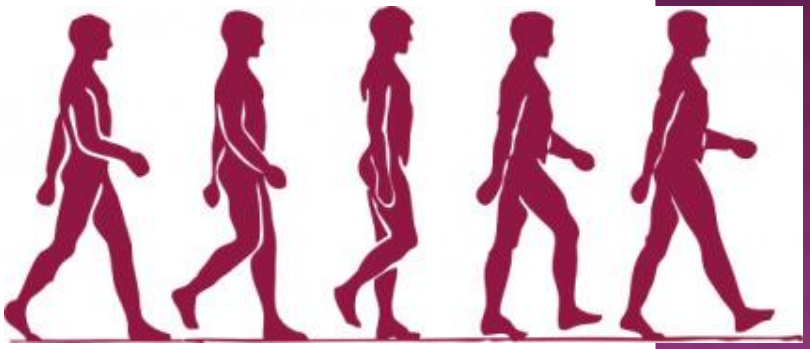
DALFYRA

WALKING IMPAIRMENT IN MS

- Walking integrates multiple functional systems, including
  - motor (pyramidal and extra pyramidal)
  - sensory (proprioception)
  - visual
  - cerebellar
  - vestibular

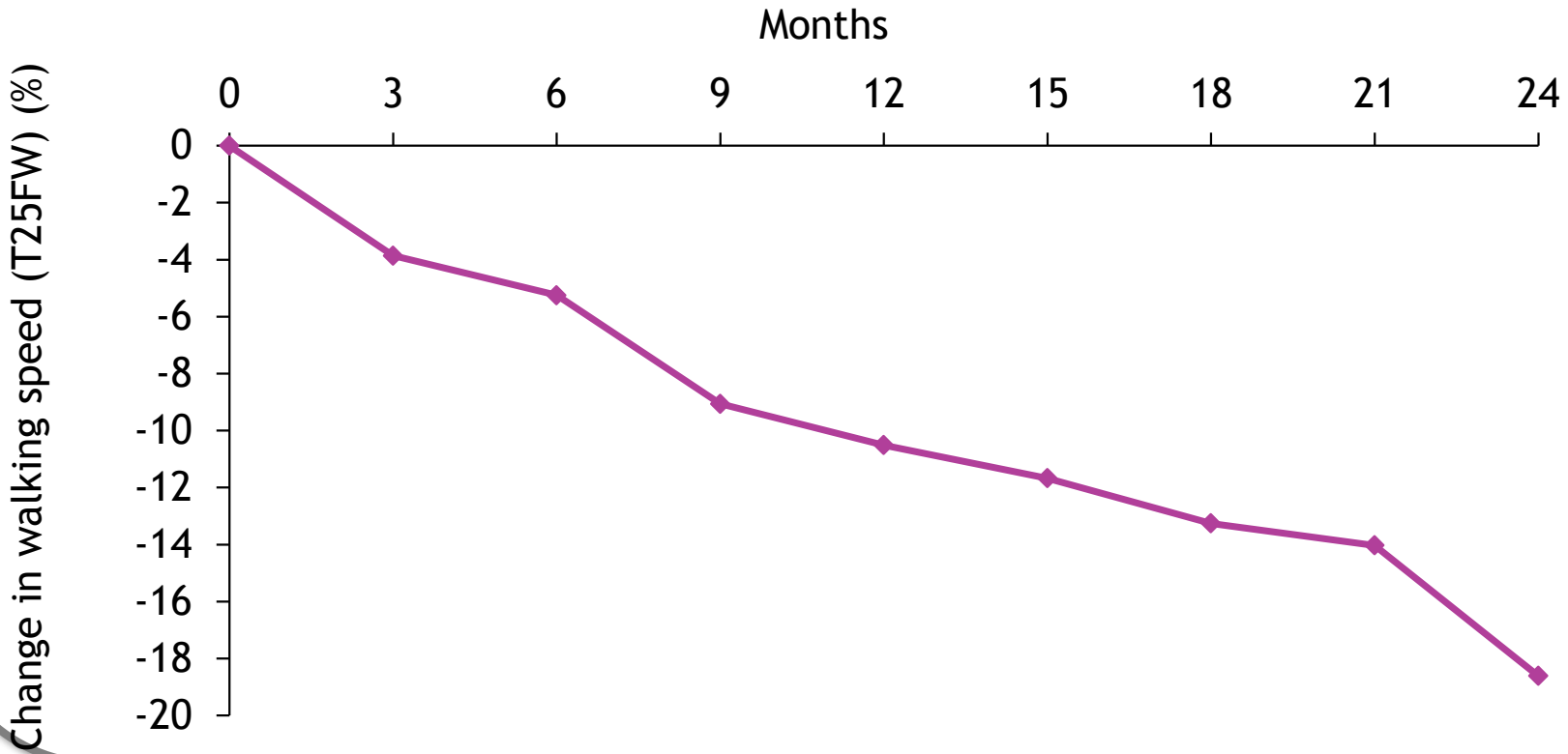


- Up to 58% of patients reported problems with some aspect of mobility in the first year following diagnosis of MS[1]
- Up to 93% of patients reported mobility problems within 10 years of diagnosis[1]
- 70% of patients with walking difficulty state that it is the most challenging aspect of their MS[2]

