Prucalopride for the Treatment of Chronic Idiopathic Constipation in Adults

October 18, 2018

Shire

Gastrointestinal Drugs Advisory Committee

Introduction

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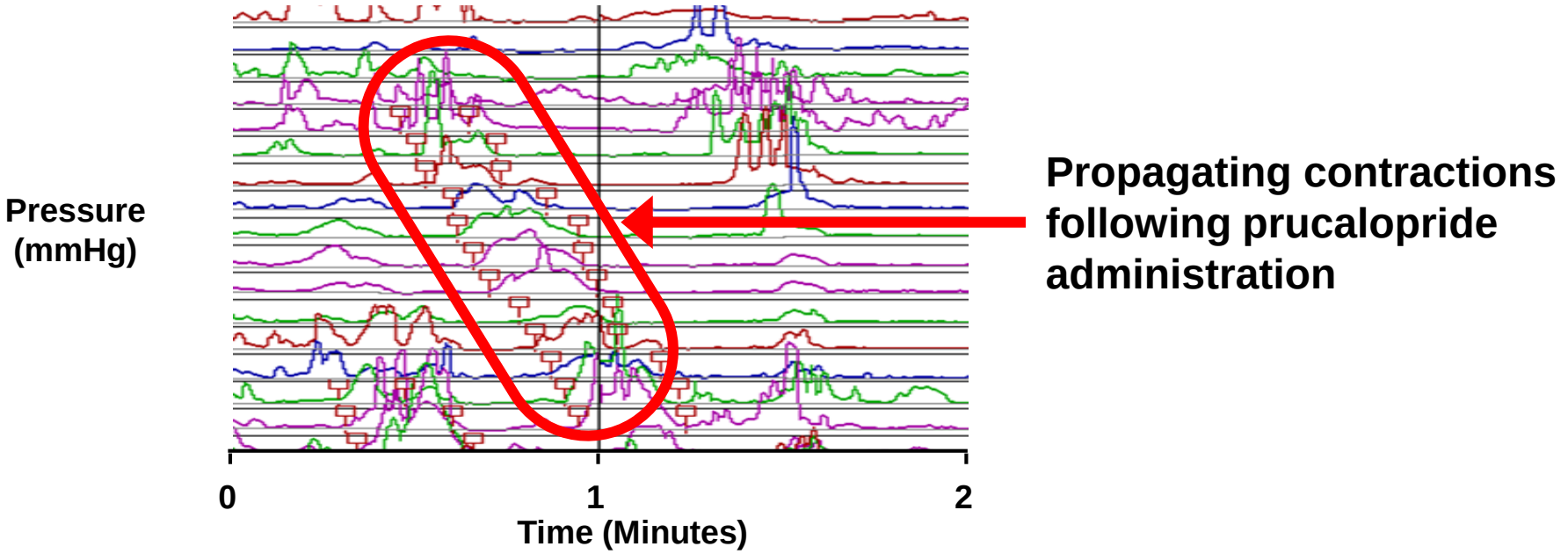
Shire

Prucalopride is a Next-Generation 5-HT_4 Receptor Agonist With Strong Prokinetic Activity

- Highly-selective 5-HT_4 agonist
- Stimulates colonic peristalsis in patients with CIC to increase intestinal motility[1]
- Prucalopride induces high-amplitude propagating contractions



1) Miner, Camilleri et al., 2016.

Prucalopride is Different from Non-Selective 5-HT_4 Receptor Agonists

Drug	5-HT_4	5-HT_3	5-HT_2	5-HT_1	D_2	hERG
Prucalopride	+					
Cisapride	+	+	+			+
Tegaserod	+	+	+	+		

+ **Clinically Relevant Affinity**

- Highly selective for 5-HT_4 receptor
- Low potential for off-target effects
- No meaningful affinity for hERG channel
- ECG studies show no effect on QT-prolongation or arrhythmias

Tack et al., 2012.

Prucalopride Safety Supported by > 8 Years of Pharmacovigilance

- Extensive experience since first approval in 2009
- Marketed in 59 countries
  - Including Canada and countries in EU, Asia and South America
- > 280,000 patient-years experience
- ~ 1 million treated patients

No Updates to CV Safety Within Prucalopride Label Since Launch

- Periodic safety reviews support existing label
  - Annual review by health authorities, including EMA's Pharmacovigilance Risk Assessment Committee (PRAC)
  - Pharmacovigilance of literature and post-marketing data
- No emerging CV safety signals detected since launch

Prucalopride US Development History

Licensed from J&J
Europe and non-US

EU Approval

Meetings with FDA to discuss NDA

Pre-NDA Meeting

GIDAC Meeting
CV Outcome Trial not required for 5-HT_4

Pharmaco-epidemiology Study 802
CV assessment

FDA Submission

76 Clinical Studies Support Prucalopride Benefit-Risk for Chronic Idiopathic Constipation (CIC)

- 16 Phase 3 and 4 studies
  - 2 pivotal
  - 4 supportive
  - 10 additional
- 14 Phase 2 studies
- 46 Phase 1 studies

Prucalopride Safe and Effective for Patients with Chronic Idiopathic Constipation

- Primary endpoint met in 5 of 6 key studies
- Consistent disease characteristics and treatment standards support generalizability to US patients
  - USA studies support safety and efficacy
- Safety well-characterized
  - Supported by clinical studies, post-marketing experience

Proposed Prucalopride Indication

- Treatment of chronic idiopathic constipation in adults

- Dosed 2 mg once-daily (QD)
  - Dosed 1 mg QD in patients with severe renal impairment

Agenda

Unmet Need in Chronic Idiopathic Constipation	**Michael Camilleri, MD** Gastroenterologist and Professor of Medicine, Pharmacology and Physiology Mayo Clinic Rochester, Minnesota
Efficacy	**Heinrich Achenbach, MD, PhD** Global Clinical Development Team Lead Shire
Safety	**John Caminis, MD** Therapeutic Area Head - Global Drug Safety Shire
Clinical Perspective	**Jan Tack, MD, PhD** Professor of Medicine Head of Clinic, Department of Gastroenterology Hospital KU Leuven, Belgium
Conclusion	**Debra Silberg, MD, PhD** Therapeutic Area Head - VP of Clinical Development Shire

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Unmet Need in Chronic Idiopathic Constipation

Michael Camilleri, MD
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Rochester, Minnesota

Chronic Idiopathic Constipation: Challenging and Persistent Problem[1,2]

- < 3 complete spontaneous bowel movements (CSBM) per week
- Chronic if lasts for at least 6 months or recurrent
- Idiopathic component frustrating for patients
  - No underlying cause for constipation

1) Dennison et al., 2005.
2) Peery et al., 2015.

Multiple Effects of CIC Can be Debilitating

- Significant impact on QoL
- Health-related QoL scores comparable to other chronic conditions
  - Musculoskeletal conditions and diabetes[1]
  - For women: heart disease, depression[2]
- May lead to increased risk for complications, comorbidities[3]
  - Fecal impaction, diverticular disease, rectal prolapse
- Patients reluctant to talk about CIC

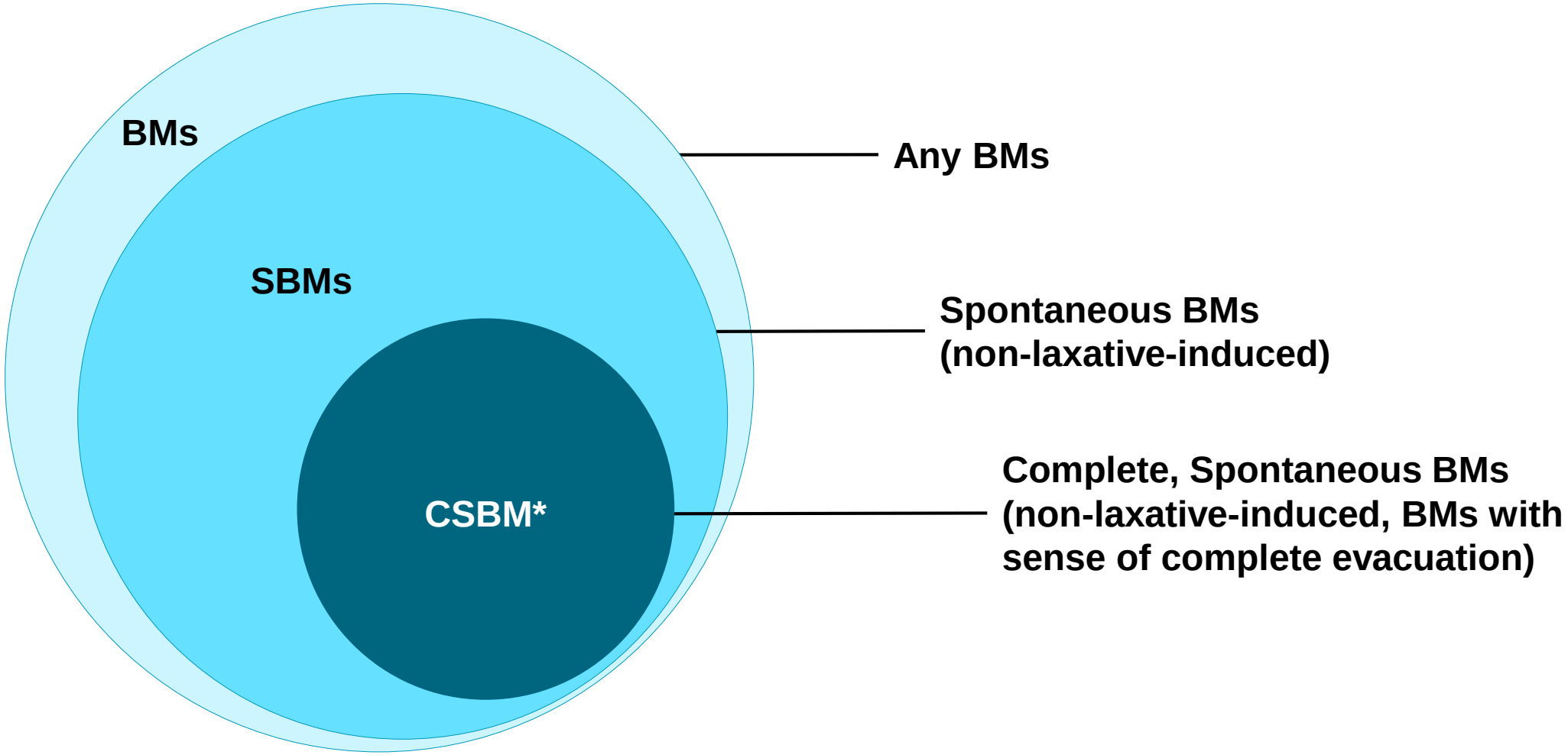
1) Belsey et al., 2010.
2) Wald et al., 2007.
3) Talley et al., 2009.

35 Million US Adults Diagnosed with CIC[1]

- Health care costs are considerable
  - All-cause costs = $11,991, gastro-related costs = $4,049[2]
  - > 3 million physician visits every year[3]
  - 92,000 hospitalizations[4]
  - Several $100 million expenditures annually on laxatives[4]
- CIC is disruptive
  - Patients missed 0.8 days of school or work per month[2]
- More prevalent in women, who also more frequently seek treatment[4]
  - > 75% of patients in referral setting are women[5]
- More common in elderly than younger adults[4]

1) Suares and Ford, 2011; 2) Camilleri et al., 2017; 3) Peery et al., 2015; 4) Lembo and Camilleri, 2003; 5) Lembo and Camilleri, 2003.

Bowel Movement Categories Differ Based on Initiation and Completeness



(C)(S)BM = (complete) (spontaneous) bowel movements

*CSBM = SCBM

Treatment Goal: Restore Normal Bowel Function (≥ 3 CSBM/week) and Improve Patient Symptoms

- Move stool out of colon, e.g., by accelerating colonic transit[1]
- Increased bowel frequency associated with improvements in symptoms
- Achieving ≥ 3 CSBMs per week clinically meaningful and life-changing for patients, both emotionally and physically

1) Emmanuel et al., 2014.

