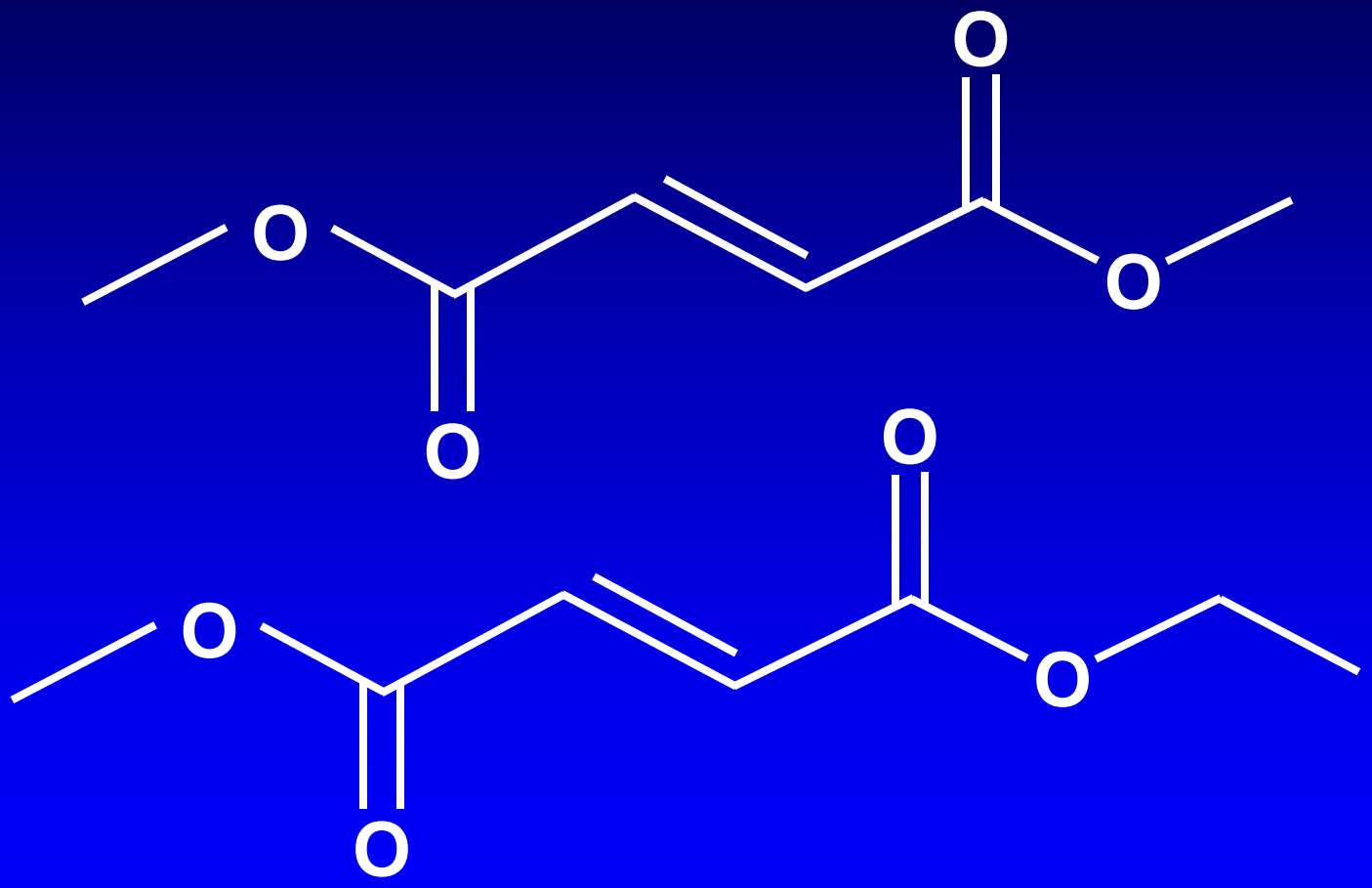
Dimethyl Fumarate and Natalizumab Update 2013

Bruce Cree, MD, PhD, MCR

Dimethyl Fumarate

** Dimethyl fumarate (BG12, Tecfidera™) was approved by the FDA for relapsing-remitting forms of MS on March 27, 2013*

Dimethyl Fumarate



Fumaric acid esters can be derived from extracts of the plant fumaria officianalis, also known as common fumatory

264. *Fumaria officinalis L.* **Gebräuchlicher oder gemeiner Erdrauch.**

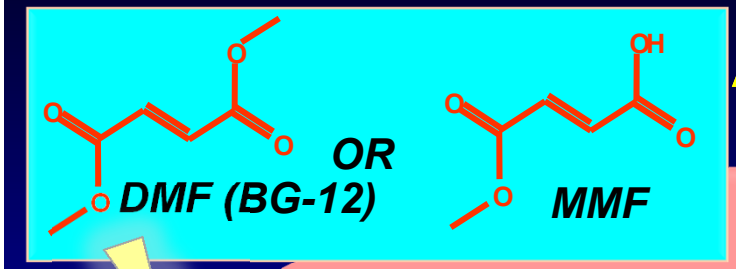
Fumarate

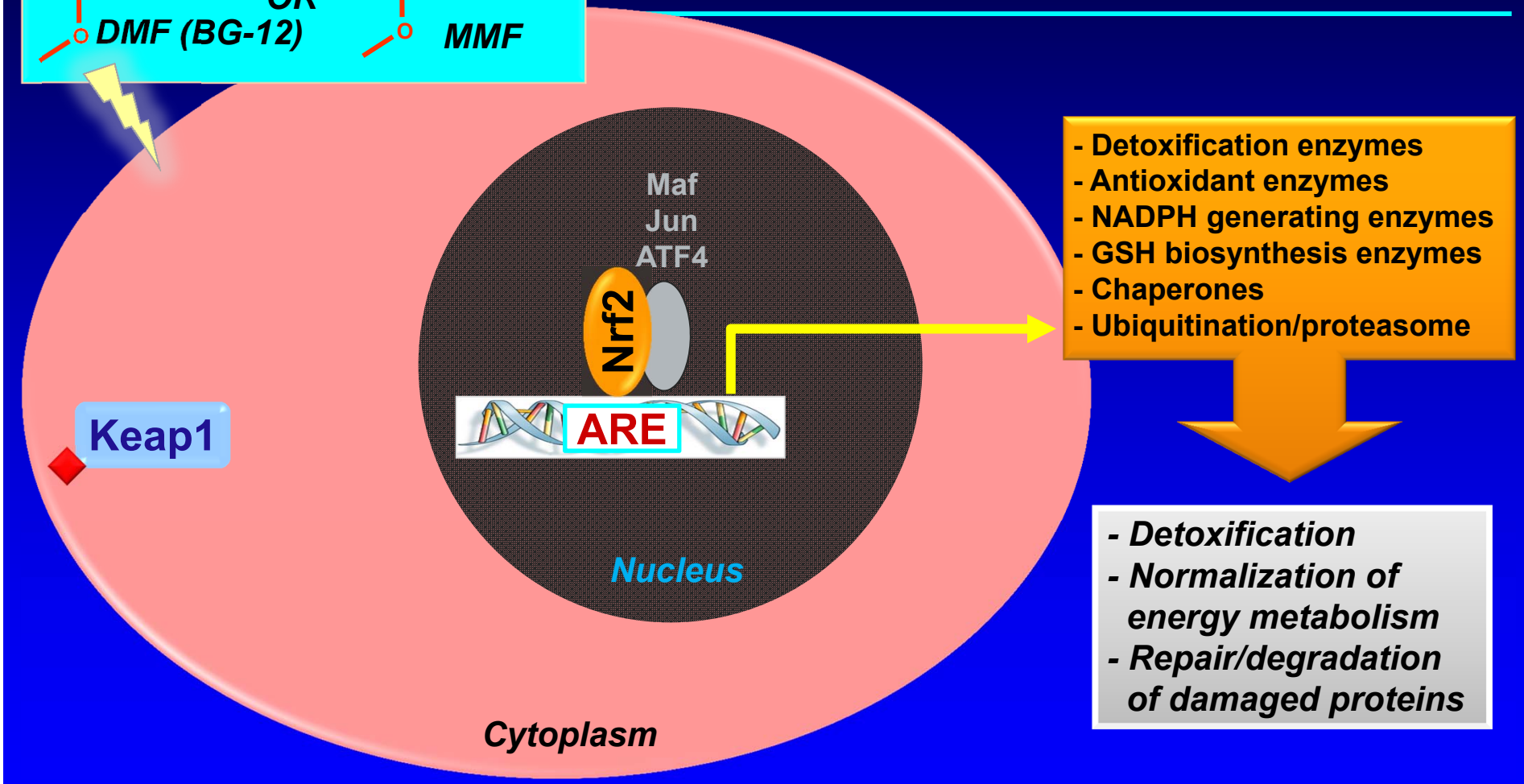
Background and Mechanism of Action

- Dimethyl fumarate is derived from Fumaderm, an oral therapy of fumaric acid esters approved to treat psoriasis in Germany
- Therapeutic mechanism of BG-12 in MS is speculative
  - In psoriasis patients, the beneficial effect of fumarates coincides with lymphocytopenia (40%-60%) and down-regulation of proinflammatory cytokine(s)
  - Increases in an anti-inflammatory cytokine (IL-10) were noted in a small pilot study of MS patients and in an EAE model
  - Data in the EAE model suggest BG-12 activates a protective antioxidant pathway in CNS

Linker RA, et al. *Expert Rev Neurotherapeutics*. 2008;8:1683-1690. Schimrigk S, et al. *Eur J Neurol*. 2006;13:604-610. Schilling S, et al. *Clin Exp Immunol.* 2006;145:101-107. Litjens NHR, et al. *Br J Dermatol*. 2003;148:444-451. Hoxtermann S, et al. *Dermatology.* 1998;196:223-230. Lukashev M, et al. *J Neurol.* 2008;255:210.

BG-12 Has Shown Nrf2 Pathway Activation

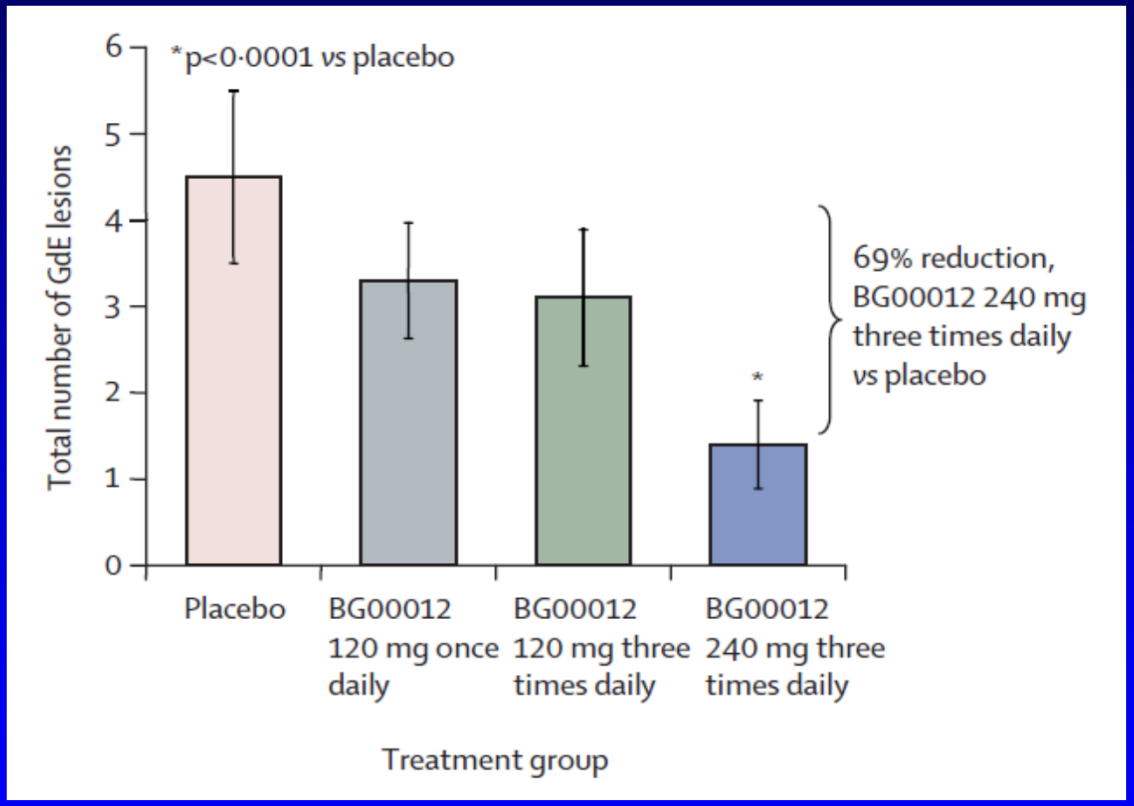




DMF=dimethyl fumarate; MMF=monomethyl fumarate.

