Drug Class Review
Disease-modifying Drugs for Multiple Sclerosis

Single Drug Addendum:
Fingolimod

Final Original Evidence Tables

February 2011

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

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Abbreviations used in evidence tables

Abbreviation	Meaning
ACT	Active-control trial
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ARR	Annualized relapse rate
bid	Twice daily
BMI	Body mass index
CCT	Controlled clinical trial
CI	Confidence interval
CNS	Central nervous system
CR	Controlled release
CV	Cardiovascular
CVS	Cardiovascular system
d	Day
DB	Double-blind
dL	Deciliter
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EEG	Electroencephalogram
EF	Ejection fraction
ER	Extended release
FDA	US Food and Drug Administration
FU	Follow-up
g	Gram
GI	Gastrointestinal
GP	General practitioner
h	Hour
HDL-C	High density lipoprotein cholesterol
HMO	Health maintenance organization
HR	Hazard ratio
HRQOL	Health-related quality of life
ICD-10	International Classification of Diseases, Tenth Revision
ICD-9	International Classification of Diseases, Ninth Revision
IR	Immediate release
ITT	Intention-to-treat
L	Liter
LA	Long acting
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last Observation Carried Forward
LS means	Least squares means
MANCOVA	Multivariate analysis of covariance

Abbreviation	Meaning
mcg	Microgram
mg	Milligram
min	Minute
mL	Milliliter
mo	Month
MS	Multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
N	Sample size (entire sample)
n	Subgroup sample size
NA	Not applicable
NR	Not reported
NS	Not significant
NSD	No significant difference
OR	Odds ratio
P	*P* value
P	Placebo
PCT	Placebo-controlled trial
PPY	Per person year
PRIMUS	Patient-Reported Indices for Multiple Sclerosis
qd	Once daily
QOL	Quality of life
RCT	Randomized controlled trial
RR	Relative risk
SAE	Serious adverse event
SB	Single-blind
SD	Standard deviation
SE	Standard error
SR	Sustained release
tid	Three times daily
URTI	Upper respiratory tract infection
VAS	Visual analog scale
vs.	Compared with (versus)
WD	Withdrawal
XR	Extended release
y	Year

Evidence Table 1. Data abstraction of fingolimod trials

Author Year Country Trial Name	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Cohen 2010 Khatri 2010 (poster) Cohen 2010 (poster) TRANSFORMS 18 countries	Men and women ages 18 to 55 years old with relapsing-remitting MS with a score of 0 to 5.5 on the EDSS, and had ≥1 relapses in the previous year or ≥2 in the previous 2 years. Excluded patients who had corticosteroid treatment within 30 days before randomization.	A: Oral fingolimod 1.25 mg qd B: Oral fingolimod 0.5 mg qd C: Intramuscular interferon beta-1a 30 µg weekly For 12 months	NR	36.2 years 67.3% female 94.1% white	Interval since first symptoms: 7.4 years Number of relapses in previous year: 1.5 Number of relapses in previous two years: 2.3	1292	127/6/1280

