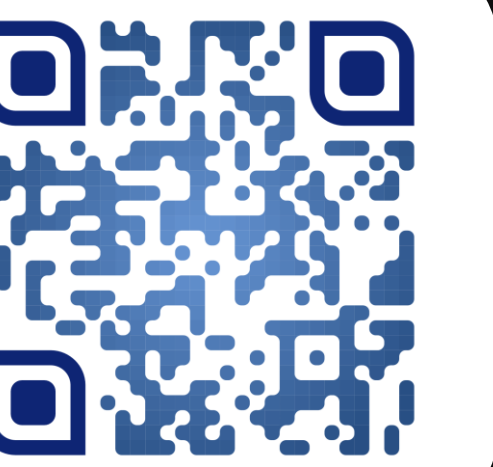


Solriamfetol (Sunosi®) for the Treatment of Excessive Daytime Sleepiness Associated with Narcolepsy or Obstructive Sleep Apnea: Post-hoc Analysis of Epworth Sleepiness Scale Items

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Key Objective

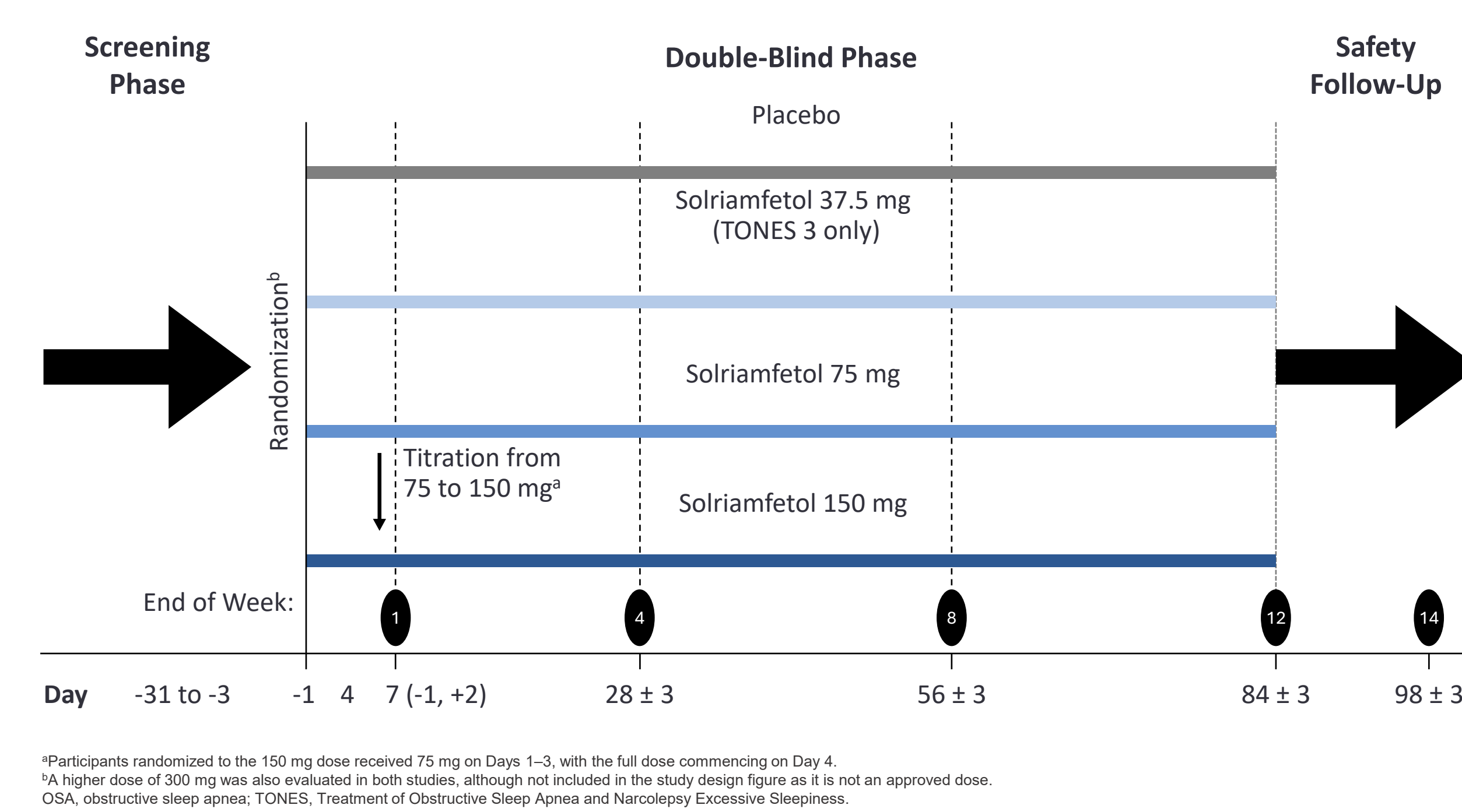
To evaluate the extent to which solriamfetol impacts various dimensions of daytime sleepiness as measured by the Epworth Sleepiness Scale using post hoc analyses from the TONES 2 and TONES 3 phase 3 trials

