TD-1211 Demonstrates Improvement in Bowel Movement Frequency and Bristol Stool Scores in a Phase 2b Study of Patients with Opioid-Induced Constipation (OIC)

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Disclosures

- **Dr. Webster is a consultant to Theravance for the TD-1211 development program**
- **In the last 12 months, Dr. Webster has received Honoraria / Travel Support from the following companies:**
  - **Covidien Mallinckrodt**
  - **Medtronic**
  - **Nektar Therapeutics**
  - **Pfizer**
  - **Salix Pharmaceuticals**
- **Theravance, Inc., is investigating TD-1211 as a potential new treatment option for OIC**

TD-1211 for Opioid-Induced Constipation

- **Theravance-discovered, multivalent, μ-opioid receptor neutral antagonist**
- **Peripherally selective**
- **Designed to normalize bowel movement frequency and quality**
- **Once daily oral dosing**

Phase 2b Study 0084 Design

- Randomized, double-blind, placebo-controlled study
- TD-1211 doses: 5, 10, 15 mg, or placebo, once daily
- Study duration: 5-weeks treatment
  - Initiation with 5 mg TD-1211 or placebo once daily for 4 days
- Non-cancer pain patients with chronic OIC
  - ≤5 SBMs during a 2-week baseline period, and
  - ≥1 additional symptom of constipation for ≥25% of bowel movements
- Chronic opioid use
  - Total daily dose of ≥30 mg morphine equivalent units
  - Stable opioid regimen ≥14 days
- Protocol-permitted rescue laxative

SBM = spontaneous bowel movement

Patient Demographics

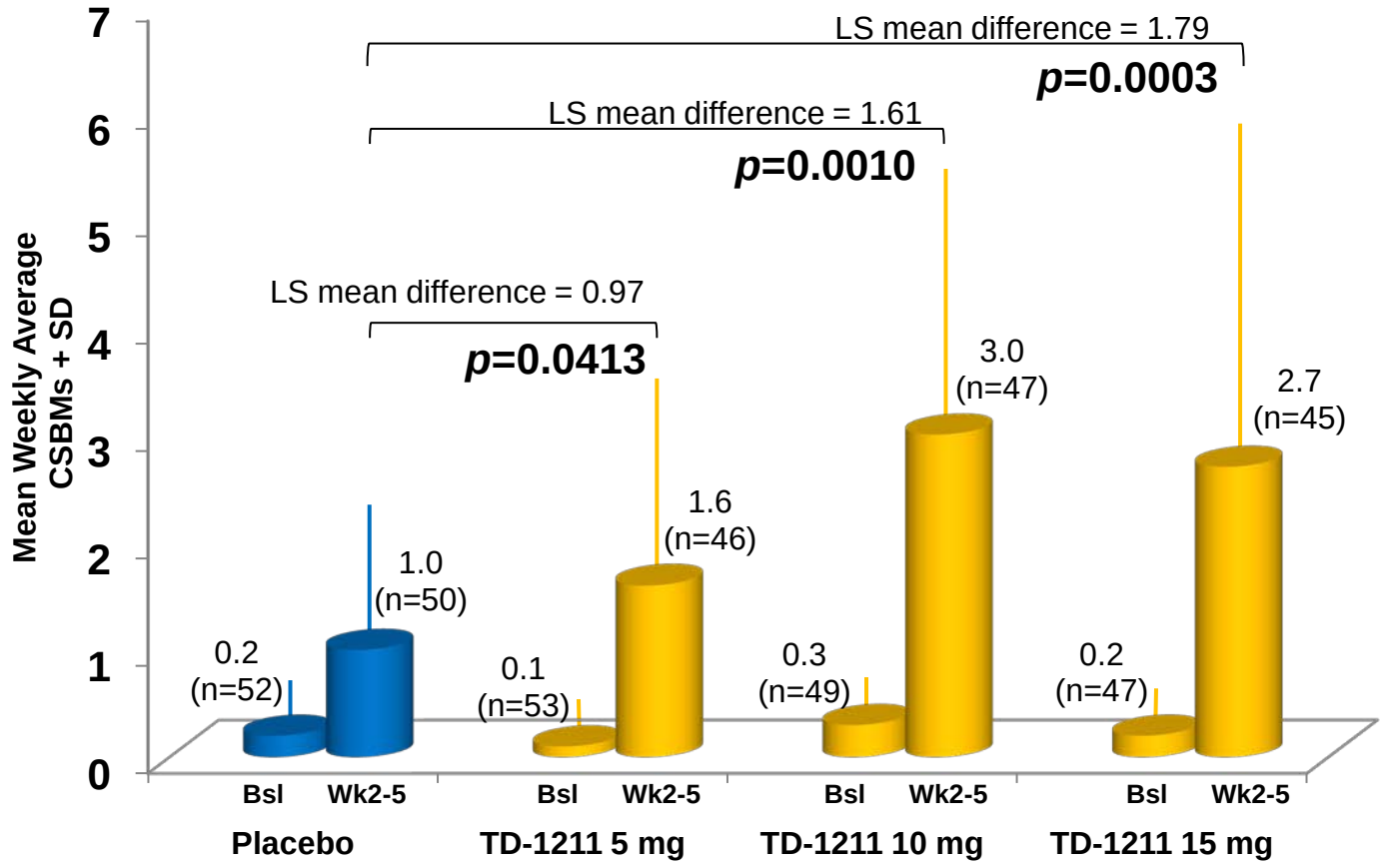
- **Baseline characteristics similar across all treatment groups**