Scannevin R, et al. Poster presented at ECTRIMS October 13–16, 2010. Gothenburg, Sweden. P887.
Feinstein D, et al. Poster presented at ECTRIMS October 13–16, 2010. Gothenburg, Sweden. P879.

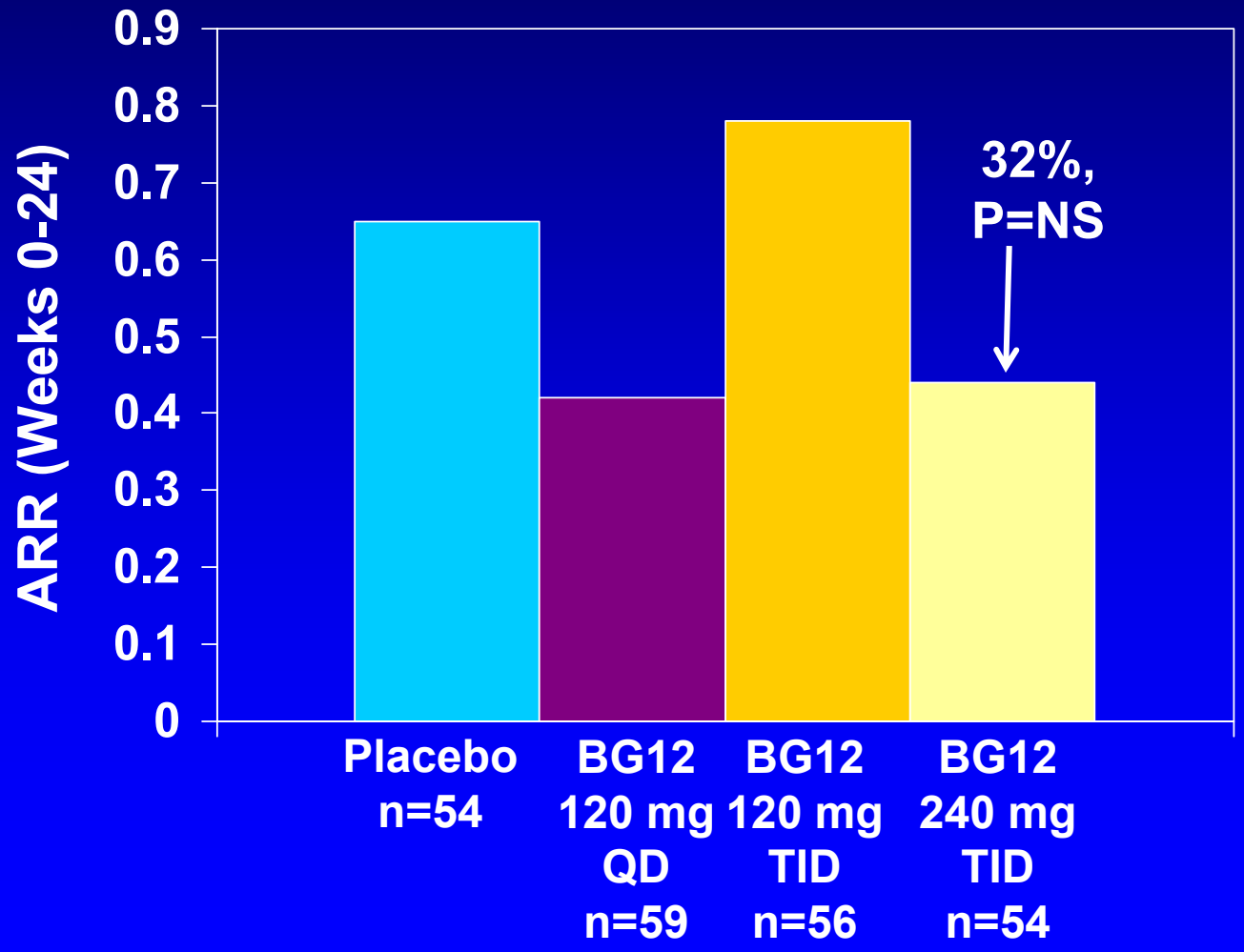
Fumarate: Phase II
Primary Endpoint



- Mean total number of GdE lesions from scans at Weeks 12, 16, 20, and 24 combined

Kappos L, et al. *Lancet.* 2008;372:1463-1472.

Fumarate: Relapse Rate



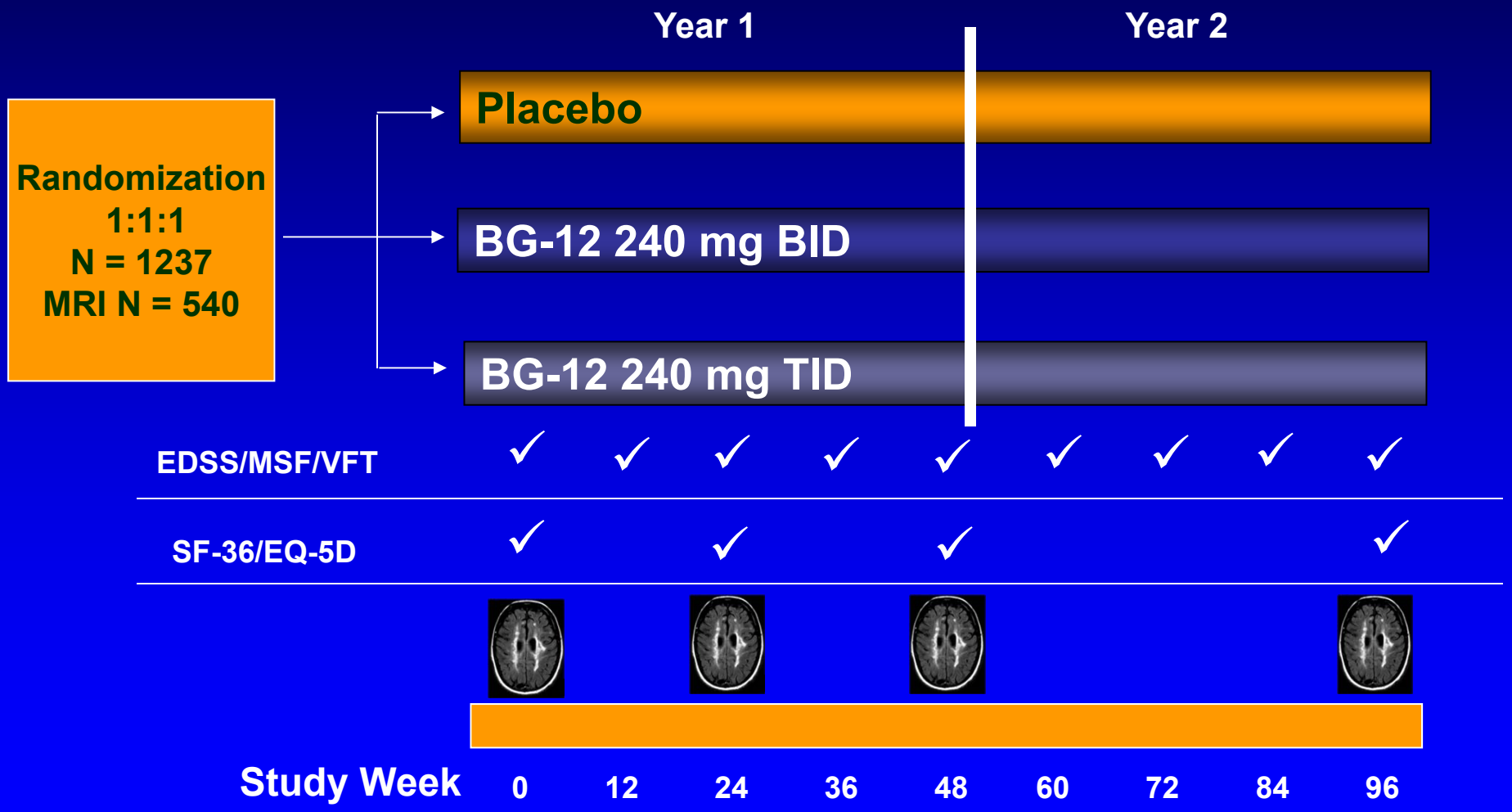
Fumarate: Safety and Tolerability

Oral – 240 mg three times daily (720 mg total daily dose)

- GI-related problems and flushing are the two most common AEs[1,2]
  - Phase IIb (240 mg tid) – AEs more common vs placebo: headache (21%), flushing (40%), pruritus (10%), diarrhea (11%), abdominal pain (14%), nausea (16%)[1,2]
  - Incidence of flushing and GI events decreased over 12 months of treatment, with notable decrease after first month[2]
- Incidence of infection was not significantly different from placebo[2]
- >30 years of use of fumaric acids in treatment of psoriasis (both topical and oral dosing)[3]