Introduction

- Solriamfetol (Sunosi®) is a dopamine-norepinephrine reuptake inhibitor with agonistic properties at the trace amine-associated receptor 1 (TAAR1) and serotonin 1A (5-hydroxytryptamine 1A [5-HT1A]) receptors^{1,2}, approved for use in adults in the United States, Canada, and select countries in Europe for the treatment of excessive daytime sleepiness (EDS) associated with narcolepsy (75–150 mg/day) or obstructive sleep apnea (OSA; 37.5–150 mg/day)^{3–5}
- TONES 2 and TONES 3 were double-blind, randomized, placebo-controlled, parallel-group, 12-week trials evaluating the safety and efficacy of solriamfetol for the treatment of EDS among patients with narcolepsy or OSA, respectively^{1,2}
- A previously published study found that a greater percentage of participants treated with solriamfetol achieved total Epworth Sleepiness Scale (ESS) scores within the normative range (score ≤ 10) or clinically meaningful improvements (≥ 25% reduction relative to baseline) on the ESS compared with those receiving placebo⁶
- However, the clinical significance of impairment across individual ESS domains can vary (eg EDS symptoms impacting driving or public activities may result in a greater disease burden than those impacting activities while at home) and have not been evaluated

Methods and Study Design

Figure 1. TONES 2¹ (Narcolepsy) and TONES 3² (OSA) Study Design



^aParticipants randomized to the 150 mg dose received 75 mg on Days 1–3, with the full dose commencing on Day 4.
^AA higher dose of 300 mg was also evaluated in both studies, although not included in the study design figure as it is not an approved dose.
OSA, obstructive sleep apnea; TONES, Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness.

- TONES 2 (n = 177) and TONES 3 (n = 356) were double-blind, randomized, placebo-controlled, 12-week trials (**Figure 1**) that evaluated both the safety and efficacy of solriamfetol for the treatment of EDS in patients with narcolepsy or OSA, respectively^{1,2}
- In both trials, co-primary efficacy endpoints were change from baseline to Week 12 in the ESS and Maintenance of Wakefulness Test (MWT)^{1,2}
- This analysis focuses on the results of the ESS at week 12 obtained in participants randomized to solriamfetol doses of 75 mg and 150 mg which are the currently approved doses for the treatment of EDS in adults with narcolepsy or OSA, in addition to the 37.5 mg dose approved only for EDS in adults with OSA; a higher dose of 300 mg was also evaluated in both studies, although not included in the current reported analysis as it is not an approved dose
- Participants rated their likelihood of dozing during 8 activities on the ESS (from 0 [“never”] to 3 [“high”]); ESS items included:
 - Passenger in a car for an hour without a break
 - In a car while stopped for a few minutes in traffic
 - Watching TV
 - Lying down to rest in the afternoon
 - Sitting quietly after lunch
 - Sitting and talking to someone
 - Sitting inactive in a public place
 - Sitting and reading
- Outcomes evaluated in this analysis included:
 - Least square mean difference vs placebo within each individual ESS item
 - Percentage of participants with ≥1 point improvement within each individual ESS item