Range of Interventions – Lifestyle Modifications, Over-The-Counter, Prescription Therapies

- No one approach works for all – high patient dissatisfaction[1]

LIFESTYLE MODIFICATIONS	OVER-THE-COUNTER	PRESCRIPTION THERAPIES

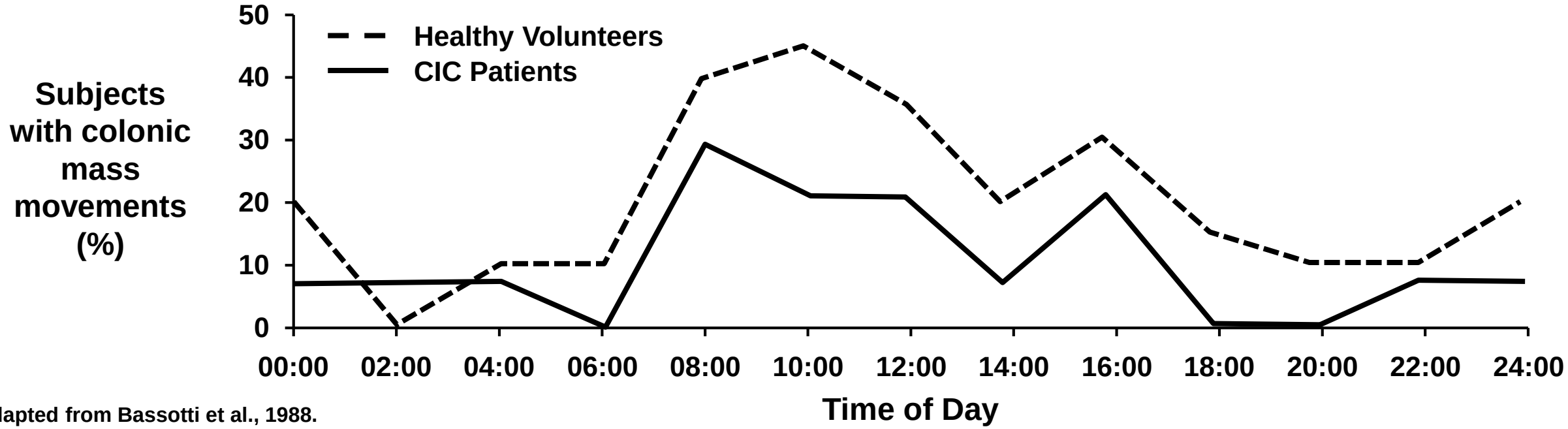
▪ Diet changes
▪ Increasing fluid intake
▪ Exercise
▪ Increase dietary fiber
	▪ Laxatives (e.g., PEG)
	▪ Bulking agents
	▪ Stool softeners
	▪ Stimulants
		▪ Prosecretory agents
		  ▪ Lubiprostone
		  ▪ Linaclotide
		  ▪ Plecanatide
		(Treatment effect ~8-17%)

- Current prescription agents have no direct effect on colonic peristalsis

1) Johanson et al., 2007.

Propulsion of Colonic Content Regulated in Part by High-Amplitude Propagating Contractions (HAPCs)

- Healthy individuals experience HAPCs about 6 times per day
  - After waking up and eating
  - Followed by urge to defecate
- HAPC frequency reduced in patients with CIC

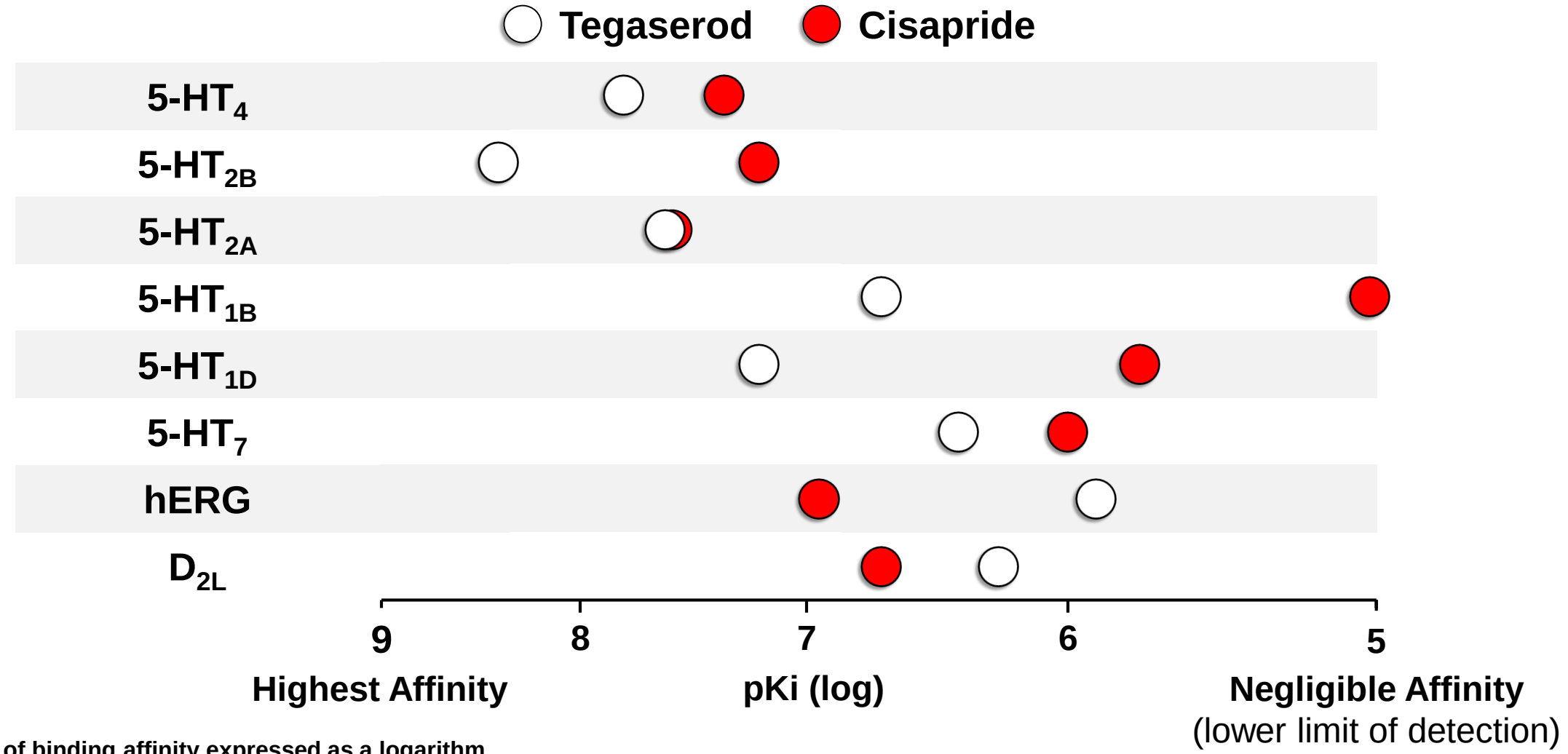


Adapted from Bassotti et al., 1988.

First Generation, Non-Selective 5-HT_4 Agonists Withdrawn from US Market

- Provided relief to many patients with gut motility dysfunction
  - Safety concerns versus benefits

First Generation 5-HT$_4$ Agonists Non-Specificity Creates Risk for Off-Target Effects, Potential CV Risk



pKi: Measure of binding affinity expressed as a logarithm

DeMaeyer et al., 2008; McKinnell et al., 2013.

Unmet Medical Need for Adults Living with Chronic Idiopathic Constipation

- CIC takes a toll on patients, often live in silence for years
- Once they seek medical help, many still unable to get sustained relief
- Patients looking for safe and effective treatment
  - Increases stool frequency
  - Uses different MoA than secretory agent
  - Improve symptoms

Prucalopride Efficacy Results

Heinrich Achenbach, MD, PhD

Global Clinical Development Team Lead

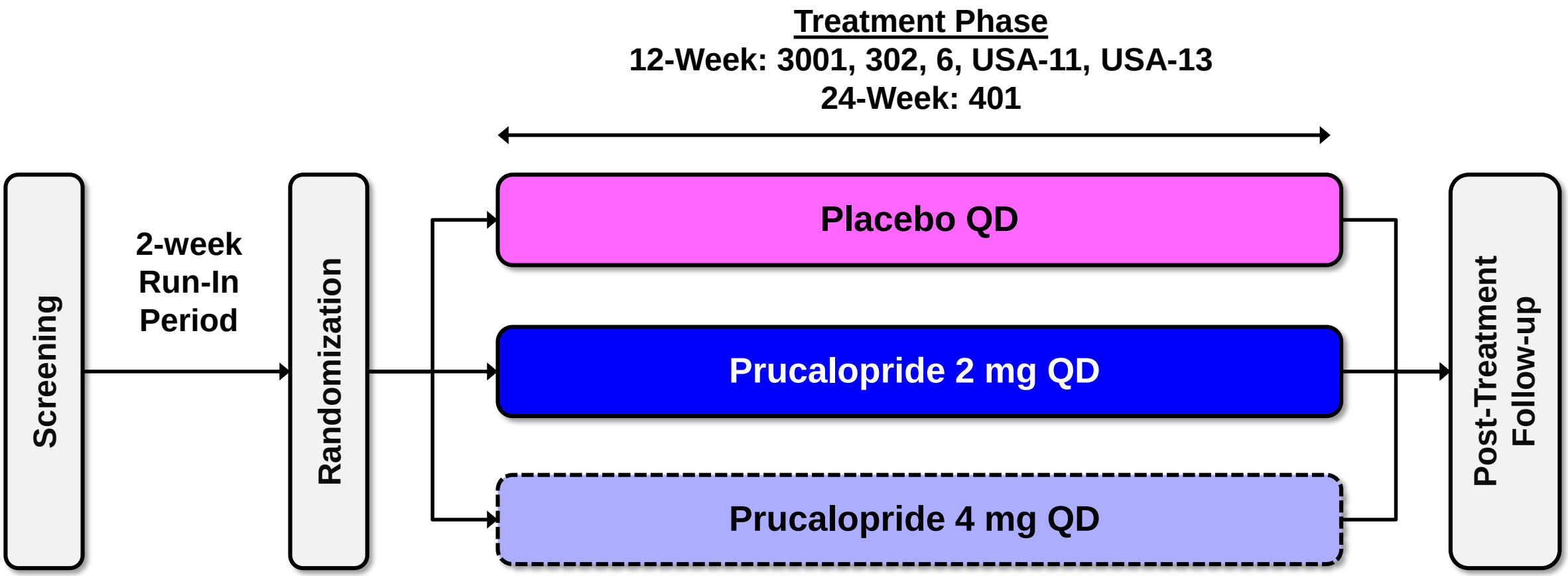
Shire

Primary Efficacy Evidence Supported by 6 Randomized, Double-Blind Placebo-Controlled Studies

Study 3001	Study 302	Study 6	Study USA-11	Study USA-13	Study 401
(N=501)	(N=374*)	(N=712)	(N=570)	(N=641)	(N=340)
12 weeks	12 weeks	12 weeks	12 weeks	12 weeks	24 weeks
Prucalopride (N=249)	Prucalopride (N=187)	Prucalopride (N=236)	Prucalopride (N=190)	Prucalopride (N=214)	Prucalopride (N=171)
Placebo (N=252)	Placebo (N=187)	Placebo (N=240)	Placebo (N=193)	Placebo (N=212)	Placebo (N=169)

*All randomized

Phase 3 Study Design



4 mg dose included in Studies 6, 11 and 13; later omitted from studies due to no increased efficacy compared to 2 mg

Patients with History of CIC Enrolled Based on Modified Rome Criteria for Functional Constipation

- ≤ 2 spontaneous bowel movements per week
  - Resulting in feeling of complete evacuation (CSBM)
- ≥ 1 of the following in > 25% of BMs
  - Very hard and/or hard stools
  - Sensation of incomplete evacuation
  - Straining at defecation
  - Sensation of anorectal obstruction/blockage
  - Manual maneuvers to facilitate evacuation
- Symptoms must occur
  - ≥ 6 months prior to diagnosis; present during last 3 months

Complete Spontaneous Bowel Movements Clinically Meaningful Outcome in CIC

- Primary endpoint
  - Proportion with average of ≥ 3 CSBMs/week over 12 weeks
- Prespecified secondary and additional endpoints
  - Average increase of ≥ 1 CSBMs per week over 12 weeks
  - Time-to-first SBM

Statistical Powering Assumptions

- Assumptions for proportion of patients with average of ≥ 3 CSBMs/week
  - Prucalopride: 27-30% response rate
  - Placebo: 14-15% response rate

  } 12-15% Treatment effect

- All 90% power at 2-sided significance level of 0.05

6 Randomized DBPC Studies Conducted in Different Regions

- USA
  - Studies USA-11, USA-13
- Europe
  - Studies 302, 401
- Global (EU, CAN, ZA, AUS)
  - Study 6
- Asia / Pacific
  - Study 3001

