How to Read Scientific Papers

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How to read Scientific papers

(1) **Reporting:** Is the information provided in the paper sufficient to allow a reader to make an unbiased assessment of the findings of the study.
(2) **External validity:** to which extent can the findings from the study be generalised to the population from which the study subjects were derived.
(3) **Bias:** Are there biases in the measurement of the intervention and the
outcome.
(4) **Confounding:** Bias in the selection of study subjects.
(5) **Power :** Could the (negative) findings from the study be due to chance.

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(1) **Reporting:** Is the information provided in the paper sufficient to allow a reader to make an unbiased assessment of the findings of the study:

1. The hypothesis/aim/objective of the study
2. The main outcomes to be measured
3. Characteristics of the patients included in the study
4. The interventions of interest
5. The distributions of principal confounders in each group of subjects to be compared
6. The main findings of the study

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(1) **Reporting:** Is the information provided in the paper sufficient to allow a reader to make an unbiased assessment of the findings of the study.

7. Estimates of the random variability in the data for the main outcomes?
8. All important adverse events that may be a consequence of the intervention
9. The characteristics of patients lost to follow-up
10. Actual probability values (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001

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(2) **External validity:** to which extent can the findings from the study be generalised to the population from which the study subjects were derived.

1. Were the subjects asked to participate in the study and those prepared to participate representative of the entire population from which they were recruited?
2. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?

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(3) Internal validity / Bias: Are there biases in the measurement of the intervention and the outcome.

1. Blinding of subjects
2. Blinding of assessments
3. Analyses prospectively planned? “data dredging”?
4 Do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls ?
5. Statistical tests used to assess the main outcomes appropriate? (non parametric tests, data distribution)
6. Compliance with the intervention/s reliable?
7. main outcome measures used accurate (valid and reliable)?

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(4) **Internal validity / Confounding:** Bias in the selection of study subjects.

1. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?
2. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?
3. Were study subjects randomised to intervention groups?
4. Was the randomised intervention assignment concealed from both patients and staff until recruitment was complete and irrevocable?
5. Adequate adjustment for confounding in the analyses (intention to treat or treated, losses to follow-up)

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(5) Power : Could the (negative) findings from the study be due to chance.

Propability to detect a clinically important effect (beta > 80%)