1. Van Asch P. *European Neurol Rev* 2011;6:115–120; 2. LaRocca NG. *Patient* 2011;4:189–201

IN A COHORT OF SPMS PATIENTS, WALKING SPEED DECLINED BY 19% OVER 2 YEARS

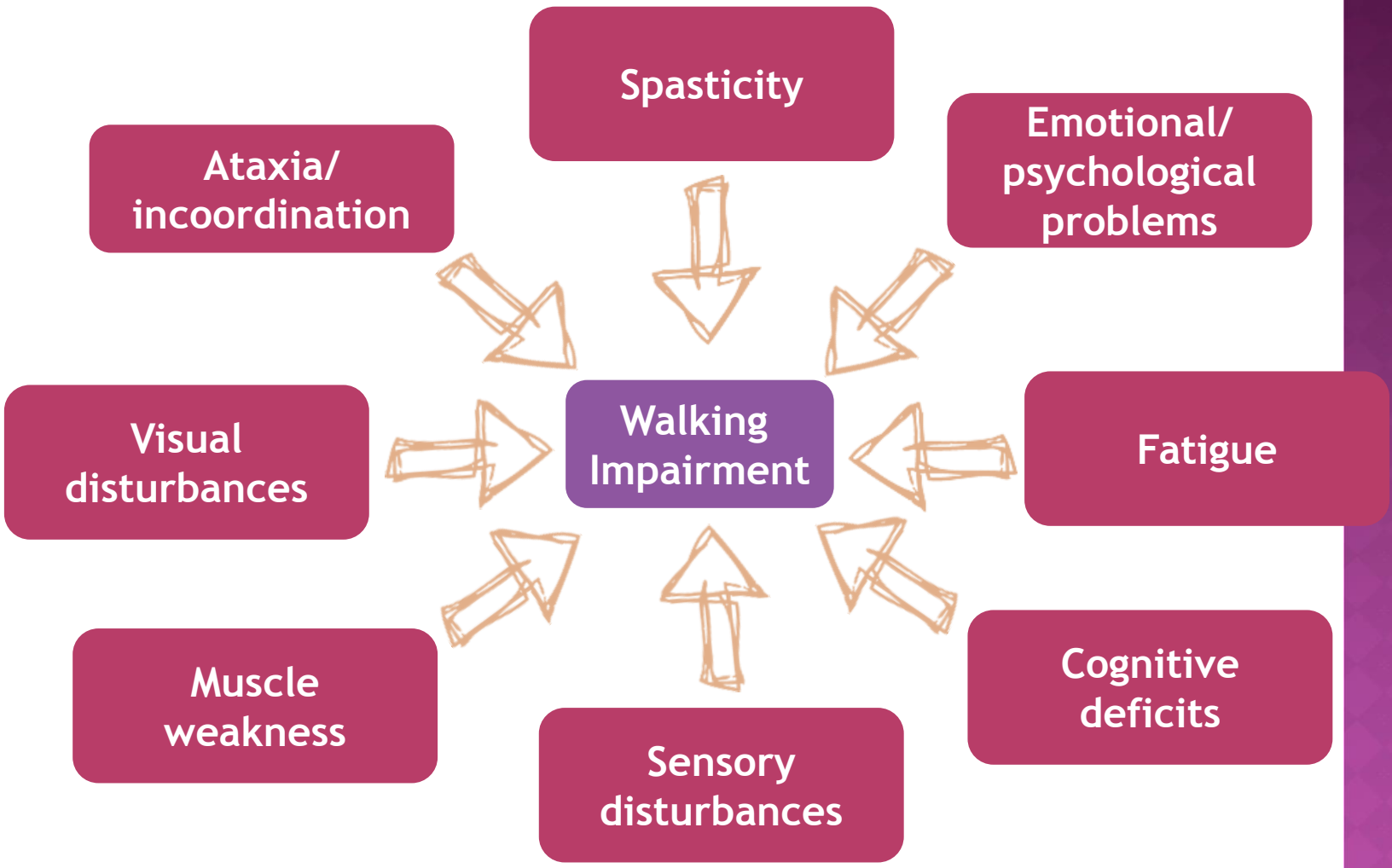
Patients with SPMS from the placebo arm of IMPACT trial of IFN beta-1a IM vs placebo (n=219)
Mean EDSS score at baseline = 5.2 (51% EDSS 6.0 or 6.5)



EDSS = Expanded Disability Status Scale; SPMS = Secondary Progressive Multiple Sclerosis; T25FW = Timed 25-Foot Walk

Biogen Idec, data on file; and Krishnan A, et al. P07.096. Presented at the American Academy of Neurology 2012 Annual Meeting, New Orleans, Louisianna

MULTIPLE FACTORS CAN CAUSE WALKING IMPAIRMENT



- Fampyra is a slow-release oral tablet indicated for the improvement of walking in adult patients with multiple sclerosis with walking disability

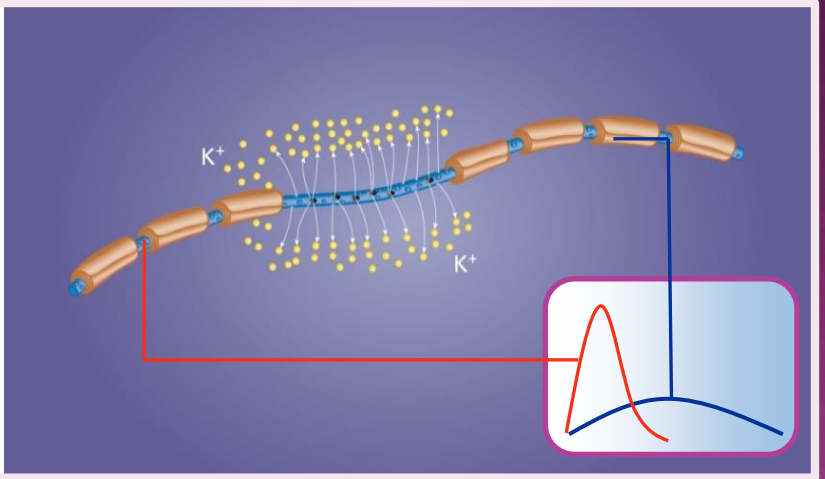
- The tablet contains a sustained release formula of 4-Aminopyridine, which blocks tiny pores, or potassium channels, on the surface of nerve fibers.


