TD-1211 Phase 2b Study Demonstrates Increased Bowel Movement Frequency and Constipation-Related Symptom Improvement in Patients with Opioid-Induced Constipation

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Disclosures

- **Dr. Canafax is an employee of Theravance, Inc.**

- **Theravance, Inc., is investigating TD-1211 as a potential new treatment option for Opioid-Induced Constipation (OIC)**

TD-1211 for Opioid-Induced Constipation

- Theravance-discovered, multivalent, μ-opioid receptor neutral antagonist
- Designed to be peripherally selective
  - Non-opioid core
  - Polar
  - Hydrophilic
  - P-gp substrate
- Goal to normalize bowel movement frequency and quality
- Once daily oral dosing

TD-1211 OIC Phase 2b Study 0084 Design

- Randomized, double-blind, placebo-controlled study
- Non-cancer pain patients with chronic OIC
  - Onset of constipation after starting opioid
  - ≤5 SBMs in 2-week baseline period, and
  - ≥1 symptom of constipation for ≥25% of bowel movements
- Chronic opioid use
  - Daily dose ≥30 mg morphine equivalent units
  - Taking opioid ≥ 3 months
- TD-1211 oral doses: 5, 10, 15 mg, or placebo, once daily
  - Initiation 5 mg TD-1211 or placebo daily for 4 days
- Study treatment duration 5-weeks
- Rescue laxatives permitted

SBM = spontaneous bowel movement

Patient Characteristics

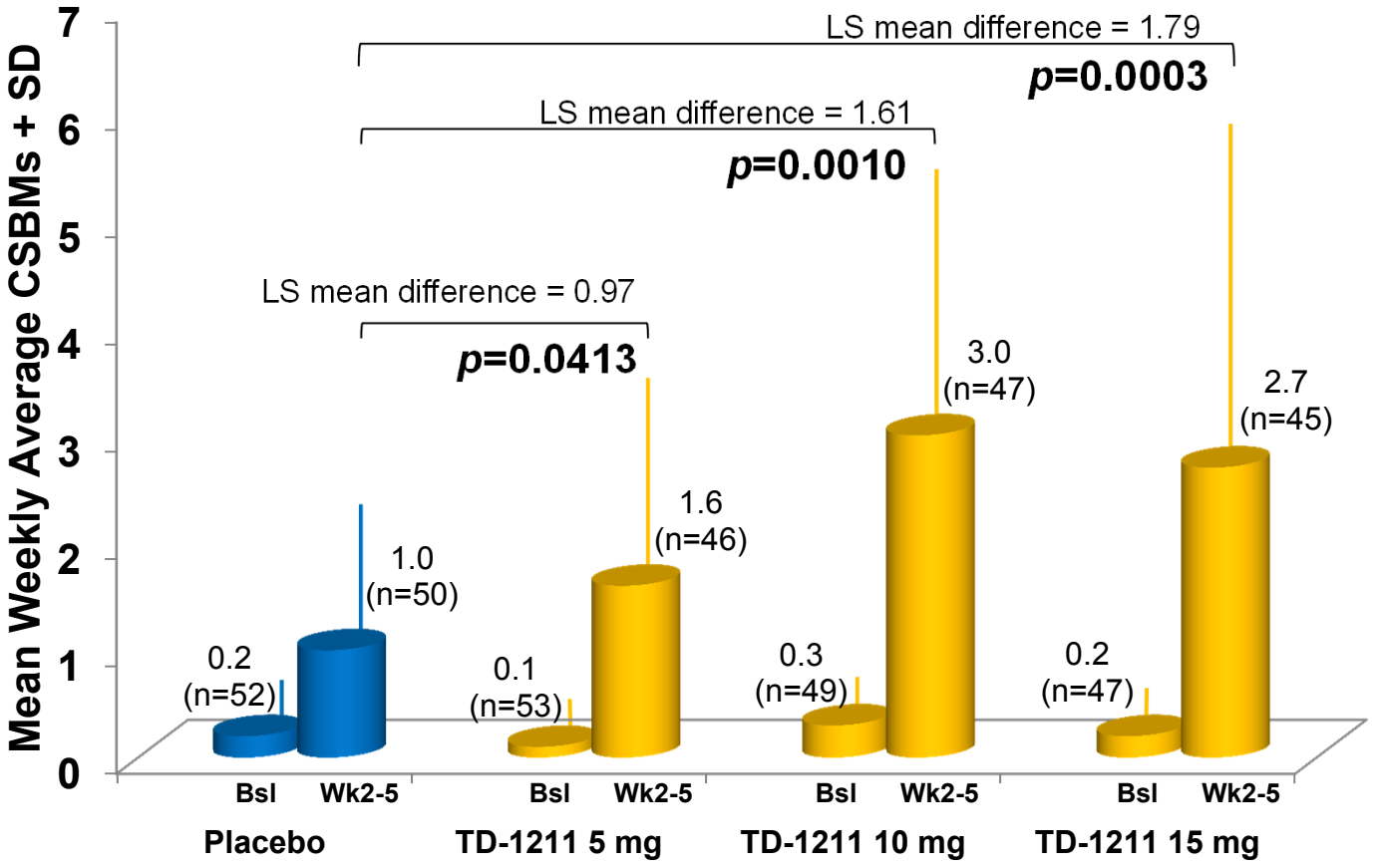
Patients randomized (# treated)	217 (215)
Mean age, years (range)	49 (21–65)
% Female	59%
Mean duration of OIC, years ± SD	6.0 ± 5.6
Mean baseline SBMs/week	1.1–1.2
Mean baseline CSBMs/week	0.1–0.3
Mean opioid dose, MEU (range)	145 (30–1740)
Most common reason for chronic opioid use	Back pain, 43%