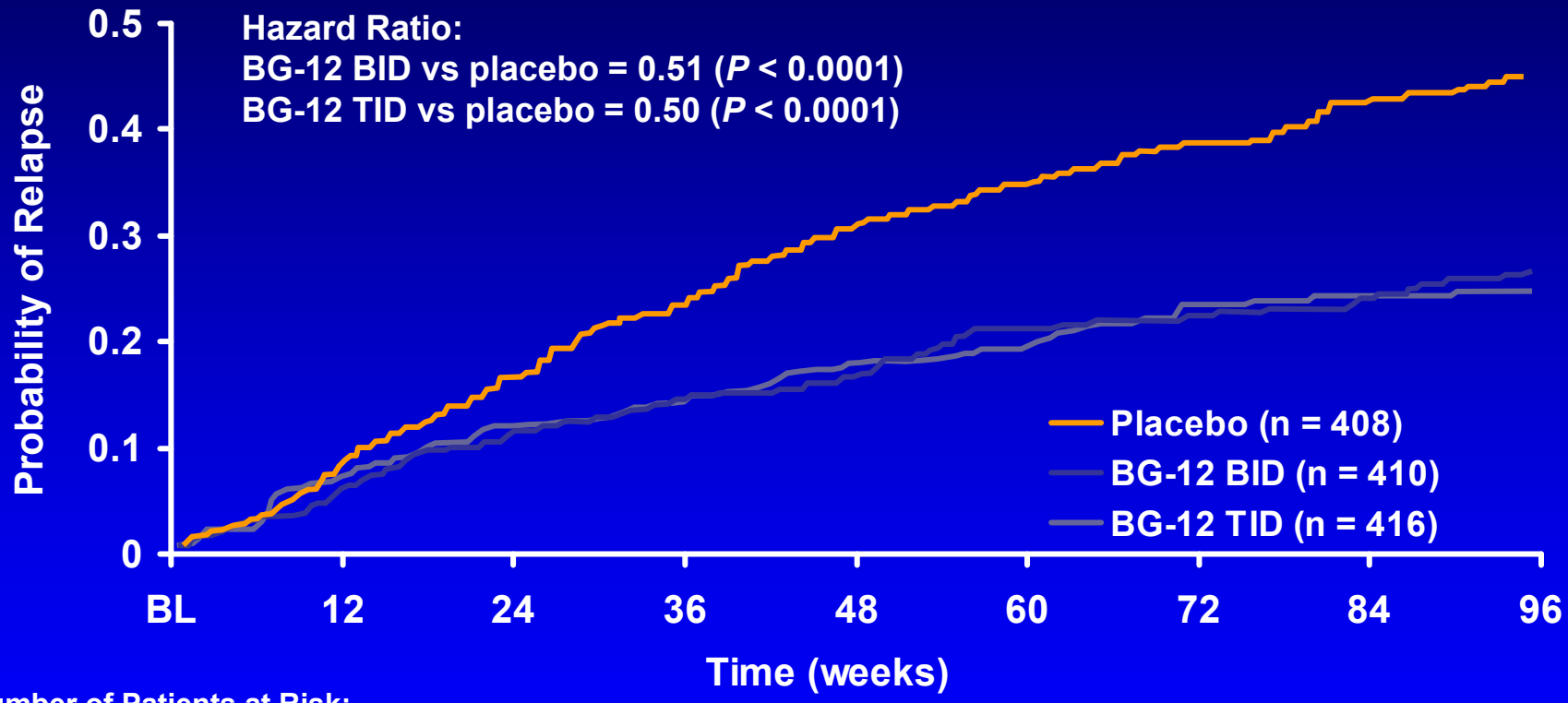
1. Kappos L, et al. *Lancet.* 2008;372:1463-1472. 2. Gold R, et al. Presented at: WCTRIMS, September 17-20, 2008; Montréal, Canada. [Poster P50]. 3. Gasperini C, et al. *Expert Opin Emerging Drugs.* 2008;13:465-477.

DEFINE (BG-12/Dimethyl Fumarate) : Study Design



Gold R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 95]

DEFINE: Cumulative Probability of Relapse (1° Endpoint)

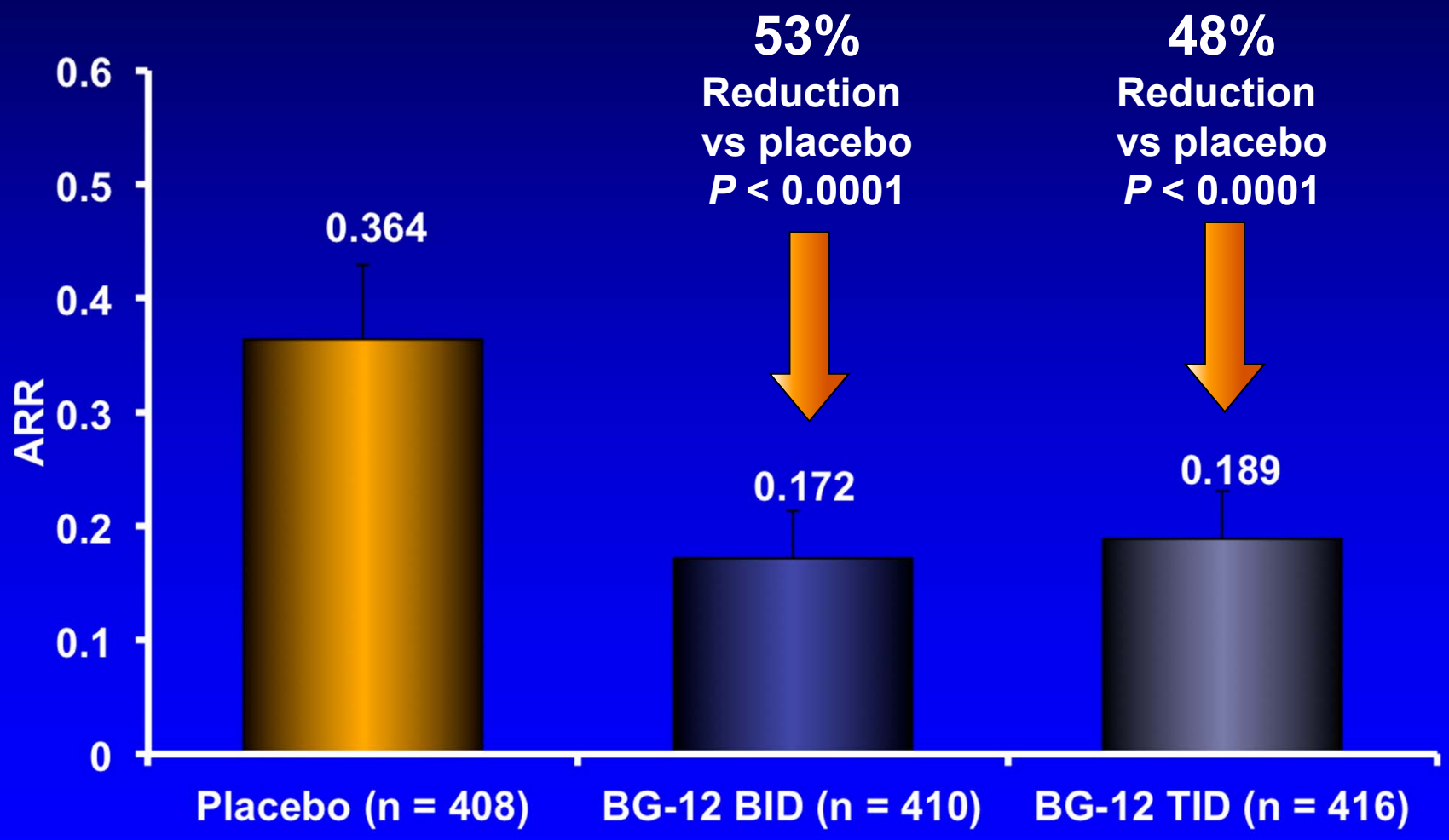


Number of Patients at Risk:								
Placebo	406	358	321	282	243	224	205	190
BG-12 BID	410	353	324	303	288	287	255	243
BG-12 TID	416	348	322	301	288	270	251	244

Patients were censored if they withdrew from study or switched to alternative MS medication without a relapse.

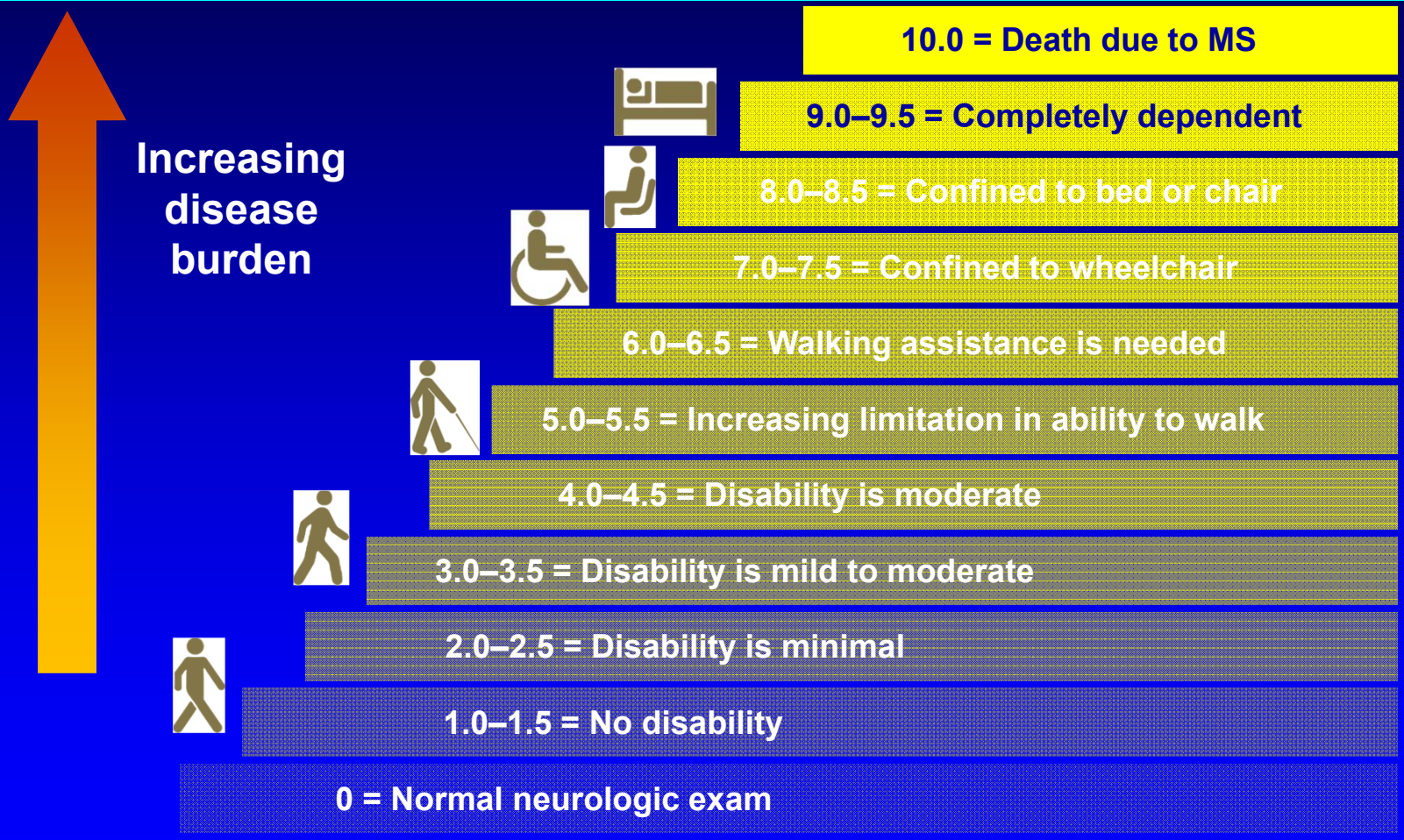
Gold R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 95]