Dalfyra™ E.R.
Fampridine 10 mg
60 Extended Release Tablets

PR-FAMPRIDINE: MECHANISM OF ACTION

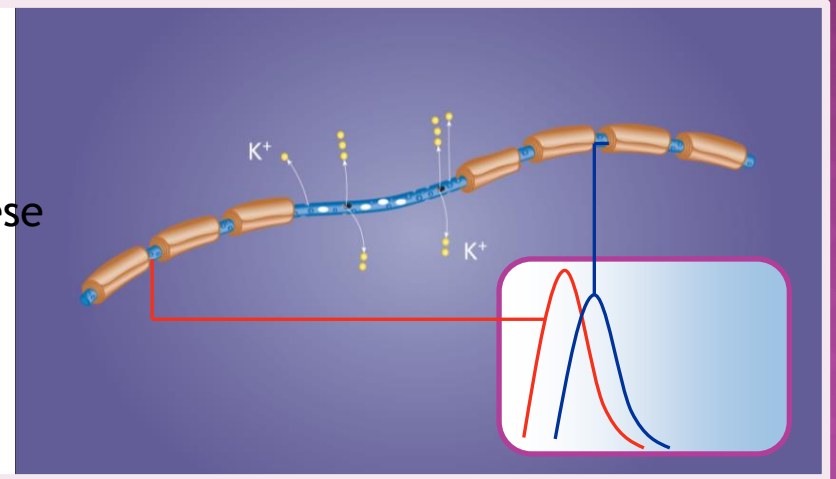
Without PR-fampridine

- Action potentials propagate more slowly along demyelinated axons than in myelinated axons



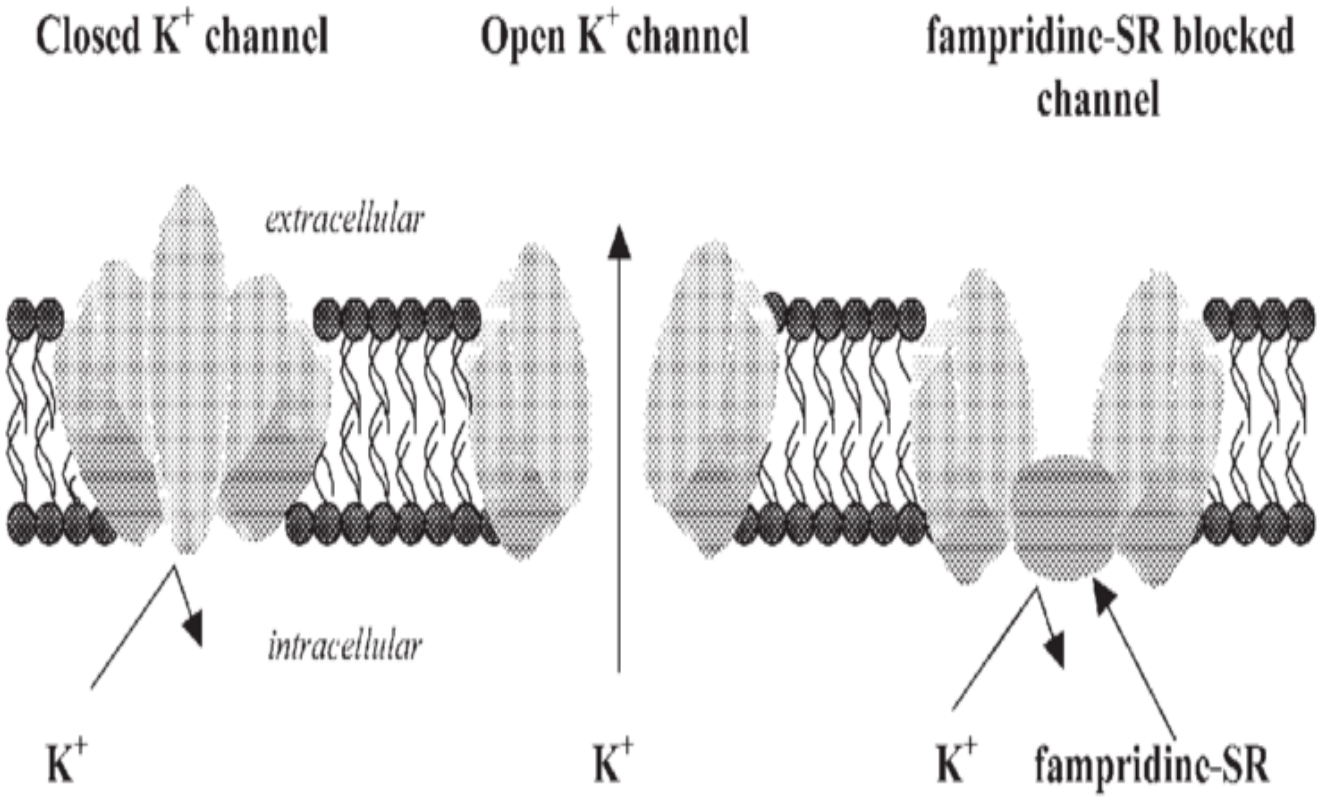
With PR-fampridine

- PR-fampridine is a K^+ channel blocker that reduces the leakage of ionic current through these channels
- This improves action potential propagation in demyelinated axons



