

# The Dalfampridine Story

Eric Bastings, MD  
Deputy Division Director  
Division of Neurology Products  
CDER



# Dalfampridine (fampridine SR)

- Sustained-release formulation of 4-aminopyridine (potassium channel blocker)
- Proposed mechanism of action: ↑ conduction of action potentials in demyelinated axons
- Approved in January 2010, “indicated to improve walking in patients with multiple sclerosis. This was demonstrated by an increase in walking speed.”



# The Story Behind It

- 4-aminopyridine “immediate release” (IR) studied by research and pharmaceutical sponsors since 80’s
- At the time, seizures already identified as drug related toxicity, believed to occur mostly at doses  $> 20\text{mg/day}$
- Narrow therapeutic index, risk of seizures likely related to  $C_{\text{max}}$   $\rightarrow$  development of sustained-release formulation, dalfampridine

# Overview of Development Program

- 1991-1998: sustained release formulation developed by Elan; orphan designation
- 1998-2004: Acorda sponsored phase 2 studies; end-of-phase 2 meeting
- 2005-2008: pivotal studies under special protocol assessment (SPA); pre-NDA meeting
- 2009: NDA filed; priority review; advisory committee meeting
- 2010: FDA approval



# Phase 2

Study MS-F201

Study MS-F202



# Study MS-F201

- Multi-center, double-blind, placebo-controlled
- Primary objective: assess tolerability of escalating doses of dalfampridine 10, 15, 20, 25, 30, 35 and 40 mg administered twice daily for 8 weeks (N=36)
- 2 AEs of seizures (30-40 mg b.i.d)
- Frequent discontinuations at doses  $\geq 25$  mg b.i.d.
- Future development focused on 10-20 mg b.i.d range



# Study MS-F202

- Double-blind, placebo-controlled, parallel group, 20-week study (12 weeks stable dose)
- 206 patients, randomized to placebo, dalfampridine 10 mg, 15 mg, or 20 mg b.i.d.
- Primary efficacy variable: percent change from baseline in average walking speed (Timed 25-Foot Walk Test).



# Timed 25 foot Walk

- Patient directed at one end of a clearly marked 25-foot course
- Patient instructed to walk as quickly as possible, but safely
- Task immediately repeated
- Administered by trained examiner
- Average score of two completed trials



# Study MS-F202 Results

- Results numerically favoring dalfampridine, but no statistically significant difference ( $p \geq 0.4$ )
- Clinical significance of dalfampridine/placebo walking speed difference ( $< 0.18$  ft/sec) unclear
- 2 AEs of seizures on 20 mg b.i.d., plus one case of “altered mental state” on 15 mg b.i.d.

# End of Phase 2 Meeting (08/2004)

- Proposed primary endpoint for Phase 3: change from baseline in walking speed (25-ft WT)
- Because of a lack of understanding of the clinical significance of changes on 25-ft WT, FDA required a co-primary “global” outcome measure, or data to validate the functional significance of changes on the 25-ft WT.
- Proposed dose: dalfampridine 15mg b.i.d.



# End of Phase 2 Meeting (08/2004)

- FDA concerned about seizures, seen at doses close to those proposed for pivotal studies
- FDA noted that even though this represents an expected side effect with a drug of this class, this may be a significant issue if the drug is not shown to have a robust and significant clinical benefit.



# Post-Hoc Analyses after EOP2 meeting

- Responder criterion: increase in walking speed in  $\geq 3$  visits out of 4 visits on drug compared to the fastest walking speed during visits off drug
- Responders experienced  $>25\%$  average increase in walking speed over treatment period
- Sponsor proposed to use that responder definition as a primary outcome measure in phase 3.

# December 2004 Telecon

- Clinical meaningfulness of the proposed responder definition unknown
  - Need to validate the proposed primary outcome before conducting the proposed study, or
  - Prospectively define a co-primary endpoint to support the clinical meaningfulness of changes.
- Progressive decline in effect during study possible
  - Patients may have no positive drug effect at the last visit, and still be declared responders.