DEFINE: Annualized Relapse Rates



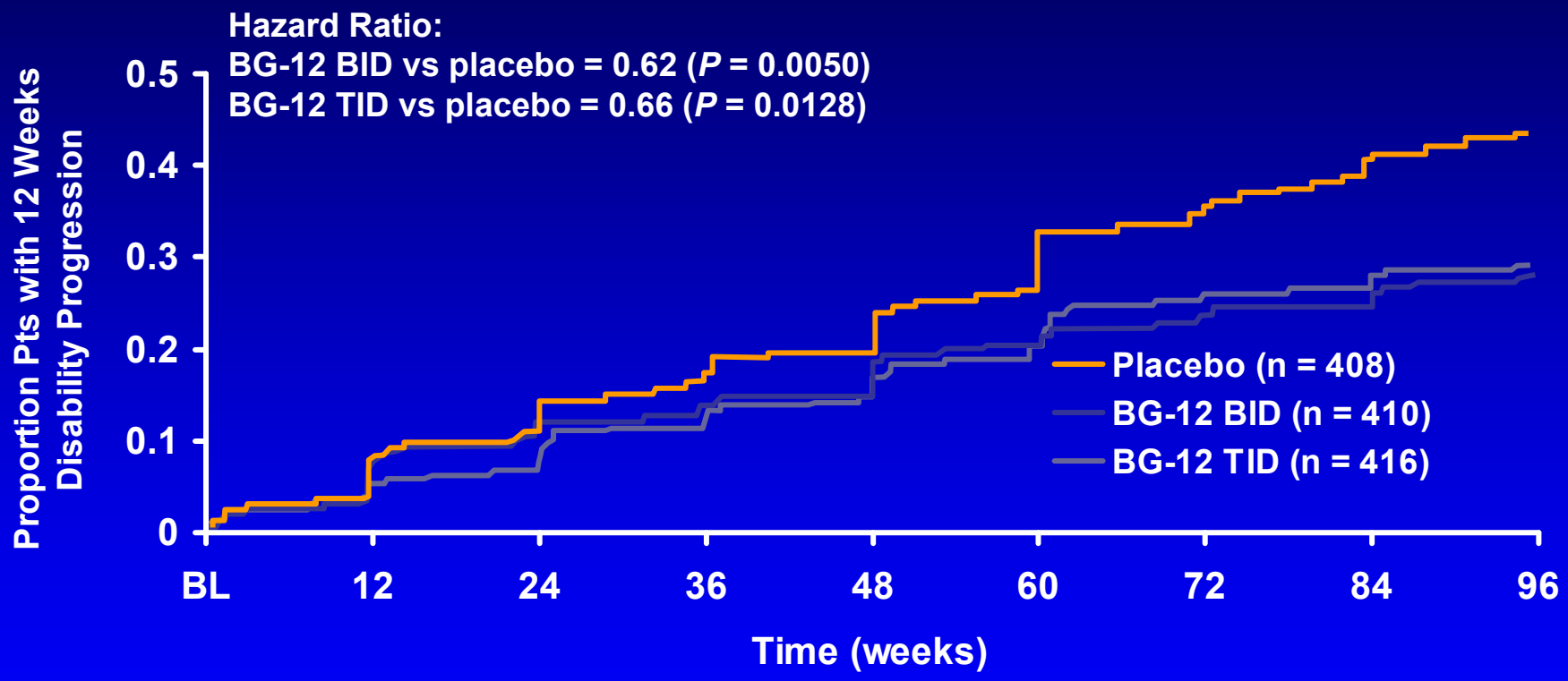
Gold R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 95]

Progression of Disability: EDSS



EDSS = Expanded Disability Status Scale.
Kurtzke JF. *Neurology*. 1983;33:1444-1452.

DEFINE: Time to 12-Week Confirmed Disability Progression

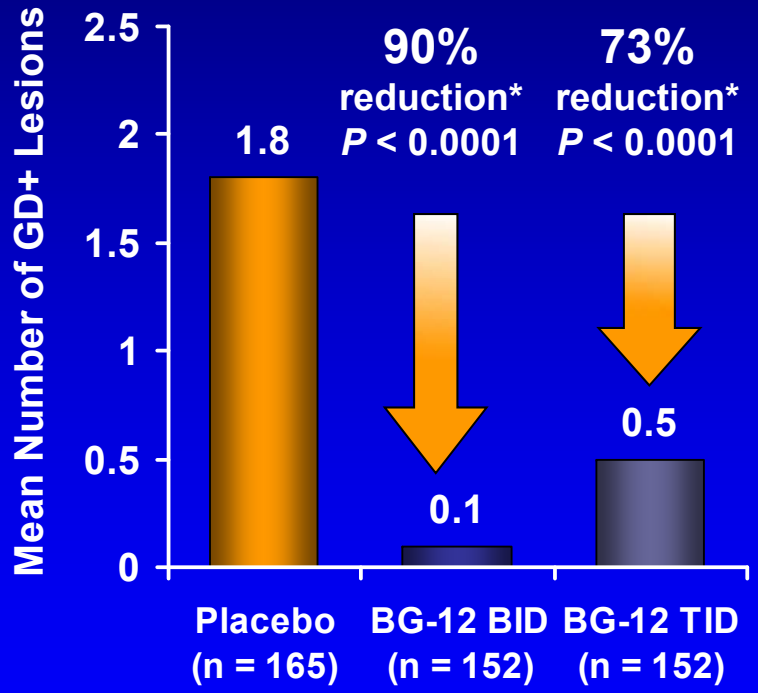


Number of Patients at Risk:								
Placebo	408	375	345	319	291	285	242	224
BG-12 BID	409	359	333	328	304	290	278	267
BG-12 TID	416	360	346	325	324	291	276	265

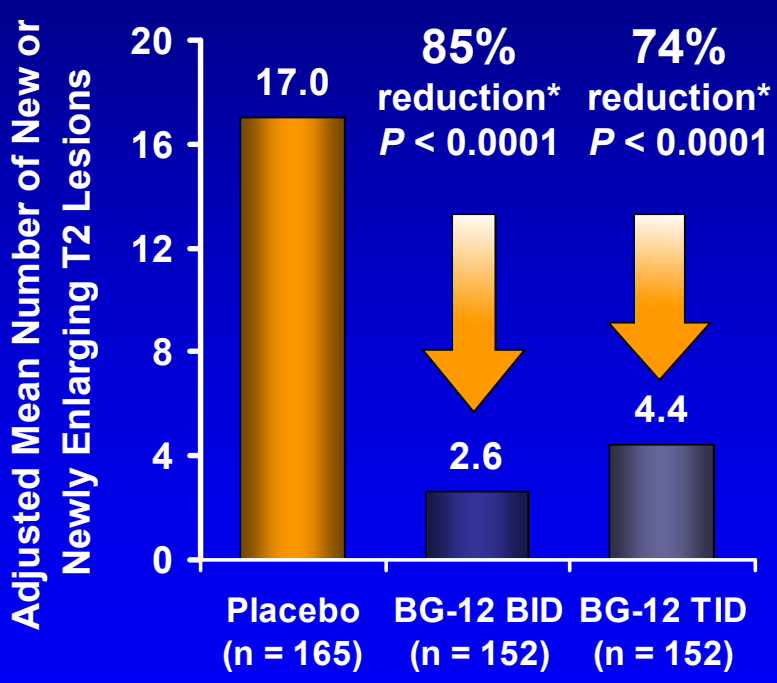
Gold R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 95]

DEFINE: 2 Years MRI Outcomes

Gd-enhancing lesions



New or newly enlarging T2 lesions



Arnold DL, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [P831]

DEFINE: Adverse Events

AE n (%)	Placebo (n = 408)	DMF 240 mg BID (n = 410)	DMF 240 mg TID (n = 416)
Any event	387 (96)	395 (96)	396 (95)
Flushing*	20 (5)	154 (38)	132 (32)
MS relapse	189 (46)	111 (27)	114 (27)
Nasopharyngitis	101 (25)	108 (26)	109 (26)
Headache	80 (20)	81 (20)	80 (19)
Diarrhea*	55 (13)	62 (15)	78 (19)
Fatigue	54 (13)	57 (14)	63 (16)
Upper respiratory tract infection	53 (13)	63 (15)	51 (12)
Urinary tract infection	53 (13)	55 (13)	54 (13)
Nausea*	38 (9)	53 (19)	54 (13)
Back pain	57 (14)	59 (14)	46 (11)
Upper abdominal pain*	28 (7)	40 (10)	52 (13)
Proteinuria*	34 (8)	38 (9)	50 (12)
Abdominal pain*	22 (5)	46 (11)	37 (9)
Arthralgia	39 (10)	46 (11)	37 (9)
Influenza	39 (10)	34 (18)	48 (12)
Pruritus*	19 (5)	42 (10)	34 (8)
Vomiting*	24 (6)	40 (10)	30 (7)

*Indicates an incidence ≥ 3% higher in either BG-12 group.

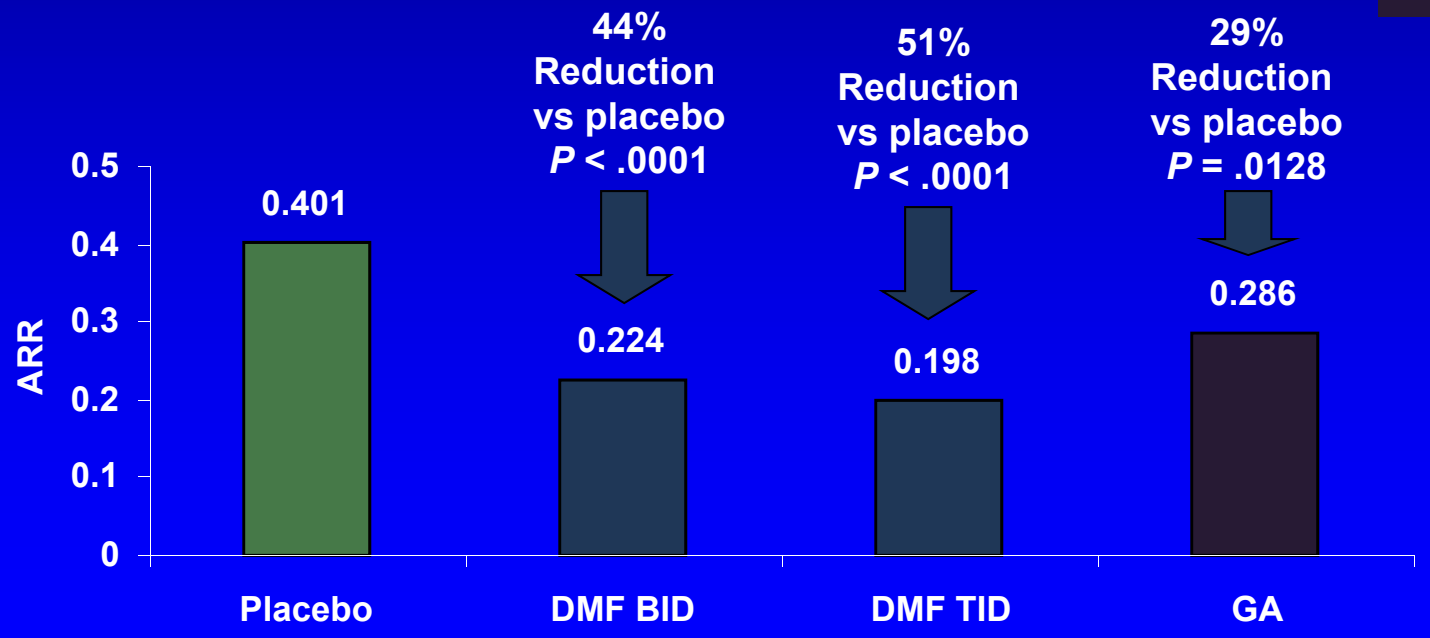
Selmaj K, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [P994]

CONFIRM: A Phase 3 Trial of DMF With an Active Comparator in Patients With MS[1]

- N = 1,417
- Ages 18-55 years
- RRMS
- EDSS 0.0 to 5.0
- 2-year study

R

- DMF 240 mg BID
- DMF 240 mg TID
- Placebo
- GA 20 mg/day



EDSS: Expanded Disability Status Scale; GA: glatiramer acetate.

