939, Withdrawn: 229, LostToFU: 73, Analyzed: 939	18-65 years clinically definite or laboratory supported definite MS of at least 2years duration history of at least one relapse followed by progressive deterioration sustained for at least 6 months an EDSS score at screening of 3.0-6.5 inclusive an increase	Received treatment with systemic corticosteroids or adrenocorticotropic hormone within 60 days before the screening visit previous treatment with any IFNB, monoclonal antibody, cladribine, or total lymphoid radiation, received cytotoxic or immunosuppressive therapy, glatiramer acetate, or other investigational drug within 6 months before screening visit	N=939 37.38% male 62.62% female
Sibley 1996 US/Canada	same as IFNB 1993	same as IFNB 1993	same as IFNB 1993	same as IFNB 1993	same as IFNB 1993	same as IFNB 1993

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
European Study Group on Interferon (ESG) 1998 **Europe-Switzerland** Efficacy quality: Good Adverse event quality: Good	Interferon beta-1b (Betaseron) injection 8 million IU every other day, over 36 months N=360 Male: 151 (42%) Female: 209 (58%) Mean age (SD): 41 (7.2)	Total withdrawals: 90 (25%) AE withdrawals: 45 (12.5%)	Proportion of patients with confirmed progression: 38.9% at 33 months, p-value: 0.0048 Time to confirmed progression: 893 days at 33 months, CI: 726-undetermined Mean change in EDSS: 0.47 at 33 months, p-value: 0.0299 Loss of mobility: 0.77 at 33 months, p-value: 0.0133 Mean Annual Relapse Rate: 0.44 at 33 months, p-value: 0.0002 Median time to first exacerbation in days: 644, p-value: 0.0030	Flu-like illness: 213/360 (59.2%) Hypertension: 14/360 (3.9%) Injection site inflammation: 180/360 (50%) Injection site necrosis: 17/360 (4.7%) Suicide or suicide attempts: 3/360 (0.8%)

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Comments
European Study Group on Interferon (ESG) 1998 Europe-Switzerland	On intervention: Mean baseline values Inf 1b; placebo: EDSS: 5.1; 5.2 Time since evidence of progressive deterioration: 3.8 years for both groups Disease duration SPMS course: 2.2 years; 2.1 years Disease duration RRMS: 8.1 years; 8.2 years

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
European Study Group on Interferon (ESG) 1998 **Europe-Switzerland** Efficacy quality: Good Adverse event quality: Good	Placebo N=358 Male: 129 (36%) Female: 229 (64%) Mean age (SD): 41 (7.2)	Total withdrawals: 97 (27.1%) AE withdrawals: 15 (4.2%)	Proportion of patients with confirmed progression: 49.7% at 33 months Time to confirmed progression: 549 days at 33 months, CI: 463-642 Mean change in EDSS: 0.60 at 33 months Loss of mobility: 0.66 at 33 months Mean Annual Relapse Rate: 0.64 at 33 months Median time to first relapse (days): 403	Flu-like illness: 133/358 (37.2%) Hypertension: 3/358 (0.8%) Injection site inflammation: 15/358 (4.2%) Injection site necrosis: 0/358 (0%) Suicide or suicide attempts: 5/358 (1.4%)
Freeman 2001 **Europe** Additional analysis of ESG data. Not quality assessed.	Interferon beta 1b injection 8 million IU every other day, over 36 months	Same as European Study Group on Interferon beta-1b in Secondary Progressive MS, 1998	Sickness Impact Profile: 15.9 at baseline -0.1 at 6 month -0.3 at 12 month -0.4 at 18 month 0.2 at 24 month 0.3 at 30 month 1.8 at 36 month 0.4 at Final	Same as European Study Group on Interferon beta-1b in Secondary Progressive MS, 1998

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Comments
European Study Group on Interferon (ESG) 1998 Europe-Switzerland	
Freeman 2001 Europe Additional analysis of ESG data. Not quality assessed.	On outcome: Sickness Impact Profile scale 0-100, with 0 as best possible HrQoL and 100 as worst possible HrQoL. After baseline, SIP is reported as mean change

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Freeman 2001 Europe (Additional analysis of ESG data)	Placebo	Same as European Study Group on Interferon beta-1b in Secondary Progressive MS, 1998	Sickness Impact Profile: 16.1 at baseline 0.4 at 6 month 0.7 at 12 month 1.0 at 18 month 0.5 at 24 month 1.7 at 30 month 2.1 at 36 month 1.8 at Final	Same as European Study Group on Interferon beta-1b in Secondary Progressive MS, 1998
IFNB MS Study Group 1993 USA and Canada Efficacy quality: Good Adverse event quality: Poor/Fair	Interferon beta-1b injection 1.6 million IU every other day, over 2 years N=125 Male: 40 (32%) Female: 85 (68%) Mean age (SD): 35	Total withdrawals: 24 (19%) AE withdrawals: 10 (8%)	Annualized relapse rate: 1.17 at 2 years, p-value: 0.0001 Annualized relapse rate: 1.05 at 3 years, p-value: 0.0004 Exacerbation requiring hospitalization: 53 at 3 years Median time to first exacerbation in days: 199 at 3 years, p-value: 0.028 Median time to first exacerbation in days: 180 at 2 years, p-value: 0.015 Proportion of relapse-free patients: 21% at 2 years Proportion of relapse-free patients: 18% at 3 years, p-value: 0.097	Fever: 44/111 (39.6%) Injection site inflammation: 70/111 (63.1%) Myalgia: 27/111 (24.3%)

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Comments
Freeman 2001 Europe (Additional analysis of ESG data)	
IFNB MS Study Group **1993** **USA and Canada** Efficacy quality: Good Adverse event quality: Poor/Fair	On intervention: Mean baseline values 1.6 MU; 8 MU; placebo EDSS: 2.9; 3.0; 2.8 Relapses 2 years preceding study entry: 3.3; 3.4; 3.6 Disease duration: 4.7 years; 4.7 years; 3.9 years On adverse event: Adverse events reported in %, calculated with total n for 2 years

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
IFNB MS Study Group **1993** **USA and Canada** Efficacy quality: Good Adverse event quality: Poor/Fair	Interferon beta-1b injection 8.0 million IU every other day, over 2 years N=124 Male: 38 (31%) Female: 86 (69%) Mean age (SD): 35	Total withdrawals: 18 (15%) AE withdrawals: 5 (4%)	Annualized relapse rate: 0.84 at 2 years, p-value: 0.0001 Annualized relapse rate: 0.84 at 3 years, p-value: 0.0004 Exacerbation requiring hospitalization: 37 at 3 years, p-value: 0.046 . Median time to first exacerbation in days: 264 at 3 years, p-value: 0.028 Median time to first exacerbation in days: 295 at 2 years, p-value: 0.015 Proportion of relapse-free patients: 31% at 2 years Proportion of relapse-free patients: 22% at 3 years, p-value: 0.097	Fever: 67/115 (58.3%) Injection site inflammation: 79/115 (68.7%) Myalgia: 47/115 (40.9%)

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Comments
IFNB MS Study Group **1993** **USA and Canada** Efficacy quality: Good Adverse event quality: Poor/Fair	

