# *Clinician's view of Benefit-Risk*

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# *Clinician's View of Benefit-Risk: a need for reliable metrics*

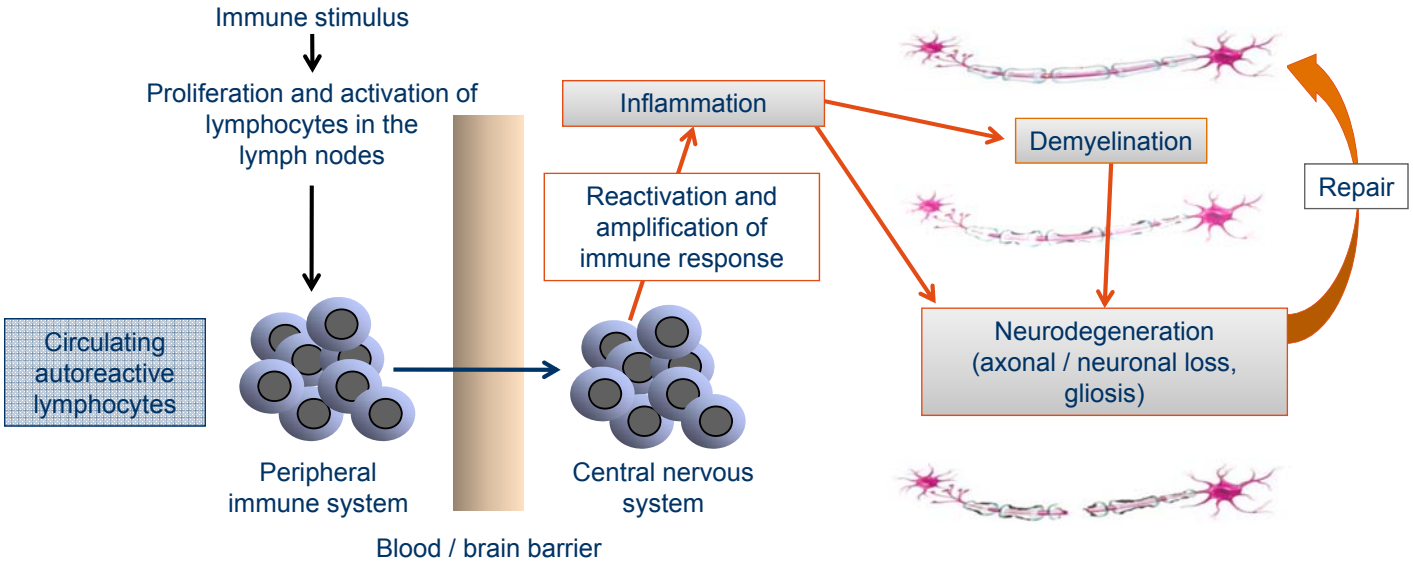
- A tale of 3 drugs
  - Natalizumab
    - MS
    - Crohn's Disease
  - Fingolimod in MS
  - Cladribine in MS

# *MS – the disease*

# *Multiple Sclerosis*

- Chronic dysimmune inflammatory disease of the CNS
  - Genetic and environmental factors likely relevant
- Affects up to 2.5 million people worldwide (~400,000 US)
  - Caucasian predominance
  - Typical onset 20 to 40 years of age (median 29)
  - Female preponderance (2:1 ratio)
- Disease has profound effects on an individual's daily activities
  - Uncertainty regarding prognosis
  - Quality of life reduced early in the course of the disease
  - Cognitive and physical disability associated to relapses and progression lead to severe limitations related to work and social functioning
  - Within 15 years of onset, if untreated, 50% will require aids for ambulation or worse
- Long term, virtually all (≥85% by 25 years) will evolve into an inexorably progressive phase of disease
  - Prevention of disease activity in early stages is likely to positively impact long term disability progression

