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“Successful” Application of Patient Reported Outcome in Multiple Sclerosis

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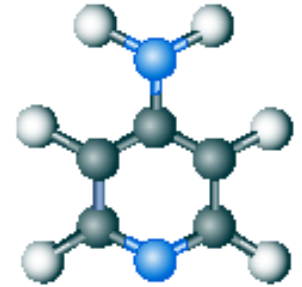


RARE DISEASE WORKSHOP SERIES
Improving the Clinical Development Process

June 15, 2011

Dalfampridine

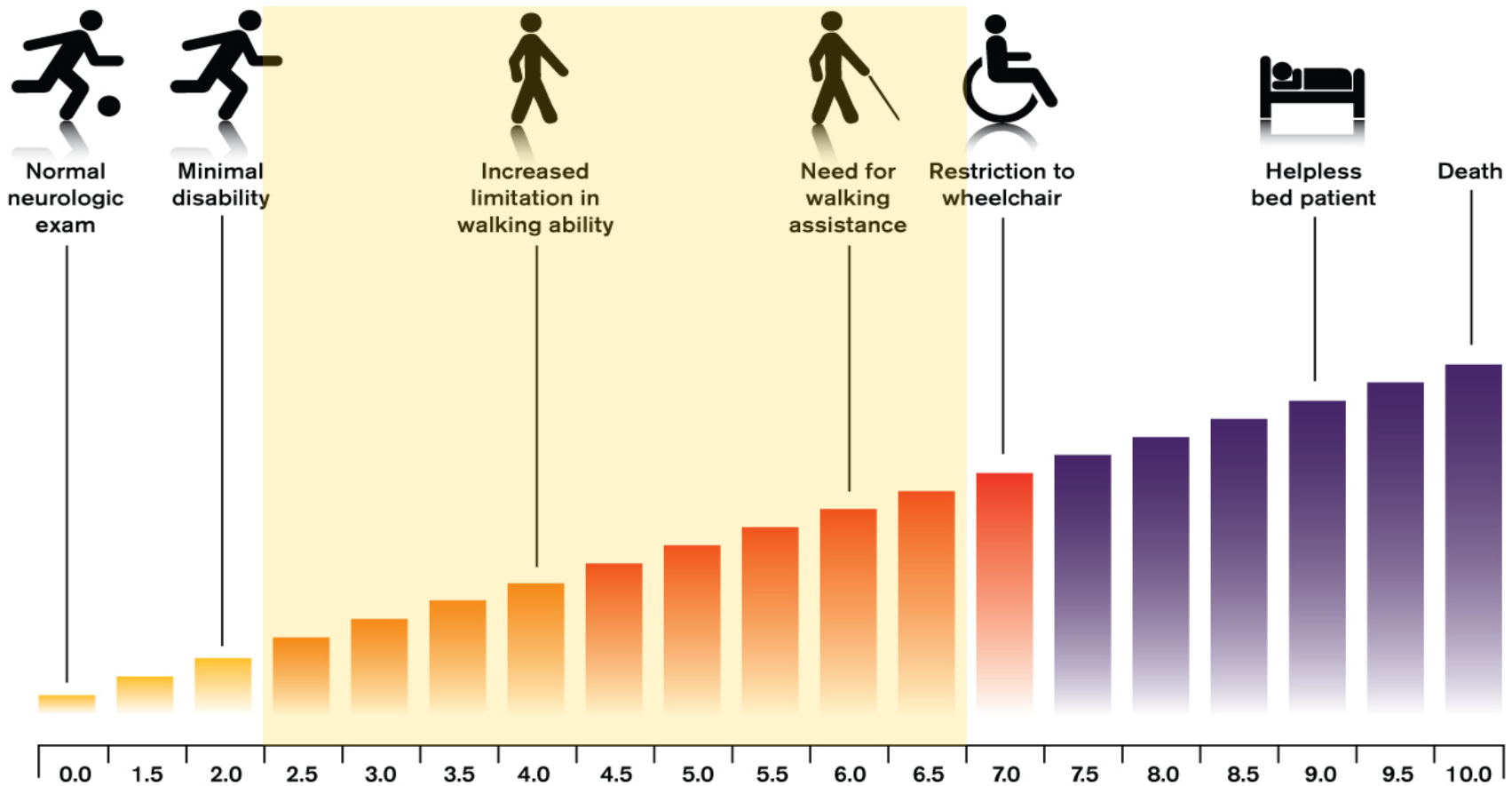
- **USAN (generic) name of 4-aminopyridine (4-AP)**
- **Blocks voltage-dependent K⁺ channels**
- **AMPYRA™ (Dalfampridine extended-release tablets) approved by FDA in Jan 2010**
 - indicated to improve walking in patients with multiple sclerosis (MS). This was demonstrated by an increase in walking speed.