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
IFNB MS Study Group **1993** **USA and Canada** Efficacy quality: Fair Adverse event quality: Poor/Fair	Placebo N=123 Male: 35 (28%) Female: 88 (72%) Mean age (SD): 36	Total withdrawals: 23 (19%) AE withdrawals: 1 (1%)	Annualized relapse rate: 1.21 at 3 years, p-value: 0.0004 Annualized relapse rate: 1.27 at 2 years, p-value: 0.0001 Exacerbation requiring hospitalization: 65 at 3 years, p-value: 0.046 Median time to first exacerbation in days: 153 at 2 years, p-value: 0.015 Median time to first exacerbation in days: 147 at 3 years, p-value: 0.028 Proportion of relapse-free patients: 14% at 3 years, p-value: 0.097 Proportion of relapse-free patients: 16% at 2 years	Fever: 38/112 (33.9%) Injection site inflammation: 7/112 (6.2%) Myalgia: 27/112 (24.1%)

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Comments
IFNB MS Study Group 1993 USA and Canada	

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
INFB MS Study Group (1) 1995 (5 year data from IFNB trial)	Interferon beta-1b (Betaseron) injection 1.6 mill IU every other day, 5 years N=125	Total withdrawals: 57 (46%)	Median annual change in EDSS: 0.20 at 5 years Annualized relapse rate: 1.22 at year 1 1.04 at year 2 0.80 at year 3 0.68 at year 4 0.66 at year 5	See comments
INFB MS Study Group (1) 1995 (5 year data from IFNB trial)	Interferon beta-1b (Betaseron) injection 8 mill IU every other day, 5 years	N=124 Total withdrawals: 48 (39%)	Median annual change in EDSS: 0.00 at 5 years Annualized relapse rate: 0.96 at year 1, p-value: <0.001 0.85 at year 2, p-value: 0.030 0.66 at year 3, p-value: 0.084 0.67 at year 4, p-value: 0.166 0.57 at year 5, p-value: 0.393	See comments

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Comments
INFB MS Study Group (1) 1995 (5 year data from IFNB trial)	On Adverse events:AEs reported as percentages only; unclear total number of patients: Depressive symptoms at yr 5:1.6 MU - 5.5%, 8 MU - 11.1%, placebo - 5.1%. Suicide attempts: 1.6 MU - 0%, 8 MU - 0%, placebo - 0% On outcome: P values are 8 million IU versus Placebo. Subgroups: patients w with confirmed progression - Baseline EDSS <3.0, 1.6 MU 30/59 (51%), 8 MU 20/55 (36%), placebo 26/58 (45%), patients w/confirmed progression - Baseline EDSS >3.0, 1.6 MU 29/66 (44%), 8 MU 23/67 (34%), placebo 30/64 (47%)
INFB MS Study Group (1) 1995 (5 year data from IFNB trial)	

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
INFB MS Study Group (1) 1995 (5 year data from IFNB trial)	Placebo	N=123 Total withdrawals: 49 (40%)	Median annual change in EDSS: 0.11 at 5 years Annualized relapse rate: 1.44 at year 1 1.18 at year 2 0.92 at year 3 0.88 at year 4 0.81 at year 5	See comments
Kappos 2001 Europe-Switzerland (Additional data from ESG trial)	Interferon beta 1b N=360	Total withdrawals: 143 AE withdrawals: NR	Proportion of patients with confirmed progression: 37.3% (EDSS<3.5) Proportion of patients with confirmed progression: 47.7% (EDSS >6.0) Proportion of patients with confirmed progression: 46.4% (EDSS 4.0-5.5) Mean change in EDSS: 0.47 at 33 months, p-value: 0.003 Mean EDSS scores: 5.58 at 33 months, p-value: 0.007 Proportion of patients becoming wheelchair bound: 18.6 at 33 months, p-value: 0.007 Mean Annual Relapse Rate: 0.42, p-value: 0.003	Same as European Study Group on Interferon beta-1b in Secondary Progressive MS, 1998

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Comments
INFB MS Study Group (1) 1995 (5 year data from IFNB trial)	
Kappos 2001 Europe-Switzerland (Additional data from ESG trial)	

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Kappos 2001 Europe-Switzerland (Additional data from ESG trial)	Placebo N=358	Total withdrawals: 165 AE withdrawals: NR	Proportion of patients with confirmed progression: 54.9% (EDSS 4.0-5.5) Proportion of patients with confirmed progression: 44.7% (EDSS<3.5) Proportion of patients with confirmed progression: 55.6% (EDSS >6.0) Mean change in EDSS: 0.69 at 33 months, p-value: 0.003 Mean EDSS scores: 5.93 at 33 months, p-value: 0.007 Proportion of patients becoming wheelchair bound: 28.5% at 33 months, p-value: 0.007 Mean Annual Relapse Rate: 0.57, p-value: 0.003	Same as European Study Group on Interferon beta-1b in Secondary Progressive MS, 1998

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Comments
Kappos 2001 Europe-Switzerland (Additional data from ESG trial)	

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Kappos 2004 Not quality assessed; reanalysis	See original trials for details of populations, comparison of trial populations; EU had significantly lower age at entry, lower age at onset, lower duration of MS, greater number of relapses in prior 2 years, greater change in EDSS in prior 2years, and lower percentage of patients that were relapse free in prior 2 years when compared to NA trial population. There were no significant differences in duration of SPMS, or baseline EDSS	NR	Combined Subgroup analysis, comparison between treatment groups:, all patients: 0.79, p=0.0076, patients with relapses: 0.70, p=0.0024, patients with change in EDSS greater than 1: 0.63, p=0.0006, patients with relapses or change in EDSS greater than 1: 0.72, p=0.0011, patients with relapses and change in EDSS greater than 1: 0.53, p=0.0006, NSD for relapses and change in EDSS less than 1 or without relapses but change in EDSS greater than 1, pooled analysis population Patients with at least one relapse in the 2 years before study entry or pronounced EDSS progression had a risk reduction to experience disability progression of 30-40%	NR
Kappos 2006 **Multiple European; Canada; Israel** **BENEFIT** Efficacy Quality :Good Adverse Event Quality: Fair/Good	Interferon beta-1b (Betaseron) 250 Ug, subcutaneous, every other day upto 2 years N=292 Male: 85 (29%) Female: 207 (71%) Mean age (SD): 30	Total withdrawals: 65(22%) AE Withdrawals: 32 (11%)	Patients progressing to CDMS: 75 patients Patients progressing to McDonald criteria MA: 191 patients	Injection site reaction:141/292 (48.3%) Flu-like illness:129/292 (44.2%) Depression:30/292 (10.3%) Abnormal liver function test(ALT): 52/292 (18%) Abnormal liver function test (AST): 18/292 ((6.2%)

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Comments
Kappos 2004 Not quality assessed; reanalysis	Pooled analysis of the EU-SPMS and NA-SPMS trials, see original trials for inclusion and exclusion criteria
Kappos 2006 **Multiple European; Canada; Israel** **BENEFIT**	On design: 13 interferon beta-1b and 6 placebo pts were randomized but never received treatment. On population: Only white race reported. Other 2% of pts not described by race On Withdrawals: Includes patients lost to follow up and withdrawals