# Therapies are needed that target both inflammation and neurodegeneration

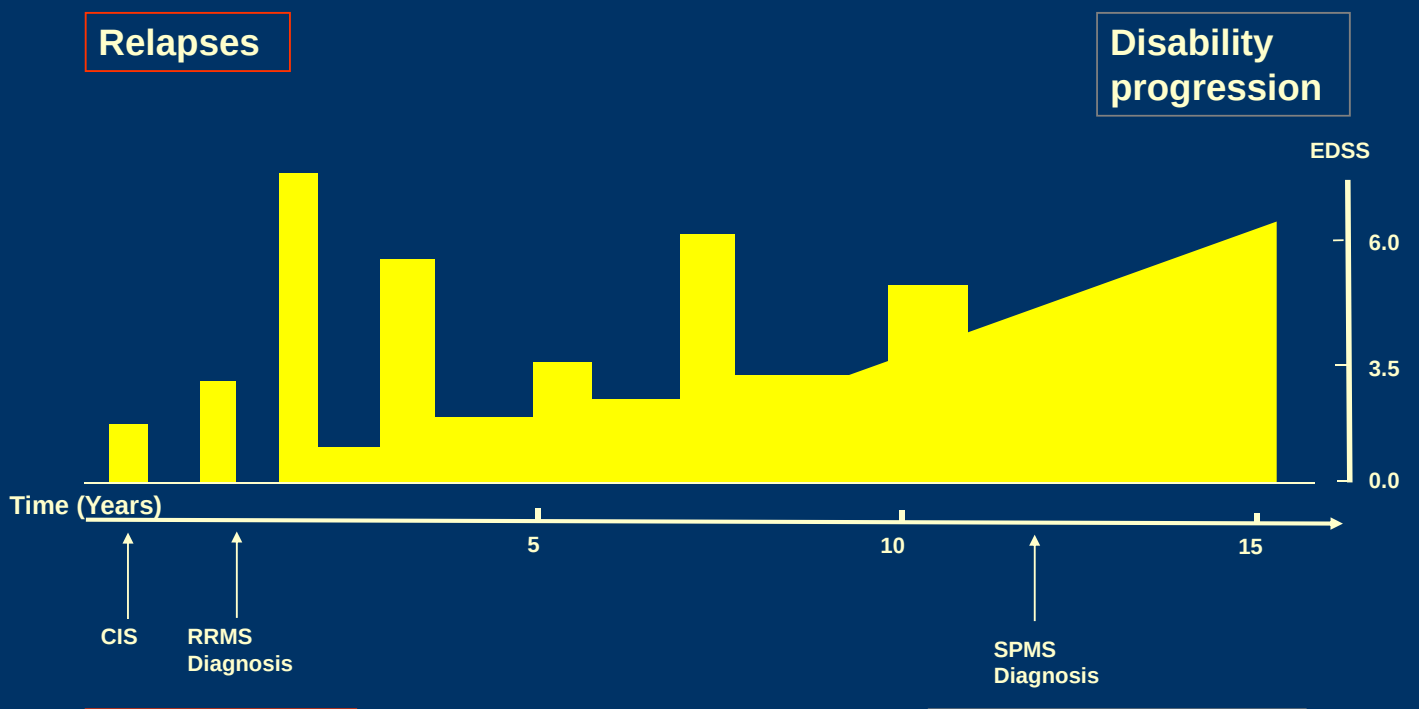



**The balance between CNS tissue injury and repair plays a critical role in progression of MS disease**

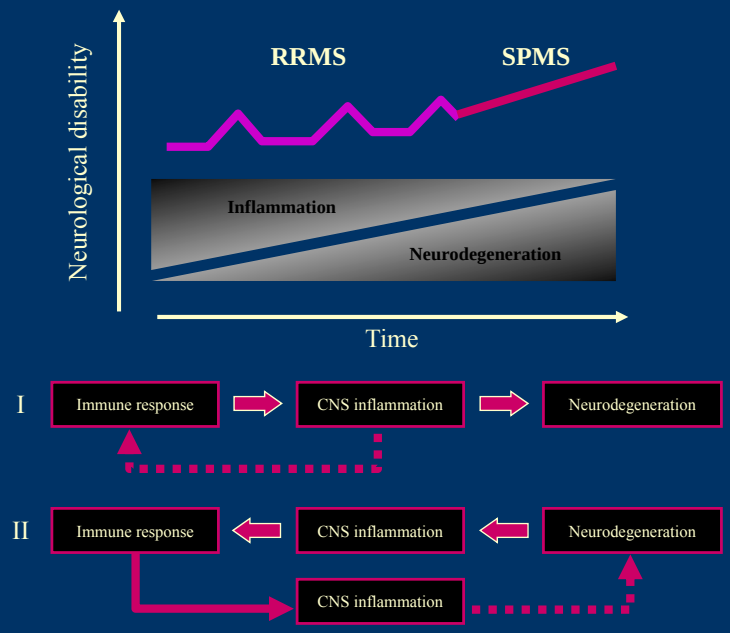
Chun J, Hartung HP. *Clin Neuropharmacol* 2010; Mehling M *et al. Neurology* 2010; Aktas O *et al. Nature Reviews* 2010

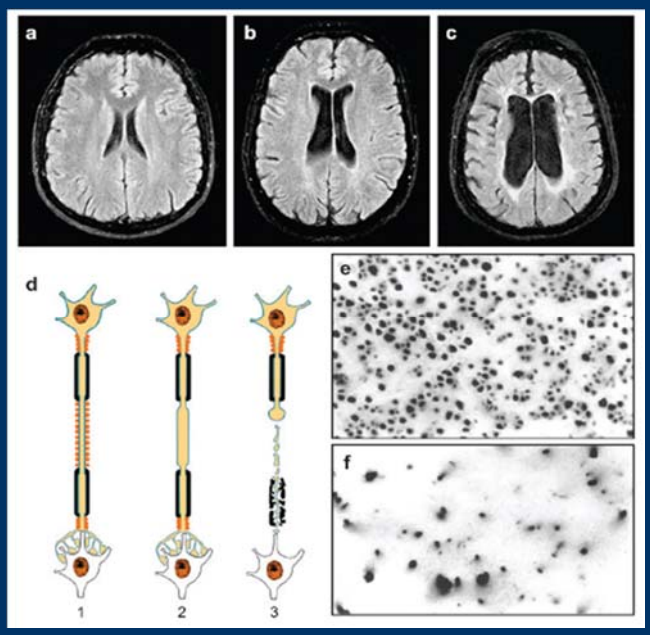


# *Multiple Sclerosis disease course*



# Neurodegeneration

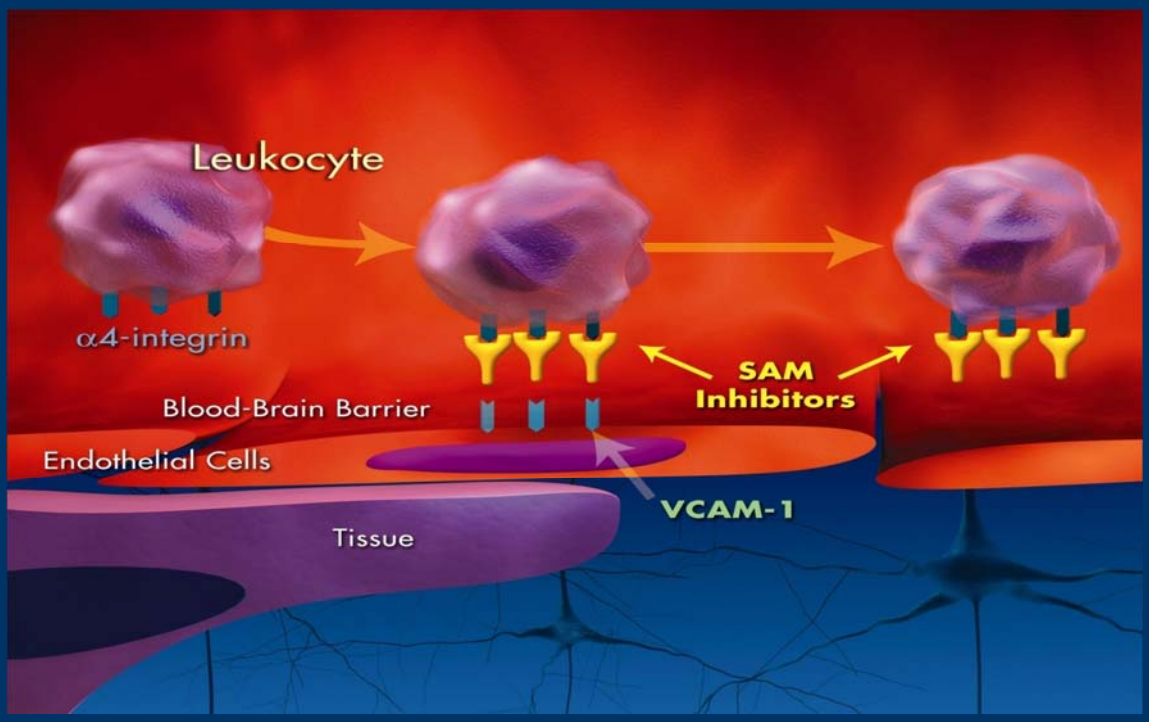



Oksenberg JR and Barcellos LF. *Genes Immun* 2005; Trapp BD and Nave KA. *Annu Rev Neurosci* 2008

# *Natalizumab in MS*

# *Natalizumab*
# *Blockade of adhesion molecule interaction*




## Natalizumab Ph III Efficacy Summary

| | AFFIRM (n=942, 2-yr data) | | SENTINEL (n=1171, 2-yr data) | |
|---|---|---|---|---|
| | Nataliz. v PBO | Rel. Red. | Nat+IFN vs IFN | Rel. Red. |
| ARR | 0.23 vs 0.73 | **67%** | 0.34 vs 0.75 | **55%** |
| Disability | 17% vs 29% | **42% (1-HR)** | 23% vs 29% | **24% (1-HR)** |
| Active T2 | 1.9 vs 11 | **83%** | 0.9 vs 5.4 | **83%** |
| T1-Gad | 0.2 vs 2.4 | **92%** | 0.1 vs 0.9 | **89%** |
| Brain volume | (n.s. 0-24 mos) | | -- | |
| | *Polman CH, et al. N Engl J Med. 2006;354:899-910.* | | *Rudick RA, et al. N Engl J Med. 2006;354:911-923* | |
| Safety considerations | • PML risk, appears dependent on prior JCV exposure, treatment duration w/ majority of cases after 25-48 infusions<br>• Mab removal via PLEX complicated by IRIS (immune reconstitution inflammatory syndrome)<br>• Herpes virus infections (post-marketing)<br>• Hypersensitivity reactions<br>• Rebound activity<br>• Persistent anti-natalizumab antibodies in ~6% with decreased efficacy, incr. IRR | | | |

# *Tysabri in MS – US/EU*

**1.1 Multiple Sclerosis (MS)**

TYSABRI is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. The efficacy of TYSABRI beyond two years is unknown.

Because TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability, TYSABRI is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate multiple sclerosis therapy [see *Boxed Warning,*

# *Tysabri in Europe*

TYSABRI is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following patient groups:

- Patients with high disease activity despite treatment with a beta-interferon.