The Measurement Problem

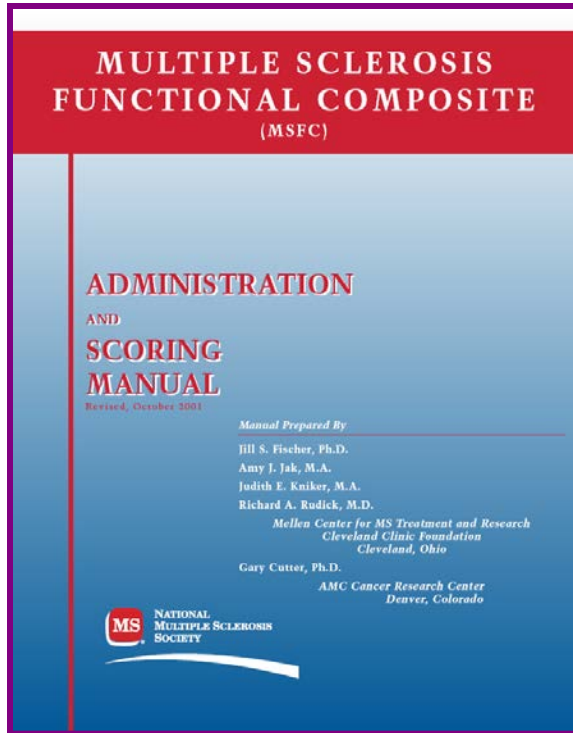
- We want to determine whether a treatment has a meaningful beneficial effect on a temporally variable symptom of disease
- We expect the treatment to change neurological function but it is only important if (downstream, with the addition of many other variables) it makes a difference in the patient's life
 - How much functional change is clinically relevant?
- Only a subset of patients is expected to be biologically susceptible to treatment benefit
 - Mean changes in the whole treatment group may (grossly) underestimate the treatment effect size in those who actually benefit

Progression of Disability in MS



Adapted from Kurtzke. *Neurology*. 1983;33:1444.

Timed 25-Foot Walk



Independent Studies Report a 20% Change in Timed 25FT Walk to be Clinically Relevant

- T25FW varied by <20% on repeated testing¹, thus >20% change is considered a real change^{1,2}
- Worsening of >20% was perceived as increased disability in daily life by MS patients, using a Patient Reported Outcome measure^{3,4}
- Improvement of >20% was reflected in subjective improvement by patients⁵

1. Schwid *Neurology* 2002; 58:1294-1296

2. Kaufman *Mult Scler* 2000; 6: 286-290.5. van Winsen *Mult Scler* 2010; 14 (5) 604-6

3. Hoogervorst *Mult Scler* 2004; 10: 55-60

4. Kragt *Mult Scler* 2006; 12: 594-598

MSWS-12 Questionnaire

Over the last 2 weeks, how much has your MS:

1. Limited your ability to walk?
2. Limited your ability to run?
3. Limited your ability to climb up and down stairs?
4. Made standing when doing things more difficult?
5. Limited your balance when standing or walking?
6. Limited how far you are able to walk?
7. Increased the effort needed for you to walk?
8. Made it necessary for you to use support when walking indoors?
9. Made it necessary for you to use support when walking outdoors?
10. Slowed down your walking?
11. Affected how smoothly you walk?
12. Made you concentrate on your walking?

Patient Reported Impact of Walking Disability: 12-item MS Walking Scale (MSWS-12)¹

- Developed from qualitative research with people with MS to define the important aspects of walking from the patient's perspective
- Defines walking function and quality through 12 different rated aspects
- Scientifically strong measurement properties supported by multiple studies independent of dalfampridine development¹⁻³
- MSWS-12 complements T25FW as it measures a different aspect of walking (disability vs. speed) from a different perspective (subjective vs. objective)
- As such, the correlations between these two endpoints are expected to be, and found to be, moderate

Phase 3 Trials Overview

Studies MS-F203 and MS-F204

- Conducted under Special Protocol Assessments (SPA)
 - Primary outcome
 - Consistent improvement in walking speed on Timed 25-foot Walk (“Timed Walk Response”)
 - Additional requirement in MS-F203
 - MSWS-12* improvement among TW Responders, to show that the response criterion is clinically relevant

*12-Item MS Walking Scale

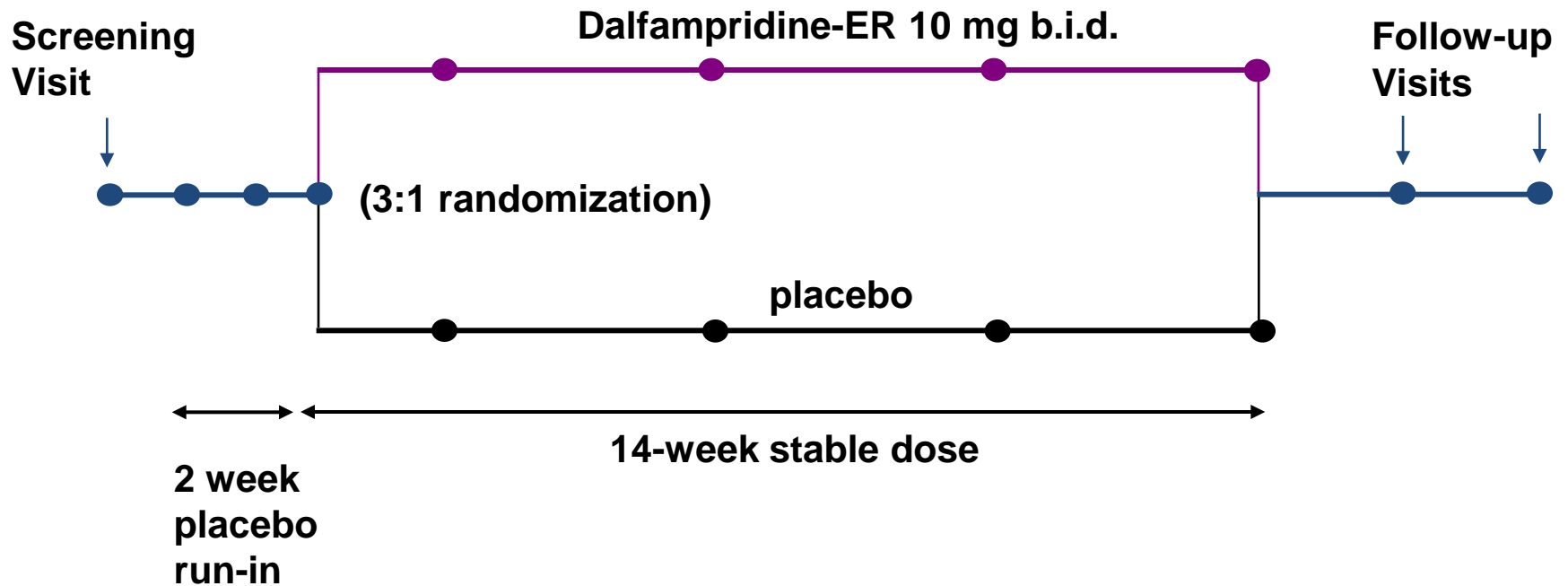
Why “Responder Analysis”?