Results

Baseline Sleep Characteristics

- A total of 177 and 356 participants were included in the current analysis of the safety populations, from the TONES 2 and TONES 3 trials, respectively; baseline demographics have been presented previously and were consistent across treatment groups within each trial^{1,2}

Table 1. Baseline ESS Score	TONES 2 (Narcolepsy)			TONES 3 (OSA)			
	Placebo (n = 59)	Solriamfetol 75 mg (n = 59)	Solriamfetol 150 mg (n = 59)	Placebo (n = 119)	Solriamfetol 37.5 mg (n = 58)	Solriamfetol 75 mg (n = 62)	Solriamfetol 150 mg (n = 117)
Total ESS score, mean (SD)	17.3 (2.8)	17.3 (3.5)	16.9 (3.7)	15.6 (3.3)	15.1 (3.5)	14.8 (3.5)	15.1 (3.4)
Passenger in a car for an hour without a break	2.1 (0.82)	2.1 (1.00)	2.2 (0.93)	2.2 (0.76)	2.1 (0.82)	2.1 (1.00)	2.2 (0.93)
In a car while stopped for a few minutes in traffic	1.2 (0.90)	1.2 (0.91)	0.9 (0.91)	1.2 (0.96)	1.2 (0.90)	1.2 (0.91)	0.9 (0.91)
Watching TV	2.3 (0.67)	2.1 (0.88)	2.2 (0.71)	2.2 (0.76)	2.3 (0.67)	2.1 (0.88)	2.2 (0.71)
Lying down to rest in the afternoon	2.8 (0.41)	2.8 (0.50)	2.8 (0.37)	2.8 (0.42)	2.8 (0.41)	2.8 (0.50)	2.8 (0.37)
Sitting quietly after lunch	2.1 (0.82)	2.1 (0.91)	2.0 (0.73)	2.0 (0.81)	2.1 (0.82)	2.1 (0.91)	2.0 (0.73)
Sitting and talking to someone	0.8 (0.79)	0.8 (0.87)	0.7 (0.71)	0.7 (0.75)	0.8 (0.79)	0.8 (0.87)	0.7 (0.71)
Sitting inactive in a public place	1.7 (0.80)	1.8 (0.97)	1.7 (0.93)	1.7 (0.90)	1.7 (0.80)	1.8 (0.97)	1.7 (0.93)
Sitting and reading	2.4 (0.64)	2.3 (0.67)	2.5 (0.75)	2.4 (0.69)	2.4 (0.64)	2.3 (0.67)	2.5 (0.75)

- All ESS items had moderate impairment (score > 2) at baseline except in a car while stopped for a few minutes in traffic, sitting and talking to someone, and sitting inactive in a public place (**Table 1**)

ESS, Epworth Sleepiness Scale.