Baseline characteristics similar for all treatment groups

CSBM = complete spontaneous bowel movement. MEU = morphine equivalent unit.

Change From Baseline in Average Weekly CSBMs Over Weeks 2 to 5 of Treatment (Primary Endpoint)

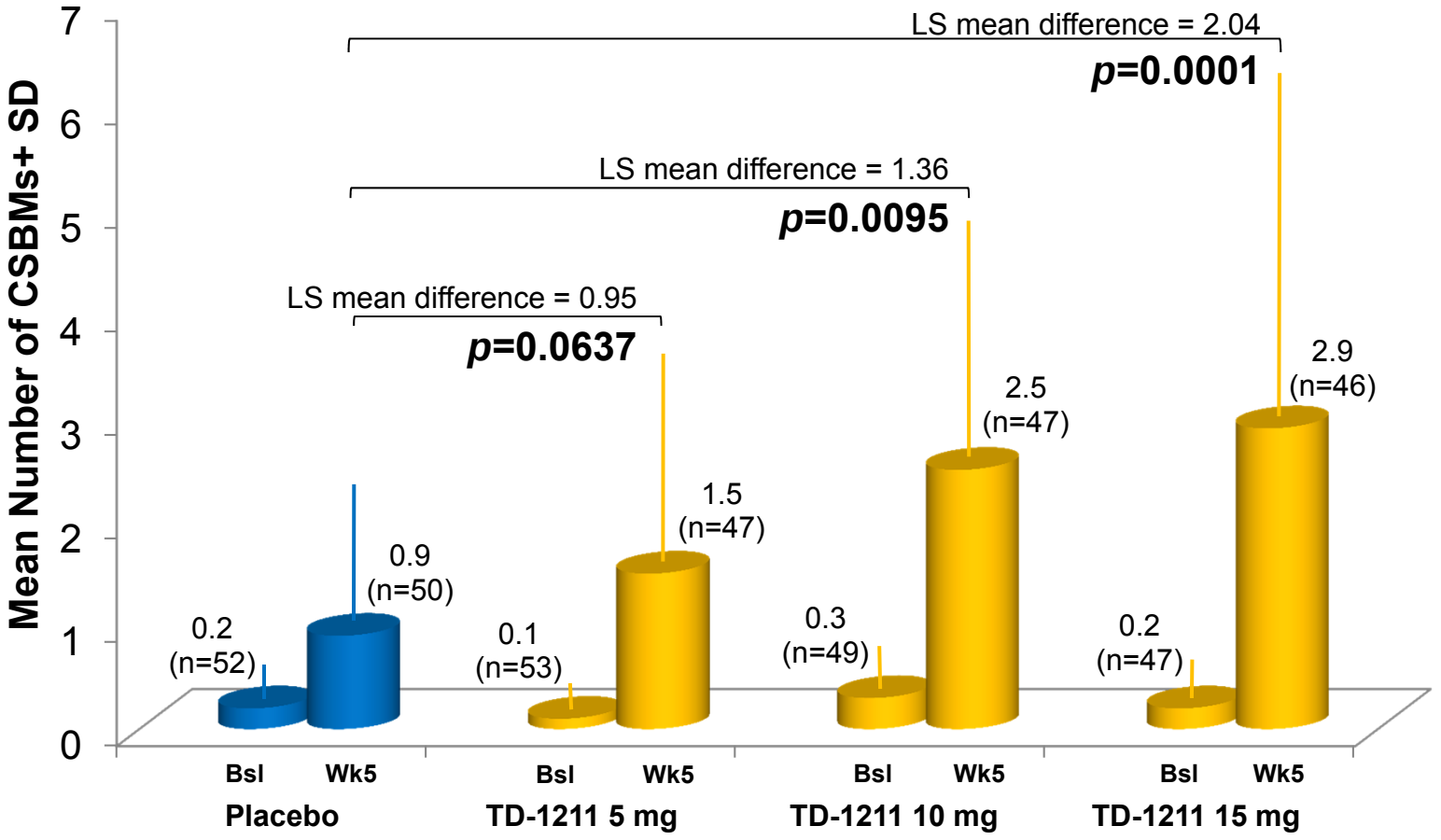
Complete Spontaneous Bowel Movements (CSBMs)



LS means difference = least squares mean difference from placebo.
Efficacy Analysis (EA) population = compliant with medication and diary entries per protocol

Change From Baseline in Weekly CSBMs During Week 5 (End of Treatment)