# Phase 3

Special Protocol Assessments (SPAs) for

Study MS-F203

Study MS-F204

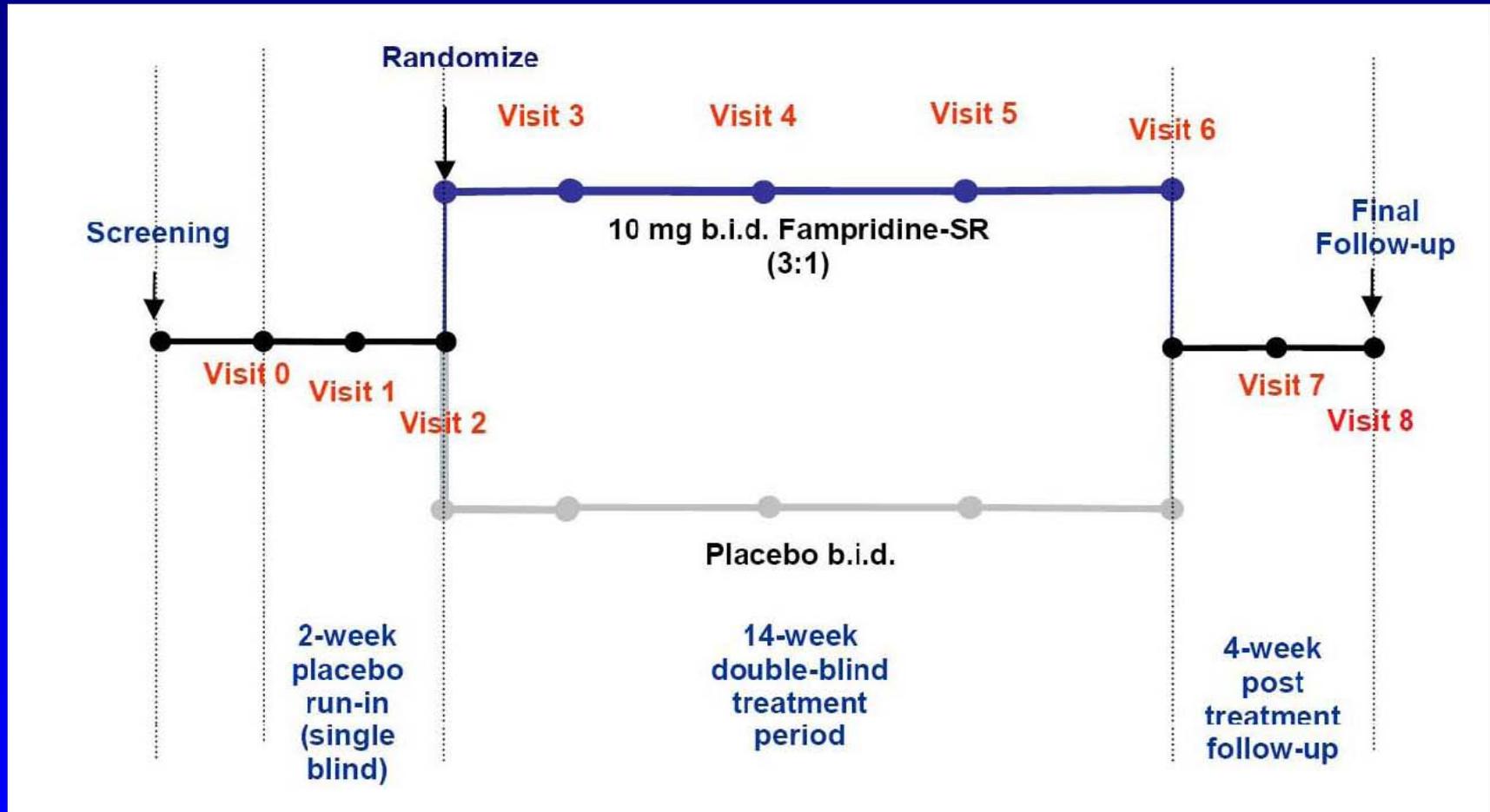


# Special Protocol Assessment (SPA)

- Reserved for protocols of clinical trials that will form the primary basis of efficacy
- Usually follow a meeting (e.g. end-of-phase 2 meeting) in which the drug development program is discussed
- Binding FDA comments within 45 days



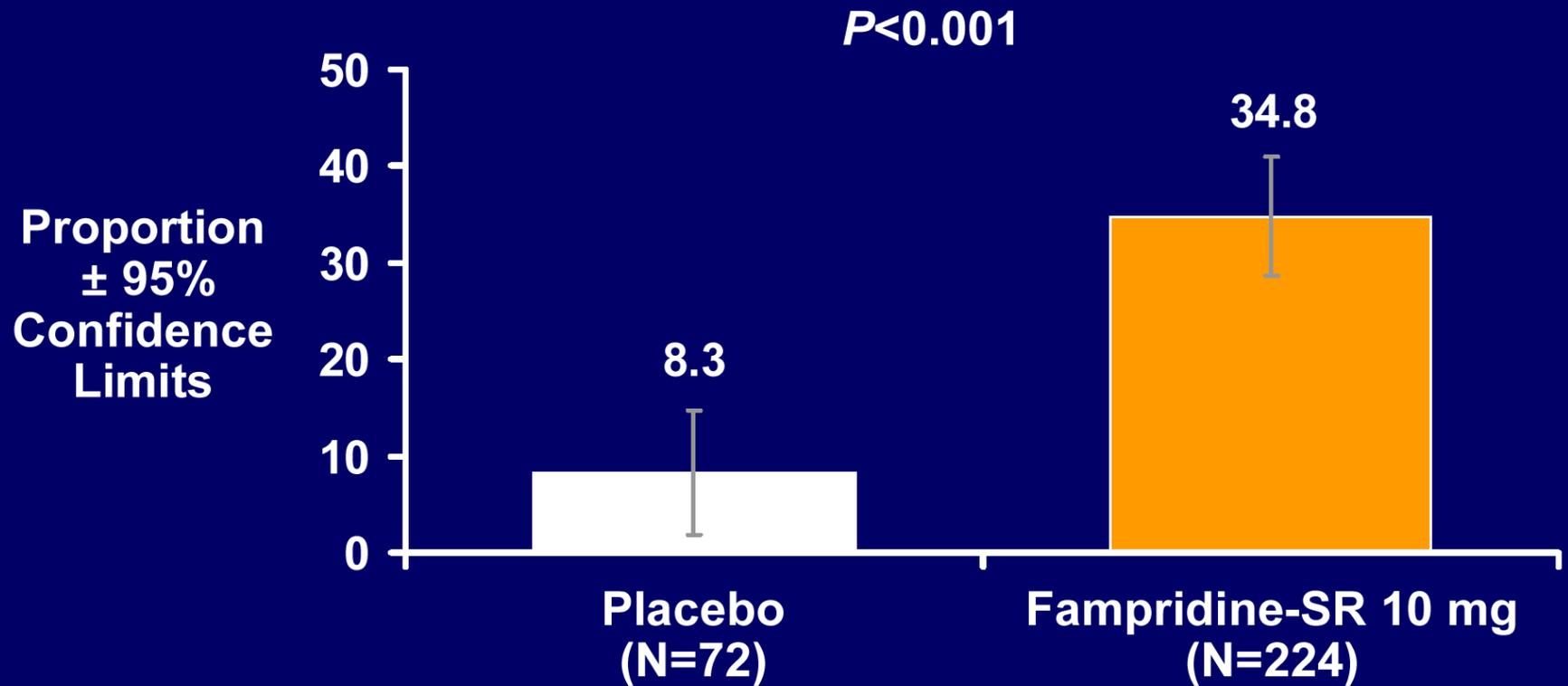
# Study MS-F203: Double-blind, placebo-controlled, parallel group study (N=301)