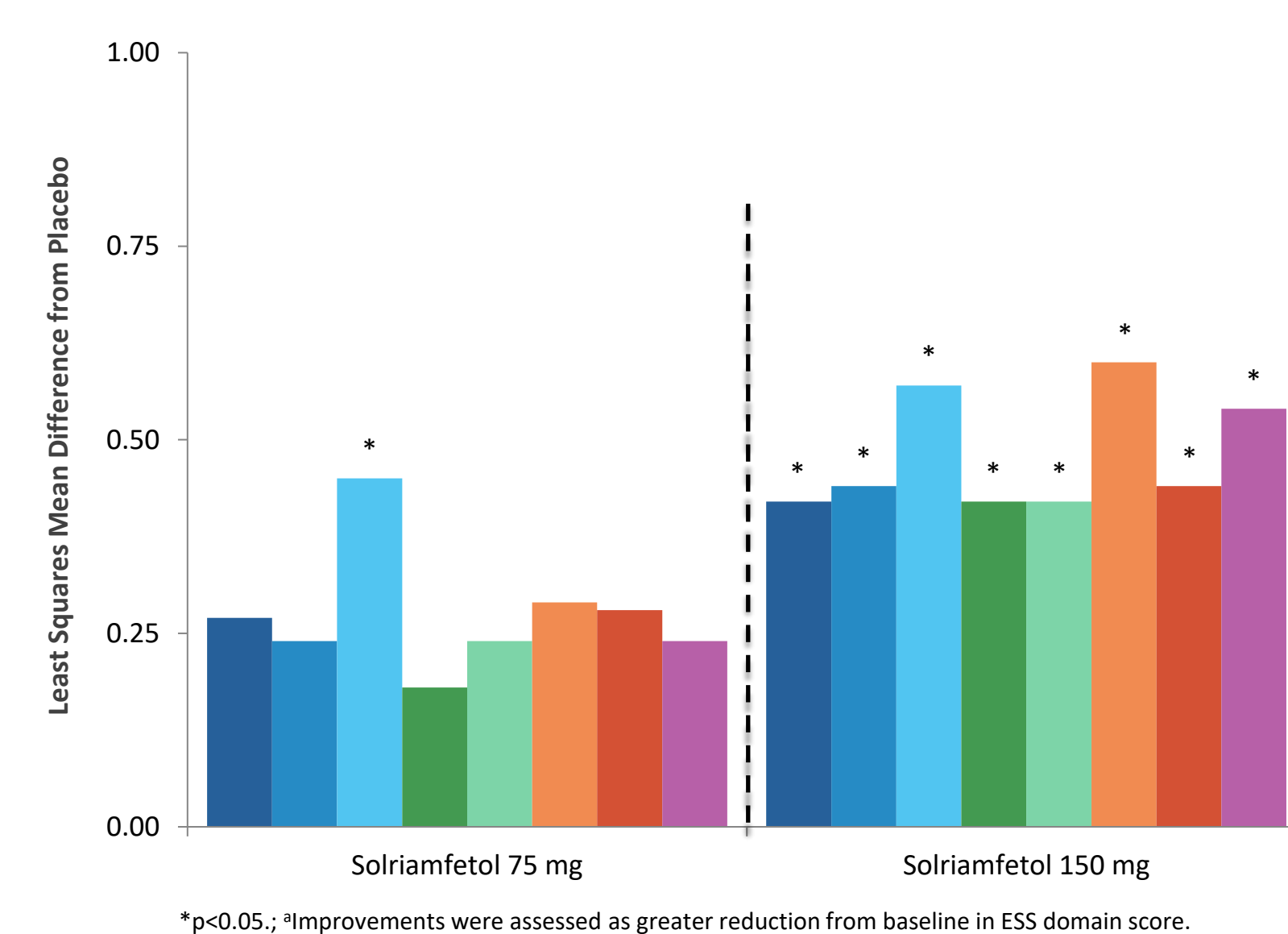
Safety

- Safety data for the TONES 2 and TONES 3 trials have been previously published^{1,2}
- Most common adverse reactions (incidence ≥ 5%) reported more frequently with the use of solriamfetol than placebo in either trial were headache, nausea, decreased appetite, anxiety, and insomnia
- In the 12-week placebo-controlled clinical trials, 11 of the 396 participants (3%) who received solriamfetol discontinued because of an adverse reaction, compared to 1 of the 226 participants (< 1%) who received placebo
 - Adverse reactions resulting in discontinuation that occurred in more than one solriamfetol-treated participant and at a higher rate than placebo were: anxiety, palpitations, and restlessness (n = 2/396; < 1% for each)