  These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

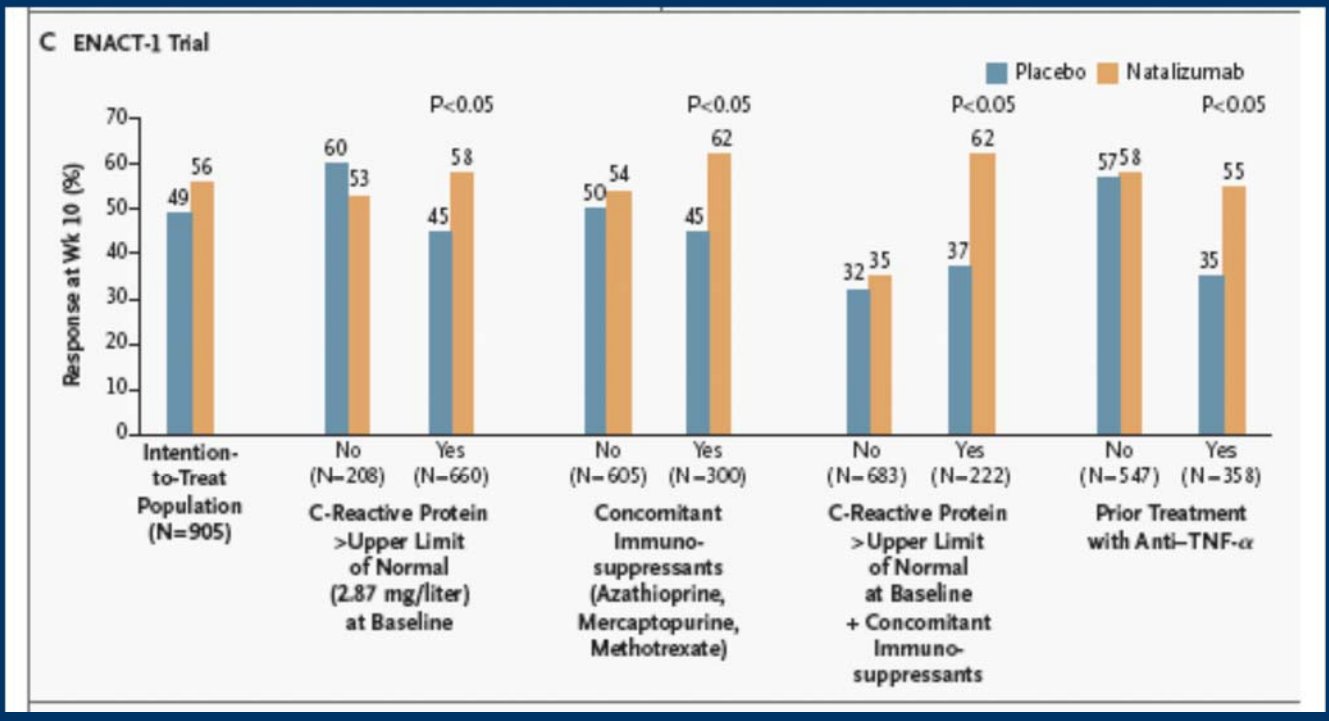
or

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

# *Natalizumab in Crohn's Disease*

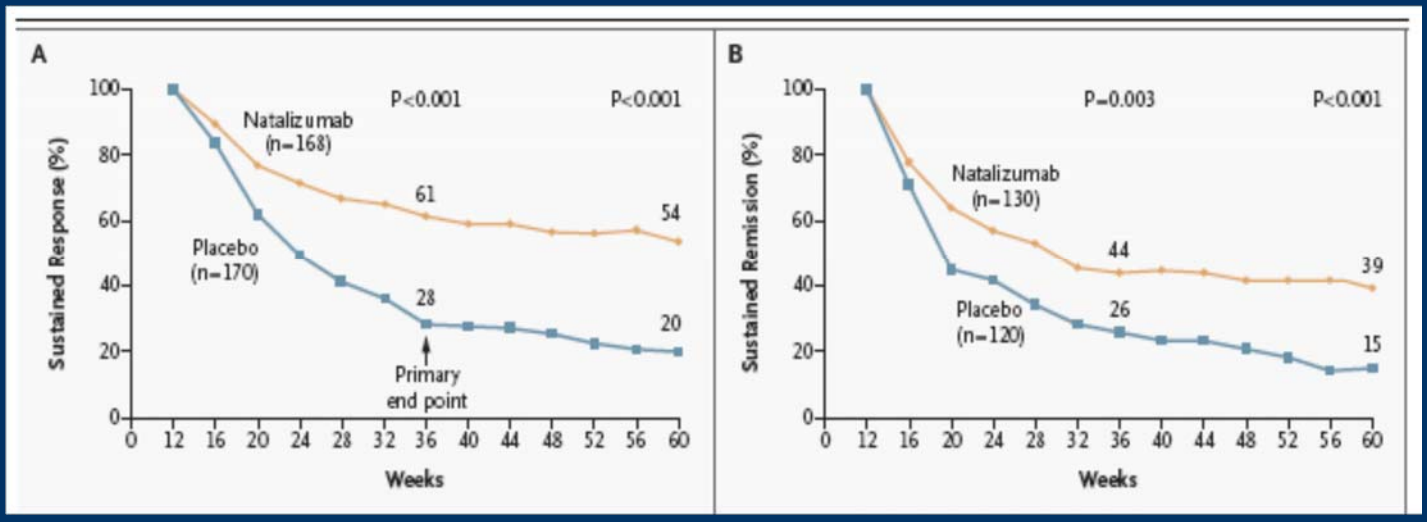
## Natalizumab Induction and Maintenance Therapy for Crohn's Disease

N Engl J Med 2005;353:1912-25.



# Natalizumab Induction and Maintenance Therapy for Crohn's Disease

N Engl J Med 2005;353:1912-25.




# *Tysabri for Crohn's Disease - US*

**1.2 Crohn's Disease (CD)**

TYSABRI is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. TYSABRI should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α [see *Boxed Warning, Warnings and Precautions (5.1)*].

# *Tysabri for Crohn's Disease - EU*

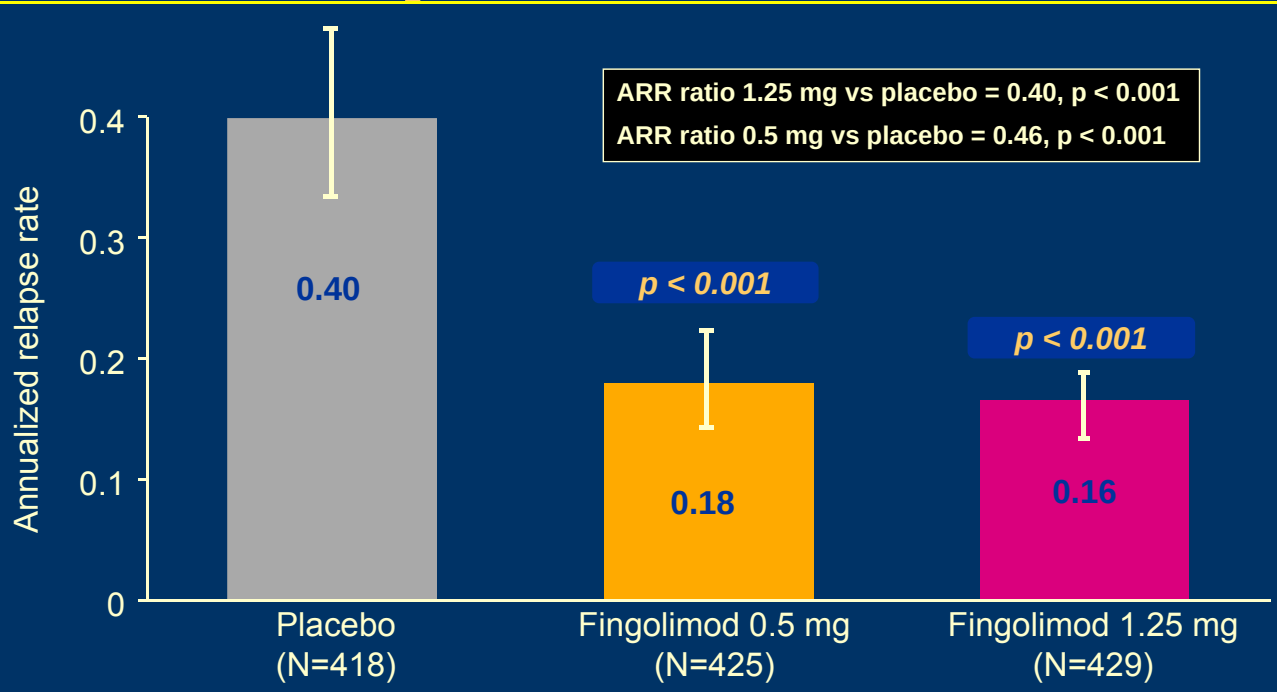
The applicant has not convincingly demonstrated efficacy with regard to maintenance of remission in the proposed restricted population failing prior therapy with corticosteroids, immunosuppression and TNF-alpha inhibitor therapy.