Fox R et al. N Engl J Med. 2012 Sep 20;367(12):1087-97

CONFIRM: Additional Outcomes

Endpoint	DMF BID (vs Placebo)	DMF TID (vs Placebo)	GA (vs Placebo)
Risk of relapse	−34% (P = .002)	−45% (P < .0001)	−29% (P = .0097)
New/enlarging T2 lesions	−71% (P < .0001)	−73% (P < .0001)	−54% (P < .0001)
New T1 hypointense lesions	−57% (P < .0001)	−65% (P < .0001)	−41% (P = .0021)
T1-GdE lesions	−74% (P < .0001)	−65% (P = .0001)	−61% (P = .0003)
12-Wk CDP	−21% (P = .2536)	−24% (P = .2041)	−7% (P = .7036)

- Similar to the DEFINE trial, incidence of flushing and GI events (ie, nausea, vomiting, diarrhea) higher in DMF–treated patients vs patients on placebo, as well as vs patients on GA

CDP: confirmed disability progression.

Fox R et al. N Engl J Med. 2012 Sep 20;367(12):1087-97

DMF: Integrated Efficacy Analysis of DEFINE and CONFIRM

Endpoint (at 2 years)	Placebo (n = 771)	DMF BID (n = 769)	DMF TID (n = 761)
Annualized relapse rate (ARR) Reduction vs placebo	0.37	0.19* 49%	0.19* 49%
Proportion of patients relapsed HR vs placebo		0.57*	0.53*
Time to 12-week confirmed disability progression HR vs placebo		0.68*	0.70*
Time to 24-week confirmed disability progression HR vs placebo		0.71*	0.68*

*Statistically significant vs placebo.

Fox RJ, et al. Presented at AAN; March 16-23, 2013; San Diego, CA. Abstract P07.097.

Slide 19

5 For the BG12 data I would include only the information on 240 mg twice daily. The 240 mg three time daily dose will not be used in clinical practice and is not relevant for practical educational purposes. This commnent applies ot the next series of slides.
Bruce Cree, 4/12/2013

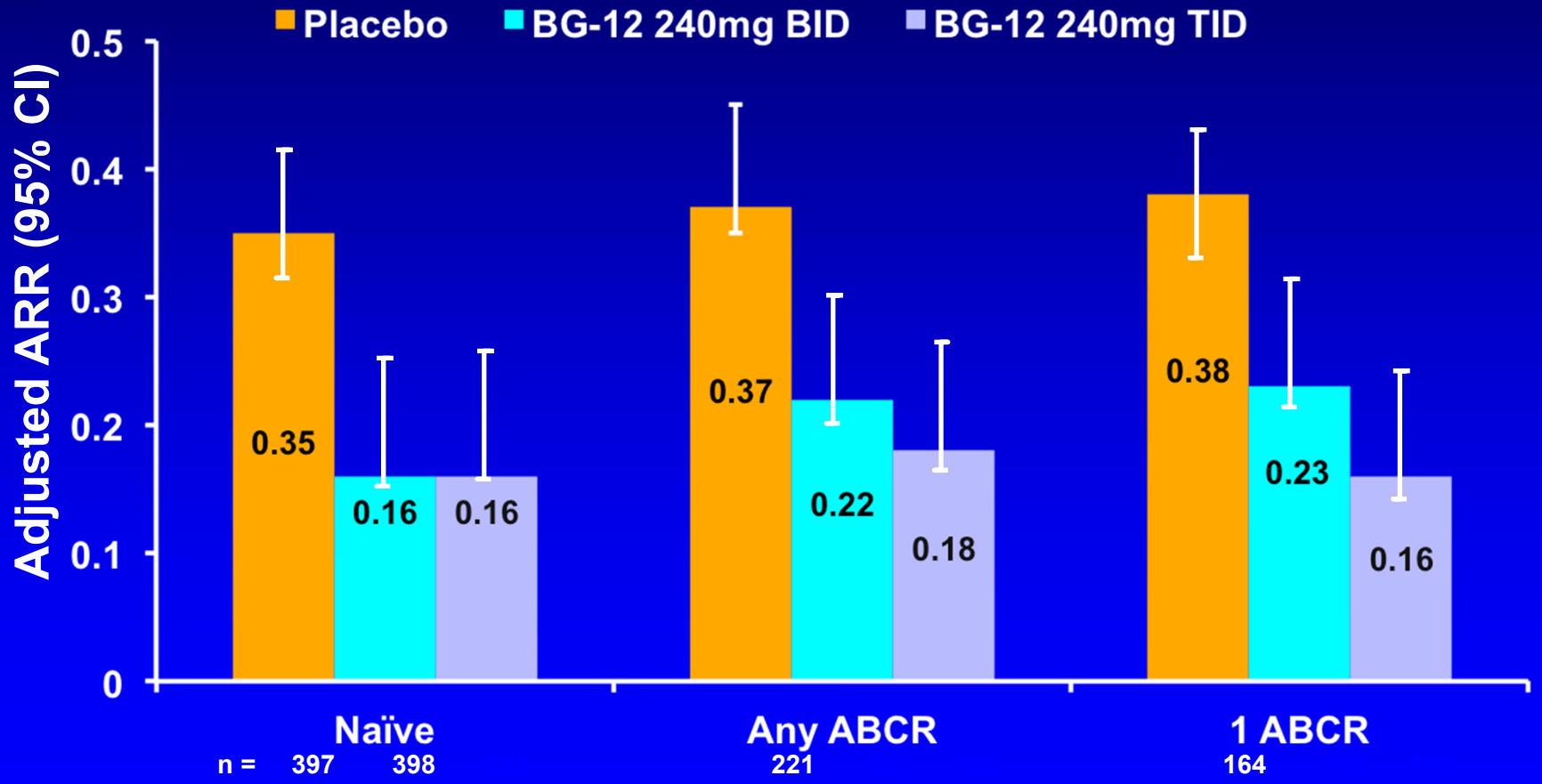
Timecourse of Treatment Effects of DMF in RRMS

- DMF significantly reduced proportion of patients relapsed and ARR by week 12
  - HR for relapse risk vs placebo:
    - 0.68 DMF BID (P = 0.028)
    - 0.70 DMF TID (P = 0.046)
  - ARR:
    - 0.66 DMF BID (P = 0.015)
    - 0.68 DMF TID (P = 0.030)
  - Significant separation maintained thereafter
- Significant improvements in MRI parameters seen at week 24 (first post-treatment assessment) that were maintained at 2 years

Kappos L, et al. Presented at AAN 2013; March 16–23, 2013; San Diego, CA. Abstract S41.005.

DMF: Integrated Analysis of Pooled Phase III Trials Based on Previous Therapy

ARR by Prior TX Subgroups



ABCR = Avonex/Betaseron/Copaxone/Rebif

Hutchinson M, et al. Presented at AAN; March 16-23, 2013; San Diego, CA. Abstract P07.128.

DMF: Integrated Safety Analysis from Phase II/III Studies

Safety population total N = 2,428

Adverse events, %	Placebo (n = 836)	BG-12 BID (n = 769)	BG-12 TID (n = 823)
Overall	92%	95%	93%
Leading to discontinuation	11%	14%	14%
Serious	21%	18%	15%
Serious infections	1%	2%	2%
Malignancies	<1%	<1%	<1%

- AEs with incidence ≥5% higher in either DMF group vs placebo:
  - Flushing and related events (hot flush, erythema)
  - Gastrointestinal events (diarrhea, nausea, abdominal pain)
  - Rash
- No opportunistic infections reported
- Overall rates of hepatic and renal events similar across groups
- In DMF groups, lymphocyte counts decreased ~25–30% over first yr, then plateaued and remained within normal limits
- Four deaths (none thought tx-related)

Phillips JT, et al. Presented at AAN; March 16-23, 2013; San Diego, CA. Abstract S30.003.

Ongoing Long-Term Safety and Tolerability of DMF: ENDORSE

- 5-yr extension study of DEFINE and CONFIRM
- At interim analysis, safety profile similar for those who continued DMF from parent studies, and those new to DMF
- Rate of both serious infections and hepatic AEs low (≤2%) in any tx group
- No evidence of increased risk of renal dysfunction
- Two patients developed renal cell carcinomas
  - Cause effect relationship with DMF is not known

Phillips JT, et al. Presented at AAN 2013; March 16–23, 2013; San Diego, CA. Abstract P01.162.

Slide 23

6 So the most inbteresting observation i this study was the identification of two patients who developed renal cell carcinomas in the extension study. This may be unrelated to treatment and due to chance but needs to be mentioned.
Bruce Cree, 4/12/2013

Additional DMF Data

- In the integrated analysis, compared with placebo DMF significantly:
  - Reduced relapses requiring IV steroids and hospitalizations
  - Led to improvements in physical and mental aspects of health and functioning, general well-being, and overall health status (QoL)
- No evidence of increased risk of fetal abnormalities or adverse pregnancy outcomes associated with gestational exposure during first trimester, although data limited
- Pregnancy class C

Giovannoni G, et al. Presented at AAN 2013; March 16–23, 2013; San Diego, CA. Abstract P07.121.
Kita M, et al. Presented at AAN 2013; March 16–23, 2013; San Diego, CA. Abstract P07.092.
Gold R, et al. Presented at AAN 2013; March 16–23, 2013; San Diego, CA. Abstract P02.129.

DMF Summary

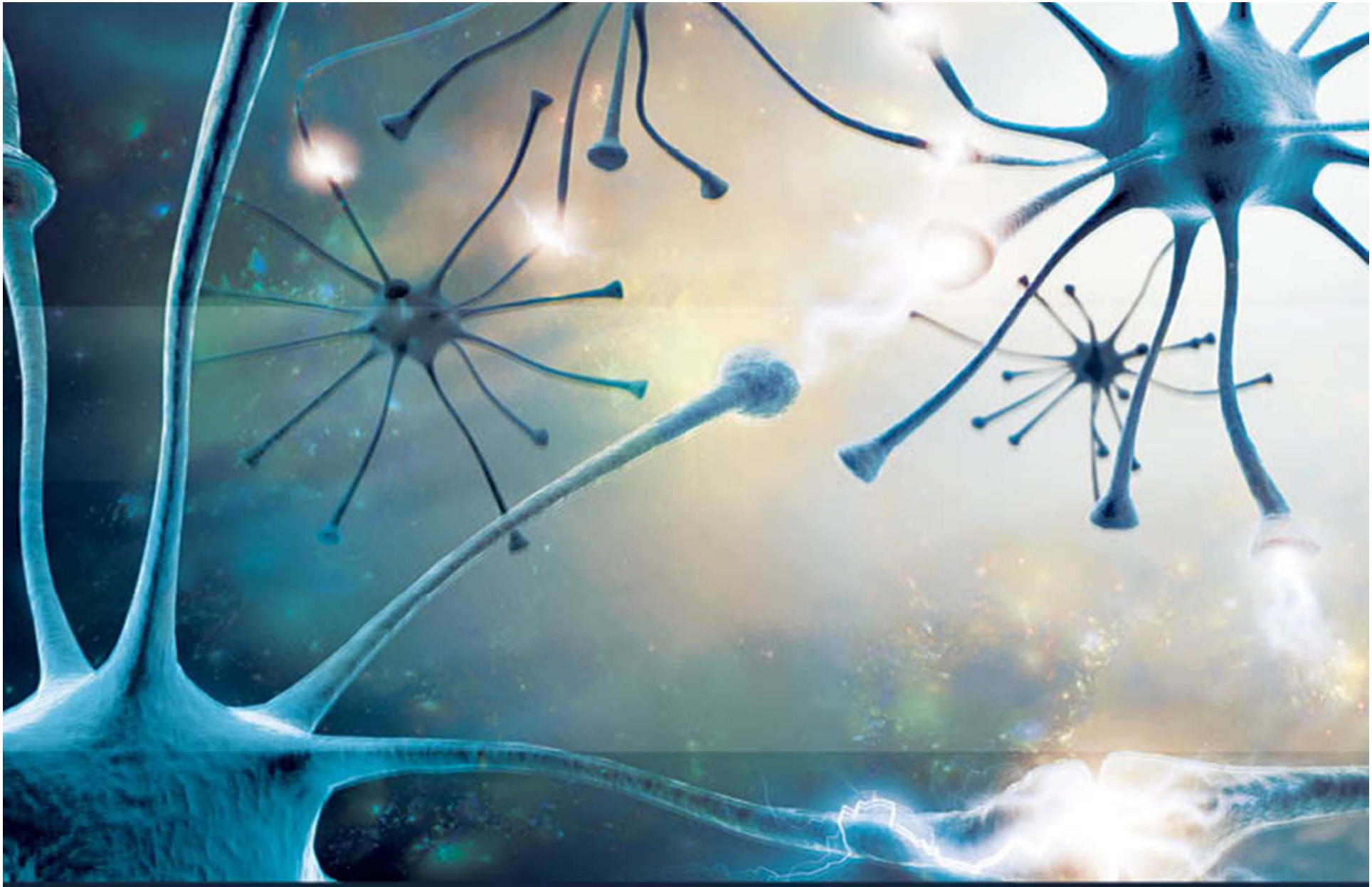
- Compared to placebo DMF showed significant reductions with respect to the probability of experiencing a relapse, the annualized relapse rate, disability progression and accumulation of gadolinium enhancing or new T2 lesions on MRI
- There did not appear to be substantial difference between the BID and TID treatments and the 240 mg BID formulation is now commercially available

Who Should Use DMF?

