XP13512 Improves Symptoms and Sleep Disturbance in Restless Legs Syndrome (RLS) Patients: Results of a 2-Week, Randomized, Double-Blind, Placebo-Controlled, Cross-Over Polysomnography Trial

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Proposed RLS Etiologies

- Genetic predisposition (chromosomal loci 12q, 14q, and 9p)[1-3]
- Decreased dopamine measures in the striatal area of the brain in positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies[4]
- Decreased substantia nigra and putamen iron levels[5]
- Subset of RLS patients with small sensory fiber loss[6]
- Hyperalgesia without allodynia[7]

[1]Desautels A, et al. *Am J Hum Genet.* 2001;69:1266-1270.
[2]Bonati MT, et al. *Brain*. 2003;126:1485-1492.
[3]Winkelmann J, et al. *Mov Disord.* 2006;21:28-33.
[4]Michaud M, et al. *J Neurol.* 2002;249:164-170.
[5]Allen RP and Earley CJ. *Sleep Med.* 2000;1:11-19.
[6]Polydefkis M, et al. *Neurology.* 2000;55:1115-1121.
[7]Stiasny-Kolster K, et al. *Brain*. 2004;127:773-782.

Gabapentin RLS Patient Studies

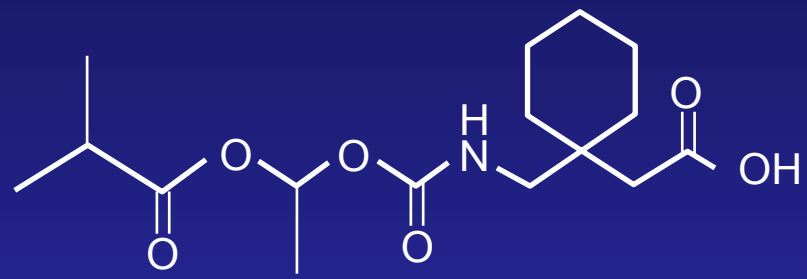
First Author (Year)	Trial Design	N	Baseline RLS Severity	Results for GBP-Treated Patients
Micozkadioglu (2004)[1]	RCT, OL	14*	Moderate	Decrease in RLS severity in all patients† Improvements in sleep quality,‡ sleep latency,‡ and sleep duration‡
Happe (2003)[2]	RCT, OL	16	Moderate to severe	Decrease in RLS severity in all patients† Reduction in PLMS†
Garcia-Borreguero (2002)[3]	RCT, DB, CO	22	Moderate to severe	Decrease in RLS severity§ and stage 1 sleep† Reduction in PLMS† and improvements in increased total sleep time,‖ sleep efficiency,¶ and slow wave sleep†
Thorp (2001)[4]	RCT, DB, CO	13*	Not defined	12 of 13 patients had relief of RLS symptoms#
Happe (2001)[5]	OL	9	Moderate to severe	8 of 9 patients had relief of RLS symptoms,** increased sleep quality,** and decreased daytime sleepiness†† Reduction in PLMS‡‡
Adler (1997)[6]	OL	8	Not defined	4 of 8 patients had relief of RLS symptoms

*Hemodialysis patients; †$p \leq 0.05$; ‡$p < 0.001$; §$p < 0.0005$; ‖$p = 0.01$; ¶$p < 0.0001$; #$p < 0.01$; **$p = 0.004$; ††$p = 0.034$; ‡‡$p = 0.003$.
Abbreviations: GBP indicates gabapentin; RCT, randomized controlled trial; OL, open-label; PLMS, periodic leg movements of sleep; DB, double-blind; CO, cross-over.

[1]Micozkadioglu H, et al. *Ren Fail*. 2004;26:393-397. [2]Happe S, et al. *Neuropsychobiology.* 2003;48:82-86.
[3]Garcia-Borreguero D, et al. *Neurology.* 2002;59:1573-1579. [4]Thorp ML, et al. *Am J Kidney Dis*. 2001;38:104-108.
[5]Happe S, et al. *Neurology.* 2001;57:1717-1719. [6]Adler CH. *Clin Neuropharmacol.* 1997;20:148-151.

XP13512 - Overview

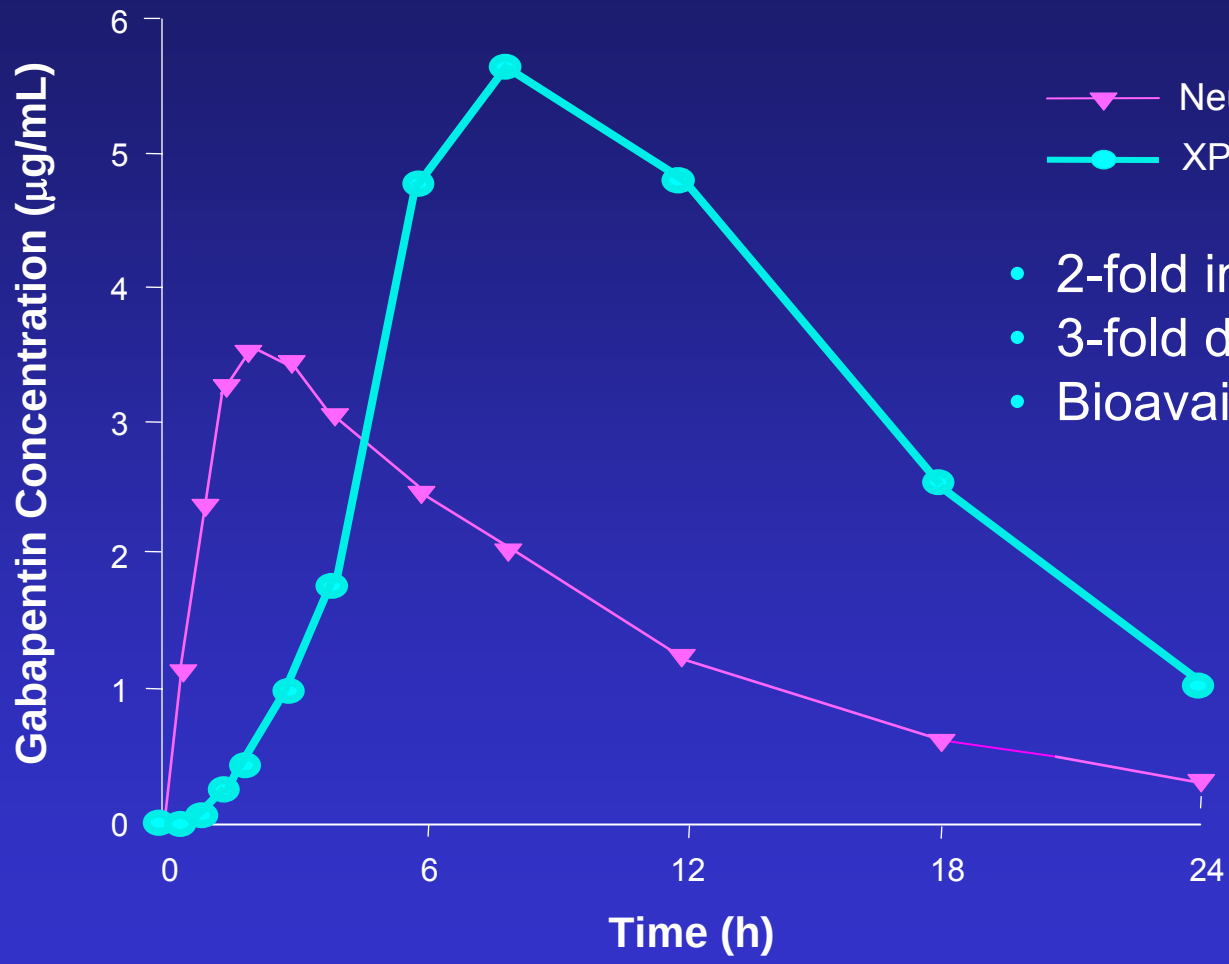
- Gabapentin prodrug, which is actively transported by MCT1 and SMVT
- Well absorbed throughout gastrointestinal (GI) tract