Outcomes from the TONES 2 (Narcolepsy) Trial

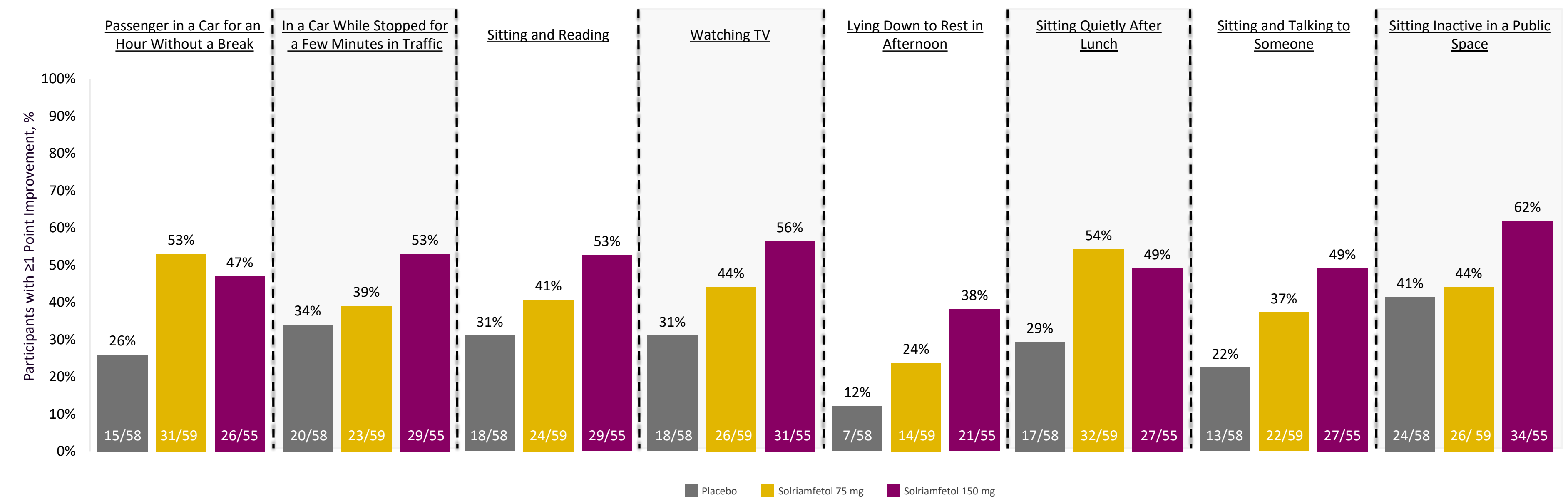
- At week 12, treatment with solriamfetol produced improvements^a vs placebo in all ESS items; improvements were significant and greatest for solriamfetol 150 mg for all ESS items (**Figure 2**)
- Numerically greater proportions of participants treated with solriamfetol 150 mg achieved ≥1 point improvement in all ESS items vs placebo, and for 6/8 ESS items vs solriamfetol 75 mg at week 12 (**Figure 3**)

Figure 2. Least Squares Mean Difference vs Placebo at Week 12 for Individual ESS Items in TONES 2



*p<0.05; ^aImprovements were assessed as greater reduction from baseline in ESS domain score.

