Efficacy and safety of mirabegron vs. placebo add-on therapy in men with overactive bladder symptoms receiving tamsulosin for underlying benign prostatic hyperplasia (PLUS)

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Potential Conflict of Interest Disclosure

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Sender Herschorn				Astellas Pharma Ipsen Ixaltis Allergan				Astellas Pharma Pfizer

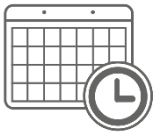
Introduction

- **Tamsulosin**
  - Effective for treatment of symptoms associated with BPH[1,2]
- **Mirabegron**
  - β3-adrenoreceptor agonist
  - Alternative to antimuscarinics for treating OAB symptoms[3]
  - Effective and well-tolerated treatment in adults[4,5]
- **OAB symptoms commonly overlap with those of BPH in men[6]**
  - Limited data available on the use of OAB medications in patients with BPH
  - MATCH study: efficacy of tamsulosin + mirabegron was superior to tamsulosin + placebo in 565 men with BPH and OAB symptoms[7]
  - Tamsulosin + mirabegron was effective and well-tolerated in a Japanese study of 94 patients with BPO and OAB symptoms[8]

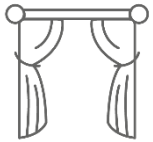
1. Barry MJ, et al. J Urol 1992;148:1549–1557; 2. Abrams P, et al. Br J Urol 1997;80:587–596; 3. Kelleher C, et al. Eur Urol 2018;74:324–333; 4. Herschorn S, et al. Urology 2013;82:313–320;
5. Nitti VW, et al. Int J Clin Pract 2013;67:619–632; 6. Suarez O, et al. Curr Urol Rep 2013;14:580–584; 7. Kakizaki H, et al. J Urol 2018;199 (suppl):e988;
8. Ichihara K, et al. J Urol 2015;193:921–926. BPH, benign prostatic hyperplasia; BPO, benign prostatic obstruction; OAB, overactive bladder.