- Correspondence to clinical practice and clinical experience
- Allows effect size to be examined in the individuals who actually benefit
- Consistent with expected biological mechanism
- May facilitate regulatory judgment

An “Unusual” Response Criterion

- Responder analyses depend on a defining criterion for “response”
- This criterion is usually designed:
 - To identify differences of meaningful magnitude (i.e. a worthwhile change from the expected)
 - Not to identify a causal relationship between treatment and effect (i.e. a true “response”)
- If we are unsure of what is meaningful, we can try to identify related changes and then determine if they are meaningful to patients

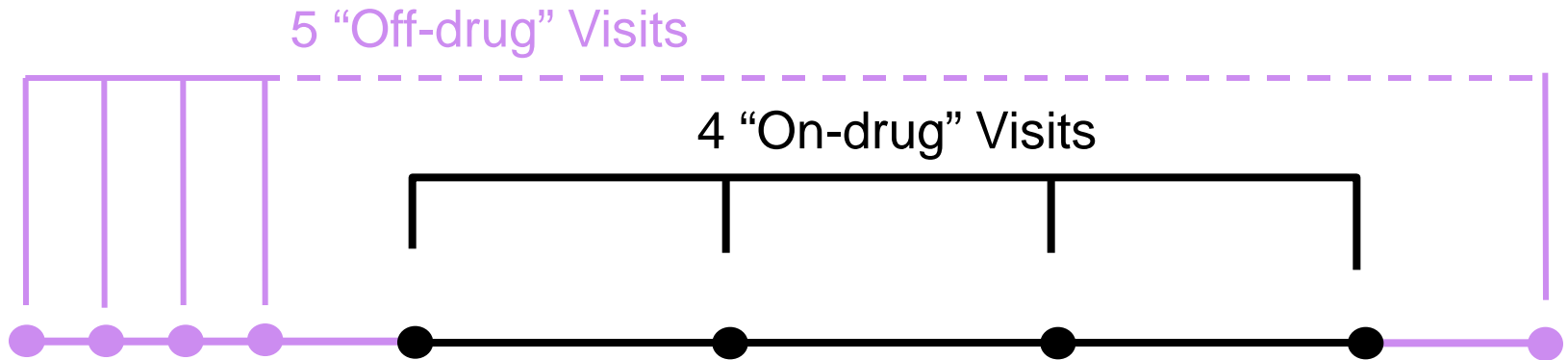
Overall Trial Design



1. Goodman AD et al. *Lancet*. 2009;373:732–738.

Primary Endpoint – Response Criterion

A Timed Walk Responder is a subject whose walking speed on at least 3 of the 4 “on-drug” visits is faster than the fastest speed during any of 5 “off-drug” visits