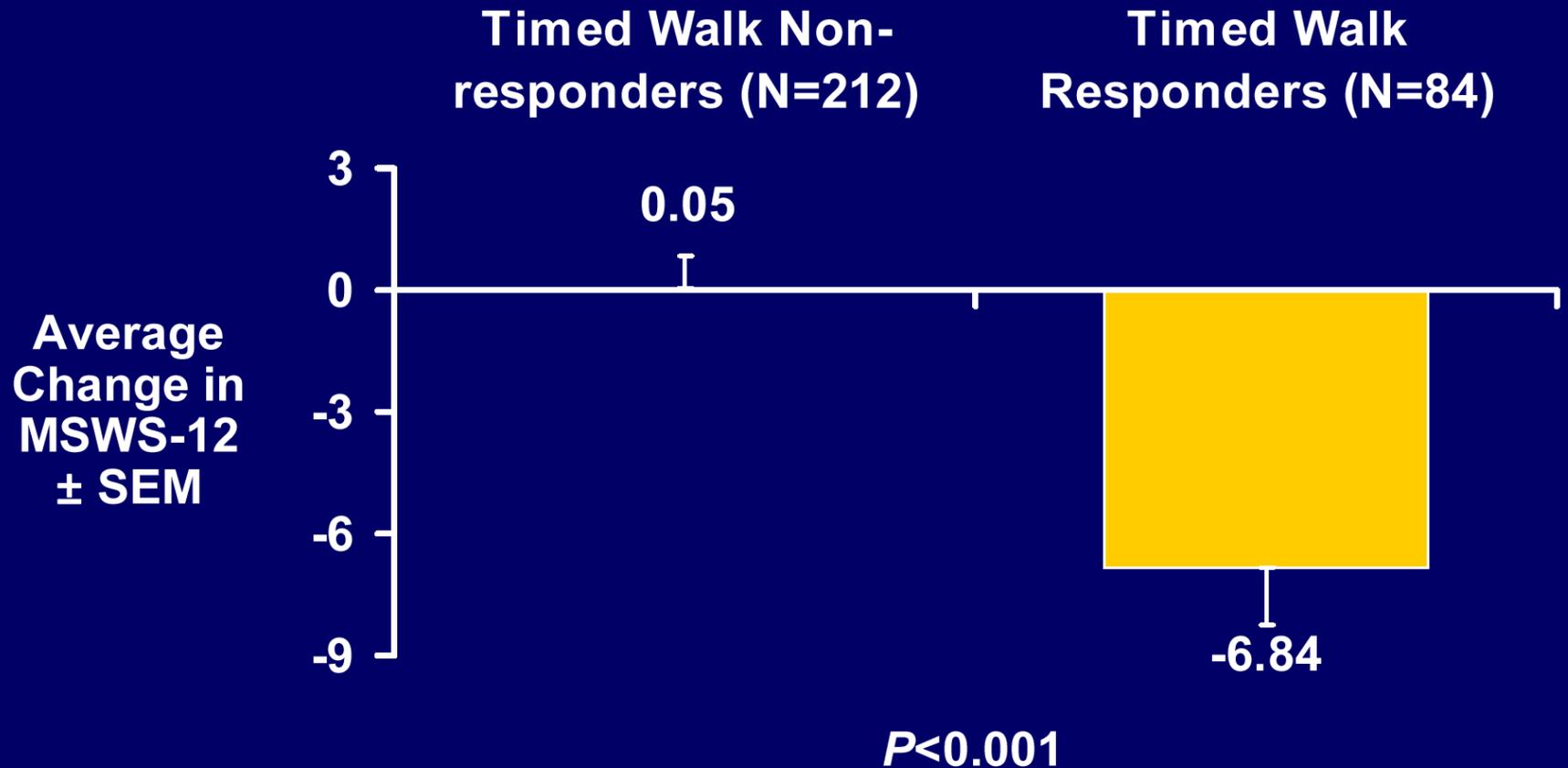
# Study MS-F203 Sequential Analysis

1. Proportion of responders (dalfampridine vs. placebo)
  2. Compare MSWS-12 score changes in responders vs. non-responders (measure of the global impact of walking impairment on perceived disability)
  3. Compare walking speed at last visit on drug for dalfampridine responders vs. placebo (responders + non-responders).
- Agreement reached after April 2005 telecon