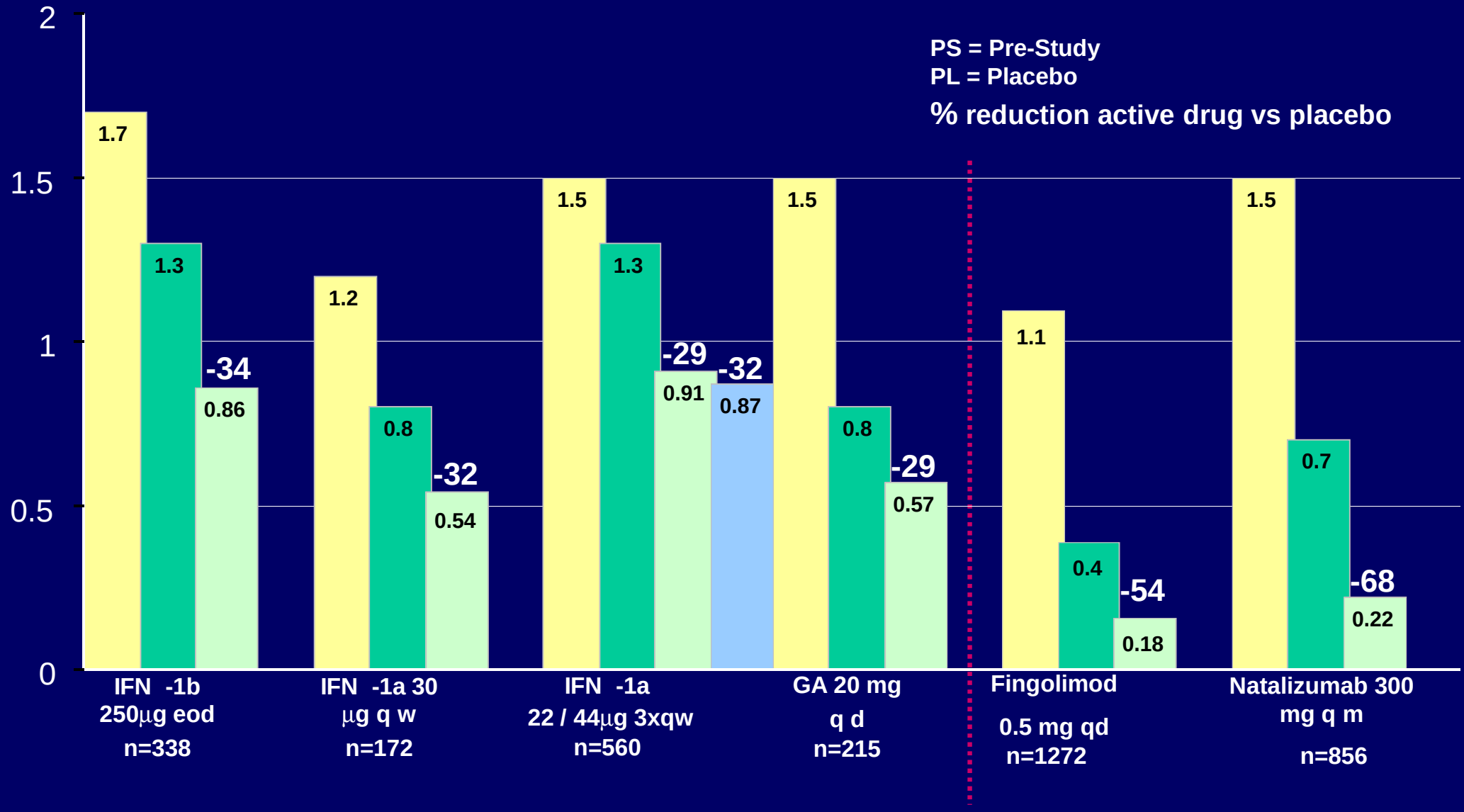
vs

probability for the difference being due to chance (alpha < 5%)

The necessity of internal, randomized controls

- **We need trials with internal randomized controls *(placebo or active)* - adjustment for baseline characterisitics may not be sufficient! Especially as long as we do not have better selection criteria / prognostic factors !**
  - ***Similar inclusion criteria have resulted in different patient populations:***
    - **Experience in SPMS trials**
    - **Relapse rates at baseline and in study**
    - **Disease progression**
    - **MRI …**

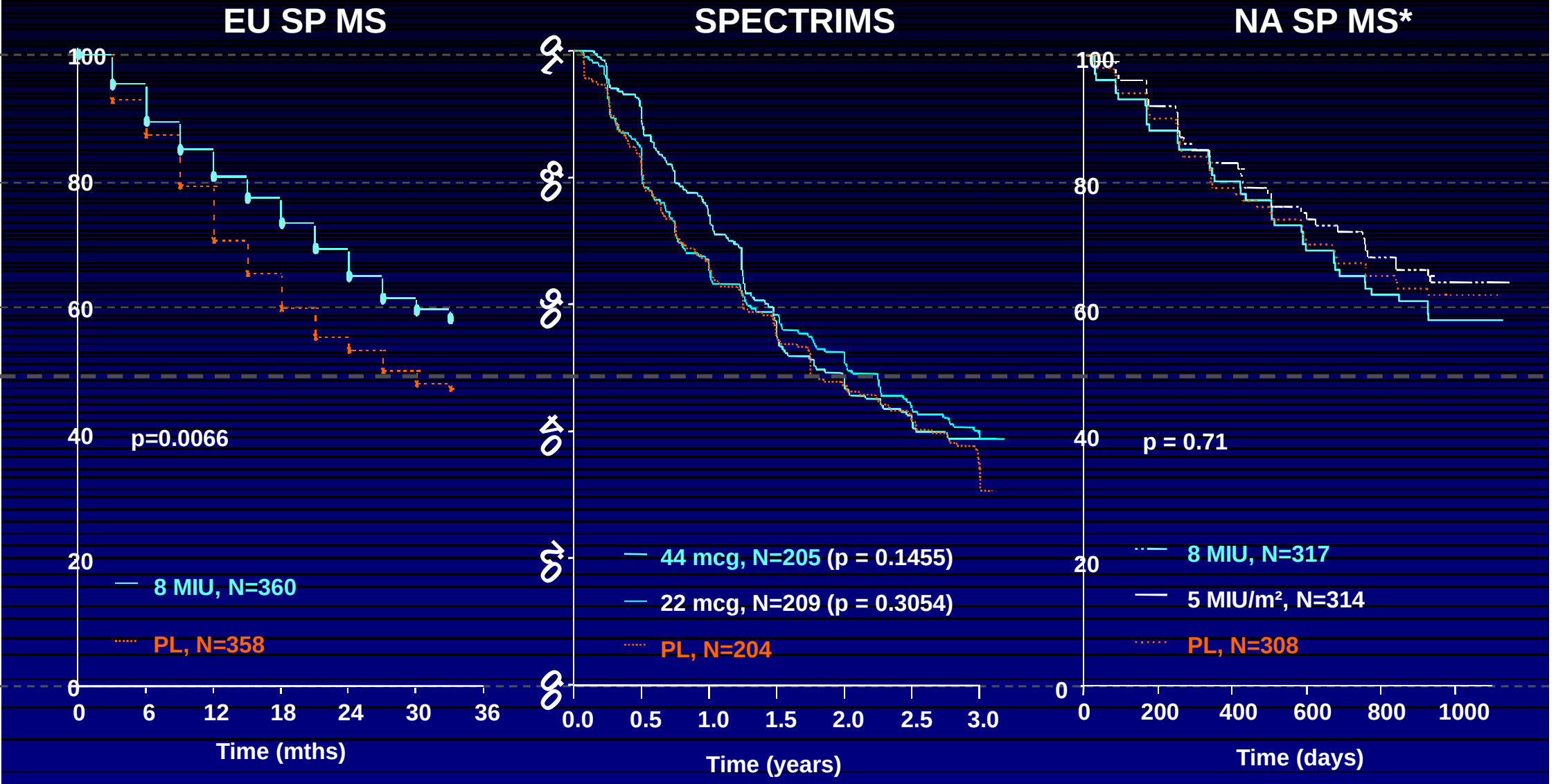
Annualized Relapse Rates in Pivotal Studies
(all Patients with 24 M on Study)