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Kappos 2006 Multiple European; Canada; Israel BENEFIT Efficacy Quality :Good Adverse Event Quality: Fair/Good	Placebo subcutaneous, every other day upto 2 years N=176 Male: 2 (1%) Female: 174 (99%) Mean age (SD): 30	Total withdrawals:28 (16%) Adverse event withdrawals: 1 (0.5%)	Patients progressing to CDMS: 77 patients Patients progressing to McDonald criteria MA: 142 patients	Injection site reaction: 15/176 (9%) Flu-like illness: 32/176 (18.2%) Depression: 20/176 (11.4%) Abnormal liver function test(ALT): 8/176 (5%) Abnormal liver function test (AST): 1/176 (0.56%)
Knobler 1990 Efficacy quality: Fair Adverse event quality: Fair	Interferon beta-1b (Betaseron) injection 0.8 mill IU 3 times per week, 24 weeks N=6 Male: 2 (33%) Female: 4 (67%) Mean age (SD): 34	Total withdrawals: 1 AE withdrawals: 1	Annualized relapse rate: 0.8 at 24wks, CI: 0.1-2.5 Total no. of patients experiencing an exacerbation: 2 at 24wks	Adverse event rates apply to first 3 yrs. Rates are only stratified by placebo and betaseron; there is no AE information by dose. AE reported under 8 mill IU arm and placebo arm

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Comments
Kappos 2006 Multiple European; Canada; Israel BENEFIT	
Knobler 1990	On intervention: Mean baseline values: 0.8 MU; 4 MU; 8 MU; 16 MU; placebo EDSS: 2.8; 4.0; 2.7; 2.9; 3.1, Relapses 2 years preceding study: 2.7; 3.3; 4.0; 2.0; 2.3 Disease duration: 6.2; 8.2; 4.2; 7.3; 7.0

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Knobler 1990 Efficacy quality: Fair Adverse event quality: Fair	Interferon beta-1b (Betaseron) injection 4 mill IU 3 times per week, 24 weeks N=6 Male: 4 (67%) Female: 2 (33%) Mean age (SD): 38	Total withdrawals: 0 AE withdrawals: 0	Annualized relapse rate: 2.2 at 24wks, CI: 0.9-4.3 Total no. of patients experiencing an exacerbation: 4 at 24 wks	Adverse event rates apply to first 3 yrs. Rates are only stratified by placebo and betaseron; there is no AE information by dose. AE reported under 8 mill IU arm and placebo arm
Knobler 1990 Efficacy quality: Fair Adverse event quality: Fair	Interferon beta-1b (Betaseron) injection 8 mill IU 3 times per week, 24 weeks N=6 Male: 4 (67%) Female: 2 (33%) Mean age (SD): 35	Total withdrawals: 1 AE withdrawals: 0	Annualized relapse rate: 0.9 at 24wks, CI: 0.2-2.7 Total no. of patients experiencing an exacerbation: 4 at 24wks	Depression: 12/24 (50%) Flu-like illness: 4/24 (16.7%) Headache: 18/24 (75%) Injection site inflammation: 23/24 (95.8%) Injection site pain: 20/24 (83.3%)

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Comments
Knobler 1990	
Knobler 1990	

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Knobler 1990 Efficacy quality: Fair Adverse event quality: Fair	Interferon beta-1b (Betaseron) injection 16 mill IU 3 times per week, 24 weeks N=6 Male: 4 (67%) Female: 2 (33%) Mean age (SD): 36	Total withdrawals: 1 AE withdrawals: 1	Annualized relapse rate: 0 at 24wks, CI: 0.0-1.2 Total no. of patients experiencing an exacerbation: 0 at 24wks	Adverse event rates apply to first 3 years. Rates are only stratified by placebo and betaseron; there is no AE information by dose. AE reported under 8 mill IU arm and placebo arm
Knobler 1990 Efficacy quality: Fair Adverse event quality: Fair	Placebo N=7 Male: 2 (29%) Female: 5 (71%) Mean age (SD): 34	Total withdrawals: 1 AE withdrawals: 0	Annualized relapse rate: 1.8 at 24wks, CI: 0.7-3.7 Total no. of patients experiencing an exacerbation: 4 at 24wks	Depression: 2/6 (33.3%) Flu-like illness: 4/6 (66.7%) Headache: 6/6 (100%) Injection site inflammation: 2/6 (33.3%) Injection site pain: 3/6 (50%)

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Comments
Knobler 1990	
Knobler 1990	

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Montalban 2004 Europe Efficacy quality: Poor Adverse event quality: Poor	Interferon beta 1b 8 million IU every other day, 2 years N=36		See comments on outcome	No details reported, only that frequency of treatment-related adverse events (flu-like symptoms, leucopenia and injection-site reactions) were greater in the Interferon group.

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Comments
Montalban 2004 Europe	On outcome: Primary outcome-sustained progression defined as EDSS of at least 1.0 or more for 6 months in patients with baseline 5.0 or less and 0.5 or more for 6 months in patients with baseline of 5.5 or more. No primary outcome values reported On population: Population included 49 with PPMS and 24 with transitional MS, defined as progressive disease with history of a single episode of relapse prior to, at the onsetof, or during the progressive phase

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
North American Study Group on SPMS (1) 2004 Efficacy quality: Good Adverse event quality: Fair	Interferon beta 1b injection 5 million IU every other day, 3 years N=314 Male: 121 (39%) Female: 193 (61%) Mean age (SD): 47 (0.47)	Total withdrawals: 75 (24%) AE withdrawals: 23 (7%)	Time to confirmed progression: 668 days at 6 months or more p-value: 0.261	Headache: 182/314 (58%) Injection site reaction: 173/314 (55%) Flu-like illness: 141/314 (50%) Injecton site inflammation:165/314 (53%) Chills: 69/314 (22%) Myalgia: 75/314 (24%)

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Comments
North American Study Group on SPMS (1) 2004	On outcome: Confirmed progression was number of days from the start of treatment to the first recorded increase of 1.0 point or more from the baseline EDSS score (0.5 point EDSS score for baseline 6.0-6.5) confirmed at two scheduled examinations spanning 6 months or more from the onset of progression. P-values for time to progression are compared to placebo. Other secondary outcomes are measured as placebo vs. pooled IFNB-1b group. The study reported a significant treatment benefit for reduction in annual relapse rate 36% vs. 43%, placebo vs. 8 MIU respectively. On intervention: Mean baseline values Inf 1b 250ug; Inf 1b 160ug; placebo, EDSS: 5.2; 5.1; 5.1, Relapses 2 years preceding study: 0.8; 0.9; 0.8, Disease duration SPMS course: 4.0 years; 4.0 years; 4.1 years, Disease duration MS diagnosis: 14.6 years; 14.5 years; 14.9 years.