K+ = potassium; PR = prolonged-release

Hayes KC. *CNS Drug Rev* 2004;10:295–316

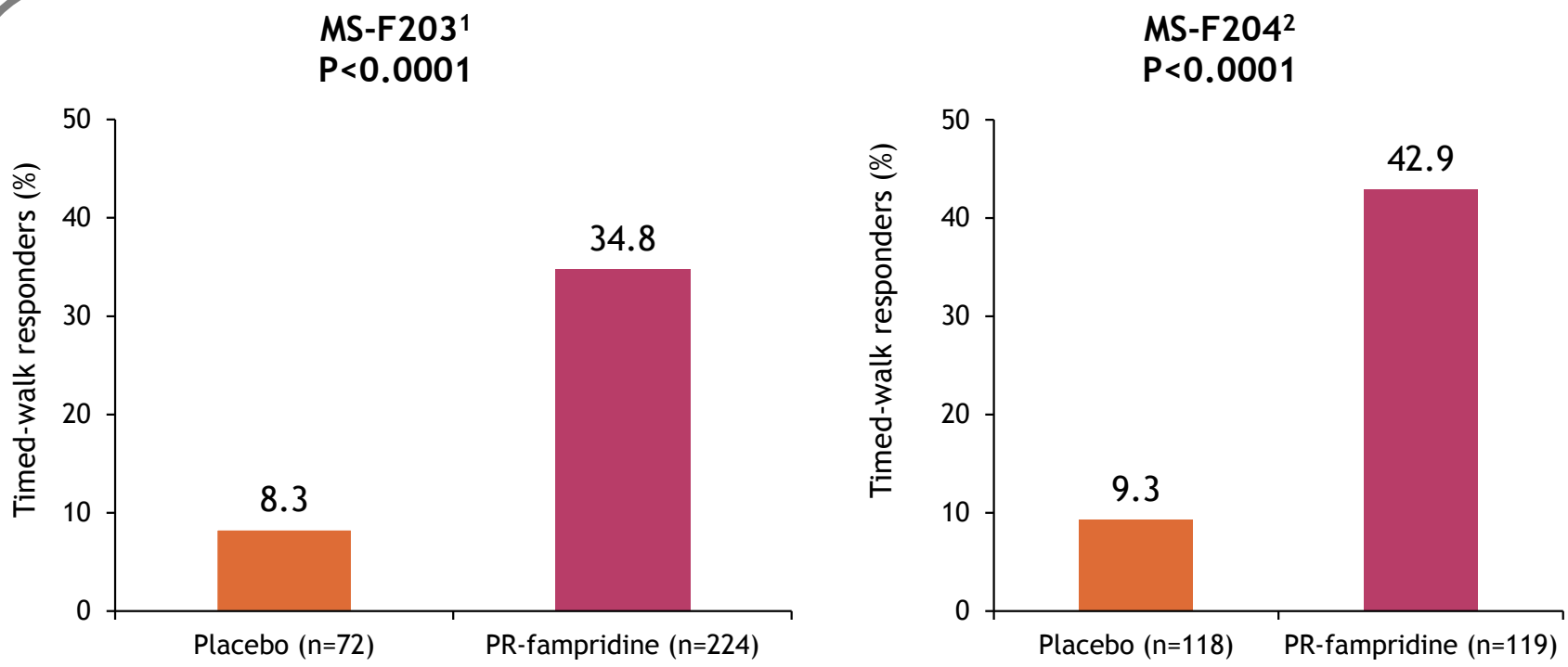

Closed K+ channel
Open K+ channel
fampridine-SR blocked channel
extracellular
intracellular
K+
K+
K+
fampridine-SR

- Taking Fampyra does not change the underlying course of the disease or limit the damage caused by the disease.

- Fampyra is administered orally by tablet twice a day, 12 hours apart.
- It should be taken without food.