Placebo effects on relapse rates in randomized MS trials (increasing…) :

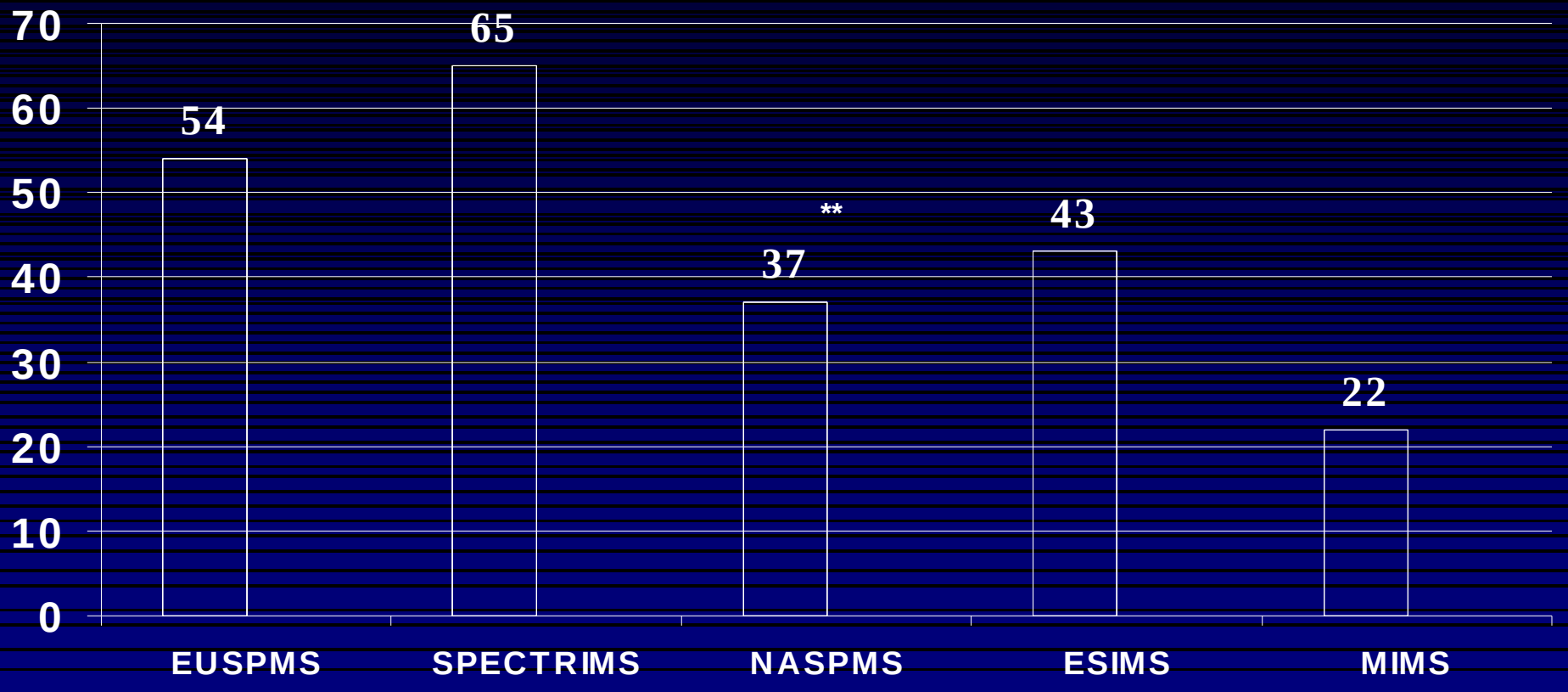
- 25 to >50% …
- genuine placebo effect?
- more stringent definition…
- dependent on blinding efficiency…
- regression to the mean?
- comprehensive care?