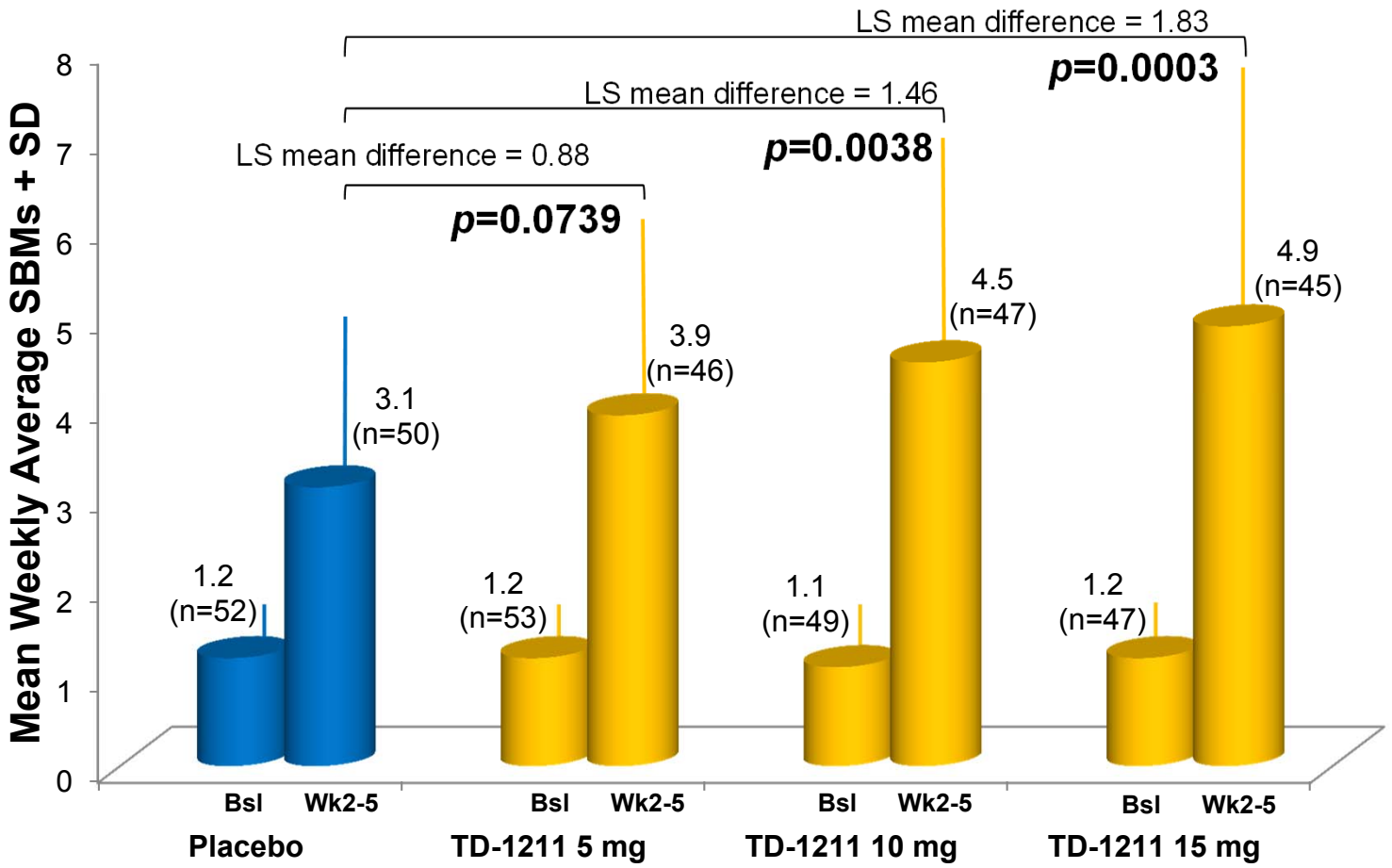
Complete Spontaneous Bowel Movements (CSBMs)