Evidence Table 1. Data abstraction of fingolimod trials

Author Year Country Trial Name	Efficacy/effectiveness outcomes
Cohen 2010 Khatri 2010 (poster) Cohen 2010 (poster) TRANSFORMS 18 countries	Fingolimod 1.25 mg vs Fingolimod 0.5 mg vs Interferon Beta-1a ARR, number (95% CI): 0.20 (0.16 to 0.26) vs 0.16 (0.12 to 0.21) vs 0.33 (0.26 to 0.42); P<0.001 Rate for patients who had no previous disease-modifying therapy, number (95% CI): 0.17 (0.11 to 0.25) vs 0.15 (0.10 to 0.23) vs 0.31 (0.22 to 0.41) Rate for patients who had previous disease-modifying therapy, number (95% CI): 0.33 (0.26 to 0.42) vs 0.26 (0.19 to 0.34) vs 0.53 (0.43 to 0.65) Impact of treatments on ARR of relapses requiring hospitalization: 0.039 vs 0.022 vs 0.077; P=0.049 for 1.25 mg vs interferon, P=0.001 for 0.5 mg vs interferon Impact of treatments on ARR for relapses requiring steroid treatment, but not hospitalization: 0.115 vs 0.084 vs 0.176; P<0.012 for 1.25 mg vs interferon, P<0.001 for 0.5 mg vs interferon Patients with no confirmed relapse, percent (95% CI): 79.8 (75.9 to 83.7) vs 82.6 (79.0 to 86.3) vs 69.3 (64.8 to 73.8); P<0.001 Number of patients with confirmed relapse: 0 relapse: 338 (80.5%) vs 354 (82.5%)vs 302 (70.1%); P<0.001 1 relapse: 61 (14.5%) vs 63 (14.7%) vs 90 (20.9%) 2 relapses: 19 (4.5%) vs 11 (2.6%) vs 30 (7.0%) ≥3 relapses: 2 (0.5%) vs 1 (0.2%) vs 9 (2.1%) Patients with no confirmed disability progression, percent (95% CI): 93.3 (90.9 to 95.8) vs 94.1 (91.8 to 96.3) vs 92.1 (89.4 to 94.7) Mean change from baseline in EDSS score: -0.11 vs -0.08 vs 0.01; P=0.02 for 1.25 mg vs interferon, P=0.06 for 0.5 mg vs interferon Mean change from baseline in MSFC z score: 0.08 vs 0.04 vs -0.03; P<0.001 for 1.25 mg vs interferon, P=0.02 for 0.5 mg vs interferon Mean change from baseline in PRIMUS-Activities scores: 0.12 vs 0.08 vs 0.43; P=0.029 for 1.25 mg vs interferon, P=0.034 for 0.5 mg vs interferon Responder analysis of PRIMUS-Activities score change from baseline at month 12 (≥2 point change): Improvement: 19.6% vs 17.5% vs 14.1% Worsening: 19.6% vs 17.9% vs 24.1%

Evidence Table 1. Data abstraction of fingolimod trials

Author Year Country Trial Name	Harms	Total withdrawals; withdrawals due to adverse events
Cohen 2010 Khatri 2010 (poster) Cohen 2010 (poster) TRANSFORMS 18 countries	Fingolimod 1.25 mg vs Fingolimod 0.5 mg vs Interferon Beta-1a Any event: 380 (90.5%) vs 369 (86.0%) vs 395 (91.6%) Any serious event: 45 (10.7%) vs 30 (7.0%) vs 25 (5.8%) Headache: 96 (22.9%) vs 99 (23.1%) vs 88 (20.4%) Fatigue: 59 (14.0%) vs 44 (10.3%) vs 45 (10.4%) Pyrexia: 15 (3.6%) vs 18 (4.2%) vs 77 (17.9%) Influenza-like illness: 15 (3.6%) vs 15 (3.5%) vs 159 (36.9%) Infection: Nasopharyngitis: 93 (22.1%) vs 88 (20.5%) vs 88 (20.4%) URTI: 36 (8.6%) vs 31 (7.2%) vs 27 (6.3%) Influenza: 28 (6.7%) vs 29 (6.8%) vs 32 (7.4%) Urinary tract infection: 24 (5.7%) vs 26 (6.1%) vs 22 (5.1%) Herpesvirus infection: 23 (5.5%) vs 9 (2.1%) vs 12 (2.8%)	Fingolimod 1.25 mg vs Fingolimod 0.5 mg vs Interferon Beta-1a Total withdrawals: 62 (14.8%) vs 44 (10.3%) vs 51 (11.8%) Due to AE: 32 (7.6%) vs 16 (3.7%) vs 912 (2.8%)