Comparison of 3 SPMS-Studies:
Time to Confirmed Progression (6 mths)



*** confirmed at 3 and 6 mths; Examinations during relapses included*

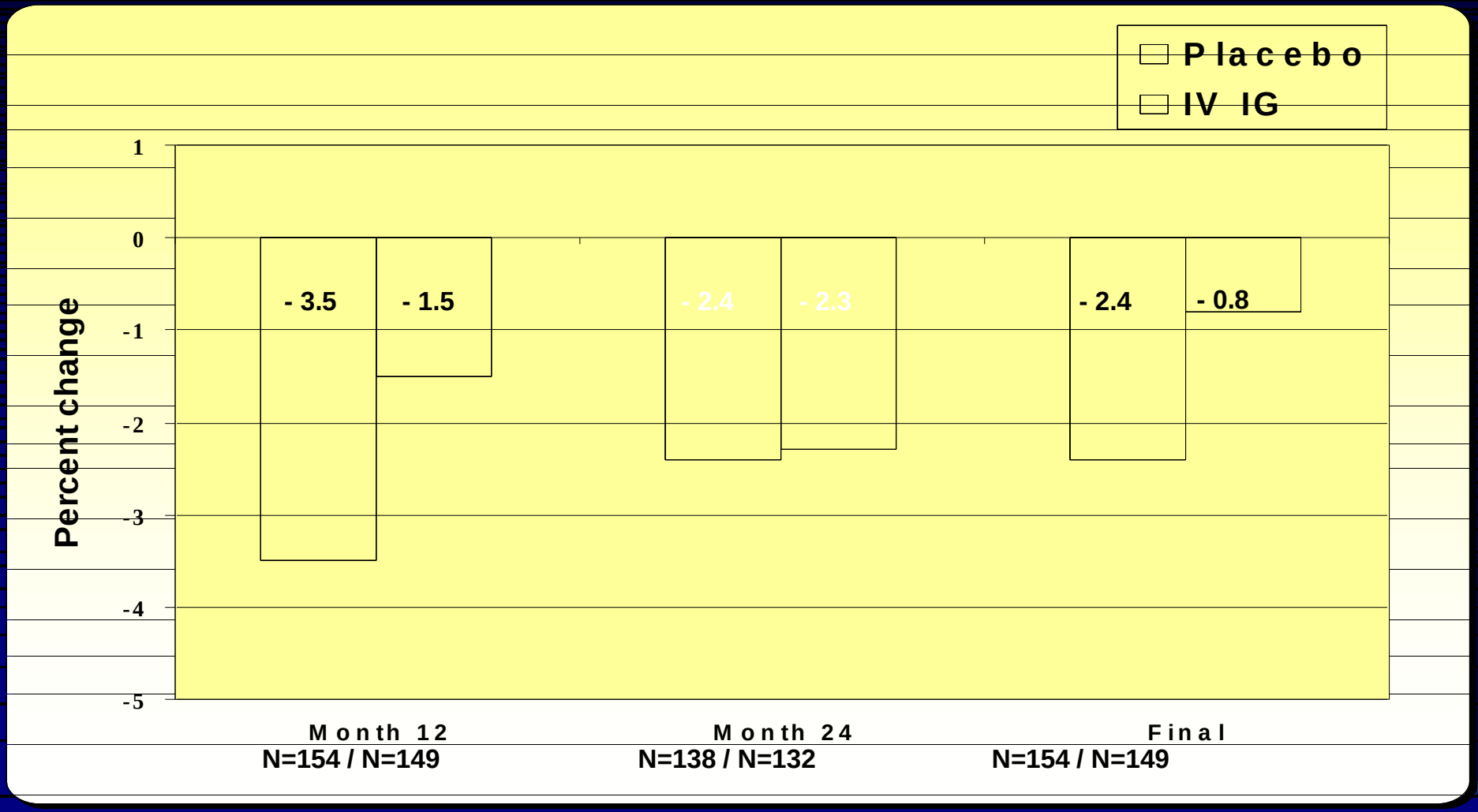
% confirmed* Progression in SP-MS Studies (Placebo)