Demographics and Results

Enrolled Populations Varied Across Studies, Balanced Within Each Study

- **Age**
  - Mean age 41-58 years (Range 18-75)
  - 10-19% age ≥ 65 years (Studies 6, USA-11, USA-13, 401)
  - Age ≤ 65 years (Study 3001)
- **Sex**
  - 85-93% female (Studies 3001, 6, USA-11, USA-13, 401)
  - 100% male (Study 302)
- **Race**
  - 86-96% White, 1-11% Black (Studies 302, 6, USA-11, USA-13, 401)
  - 92% Asian, 6% White (Study 3001)

Population consistent with study reports:
All treated patients (USA-11, USA-13 and INT-6), safety population (401), modified intent-to-treat (mITT, 302) and intent-to-treat population (ITT, 3001)

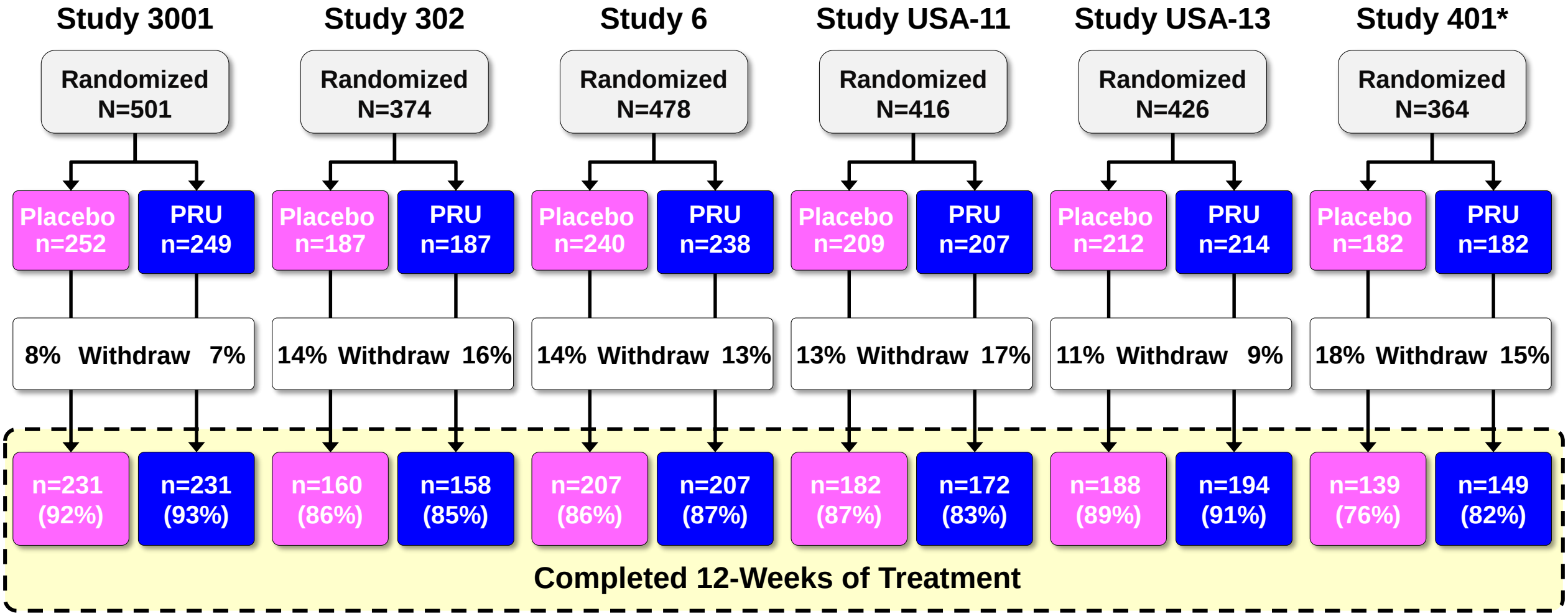
Baseline Disease Characteristics Demonstrate Significant CIC

	Study 3001		Study 302		Study 6		Study USA-11		Study USA-13		Study 401	
	Placebo (N=252)	PRU (N=249)	Placebo (N=187)	PRU (N=187)	Placebo (N=240)	PRU (N=236)	Placebo (N=193)	PRU (N=190)	Placebo (N=212)	PRU (N=214)	Placebo (N=171)	PRU (N=169)
Duration of constipation, mean (years)	**13**	**13**	**9**	**9**	**18**	**16**	**22**	**21**	**21**	**23**	**14**	**16**
Baseline CSBMs/week, mean	**0.3**	**0.3**	**0.4**	**0.5**	**0.4**	**0.4**	**0.4**	**0.5**	**0.4**	**0.4**	**0.4**	**0.4**

- Achieving primary endpoint requires 10-fold improvement

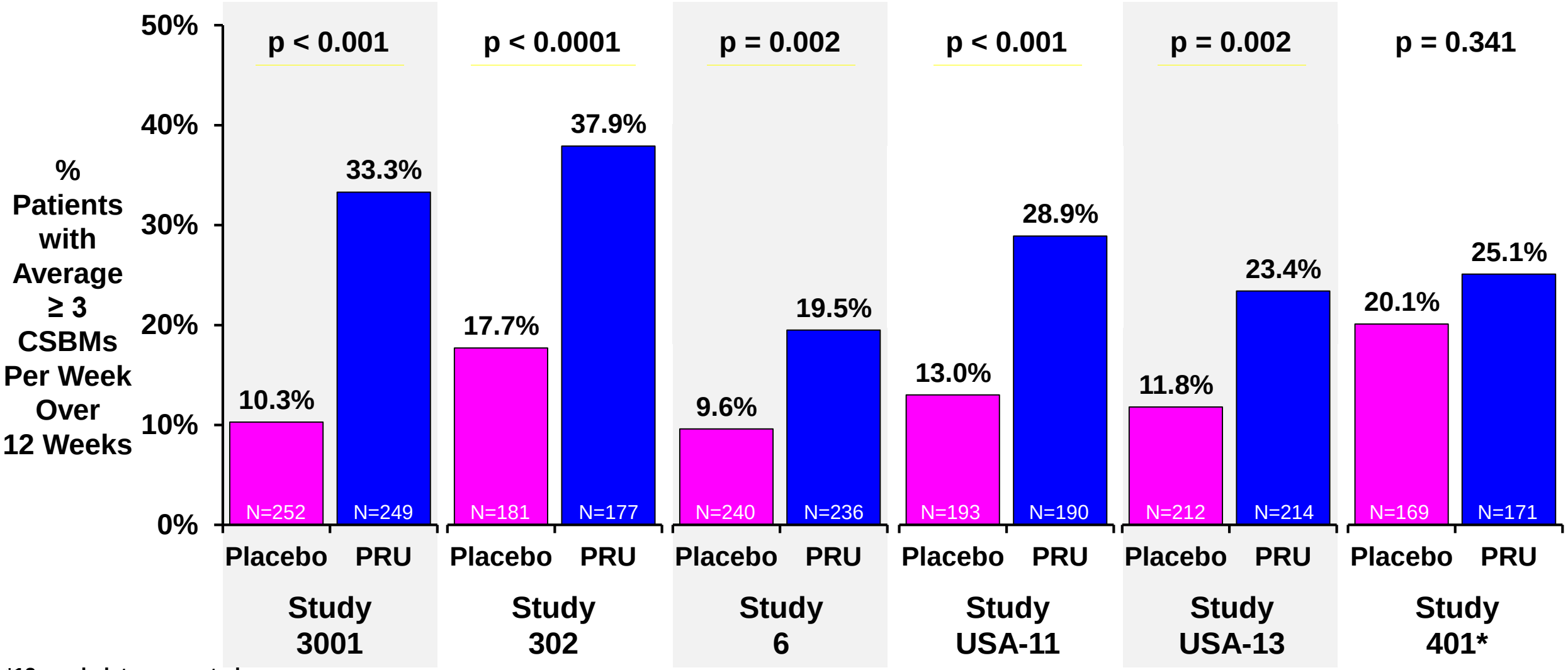
PRU = Prucalopride

Similar Disposition Across Studies



*12-week data presented

Primary Endpoint Results Across All Studies Support Benefit of Prucalopride



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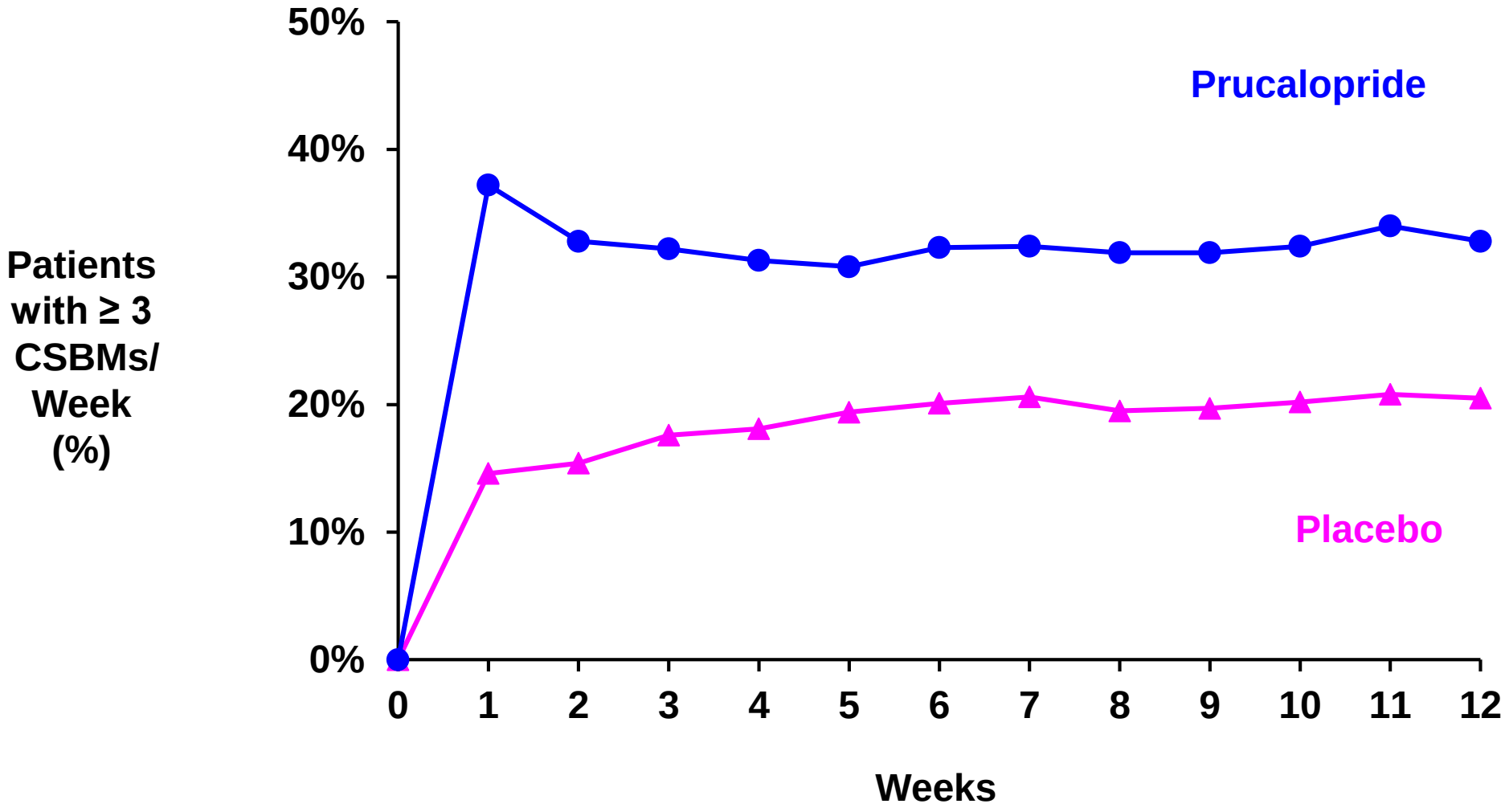
Prucalopride Response Maintained Throughout Treatment Period