- Immediately releases gabapentin in blood
- Linear pharmacokinetics (no saturable absorption of gabapentin)
- Successfully formulated for sustained release (SR)
- 2 mg of XP13512 produces ~1 mg of gabapentin

MCT1 indicates monocarboxylate transporter type 1; SMVT, sodium-dependent multivitamin transporter.

Mean Concentrations of Gabapentin in Blood After Oral Near-Equal XP13512 SR or Neurontin® Doses in Healthy Adults



- 2-fold increase in AUC
- 3-fold delay in T_{max}
- Bioavailability, 75%

2 mg of XP13512 produces ~1 mg of gabapentin.

AUC indicates the area under the plasma concentration-time curve; T_{max}, time to maximum plasma concentration.
XenoPort, Inc., Study XP022, data on file.

Phase 2b Double-Blind, Placebo-Controlled, Randomized, Parallel-Group Study

- A 2-week, randomized, double-blind, placebo-controlled exploratory trial
  - Study drug (XP13512 600 mg or 1200 mg) taken at 5 PM daily with food
- XP13512 1200 mg resulted in a significant decrease in the International Restless Legs Syndrome (IRLS) Rating Scale scores
  - Significant improvements were also evident in sleep quality, pain, mood, and Clinical Global Impression (CGI) of change
- XP13512 was generally well tolerated
  - No serious adverse events were observed with doses of either 600 mg or 1200 mg
  - Adverse events (somnolence, dizziness) were generally transient and mild to moderate in severity

XenoPort, Inc., Study XP045, data on file.

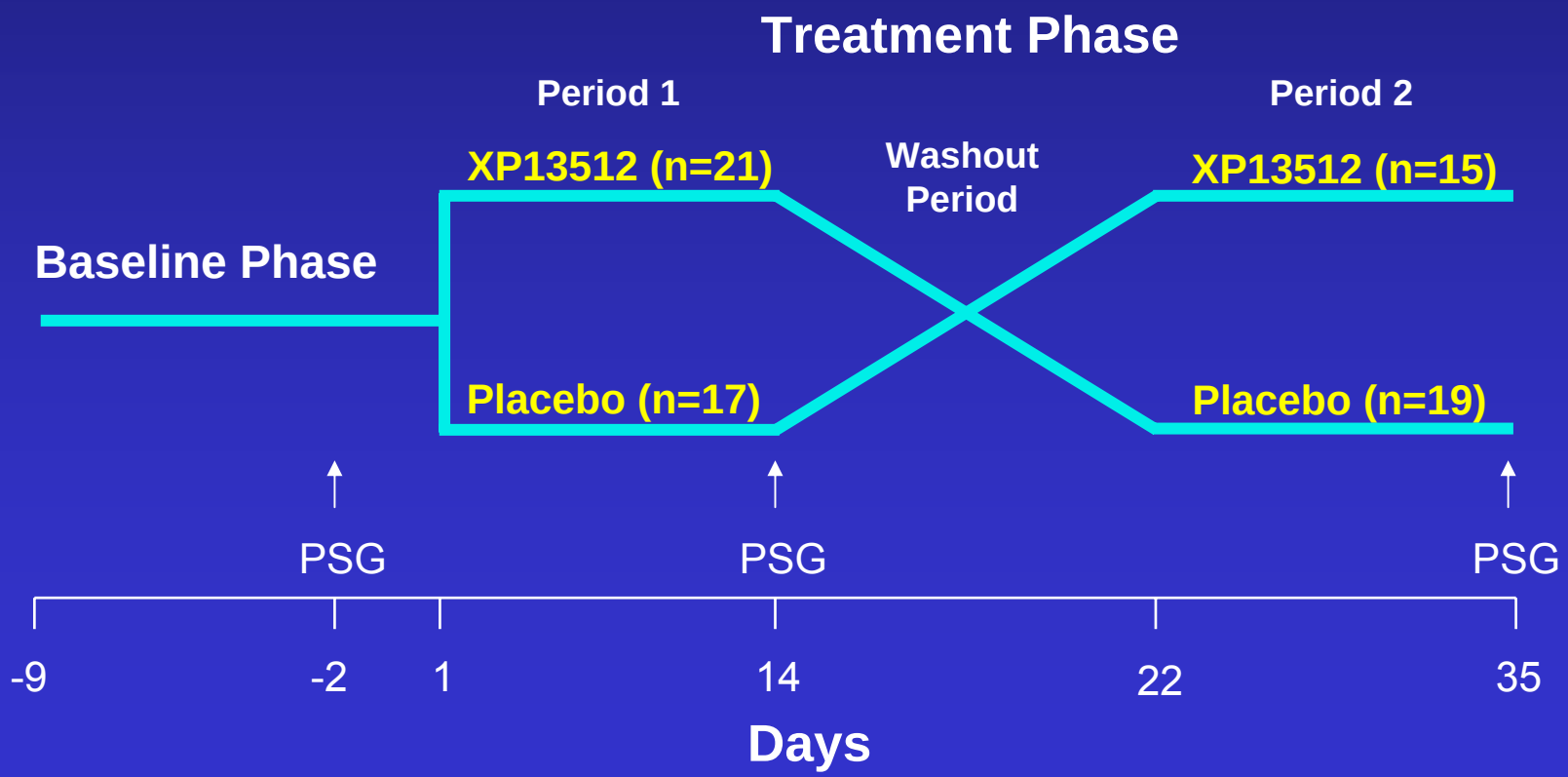
Study Objectives

- Primary objective
  - Assess the efficacy of XP13512 versus placebo for the treatment of patients with RLS using IRLS Rating Scale scores
- Secondary objectives
  - Assess the efficacy of XP13512 for reducing PLMS and improving sleep quality and architecture
  - Evaluate the safety of XP13512