The proposed risk management measures proposed by the applicant are considered insufficient to reduce the risk to an acceptable level.

Having considered the grounds for the re-examination from the applicant, the discussion during the Ad-Hoc Expert Group meeting and the CHMP members' discussion during the oral explanation, the CHMP is of the opinion that the benefit/risk for Natalizumab Elan Pharma in the claimed indication remains negative.

# *Fingolimod*

# FREEDOMS - Primary Endpoint: Annualized Relapse Rate

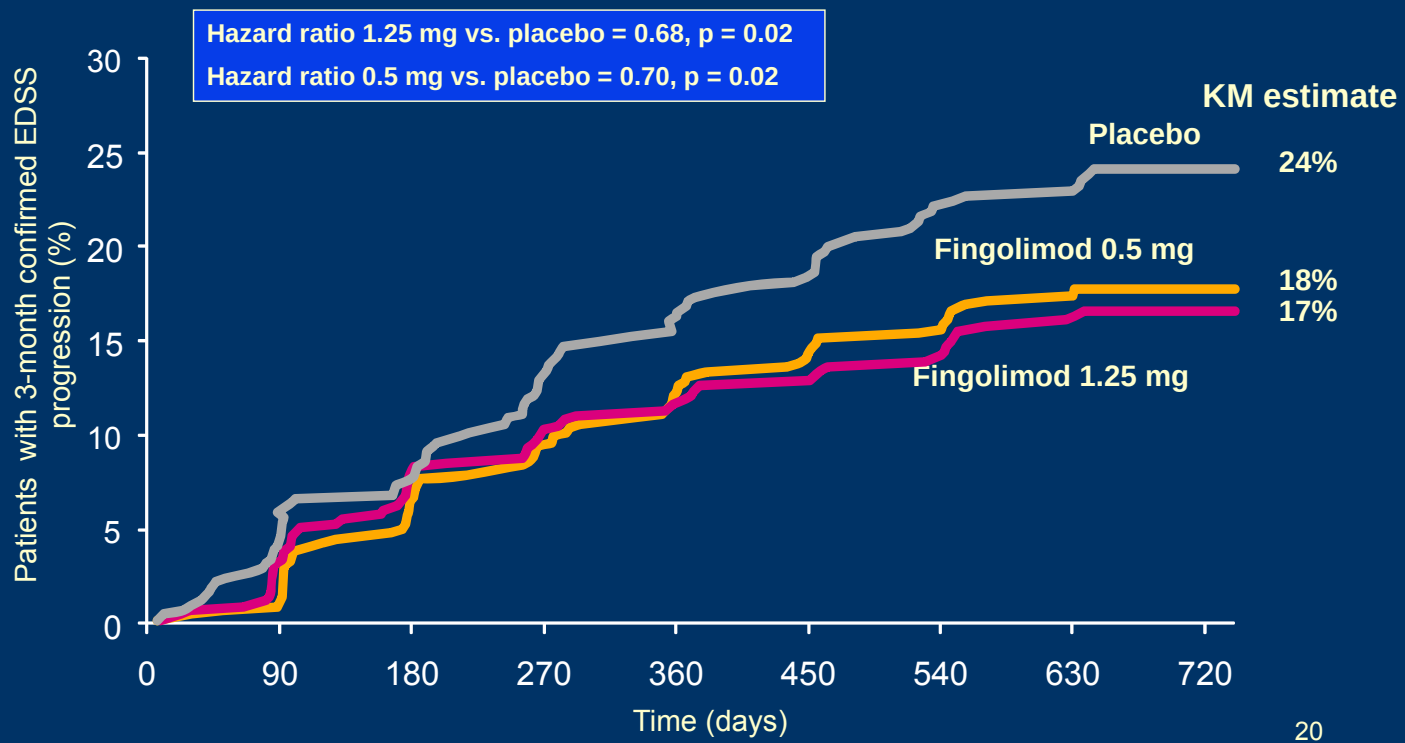



**ARR was reduced in both treatment-naïve patients and patients previously treated with DMT (*p < 0.01* for all comparisons)**

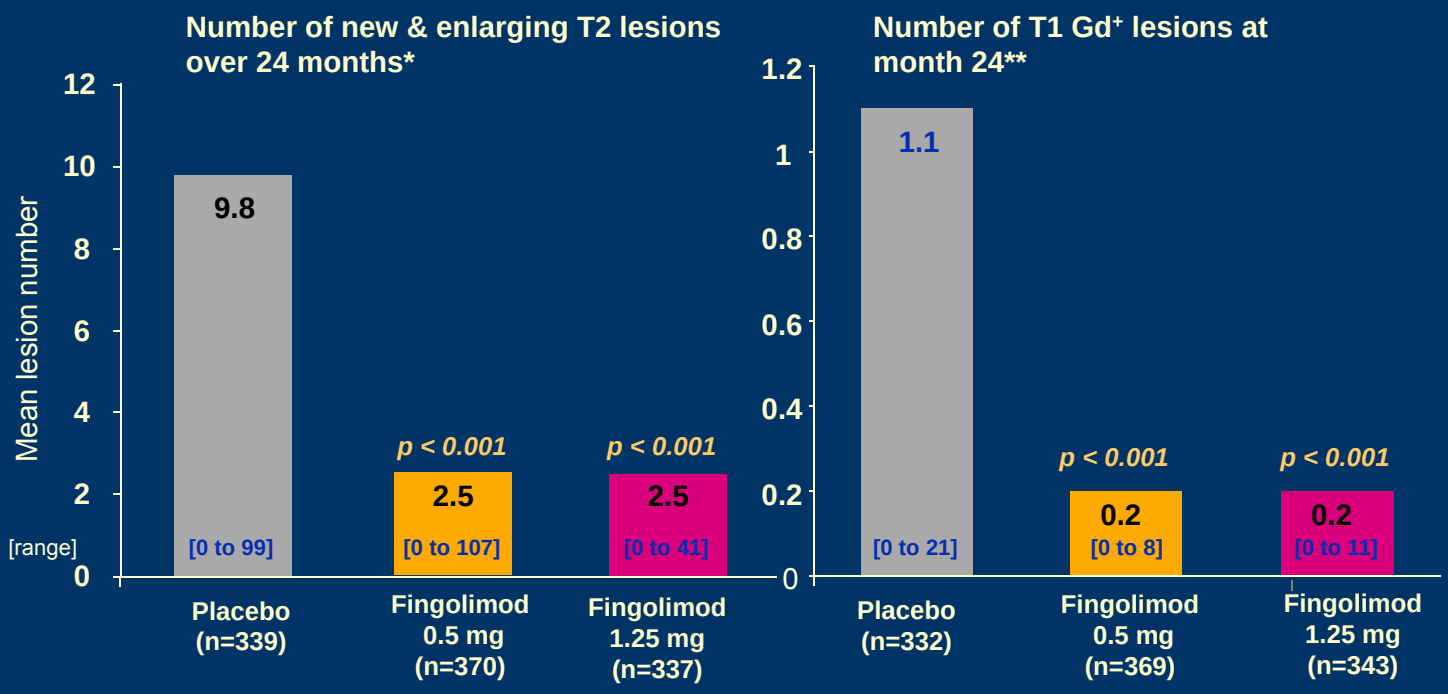
Negative binomial regression model adjusted for treatment group, country, number of relapses in previous two years and baseline Expanded Disability Status Scale. Bars represent the 95% CI