Pooled Data: Study 3001, 302, 6, USA-11, USA-13 and 401

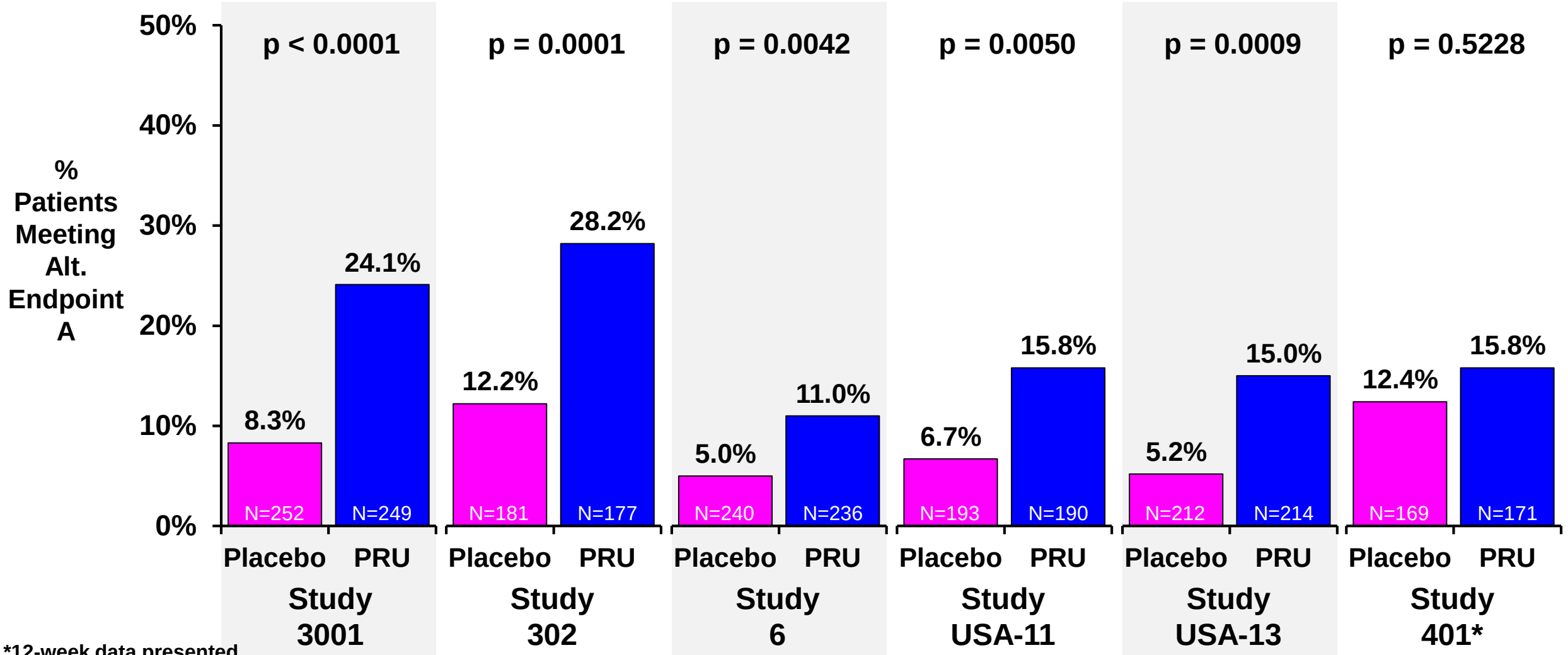
FDA Requested Post-Hoc Analysis: Alternative Endpoint A

- Proportion of patients with
  - ≥ 3 CSBMs/week

    AND
  - Increase from baseline of ≥ 1 CSBM/week

    FOR
  - ≥ 9 of 12 weeks, including at least 3 in the last 4 weeks

Alternative Endpoint A Results Consistent with Primary Endpoint Results



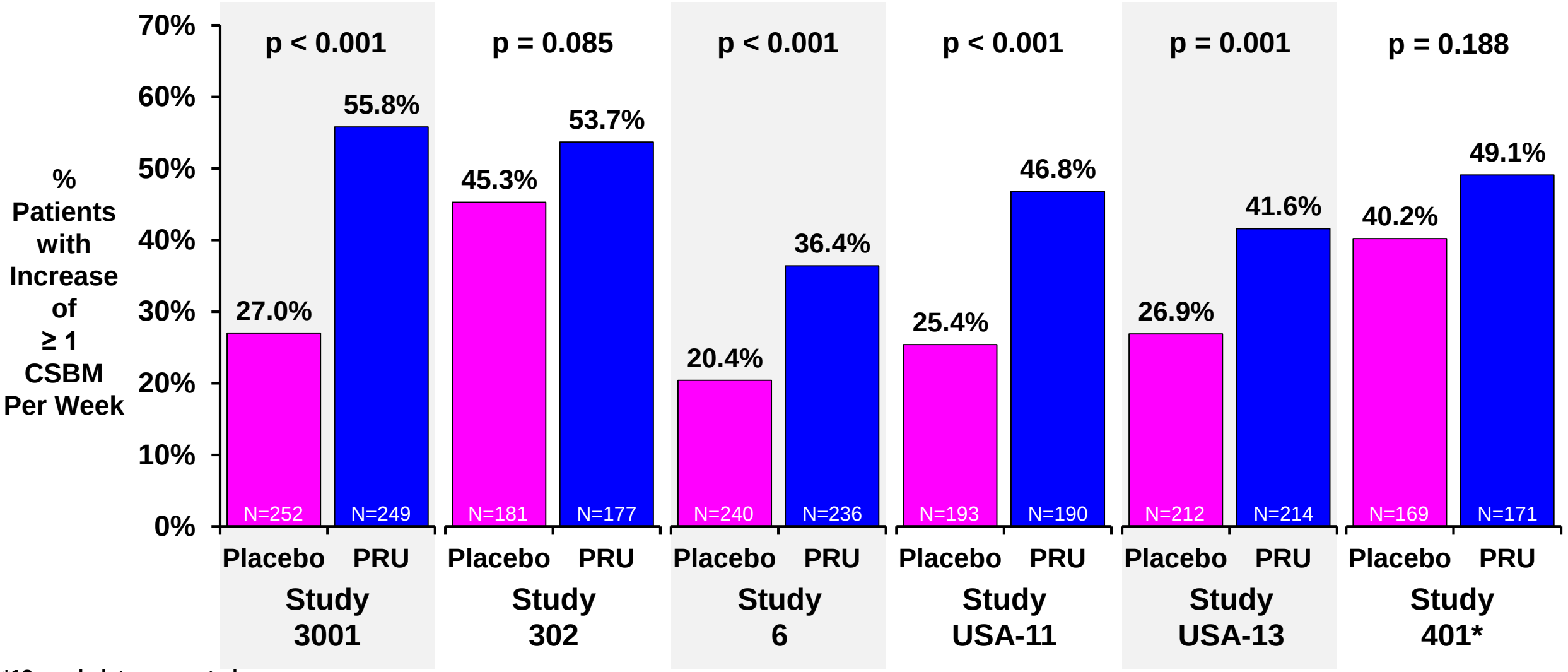
*12-week data presented

Alternative Endpoint A: Proportion of patients with ≥ 3 CSBMs per week and an increase of ≥ 1 CSBM/week for 9 out of 12 weeks including 3 of last 4 weeks

Evaluation Unable to Find Causal Factor for Study 401 Result

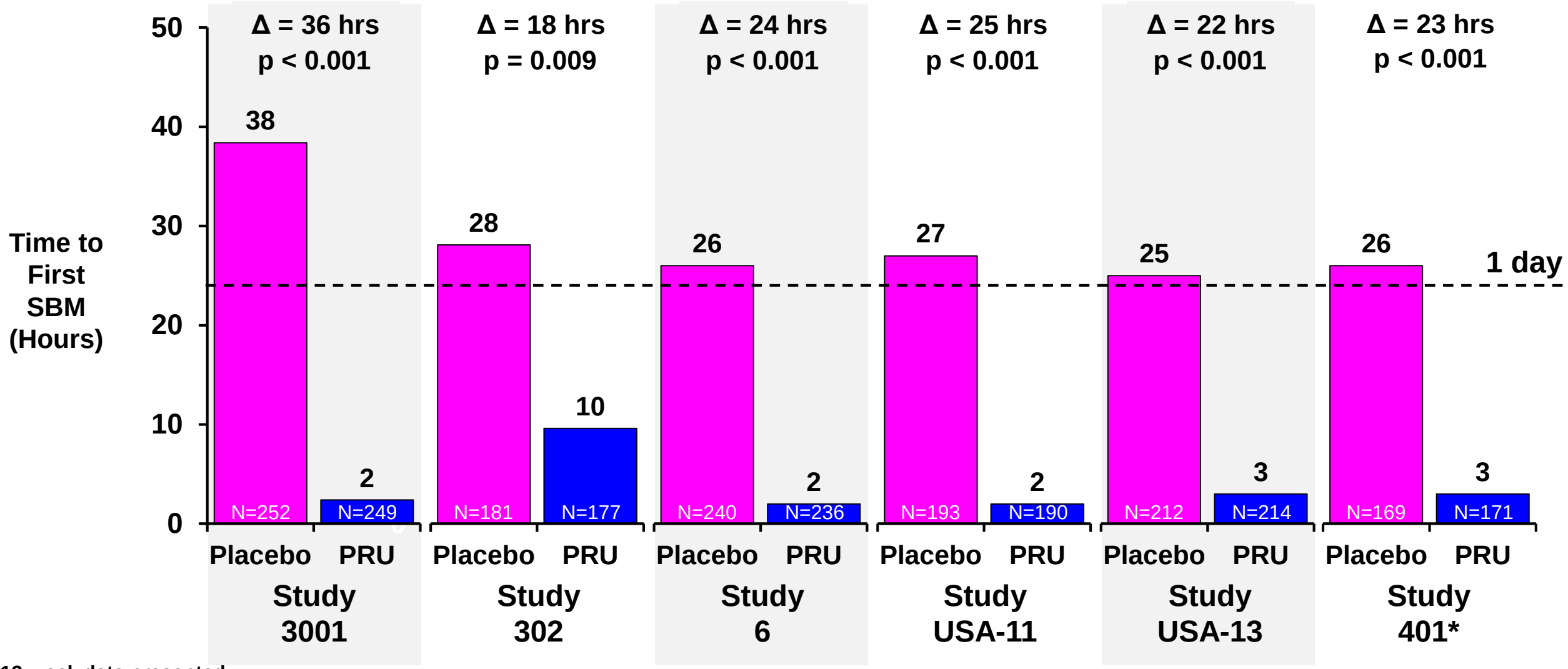
- Primary results not statistically significant at Week 12 or 24
- Evaluations of demographics, disease characteristics and rescue medication use unable to explain finding
- Placebo response highest among all prucalopride studies
- Based on powering assumptions, 10% probability that results will not show statistical significance

Higher Proportion of Patients with Average Increase of ≥ 1 CSBM/week



*12-week data presented

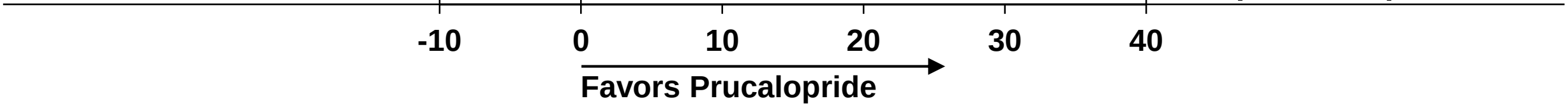
Prucalopride Decreases Time to First SBM