Patients randomized	**217**
Mean age, yrs (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 opioid dose, MEU (range)	**145 (30–1740)**
Most common reason for chronic opioid use	**Back pain, 43%**

MEU = morphine equivalent unit

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

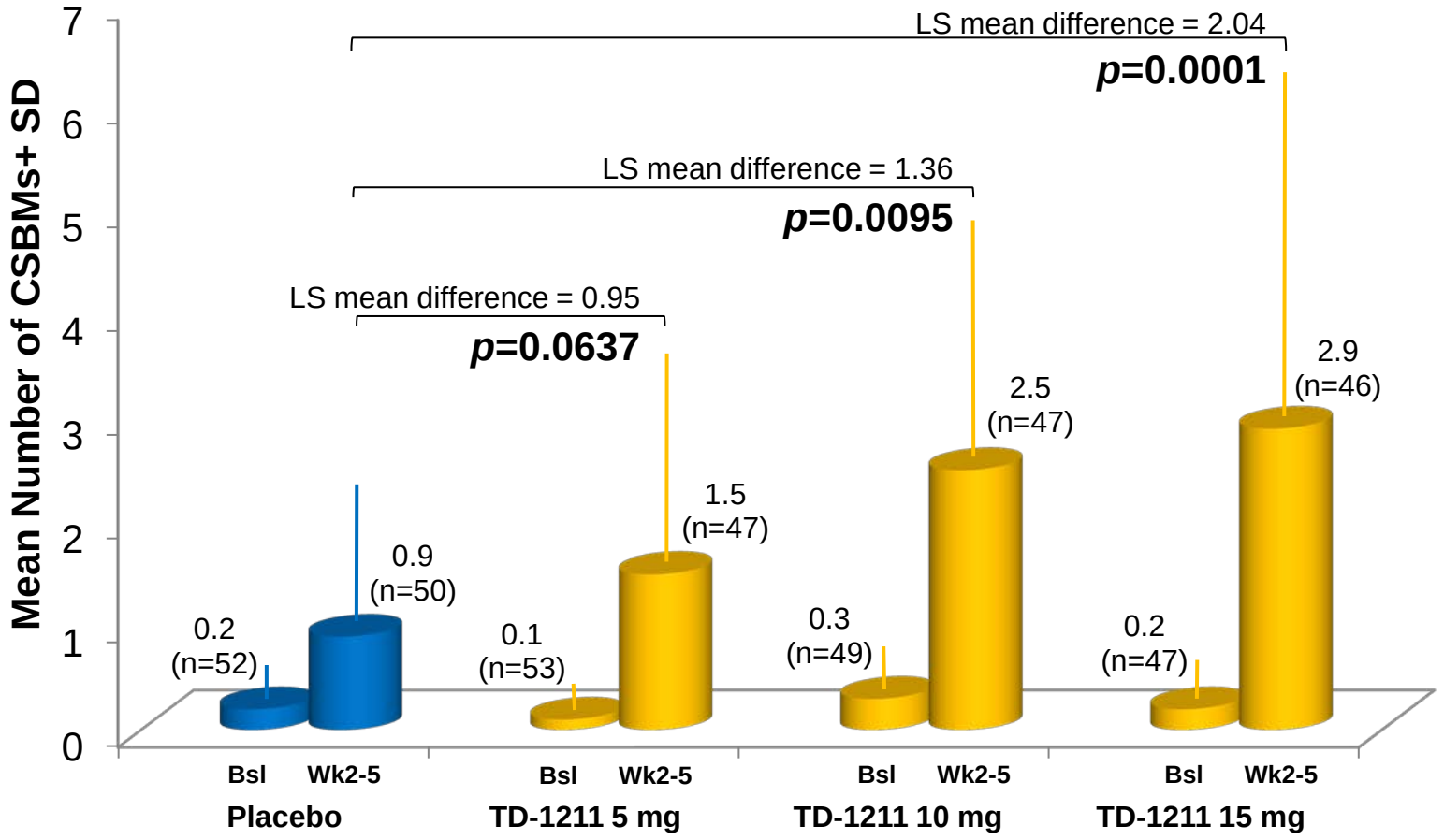
Complete Spontaneous Bowel Movements (CSBMs)