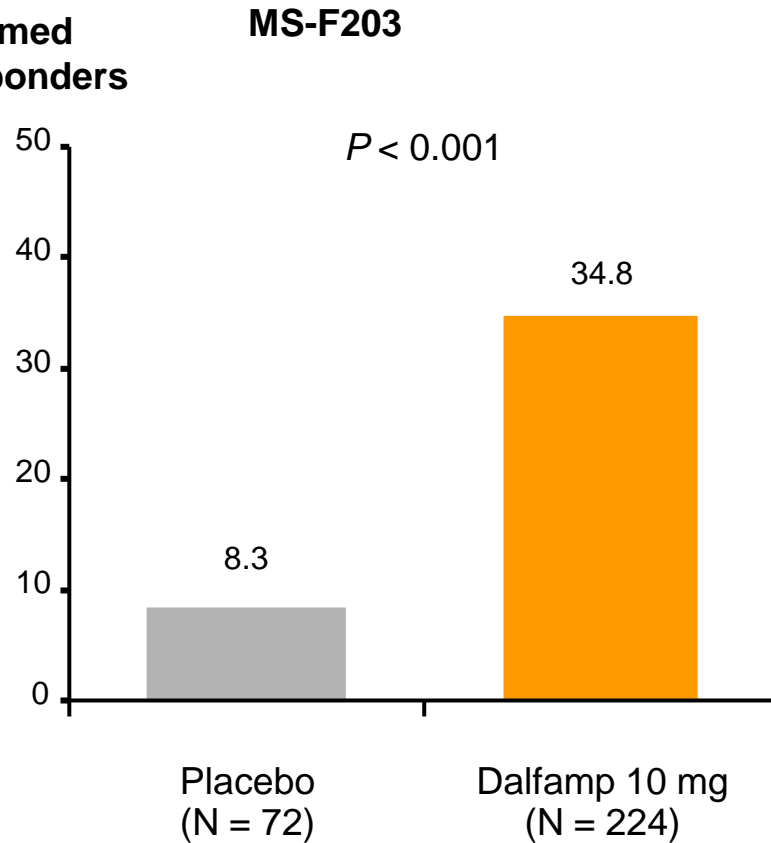


Timed Walk Response Criterion

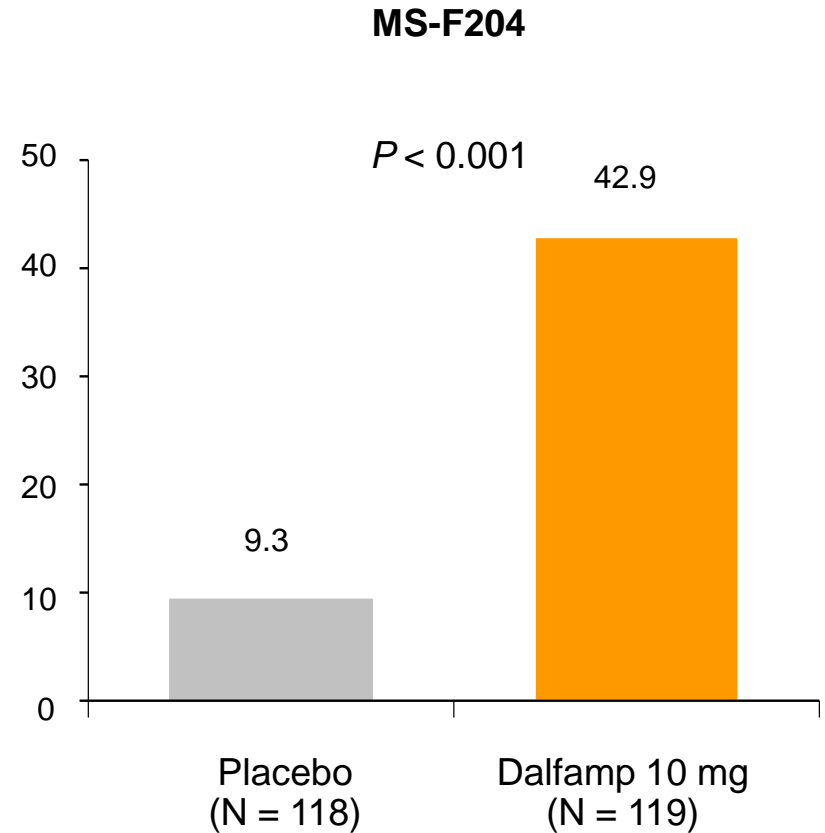
- Designed to identify treatment-related changes, for a true separation of treatment responders and non-responders
- Not based on an arbitrarily selected threshold of clinical significance
- Threshold for response varies with the baseline variability of the individual subject
- Additional characterization of Timed Walk Responders within the studies was required by protocol to show associated change in patient reported disability (MSWS-12 score)

Significant Increase in Timed Walk Response with Dalfampridine

Percent Timed Walk Responders



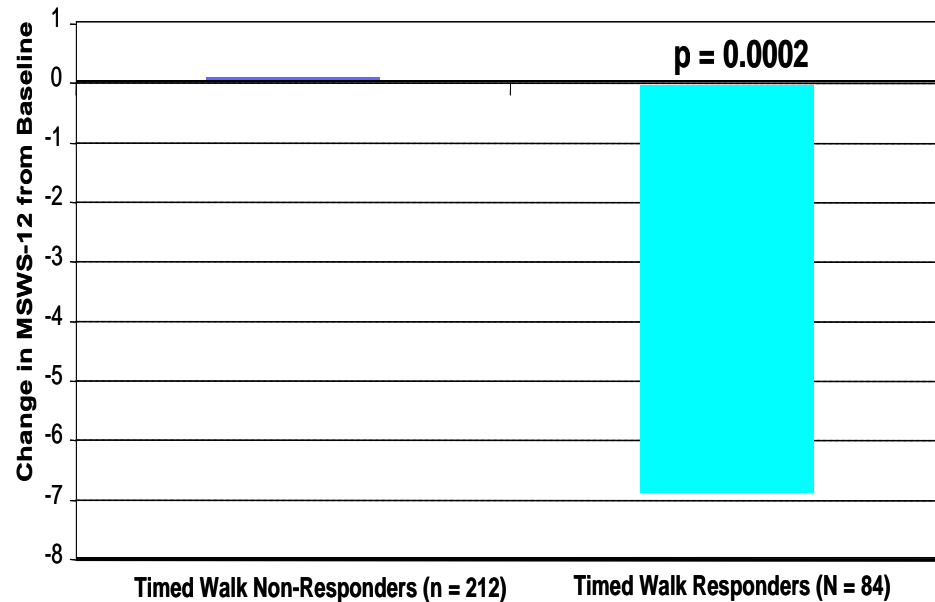
Goodman AD et al. *Lancet*. 2009;373:732–738.