* confirmed after 3 Mths
** confirmed after 6 Mths

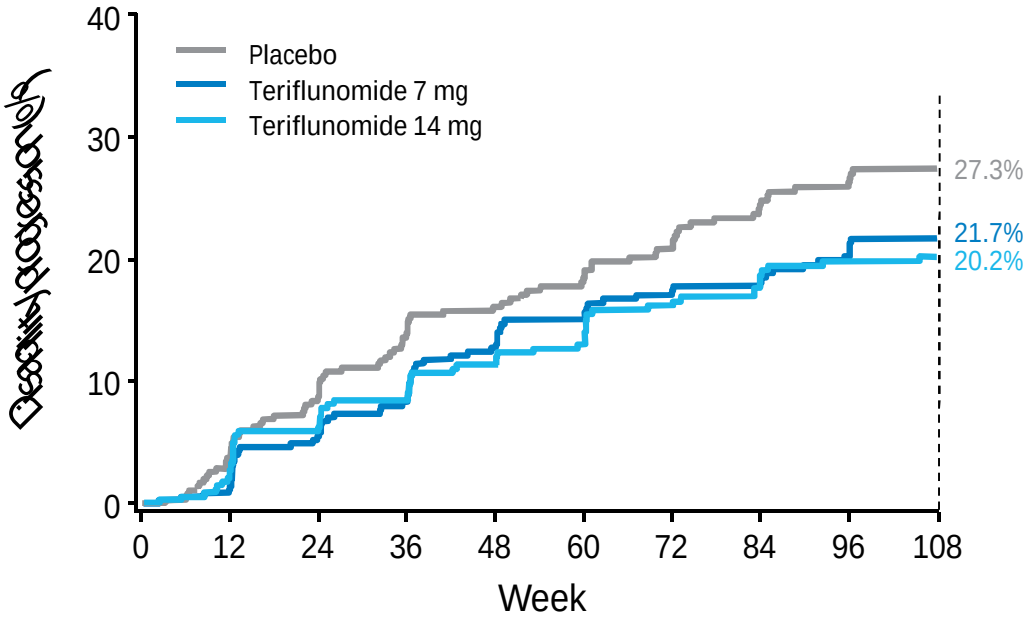
ESIMS(Fazekas et al)

Lesion volume - median percent change from baseline

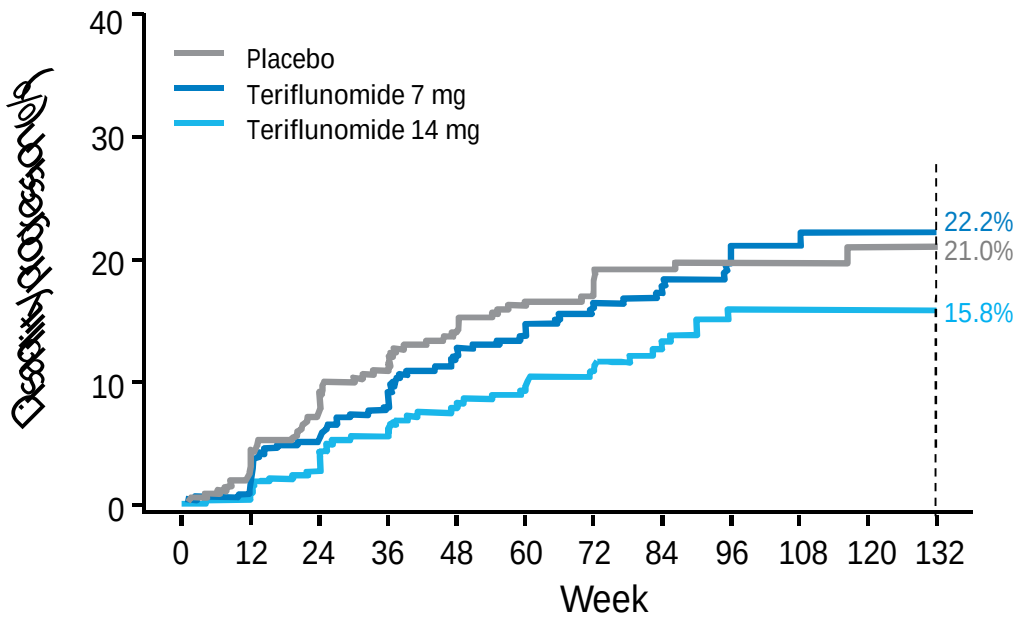


Teriflunomide:
EDSS progression (12-Week confirmed) in 2 Phase III studies

TEMSO[1]



TOWER[2]



	TEMSO	TOWER
7 mg *vs* placebo	HR 0.763 p=0.0835	HR 0.955 p=0.7620
14 mg vs placebo	HR 0.702 p=0.0279	HR 0.685 p=0.0442