LS means difference = least squares mean difference from placebo; Efficacy Analysis (EA) population

Change From Baseline in Weekly CSBMs During Week 5 of Treatment

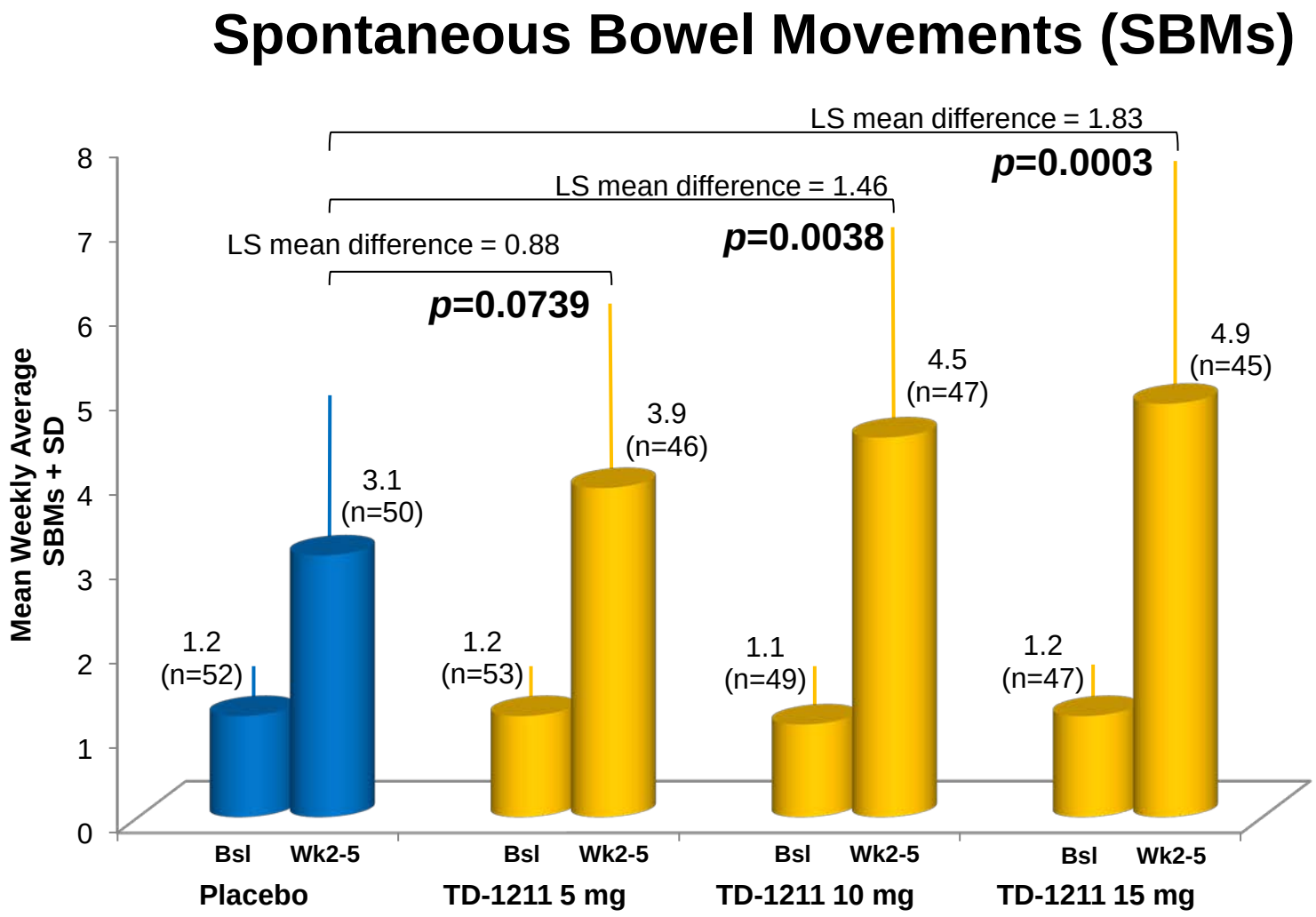
Complete Spontaneous Bowel Movements (CSBMs)