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
North American Study Group on SPMS (1) 2004 Efficacy quality: Good Adverse event quality: Fair	Interferon beta 1b injection 8 million IU every other day, 3 years N=317 Male: 107 (34%) Female: 210 (66%) Mean age (SD): 46 (0.45)	Total withdrawals: 79 (25%) AE withdrawals: 22 (7%)	Time to confirmed progression: 981 days at 6 months or more p-value: 0.606	Headache:174/317 (55%) Injection site reaction: 165/317 (52%) Flu-like illness: 137/317 (43.2%) Injecton site inflammation: 160/317 (50%) Chills: 70/317 (22%) Myalgia:92/317 (29%)
North American Study Group on SPMS (1) 2004 Efficacy quality: Good Adverse event quality: Fair	Placebo N=308 Male: 123 (40%) Female: 185 (60%) Mean age (SD): 48 (0.46)	Total withdrawals: 75 (24.3%) AE withdrawals: 28 (9%)	Time to confirmed progression: 750 days at 6 months or more	Headache:141/308 (46%) Injection site reaction: 43/308 (14%) Flu-like illness: 102/308 (33%) Injection site inflammation: 20/308 (6%) Chills: 36/308 (12%) Myalgia: 57/308 (19%)

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Comments
North American Study Group on SPMS (1) 2004 Efficacy quality: Good Adverse event quality: Fair	
North American Study Group on SPMS (1) 2004	

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events
Sibley 1996 US/Canada (Additional analysis of IFNB 1993)	Interferron beta 1-b 8MU	NR	Annualized relapse rate: 0.96 at 3 years	NR
Sibley 1996 US/Canada (Additional analysis of IFNB 1993)	Interferon beta 1-b 1.6MU	NR	Annualized relapse rate: 0.96 at 3 years	NR
Sibley 1996 US/Canada (Additional analysis of IFNB 1993)	Placebo	NR	Annualized relapse rate: 1.12 at 3 years	NR

Evidence Table 7. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Comments
Sibley 1996 US/Canada (Additional analysis of IFNB 1993)	On outcome:These data represent pooled "annual exacerbation rates" however they do not match the data in INFB 1993 (the main publication for this trial.) For 'exacerbation rate" at 3 yrs, those data are: 1.6 MU - 1.05, 8 MU - 0.84, placebo - 1.21, The reason for these discrepant figures is unclear.
Sibley 1996 US/Canada (Additional analysis of IFNB 1993)	
Sibley 1996 US/Canada (Additional analysis of IFNB 1993)	

Evidence Table 8. Placebo-controlled trials of glatiramer acetate

Study	Population type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
Bornstein 1987	RRMS	Double Blind Parallel Center: NR Setting: NR	Screened:140 Eligible:NR Enrolled:50 Withdrawn:7 Loss to F/U:2 Analyzed:48	Definite MS diagnosis; age 20-35; at least 2 'well-demarcated' and well-documented exacerbations 2 yr prior to study entry; EDSS </=6; emotionally stable as determined by psychosocial evaluation	NR; authors report screened patients excluded for the following reasons: age, low frequency of exacerbations, lack of documentation, psychosocial inadequacy, transition to a chronic progressive course, distance from the clinic and pregnancy	N=50 Mean age (SD): 30.5 (NR) (range: NR) 42% male 58% female 96% white 4% other
Comi 2001 6 European countries; Canada	RRMS	Double Blind Parallel Multicenter Setting: NR	Screened: 485 Eligible: 272 Enrolled: 239 Withdrawn:14 Loss to F/U: 2 Analyzed: Unclear	RRMS diagnosis for at least 1 year; at least 1 documented relapse in 2 years preceding study entry; age 18-50 years; baseline EDSS 0-5; at least on enhancing lesion on MRI. Clinically relapse-free and without steroid treatment 30 days prior to MRI	Previous use of GA or oral myelin; prior lymphoid irradiation, use of immunosuppressant or cytotoxic agents in 2 years preceding study entry, use of azathioprine, cyclosporine, interferons, deoxyspergualine or chronic corticosteroid use during 6 months prior to study entry; concomitant therapy with an experiemental MS drug; serious intercurrent systemic or psychiatric illnesses, pregnancy or unwilling/unable to practice contraception during study enrollment; known hypersensitiviy to gadolinium-DTPA; unable to undergo repeated MRI scans.	N=239 Mean age (SD): 34.0 (7.5) NR% male NR% female

Evidence Table 8. Placebo-controlled trials of glatiramer acetate

Study	Population type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
Johnson 1995	RRMS	Double Blind Parallel Multicenter Research Center	Screened: 284 Eligible: NR Enrolled:251 Withdrawn:36 Loss to F/U: 0 Analyzed: 251	Clinically definite or lab supported RRMS; age 18-45 years; baseline EDSS 0-5; at least two relapses in 2 years prior to study entry; onset of 1st relapse at least 1 year prior to randomization; period of neurologic stability no use of steroids 30 days prior	Previous use of Cop 1 (glatiramer), immunosuppresive therapy with cytotoxic chemotherapy or lymphoid irradiation; pregnancy or lactation; insulin-dependent diabetes; HIV or HTLV-1 positive; evidence of Lyme disease, required use of aspirin or chronic NSAIDs	N=251 Mean age (SD): 34.4 (6.3) 26.69% male 73.31% female 94% white 6% other

Evidence table 9. Effectiveness and adverse events in placebo-controlled trials of glatiramer acetate

Source	Dosage, Population	Withdrawals	Outcomes	Adverse Events	Comments
Bornstein (1) 1987 Efficacy Quality:Fair Adverse event Quality: Fair	Glatiramer acetate (Copolymer 1) self-injection 20 mg qd n=25	NR	Proportion of patients with confirmed progression: 20% at 2 years; p=<0.005 Mean relapse rate: 0.6 at 2 years Proportion of relapse-free patients: 56% at 2 years Total no. of relapses: 16 at 2 years	Arthralgia (joint pain): 10/25 (40%) Headache: 8/25 (32%) Injection site itching: 16/25 (64%) Injection site redness: 19/25 (76%) Injection site soreness: 23/25 (92%) Injection site swelling: 22/25 (88%) Patterned reaction: 2/25 (8%)	On population: Population reported as 'exacerbating-remitting' by study authors - here reported as 'RRMS'; Black/Hispanic reported as a single group by study authors - here reported as 'Other'; baseline EDSS 2.9 GA; 3.1 placebo On outcome: Subgroup analyses found that baseline EDSS and treatment group both significantly affected likelihood that a patient would be relapse-free (p=0.003 for baseline EDSS; p=0.036 for treatment group) On adverse event: Patterned reactions consist of flushing, sweating, palpitations, tightness in the chest, difficulty breathing, anxiety beginnning during/immediately after injection and lasting 5-15 mins On Withdrawal: 7 patients identified as having stopped treatment, including 2 in placebo group whose data was deemed unusable. Other 5 patients not identified by treatment group.