LS means difference = least squares mean difference from placebo; EA population

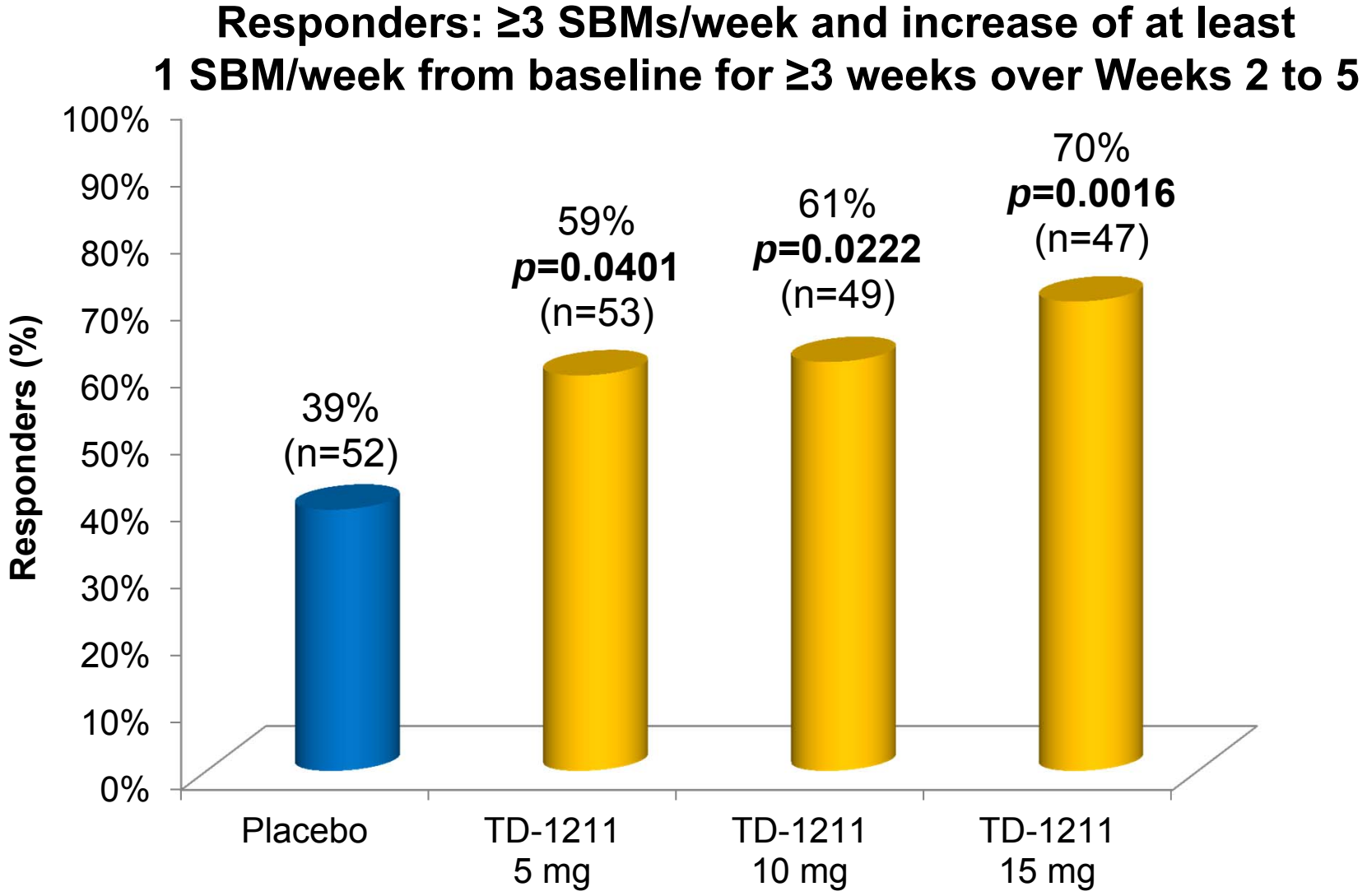
Change From Baseline in Average Weekly SBMs Over Weeks 2 to 5 of Treatment