Evidence Table 1. Data abstraction of fingolimod trials

Author Year Country Trial Name	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Kappos 2006 10 European countries and Canada	18 to 60 year olds with relapsing MS and ≥2 documented relapses in previous 2 years, and ≥1 documented gadolinium-enhanced lesions detected on MRI. Additionally, participants had a score of 0 to 6 on EDSS and were in neurologically stable condition with no evidence of relapse for at least 30 days before screening and during screening and baseline. Excluded patients for use of corticosteroids (within the previous 30 days), immunomodulatory therapy (within the previous 3 months), or immunosuppressive treatment (e.g., azathioprine or methotrexate within 6 months, cyclophosphamide within 12 months, or mitoxantrone or cladribine within 24 months).	A: Oral fingolimod 1.25 mg qd B: Oral fingolimod 5.0 mg qd C: Placebo For 6 months	Relapses were managed by the treating physician according to a standardized scheme, with up to 1000 mg/d of methylprednisolone given intravenously for 3 to 5 days.	37.8 years 70.8% female Ethnicity NR	Interval since first symptoms: 8.7 years Number of relapses in previous year: 1.3 Number of relapses in previous two years: 1.9 Time since most recent relapse: 7.6 months Course of disease: Relapse-remitting: 88.8% Secondary progressive: 11.2%	281	26/NR/277

Evidence Table 1. Data abstraction of fingolimod trials

Author Year Country Trial Name	Efficacy/effectiveness outcomes
Kappos 2006 10 European countries and Canada	Placebo vs Fingolimod 1.25 mg vs Fingolimod 5.0 mg ARR: 0.77 vs 0.35 vs 0.36; P=0.01 Relative reduction in relapse rate vs placebo: NA vs 55% (95% CI, 18 to 75) vs 53% (95% CI, 14 to 74) Patients free of relapse at 6 months: 66 (71.7%) vs 86 (92.5%) vs 86 (93.5%); P=0.004 Confirmed relapses: 34 (37%) vs 16 (17.2%) vs 16 (17.4%) All relapses: 40 (43.5%) vs 21 (22.6%) vs 18 (19.6%) Confirmed relapses with complete clinical recovery: 12 (35%) vs 12 (75%) vs 7 (44%) Number of hospitalizations due to relapse: 4 vs 2 vs 1 Mean EDSS score: 2.7 vs 2.6 vs 2.6 Categorical change from baseline in EDSS score: Improved or stable: 71 (80%) vs 84 (90%) vs 75 (85%); P= 0.06 for 1.25 mg vs placebo Worse: 18 (20%) vs 9 (10%) vs 13 (15%) Actual Use Patients who received corticosteroid therapy: 44 (16%) Cumulative dose (mg/kg of body weight): 1313 Placebo vs Fingolimod 1.25 mg vs Fingolimod 5.0 mg Patients who received corticosteroid therapy: 23 (25%) vs 11 (12%0 vs 10 (11%); P=0.02 Cumulative dose (mg/kg of body weight): 2372 vs 848 vs 725; P=0.2

Evidence Table 1. Data abstraction of fingolimod trials

Author Year Country Trial Name	Harms	Total withdrawals; withdrawals due to adverse events
Kappos 2006 10 European countries and Canada	Placebo vs Fingolimod 1.25 mg vs Fingolimod 5.0 mg Any event: 76 (82%) vs 79 (84%) vs 90 (96%); P<0.05 for 5.0 mg vs placebo Nasopharyngitis: 14 (15%) vs 16 (17%) vs 26 (28%); P<0.05 for 5.0 mg vs placebo Headache: 13 (14%) vs 22 (23%) vs 18 (19%) Dyspnea: 1 (1%) vs 4 (4%) vs 12 (13%); P<0.05 for 5.0 mg vs placebo Diarrhea: 2 (2%) vs 9 (10%) vs 11 (12%); P<0.05 for 5.0 mg vs placebo Nausea: 2 (2%) vs 8 (9%) vs 10 (11%); P<0.05 for 5.0 mg vs placebo Confirmed increase in ALT: 1 (1%) vs 9 (10%) vs 11 (12%); P<0.05 Gastroenteritis: 0 (0%) vs 3 (3%) vs 5 (5%) Leukopenia: 0 (0%) vs 2 (2%) vs 5 (5%) Pharyngitis: 2 (2%) vs 7 (7%) vs 3 (3%) Posterior reversible encephalopathy syndrome: 0 (0%) vs 0 (0%) vs 1 (1%)	Placebo vs Fingolimod 1.25 mg vs Fingolimod 5.0 mg Total withdrawals: 7 (7.5%) vs 6 (6.4%) vs 13 (13.8%) Due to AE: 4 (4%) vs 5 (5%) vs 8 (9%)