Phase 2a Randomized, Double-Blind, Placebo-Controlled Cross-Over Study

Study Design (N=38)

In Periods 1 and 2, XP13512 was titrated over 5 days to 1800 mg daily (600 mg at 5:00 PM, 1200 mg 1 hour before bedtime)



PSG indicates polysomnogram.

Inclusion/Exclusion Criteria

- RLS based on IRLSSG diagnostic criteria[1]
- Aged 18 to 69 years
- RLS symptoms for ≥4 of the 7 nights in baseline study period
- Total RLS severity score of ≥15 on the IRLS Rating Scale at the end of baseline period
- No other primary sleep disorders that may significantly affect RLS symptoms

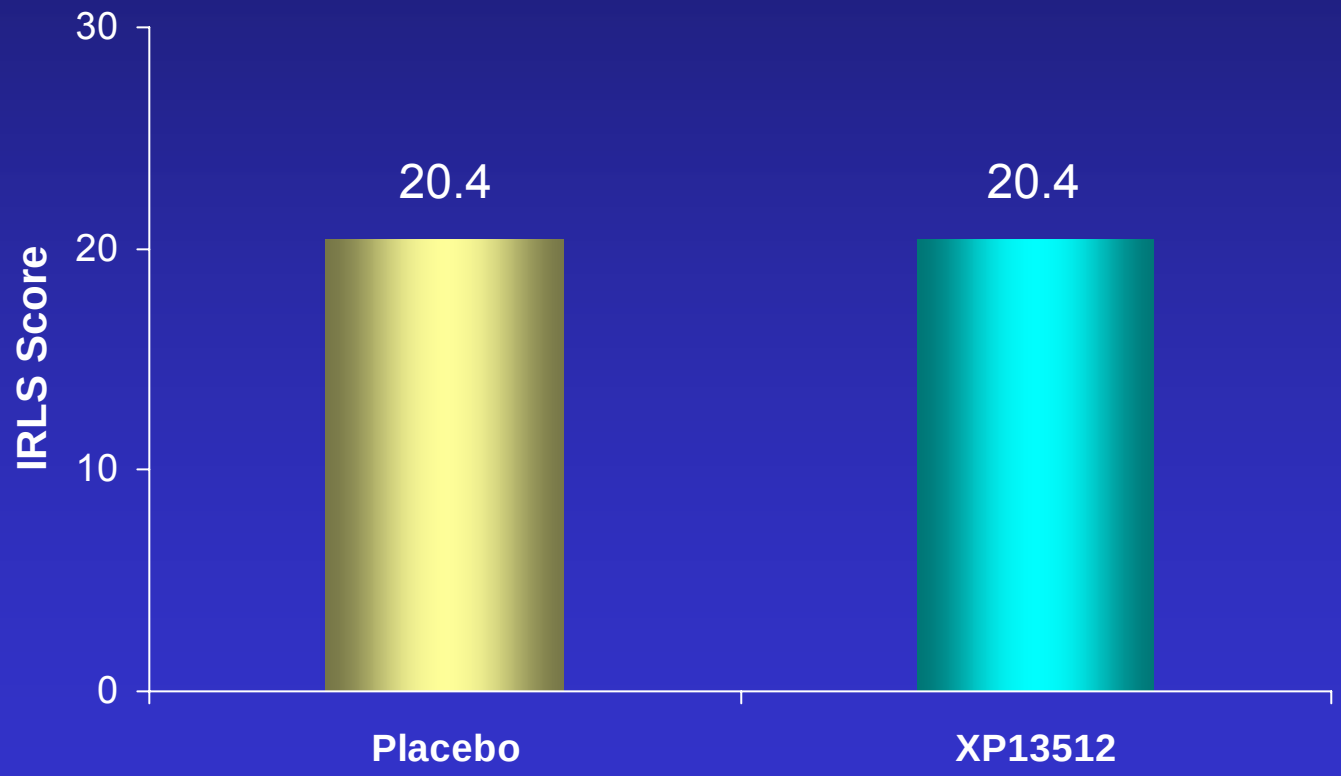
[1]Allen RP, et al. *Sleep Med*. 2003;4:101-119; International Restless Legs Syndrome Study Group (IRLSSG).

Patient Demographic and Baseline Characteristics

N=38	All Patients
Gender, n (%)	
Male	16 (42.1)
Female	22 (57.9)
Race, n (%)	
White/Caucasian	34 (89.5)
Age, years	
Mean (SD)	50.1 (13.2)
Range	19.7-72.7
Days with RLS symptoms (from 7-day RLS record)	
Mean (SD)	6.0 (1.1)
Range	4-7
Duration of RLS symptoms, years	
Mean (SD)	14.3 (14.1)
Range	0.0-57.0