HR, hazard ratio. 1. O'Connor et al. *N Engl J Med* 2011;365:1293–303; 2. Kappos et al. *Mult Scler J* 2012; 18:9–53
Disability progression is defined as an increase from baseline of ?Ë.0 point on the EDSS, confirmed for at least 12 weeks

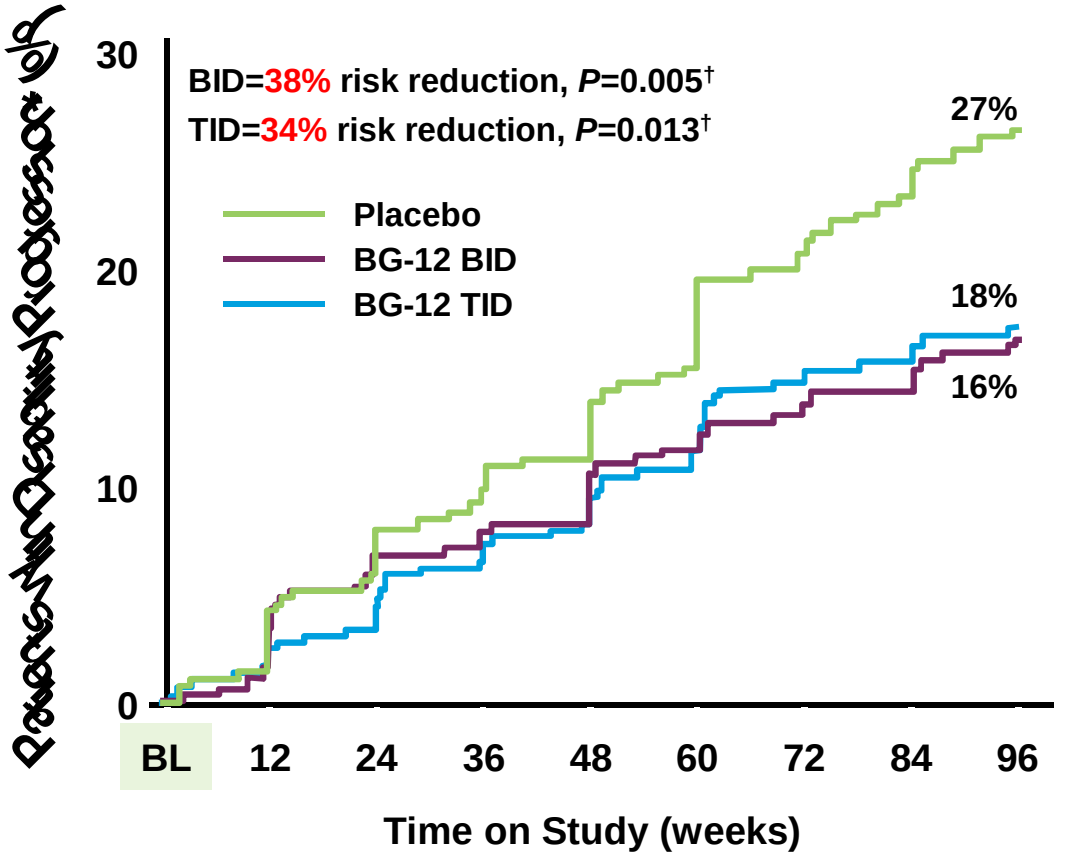
Teriflunomide: Baseline patient and disease characteristics in 2 Phase III studies

	TEMSO	TOWER
Age, years Mean (SD) Median (range)	 37.9 (8.8) 38.0 (18–55)	 37.9 (9.3) 38.0 (18–56)
Female, n (%)	785 (72.2)	831 (71.1)
Race, n (%) Caucasian/White Asian Other	 1058 (97.5) 15 (1.4) 12 (1.1)	 960 (82.1) 169 (14.5) 40 (3.4)
Time since first symptom of MS, years Mean (SD) Median (range)	 8.7 (6.9) 6.8 (0.3–35.7)	 8.0 (6.7) 6.3 (0.1–36.9)
Number of relapses within past 2 years Mean (SD) Median (range)	 2.2 (1.1) 2.0 (1–12)	 2.1 (1.2) 2.0 (1–9)
MS subtype, n (%) Relapsing–remitting Secondary progressive Progressive relapsing	 995 (91.5) 51 (4.7) 42 (3.9)	 1138 (97.5) 9 (0.8) 20 (1.7)
Baseline EDSS score Mean (SD) Median (range)	 2.68 (1.3) 2.50 (0–6.0)	 2.70 (1.4) 2.50 (0–6.5)
Previous DMT received in past 2 years, n (%)	294 (27.0)	384 (32.8)