MS-F203/204: PRIMARY EFFICACY OUTCOME
PERCENTAGE OF TIMED-WALK RESPONDERS

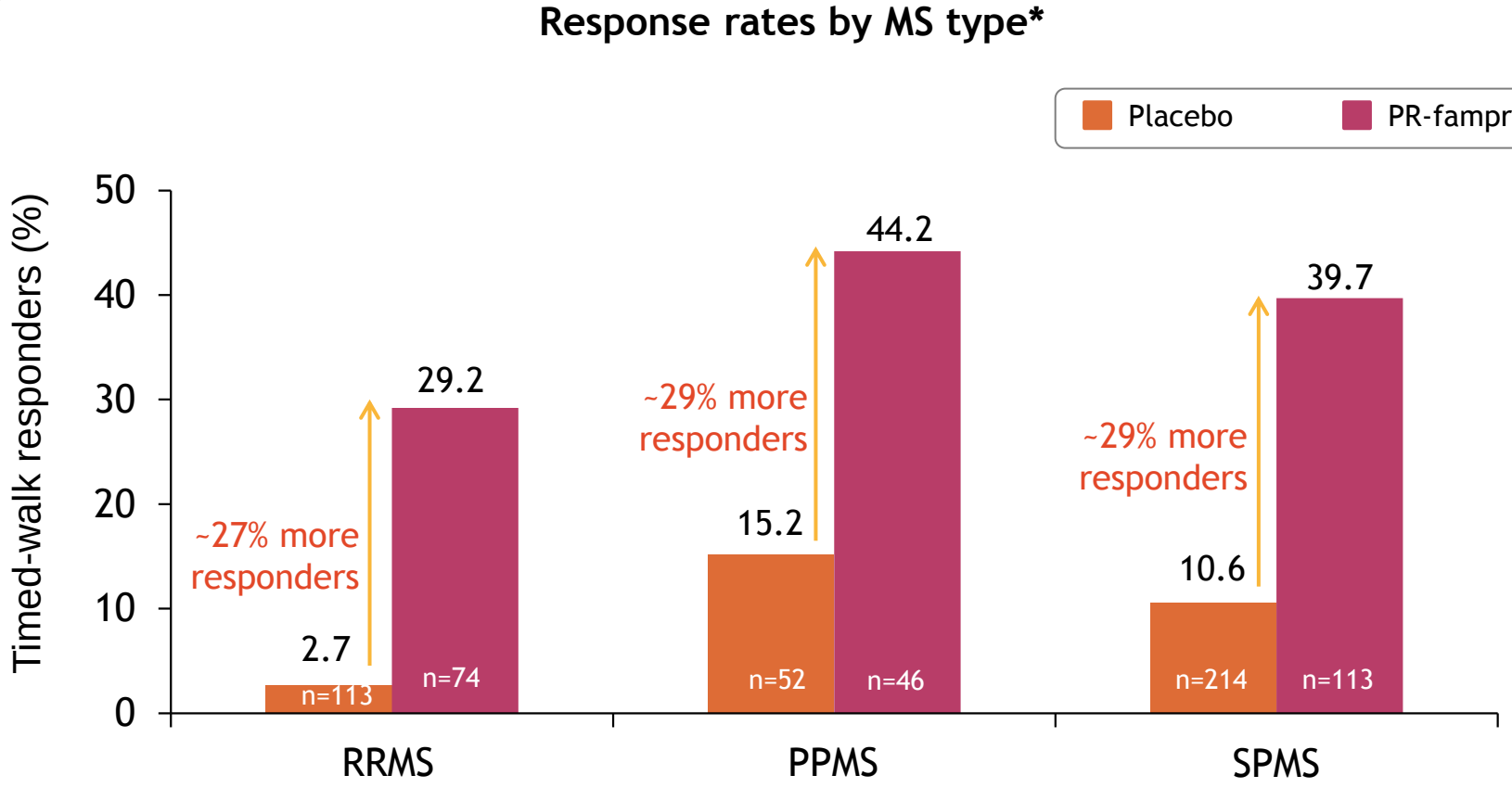
- Across trials, ~38%[3] of patients showed a consistent increase in walking speed (timed-walk responders)



PR = prolonged-release

1. Goodman AD, et al. *Lancet* 2009;373:732–738; 2. Goodman AD, et al. *Ann Neurol* 2010;68:494–502; 3.EMEA Assessment Report, Fampyra 2011

MS-F202/3/4: POOLED PRIMARY EFFICACY OUTCOME DATA
PR-FAMPRIDINE TIMED-WALK RESPONSE RATES ARE CONSISTENT REGARDLESS OF MS TYPE



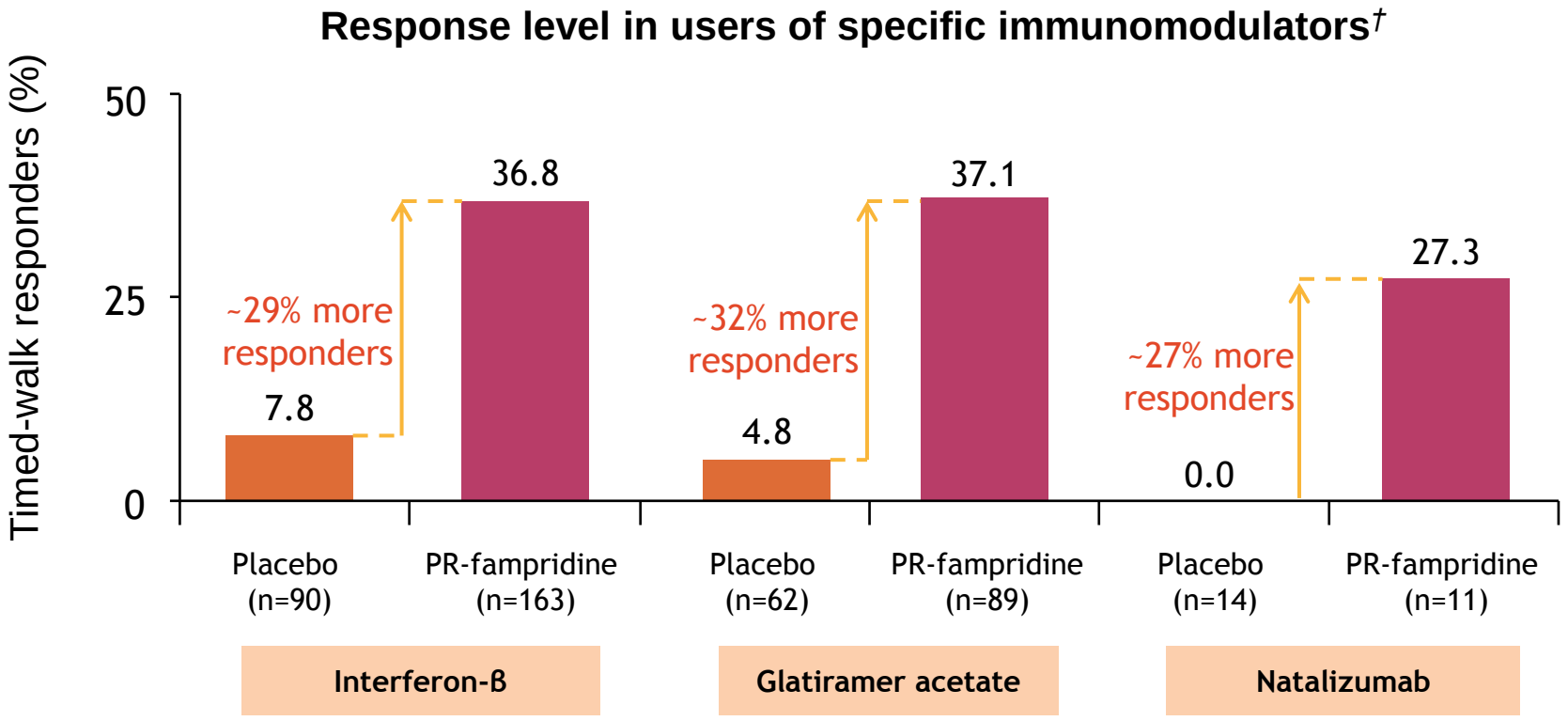
*Data from *post-hoc* pooled analysis of MS-F202, MS-F203 and MS-F204