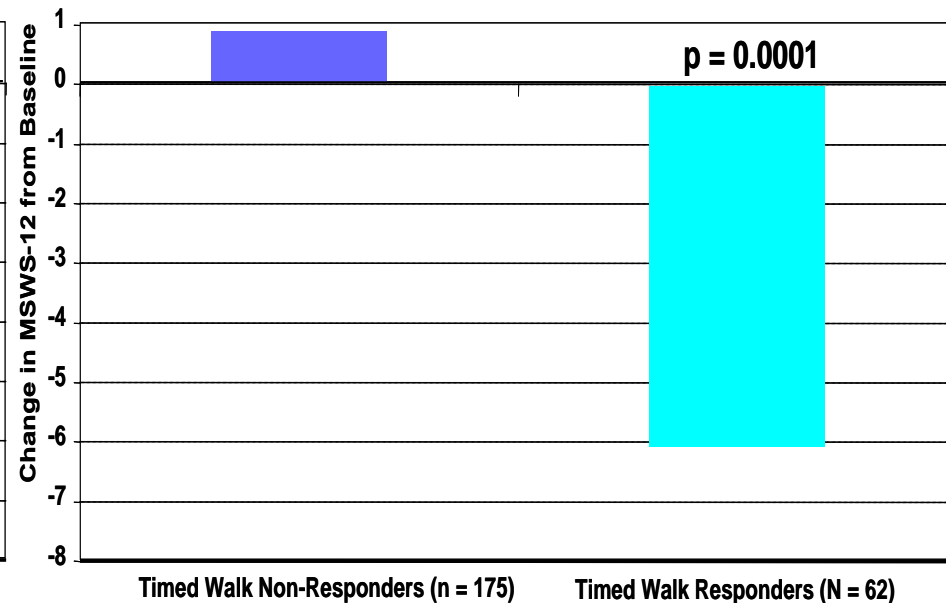
Goodman AD et al. *Ann. Neurol*. 2010; 68:494–502.

Decrease in Self-Assessed Walking Disability Among Timed Walk Responders – Protocol Specified Analysis of Correlation

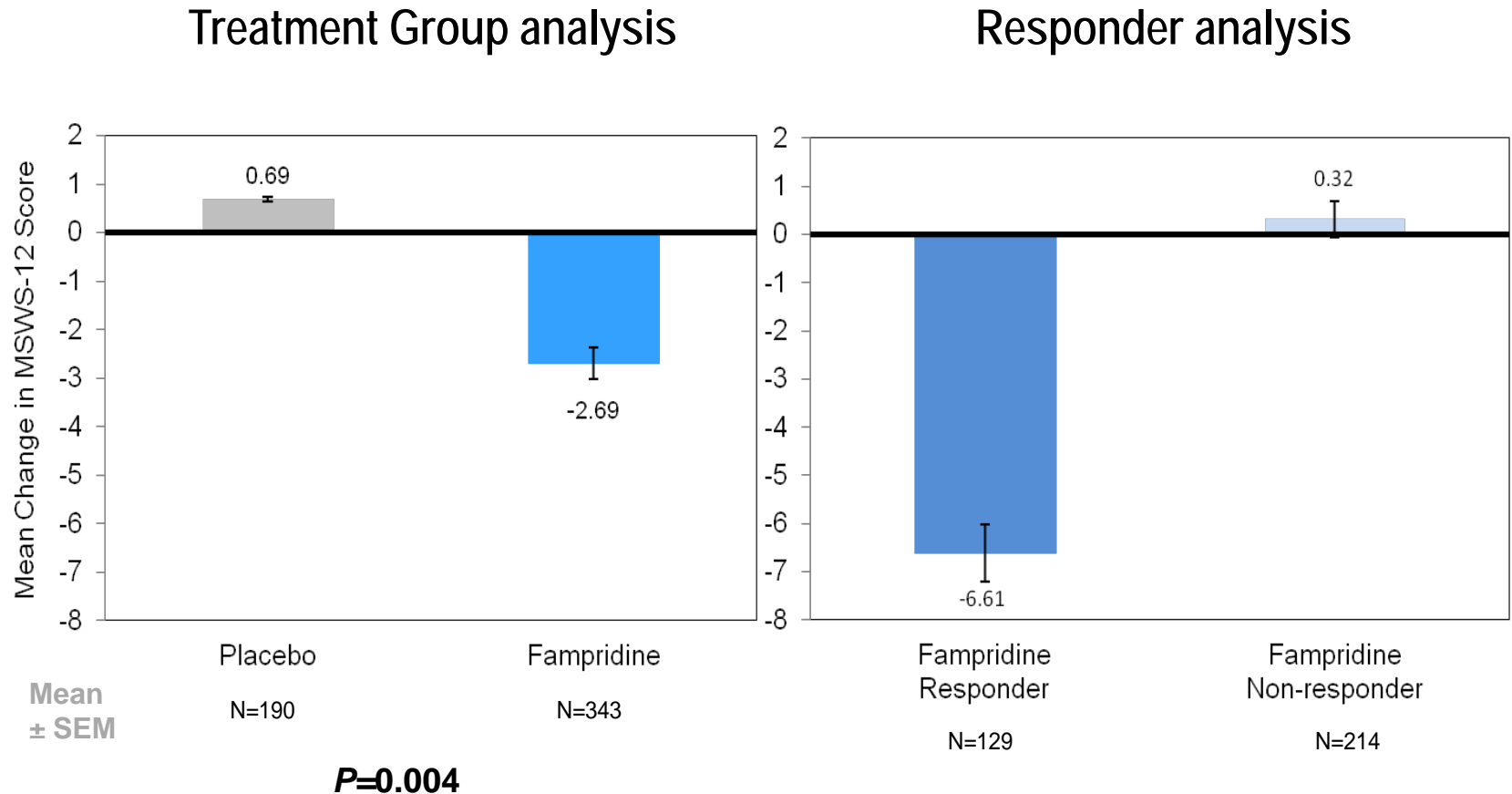
MS-F203
12-Item MS Walking Scale
ITT Population