# FREEDOMS - Time to 3-month Confirmed Disability Progression



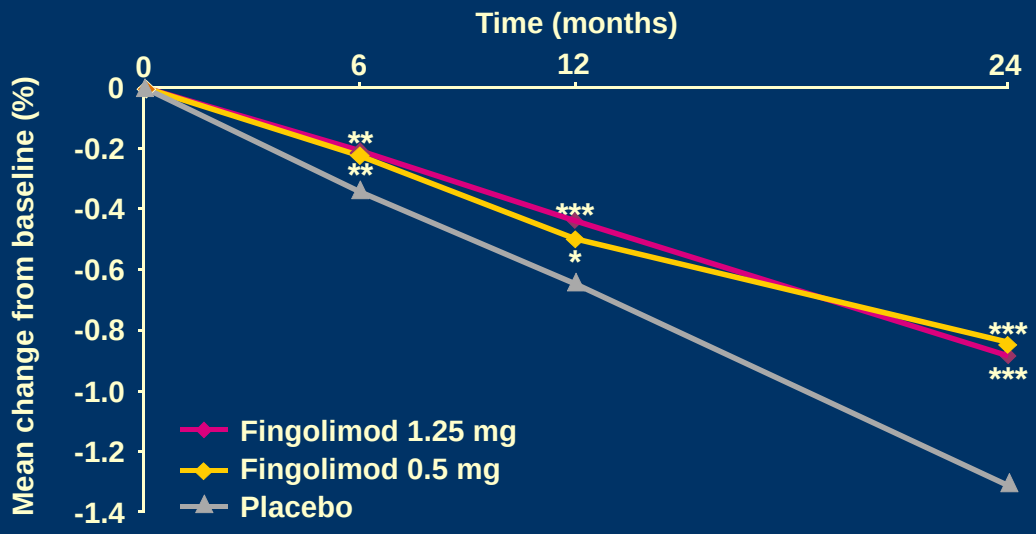
# FREEDOMS - MRI lesion activity




*Analysis performed using a negative binomial regression model adjusted for treatment group and country
**Analysis performed using rank ANCOVA adjusted for treatment group, country and number of lesions at baseline

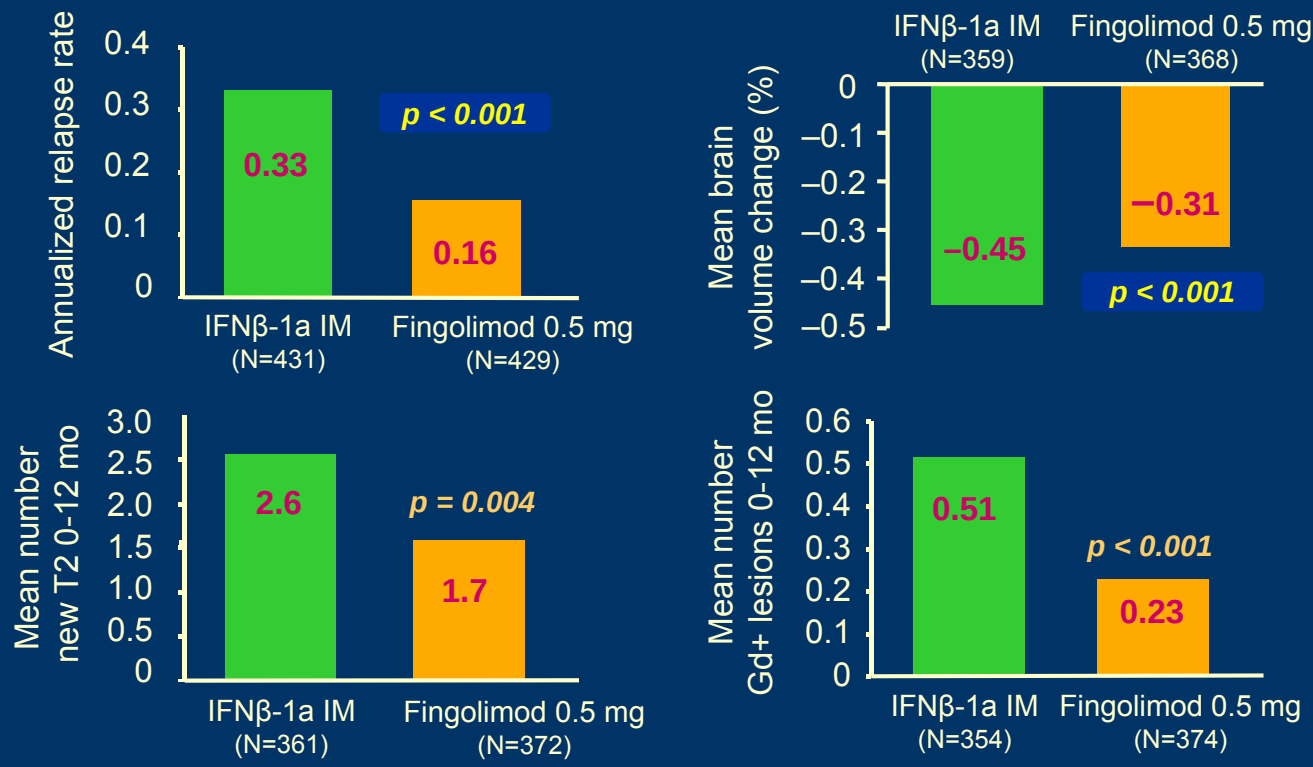


# FREEDOMS - Brain volume change




For fingolimod vs placebo: *$p$<0.05; **$p$<0.0; ***$p$≤0.001
Rank ANCOVA adjusted for treatment group, country, and baseline normalized brain volume
ITT population with available scans

# *Efficacy Compared to an Approved 1st-line Therapy - TRANSFORMS Outcomes*




Modified intention-to-treat population: all patients who underwent randomization and received one dose of a study drug
Negative binomial regression model adjusted for study group, country, baseline number of relapses in previous 2 years and baseline disability score. p = 0.16 for fingolimod 0.5 mg vs 1.25 mg. Bars represent the 95% CI
Analysis included patients with available magnetic resonance imaging (MRI) scans



# Fingolimod Adverse Event Experience

| | Phase III placebo-controlled (D2301) | | | All studies+ | |
|---|---|---|---|---|---|
| | Placebo | Fingolimod | | Fingolimod | |
| | | 0.5 mg | 1.25 mg | 0.5 mg | 1.25 mg |
| Number of patients | 418 | 425 | 429 | 1176 | 1302 |
| Exposure (pt-years) | 703.2 | 750.2 | 682.8 | 1878.0 | 2218.3 |
| **Event, N (%)** | | | | | |
| At least one adverse event | 387 (92.6) | 401 (94.4) | 404 (94.2) | 1054 (89.6) | 1203 (92.4) |
| Adverse event leading to study drug discontinuation* | 32 (7.7) | 32 (7.5) | 61 (14.2) | 92 (7.8) | 186 (14.3) |
| Any serious adverse event | 56 (13.4) | 43 (10.1) | 51 (11.9) | 111 (9.4) | 170 (13.1) |
| Deaths | 2 (0.5) | 0 | 1 (0.2) | 0 | 5 (0.3) |