Spontaneous Bowel Movements (SBMs)



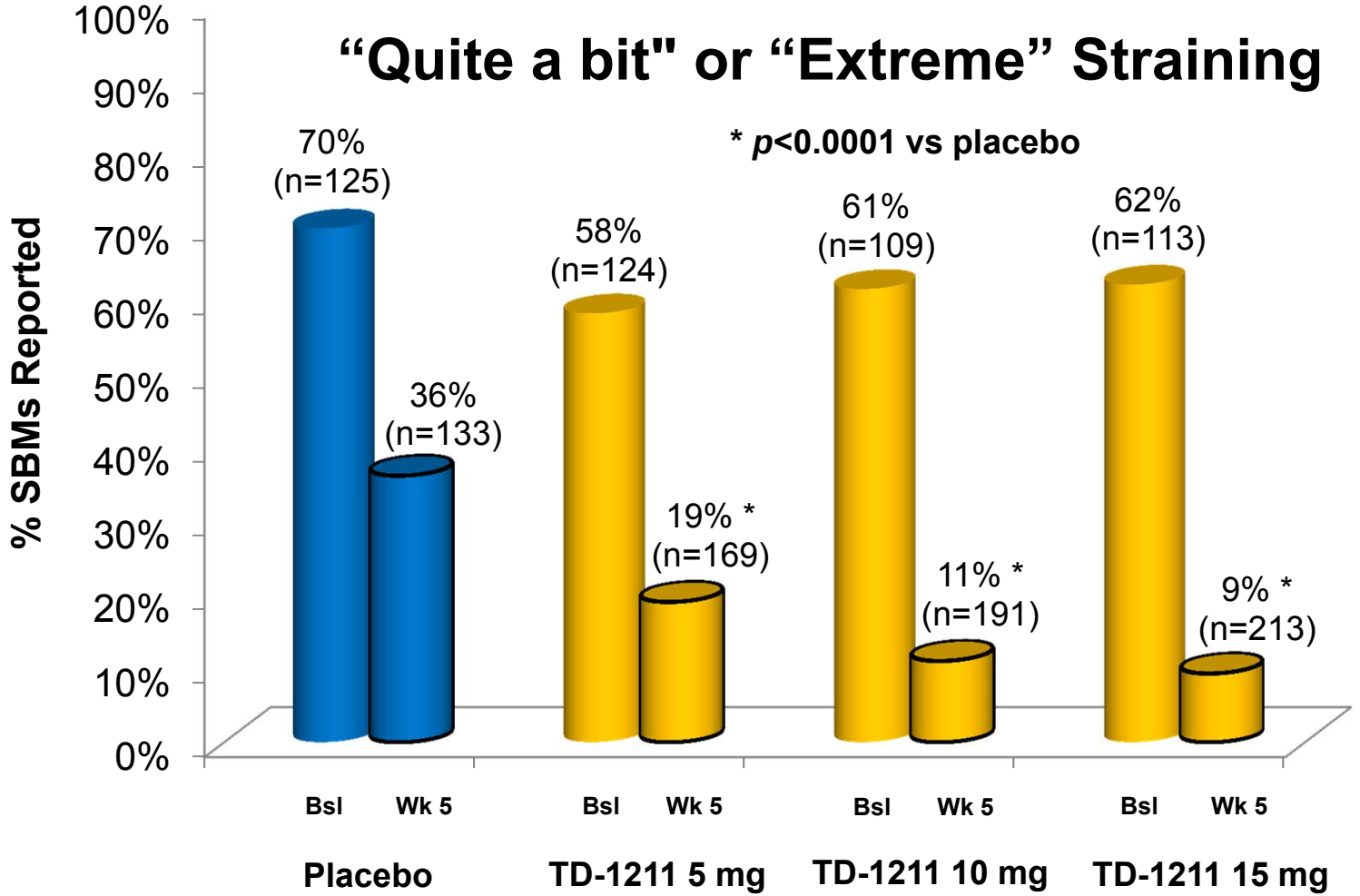
LS means difference = least squares mean difference from placebo; EA population