MS-F204
12-Item MS Walking Scale
ITT Population



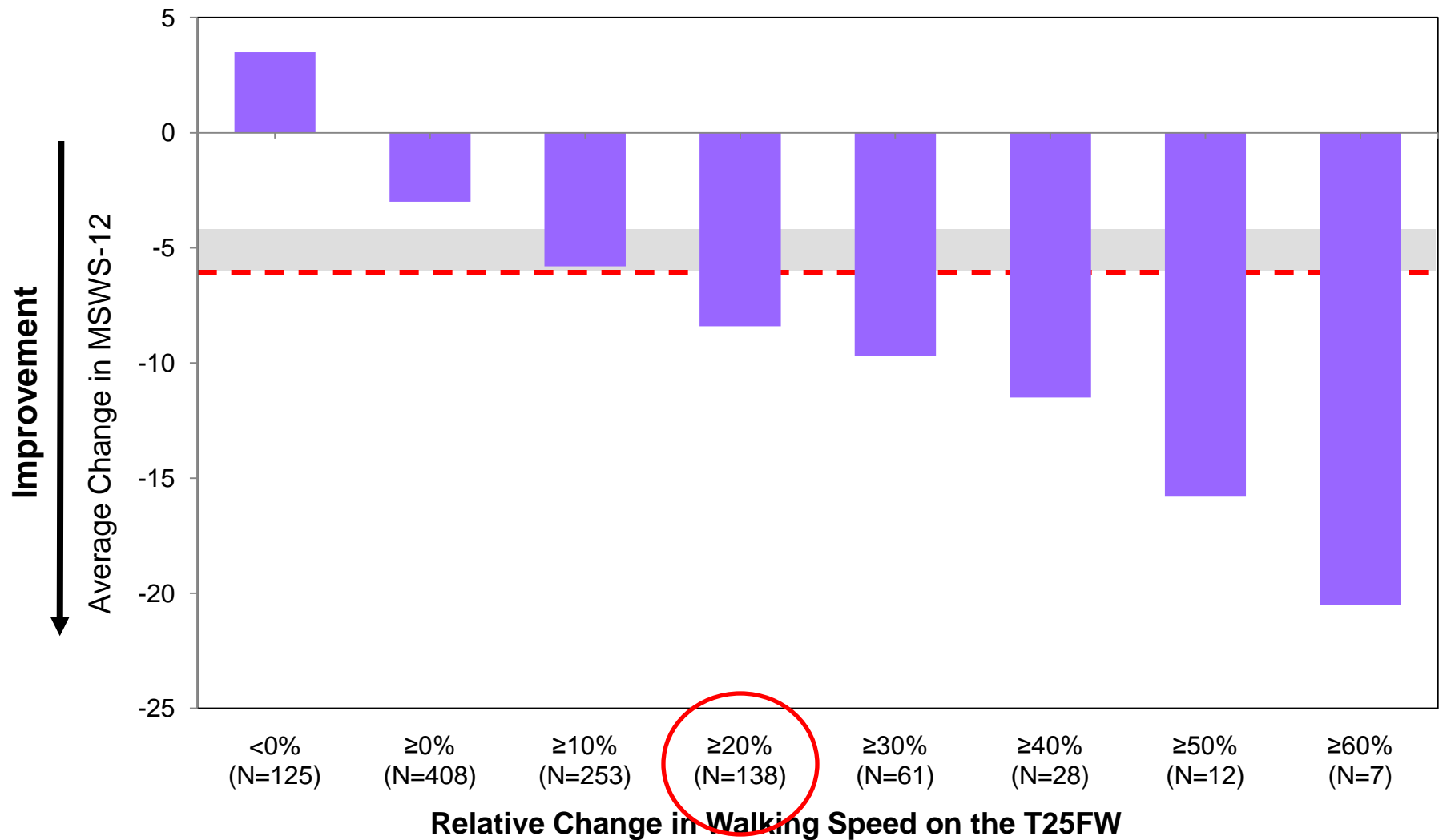
MSWS-12 Score: Treatment Effect Driven by Responder Group