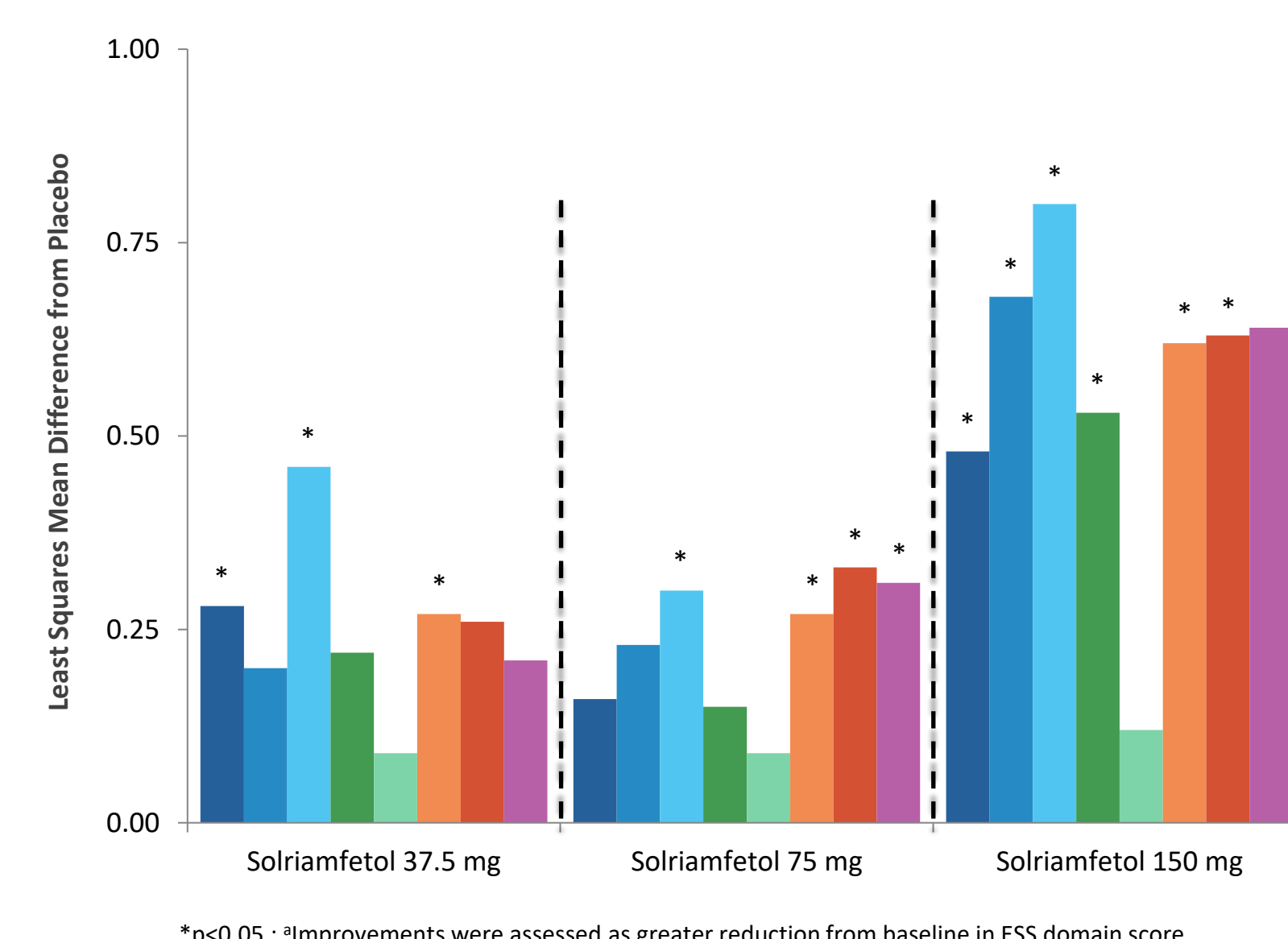
Figure 3. Percentage of Participants with ≥1 Point Improvement at Week 12 for Individual ESS Items in TONES 2