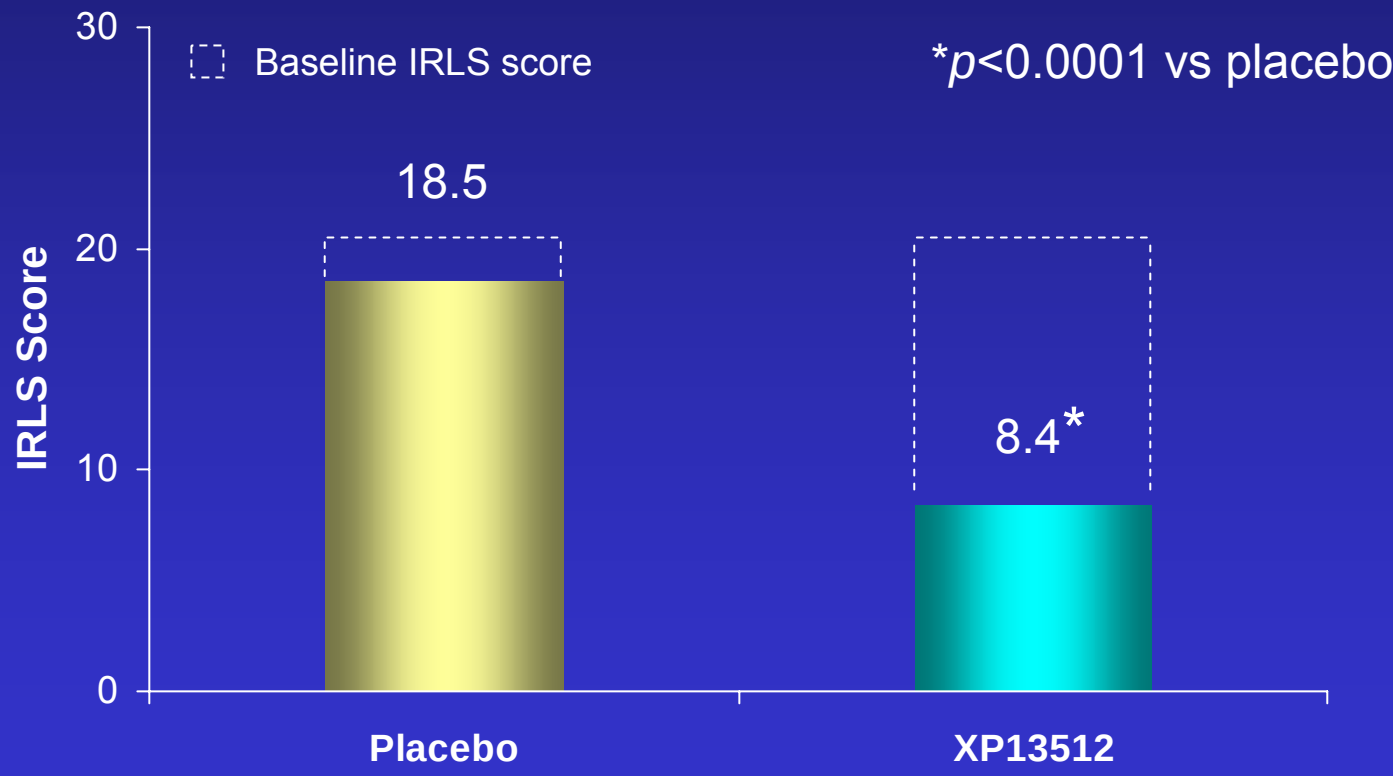
IRLS Rating Scale Score

Baseline (n=34)



IRLS Rating Scale Score

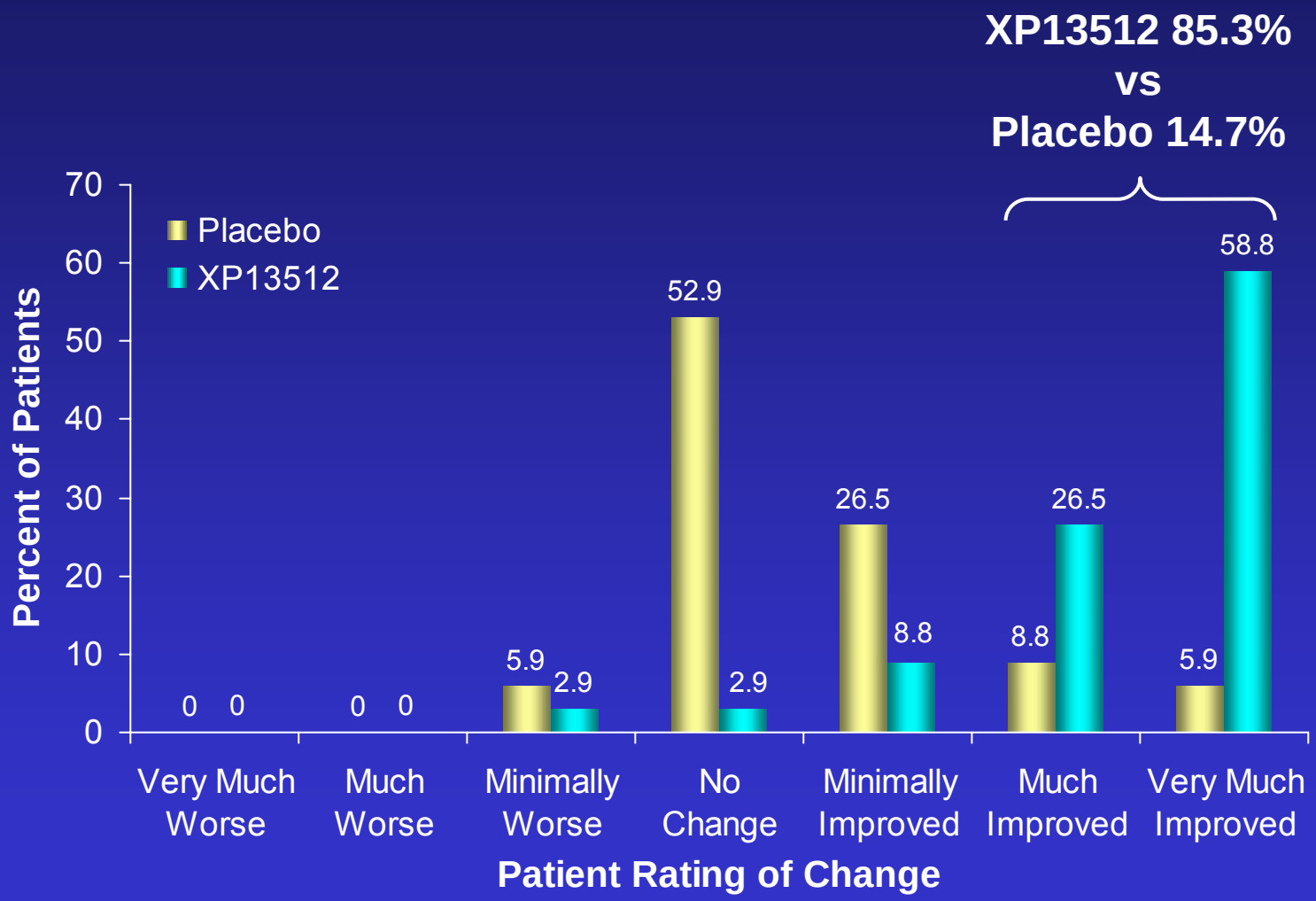
End of Week 2 (n=34)



