



GI ReConnect

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Faculty Disclosure

Brooks Cash, MD

- Speaker/Consultant: Abbvie, Salix, Takeda

Pharmacotherapy for IBS-C/CIC: The Role of OTCs versus Prescription Therapies

Brooks D. Cash, MD, AGAF, FACG, FASGE

Dan and Lillie Sterling Professor of Medicine

Division Chief, Gastroenterology, Hepatology, and Nutrition

University of Texas Health Science Center at Houston

Chronic Constipation in the US

- Prevalence \approx 8-15%
 - \approx 1/3 seek consultation
- Cumulative incidence: 17% over 12 years

| | Economic Impact |
|------------------|--|
| OTC laxatives | Approximately \$800 million annually (2007) |
| Direct costs | More \$230 million; \$64,000/person over 15 years |
| Physician visits | 8 million ambulatory visits annually |
| Hospital costs | \$4.25 billion (2010) |
| ED visits | Increased 41.5% from 2006-2011; costs increased 121.4% |

Current Insights About Constipation Survey*

- 75% of people with CIC spend ≥ 1 hour using the toilet daily.
 - 9% spend 3 to 4 hours and 10% spend ≥ 5 hours on the toilet on average daily.
- 84% said others underestimate CIC's negative impact on everyday life
- 71% reported that CIC interferes with enjoyable activities
- People with CIC missed 7 workdays, 5 social events, and 4 of their children's events on average per year
- CIC negatively affects self-confidence (60%), ability to engage in hobbies they enjoyed in the past (59%), partnership relationships and intimacy (54%), and job/career or ability to work (47%).
- CIC symptoms were experienced for an average of 2.7 years before receiving a diagnosis; 56% reported making about 5 visits to a healthcare provider before definitive diagnosis

N=881*

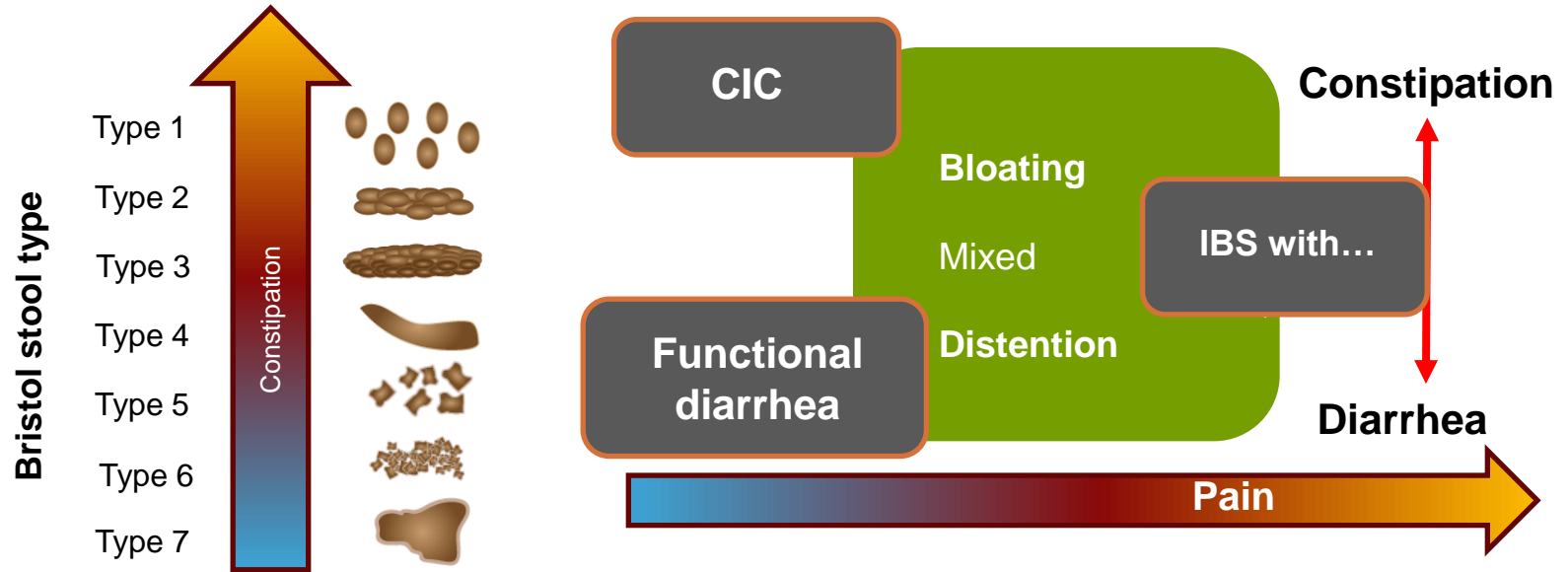
Current Insights about Constipation Survey; December 7, 2018.

multivu.com/players/English/8374951-national-cic-chronic-idiopathic-constipation-survey/.