PPMS = primary progressive MS; PR = prolonged-release; RRMS = relapsing remitting MS; SPMS = secondary progressive MS

Adapted from: Brown T, et al. Poster P921. Presented at ECTRIMS;13-16 October 2010

MS-F202/3/4: POOLED PRIMARY EFFICACY OUTCOME DATA

*PR-FAMPRIDINE TIMED-WALK RESPONSE RATES ARE CONSISTENT REGARDLESS OF TYPE OF CONCOMITANT DMT USE**



*Interaction P value = 0.076

†Data pooled from MS-F202, MS-F203 and MS-F204

DMT = disease modifying therapy; PR = prolonged-release

Brown TR, et al. Poster P06.136. Presented at ANN;10-17 April 2010

- The results of these two studies indicate that:
- between one third to one half of people with walking difficulties will see an improvement in their walking speed after taking Fampridine PR.
- An average improvement of about 25% of walking speed would be expected from those that respond to the treatment.

- Patients should be evaluated after two weeks and treatment should be stopped for those who have not shown an improvement

- Treatment should also be stopped if a patient's walking ability worsens or if the patient does not report any benefit.

- Fampyra should not be taken by people who may be hypersensitive (allergic) to fampridine or any of the other ingredients.

- It shouldnot be administered to patients who have seizures or have ever had seizures or in patients with kidney problems.

- It should not be used with other medicines that contain fampridine or medicines known as ‘inhibitors of organic cation transporter 2’ such as Cimetidine.

SAFETY AND TOLERABILITY: DISCONTINUATION

- In the Phase III trials (MS-F203/204)[1,2] PR-fampridine was generally well tolerated
- The majority of AEs were mild to moderate in severity and in general did not lead to treatment discontinuation
  - Low discontinuation rate due to AEs in three placebo-controlled MS studies
    - 4% for PR-fampridine
    - 2% for placebo

AE = adverse event; PR = prolonged-release

1. Goodman AD, et al. *Lancet* 2009;373:732–738; 2. Goodman AD, et al. *Ann Neurol* 2010;68:494–502; Ampyra PI, May 2012

PHASE III (MS-F203/4): ADVERSE EVENTS OF INTEREST

	Placebo (n=191)	PR-fampridine 10mg BID (n=148)
Urinary tract infection	10.5%	14.9%
Falls	16.2%	14.4%
Insomnia	2.6%	8.9%
Dizziness	2.6%	8.3%
Headache	2.6%	6.9%
Nausea	2.1%	6.9%
Asthenia	4.7%	6.6%
Upper respiratory tract infection	7.9%	6.0%
Back pain	1.6%	5.7%
Balance disorder	2.1%	5.7%
Fatigue	3.1%	5.2%

All AEs seen in >5% of PR-fampridine patients

- Seizure rates were similarly low in the placebo and PR-fampridine groups (1/191 [0.4%] vs 1/348 [0.3%] respectively)
- 5% discontinued due to AEs in MS-F203 and 3% in MS-F204
- Overall discontinuations were 8.8% in MS-F203 and 6.7% in MS-F204

AE = adverse event; PR = prolonged-release

Adapted from: Goodman AD, et al. *Lancet* 2009;373:732–738; Goodman AD, et al. *Ann Neurol* 2010;68:494–502

- No adverse effects on fertility were observed in rats following oral doses of fampridine up to 9 mg/kg/day in males and females treated prior to and during mating, continuing in females to late gestation or weaning.

- Adequate and well controlled studies in pregnant women have not been conducted.

- It is not known whether fampridine is excreted in human milk and the excretion of fampridine in milk has not been studied in animals.

INT J NEUROSCI. 2017 OCT;127(10):915-922.

EXPERIENCE WITH FAMPRIDINE IN CLINICAL PRACTICE: ANALYSIS OF A POSSIBLE MARKER OF CLINICAL RESPONSE.