- **Durable response observed through Week 5**

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



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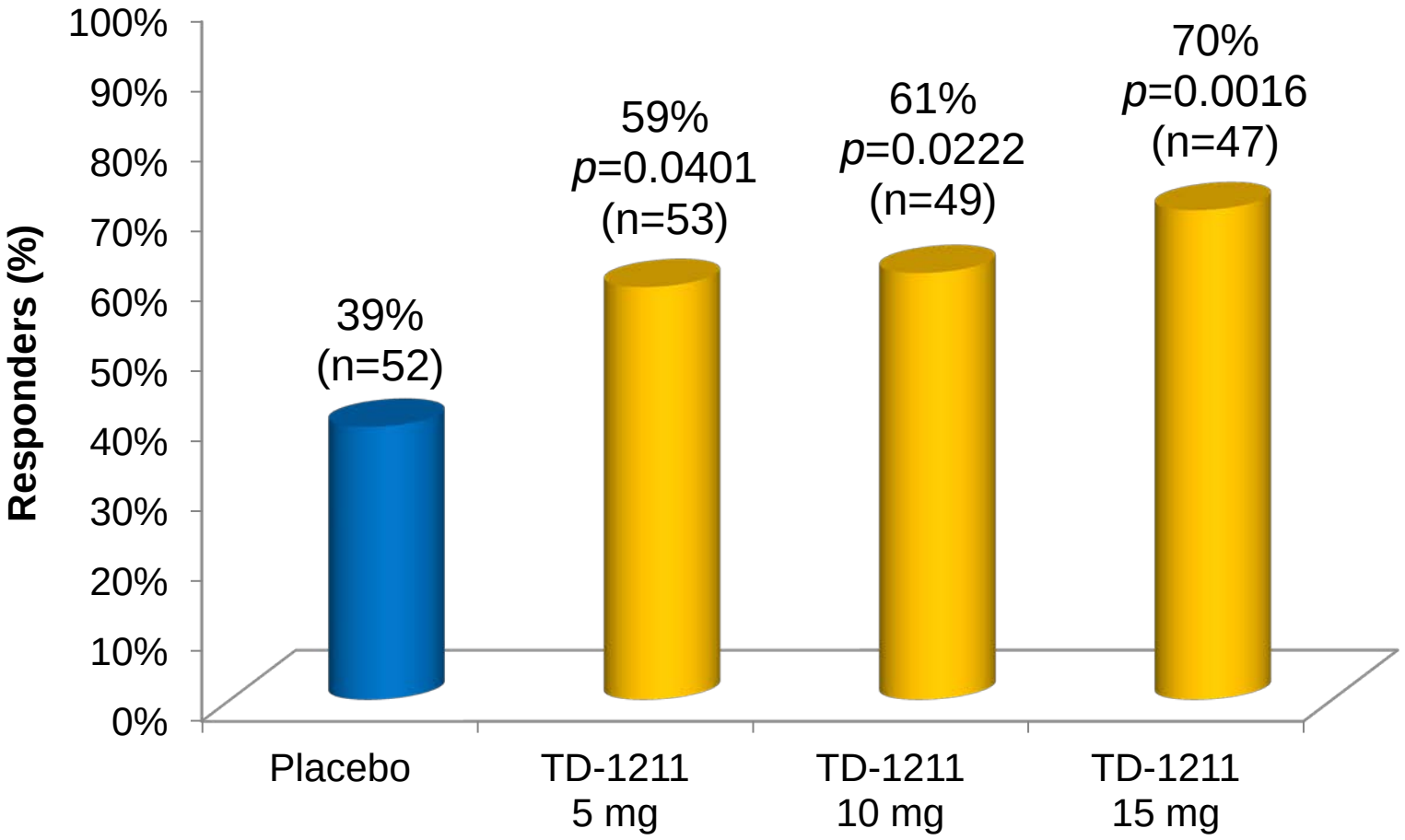