Investigator Clinical Global Impression of Change

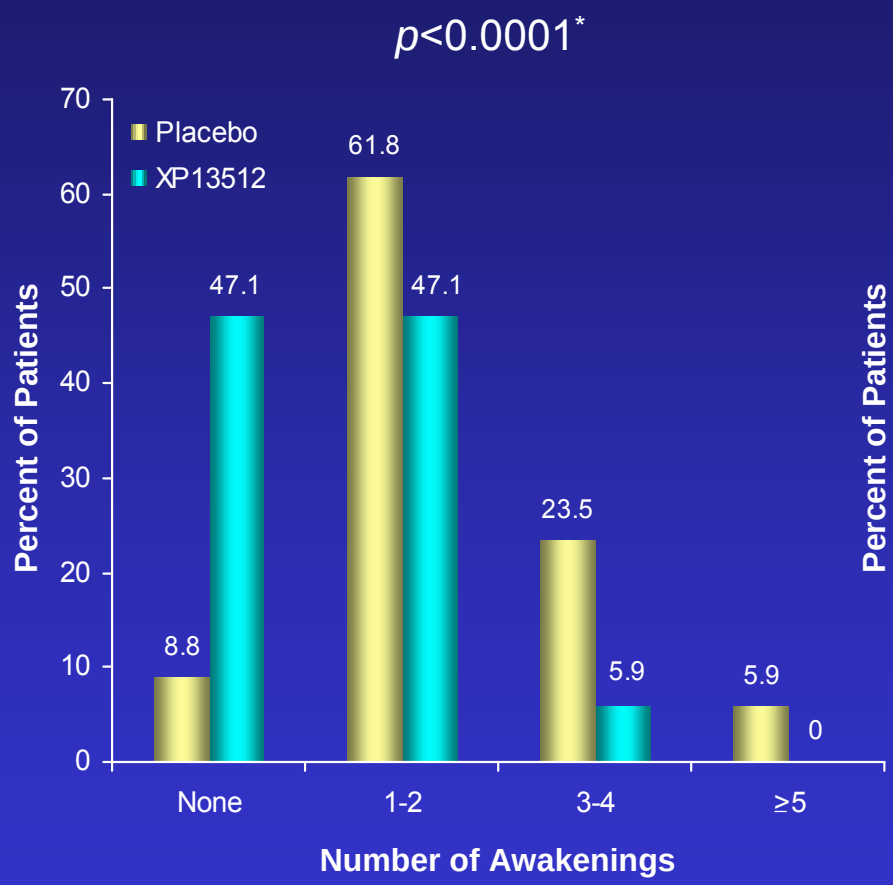
XP13512 vs placebo: $p<0.0001$, comparison across total distribution.

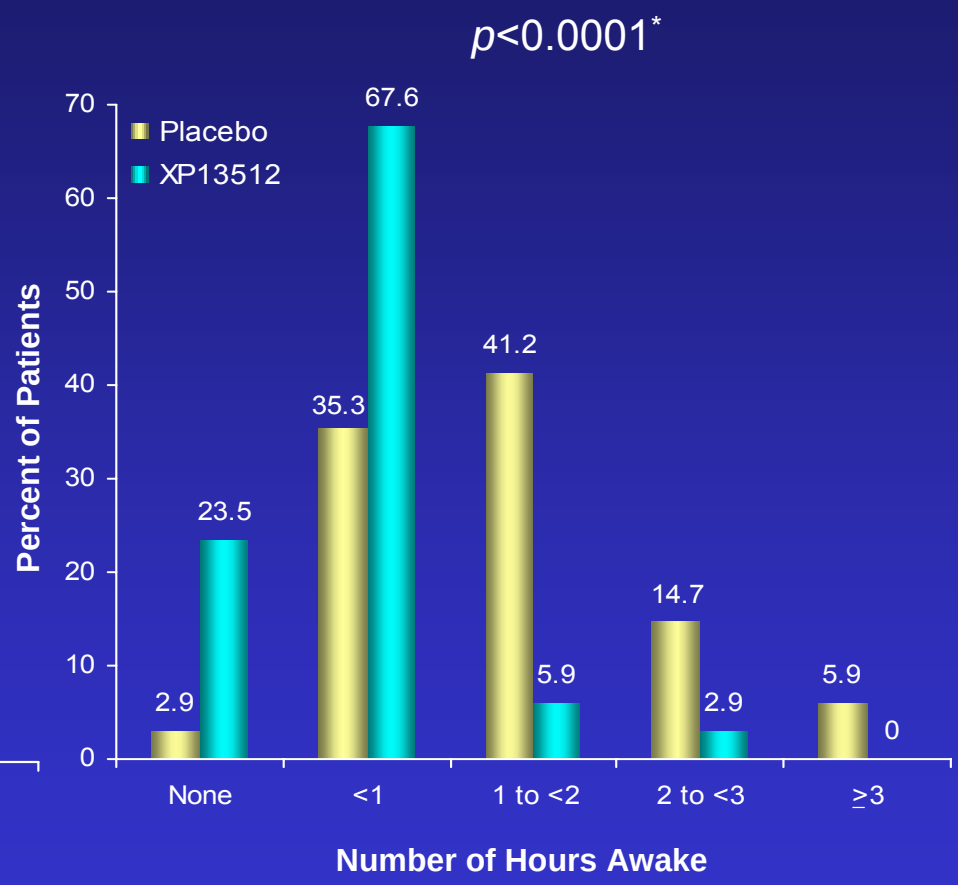
Patient Clinical Global Impression of Change



XP13512 vs placebo: $p<0.0001$, comparison across total distribution.