MS-F203 and MS-F204, pooled

MSWS-12=12-item Multiple Sclerosis Walking Scale; SEM=standard error of the mean

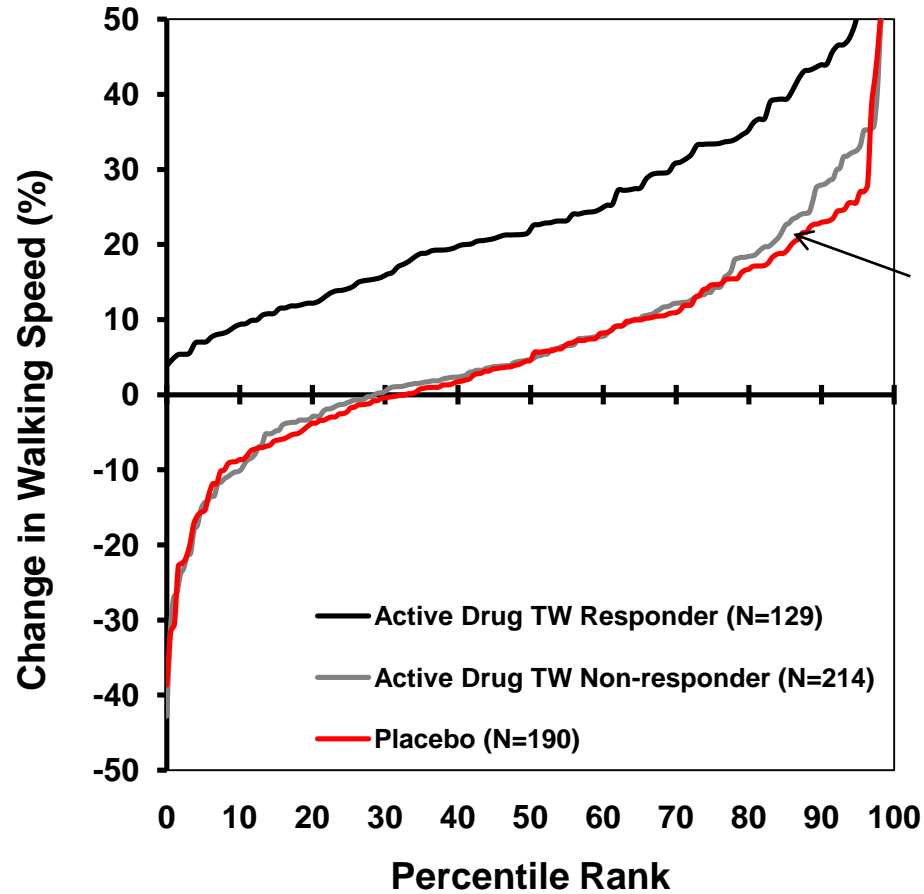
~ 20% Change in T25FW (still!) Appears to be a Clinically Relevant Threshold*



*MS-F203 and MS-F204 combined data (placebo and dalfampridine)

† Hobart *Mult Scler* 2010(Suppl)