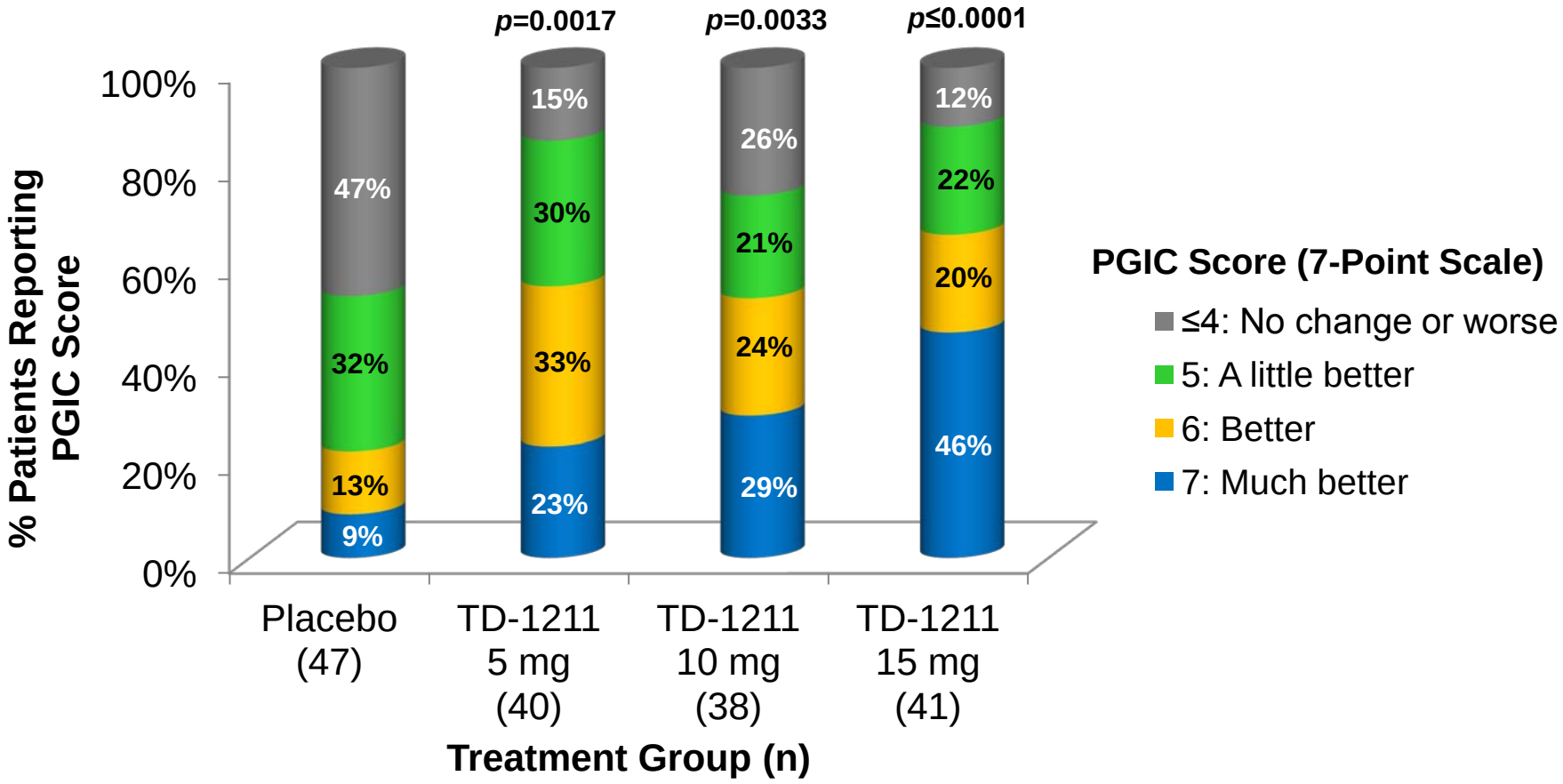
Pre-Specified Responder Analysis



Responder definition: ≥3 SBMs per week and an increase of at least 1 SBM per week from baseline for ≥3 weeks over Weeks 2 to 5