Evidence Table 1. Data abstraction of fingolimod trials

Author Year Country Trial Name	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Kappos 2010 Kappos 2010 (presentation) O'Connor 2010 (poster) von Rosenstiel 2010 (poster) 22 countries FREEDOMS	Men and women ages 18 to 55 years old with relapsing-remitting MS with a score of 0 to 5.5 on the EDSS, and had ≥1 relapses in the previous year or ≥2 in the previous 2 years. Excluded patients who had corticosteroid treatment within 30 days before randomization, interferon-beta or glatiramer acetate therapy within 3 months before randomization.	A: Oral fingolimod 1.25 mg qd B: Oral fingolimod 0.5 mg qd C: Placebo For 24 months	NR	37.1 years 69.9% female Ethnicity NR	Interval since first symptoms: 8.2 years Number of relapses in previous year: 1.5 Number of relapses in previous two years: 2.1 No history of disease-modifying treatment: 59.1%	1272	238/15/1272

Evidence Table 1. Data abstraction of fingolimod trials

Author Year Country Trial Name	Efficacy/effectiveness outcomes
Kappos 2010 Kappos 2010 (presentation) O'Connor 2010 (poster) von Rosenstiel 2010 (poster) 22 countries FREEDOMS	Fingolimod 1.25 mg vs Fingolimod 0.5 mg vs Placebo ARR over 24 months: 0.16 vs 0.18 vs 0.40; P<0.001 ARR subgroup analyses: Treatment-naive subjects: 0.17 (62% reduction vs placebo, P<0.001) vs 0.17 (64% reduction vs placebo, P<0.001) vs 0.45 Previously treated subjects: 0.21 (59% reduction vs placebo, P<0.001) vs 0.28 (46% reduction vs placebo, P<0.001) vs 0.5 Duration of MS since first symptom ≤6.7 years: 0.19 vs 0.18 vs 0.52 Duration of MS since first symptom >6.7 years: 0.19 vs 0.25 vs 0.42 0 or 1 relapses in previous year: 0.15 (59% reduction vs placebo, P<0.001) vs 0.19 (48% reduction vs placebo, P<0.001) vs 0.36 >1 relapses in previous year: 0.27 (62% reduction vs placebo, P<0.001) vs 0.26 (63% reduction vs placebo, P<0.001) vs 0.70 1 relapse in previous 2 years: 0.15 (60% reduction vs placebo, P<0.001) vs 0.14 (63% reduction vs placebo, P<0.001) vs 0.38 2–3 relapses in the previous 2 years: 0.20 vs 0.21 vs 0.47 ≥4 relapses in the previous 2 years: 0.24 vs 0.43 vs 0.70 Female: 0.18 (60% reduction vs placebo, P<0.001) vs 0.23 (50% reduction vs placebo, P<0.001) vs 0.45 Male: 0.21 (63% reduction vs placebo, P<0.001) vs 0.18 (67% reduction vs placebo, P<0.001) vs 0.56 ≤ 40 years old: 0.19 (65% reduction vs placebo, P<0.001) vs 0.18 (67% reduction vs placebo, P<0.001) vs 0.56 >40 years old: 0.19 (49% reduction vs placebo, P<0.001) vs 0.28 (24% reduction vs placebo, P=NS) vs 0.37 High disease activity at baseline: 0.33 (65% reduction vs placebo, P<0.001) vs 0.35 (63% reduction vs placebo, P<0.001) vs 0.93 Not high disease activity at baseline: 0.16 vs 0.19 vs 0.40 Baseline EDSS score of 0.0-3.5: 0.16 (63% reduction vs placebo, P<0.001) vs 0.21 (52% reduction vs placebo, P<0.001) vs 0.44 Baseline EDSS score of >3.5: 0.33 (54% reduction vs placebo, P<0.001) vs 0.24 (66% reduction vs placebo, P<0.001) vs 0.71 Absence of relapse during the 24-month period, percent (95% CI): 74.7 (70.4 to 78.9) vs 70.4 (66.0 to 74.8) vs 45.6 (40.7 to 50.6); P<0.001 HR vs placebo: 0.38 (95% CI, 0.30 to 0.48) vs 0.48 (95% CI, 0.39 to 0.61) vs NA; P<0.001 Absence of disability progression, confirmed after 3 months, during the 24-month period, percent (95% CI): 83.4 (79.7 to 87.1) vs 82.3 (78.6 to 86.1) vs 75.9 (71.7 to 80.2); P<0.03 HR vs placebo: 0.68 (95% CI, 0.50 to 0.93) vs 0.70 (95% CI, 0.52 to 0.96) vs NA; P=0.02 Absence of disability progression, confirmed after 6 months, during the 24-month period, percent (95% CI): 88.5 (85.3 to 91.6) vs 87.5 (84.3 to 90.7) vs 81.0 (77.1 to 84.9); P<0.01 HR vs placebo: 0.60 (95% CI, 0.41 to 0.86) vs 0.63 (95% CI, 0.44 to 0.90) vs NA; P<0.01 EDSS score at 24 months: -0.03 vs 0.00 vs 0.13; P=0.02 MSFC z score at 24 months: 0.01 vs 0.03 vs -0.06; P<0.02