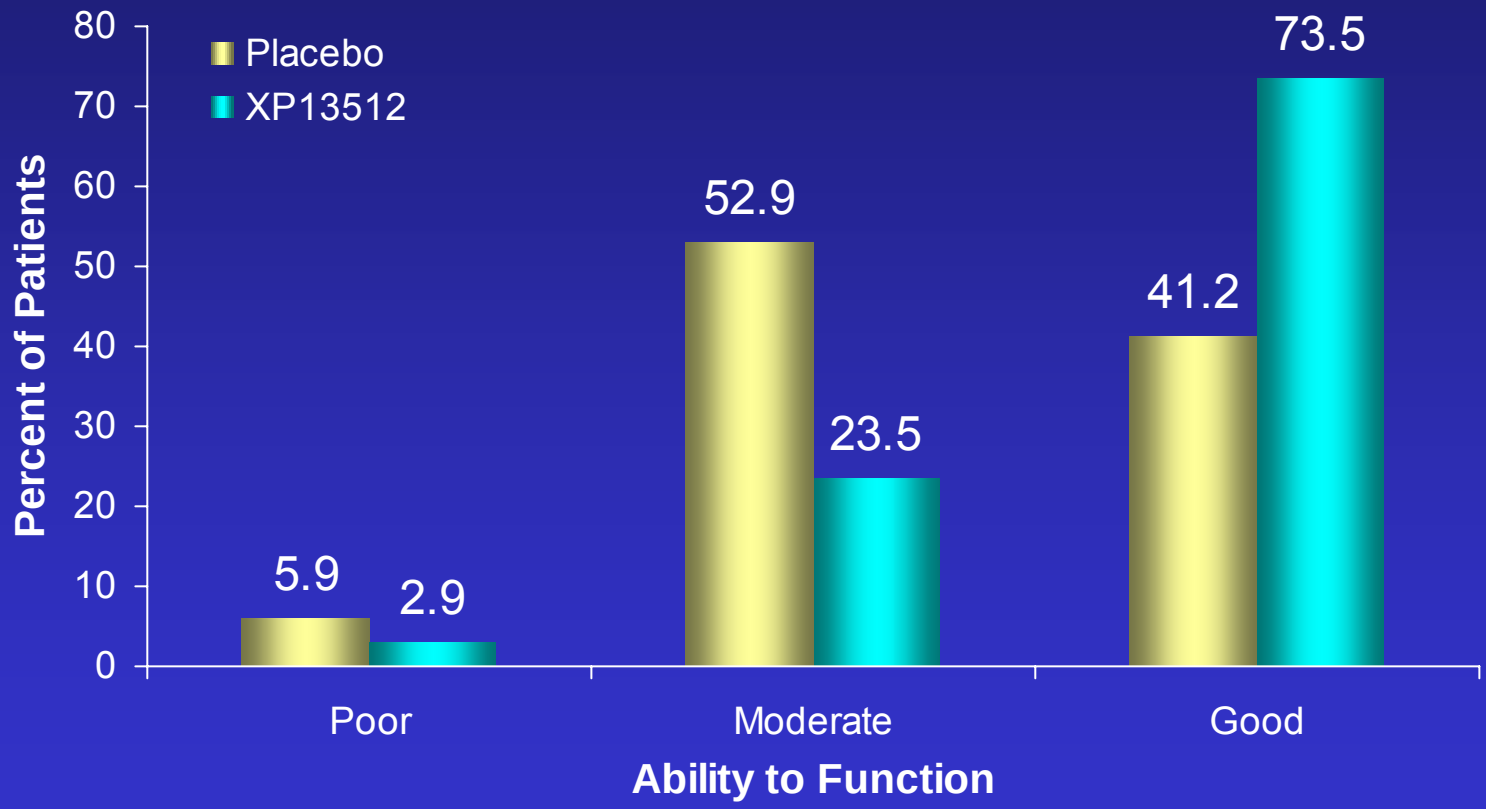
Reduction in Number of Awakenings and Hours Awake at Night Due to RLS Symptoms in Past Week (Week 2)





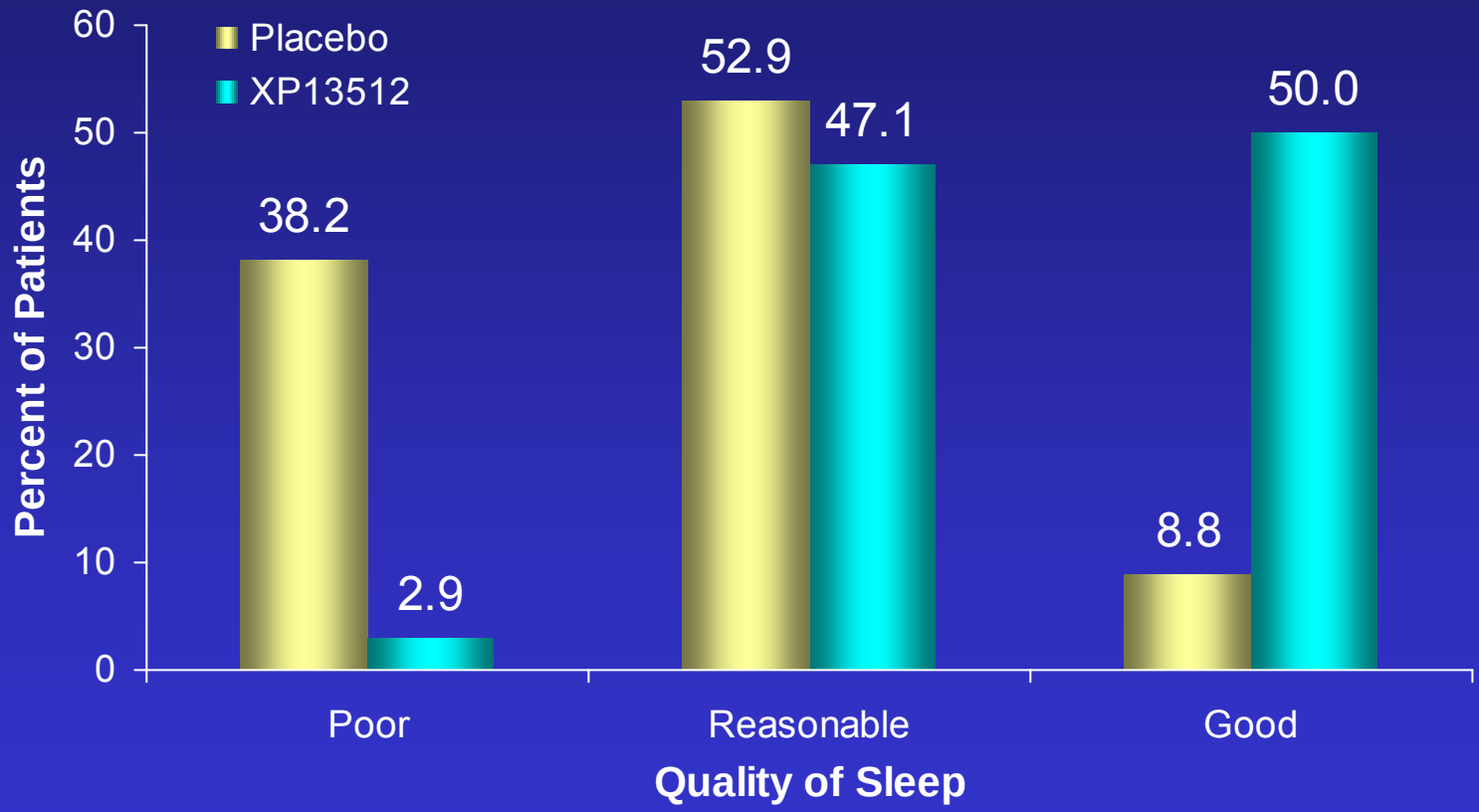
*Repeated measures Cochran-Mantel-Haenszel test.