Evidence table 9. Effectiveness and adverse events in placebo-controlled trials of glatiramer acetate

Source	Dosage, Population	Withdrawals	Outcomes	Adverse Events	Comments
Bornstein (1) 1987 Efficacy Quality:Fair Adverse event Quality: Fair	Placebo self-injection qd n=25	NR	Proportion of patients with confirmed progression: 48% at 2 years Mean relapse rate: 2.7 at 2 years Proportion of relapse-free patients: 26% at 2 years Total no. of relapses: 62 at 2 years	Arthralgia (joint pain): 9/23 (39.1%) Headache: 9/23 (39.1%) Injection site itching: 5/23 (21.7%) Injection site redness: 11/23 (47.8%) Injection site soreness: 8/23 (34.8%) Injection site swelling: 4/23 (17.4%) Patterned reaction: 0/23 (0%)	
Comi 2001 **6 European countries; Canada** Efficacy Quality:Fair Adverse event Quality: Fair/Good	Glatiramer acetate (Copolymer 1) injection 20 mg qd n=119 Mean age (SD): 34 (7.4)	Total withdrawals: 7 (5.8%) AE withdrawals: 3 (2.5%)	Use of rescue medications: 33.6% at 9 months Annualized relapse rate: 0.81 at 1 year (projection) Exacerbation requiring hospitalization: 16/119 at 9 months Mean relapse rate: 0.51 at 9 months; p=0.012 Proportion of relapse-free patients: 55.5% at 9 months; p=0.175	Injection site reactions: 84/119 (70.6%) Patterned reaction: 45/119 (37.8%)	On population: Baseline EDSS 2.4 (SD 1.2)

Evidence table 9. Effectiveness and adverse events in placebo-controlled trials of glatiramer acetate

Source	Dosage, Population	Withdrawals	Outcomes	Adverse Events	Comments
Comi 2001 **6 European countries; Canada** Efficacy Quality:Fair Adverse event Quality: Fair/Good	Placebo N=120 Mean age (SD): 34 (7.5)	Total withdrawals: 7 (5.8%) AE withdrawals: 2 (1.7%)	Use of rescue medications: 39.2% at 9 mos Annualized relapse rate: 1.21 at 1 yr (projection) Exacerbation requiring hospitalization: 30/120 at 9 mos Mean relapse rate: 0.76 at 9 mos Proportion of relapse-free patients: 49.2% at 9 mos	Injection site reactions: 34/120 (28.3%) Patterned reaction: 16/120 (13.3%)	
Johnson 1995 Efficacy quality: Good Adverse event quality: Fair	Glatiramer acetate (Copolymer 1) injection 20 mg qd N=125 Male: 37 (30%) Female: 88 (70%) Mean age (SD): 35 (6.0)	Total withdrawals: 19 (15%) AE withdrawals: 4 (3%)	Mean change in EDSS: -0.05 (SD 1.13) at 2 years; p=0.023 Proportion of pts EDSS progression-free: 78.4% at 2 years; p=NS Ambulation index: 0.27 (SD 0.94) at 2 years; p=NS Annualized relapse rate: 0.59 Mean relapse rate: 1.19 at 2 years; p=0.007 Median Time to first relapse (days): 287; p=0.097 Proportion of relapse-free patients: 33.6% at 2 years; p=0.098	Injection site reactions: 113/125 (90.4%) Patterned reaction: 19/125 (15.2%)	On population: Mean baseline EDSS (SD): 2.6 (1.3); 2-yr relapse rate preceding study: 2.9; Race only listed as 'white' and 'other'

Evidence table 9. Effectiveness and adverse events in placebo-controlled trials of glatiramer acetate

Source	Dosage, Population	Withdrawals	Outcomes	Adverse Events	Comments
Johnson 1995 Efficacy quality: Good Adverse event quality: Fair	Placebo N=126 Male: 30 (24%) Female: 96 (76%) Mean age (SD): 34 (6.5)	Total withdrawals: 17 (14%) AE withdrawals: 1 (0.8%)	Mean change in EDSS: 0.21 (SD 0.99) at 2 years Proportion of pts EDSS progression-free: 75.4% at 2 years Ambulation index: 0.28 (SD 0.93) at 2 years Annualized relapse rate: 0.84 Mean relapse rate: 1.68 at 2 years Median Time to first relapse (days): 198 Proportion of relapse-free patients: 27.0% at 2 years	Injection site reactions: 74/126 (58.7%) Patterned reaction: 4/126 (3.2%)	

Evidence Table 10. Placebo controlled trials of natalizumab

Study	Population Type	Design	Recruitment	Eligibility	Exclusion
Miller (2) **2003** **US, Canada, UK**	RRMS, SPMS	Double Blind Parallel Multicenter Specialty Clinic	Screened:NR Eligible:NR Enrolled:213 Withdrawn:18 Lost to F/U:10 Analyzed: 205	18-65 years clinically or lab supported diagnosis of RR or SPMS with at least 2 relapses within previous 2 years EDSS 2.0-6.5 with a minimum of 3 brain lesions on MRI.	Use of immunosuppressive or immunomodulating treatments w/in 3 months prior to study entry; relapse within 30 days; use of systemtic corticosteroids within 30 days.
Polman **2002** **AFFIRM**	RRMS	Double Blind Parallel Multicenter Specialty Clinic	Screened:NR Eligible:NR Enrolled:942 Withdrawn:83 Lost to F/U:12 Analyzed: 942	Adults age 18-50 years with diagnosis of RRMS and EDSS score 0-5, MRI lesions consistent with MS diagnosis, at least 1 relapse in preceding 12 months.	PP, SP or progressive relapsing MS diagnosis; relapse within 50 days prior to drug administration; treatment with cyclophosphamide or mitoxantrone w/in previous year, treatment with interferon beta, glatiramer, cyclosporine, asathioprine, methotrextate or IIG within 6 months; previous treatment with interferon beta, glatiramer or both for more than 6 months.
Rudick **2006** **US, Europe** **SENTINEL**	RRMS	Double Blind Parallel Multicenter Specialty Clinic	Screened:NR Eligible:NR Enrolled:1196 Withdrawn:168 Lost to F/U:9 Analyzed:1171	18-55 years; diagnosis of RRMS; EDSS 0-5.0; MRI confirmed brain lesions consistent with MS diagnosis; previous use of Interferon beta-1a for at least 12 months prior to study entry; at least 1 relapse in 12 months preceding randomization.	Diagnosis of PP, SP or PRMS; relapse within 50 days of study entry; treatment with any DM therapy other than beta-1a within 12 months prior to randomization.

Evidence Table 10. Placebo controlled trials of natalizumab

Study	Sample Size, Age, Gender, Ethnicity
Miller (2) **2003** **US, Canada, UK**	N=213 Mean age (SD): 43.6 (range: 22-66) 28.64% male 71.36% female
Polman **2002** **AFFIRM**	N=942 Mean age (SD): 36.0 (8.3) (range: 18-50) 29.94% male 70.06% female 95% white 5% other
Rudick **2006** **US, Europe** **SENTINEL**	N=1171 Mean age (SD): 38.9 (7.7) (range: 18-55) 26.39% male 73.61% female 93% white 7% other

Evidence Table 10. Placebo controlled trials of natalizumab

Study	Population Type	Design	Recruitment	Eligibility	Exclusion
Sheremata 1999 US	RRMS, SPMS	None reported	Screened:NR Eligible:NR Enrolled:28 Withdrawn:0 Loss to F/U:0 Analyzed:28	Clinically-definite RR or SPMS between 19-55years within 15% ideal body weight range. Baseline EDSS</=5.5	Patients with MS exacerbations or infections, immunomodulatory or investigational drug recipients; pregnancy, breastfeeding or failure to use adequate birth control; regular blood donors, heavy smokers, drinkers other medical disorders; known drug hypersensitivity.
Tubridy 1999 UK	RRMS, SPMS	Double Blind Parallel Multicenter Specialty Clinic	Screened:NR Eligible:NR Enrolled:72 Withdrawn:2 Loss to F/U:0 Analyzed:70	Clinically definite RR or SPMS; age 18-55 years; <90kg (198 lbs); EDSS 2.0-7.0; 2+ exacerbations in 18 months preceding study; >4 weeks since last exacerbation	PPMS; pregnant, breastfeeding or women of childbearing age not using birth control; normal T2 weighted MRI at week -4; use of immunosuppressive drug within 6 months (including azathioprine, cyclophosphamide and beta-interferon); use of methylprednisolone and/or oral prednisone in 4 weeks preceding 1st visit; previous treatment with anti-CD4 antibodies, other monoclonal antibodies or total lymphoid irradiation at any timel previous exposure to products containing murine protein; alcohol consumption >21 units/week or abuse of other drugs