Evidence Table 1. Data abstraction of fingolimod trials

Author Year Country Trial Name	Harms	Total withdrawals; withdrawals due to adverse events
Kappos 2010 Kappos 2010 (presentation) O'Connor 2010 (poster) von Rosenstiel 2010 (poster) 22 countries FREEDOMS	Fingolimod 1.25 mg vs Fingolimod 0.5 mg vs Placebo At least one AE: 404 (94.2%) vs 401 (94.4%) vs 387 (92.6%) Any serious adverse event: 51 (11.9%) vs 43 (10.1%) vs 56 (13.4%) Headache: 114 (26.6%) vs 107 (25.2%) vs 96 (23.0%) Back pain: 45 (10.5%) vs 50 (11.8%) vs 29 (6.9%) Diarrhea: 40 (9.3%) vs 50 (11.8%) vs 31 (7.4%) Abnormal laboratory liver-function test: 80 (18.6%) vs 67 (15.8%) vs 21 (5.0%) Fatigue: 47 (11.0%) vs 48 (11.3%) vs 45 (10.8%) Infections: URTI: 206 (48.0%) vs 212 (49.9%) vs 211 (50.5%) Nasopharyngitis: 112 (26.1%) vs 115 (27.1%) vs 115 (27.5%) Sinusitis: 27 (6.3%) vs 28 (6.6%) vs 19 (4.5%) Pharyngitis: 25 (5.8%) vs 27 (6.4%) vs 24 (5.7%) Rhinitis: 18 (4.2%) vs 25 (5.9%) vs 25 (6.0%) Influenza virus infection: 40 (9.3%) vs 55 (12.9%) vs 41 (9.8%) Lower respiratory tract or lung infection: 49 (11.4%) vs 41 (9.6%) vs 25 (6.0%) Bronchitis: 39 (9.1%) vs 34 (8.0%) vs 15 (3.6%) Pneumonia: 8 (1.9%) vs 4 (0.9%) vs 3 (0.7%) Herpesvirus infection: 25 (5.8%) vs 37 (8.7%) vs 33 (7.9%) Urinary tract infection: 21 (4.9%) vs 34 (8.0%) vs 47 (11.2%)	Fingolimod 1.25 mg vs Fingolimod 0.5 mg vs Placebo Total withdrawals: 131 (30.5%) vs 80 (18.8%) vs 115 (27.5%) Due to AE: 31 (7.2%) vs 15 (3.5%) vs 24 (5.7%)