ALVAREZ-PAYERO M[1], VALEIRAS-MUÑOZ C[2], LION-VÁZQUEZ S[3], PIÑEIRO-CORRALES G[1], MUÑOZ-GARCÍA D[4], MIDAGLIA L[4].

- Six-month prospective study of fampridine in patients with multiple sclerosis.

- Of all patients, 70.9% demonstrated clinical benefit based on response criteria established, at the 14-d follow-up, 61.8% at 3 months and 45.5% at 6 months.

- A significant decrease in the mean (SD) EDSS score was observed in responders at 6 months (6.1 [0.9] vs. 5.64 [0.1], $p < 0.05$).

- Adverse effects were recorded in 50.9%, although most were mild-moderate and resolved completely.

MULT SCLER J EXP TRANSL CLIN. 2017 NOV 8;3(4):2055217317740145.

RANDOMIZED, PLACEBO-CONTROLLED CROSSOVER STUDY OF DALFAMPRIDINE EXTENDED-RELEASE IN TRANSVERSE MYELITIS.

SCHWARTZ K[1], WYMBS NF[1], HUANG H[1], MEALY MA[1], PARDO CA[1], ZACKOWSKI K[1], LEVY M[1].

- Sixteen adult study participants with monophasic TM confirmed by MRI were enrolled if their baseline timed 25-foot walking speed was between 5 and 60 seconds.

- Of 16 enrolled participants, three withdrew and 13 completed the trial.

- Among the 13 completers, nine individuals showed an average timed walk that was faster in the D-ER arm compared to the placebo arm, but only four participants met the stricter statistical threshold to be classified as a responder.

- Analyses of secondary clinical outcome measures including strength, balance assessments, spasticity, and EDSS score showed trends toward improvement with D-ER.

NEUROLOGY. 2017 FEB 28;88(9):832-841.

MONITORING LONG-TERM EFFICACY OF FAMPRIDINE IN GAIT-IMPAIRED PATIENTS WITH MULTIPLE SCLEROSIS.

FILLI L[1], ZÖRNER B[2], KAPITZA S[2], REUTER K[2], LÖRINCZ L[2], WELLER D[2], SUTTER T[2], KILLEEN T[2], GRUBER P[2], PETERSEN JA[2], WELLER M[2], LINNEBANK M[2].

- Fifty-three PwMS who completed the FAMPKIN core study were included in this extension trial.
- Drug efficacy was assessed in an open-label and randomized double-blind, placebo-controlled study design with regular baseline assessments over a period of 2 years using the Timed 25-Foot Walk (T25FW), 6-Minute Walk Test (6MWT), and 12-item MS Walking Scale (MSWS-12) as outcome measures.

- The data showed good tolerability and persisting efficacy of PR fampridine during long-term treatment in PwMS.

- Significant improvements in walking speed, endurance, and self-perceived ambulatory function were observed during open-label and double-blind controlled treatment with PR fampridine

- Several patients showed changes in drug responsiveness over time, resulting in an increased proportion of patients exceeding 10% or 20% improvements in walking measures after long-term treatment.

- The considerable proportion of patients in whom responsiveness to
  PR fampridine changed over time emphasizes the importance of regular reassessment of drug efficacy in clinical practice to optimize treatment.
- Such reassessments seem to be particularly important in patients with poor initial drug responses, as this group demonstrated enhanced responsiveness after long-term treatment.

Ann Phys Rehabil Med. 2016 Sep;59S:e40. "Gait responder" to fampridine, a too restrictive concept? Christopher M, Sagawa Y Jr, Bernard C, Moulin T, Magnin E, Decavel P.

- 60 PwMS with an EDSS score between 4 and 7 were included in a prospective monocentric open label trial.

- Two identical measures were conducted a week apart before initiating treatment in order to take into account the test-retest effect.

- Then, patients were treated for at least 14 days and were evaluated twice (again a week apart).
- Two tests were used to measure IPS: symbol digit modalities test (SDMT) and verbal fluencies test (VFT).
- The gait was measured at fast condition and the fatigue was evaluate using the modified fatigue impact scale (EMIF-SEP).

- Patients were divided into two groups regarding to the increase of gait speed after treatment: gait responders (GR) (more than 17.2%) and non-gait responders-NGR (less than 17.2%).
- The second group was also divided into two groups: those continuating treatment (on clinician appreciation) called others responders (OR) and those who stopped treatment called no responders (NR)

- Mean EDSS was 5.25±1.07.
- 24% of PwMS were qualified as gait responder (mean speed improvement of 49.4%).
- Those who improved their gait velocity were the most affected by the disease (regarding to EDSS).

- Fatigue and IPS improvement was found in GR, NGR and OR after treatment.

- Our results suggest that fampridine could have an effect on cognition disorders and fatigue even on those who are not gait responder.

BRAIN BEHAV. 2017 JAN; 7(1): E00559.

DALFAMPRIDINE EFFECTS ON COGNITION, FATIGUE, AND DEXTERITY

MELANIE KORSEN, [1] RHINA KUNZ, [1] ULF SCHMINKE, [1] UWE RUNGE, [1] THOMAS KOHLMANN, [2] AND ALEXANDER DRESSEL

- Here, we investigated whether the responder status with respect to mobility measures would determine whether dalfampridine treatment exerts a beneficial effect on other MS symptoms.

- We therefore assessed walking ability, upper limb function, cognition, fatigue, VEPs, depression, and quality of life in patients before and after dalfampridine treatment.