PLUS: Overview

Study outline

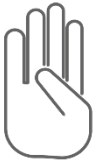


12-week



Double-blind

Randomized



Phase IV

Multi-centre

North America

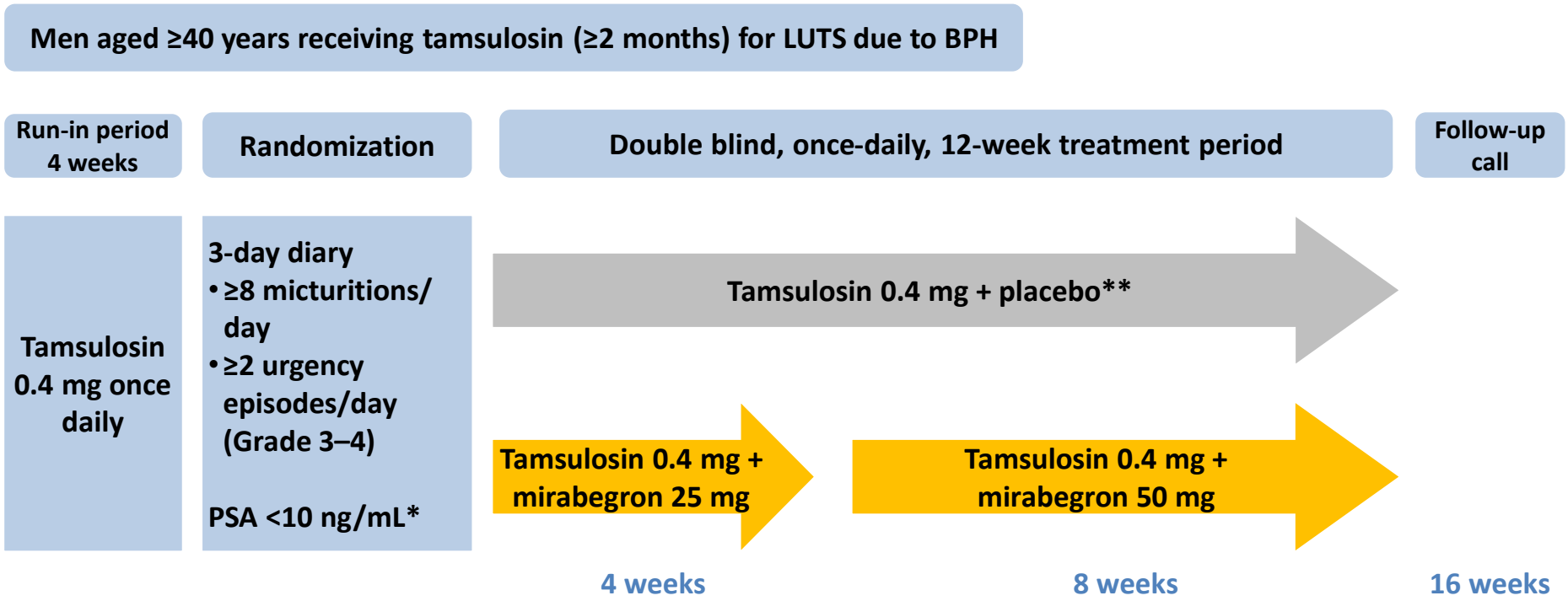
Europe

Study objective

Evaluate the efficacy and safety of mirabegron vs. placebo for treating OAB symptoms in men concurrently receiving tamsulosin for LUTS due to underlying BPH

LUTS, lower urinary tract symptoms.

PLUS: Study Design



*Patients had to have a PSA of <4 ng/mL or a PSA of ≥4–<10 ng/mL with a negative prostate biopsy in the past 2 years.
**After 4 weeks of the treatment period, placebo administration was adjusted to be equivalent to mirabegron 50 mg.
PSA, prostate specific antigen.