SBM Responder Analysis (Pre-Specified)



EA population

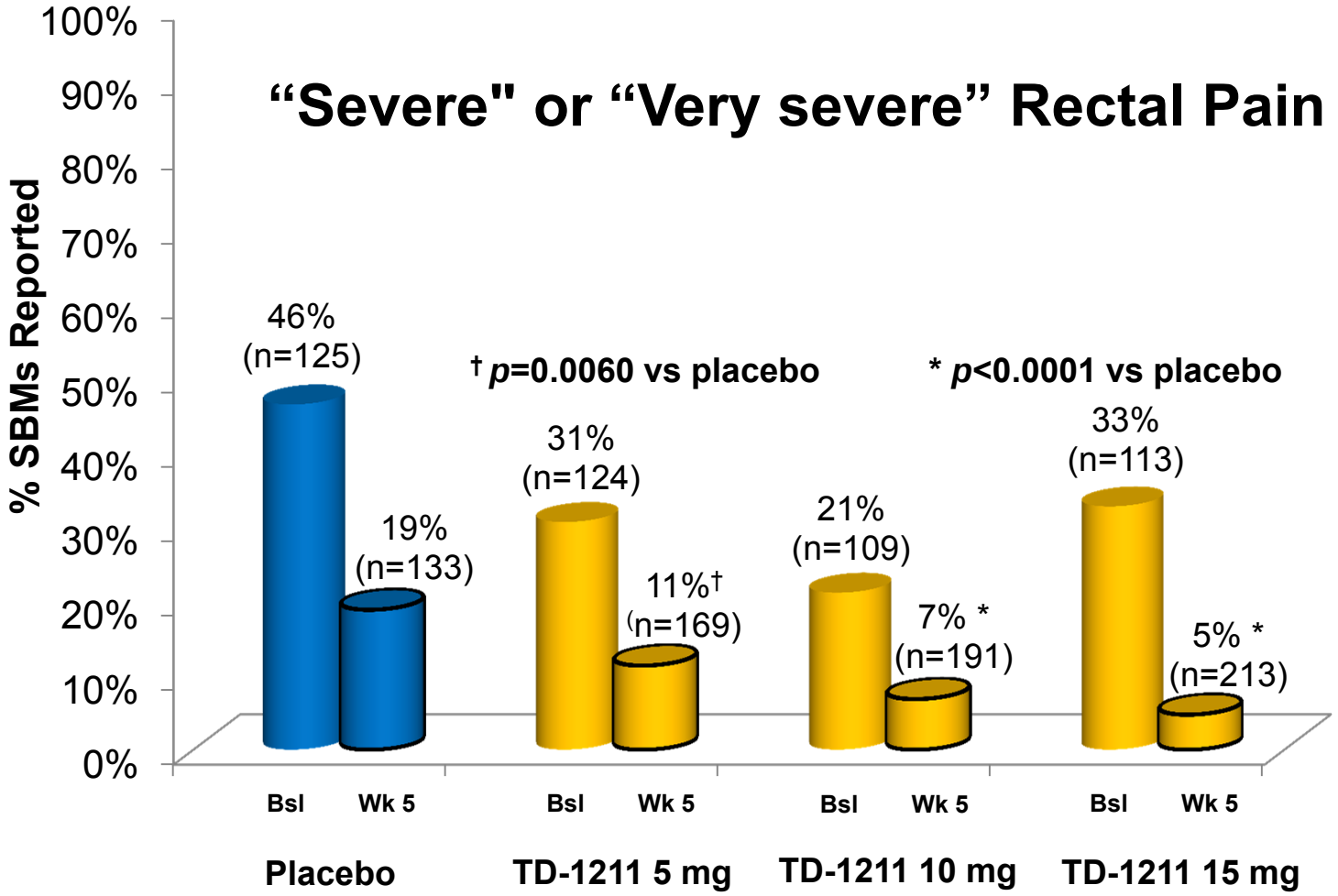
Straining Improvement with SBMs



Patients reported amount of straining for each SBM on a 5-point scale with "not at all" and "extreme" as anchors

EA population

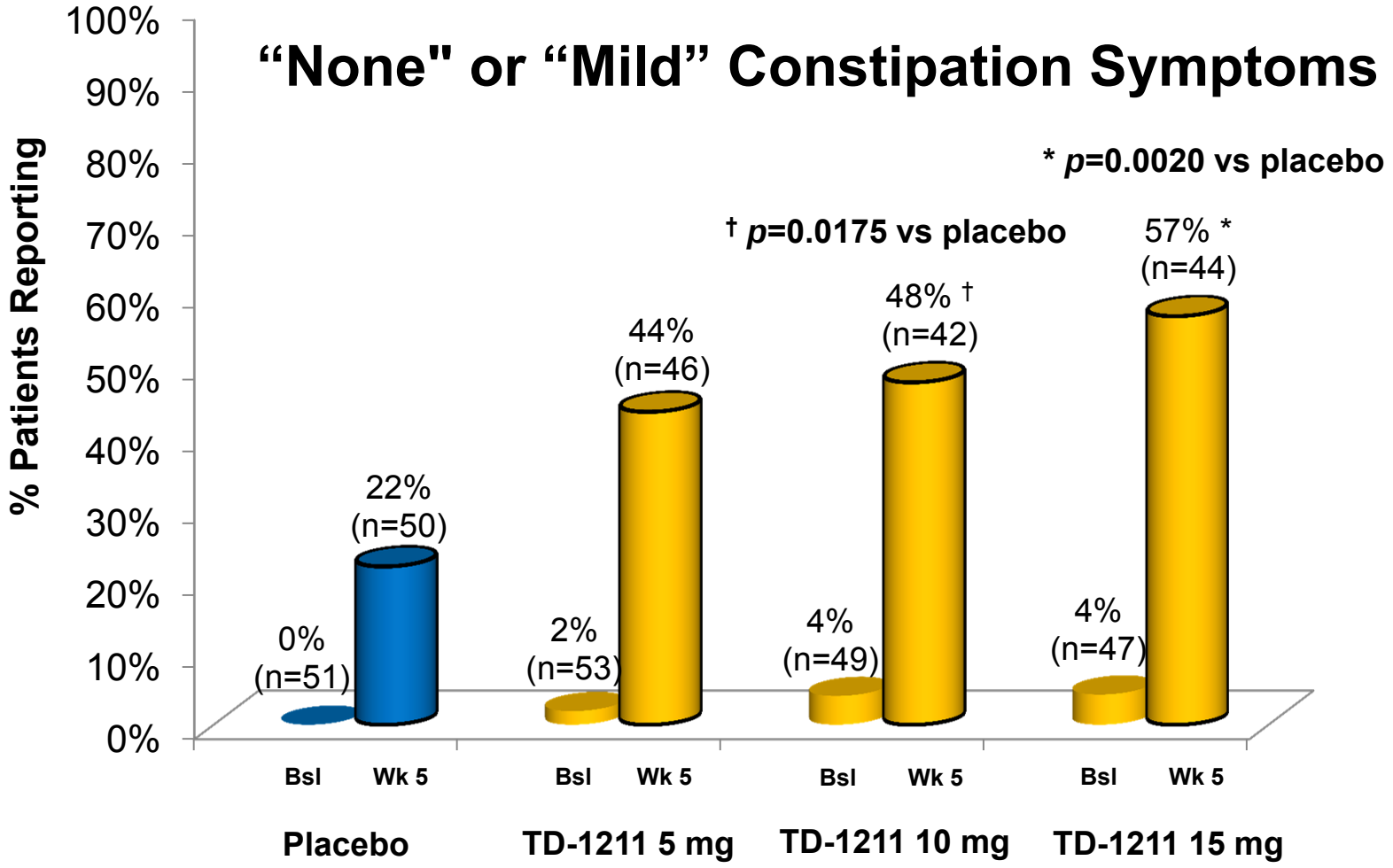
Rectal Pain Improvement with SBMs



Patients reported amount of rectal pain with each SBM on a 5-point scale with "none" and "very severe" as anchors