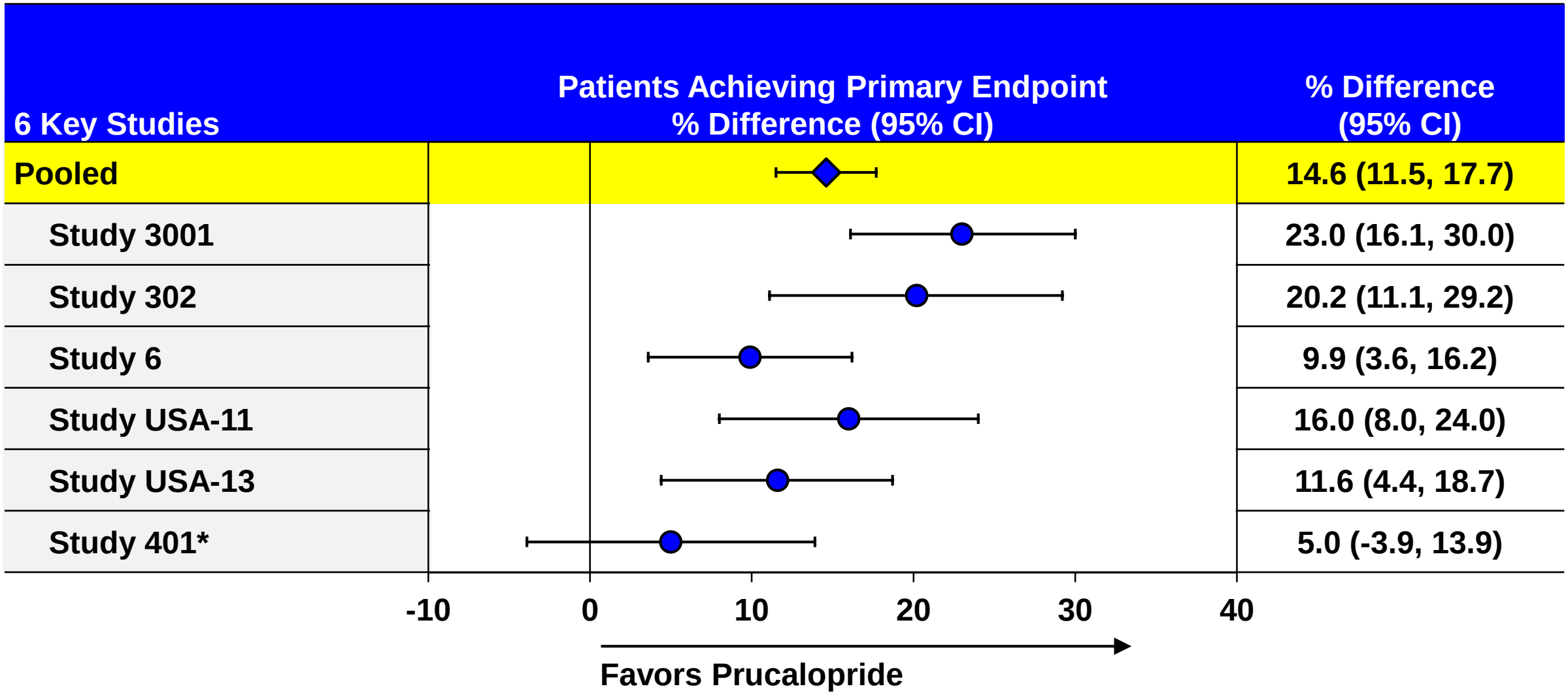
*12-week data presented

Benefit of Prucalopride Treatment Observed Regardless of Baseline Demographics

Subgroup		Patients Achieving Primary Endpoint % Difference (95% CI)	% Difference (95% CI)	p-value
Overall			**14.6 (11.5, 17.7)**	**< 0.001**
Age	< 65 years		15.1 (11.8, 18.5)	< 0.001
	≥ 65 years		11.2 (2.9, 19.6)	0.004
Sex	Female		14.5 (10.9, 18.0)	< 0.001
	Male		15.0 (8.2, 21.7)	< 0.001
Race	White		13.5 (9.8, 17.0)	< 0.001
	Non-White		18.9 (12.7, 25.2)	< 0.001
Region	North America		14.0 (9.0, 18.9)	< 0.001
	Western Europe		11.6 (5.1, 18.2)	< 0.001
	Eastern Europe		13.3 (5.1, 21.6)	0.002
	Asia-Australia		22.9 (15.6, 30.2)	< 0.001



Overall Efficacy Evidence Supports Prucalopride Treatment for Patients with CIC



*12-week data presented

Benefit Observed Across Variety of Secondary and Post-Hoc Efficacy Endpoints

Endpoint	Study 3001	Study 302	Study 6	Study USA-11	Study USA-13	Study 401
Primary endpoint	✓	✓	✓	✓	✓	
Alternative Endpoint A	✓	✓	✓	✓	✓	
Average increase of ≥ 1 CSBMs/week	✓		✓	✓	✓	
Time-to-first SBM	✓	✓	✓	✓	✓	✓

✓ Statistically Significant Endpoint

Prucalopride Safety

John Caminis, MD

Therapeutic Area Head – GI, Endocrine & Metabolism

Global Drug Safety

Shire

Extensive Prucalopride Exposure in Studies and Post-Marketing

	# of Patients Exposed to Prucalopride
Randomized, double-blind, placebo-controlled (DBPC) studies	3,295
Open-label studies	2,759
Phase 1 studies	939
Pharmacoepidemiology Study 802	5,715

Estimated post-marketing exposure through Sept 2017
> 280,000 patient-years experience

Duration of Exposure to Prucalopride From Open-Label Studies

Duration of Prucalopride Exposure in Open-Label	# of Patients With CIC (N=2,759)
Any patient dosed	2,595
≥ 90 days	2,151
≥ 180 days	1,710
≥ 365 days	1,052

Additional Safety Data Collected During Open-Label Studies

- 86% of DBPC patients continued into open-label extension
- Data collected every 3 months
  - Adverse events
  - ECG
  - Vital signs
  - Laboratory data
  - Pharmacokinetic (months 3, 6 and 9)

Pooled Randomized DBPC: 16 Studies of ≥ 4 Weeks

- Phase 3 and 4 (n=9)
- Phase 2 (n=7)
- Safety assessment focused on
  - Placebo (N=1,973)
  - Prucalopride 2 mg (N=1,516)

Pooled Randomized DBPC: Phase 3 (Studies 3001, 302, 6, USA-11, 12, USA-13, USA-25, USA-28); Phase 4 (Study 401)
Phase 2 (Studies 1, FRA-1, 2, USA-3, GBR-4, BEL-6, USA-26)

Pooled Randomized DBPC: Most AEs Reported as Mild or Moderate, With Few SAEs

	Placebo (N=1,973)	Prucalopride 2 mg (N=1,516)
Any AE	54%	62%
Any severe AE	11%	13%
Any serious AE	2%	2%
Any AE leading to discontinuation	3%	5%
Death	0.05%	0.07%

Pooled Randomized DBPC: 16 Phase 2-4 randomized DBPC studies in CIC lasting ≥ 4 weeks

Pooled Randomized DBPC: 4 AEs Reported in ≥ 5% of Patients

	Placebo (N=1,973)	Prucalopride 2 mg (N=1,516)
Any AE	54%	62%
Headache	9%	17%
Nausea	6%	14%
Diarrhea	4%	12%
Abdominal pain	8%	10%

- Majority of events mild or moderate, and typically transient in nature

Pooled Randomized DBPC: 16 Phase 2-4 randomized DBPC studies in CIC lasting ≥ 4 weeks

Pooled Randomized DBPC: Low Rate of AEs Leading to Discontinuation (≥ 1%)

	Placebo (N=1,973)	Prucalopride 2 mg (N=1,516)
Any AE leading to discontinuation	3%	5%
Headache	0.5%	1.5%
Diarrhea	0.1%	1.5%
Nausea	0.5%	1.3%

Pooled Randomized DBPC: 16 Phase 2-4 randomized DBPC studies in CIC lasting ≥ 4 weeks

All Deaths: 3 from Pooled Randomized DBPC (N=5,278) 5 from Open-Label (N=2,759)

Age / Sex	Cause of Death	Dose	Studies	Treatment
89 / M	MI	Placebo	DBPC	On
83 / M	Lobar pneumonia	1 mg	DBPC	On
86 / F	Bronchitis	2 mg	DBPC	On
81 / M	MI	2 mg	Open-label	Off drug + 67 days
89 / F	Pneumonia	2 mg	Open-label	On
56 / M	MI	4 mg	Open-label	On
70 / M	Suicide	2 mg	Open-label	Off drug + 29 days
40 / F	Suicide	4 mg	Open-label	Off drug + 52 days

Pooled Randomized DBPC: All doses in 16 Phase 2-4 randomized DBPC studies in CIC lasting ≥ 4 weeks

Evaluation of Suicide-Related Events Concluded No Changes to Prucalopride Safety Information

- DBPC: Low incidence of psychiatric AEs and similar to placebo

Age/Sex	Event	Studies	Relevant History	Treatment Duration
70 / M	Suicide	Open-label	Depression, insomnia anti-depressants 1 mo prior to event	101 days + 29 days off drug
40 / F	Suicide	Open-label	Depression, drug abuse	242 days + 52 days off drug
29 / F	Suicide Attempt	DBPC	Depression; illicit drug use	42 days + 7 days off drug
38 / F	Suicide Attempt	Open-label	None documented: personal problems	269 days
37 / F	Suicide Attempt	Open-label	Anxiety, multiple pain diagnoses, psychiatric & pain medications	142 days
24 / M	Suicide Ideation	Open-label	Depression, insomnia, hallucinations, homicidal thoughts	452 days

- None of the events attributed to prucalopride

Cardiovascular and Major Adverse Cardiac Events (MACE) Assessments

Comprehensive Assessments Support Prucalopride CV Safety

1. Extensive nonclinical testing at supra-therapeutic doses
2. Thorough QT study and Phase 1 monitoring
3. Comprehensive review of pooled randomized DBPC studies
4. Independent, blinded expert adjudication of MACE in randomized DBPC and open-label clinical studies
5. Pharmacoepidemiology Study 802 comparing patients treated with prucalopride to patients treated with PEG
6. More than 8 years post-marketing safety experience

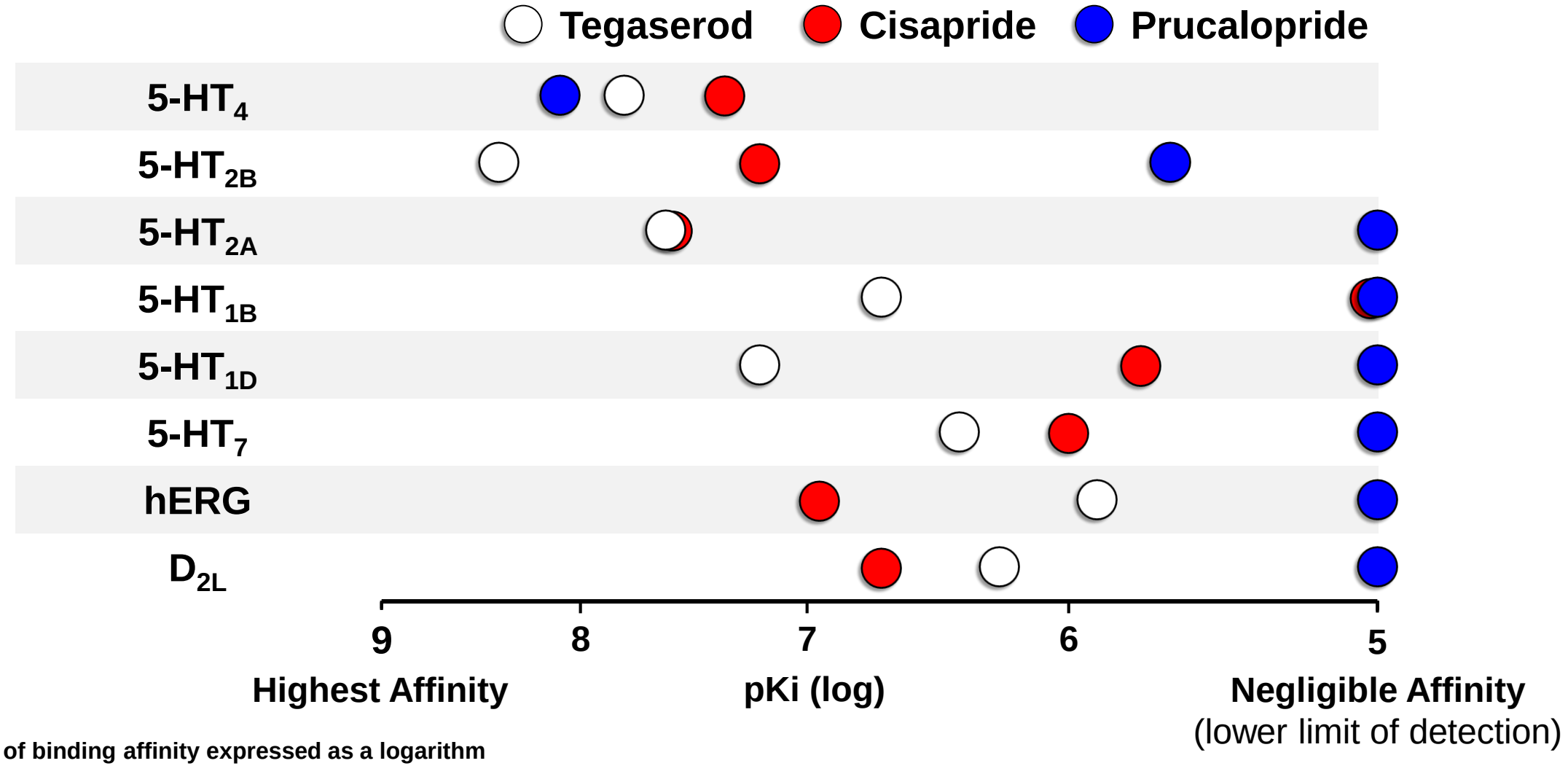
PEG = Polyethylene Glycol

52 Receptors Tested for Binding Affinity (pKi)

- 14 5-HT receptor subtypes
- 13 monoamine receptors
- 8 peptide receptors
- 5 ion channels
- 5 transporters
- 3 opiate receptors
- 4 other

pKi: Measure of binding affinity expressed as a logarithm

Prucalopride is a Highly-Selective, High-Affinity 5-HT_4 Receptor Agonist (pKi)



pKi: Measure of binding affinity expressed as a logarithm

DeMaeyer et al., 2008; McKinnell et al., 2013.