- Newly diagnosed untreated relapsing MS patients
- Relapsing treated MS patients who wish to switch to a twice daily oral therapy
- Relapsing treated MS patients who have a sub-optimal response to treatment
- Relapsing MS patients who may be candidates for treatment with natalizumab who test positive for the JC virus
- Relapsing MS patients with concomitant medical concerns in whom the risk: benefit profile for fingolimod is of concern

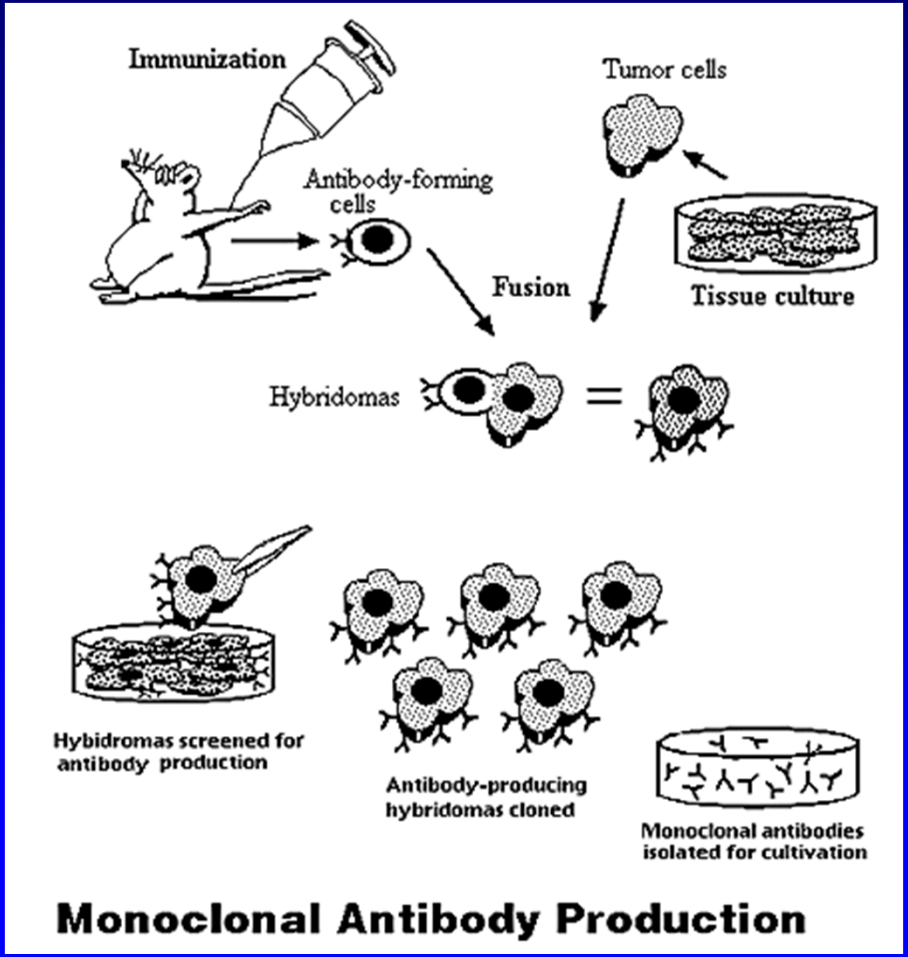
Who should not take DMF?

- DMF has not been studied in patients with progressive MS or in patients who require ambulatory assistance to walk
- Long term safety of DMF in MS is not established
- Of note, in psoriasis, 3 patients treated with Fumaderm developed PML
  - 2 were treated with Raptiva (efalizumab), a drug known to cause PML
  - 1 patient had persistent low lymphocyte counts
- Baseline and annual CBC is recommended