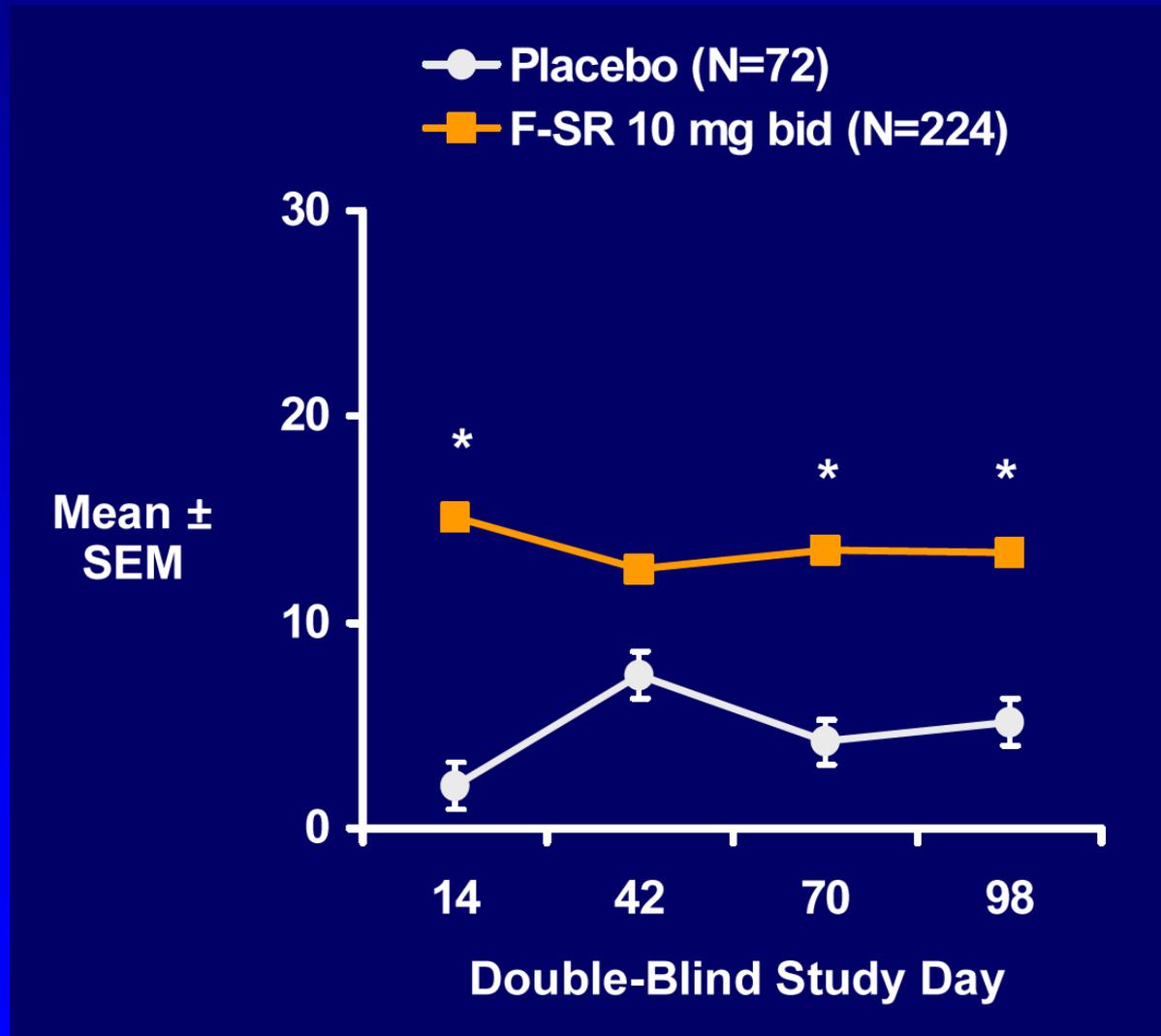
# Study MS-F203 Analysis Step 1: Proportion of Responders



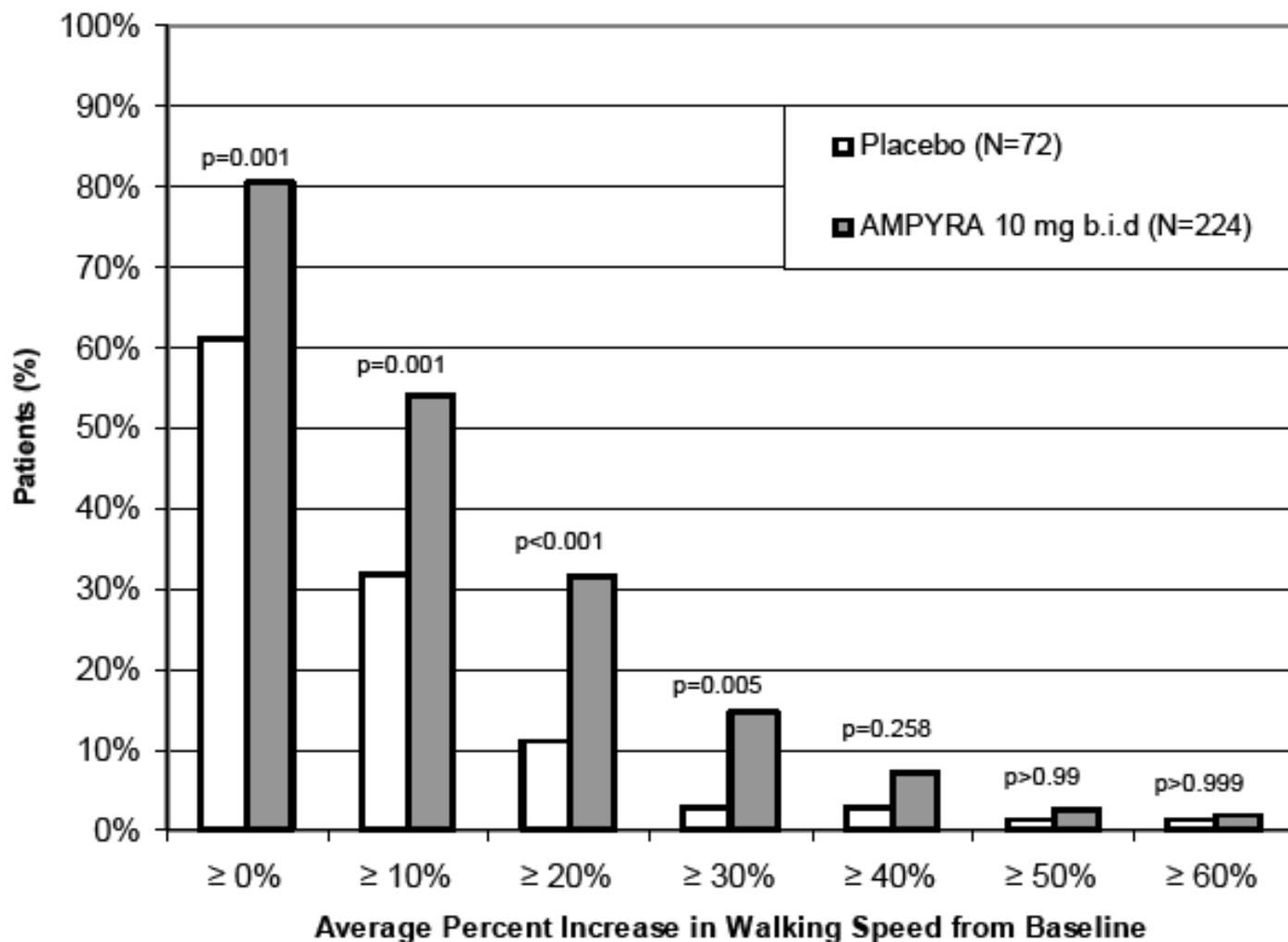
# Study MS-F203 Analysis Step 2: Comparison of MSWS-12 Score Changes