Nonclinical Evidence Show Wide Cardiovascular Safety Margin[1] and Absence of Mechanism for CV Risk

- No relevant effect on electrophysiological parameters
  - No effect on hERG channel at 50-times therapeutic concentration
  - No effects on other ion channels at 500-times therapeutic concentration
  - No proarrhythmic tendencies observed at 500-times therapeutic concentration
- No effect on platelet aggregation or coronary artery contractility

1) Conlon et. al., 2018.

TQT & Phase 1 Studies In Healthy Volunteers: No Effect on Cardiac Repolarization or Proarrhythmic Potential

- Phase 1 studies up to 20 mg with intense cardiac monitoring
- TQT studied doses 2 and 10 mg
  - No effects on repolarization
  - No electrophysiological change
- Transient change in heart rate
  - No further increases at higher doses 20mg

Comprehensive Assessments Support Prucalopride CV Safety

1. Substantive nonclinical testing at supra-therapeutic doses
2. Thorough QT study and Phase 1 monitoring
3. Comprehensive review of pooled randomized DBPC studies
4. Independent, blinded expert adjudication of MACE in randomized DBPC and open-label clinical studies
5. Pharmacoepidemiology Study 802 comparing patients treated with prucalopride to patients treated with PEG
6. More than 8 years post-marketing experience

16 Pooled Randomized DBPC and 3 Open-Label Studies: Low Incidence of CV AEs of Interest

	Placebo (N=1,973)	Prucalopride 2 mg (N=1,516)	Open-Label* (N=2,759)
Exposure time (patient-years)	389	327	2302
QT Prolongation, Ventricular Arrhythmia & Syncope			
Any AE	2.8%	1.8%	1.4%
Any serious AE	0.5%	0.3%	0.2%
Any death	0	0	0
Any AE leading to discontinuation	0	0	0.1%
Cardiovascular & Cerebrovascular Ischemic Events			
Any AE	1.3%	1.8%	1.0%
Any serious AE	0.8%	0.6%	0.6%
Any death	0.2%	0	0.9%
Any AE leading to discontinuation	0.5%	0.3%	0.9%

* Total includes all prucalopride doses from 7 open-label studies (3, 4, 10, BEL-8, FRA-1, NED-4, USA-22)

16 Pooled Randomized DBPC and 3 Open-Label Studies: Low Frequency of Ischemic Events

	Placebo (N=1,973)	Total Prucalopride (N=3,305)	Open-Label* (N=2,759)
CV ischemic-related AE, N (%)	5 (0.3%)	9 (0.3%)	23 (0.8%)
Events/100 years exposure	1.3	1.6	1.0

* Total includes all prucalopride doses from 7 open-label studies (3, 4, 10, BEL-8, FRA-1, NED-4, USA-22)

Independent Adjudication of Randomized DBPC Data Found No Indication of an Increased MACE Risk

	Placebo (N=2,019)	Total Prucalopride* (N=3,366)	Prucalopride 2 mg (N=1,516)
MACE	2 (0.1%)	2 (0.1%)	1 (0.1%)
CV death	0.05%	0	0
Non-fatal MI	0	0.03%	0
Non-fatal stroke	0.05%	0.03%	0.06%
MACE rate / 1000 patient years	5.2	3.5	3.1
Extended MACE (with unstable angina)	2 (0.1%)	4 (0.1%)	1 (0.1%)
Extended MACE rate / 1000 PYE	5.2	7.1	3.1

~31% of enrolled patients with pre-existing CV condition or disease

* Total includes all prucalopride doses for Pooled 16 Randomized DBPC studies ≥ 4 weeks plus 3 randomized DBPC studies < 4 weeks
Pooled Randomized DBPC (Studies 3001, 302, 6, USA-11, 12, USA-13, USA-25, USA-28, 401, 1, FRA-1, 2, USA-3, GBR-4, BEL-6, USA-26); plus randomized DBPC < 4 weeks duration (Studies NED-2, NED-13, USA-21)

Comprehensive and Systematic Assessments Support Prucalopride CV Safety

1. Substantive nonclinical testing at supra-therapeutic doses
2. Thorough QT study and Phase 1 monitoring
3. Comprehensive review of pooled randomized DBPC studies
4. Independent, blinded expert adjudication of MACE in randomized DBPC and open-label clinical studies
5. Pharmacoepidemiology Study 802 comparing patients treated with prucalopride to patients treated with PEG
6. More than 8 years post-marketing experience

Study 802: Robust Pharmacoepidemiology Population-Based Study

- Comparing incidence of MACE for prucalopride and PEG
  - Designed to exclude three-fold relative risk of MACE for prucalopride
- Data collected 2010-2016
  - 5 data sources from UK, Sweden and Germany
- Pooled results included data from UK and Sweden
  - Matching and propensity scores resulted in cohorts well-balanced in demographics and CV risk factors

Study 802: Demographic Characteristics

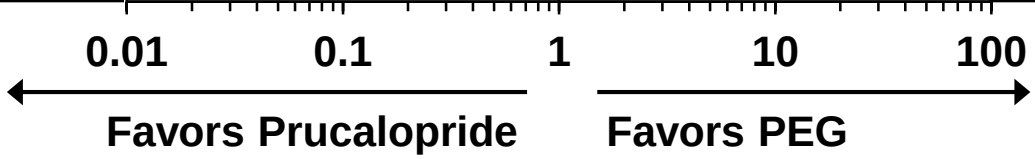
	Prucalopride (N=5,715)	PEG (N=29,372)
Sex		
Female	93%	93%
Male	7%	7%
Age (years)		
18 - 54	57%	58%
≥ 55	43%	42%
Age (years) and sex		
≥ 55 Female	39%	38%
≥ 55 Male	4%	4%
History of CV hospitalization		
Yes	6%	5%
At least 1 cardiovascular risk factor		
Yes	58%	55%

Study 802: No Increased Risk for MACE Compared to Patients Treated with PEG (Primary Analysis)

MACE	Prucalopride (N=5,715)	PEG (N=29,372)
Adjusted incidence rate / 1000 patient years (95% CI)	6.57 (3.90, 10.39)	10.24 (6.97, 14.13)
Adjusted incidence rate ratio (95% CI)	0.64 (0.36, 1.14)	

Study 802: Subgroup Analyses Align with Overall Results

		IRR (95% CI)	Prucalopride Events	PEG Events	IRR (95% CI)
Primary Analysis			18	73	0.64 (0.36, 1.14)
Sex	Female		14	61	0.56 (0.29, 1.07)
	Male		4	12	1.51 (0.45; 5.07)
Age (years)	18-54		1	9	0.20 (0.02, 1.65)
	≥ 55		17	64	0.84 (0.47, 1.50)
Age (years) & Sex	18-54 Female		1	8	0.22 (0.03, 1.90)
	≥ 55 Female		13	53	0.71 (0.37, 1.37)
	18-54 Male		0	1	--
	≥ 55 Male		4	11	2.57 (0.71, 9.26)
History of CV Hospitalization	Yes		6	23	1.10 (0.41, 2.93)
	No		12	50	0.62 (0.31, 1.24)



Study 802: Conclusion

- Did not establish increased risk of MACE with prucalopride compared to PEG
- Overall sensitivity analyses support results of primary endpoint
  - Varying outcome definitions and follow-up time
  - Analysis of potential bias

Comprehensive and Systematic Assessments Support Prucalopride CV Safety

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5. Pharmacoepidemiology Study 802 comparing patients treated with prucalopride to patients treated with PEG
6. More than 8 years post-marketing experience

Safety Profile Supported by More Than 280,000 Patient-Years Exposure (2009 – 2017*)

- Continuous monitoring and signal detection across all available sources of published and post-marketing data
- N=5,072 reported adverse events
  - 151 cardiovascular events
  - Majority non-serious
  - No change in annual reported rate since 2009

* Data cutoff: Oct 2017

No Change to CV Safety Profile Since Launch

- Shire implemented active monitoring for CV events
  - Desire for caution based on CV reports for other non-specific 5-HT_4 products
- Periodic review by Heath Authorities Bodies (e.g., EMA's PRAC)
  - Responsible for assessing all aspects of pharmacovigilance and risk management
- No CV safety signal identified from any agency

PRAC = Pharmacovigilance Risk Assessment Committee

Prucalopride Maintains Positive Benefit Risk Profile Since Launch

- Core safety information on cardiovascular risk unchanged since launched in 2009
- Most commonly reported AEs: Headache, nausea, diarrhea and abdominal pain
- Most AEs were mild to moderate in severity, occurred early and were transient in nature
- Comprehensive investigation of individual sources of data did not reveal an increase in CV risk for prucalopride
- Totality of data did not identify increase in CV risk

Clinical Perspective on Prucalopride

Jan Tack, MD, PhD

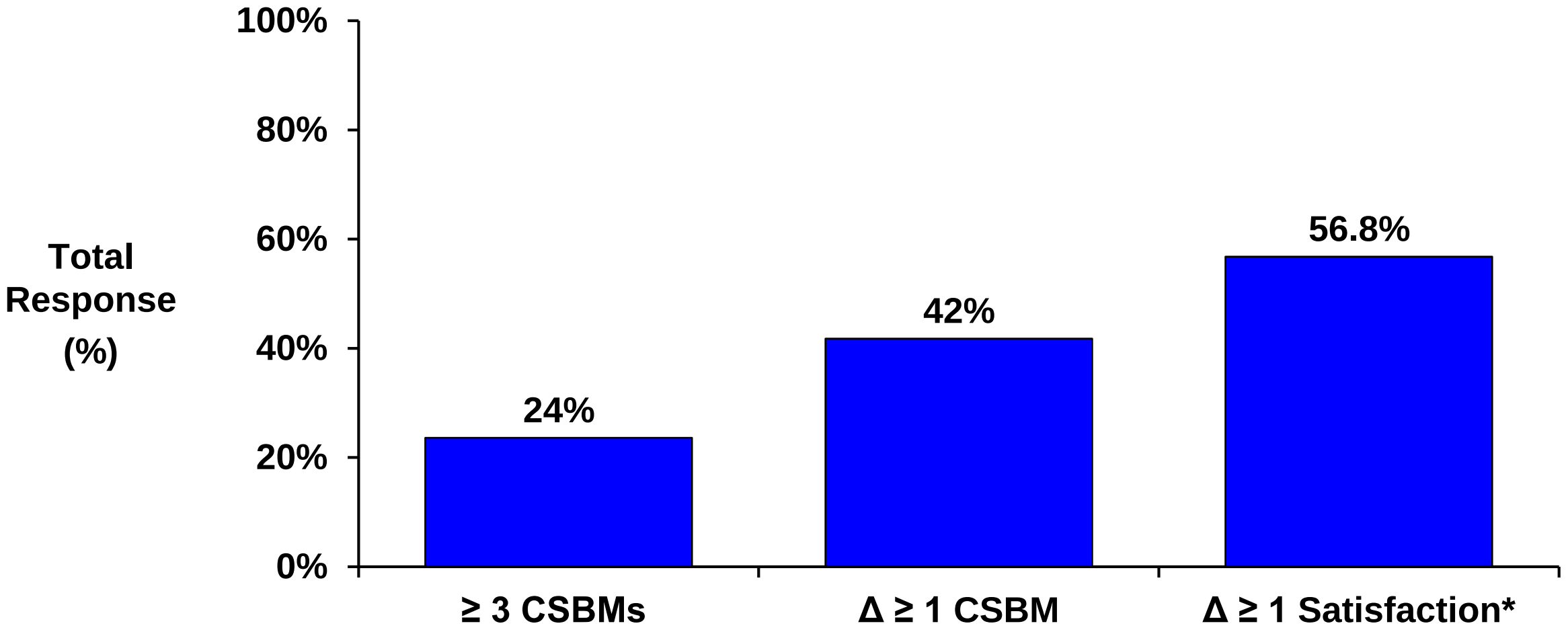
Professor of Medicine

Head of Clinic, Department of Gastroenterology
University Hospital KU Leuven, Belgium

Prucalopride Delivers Clinically Meaningful Outcomes for Patients with CIC

- Low rate of BMs = low QoL and high symptom severity
- Majority of refractory patients unable to achieve relief from laxatives
- With prucalopride
  - More than 1/3 patients achieve ≥ 3 CSBMs/week
  - Patients report symptom improvement with any increase in CSBMs
  - Improve quality of life