Evidence Table 1. Data abstraction of fingolimod trials

Author Year Country Trial Name	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
O'Connor, 2009 (24 month extension to Kappos 2006) Kappos, 2009 (48 months extension to Kappos 2006; presentation) Europe and Canada	Patients aged 18-60 years with relapsing MS with ≥1 relapses in the previous year or ≥2 in the previous 2 years, or at least one gadolinium-enhanced lesion on MRI, and an EDSS score of 0 to 6. In this extension study, placebo patients (from core study) re-randomized to one of the fingolimod doses; those receiving fingolimod remained on the initial dose; those receiving 5.0mg fingolimod were switched to 1.25mg during months 15 to 24 study visits.	A: Oral fingolimod 1.25 mg qd; same dose in core study B: Oral fingolimod 5.0 mg qd; same dose in core study C: Oral fingolimod 1.25 mg qd; Placebo in core study B: Oral fingolimod 5.0 mg qd; Placebo in core study	NR	37.3 years 70% female Ethnicity NR	Duration of fibromyalgia: 8.4 years EDSS score (mean): 2.50 Course of disease: Relapsing-remitting: 90% Secondary progressive: 10%	250	24 month Extension study: 61/2/271 48 month Extension study: 95/2/281

Evidence Table 1. Data abstraction of fingolimod trials

Author Year Country Trial Name	Efficacy/effectiveness outcomes
O'Connor, 2009 (24 month extension to Kappos 2006) Kappos, 2009 (48 months extension to Kappos 2006; presentation) Europe and Canada	Fingolimod 1.25 mg vs Fingolimod 5.0 mg vs Placebo/Fingolimod 1.25 mg vs Placebo/Fingolimod 5.0 mg (24 month Extension Study) ARR (confirmed relapses only) months 0-6: 0.36 vs 0.32 vs 0.70 vs 0.69 ARR (confirmed relapses only) months 7-12: 0.29 vs 0.23 vs 0.21 vs 0.10 ARR (confirmed relapses only) months 7-24: 0.14 vs 0.17 vs 0.26 vs 0.12 Patients free of relapse at month 24: 75% vs 77% vs 59% vs 54% Proportion of patients with 3-month confirmed disability progression: 17.1% vs 24.7% vs 18.9% vs 25.6% Fingolimod 1.25 mg vs Fingolimod 5.0 mg vs Placebo/Fingolimod (48 month Extension Study) ARR months 0-48: 0.18 vs 0.20 vs 0.25; P=0.009 for 1.25 mg vs placebo/fingolimod, P=0.014 for 5.0 mg vs placebo/fingolimod Patients free of relapse at 48 months: 63% vs 70% vs 51% Mean EDSS score at 48 months: 2.51 vs 2.32 vs 2.80