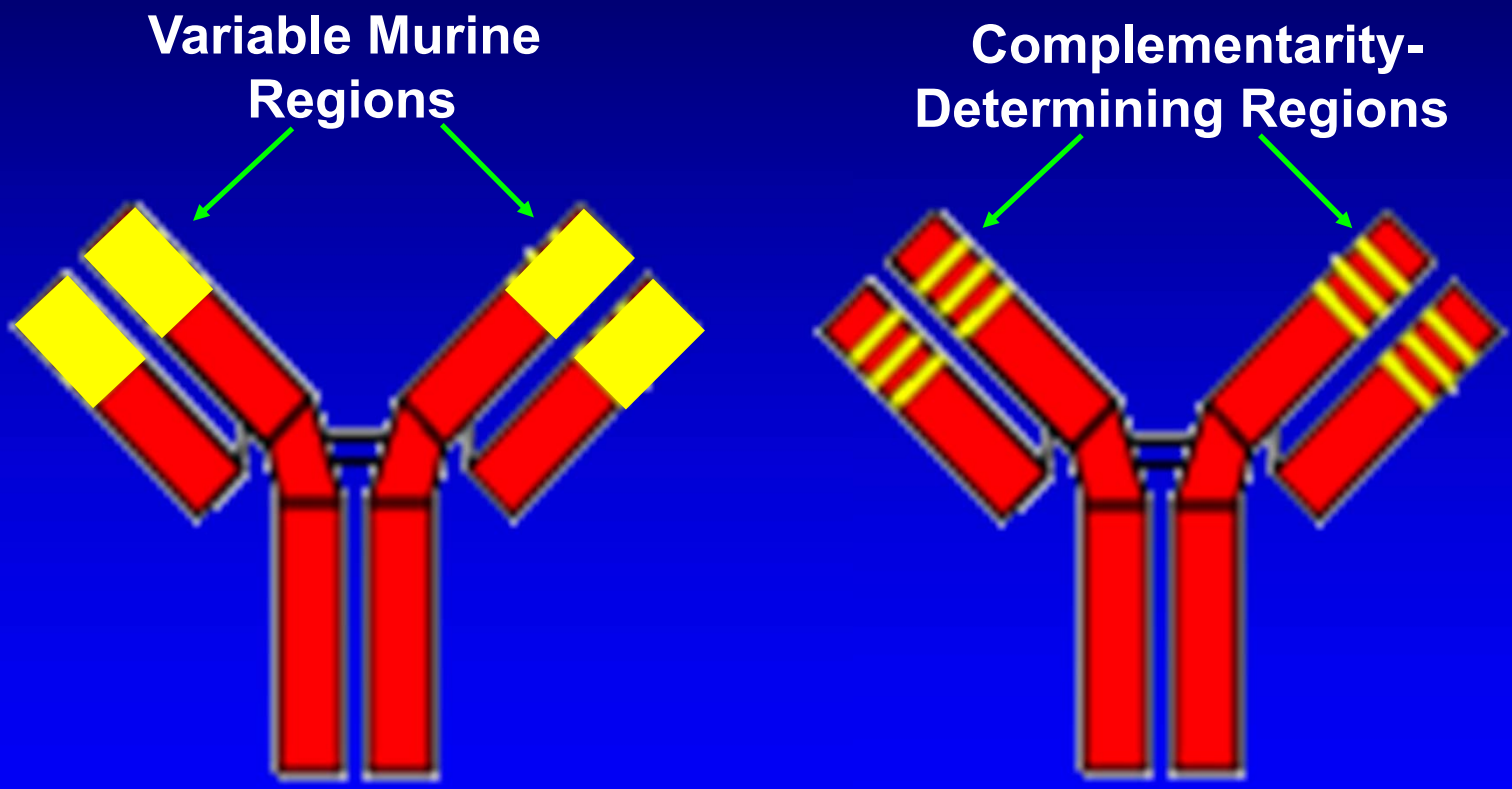


NATALIZUMAB

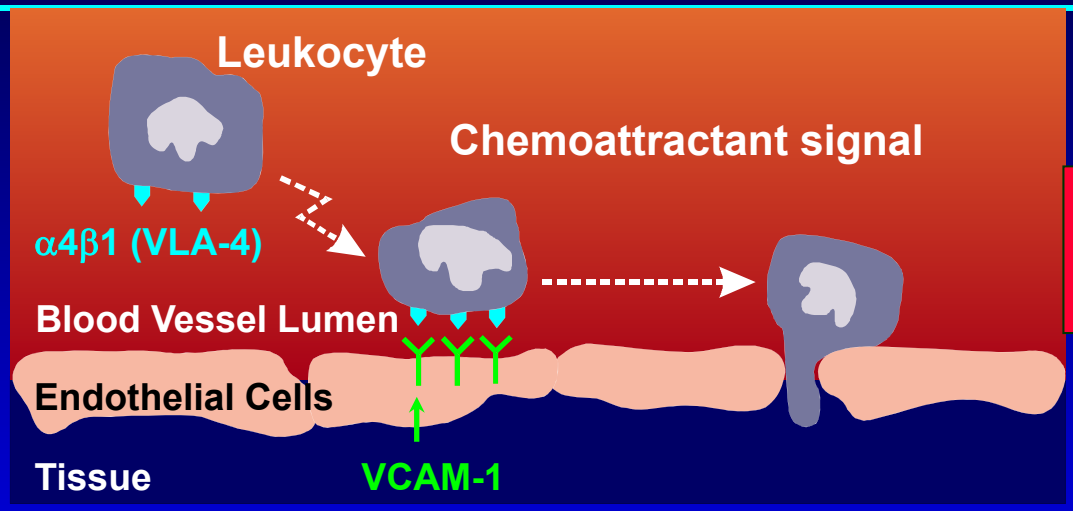
Monoclonal Antibody Production



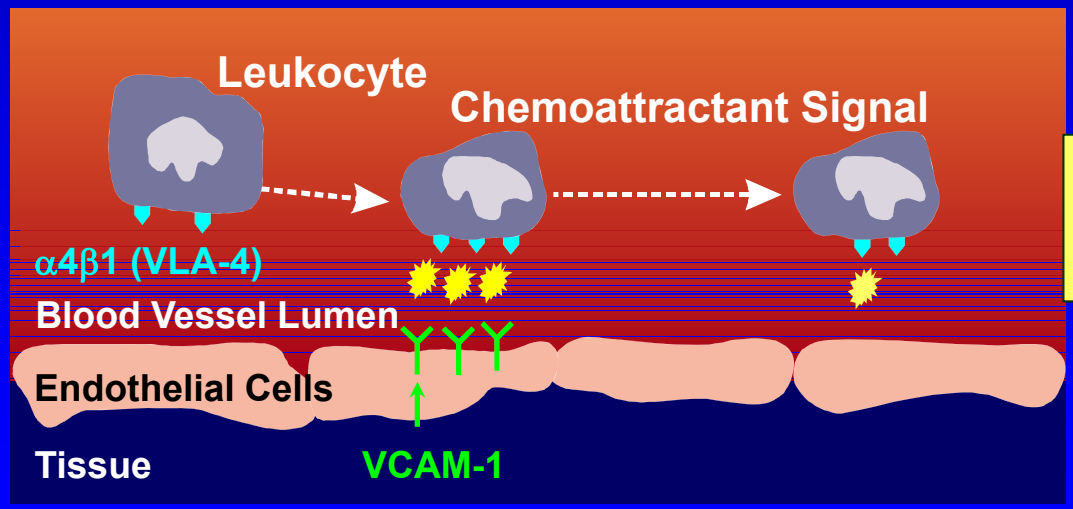
Chimeric and Humanized Antibodies



SAM Inhibition: Implications for Multiple Sclerosis Therapy



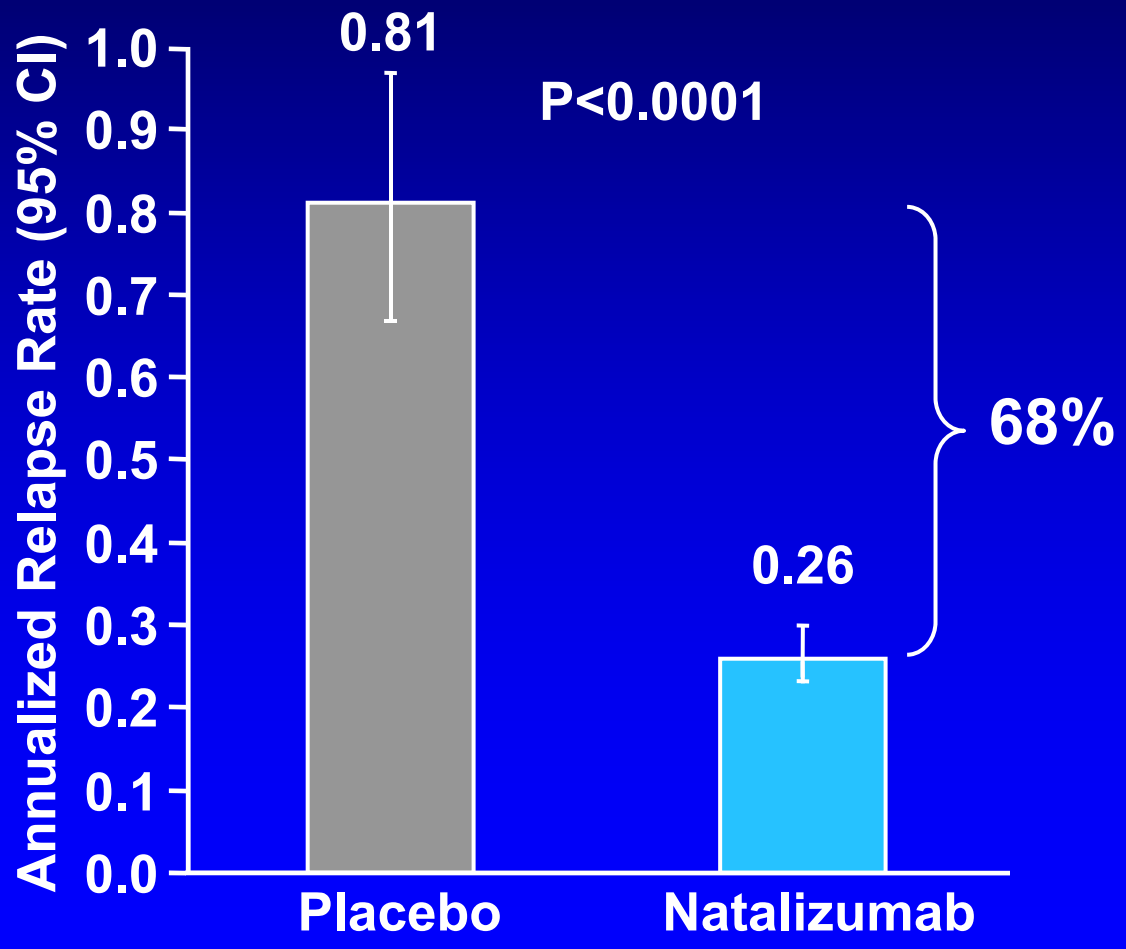
Leukocyte Infiltration and Brain Inflammation



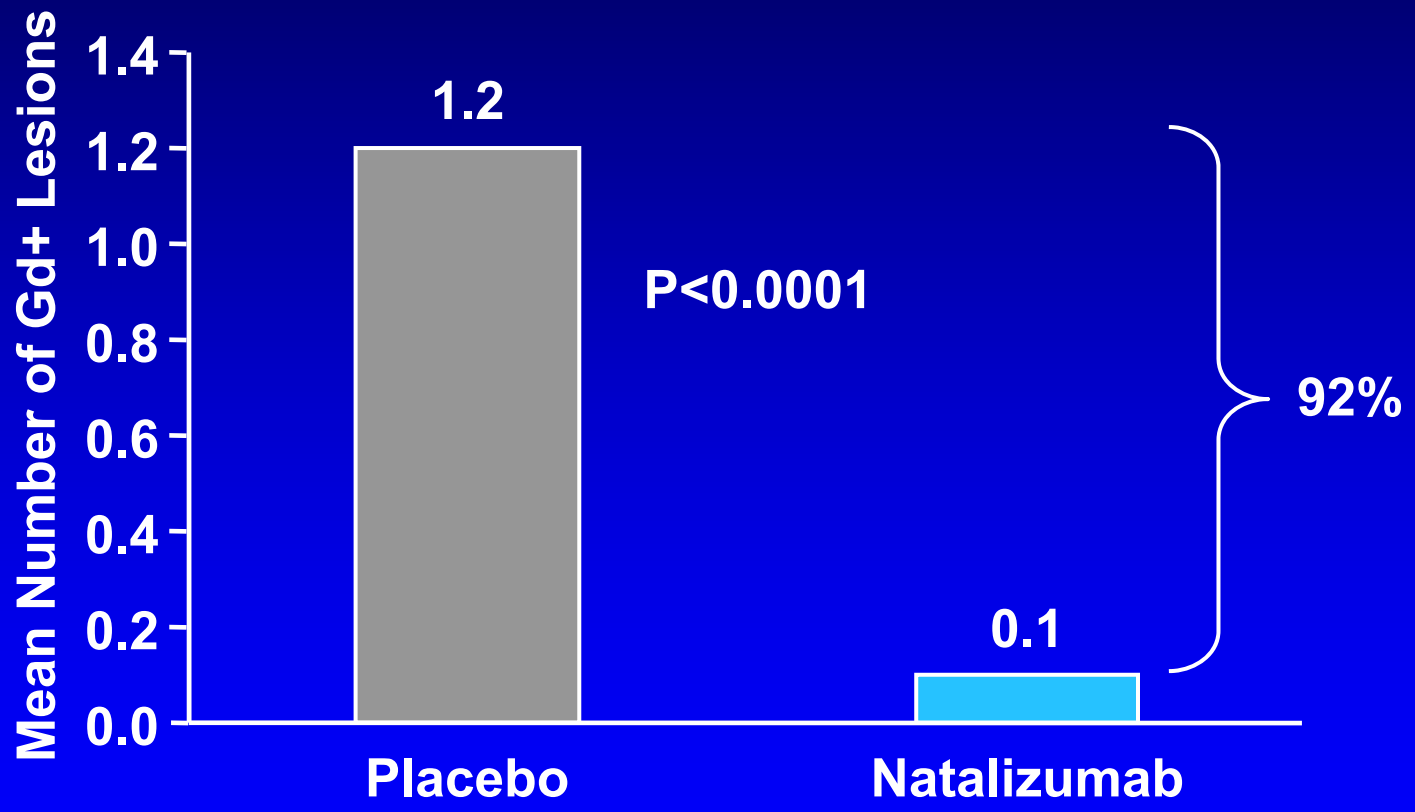
Reduced Leukocyte Infiltration and Brain Inflammation

Annualized Relapse Rate

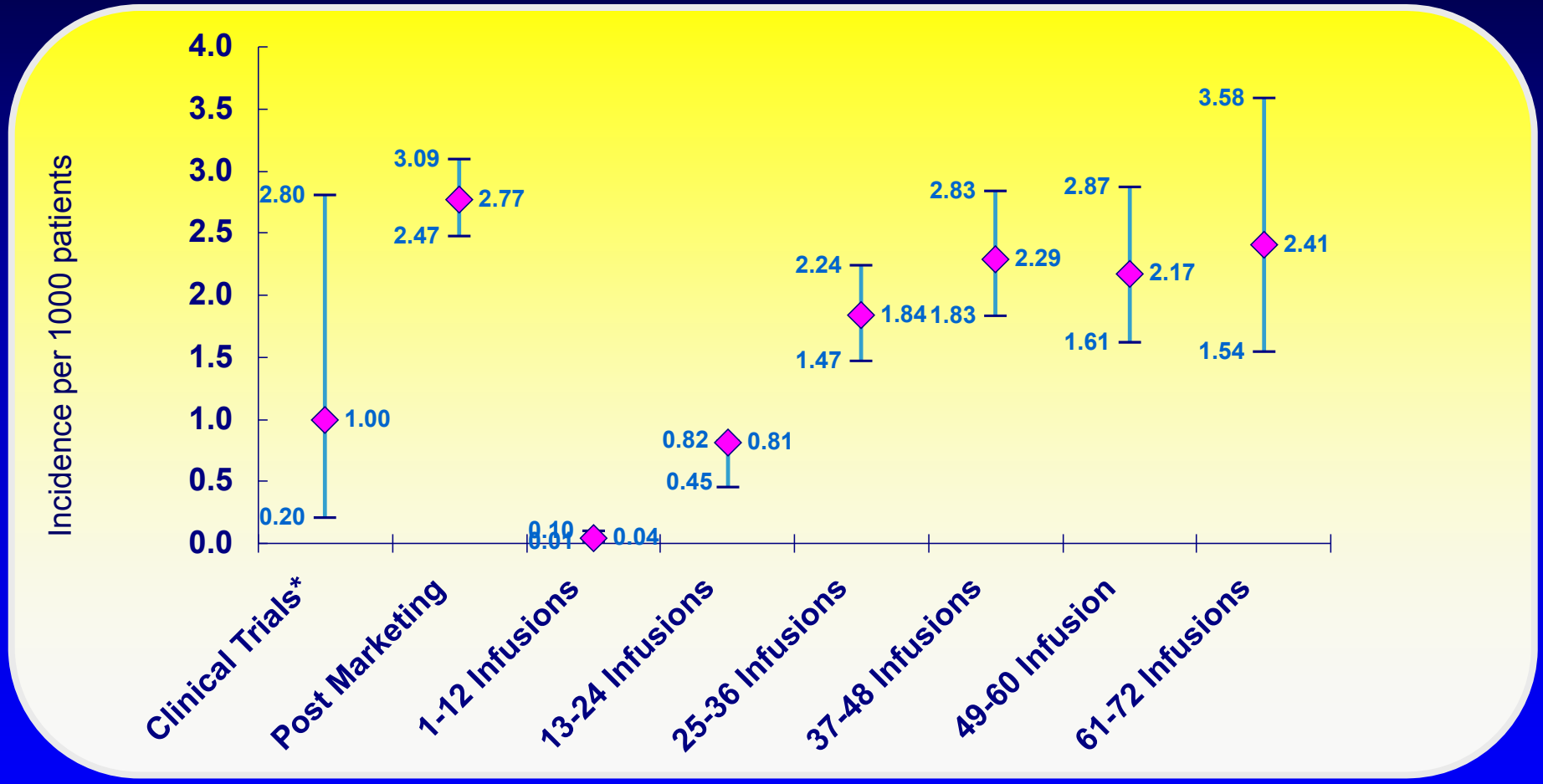
Pre-specified Primary Endpoint



Gadolinium-Enhancing (Gd+) Lesions



Natalizumab PML Incidence Estimates by Treatment Epoch



*Yousry TA, et al. *N Engl J Med.* 2006;354:924-933.