Ability to Function in Past Week (Week 2)



p=0.0143, repeated measures Cochran-Mantel-Haenszel test.

Overall Quality of Sleep in Past Week (Week 2)



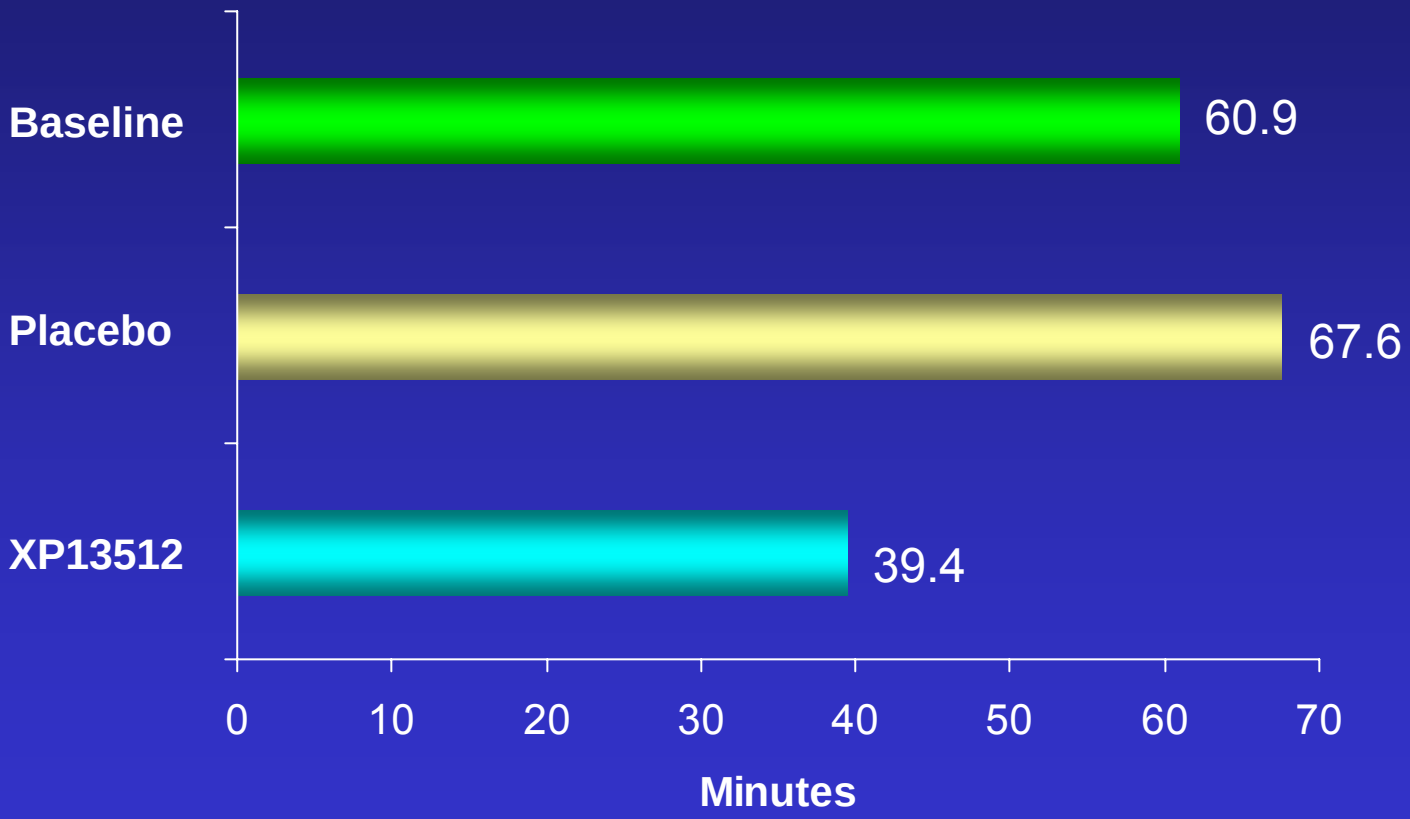
p<0.0001, repeated measures Cochran-Mantel-Haenszel test.

PSG: Sleep Measures

	Baseline (N=34)	Placebo	XP13512	*p* Value (ANOVA)
Sleep efficiency, %	81.9	81.8	87.1	0.0309
Number of awakenings	8.0	8.5	6.0	<0.0001
Number of entries to stage 1	20.6	22.4	16.5	<0.0001
Total sleep time, min	393.2	392.6	417.7	0.0317

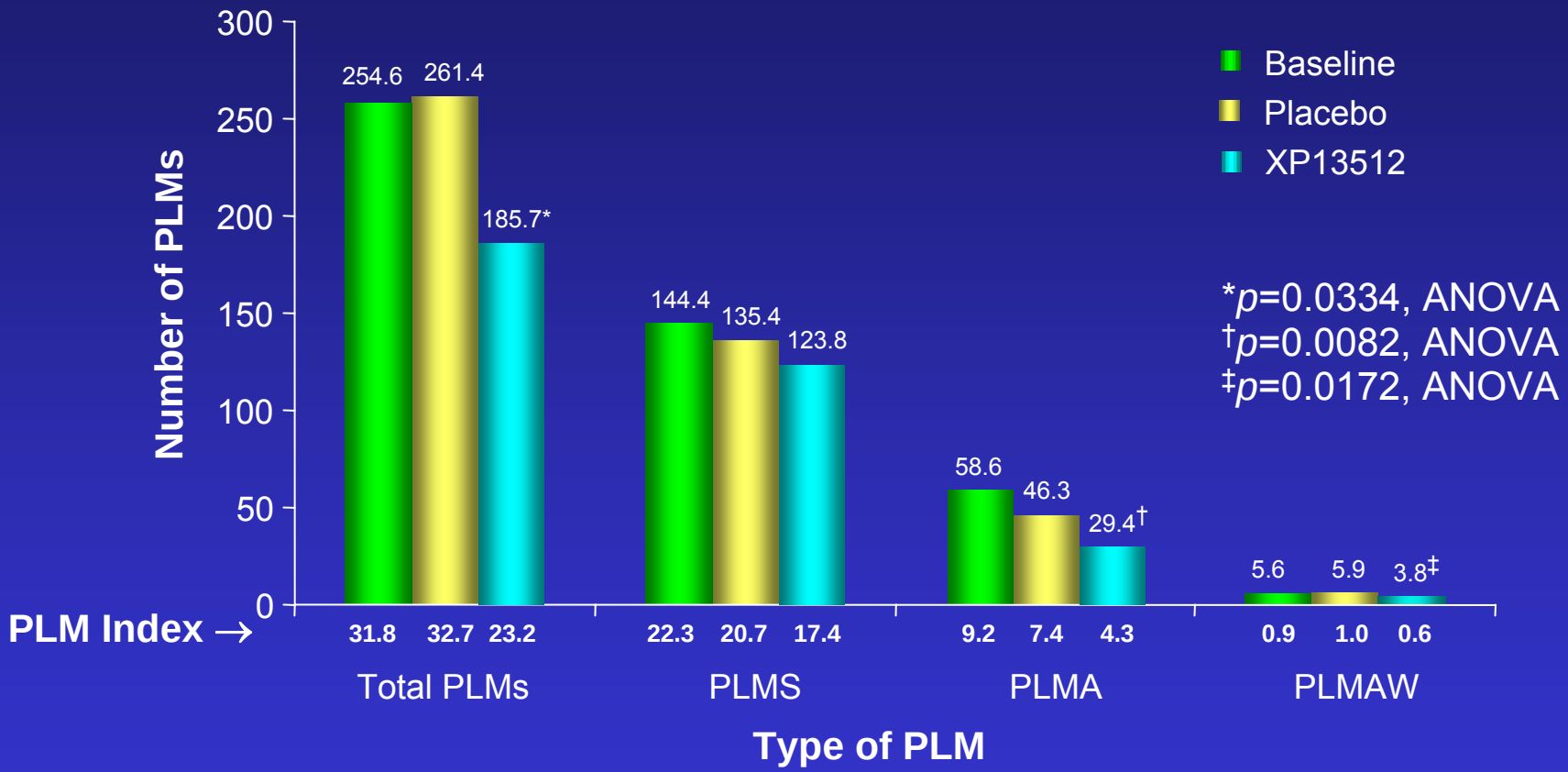
ANOVA indicates analysis of variance.
PSG analysis by Tom Roth, PhD, Sleep Disorders Center, Henry Ford Hospital, Detroit, Michigan, and staff.