Evidence Table 10. Placebo controlled trials of natalizumab

Study	Sample Size, Age, Gender, Ethnicity
Sheremata 1999 US	N=28 Mean age (SD): 40.8 (9.1) 53.57% male 46.43% female
Tubridy 1999 UK	N=72 Mean age (SD): 40.3 (range: 25-55) 36.11% male 63.89% female

Evidence Table 11. Effectiveness and adverse events in placebo controlled trials of natalizumab

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events	Comments
Miller (2) 2003 US, Canada, UK Efficacy quality: Good Adverse event quality: Fair	Natalizumab IV 3 mg/kg every 28 days, over 6 months N=68 Male: 21 (31%) Female: 47 (69%) Mean age (SD): 43	Total withdrawals: 5 (7.4%) AE withdrawals: 4 (5.9%)	Mean change in EDSS: -0.14 VAS score, mean change: 9.49 mm, p-value: 0.04 Use of rescue medication in relapsing patients: 5/13, p-value: <0.001 Total no. of relapses (physician assessed): 3, p-value: 0.004	Headache: 27/68 (39.7%) Infections: 15/68 (22.1%) Total patients reporting any AE: 5/68 (7.4%) UTI: 15/68 (22.1%) Weakness/muscle weakness: 12/68 (17.6%)	On intervention: Other baseline values - 3mg/kg; 6 mg/kg; placebo, Mean EDSS - 4.2; 4.3; 4.4, Mean relapses 2 years prior to study entry: 2.9; 3.1; 3.0 RRMS course: 47(69%); 52 (70%); 45 (63%), SPMS course: 21 (31%); 22 (30%); 26 (37%). On outcome: Relapse rates were measured 6 months after stopping treatment; no significant differences were found among three treatment groups. P values are versus placebo.
Miller (2) 2003 US, Canada, UK Efficacy quality: Good Adverse event quality: Fair	Natalizumab IV 6 mg/kg every 28 days, over 6 months N=74 Male: 15 (20%) Female: 59 (80%) Mean age (SD): 45	Total withdrawals: 8 (10.8%) AE withdrawals: 3 (4.1%)	Mean change in EDSS: -0.03 VAS score, mean change: 6.21 mm, p-value: 0.03 Use of rescue medication in relapsing patients: 7/14, p-value: 0.002 Total no. of relapses (physician assessed): 8, p-value: 0.11	Headache: 20/74 (27%) Infections: 14/74 (18.9%) Total patients reporting any AE: 4/74 (5.4%) UTI: 13/74 (17.6%) Weakness/muscle weakness: 7/74 (9.5%)	
Miller (2) 2003 US, Canada, UK Efficacy quality: Good Adverse event quality: Fair	Placebo IV every 28 days, over 6 months N=71 Male: 25 (35%) Female: 46 (65%)	Total withdrawals: 5 (7.0%) AE withdrawals: 3 (4.2%)	Mean change in EDSS: 0.03 VAS score, mean change: -1.38 mm Use of rescue medication in relapsing patients: 22/27 Total no. of relapses (physician assessed): 18	Headache: 27/71 (38%) Infections: 11/71 (15.5%) Total patients reporting any AE: 7/71 (9.9%) UTI: 11/71 (15.5%) Weakness/muscle weakness: 11/71 (15.5%)	

Evidence Table 11. Effectiveness and adverse events in placebo controlled trials of natalizumab

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events	Comments
Polman 2002 AFFIRM Efficacy quality: Good Adverse event quality: Good	Natalizumab IV 300mg every 4 weeks up to 116 weeks N=627 Male: 178 (28%) Female: 449 (72%) Mean age (SD): 36 (8.5)	Total withdrawals: 52 (8.3%) AE withdrawals: 15 (2.4%)	Cumulative prob. of disease progression: 17%; HR 0.58 at 2 yrs, p-value: <0.0001, CI: 0.43-0.77 Annualized relapse rate: 0.27 at 1 yr, p-value: <0.001, CI: 0.21-0.33 Annualized relapse rate: 0.23 at 2 yrs, p-value: <0.001, CI: 0.19-0.28 Proportion of relapse-free patients: 77% at 1 yr, p-value: <0.001 Proportion of relapse-free patients: 67% at 2 yrs, p-value: <0.001	Arthralgia (joint pain): 119/627 (19%) Depression: 119/627 (19%) Fatigue/Tiredness: 169/627 (27%) Headache: 238/627 (38%) Injection site reactions (e.g. bleeding): 19/627 (3%) Respiratory infections: 107/627 (17.1%) Total patients reporting any AE: 596/627 (95.1%) UTI: 125/627 (19.9%)	On population: Mean disease duration: 5 yrs, Mean EDSS at baseline: 2.3 (+/- 1.2), Mean relapse rate/year at baseline: 1.52(+/- 0.86) On outcome: 3 randomized patients who never received treatment were included for efficacy but not safety outcomes On adverse events:No SS differences between natalizumab and placebo for serious AEs and non-serious AEs. Serious AEs: cholelithiasis reported in <1% of pts in both groups (p=0.435). On withdrawals: 24 additional natalizumab pts and 15 additional placebo pts discontinued drug due to AEs but completed follow-up; not counted as withdrawals by authors

Evidence Table 11. Effectiveness and adverse events in placebo controlled trials of natalizumab

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events	Comments
Polman 2002 AFFIRM Efficacy quality: Good Adverse event quality: Good	Placebo IV every 4 weeks up to 116 weeks N=315 Male: 104 (33%) Female: 211 (67%) Mean age (SD): 37 (7.8)	Total withdrawals: 31 (9.8%) AE withdrawals: 6 (1.9%)	Annualized relapse rate: 0.73 at 2 yrs, p-value: <0.001, CI: 0.62-0.87 Cumulative prob. of disease progression: 29% HR 0.58 at 2 yrs, p-value: <0.0001, CI: 0.43-0.77 Annualized relapse rate: 0.78 at 1 yr, p-value: <0.001, CI: 0.64-0.94 Proportion of relapse-free patients: 56% at 1 yr, p-value: <0.001 Proportion of relapse-free patients: 67% at 2 yrs, p-value: <0.001	Arthralgia (joint pain): 44/312 (14.1%) Depression: 50/312 (16%) Fatigue/Tiredness: 66/312 (21.2%) Headache: 103/312 (33%) Injection site reactions (e.g. bleeding): 6/312 (1.9%) Respiratory infections: 50/312 (16%) Total patients reporting any AE: 300/312 (96.2%) UTI: 53/312 (17%)	