EA population

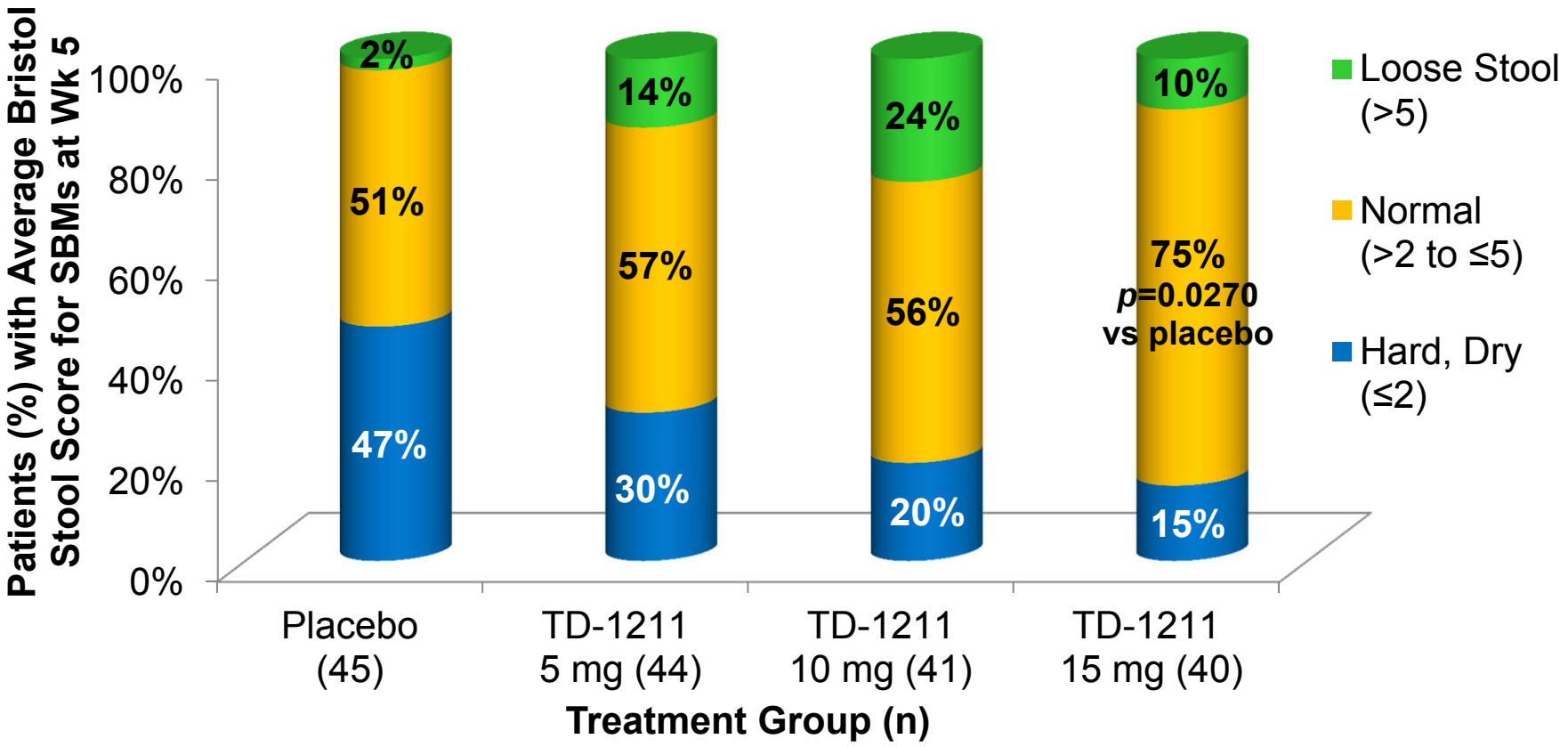
Constipation Symptoms Global Assessment



Patients rated their constipation symptoms over the past 7 days on a 5-point scale with "none" and "very severe" as anchors

EA population

Bristol Stool Scale Scores for SBMs at Week 5 (End of Treatment)



- **At baseline, 54-67% of patients across treatment groups had "hard, dry" average BSS scores and 29-43% had "normal" scores**