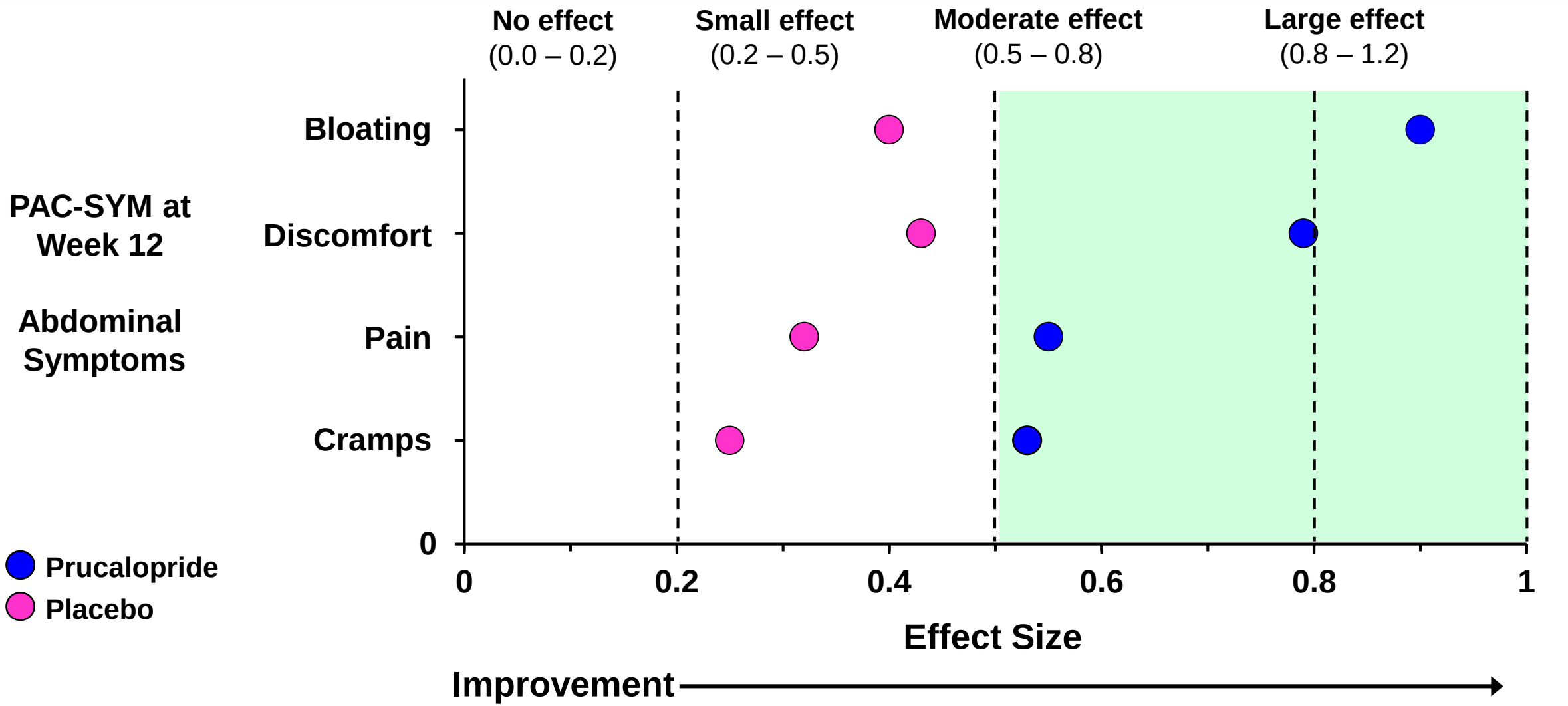
Patient Satisfaction Extends Beyond 3 CSBMs



Stanghellini, Vandeplassche, Kerstens, UEGW, 2010.
Includes Studies 6, USA-11 and USA-13

*MCID 0.36 to 0.80

Prucalopride Improves Difficult-to-Manage Symptoms



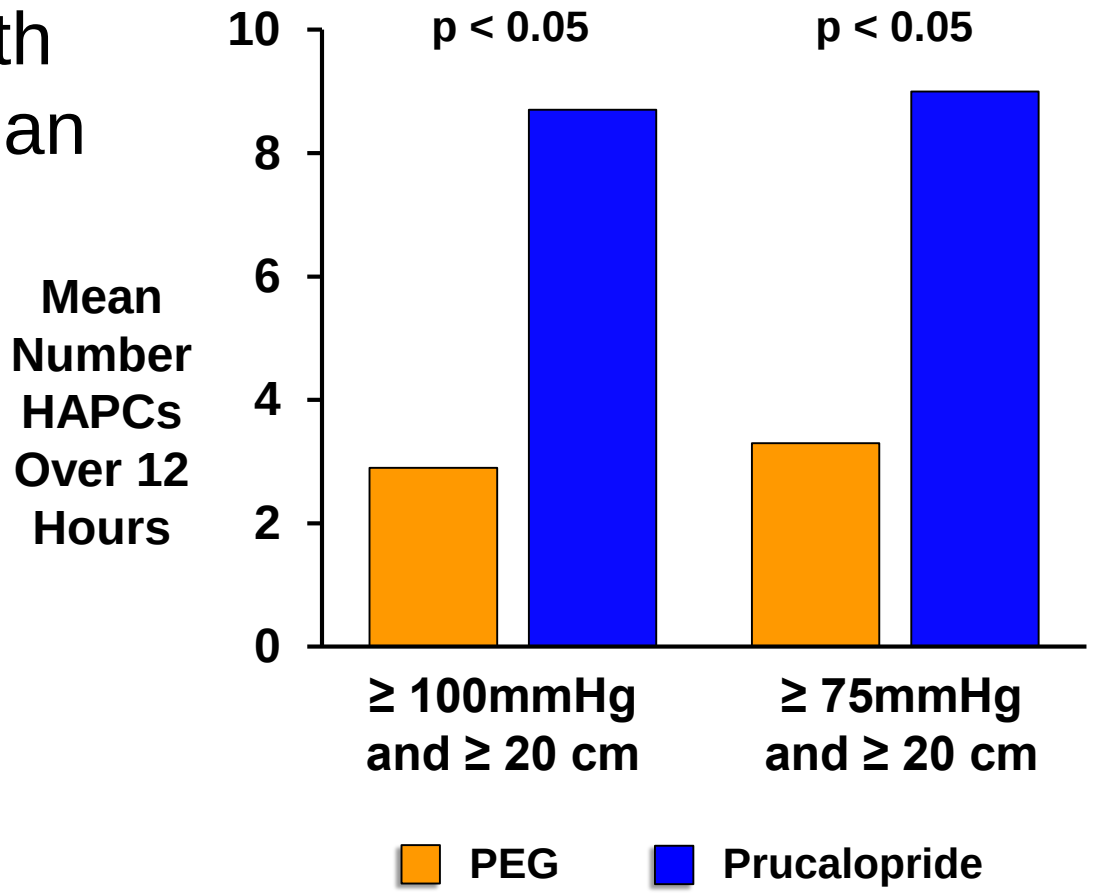
Tack et al., 2014.

Daily Regularity Important for Patients and Result of Prucalopride's Mechanism of Action

- Prucalopride's physiological response reflects MoA
  - Not seen with other treatments
- Patients generally have bowel movement in morning
- Becomes normal stool pattern
  - No longer worry about when, or stay close to bathroom

Prucalopride Induces Colonic High Amplitude Propagating Contractions (HAPC), Alleviating CIC

- Patients with CIC have fewer HAPCs
- Contractions greater in patients with constipation taking Prucalopride than PEG
  - HAPC frequency similar to healthy volunteers
- More HAPCs corresponds with increase in BMs



Miner and Camilleri et al., 2016.

Managing Risks in Practice

- Inform patients about headache, diarrhea and abdominal symptoms
  - Usually transient
  - Rarely cause discontinuation

Prucalopride Fills Gap in Treatment Landscape

- Available therapeutic options mainly target secretion
- Prucalopride's unique MoA addresses motility
- Patients can experience
  - Increased stool frequency
  - Ease and regularity of defecation
  - Decrease in abdominal symptoms
  - Increase in satisfaction
- Safe and well-tolerated

Concluding Remarks

Debra Silberg, MD, PhD

Therapeutic Area Head – VP of Clinical Development

Shire

Unique NDA

- Real world experience since 2009
- Available in 59 countries
- ~ 1 million patients have taken prucalopride
- Post-marketing experience supports use of pharmacoepidemiology study to examine CV safety
  - Rather than prospective 12-month RCT

> 8 Years of Dedicated Post-Marketing CV Monitoring Finds No Signal for CV Events in Patients

- Includes pharmacovigilance and pharmacoepidemiology Study 802, specifically designed to look at CV events
- No changes in CV safety profile since approval

Real World Data Supported by Large Development Program

- Nonclinical and Phase 1 studies show no biologic plausibility for cardiovascular risk
- Double blind placebo controlled trials and long-term extension studies showed low rates of CV events

Totality of Data Supports Prucalopride's Positive Benefit/Risk Profile

- Prucalopride is a highly selective, 5-HT_4 receptor agonist
- Promotes high amplitude propagating contractions
- Pro-kinetic agent would give new, efficacious treatment option with different MoA
- Approval would fill gap for treating CIC and provide relief for many patients

Q&A Moderator

Debra Silberg, MD, PhD

Therapeutic Area Head – VP of Clinical Development

Shire

Prucalopride for the Treatment of Chronic Idiopathic Constipation in Adults

October 18, 2018

Shire

Gastrointestinal Drugs Advisory Committee

Backup Slides Shown

Post Marketing: Cases Reporting Concomitant GI Medication use with Prucalopride

GI medication	Post Marketing Cases	
	Cases	Serious Cases
Lactulose	20	4
Senna/Senokot	13	3
Laxatives	10	1
Bisacodyl	9	2
Magnesium/magnesium oxalate/magnesium glycinate	6	2
Psyllium	3	0
PEG / Polyethylene glycol	2	1
Linaclotide/Linzess	0	0
Plecanatide/Trulance	0	0
Lubiprostone/Amitiza	0	0

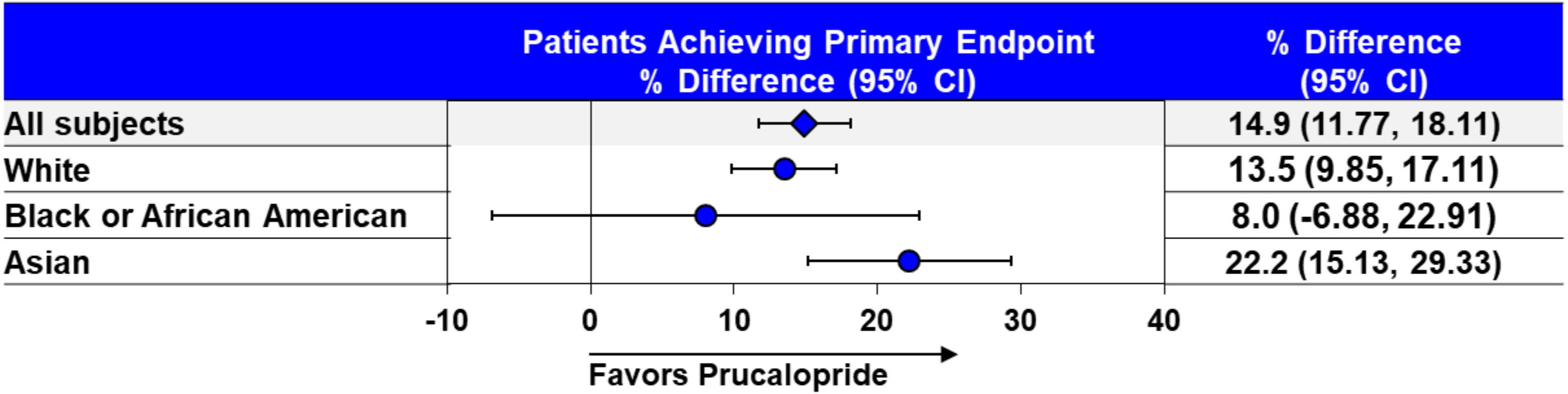
There were patients who were taking more than 1 concomitant medication.