PLUS: Endpoints

Primary endpoint
Change from Baseline to EoT in mean number of micturitions/day

- **Secondary endpoints included**
  - Change from Baseline in
    - MVV/micturition
    - Mean number of urgency episodes/day
    - TUFS
    - Total IPSS
  - Safety
    - Occurrence of TEAEs
    - Changes from Baseline/Screening in post-void residual volume and maximum urinary flow

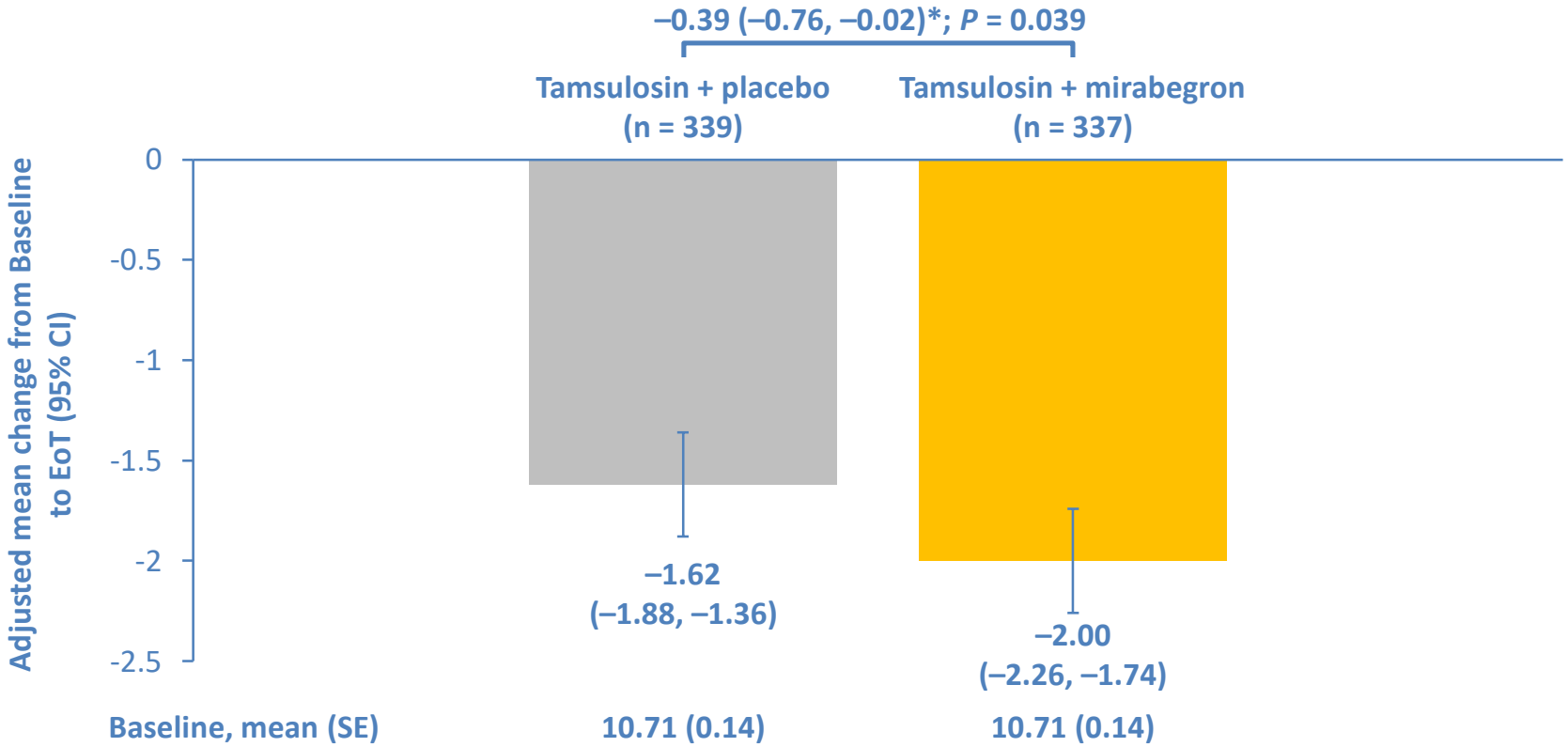
EoT, end of treatment; IPSS, International Prostate Symptom Score; MVV, mean volume voided; TEAE, treatment-emergent adverse event; TUFS, total urgency and frequency score.