- Of the 34 patients who completed the study, 22 patients were responders and 12 patients nonresponders, according to their performance in mobility measures.

- Treatment effects for the entire patient cohort were observed for PASAT (p = .029) and BDI (p = .032).

- In this study, we observed beneficial effects of dalfampridine on cognition, depression, and fatigue.
- These effects were not limited to patients who responded to dalfampridine with improved mobility measures.
- These findings underscore the need to assess the beneficial effects of dalfampridine on neurological deficits in MS patients in additional randomized clinical trials.

J NEUROL. 2015 AUG;262(8):1936-45.

SUSTAINED-RELEASED FAMPRIDINE IN MULTIPLE SCLEROSIS: EFFECTS ON GAIT PARAMETERS, ARM FUNCTION, FATIGUE, AND QUALITY OF LIFE.

ALLART E[1], BENOIT A, BLANCHARD-DAUPHIN A, TIFFREAU V, THEVENON A, ZEPHIR H, OUTTERYCK O, LACOUR A, VERMERSCH P.

- 120 consecutive, eligible patients with MS were evaluated at baseline (D0) and after two weeks (D14) of fampridine-SR.
- Lastly, D14 responders were again evaluated after three months (M3).
- Response to treatment was defined as a 15% improvement in at least one of the following tests: the Timed 25-Foot-Walk (T25FW), the 2-min walk test (2MWT) and the Multiple Sclerosis Walking Scale (MSWS-12).

- Eighty-three patients (74%) were found to be responders.

- The response rate was lower when assessed as a 20% improvement in the T25FW (50.9%), and this difference was particularly marked for fast-walking subjects (i.e. T25FW <8 s at baseline).

- Responders showed also significant, lasting reductions in fatigue and significant, lasting improvements in hand function

- In conclusion, several MS-induced symptoms other than gait velocity may be improved by fampridine-SR, even if this remains to be more specifically evaluated in future studies.

MULT SCLER RELAT DISORD. 2018 DEC 19;28:117-124.
EFFECTS OF 4-AMINOPYRIDINE ON ATTENTION AND EXECUTIVE FUNCTIONS OF PATIENTS WITH MULTIPLE SCLEROSIS: RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL. PRELIMINARY REPORT.
ARREOLA-MORA C[1], SILVA-PEREYRA J[2], FERNÁNDEZ T[3], PAREDES-CRUZ M[4], BERTADO-CORTÉS B[5], GRIJALVA I[6].

- Twenty-four patients were recruited of which 21 completed the trial, 11 with 4-aminopyridine and 10 with placebo treatment.

- No significant differences between groups in the initial assessments were observed.

- In terms of efficacy, the experimental group achieved significantly higher scores in attention span, verbal fluency, planning and graphics and constructive motion.

SPRINGERPLUS. 2016 JUL 13;5(1):1070. FAMPRIDINE AND QUALITY OF LIFE IN INDIVIDUALS WITH MULTIPLE SCLEROSIS. SAGAWA Y JR[1], MAGNIN E[2], PAILLOT L[3], MOULIN T[4], DECAVEL P[1].

- Fifty pwMS were included in this study.
- QoL was evaluated 7 days before fampridine (Pre1), on the day the fampridine treatment was initiated (Pre2), and 14 and 21 days after fampridine (Post1 and Post2 respectively)
- The QoL of pwMS improved after fampridine, suggesting a real benefit in their lives.

EUR NEUROL. 2015;74(5-6):243-50.
VERBAL FLUENCIES AND FAMPRIDINE TREATMENT IN MULTIPLE SCLEROSIS.
MAGNIN E[1], SAGAWA Y JR, CHAMARD L, BERGER E, MOULIN T, DECAVEL P.

- Verbal fluencies were significantly higher after fampridine treatment.
- Gait responders and gait non-responders did not present significant differences in verbal fluency performance and fatigue score.
- No correlation between gait velocity improvement and fatigue improvement compared with verbal fluency improvement was observed.

CNS DRUGS. 2018 JUL 10. RESTORING AXONAL FUNCTION WITH 4-AMINOPYRIDINE: CLINICAL EFFICACY IN MULTIPLE SCLEROSIS AND BEYOND. LEUSSINK VI[1], MONTALBAN X[2,3], HARTUNG HP[4].

- Downbeat Nystagmus
- This lack of subjective improvement may be overcome with the sustained-release form of 4-aminopyridine, which has shown efficacy in an observational study.

- Therefore, further trials on the sustained-release formulation are needed to better understand the clinical efficacy and long-term effects of 4-aminopyridine.

EPISODIC ATAXIA TYPE 2

- A randomized, placebo-controlled trial investigated theclinical efficacy of 4-aminopyridine in ten subjects with EA2.
- During the study, the median monthly attack frequency under placebo was 6.5 and decreased to 1.65 (p = 0.03) under treatment with 4-aminopyridine.
- In addition, the median monthly attack duration decreased from 13.65 h with placebo to 4.45 h with 4-aminopyridine (p = 0.08) and quality of life, measured via the Vestibular Disorders Activities ofDaily Living Scale, improved.

CEREBELLAR ATAXIAS

- Sustained-release 4-aminopyridine revealed modest short-term improvements in a short-term trial in 16 patients with cerebellar ataxia (sporadic adult-onset ataxia of unknown etiology [SAOA], spinocerebellar ataxia types 1–3, 6 [SCA1/3/6], POLG mutation)