BSS = Bristol Stool Scale; SBMs = spontaneous bowel movements; EA Population

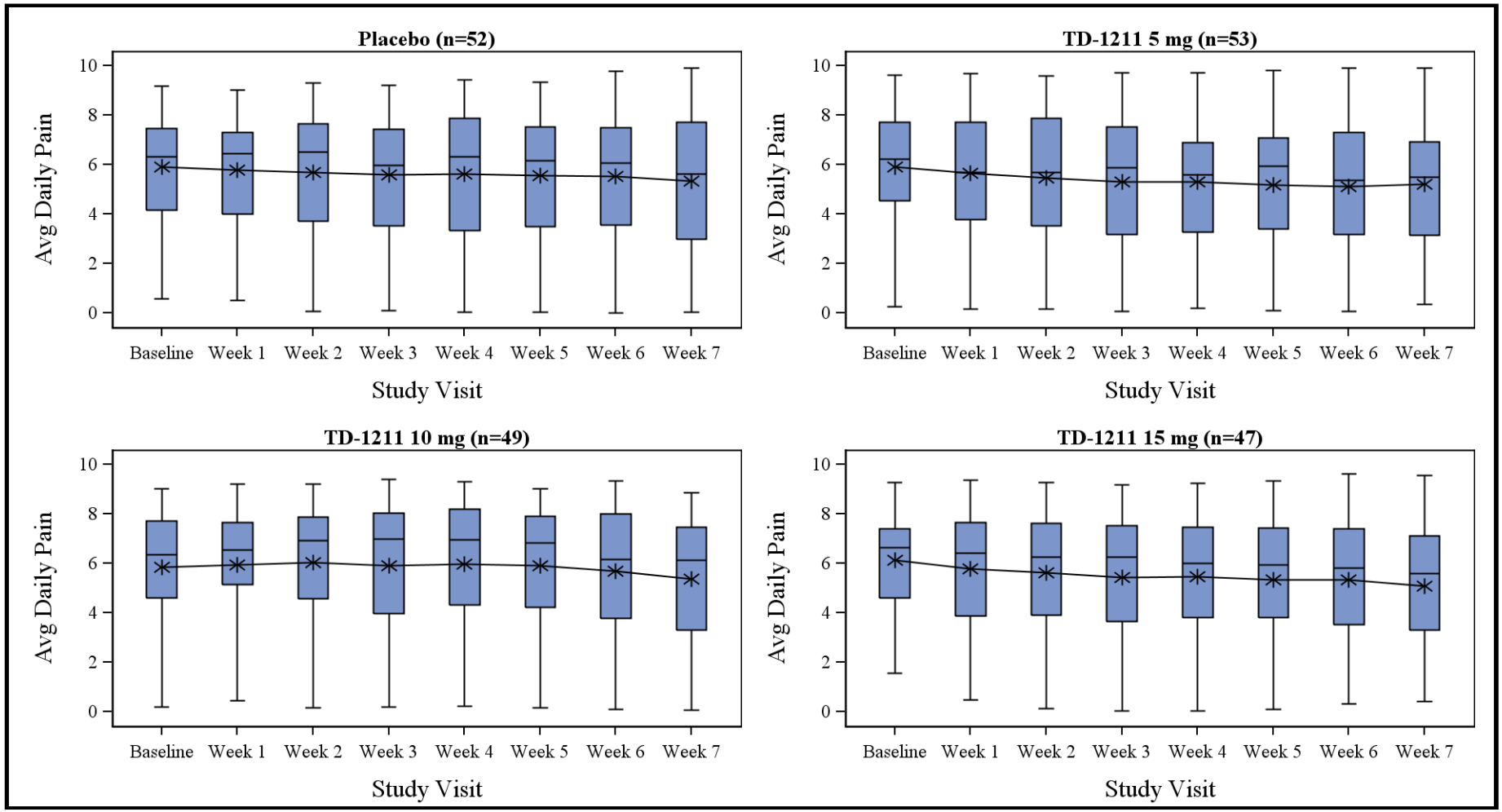
Adverse Events

Safety Population	Patients, n (%)				
	Placebo n=54	TD-1211 Dose Group			All TD-1211 n=161
		5 mg n=56	10 mg n=53	15 mg n=52	
Any TEAE	**24 (44)**	**22 (39)**	**29 (55)**	**22 (42)**	**73 (45)**
GI disorders (occurring in ≥2 patients in any group)	**11 (20)**	**13 (23)**	**15 (28)**	**14 (27)**	**42 (26)**
Abdominal pain (cramps)	6 (11)	7 (13)	6 (11)	8 (15)	21 (13)
Abdominal pain upper	1 (2)	2 (4)	3 (6)	2 (4)	7 (4)
Diarrhea	0	4 (7)	6 (11)	4 (8)	14 (9)
Flatulence	3 (6)	1 (2)	2 (4)	1 (2)	4 (3)
Nausea	2 (4)	4 (7)	8 (15)	3 (6)	15 (9)
Vomiting	1 (2)	4 (7)	1 (2)	0	5 (3)

- **Majority of GI adverse events:**
  - **Associated with treatment initiation**
  - **Resolved in a few days**
  - **Were mild/moderate**

TEAEs = treatment-emergent adverse event; GI = gastrointestinal

Average Daily Pain Scores (0-10 Scale) Per Week



EA population. Weeks 6 +7 = follow-up period

Summary of TD-1211 OIC Study 0084

- TD-1211 increased BM frequency during 5 weeks of therapy
  - Placebo adjusted increase in CSBMs (1.79/wk) and SBMs (1.83/wk) at 15 mg QD
  - SBM responder rate of 70% at 15 mg QD versus 39% with placebo
- Patients reported improvement in measures of constipation-related symptoms, including straining, rectal pain, and global assessment
- TD-1211 was generally well tolerated
- No clinically significant laboratory, ECG, or vital sign abnormalities
- No treatment-related SAEs
- No evidence of CNS penetration, interference with analgesia, or central opioid withdrawal
- Results support further development of TD-1211 as a peripherally-selective μ-opioid antagonist for treatment of OIC