# Study MS-F203 Analysis Step 3: Maintenance of Drug Effect

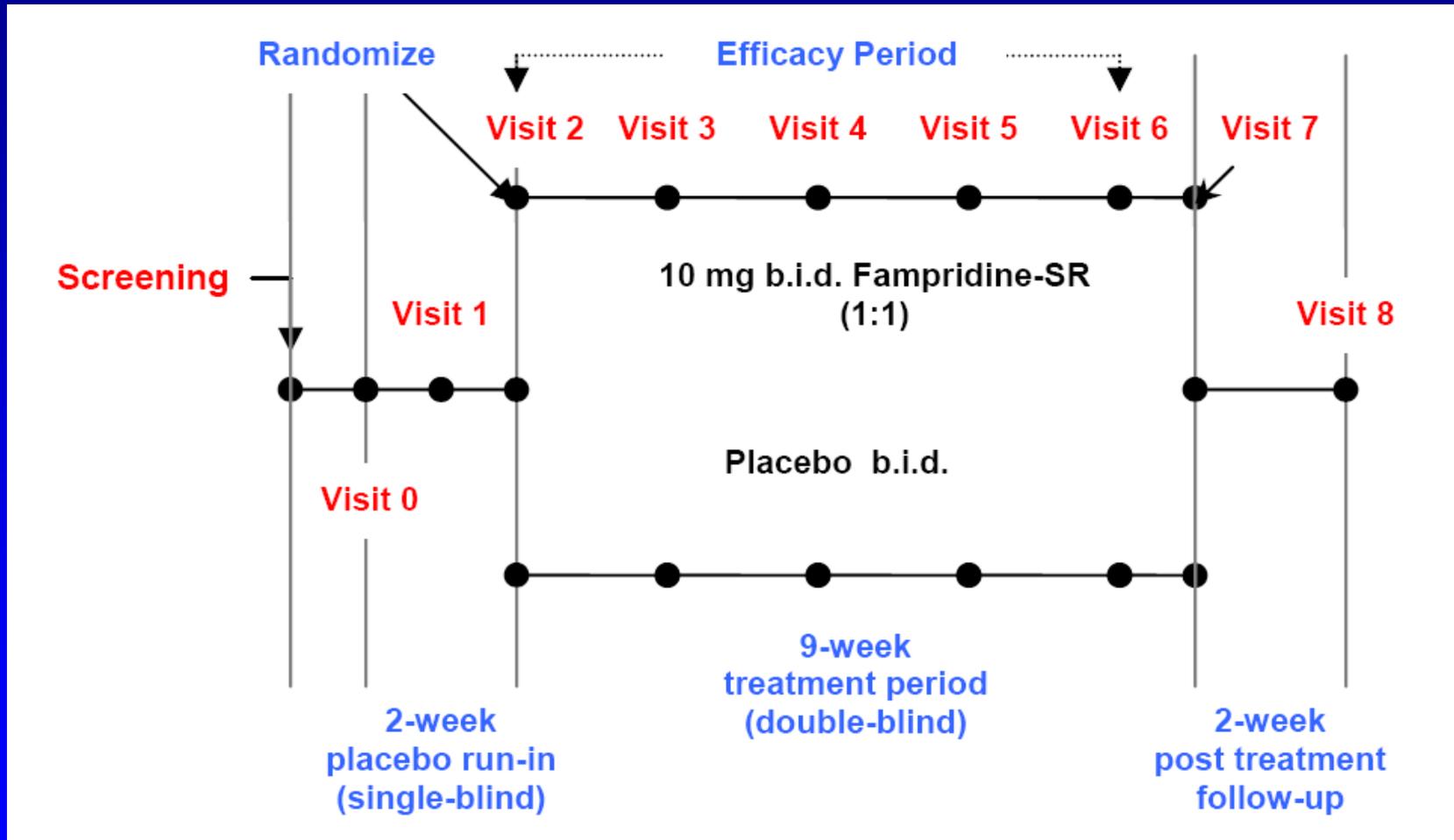


**Figure 1: Average walking speed change (%) from baseline during the double-blind phase of Trial 1**



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

# Study MS-F204 (N=239)

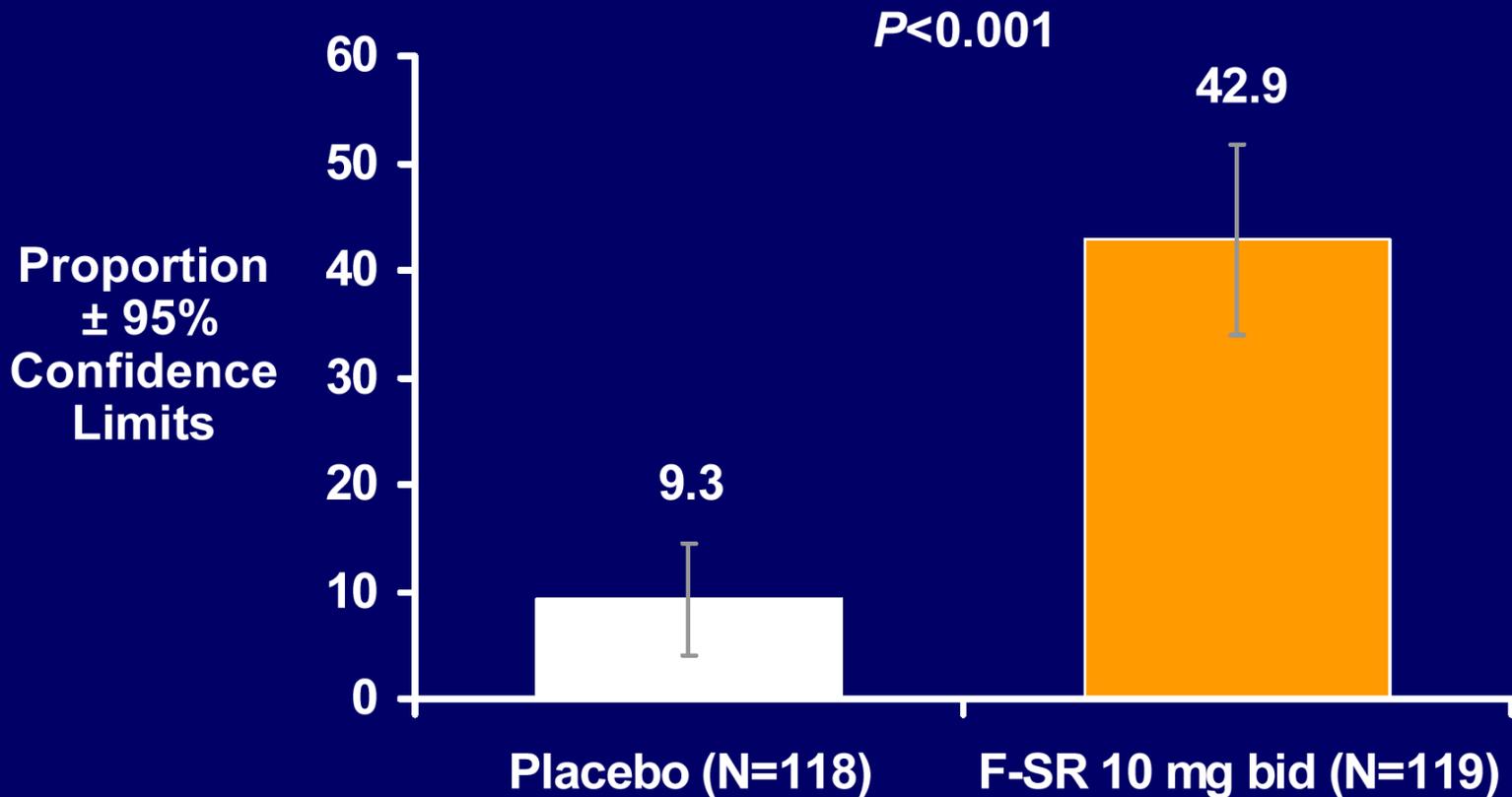


# 2006 Special Protocol Assessment: Study MS-F204

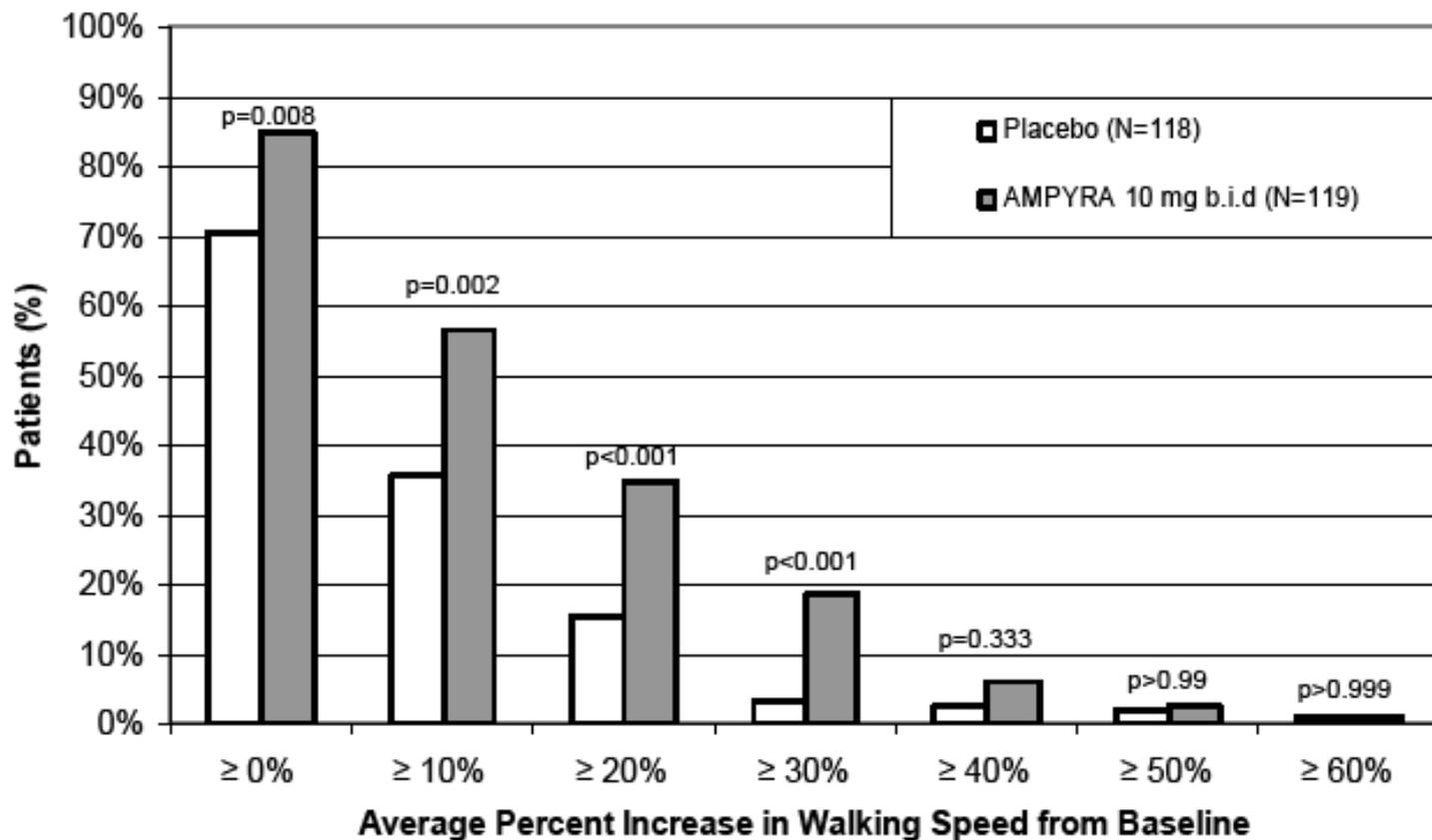
- Design similar to Study MS-F203 (same responder definition); shorter duration (13 weeks)
- FDA asked to evaluate whether the drug effect is present throughout the dosing interval
  - By evaluating patients at various times during the dosing interval during one visit
  - Or by evaluating patients at different times at the various visits, to cover the dosing interval.
- Agreement reached in May 2007 (after telecon)