Evidence Table 11. Effectiveness and adverse events in placebo controlled trials of natalizumab

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events	Comments
Rudick 2006 **US, Europe** **SENTINEL** Efficacy quality: Good Adverse event quality: Fair	Interferon beta-1a (Avonex) injection 30ug once/week up to 116 doses N=589 Male: 147 (25%) Female: 442 (75%) Mean age (SD): 39 (7.7)	Total withdrawals: 73 (12%) AE withdrawals: 17 (3%)	Cumulative prob. of disease progression: 23% at 2 years, p-value: 0.02 Annualized relapse rate: 0.34 at 2 years, p-value: 0.001, CI: 0.29-0.39 Annualized relapse rate: 0.38 at 1 year, p-value: <0.001, CI: 0.32-.045 Proportion of relapse-free patients: 61% at 2 years, p-value: <0.001	Depression: 124/589 (21.1%) Flu-like illness: 118/589 (20%) Headache: 271/589 (46%) Other psychiatric event (anxiety, mania, etc.): 71/589 (12.1%) Respiratory infections: 47/589 (8%) Total patients reporting any AE: 584/589 (99.2%)	On Design:25 post-randomization exclusions due to "data irregularities" at one study site. On population:Population figues exclude 25 patients from one center whose data was not counted in analysis due to data irregularities. On Outcome: Sustained disability progression over 2 yrs: HR 0.76 (95% CI, 0.61-0.96; p=0.02), Risk of relapse: HR 0.50 (95% CI, 0.43-0.59; p<0.001), Comments: Proportion of relapse-free patients reported in text as 54% and 32% respectively; does not match values in Table 2 (61% and 37%)

Evidence Table 11. Effectiveness and adverse events in placebo controlled trials of natalizumab

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events	Comments
Rudick 2006 **US, Europe** **SENTINEL** Efficacy quality: Good Adverse event quality: Fair	Natalizumab IV 300mg every 4 weeks up to 29 doses N=589 Male: 147 (25%) Female: 442 (75%) Mean age (SD): 39 (7.7)	Total withdrawals: 73 (12%) AE withdrawals: 17 (3%)	Cumulative prob. of disease progression: 23% at 2 years, p-value: 0.02 Annualized relapse rate: 0.34 at 2 years, p-value: 0.001, CI: 0.29-0.39 Annualized relapse rate: 0.38 at 1 year, p-value: <0.001, CI: 0.32-.045 Proportion of relapse-free patients: 61% at 2 years, p-value: <0.001	Depression: 124/589 (21.1%) Flu-like illness: 118/589 (20%) Headache: 271/589 (46%) Other psychiatric event (anxiety, mania, etc.): 71/589 (12.1%) Respiratory infections: 47/589 (8%) Total patients reporting any AE: 584/589 (99.2%)	On design: 25 post-randomization exclusions due to "data irregularities" at one study site. On population: Population figues exclude 25 patients from one center whose data was not counted in analysis due to data irregularities. On outcome:Sustained disability progression over 2 years: HR 0.76 (95% CI, 0.61-0.96; p=0.02), Risk of relapse: HR 0.50 (95% CI, 0.43-0.59; p<0.001), Proportion of relapse-free patients reported in text as 54% and 32% respectively; does not match values in Table 2 (61% and 37%)
Rudick 2006 **US, Europe** **SENTINEL** Efficacy quality: Good Adverse event quality: Fair	Interferon beta-1a (Avonex) injection 30ug once/wk up to 116 weeks N=582 Male: 162 (28%) Female: 420 (72%) Mean age (SD): 39 (7.6)	Total withdrawals: 95 (16%) AE withdrawals: 14 (2%)	Cumulative prob. of disease progression: 29% at 2 years, p-value: 0.02 Annualized relapse rate: 0.75 at 2 years, p-value: 0.001, CI: 0.67-0.84 Annualized relapse rate: 0.81 at 1 year, p-value: <0.001, CI: 0.72-0.92 Proportion of relapse-free patients: 37% at 2 years, p-value: <0.001	Depression: 105/582 (18%) Flu-like illness: 111/582 (19.1%) Headache: 256/582 (44%) Other psychiatric event (anxiety, mania, etc.): 47/582 (8.1%) Respiratory infections: 41/582 (7%) Total patients reporting any AE: 578/582 (99.3%)	

Evidence Table 11. Effectiveness and adverse events in placebo controlled trials of natalizumab

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events	Comments
Rudick 2006 **US, Europe** **SENTINEL** Efficacy quality: Good Adverse event quality: Fair	Placebo IV every 4 weeks up to 29 weeks N=582 Male: 162 (28%) Female: 420 (72%) Mean age (SD): 39 (7.6)	Total withdrawals: 95 (16%) AE withdrawals: 14 (2%)	Cumulative probability of disease progression: 29% at 2 years, p-value: 0.02 Annualized relapse rate: 0.75 at 2 years, p-value: 0.001, CI: 0.67-0.84 Annualized relapse rate: 0.81 at 1 year, p-value: <0.001, CI: 0.72-0.92 Proportion of relapse-free patients: 37% at 2 years, p-value: <0.001	Depression: 105/582 (18%) Flu-like illness: 111/582 (19.1%) Headache: 256/582 (44%) Other psychiatric event (anxiety, mania, etc.): 47/582 (8.1%) Respiratory infections: 41/582 (7%) Total patients reporting any AE: 578/582 (99.3%)	
Sheremata 1999 **US** Efficacy quality: Fair Adverse event quality: Poor	Natalizumab IV 0.03-3.0 mg/kg 1x, single dose N=21	Total withdrawals: 0 (0%) AE withdrawals: 0 (0%)	NR	Total patients reporting any AE: 17/21 (81%)	On population: Other baseline values:RRMS: 20/28 (71%), SPMS: 8/20 (29%), Relapse rate 2 yrs prior to study entry: 0.7-2.3 (no mean provided)
Sheremata 1999 **US** Efficacy quality: Fair Adverse event quality: Poor	Placebo IV single dose N=7	Total withdrawals: 0 (0%) AE withdrawals: 0 (0%)	NR	Total patients reporting any AE:6/7 (85.7%)	

Evidence Table 11. Effectiveness and adverse events in placebo controlled trials of natalizumab

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events	Comments
Tubridy 1999 UK Efficacy quality: Fair Adverse event quality: Poor/Fair	Natalizumab IV 3 mg/kg of body weight every 4 weeks, 2 doses N=37 Male: 12 (32%) Female: 25 (68%) Mean age (SD): 40	Total withdrawals: 0 (0%) AE withdrawals: 0 (0%)	Mean change in EDSS: -0.02 at 24 weeks Mean change in EDSS: -0.06 at 12 weeks Exacerbation requiring hospitalization: 4 at 24 weeks Exacerbation requiring hospitalization: 2 at 12 weeks Total no. of patients experiecing an exacerbation: 14 at 24 weeks, p-value: 0.005 Total no. of patients experiecing an exacerbation: 9 at 12 weeks, p-value: 0.57	Fatigue/Tiredness: 12/37 (32.4%) Total patients reporting any AE: 19/37 (51.4%)	On intervention:Natalizumab was diluted to 100 ml w/saline, Baseline values: natalizumab; placebo, Mean EDSS: 4.9; 4.7, RRMS: 25 (68%); 28 (80%), SPMS: 12 (32%); 7 (20%)
Tubridy 1999 UK Efficacy quality: Fair Adverse event quality: Poor/Fair	Placebo IV 100 ml saline every 4 weeks, two doses N=35 Male: 14 (40%) Female: 21 (60%) Mean age (SD): 41	Total withdrawals: 2 (6%) AE withdrawals: 0 (0%)	Mean change in EDSS: 0.02 at 24 weeks Mean change in EDSS: 0.18 at 12 weeks Exacerbation requiring hospitalization: 3 at 12 weeks Exacerbation requiring hospitalization: 0 at 24 weeks Total no. of patients experiencing an exacerbation: 11 at 12 weeks, p-value: 0.57 Total no. of patients experiencing an exacerbation: 4 at 24 weeks, p-value: 0.005	Fatigue/Tiredness: 4/35 (11.4%) Total patients reporting any AE: 24/35 (68.6%)	