Observed clinical trial rate in patients who received a mean of 17.9 monthly doses of natalizumab. The post-marketing rate is calculated as the number of PML cases since reintroduction in patients that have had at least 1 dose of natalizumab.

Incidence estimates by treatment epoch are calculated based on TYSABRI exposure through May 31, 2011 and 133 confirmed cases as of June 1, 2011. The incidence for each epoch is calculated as the number of PML cases divided by the number of patients exposed to TYSABRI (e.g. for 25 to 36 infusions all PML cases diagnosed during this period is divided by the total number of patients ever exposed to at least 25 infusions and therefore having risk of developing PML during this time). Biogen Idec, data on file.

Current Stratification of Natalizumab-Associated PML Risk

Anti-JCV Antibody Status

Negative

0.07/1000
95% CI 0 – 0.38

Positive

Prior IS Use

Natalizumab Exposure	NO	YES
1–24 mos	0.6/1,000 patients (95% CI 0.4 – 0.9)	1.8/1,000 patients (95% CI 1.1 – 2.8)
> 24 mos	5.2/1,000 patients 95% CI 4.3 – 6.2)	10.6/1,000 patients (95% CI 8.1 – 13.8)

Low body mass has recently been identified as an additional potential risk factor for the development of PML

343 cases of PML have been documented in patients treated with natalizumab as of April 1, 2013. Available at: http://chefarztfrau.de/?page_id=716

PML = progressive multifocal encephalopathy; JCV = John Cunningham virus; IS = immunosuppressant

Dong-Si T, et al. Presented at AAN; March 16–23, 2013; San Diego, CA. Abstract P04.271.
Foley J. Presented at AAN; March 16–23, 2013; San Diego, CA. Abstract S30.002.

Slide 35

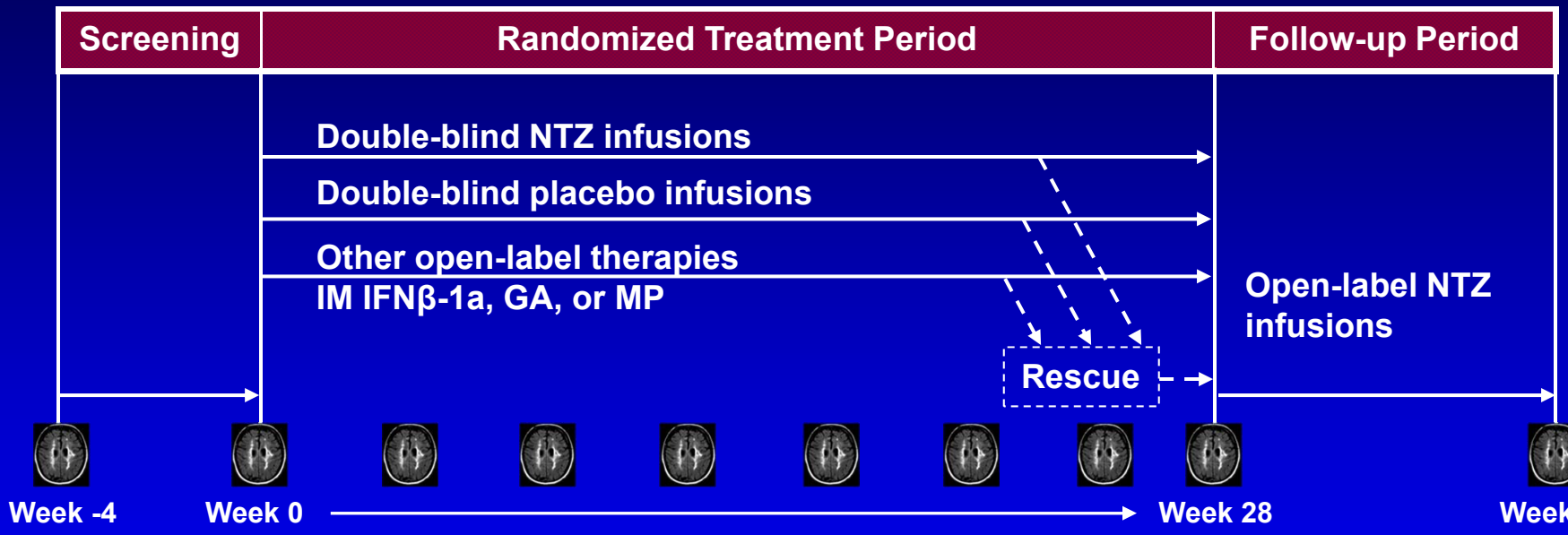
7 The abstract in the notes is for a different study.
Bruce Cree, 4/12/2013

RESTORE Study: Natalizumab

- Background:
  - NTZ efficacy in RRMS based on SENTINEL and AFFIRM phase III trials
  - Associated with PML (opportunistic infection of CNS) caused by JC virus
    - Risk increases with anti-JCV antibody (+) status, prior immunosuppressant use, and duration of NTZ treatment
- RESTORE Overview:
  - Randomized study evaluating effect of 24-week NTZ treatment interruption on immune parameters and disease activity
  - Patients treated with NTZ for ≥ 12 months (N = 175) randomized (1:1:2) to:
    - NTZ
    - Placebo
    - Other immunomodulatory therapy (IM IFNβ-1a, GA, or MP; investigator determined)

Fox R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 150]

RESTORE: Study Design



- If patient developed evidence of MS disease activity, investigators could administer high-dose corticosteroids and/or restart NTZ as rescue treatment
  - Clinical disease activity: defined by change in overall EDSS or functional system subscale scores
  - MRI disease activity: defined as 1 new Gd+ lesion of > 0.8 cm or 2 or more new GD+ lesions of any size
- Study not designed or powered to determine effect on development of PML

Fox R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 150]

Patients with Clinical Relapses or Meeting MRI Rescue Criteria After Randomization*

Patients, n/n	Clinical Relapses[a]	MRIs Meeting Rescue Criteria[b]
Total	25/167 (15%)	48/167 (29%)
Natalizumab	2/45 (4%)	0/45 (0%)
Placebo	7/41 (17%)	18/41 (44%)
Other therapies		
IM IFNβ-1a	4/14 (29%)	1/14 (7%)
GA	4/15 (27%)	8/15 (53%)
MP	8/52 (15%)	21/52 (40%)

*Interim results

[a]11 relapses (44%) occurred by 16 weeks, and 14 (56%) occurred between weeks 16-28

[b]36 of 48 patients (75%) who met rescue criteria did so at week 16 or 20

Fox R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 150]

RESTORE: Summary

- NTZ interruption resulted in a high rate of recurrence of MRI and clinical MS disease activity
  (starting clinically at ~ week 8 , radiographically ~ week 12)
- IM IFNβ-1a appeared to suppress MRI activity more than other open-label treatments, although this group had lower disease activity prior to start of NTZ
- However, study was not designed or powered to compare efficacy of alternative immunomodulatory therapies
- Monthly MP (1g IV, started 1 month after last NTZ dose) did not appear to be effective in disease suppression

Fox R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 150]

Who is a good candidate for Natalizumab?

- Relapsing MS patients who have had sub-optimal responses to other disease modifying therapies and are JCV seronegative
- Relapsing MS patients who are unable to tolerated other disease modifying therapies and are JCV seronegative
- Relapsing MS patients with highly active disease who are JCV seropositive in whom the potential benefit of treatment with natalizumab outweighs the risk of PML
- The effects of natalizumab in patients with secondary progressive MS are currently under study

Who is not a good candidate for treatment with natalizumab?

- Patients who have had prior treatment with immune suppressants, e.g. azathioprine, mycophenolate mofetil, methotrexate, mitoxantrone, cyclophosphamide, etc. and who are seropositive for the JCV
- Patients who are seropositive and have been treated with natalizumab for 2 years or more are at higher risk for PML

Patient Decisions Regarding Natalizumab Therapy

- UT Southwestern Study
  - 136/469 pts treated with natalizumab discontinued tx
    - 32.4% because of concern about PML
      - Most either anti-JCV seropositive or had >24 infusions
    - 18.4%: intolerable side effects (infusion-related or infections)
    - 9.6%: lack of perceived benefit
    - 11.8%: either worsening deficits or transitioned to secondary progression
- French Study
  - N = 292 natalizumab-treated MS pts
    - Anti-JCV serum positivity: 150 patients (51%)
    - 112 (74.4 %) of these decided to continue natalizumab, including 23 pts (15%) with 2 known PML risk factors

Beh S, et al. Presented at AAN 2013; March 16–23, 2013; San Diego, CA. Abstract P01.157.
Ongagna J-C, et al. Presented at AAN 2013; March 16–23, 2013; San Diego, CA. Abstract P01.184.

Switching From Natalizumab to Fingolimod: ENIGM Study

- 36 tertiary centers in France treating 4500 natalizumab (NTZ)-treated patients
- 177 patients switched to fingolimod (FTY) after mean 36 NTZ infusions
  - 72% seropositive for JCV
  - 50% classified in highest PML risk category
- Duration of and management during a washout period (WP) evaluated

Cohen M, et al. Presented at AAN 2013; March 16–23, 2013; San Diego, CA. Abstract S41.002.

Switching From Natalizumab to Fingolimod: ENIGM Study (cont'd)

- Results
- In the WP:
  - 55% pts did not receive any treatment
  - 45% received sequential MP infusions
  - Relapse rate in WP: 65%
    - Only predictive factor: WP duration (P = 0.002)
- At initiation of fingolimod, EDSS had slightly worsened (P = 0.004)
- 33% of patients who received FTY for >6 months had ≥1 relapse
- 3.3% stopped FTY for efficacy or tolerance issues

MP = methylprednisolone

Cohen M, et al. Presented at AAN 2013; March 16–23, 2013; San Diego, CA. Abstract S41.002.

Additional Evaluations of Switching from Natalizumab to Fingolimod

- Fingolimod reported as most effective natalizumab exit strategy (N = 75) in single MS center (LaGanke)
- FIRST Trial
- Patients received NTZ before baseline for:
  - >6 months (n = 135)
  - 3 to 6 months prior to baseline (n = 119)
- Patients discontinuing NTZ had higher relapse risk that was improved with fingolimod
  - Relapses in first month of fingolimod tx higher in pts with shorter previous NTZ exposure

LaGanke CC. Presented at AAN 2013; March 16–23, 2013; San Diego, CA. Abstract P01.206.
Comi G, et al. Presented at AAN 2013; March 16–23, 2013; San Diego, CA. Abstract P07.103.

Slide 45

2 I thought the most important study presented on fingolimod at AAN was Dr. Cohen's presentation on brain volume loss. I would include a slide from his presentation in this prgram. BAsically waht was found was that across three trials there was a significant and consistent impact of fingolimod on brain volume loss. I have attached slides from his presentation for your review.

Bruce Cree, 4/12/2013