EA population

Patient's Global Impression of Change in Constipation



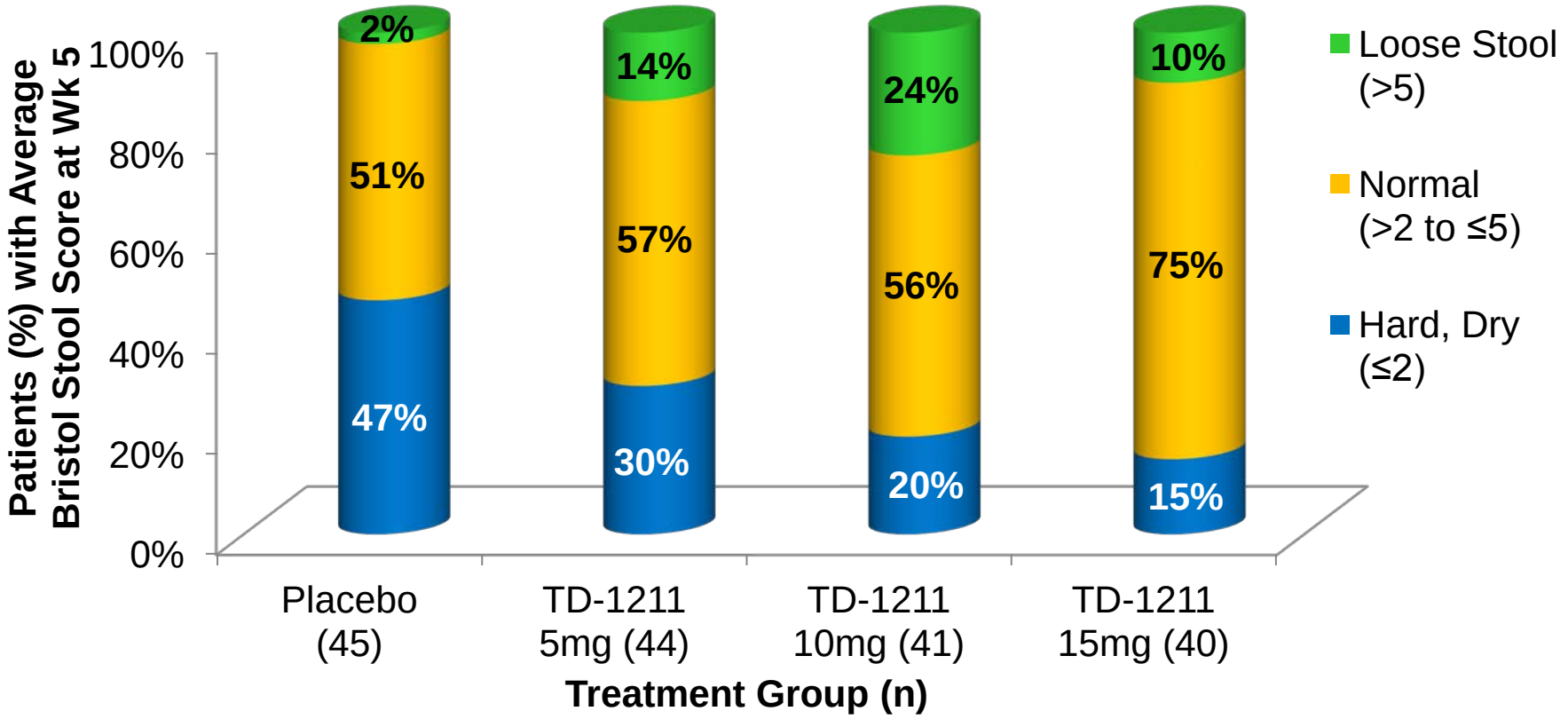
End of Treatment response to: "Since the end of the 2-week qualification period and before the first dose of study medication, how would you describe the change in your constipation?"