# Study MS-F204 Primary Endpoint Results

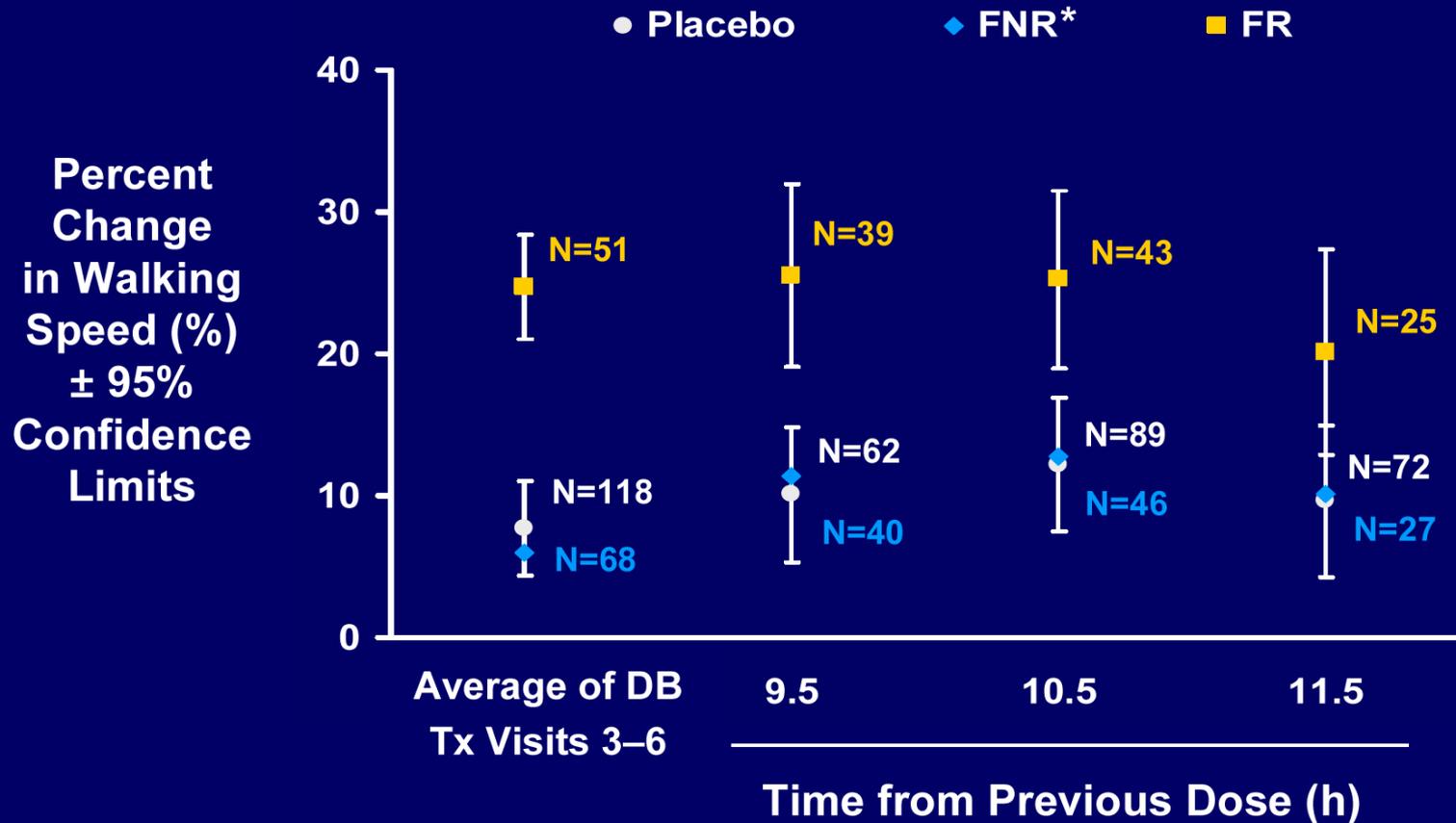


**Figure 2: Average walking speed change (%) from baseline during the double-blind phase of Trial 2**



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

# Efficacy at End of Dosing Cycle

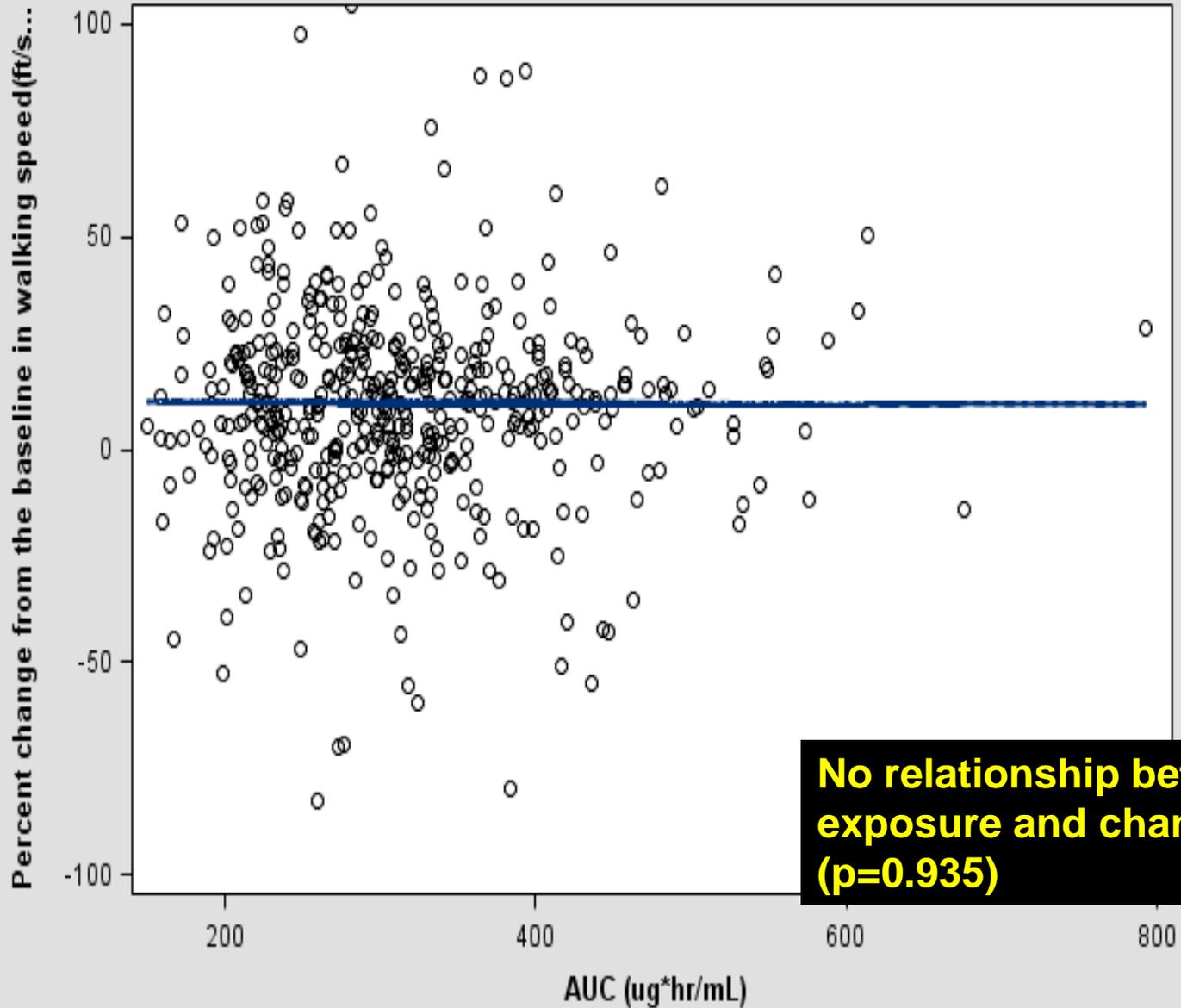


# NDA

- Pre-NDA meeting on October 27, 2008
- Submitted on April 22, 2009
- Priority review (6 months)
- Advisory meeting on October 14, 2009
- Approval on January 22, 2010



Without placebo : pooled data



**No relationship between exposure and change in WS (p=0.935)**

# Important Points

- Interaction between sponsor and FDA critical, as illustrated by multiple meetings that took place during development of dalfampridine
- Critical to use phase 2 to explore possible endpoints for pivotal trials, and define a target dose range



# Important Points

- New endpoints and new indications can be developed; study(ies) must establish that there is a clinically significant benefit to the patient
- If primary endpoint does not establish by itself the meaningfulness of benefit, several avenues are possible:
  - Co-primary “global” or functional endpoint may be necessary
  - Preliminary work can also establish meaningfulness of changes on primary outcome measure
- Indication is linked to study design and results



# Important Points

- Development program should always try to establish the lowest dose that provides a desirable treatment effect
  - Safety profile of doses investigated in development program may prove unacceptable
  - Other studies investigating lower doses may be necessary, either pre- or post-approval





FDA