Evidence Table 12. Placebo controlled trials of mitxantrone

Study	Population Type	Design	Recruitment	Eligibility	Exclusion
Bastianello 1994 Italy Efficacy quality: Fair Adverse event quality: Fair	RRMS	Double Blind Parallel Multicenter Setting: NR	Screened:NR Eligible:NR Enrolled:52 Withdrawn:0 Lost to F/U:0 Analyzed:25	A definite diagnosis of MS; a relapsing-remitting disease course defined as two or more relapses occuring in the 24 months prior to study entry; age between 18 and 45 years; disease duration between 18 and 45 years; disease duration from 1-10 years; disability no less than 2 or more than 5 on the Kurtzke Expanded Disability Status Scale (EDSS).	Patients were excluded who were HIV-positive, with previous cardiovascular disease, with left ventricular ejection fraction of less than 50% as determined by echocardiography, subjects presenting renal, liver and/or respiratory dysfunctions, diabetes, malignancy, psychitaric illness, pregnancy and women not practicing contraception, as well as patients who had taken previous immunosuppressant medications (such as azathioprine, cyclophosphamide, plasmapheresis) or were taking steroids during the 3 months before entry. Finally patients incapable of fulfilling the requirements of the study or signing the informed consent were also excluded.
Millefiorini 1996 Italy Efficacy quality: Good Adverse event quality: Good	PRMS	Blinding:NR Parallel Multicenter Setting: NR	Screened:NR Eligible:NR Enrolled:51 Withdrawn:9 Lost to F/U:NR Analyzed:51	Age between 18 and 45 years, clinically definite or laboratory supported RRMS, disease duration from 1-10 years, disability from 2 to 5 on Kurtzske Expanded Status Disability Scale (EDSS) with at least 2 exacerbations in the previous 2 years.	Exclusion of patients who were HIV-positive, with previous cardiovascular, with left ventricular ejection fraction of less than 50% as determined by echocardiography, subjects presenting renal, liver and/or respiratory dysfunction, diabetes, malignancy, psychiatric illness, pregnancy and women not practicing contraception as well as patients who where taking steroids during the 3 months before entry or previous immunosuppressant medication. Patients incapable of fulfilling the requirements of the study or signing the informed consent were also excluded.

Evidence Table 13. Effectiveness and adverse events in placebo controlled trials of mitoxantrone

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events	Comments
Bastianello 1994 Italy Efficacy quality: Fair Adverse event quality: Fair	Mitoxantrone IV 8mg/m2 30 min infusion every month, for 1 year N=13 Male: 5 (38%) Female: 8 (62%) Mean age (SD): 30 (5.2)	Total withdrawals: 0 AE withdrawals: 0	Mean change in EDSS: -0.27 at 1 year, p-value: 0.18, CI: NR Proportion of patients with EDSS deterioration: 8% at 1 year, p-value: 0.49, CI: NR Mean relapse rate: 0.54 at 1 year, p-value: 0.014, CI: NR Total no. of patients experiencing an exacerbation: 5 at 1 year, p-value: 0.02, CI: NR	Amenorrhea: 1/13 (7.7%) Diarrhoea, vomiting and slight fever: 1/13 (7.7%) Nausea: 7/13 (53.8%) Adverse events not seperated by drug. Adverse events of 25 people all together are reported.	On intervention:Mean baseline values mitoxantrone vs placebo: EDSS: 3.7 vs 3.5, Relapses 2 years prior to study entry: 2.8 vs 3.3
Bastianello 1994 Italy Efficacy quality: Fair Adverse event quality: Fair	Placebo N=12 Male: 5 (42%) Female: 7 (58%) Mean age (SD): 28 (6.5)	Total withdrawals: 0 AE withdrawals: 0	Mean change in EDSS: 0.08 at 1 year, p-value: 0.18, CI: NR Proportion of patients with EDSS deterioration: 17% at 1 year, p-value: 0.49, CI: NR Mean relapse rate: 1.67 at 1 year, p-value: .014, CI: NR Total no. of patients experiencing an exacerbation: 10 at 1 year, p-value: 0.02, CI: NR	Adverse events not seperated by treatment arm. Adverse events of 25 people all together are reported. (see adverse events under treatment arm)	

Evidence Table 13. Effectiveness and adverse events in placebo controlled trials of mitoxantrone

Study	Dosage, Population	Withdrawals	Outcomes	Adverse Events	Comments
Millefiorini 1996 Italy Efficacy quality: Good Adverse event quality: Good	Mitoxantrone IV 8mg/m2 1x/month, for 1 year N=27 Male: 10 (37%) Female: 17 (63%) Mean age (SD): 31 (6.0)	Total withdrawals: 4 (15%) AE withdrawals: NR	Mean exacerbations per person-year: 0.44 at 2 years, p-value: 0.0002, CI: 0.62-2.84 Proportion of patients with EDSS deterioration: 7% at 2 years, p-value: 0.02, CI: 8-52 Proportion of relapse-free patients: 63% at 2 years, p-value: 0.006, CI: 15-65	Amenorrhea: 5/51 (9.8%) Headache: 3/51 (5.9%) Nausea/vomiting: 9/51 (17.6%) Respiratory infections: 2/51 (3.9%) UTI: 3/51 (5.9%) (Data not seperated by treatment arms)	On intervention: Mean baseline values: mitoxantrone vs placebo: EDSS: 3.6 vs 3.5, Relapses 2 years prior to study entry: 2.8 for both groups, Disease duration: 5.7 vs 5 years, Incomplete recruitment generated an imbalance in terms of sex.
Millefiorini 1996 Italy Efficacy quality: Good Adverse event quality: Good	Placebo IV Saline solution 1x/month Total daily dose: for 1 year N=27 Male: 10 (37%) Female: 17 (63%) Mean age (SD): 31 (6.0)	Total withdrawals: 5 (21%) AE withdrawals: NR	Mean exacerbations per person-year: 1.31 at 2 years, p-value: 0.0002, CI: 0.62-2.84 Proportion of patients with EDSS deterioration: 37% at 2 years, p-value: 0.02, CI: 8-52 Proportion of relapse-free patients: 21% at 2 years, p-value: 0.006, CI: 15-65	Data not seperated by treatment arms. See adverse events under treatment arm.	