Patient Demographics and Baseline Disease Characteristics (FAS)

Parameter	Tamsulosin + placebo (n = 339)	Tamsulosin + mirabegron (n = 337)
Age in years, mean (SD)	64.9 (9.6)	64.9 (8.4)
Age group 40–<65 years, n (%)	149 (44.0)	147 (43.6)
Age group ≥65 years, n (%)	190 (56.0)	190 (56.4)
Duration of OAB symptoms in months, mean (SD) [n]		
Wet OAB	65.9 (49.9) [129]	77.7 (56.8) [132]
Dry OAB	65.5 (58.6) [210]	58.6 (43.0) [205]
Mean number of micturitions/day, n (%)		
<8	11 (3.2)	5 (1.5)
8–15	310 (91.4)	314 (93.2)
>15	18 (5.3)	18 (5.3)
Number of incontinence episodes/day, n (%)*		
0	210 (61.9)	205 (60.8)
>0–<3	102 (30.1)	85 (25.2)
≥3	27 (8.0)	47 (13.9)
Total IPSS, n (%)		
Mild (1–7)	8 (2.4)	10 (3.0)
Moderate (8–19)	229 (67.6)	235 (69.7)
Severe (20–35)	102 (30.1)	92 (27.3)

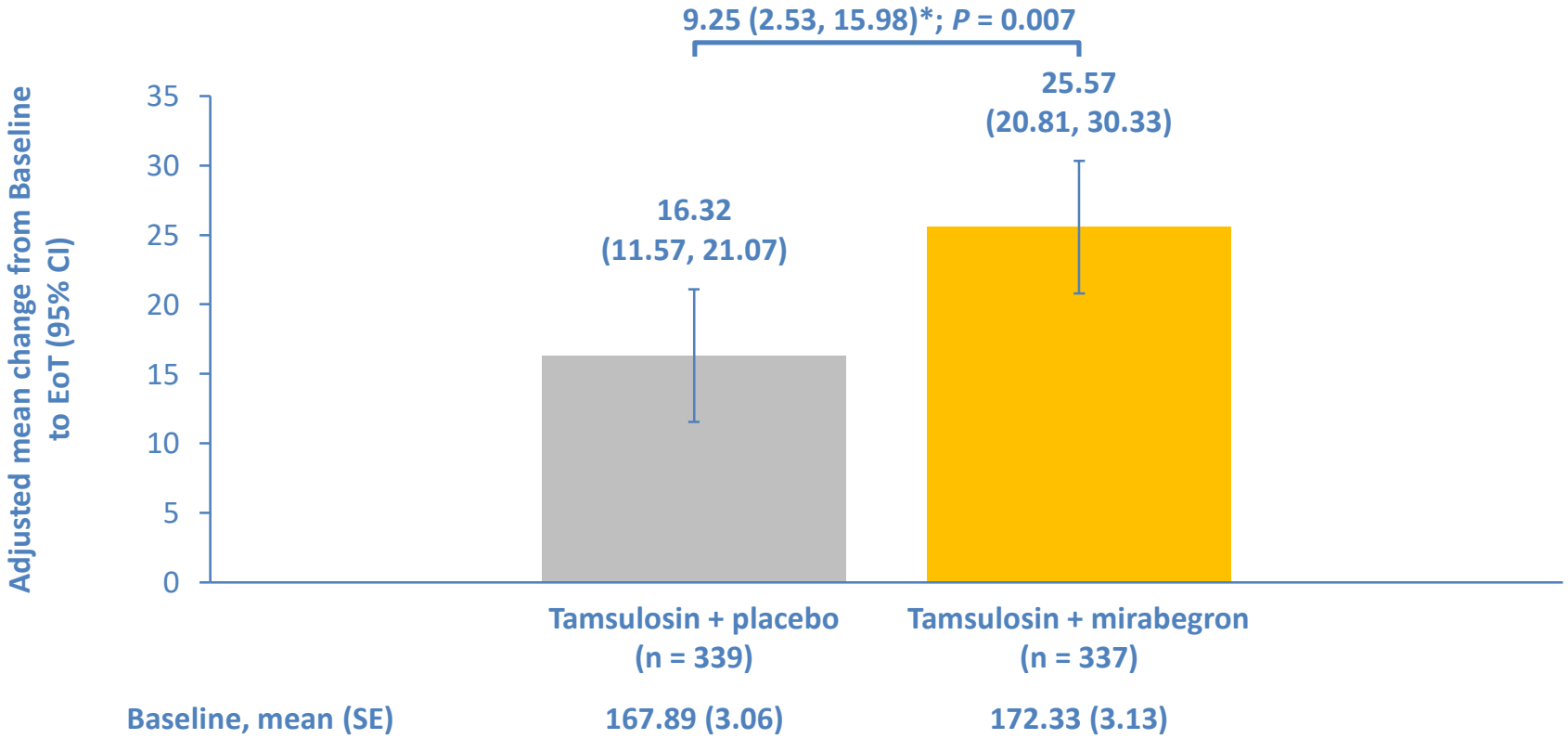
FAS, full analysis set (all patients who took ≥1 dose of double-blind treatment after randomization, reported ≥1 micturition in the Baseline diary, and ≥1 micturition post-Baseline); SD, standard deviation. *Based on 3-day diary.

Primary Endpoint: Change in Mean Number of Micturitions/Day (FAS)