+Includes all available data from Phase II and Phase III core and extension studies (2201, 2201E1, 2301, 2301E1, 2302 and 2302E1) with treatment durations varying between 1 to 6 years – data cut off from 120 day safety update.
*Includes events occurring in patients whose primary or secondary reason for discontinuing the study drug was an adverse event (including abnormal laboratory findings)

# *Safety Areas of Special Interest*

- Pharmacodynamic effects:
  - Bradyarrhythmias on treatment initiation
  - Blood Pressure increase
- Effects of uncertain mechanism:
  - Macular edema
  - Elevations of liver enzymes
- Potential risks related to the immunomodulatory effect:
  - Infections
  - Malignancies



## US label for Gilenya

GILENYA is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability

# EU label for Gilenya

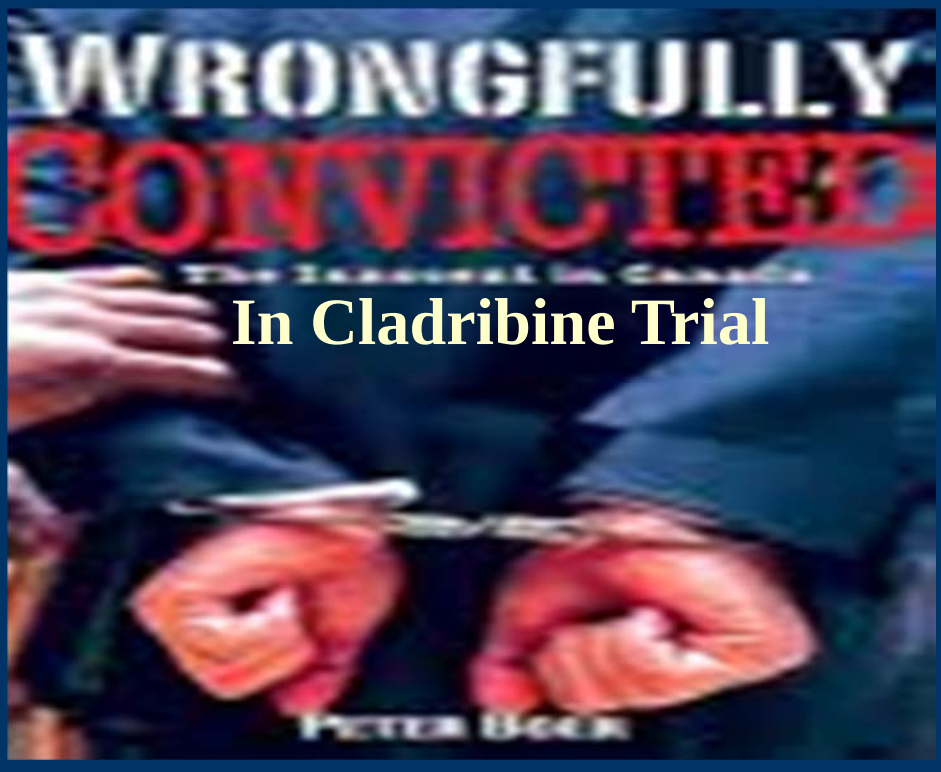
**Gilenya™ (fingolimod) is indicated as single disease-modifying therapy in highly active RRMS for the following adult patient groups:**

- Patients with high disease activity despite treatment with a IFNβ
  - failed to respond to a course of IFNβ, with ≥1 relapse in the previous year, and either ≥9 T2-hyperintense lesions or ≥1 Gd-enhancing lesion
  - non-responder: patient with an unchanged or increased relapse rate compared with the previous year

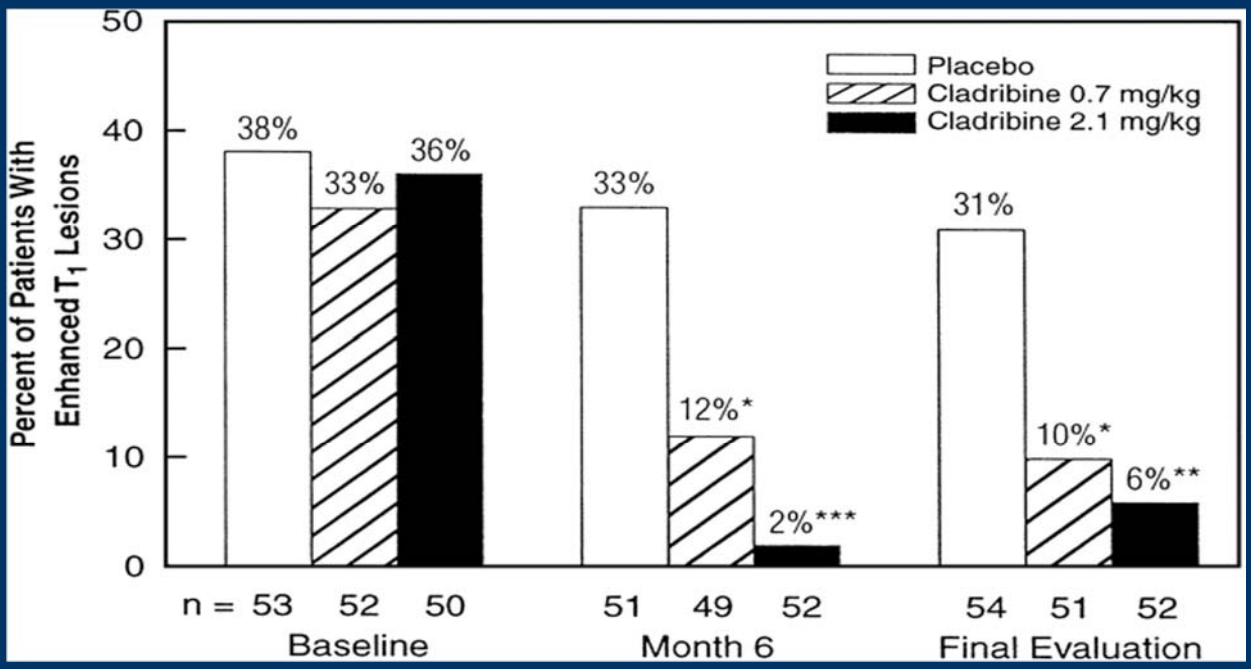
- Patients with rapidly evolving severe RRMS: ≥2 relapses in 1 year, and ≥1 Gd-enhancing lesion or a significant increase in T2 lesion load