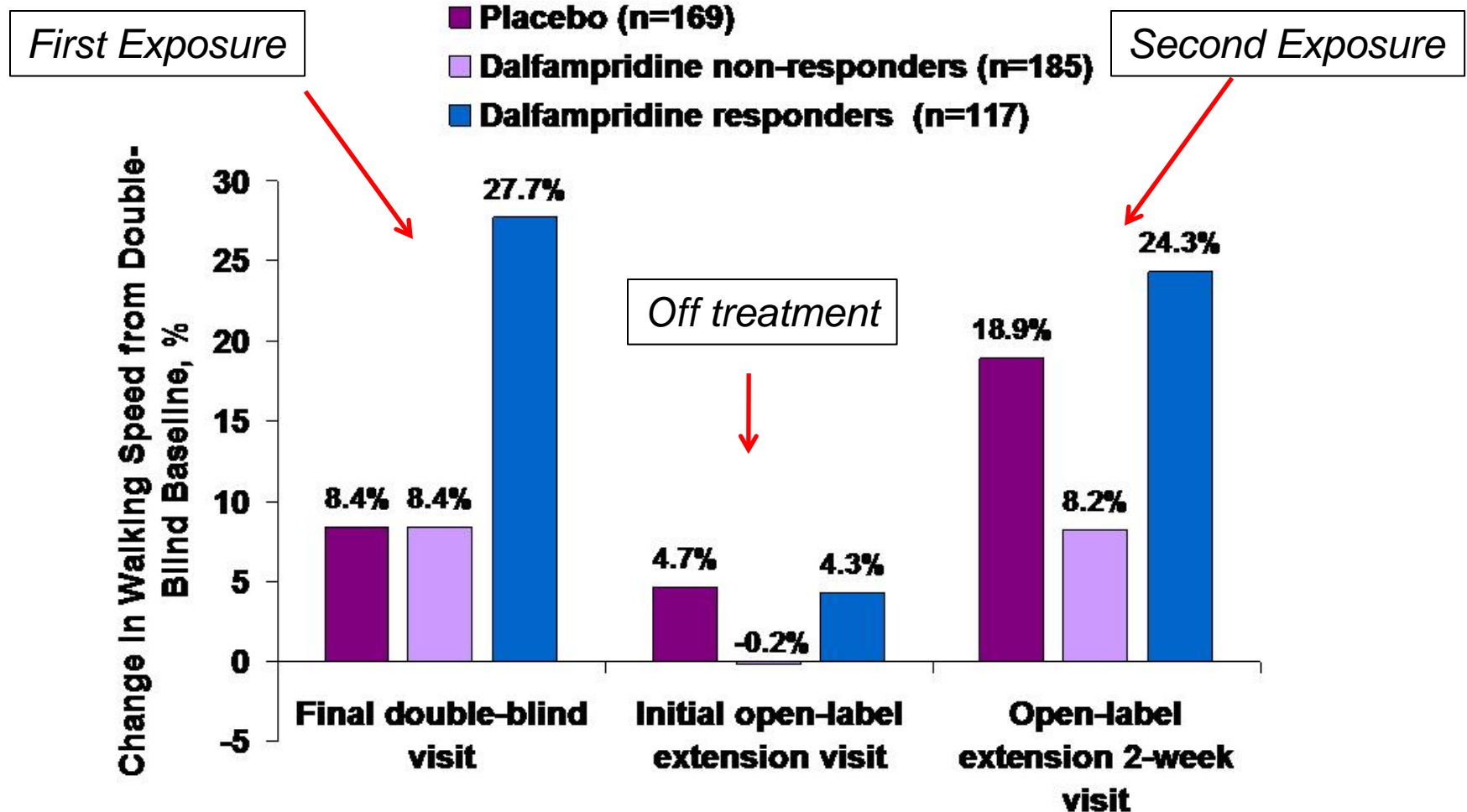
Population Analysis



Timed Walk Non-responders show distribution of changes similar to placebo patients

*Pooled data
(MS-F203
MS-F204)

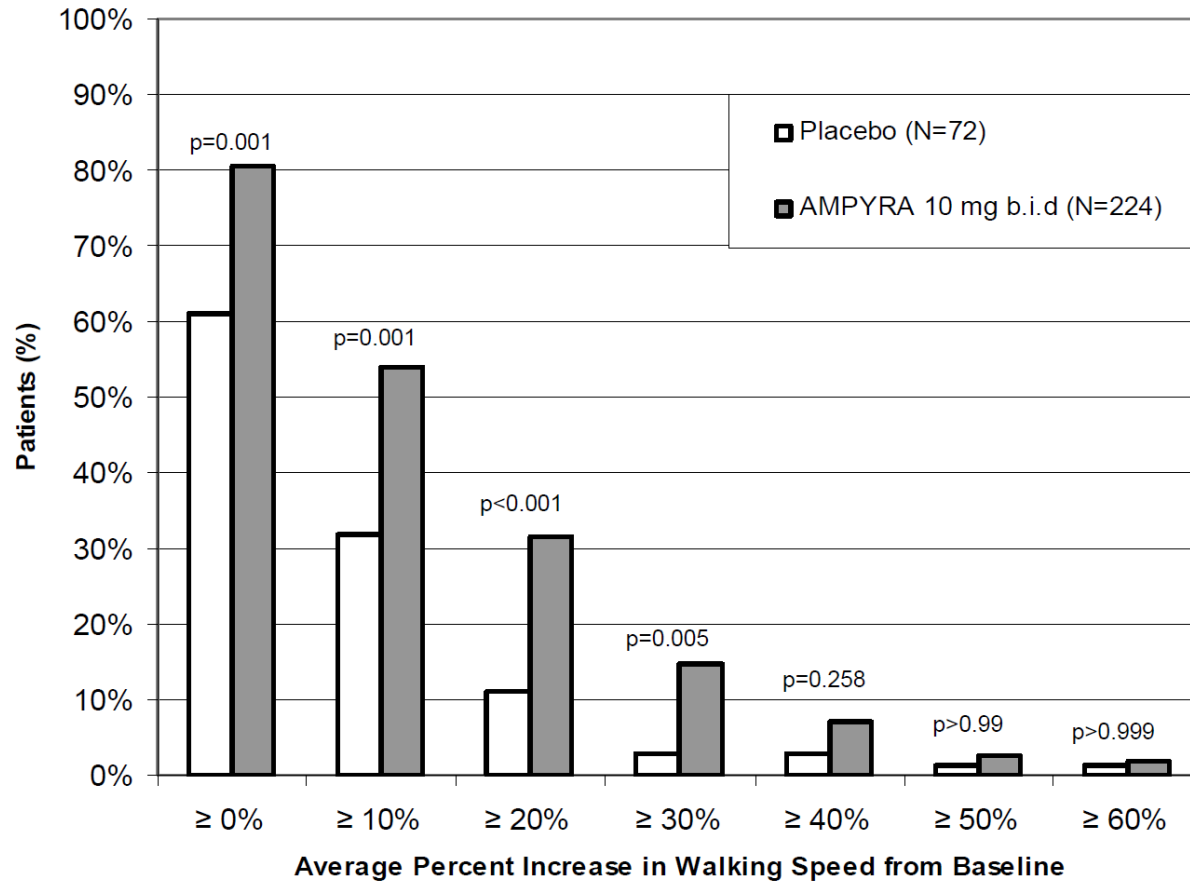
How “Real” is Responder Status?*



*Pooled data from MS-F203, MS-F204, MS-F203EXT and MS-F204 EXT

But What Resonates?*

Figure 1: Average walking speed change (%) from baseline during the double-blind phase of Trial 1



P-values provided at each threshold comparing AMPYRA to placebo.

Summary

- Consistency of change on a quantitative measure can be an effective way to identify response to treatment
- A patient-reported outcome can support the clinical relevance of a change in a functional measure
- It remains easier to “understand” the notion of response measured by a given magnitude of change from a supposed “baseline” in the whole treatment group
- This comfort may be illusory