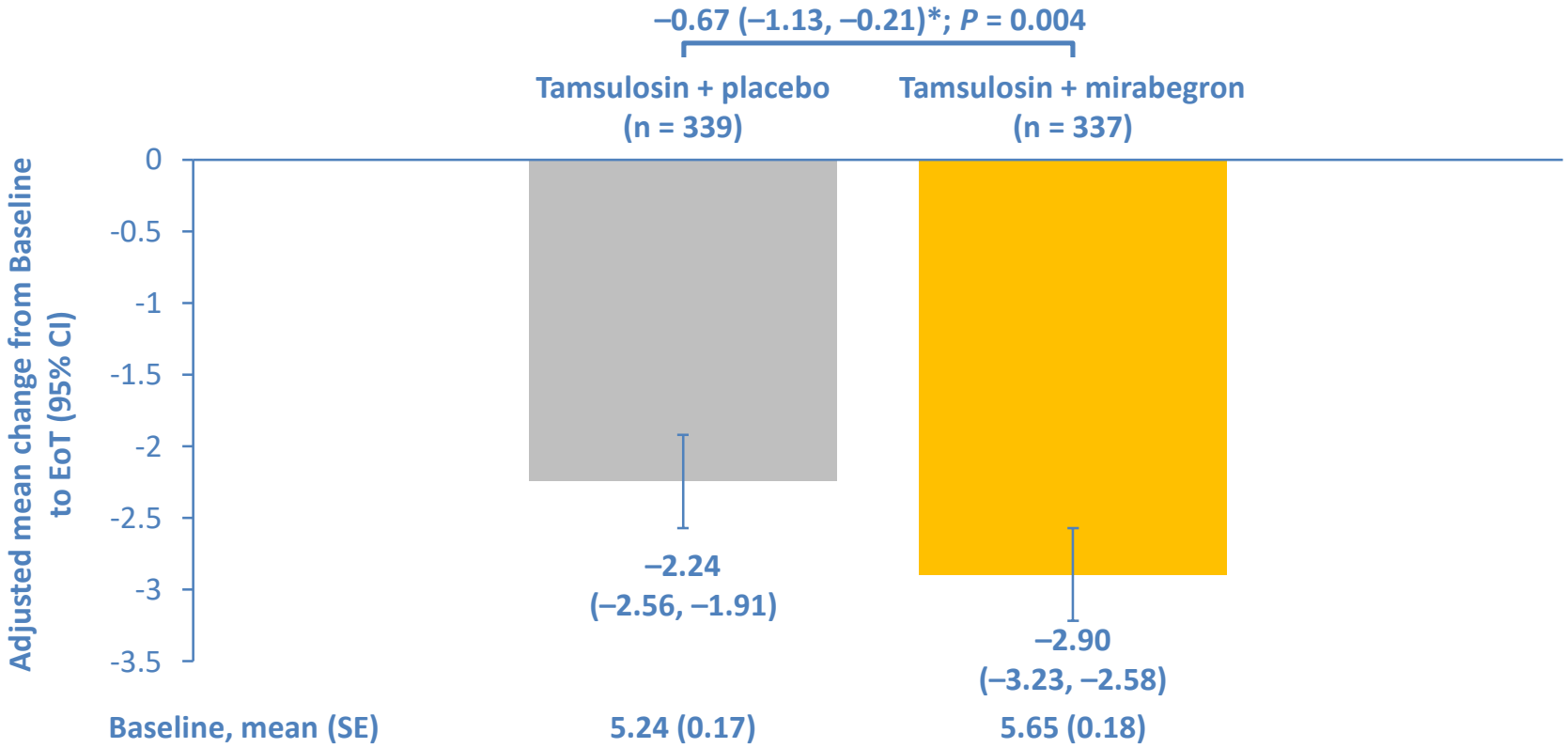
ANCOVA model including treatment group, region, and age group as fixed factors and Baseline as a covariate. ANCOVA, analysis of covariance; CI, confidence interval; SE, standard error.

Secondary Endpoint: Change in MVV/Micturition (FAS)



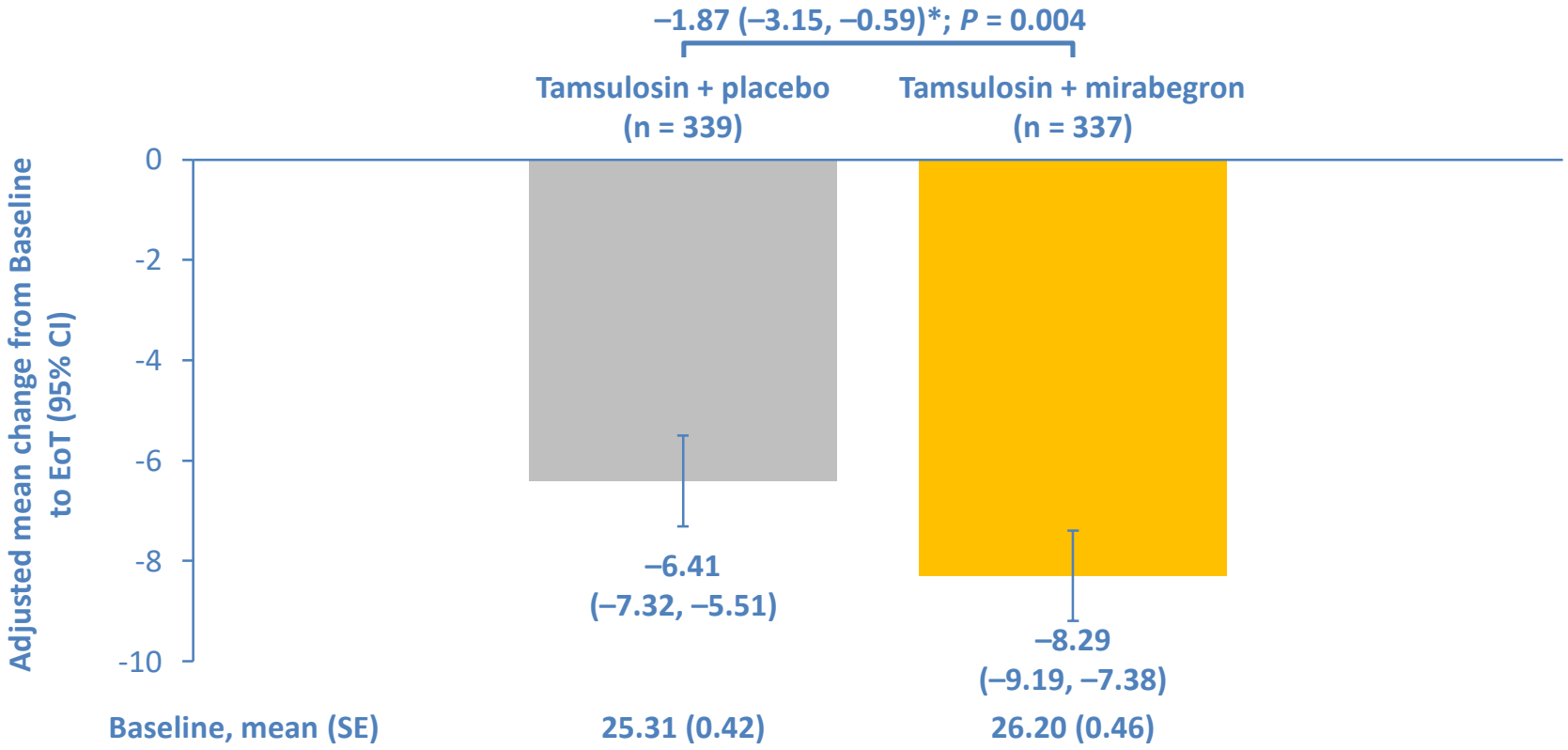
ANCOVA model including treatment group, region, and age group as fixed factors and Baseline as a covariate.