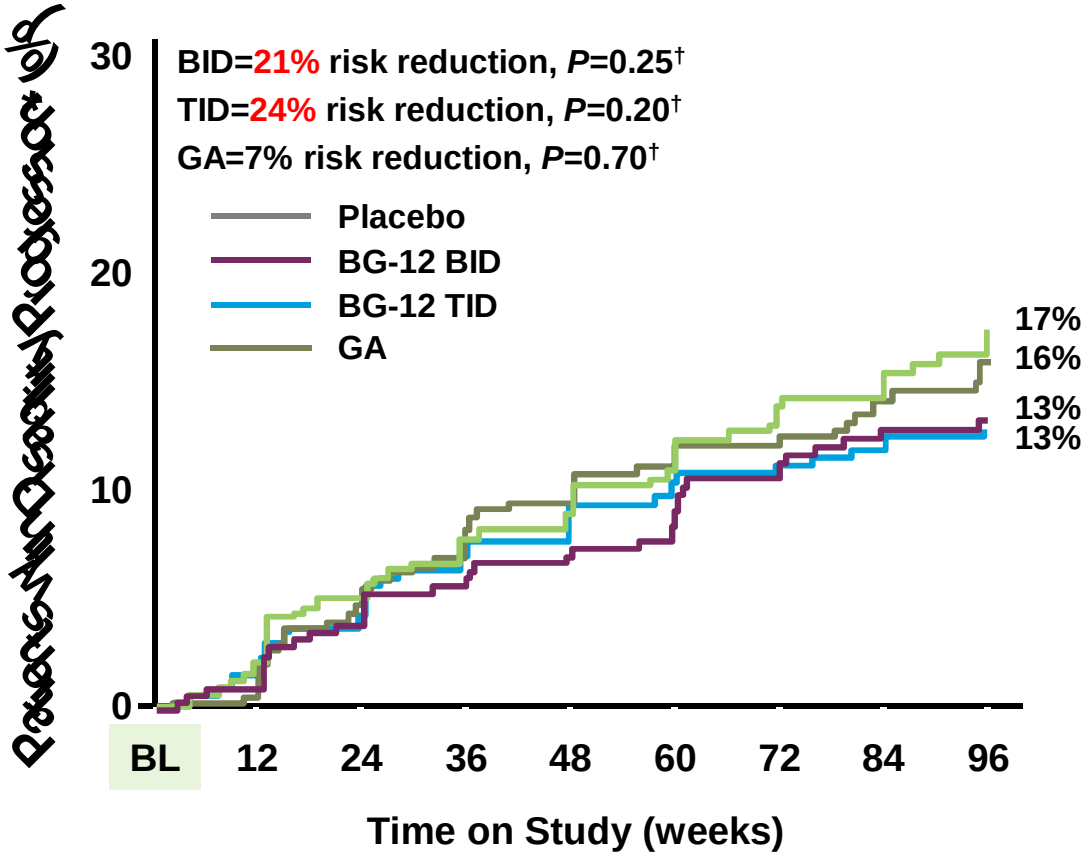
Randomised populations. DMT, disease-modifying therapy; SD, standard deviation

BG12:
EDSS Progression (12-Week Confirmed)

DEFINE*



CONFIRM**



*Estimated proportion of patients with progression and time to progression up to 96 weeks based on the Kaplan-Meier product limit method;
†based on Cox proportion hazards model, adjusted for baseline EDSS score (?2.0 vs >2.0), region, and baseline age (<40 vs ?40 years).

*Gold R et al. *N Engl J Med*. 2012;367:1098-1107; **Fox R et al. *N Engl J Med*. 2012;367:1087-1197.

BG-12 Phase III Efficacy Results

DEFINE 109MS301

% Reduction in	BG-12 (BID) vs. placebo	BG-12 (TID) vs. placebo
Annualized relapse rate	53%	48%
Number of new or newly enlarging T2-hyperintense lesions	85%	74%
Number of Gd-enhancing lesions	90%	73%
Number of new T1- hypointense lesions	72%	63%
Proportion of patients relapsed	49%	50%
12 week confirmed disability progression (EDSS)	38%	34%

CONFIRM 109MS302

BG-12 (BID) vs. placebo	BG-12 (TID) vs. placebo	GA vs. placebo
44%	51%	29%
71%	73%	54%
74%	65%	61%
57%	65%	41%
34%	45%	29%
21%*	24%*	7%*

Safety and tolerability profile consistent with that seen in published Phase II

* Top-line results only; Not a head-to-head comparison

Gold et al. *NEJM* 2012; Fox et al. *NEJM* 2012

Open label observational and long term follow up studies

- ***Important and informative but bear methodological flaws:***
  - ***usually post hoc analyses***
  - ***no internal control group***
  - ***known but also many unknown confounding variables***
  - ***selective drop out***
  - ***no blinding***