Time to First Bowel Movement

	Patients, n (%)	
	Placebo n=52	TD-1211 Combined n=149
Number of patients with at least one SBM within:		
4 hours	5 (10)	56 (38)
8 hours	**9 (17)**	**77 (52)**
16 hours	17 (33)	87 (58)
24 hours	30 (58)	99 (66)
48 hours	39 (75)	124 (83)

SBMs = spontaneous bowel movements. EA population

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



- **Patients with average BSS scores at baseline among treatment groups: 54-67% hard, dry and 29-43% normal**

BSS = Bristol Stool Scale; SBMs = spontaneous bowel movements

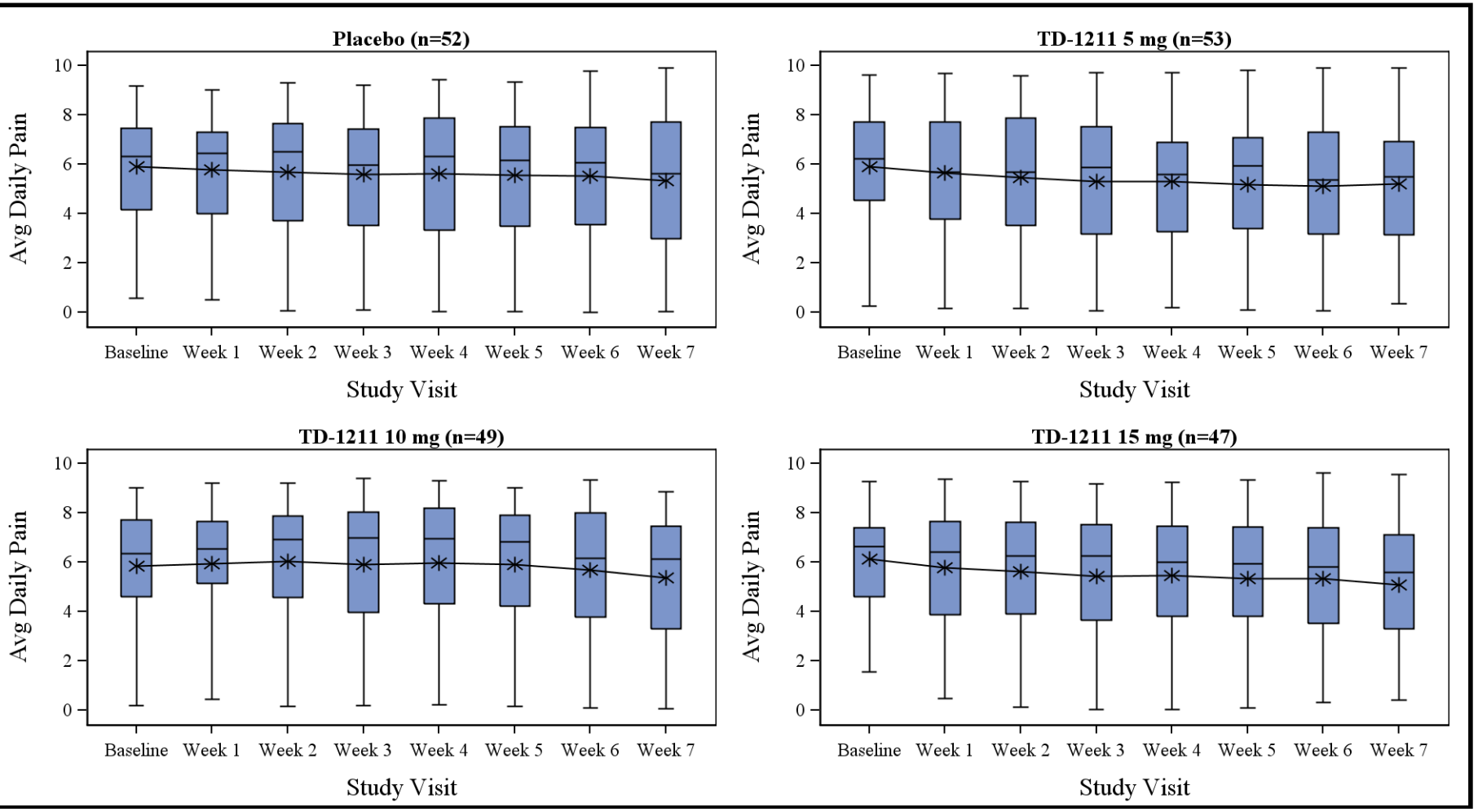
Overall TEAEs Similar Between TD-1211 and Placebo, with GI TEAEs Predominant

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)	**11 (20)**	**13 (23)**	**15 (28)**	**14 (27)**	**42 (26)**
Abdominal pain	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)

- **A majority of treatment-related GI adverse events were associated with initiation of treatment, resolved within a few days, and were mild or 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 Study 0084

- **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 withdrawal**
- **Majority of patients reported their constipation was better or much better on treatment**
- **Clinically meaningful response to treatment**