PSG: Wake Time After Sleep Onset



p=0.0009, ANOVA.

PSG (8 Hours): Periodic Leg Movements



PLMs indicates periodic leg movements; PLMS, period leg movements of sleep; PLMA, periodic leg movements of sleep with ≥3-second arousal; PLMAW, periodic leg movements of sleep with ≥30-second awakening.

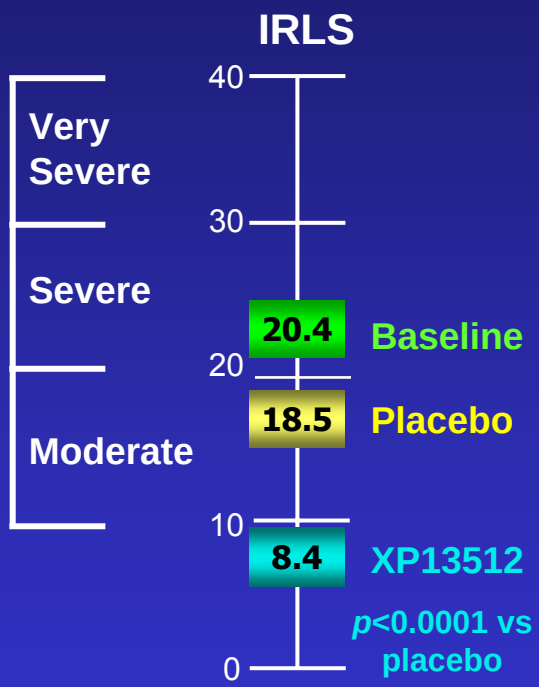
Number of Patients (≥2) With Adverse Events

Adverse Event (N=36)	Placebo, n (%)	XP13512, n (%)
All adverse events	14 (38.9)	28 (77.8)
Somnolence	1 (2.8)	11 (30.6)
Dizziness	2 (5.6)	10 (27.8)
Balance disorder	0 (0.0)	3 (8.3)
Dry mouth	0 (0.0)	2 (5.6)
Nausea	0 (0.0)	2 (5.6)
Fatigue	0 (0.0)	2 (5.6)
Headache	1 (2.8)	2 (5.6)
Hypoaesthesia	0 (0.0)	2 (5.6)
Insomnia	0 (0.0)	2 (5.6)
Nasopharyngitis	3 (8.3)	0 (0.0)

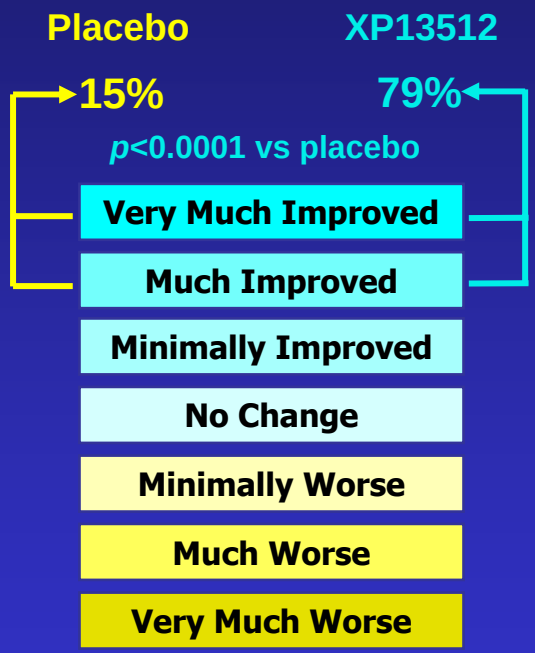
No study withdrawals due to AEs

Summary

Reduced RLS Symptoms (IRLS Rating Scale score)



Improved Investigator Rating (CGI score)



Improved Sleep Parameters (polysomnogram)

Significant improvements in

- TST and SE
- SWS
- WASO
- PLMs

All $p<0.05$ vs placebo

XP13512 was generally well tolerated in this study.

No serious adverse events were observed at a dose of 1800 mg.
Adverse events (somnolence, dizziness) were generally transient and mild to moderate in severity.

TST indicates total sleep time; SE, sleep efficiency; SWS, slow wave sleep; WASO, time awake after sleep onset.

Conclusions

- XP13512 resulted in a significant decrease in IRLS Rating Scale scores
  - Significant improvements were also evident in sleep quality and architecture, leg discomfort, and clinical global impressions of change
- XP13512 was generally well tolerated in this study
  - No serious adverse events were observed at a dose of 1800 mg
  - Adverse events (somnolence, dizziness) were generally transient and mild to moderate in severity