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Impact of Journal Quality

better reviewers and editors – thorough editorial process…

but:

selection bias…

http://www.consort-statement.org/

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Language:

- **Safety and Tolerabiity or Risks and Adverse Events?**
- **Impairment or disability?**

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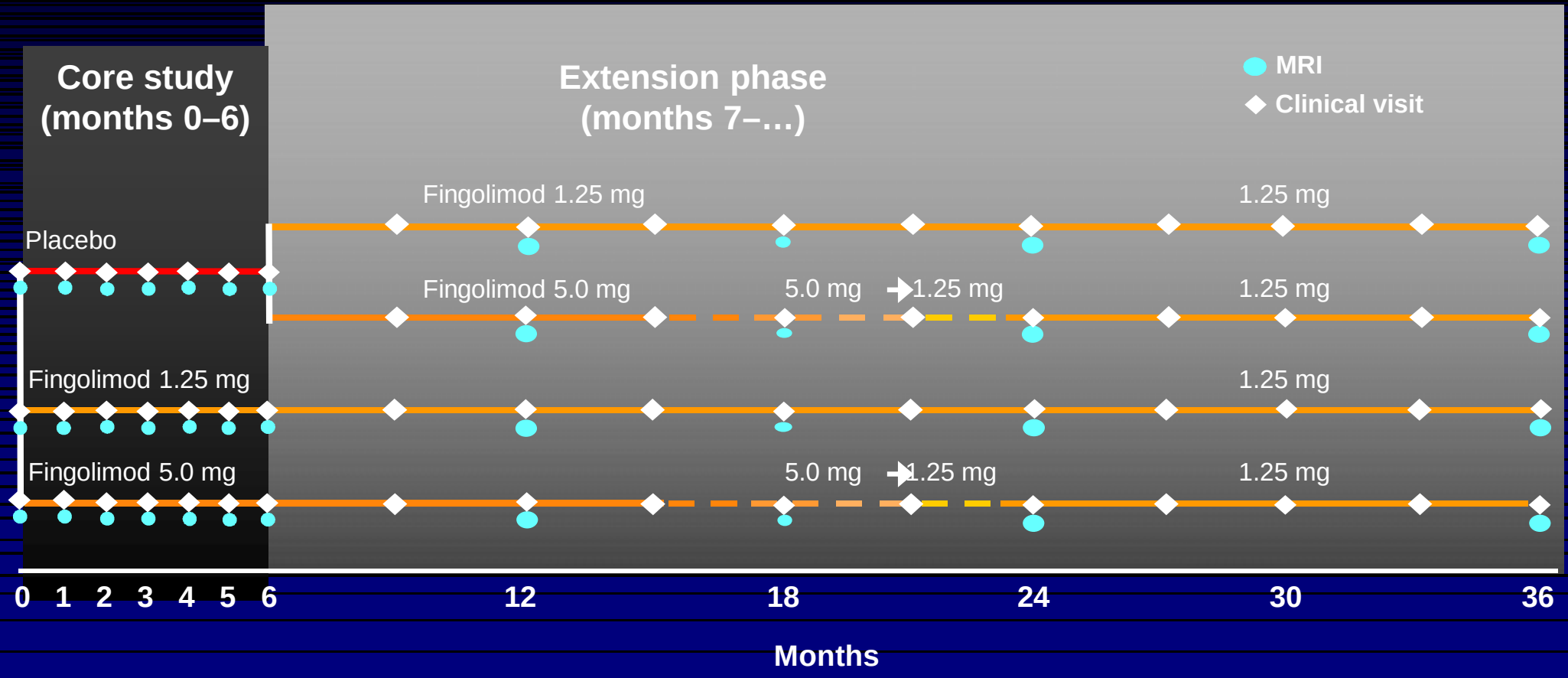
Impact of Placebo and Active Treatment Control Group Choice on the Number of Nonresponders (*Leon A.C., 2001, modified)*

- Fewer patients need to be enrolled in placebo-controlled trials, consequently, there tend to be far fewer potential non-responders in placebo-controlled trials.
- Example: New Medication B, Clinical Endpoint: Relapse Rate

	Medication B vs. A	Medication B vs. Placebo
Statistical Power	0.9	0.9
Expected Effect Size on Relapse Rate	A -30% B -50%	Placebo -10% B -50%
Enrolled per group (2-arm-design)	134	30
Expected Non-Responders	161 (60%)	42 (70%)

Typical Phase II- and Extension-Study Design for a new compound: provides first proof of concept and long term safety data



Kappos et al , NEJM, 2006

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Thank you for your attention !