Evidence Table 1. Data abstraction of fingolimod trials

Author Year Country Trial Name	Harms	Total withdrawals; withdrawals due to adverse events
O'Connor, 2009 (24 month extension to Kappos 2006) Kappos, 2009 (48 months extension to Kappos 2006; presentation) Europe and Canada	Fingolimod 1.25 mg vs Fingolimod 5.0 mg vs Placebo/Fingolimod 1.25 mg vs Placebo/Fingolimod 5.0 mg (24 month Extension Study) At least one AE: 88.5% vs 95.0% vs 87.5% vs 90.7% Any SAE: 8.0% vs 15% vs 5.0% vs 11.6% Any severe AE: 10.3% vs 13.8% vs 12.5% vs 14.0% Nasopharyngitis : 19.5% vs 26.3% vs 12.5% vs 18.6% Headache: 14.9% vs 11.3% vs 17.5% vs 18.6% Influenza: 9.2% vs 16.3% vs 17.5% vs 9.3% Lymphopenia: 11.5% vs 15.0% vs 10.0% vs 9.3% Fatigue: 9.2% vs 3.8% vs 15.0% vs 18.6% Leukopenia: 11.5% vs 13.8% vs 2.5% vs 7.0% ALT increased: 5.7% vs 5.0% vs 12.5% vs 14.0% Back Pain: 5.7% vs 3.8% vs 10.0% vs 11.6% Hypertension: 10.3% vs 5.0% vs 5.0% vs 4.7% URTI: 4.6% vs 11.3% vs 0% vs 9.3% Depression: 5.7% vs 3.8% vs 0% vs 11.6% Migraine: 3.4% vs 2.5% vs 10.0% vs 7.0% Fingolimod 1.25 mg vs Fingolimod 5.0 mg vs Placebo/Fingolimod (48 month Extension Study) At least one AE: 96.8% vs 98.9% vs 95.7% Any severe AE: 19.1% vs 23.4% vs 22.6% Any SAE: 12.8% vs 26.6% vs 17.2% Any infection: 69.1% vs 78.7% vs 68.8% Nasopharyngitis: 35.1% vs 44.7% vs 25.8% Influenza: 19.1% vs 23.4% vs 17.2% URTI: 9.6% vs 13.8% vs 11.8% Bronchitis: 12.8% vs 9.6% vs 6.5% Pharyngitis: 11.7% vs 4.3% vs 5.4% Gastroenteritis: 4.3% vs 10.6% vs 3.2% Headache: 37.2% vs 26.6% vs 30.1% Fatigue: 20.2% vs 16.0% vs 21.5% Back pain: 14.9% vs 18.1% vs 17.2% ALT increase: 12.8% vs 16.0% vs 16.1% Diarrhea: 17.0% vs 16.0% vs 9.7% Cough: 13.8% vs 17.0% vs 11.8%	Fingolimod 1.25 mg vs Fingolimod 5.0 mg vs Placebo/Fingolimod 1.25 mg vs Placebo/Fingolimod 5.0 mg (24 month Extension Study) Total withdrawals: 22 (25.3%) vs 20 (25%) vs 9 (22.5%) vs 8 (18.6%) Due to AE: 9 (10.3%) vs 9 (11.3%) vs 2 (5%) vs 4 (9.3%) Fingolimod 1.25 mg vs Fingolimod 5.0 mg vs Placebo/Fingolimod (48 month Extension Study) Total withdrawals: 33 (37.9%) vs 33 (41.3%) vs 29 (34.9%) Due to AE: 15 (17.2%) vs 10 (12.5) vs 11 (13.3%)

Evidence Table 2. Quality assessment of fingolimod trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Kappos, 2006, Switzerland	Unclear	Unclear	Yes	Yes	Yes	Yes
Kappos, 2010, Switzerland	Unclear	Unclear	Yes	Yes	Yes	Yes
Cohen, 2010, United States	Unclear	Yes	Yes	Yes	Unclear - injection site reactions with interferon and first-dose adverse events with fingolimod may have unblinded	Unclear - injection site reactions with interferon and first-dose adverse events with fingolimod may have unblinded

Evidence Table 2. Quality assessment of fingolimod trials

Author, Year Country	Patient masked?	Intention-to-treat analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality rating
Kappos, 2006, Switzerland	Yes	Yes	Yes	Yes	No--more than 10% lost from time of randomization to study completion between groups	Fair
Kappos, 2010, Switzerland	Yes	Yes	Yes	Yes	No--more than 10% lost from time of randomization to study completion between groups	Fair
Cohen, 2010, United States	Unclear - injection site reactions with interferon and first-dose adverse events with fingolimod may have unblinded	Yes	Yes	Yes	No--more than 10% lost from time of randomization to study completion between groups	Fair