Outcomes from the TONES 3 (OSA) Trial

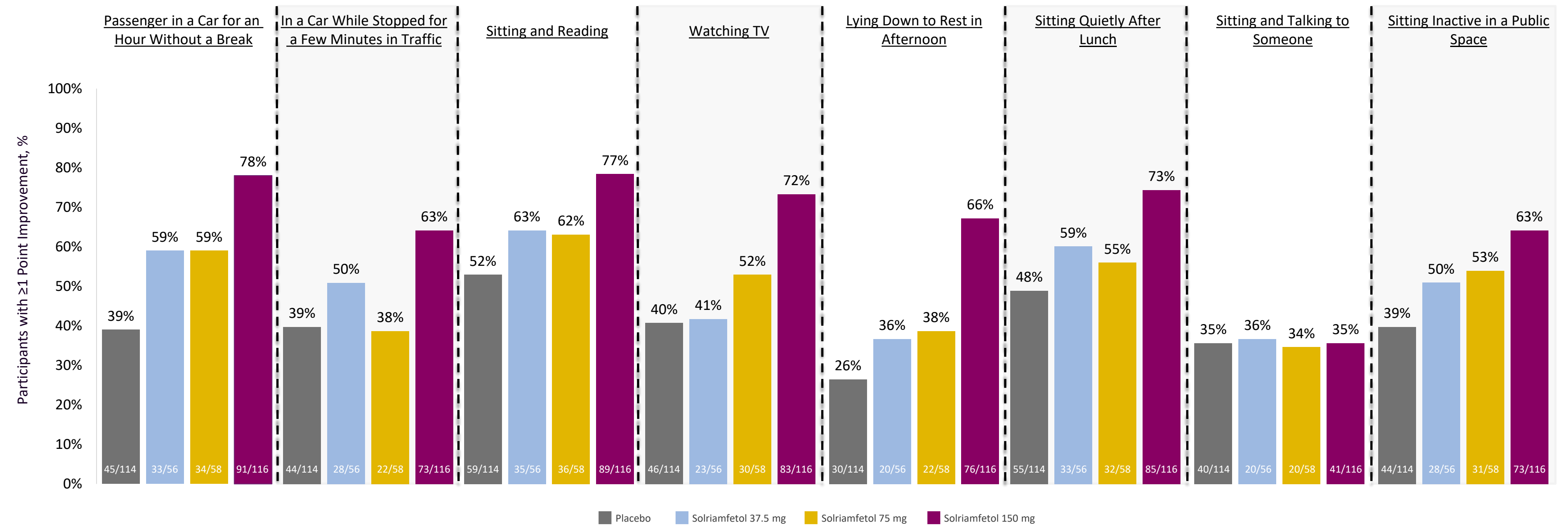
- At week 12, treatment with solriamfetol demonstrated improvements^a vs placebo in all ESS items; improvements were significant and greatest for solriamfetol 150 mg for all ESS items except sitting and talking to someone (**Figure 4**)
- Numerically greater proportions of participants treated with solriamfetol 150 mg achieved ≥1 point improvement in all ESS items except sitting and talking to someone, vs placebo, and for 7/8 ESS items vs solriamfetol 75 mg or 37.5 mg at week 12 (**Figure 5**)

Figure 4. Least Squares Mean Difference vs Placebo at Week 12 for Individual ESS Items in TONES 3



*p<0.05; ^aImprovements were assessed as greater reduction from baseline in ESS domain score.

Figure 5. Percentage of Participants with ≥1 Point Improvement at Week 12 for Individual ESS Items in TONES 3



Conclusions

- In people with narcolepsy or OSA, treatment with solriamfetol was associated with robust, dose-related, potentially clinically meaningful overall improvements in all domains of sleepiness and activity impairment as assessed by the ESS, including those which may be associated with safety-related challenges (eg driving a motor vehicle), compared with placebo
- These results further support the use of solriamfetol to improve excessive daytime sleepiness associated with narcolepsy or OSA

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Disclosures

ML is the Founder and President of SMAPP (Sleep Medicine Advanced Practice Providers) Foundation; consultant and Advisory Board Member for Avadel (Alkermes) Pharmaceuticals, Harmony Biosciences, Axsome Therapeutics, Jazz Pharmaceuticals, Takeda Pharmaceuticals, Apnimed and PWN4PWN; and has received speaker honorarium for Avadel Pharmaceuticals, Axsome Therapeutics. GE and SF are full time employees of Axsome Therapeutics, Inc. CM is the Vice President and Co-Founder of SMAPP (Sleep Medicine Advanced Practice Providers) Foundation; has received consulting fees for participation on advisory boards for Avadel Pharmaceuticals, Axsome Therapeutics, Harmony Biosciences, Jazz Pharmaceutical, and Takeda; and has served on speakers bureaus for Axsome Therapeutics, Avadel Pharmaceuticals, Jazz Pharmaceuticals, and Takeda.

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