Gilenya Summary of Product Characteristics, 4 April 2011



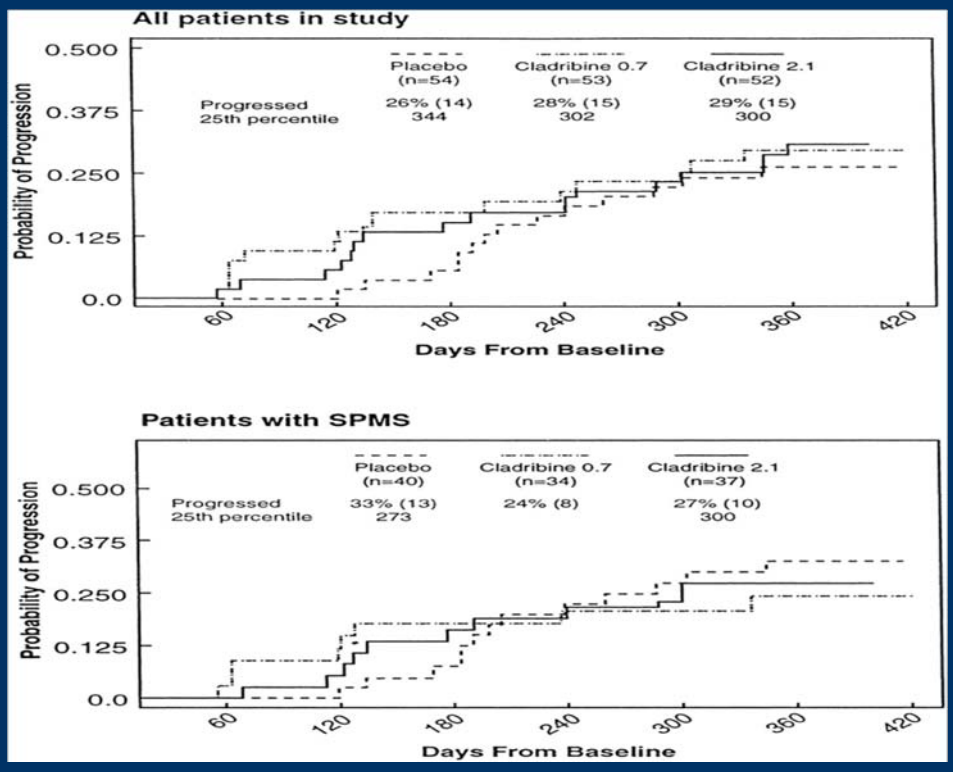


# Cladribine Phase 2 – MRI activity



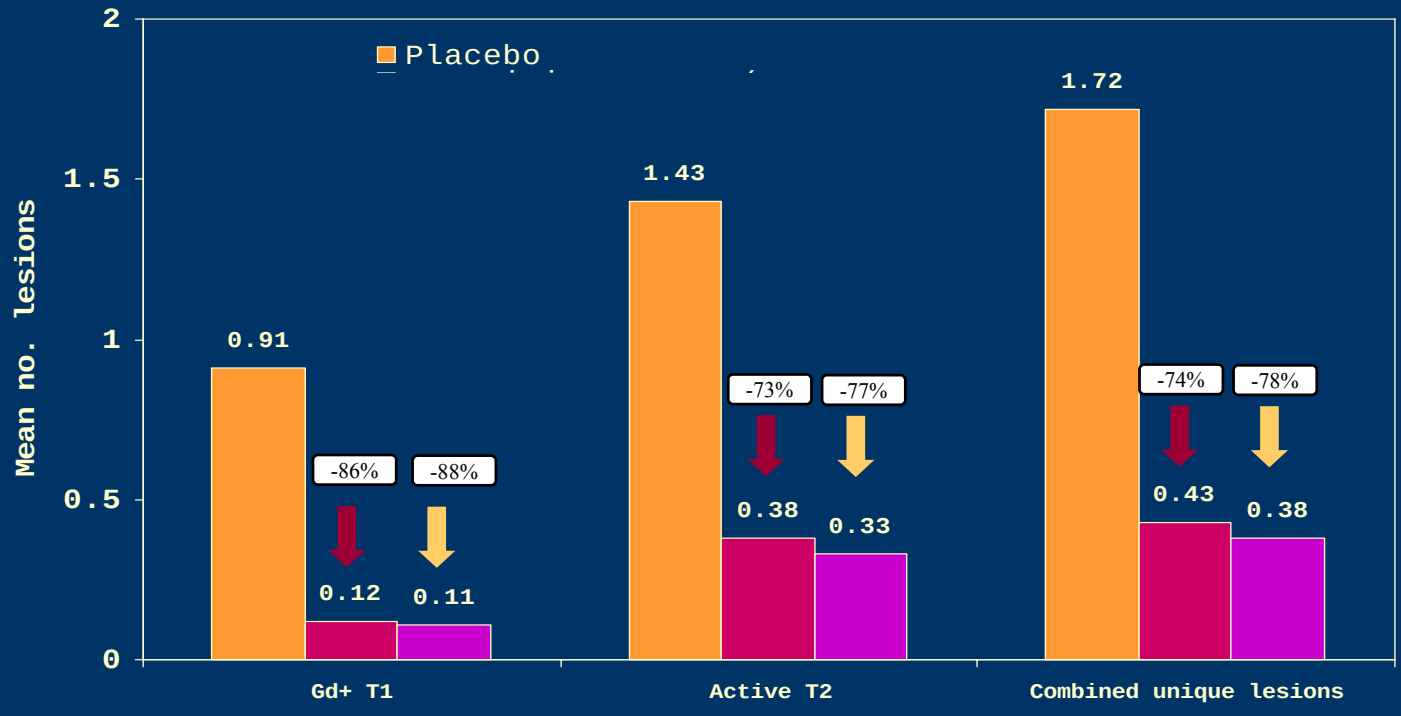

Rice, G. P. A. et al. Neurology 2000;54:1145-1155

# Cladribine Phase 2 - Disease Progression



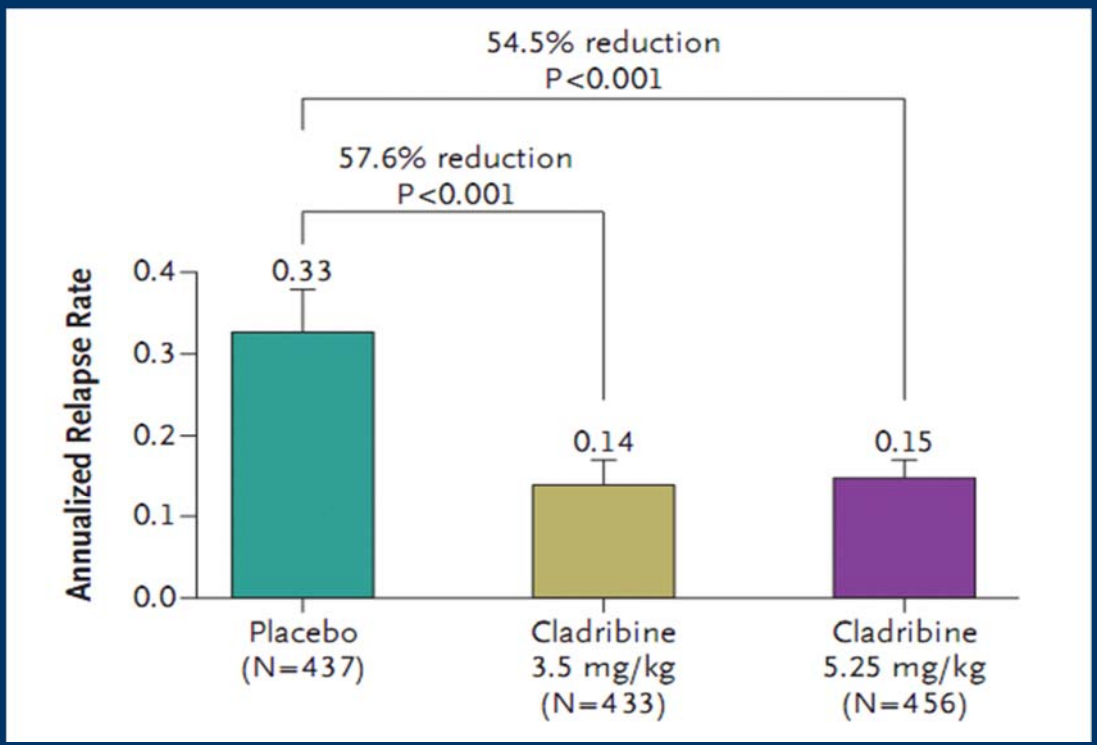

Rice, G. P. A. et al. Neurology 2000;54:1145-1155

# Phase 3 in RRMS
# Cladribine vs. Placebo on MRI Activity




Giovannoni G, et al. *New Engl J Med.* 2010;362:416-426.