In > 8 years of use the estimated postmarketing exposure is 282,535 person-years (through 30 September 2017)

Summary of Adverse Events
Phase II / IV DBPC Studies

	Placebo (N=1,973)	Prucalopride 2 mg (N=1,516)	Prucalopride 4 mg (N= 1,349)	Prucalopride Total (N=3,305)
AEs	54%	62%	71%	65%
Severe AEs	11%	13%	20%	16%
Related AEs	21.5%	35.3%	44%	37.9%
Serious AEs	2%	2%	2%	2%
AEs leading to discontinuation	3%	5%	9%	7%
Deaths (n)	1	1	0	2

Primary Endpoint Effect Size by Race



Pooled Data: Study 3001, 302, 6, USA-11, USA-13 and 401

Race Distribution of Patients on Prucalopride

CIC Open Label Studies

Race	N (%)
White	2509 (90.9)
Black or African American	189 (6.9)
Native Hawaiian or other Pacific Islander	None
Asian	13 (0.5)
American Indian or Alaska Native	None
Multiple	1 (0.06)
Other	47 (1.7)

6 Key Efficacy Studies

Race*	N (%)
White	2551 (79.5)
Black or African American	112 (3.5)
Native Hawaiian or other Pacific Islander	None
Asian	480 (15.0)
American Indian or Alaska Native	None
Multiple	None
Other	48 (1.5)

* 18 missing

*Studies PRU-CRC-3001, SPD555-302, PRUINT-6, PRU-USA-11, PRU-USA-13, and SPD555-401)

Methodology of Adjudication for MACE in DBPC Studies

- Objective: To evaluate all potential major adverse cardiovascular events (MACE) from completed Phase 2/4 clinical studies in adult subjects
- External adjudication committee Membership
  - 2 cardiologists and 1 stroke neurologist
  - retrospectively reviewed cases in a blinded manner using consistent endpoint definitions to adjudicate potential MACE
  - Process
    - The Endpoint Coordinating Team (ECT) included appointees from a CRO and Shire to ensured that all reported potential events were provided to the expert committee and adjudicated
    - The Chair of the External Adjudication Committee received a listing of SAEs and selected relevent Events for Adjudication

Total ^{14}C-labeled Prucalopride Tissue Distribution as % of Dose: Male Wistar Rats, Single Oral Dose (0.63 mg base-eq/kg)

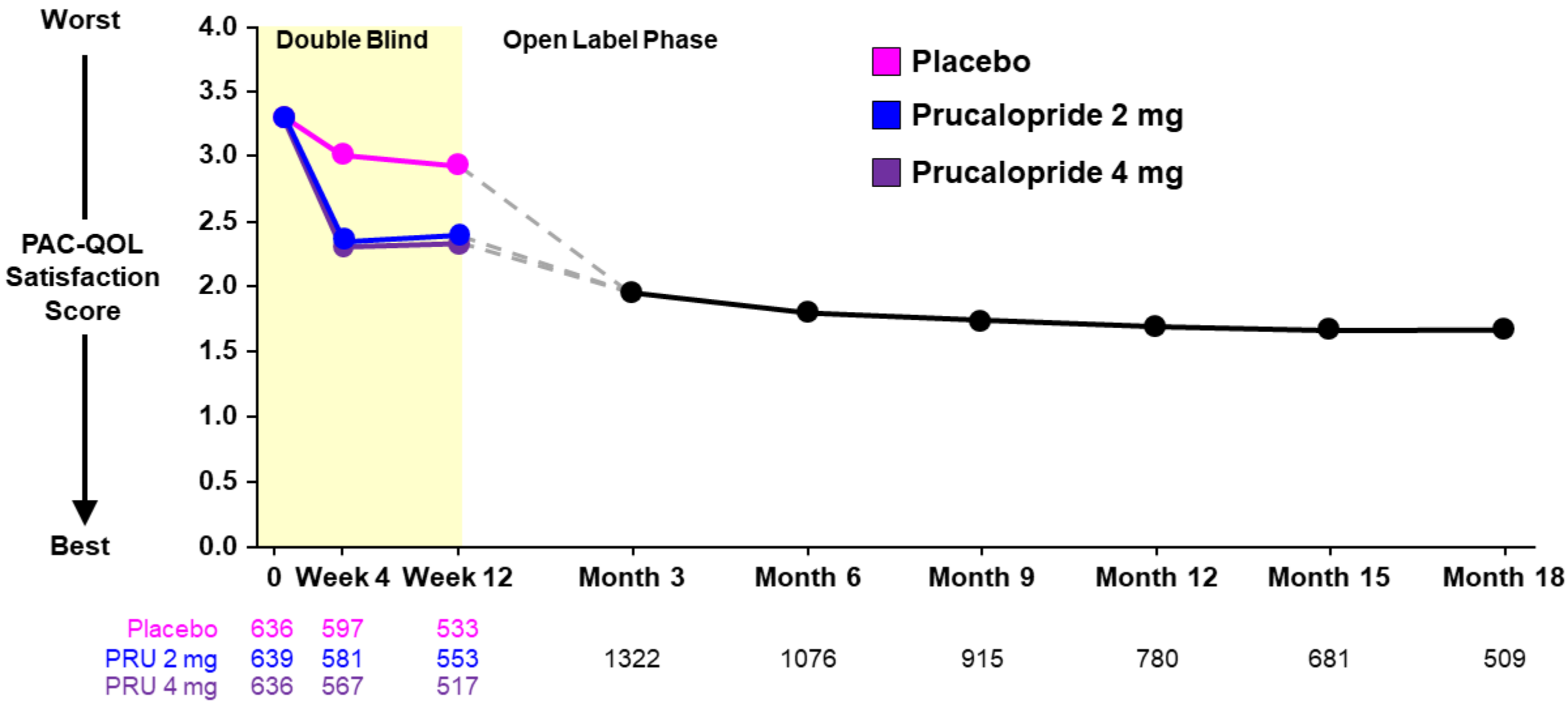
Group code Time (h)	C 0.5	D 1	E 2	F 4	G 8	H 24	I 48	J 96
Brain	0.015 ± 0.002	0.014 ± 0.001	0.010 ± 0.003	0.006 *	≤0.004	≤0.004	≤0.004	≤0.004
Heart	0.099 ± 0.015	0.070 ± 0.021	0.048 ± 0.006	0.023 ± 0.006	0.006 ± 0.004	≤0.003	≤0.002	≤0.002
Lung	0.240 ± 0.038	0.183 ± 0.044	0.147 ± 0.034	0.072 ± 0.019	0.022 ± 0.011	≤0.003	≤0.003	≤0.003
Liver	15.6 ± 2.0	14.0 ± 1.4	11.2 ± 1.4	6.86 ± 1.20	2.55 ± 0.49	0.719 ± 0.090	0.360 ± 0.037	0.207 ± 0.020
Kidney	0.808 ± 0.100	0.598 ± 0.138	0.397 ± 0.037	0.207 ± 0.057	0.067 ± 0.018	0.014 ± 0.002	0.010 ± 0.002	0.007 ± 0.001
Adrenal gland	0.006 ± 0.002	0.006 ± 0.001	0.004 ± 0.001	≤0.002 *	≤0.002 *	≤0.002	≤0.002	≤0.002
Stomach (tissue)	0.355 ± 0.036	0.245 ± 0.054	0.169 ± 0.046	0.060 ± 0.022	0.021 ± 0.016	≤0.003	≤0.003	≤0.003
Stomach (contents)	27.7 ± 4.4	17.0 ± 4.5	9.44 ± 9.69	2.40 ± 3.60	1.97 ± 2.56	≤0.03	≤0.03	≤0.03
Small intestine (tissue)	8.15 ± 1.09	6.79 ± 0.76	5.54 ± 1.11	1.65 ± 0.450	0.452 ± 0.305	0.010 *	≤0.02	≤0.02
Sm intestine (contents)	24.1 ± 2.5	33.3 ± 0.4	41.9 ± 6.8	16.6 ± 1.9	2.49 ± 0.43	0.114 ± 0.026	≤0.03	≤0.03
Large intestine (tissue)	0.322 ± 0.055	0.249 ± 0.055	0.220 ± 0.036	0.527 ± 0.079	0.292 ± 0.070	0.022 ± 0.001	≤0.006	≤0.006
Lrg intestine (contents)	0.546 ± 0.103	1.11 ± 0.15	2.14 ± 1.03	36.6 ± 1.8	33.5 ± 8.8	2.19 ± 0.061	0.074 ± 0.061	≤0.03

r4445m spd555
* median

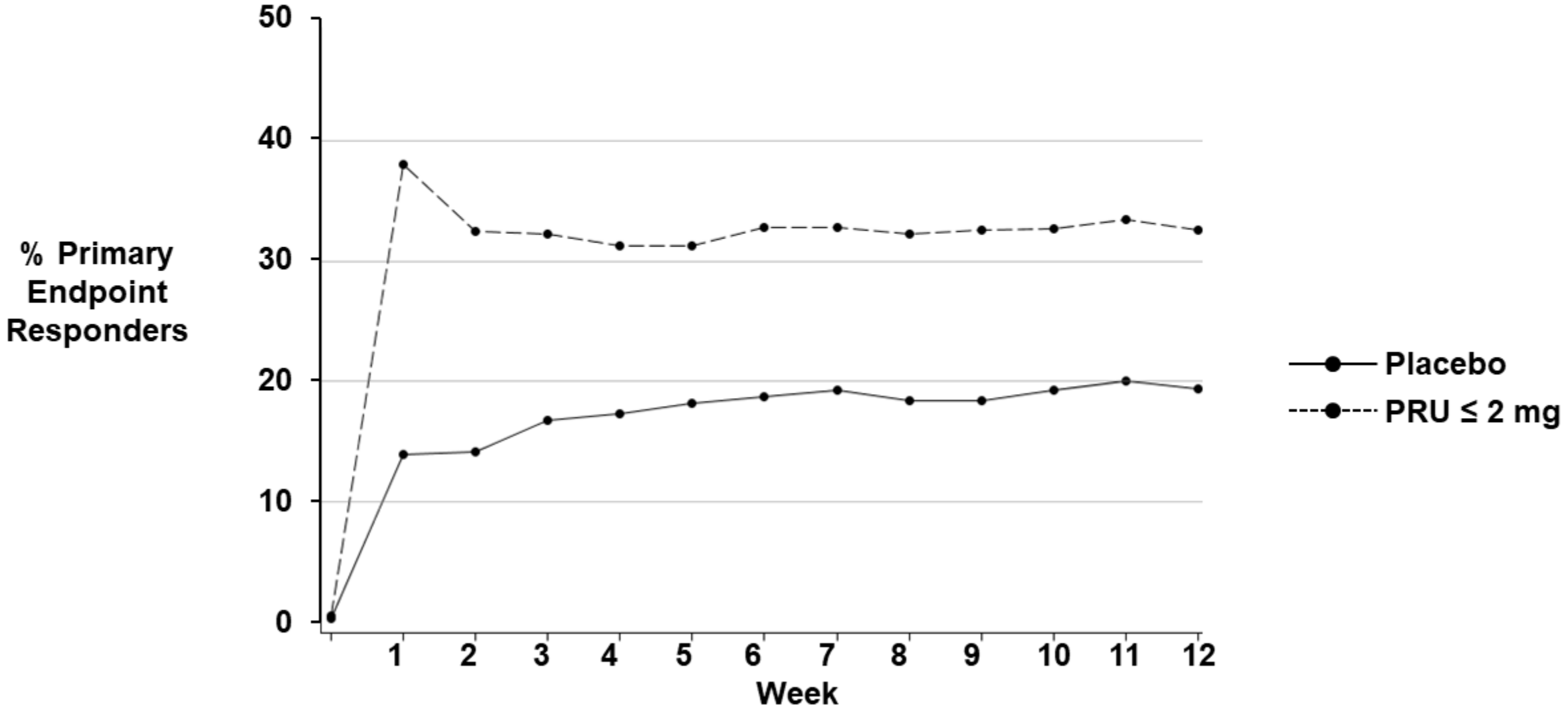
Results of Nonclinical *in vitro* and *in vivo* CNS Studies Using Supra-Therapeutic Prucalopride Doses

- Low levels of ^{14}C-prucalopride and its metabolites in brain (total radioactivity <0.02% of total dose in male rats at all time points to 8 hrs)
- No affinity for a wide array of receptors, ion channels, and monoamine transporters at neurotransmitter sites (>150x)
- No structural relationships to controlled drug substances
- Safety pharmacology studies in rats and mice, CNS-related observations were noted at very high concentrations (≥390x)
- Toxicology studies in rats and dogs, CNS-related observations were observed at very high concentrations (≥325x)

QOL Data from Phase 3 Open-Label Studies Confirm Long-Term Prucalopride Efficacy



Summary 5 Key Efficacy Studies (Without Study 401)



Completed Formal DDI Studies

Effect of prucalopride on other drugs (in vivo interaction studies):

- Warfarin
- Digoxin
- Alcohol
- Erythromycin
- Paroxetine
- Ethinylestradiol / norethisterone

Effect of other drugs on prucalopride (in vivo interaction studies):

- Probenecid
- Cimetidine
- Erythromycin
- Ketoconazole
- Paroxetine