Secondary Endpoint: Change in Mean Number of Urgency Episodes/Day (Grades 3–4; FAS)



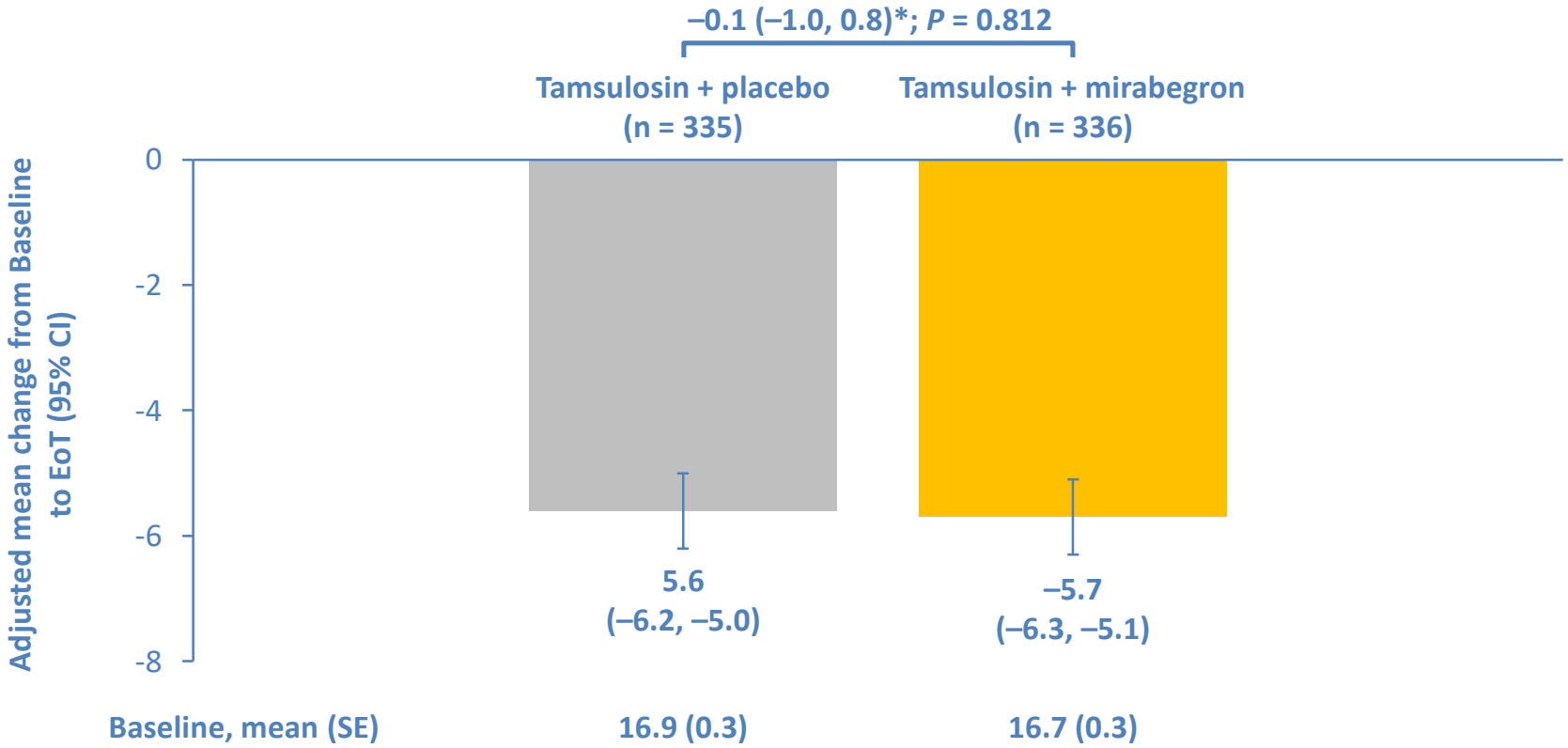
ANCOVA model including treatment group, region, and age group as fixed factors and Baseline as a covariate.