# Relapse Rate: Cladribine vs. Placebo




Giovannoni G, et al. *New Engl J Med.* 2010;362:416-426.
ARR, annualized relapse rate.

# MRI Declared "Not Guilty" on Appeal
# The Cladribine Case

...however

## *Cladribine in MS*

- Jul 2010 – Cladribine approved in Russia
- Sep 2010 – Cladribine approved in Australia
- Sep 2010 – Cladribine rejected by CHMP
- Jan 2011 – Cladribine appeal by CHMP rejected
- Feb 2011 – FDA rejects approval for Cladribine
- Jun 2011 – EMD Serono stops development of cladribine and to withdraw from Russia/Australia

# *Other Aspects to Consider in Comparative Risk-Benefit*

- Study population
- On-study placebo disease activity
  - Cross-study comparisons
  - NNT / NNH
- Patient perception of benefit and risk

# *Baseline Characteristics and On-study Relapse Rates from Pivotal Phase III Studies*

| Placebo controlled study | Age (yrs) Mean | Disease Duration (yrs) Mean/(Median) | Relapses in prior 2 years (mean) | Mean EDSS at baseline | % Gd-enhancing lesions on MRI at baseline | On-Study Placebo ARR |
|---|---|---|---|---|---|---|
| **Fingolimod**<br>**FREEDOMS (D2301)****<br>N=1272, 3 arms<br>**~40% previously Rx** | 37 | 8.3<br>(6.8) | 2.1 | 2.4 | 38% | 0.40 |
| **Natalizumab**<br>**AFFIRM**<br>N=942, 2 arms<br>**8% previously Rx** | 36 | -<br>(5.0) | 1.5* | 2.3 | 48% | 0.67 |
| **Rebif**<br>N=560, 3 arms<br>**Rx naïve** | 35 | 7.2<br>(5.3) | 3.0 | 2.5 | - | 1.3 |
| **Betaferon**<br>N=372, 3 arms<br>**Rx naïve** | 36 | 4.4† | 3.4 | 2.9 | - | 1.3 |
| **Avonex**<br>N=301, 2 arms<br>**Rx naïve** | 37 | 6.5<br>- | 1.2* | 2.4 | 54% | 0.9 |
| **Copaxone**<br>N=251, 2 arms<br>**Rx naïve** | 35 | 7.0<br>- | 2.9 | 2.6 | - | 1.7 |

***incidence only in prior year reported; ** TRANSFORMS (D2302) highly comparable to FREEDOMS**
**† since diagnosis, not onset; n.d .not done, n.r. not reported (done only in subgroup)**

# *Benefits and Risks with fingolimod 0.5mg*
# *Events avoided/induced per 1000 patients treated*

| | Type of Event | Number of events: Placebo (2 years) | Number of events: IFN (1 year) |
|---|---|---|---|
| Benefit | Relapses Avoided | 440 | 170 |
| Benefit | Patients Free of Relapse | 233 | 124 |
| Benefit | Patients Free of Disability Progression | 56 | 19 |
| Risk | Macular Edema | 3* | 1 |
| Risk | High-grade AV block | 1* | 0 |
| Risk | 5-fold ALT elevation | 9 | 0 |
| Risk | Hypertension | 23 | 18 |
| Risk | Pneumonia | 3 | 0 |

* No hubo casos en estudio 2301, data del programa completo

# Importance of benefit-to-risk assessment for drugs used in MS

**Table 5** NNT[a] values based on efficacy outcome data for products approved as first-line therapy in relapsing multiple sclerosis

| Outcome | IFN β-1b, 8 MIU on alternate days | IFN β-1a, 30 mcg qw | Glatiramer acetate, 20 mg once daily | IFN β-1a, 22 mcg tiw | IFN β-1a, 44 mcg tiw | IFN β-1a, 44 mcg tiw versus 30 mcg qw |
|---|---|---|---|---|---|---|
| Relapse count | | | | | | |
| 1 year | nr | 11 | nr | 2.0 | 1.6 | 10 |
| 2 years[b] | 2.3 | 7 | 4.1 | 2.7 | 2.4 | 10[c] |
| Relapse-free (%) | | | | | | |
| 1 year | nr | nr | 16[d] | 4 | 3 | 11 |
| 2 years[b] | 12/6[e] | 9[f] | 15 | 10 | 6 | 13[c] |
| Progression-free (%) | 13 | 8 | 33 | 13 | 10 | 100 |
| No T1 active scans (%) | – | 9[g] | 14[d] | 3.7[d] | 3.1[d] | 6[h] |

**Francis G, J Neurol (2004) 251[Suppl 5], 42-49**

# MS Patient's benefit-risk preferences: SAEs vs. Efficacy

| Benefit | PML | Liver Failure | Leukemia |
|---|---|---|---|
| | Mean (Lower Bound, Upper Bound) | Mean (Lower Bound, Upper Bound) | Mean (Lower Bound, Upper Bound) |
| Slow Progression Benefit* | 0.31 % (0.26, 0.36) | 0.30% (0.23, 0.36) | 0.35 % (0.25, 0.44) |
| Clinically Relevant Benefit** | 0.38% (0.32, 0.43) | 0.39% (0.32, 0.46) | 0.48 % (0.39, 0.58) |
| Largest Tested Benefit*** | 0.74% (0.68, 0.79) | 1.02% (0.92, 1.13) | 1.08 % (0.99, 1.18) |

* Number of relapses in the next 5 years reduced from 4 to 1, time until next disability progression increased from 5 years to 8 years
** Number of relapses in the next 5 years reduced from 4 to 1, time until next disability progression increased from 3 years to 5 years
*** Number of relapses in the next 5 years reduced from 4 to 0, time until next disability progression increased from 1 year to 8 years

**Johnson R, et al, J Neurol (2009) 256:554-562**



# MS Patient's benefit-risk preferences: SAEs vs. Efficacy

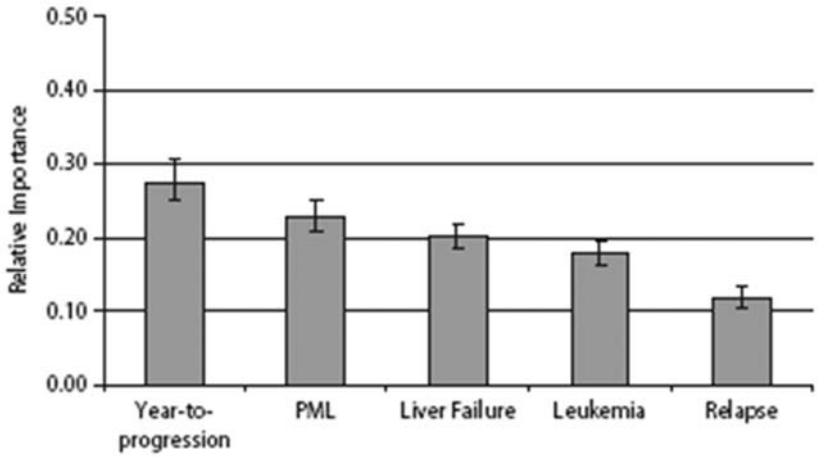



**Fig. 3** Relative importance of each attribute (with 95% confidence intervals)

**Johnson R, et al, J Neurol (2009) 256:554-562**

# *Benefit-Risk: What's needed?*

- New metrics
  - Quantifiable, objective, reproducible/reliable
- Consistency between agencies
- Increased consideration of the view of patients faced with the consequences of disease
- Acceptance of risk for benefit
  - "no pain, no gain"