Secondary Endpoint: Change in Mean TUFS (FAS)



ANCOVA model including treatment group, region, and age group as fixed factors and Baseline as a covariate.

Secondary Endpoint: Change in Mean Total IPSS (FAS)



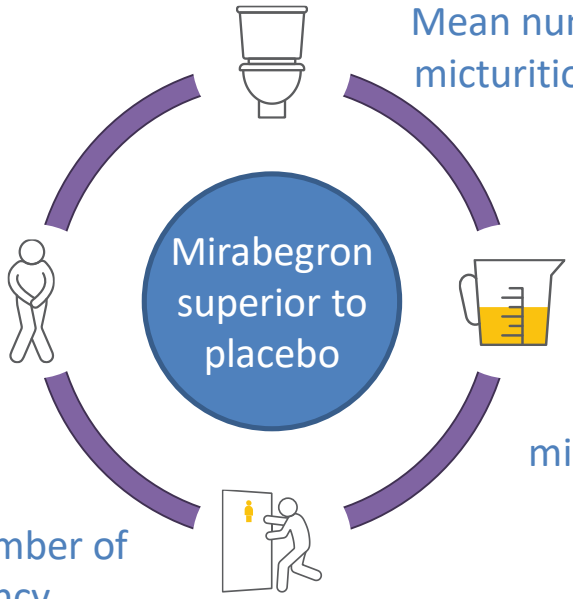
ANCOVA model including treatment group, region, and age group as fixed factors and Baseline as a covariate.

Safety Outcomes (SAF)

Safety parameter, n (%)	Tamsulosin + placebo (n = 354)	Tamsulosin + mirabegron (n = 352)
TEAEs	111 (31.4)	91 (25.9)
Drug-related TEAEs	21 (5.9)	42 (11.9)
Serious TEAEs	8 (2.3)	10 (2.8)
Drug-related serious TEAEs	1 (0.3)	2 (0.6)
TEAEs leading to study drug discontinuation	4 (1.1)	7 (2.0)
Drug-related TEAEs leading to study drug discontinuation	2 (0.6)	6 (1.7)
Urinary retention	1 (0.3)	6 (1.7)
Patients requiring catheterization	0 (0)	2 (0.6)
Post-void residual volume in mL		
Baseline, mean (SD)	30.2 (40.3)	30.6 (41.5)
Change to Week 12/EoT, mean (95% CI) [n]	3.8 (–0.9, 8.4) [331]	14.7 (8.5, 21.0) [321]
Maximum urinary flow in mL/sec		
Screening, mean (SD)	15.7 (7.87)	16.3 (15.93)
Change to Week 12/EoT, mean (95% CI) [n]	0.0 (–1.10, 1.08) [319]	–1.8 (–3.76, 0.10) [309]

SAF, safety analysis set (all patients who took ≥1 dose of double-blind treatment after randomization).

PLUS Study: Conclusions



No unexpected safety concerns

Mirabegron is a potentially useful add-on therapy to tamsulosin for men with BPH and OAB symptoms

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