Chronic Constipation: Healthcare and Pharmacotherapy Use

- Cross-sectional online US survey; N=4702 with CIC
 - 9.5 years of symptoms
 - 57.6% rated as ≥ 3 in severity (1-5 scale)
 - 47.8% took medication for CIC
 - 93.5% OTC only
 - 1.3% prescription therapy only
 - 5.2% OTC and prescription therapy

IBS-C and CIC Overlap



OTC Options for Chronic Constipation

Osmotic laxatives

- PEG
- Lactulose
- Sorbitol
- Magnesium salts
- Sodium biphosphate

Bulk laxatives*

- Psyllium
- Pectin
- Bran
- Guar
- Cellulose
- Calcium polycarbophil

Stool Softeners

- Liquid paraffin
- Docusate sodium and calcium

Stimulant laxatives

- Senna
- Bisacodyl
- Cascara
- Sodium bicarbonate + potassium bitartrate

Laxatives for Chronic Constipation: Systematic Review

- Stool softeners
 - Minimal evidence; generally considered ineffective
- Bulking agents
 - Weak evidence base; generally considered effective
- Osmotic laxatives
 - Strong evidence base; effective
 - PEG>Magnesium laxatives, lactulose
- Stimulant laxatives
 - Moderate evidence supports bisacodyl, sodium picosulfate; effective; diarrhea common AE

| | Recommendation ^b | Quality of Evidence ^c |
|---|-----------------------------|----------------------------------|
| Bulk agents | Strong | Low |
| Psyllium, methylcellulose, calcium polycarbophil, wheat dextrin | | |
| Nonabsorbed substances | | |
| PEG 3350 | Strong | High |
| Lactulose ^d | Strong | Low |
| Magnesium salts | NA | NA |
| Stimulants | | |
| Bisacodyl | Strong | Moderate |
| Senna | NA | NA |
| Secretory drugs^d | | |
| Lubiprostone | Strong | High |
| Linaclotide | Strong | High |

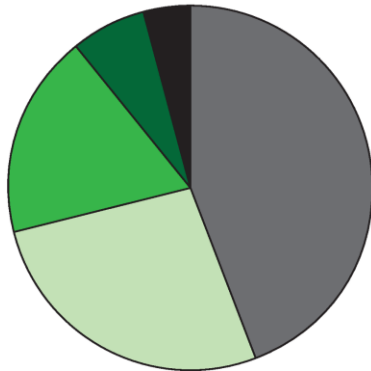
Caveats Regarding Non-Specific Laxatives

- Osmotics: unpredictable response, bloating, gas, electrolyte disturbances
 - Mg oxide: 2005-8: 15 cases of hypermagnesemia reported in Japan (hypotension, bradycardia, atrial fibrillation, altered mentation, respiratory depression, and cardiac arrest; 2 deaths; 10/15 had renal disease)
 - Tatsuki et al: 25% Japanese children with hyperMg; no correlation with dose or duration
- Stimulants: abdominal cramping; colon ischemia

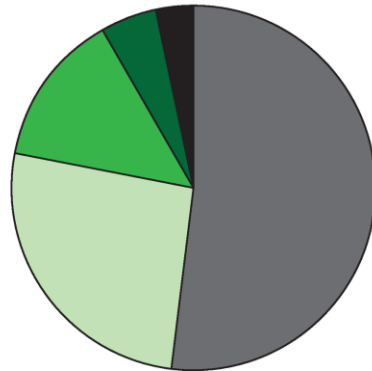
Satisfaction With OTCs for CIC

- Post-hoc analysis of patient-reported data from a questionnaire administered during screening for a prospective Phase 3b clinical trial in patients with CIC (N=1482)

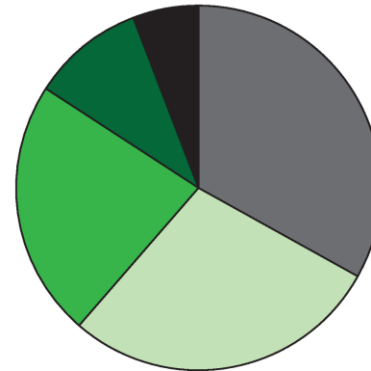
Abdominal discomfort



Abdominal bloating



Constipation



Prescription Therapies for IBS-C/CIC

IBS-C

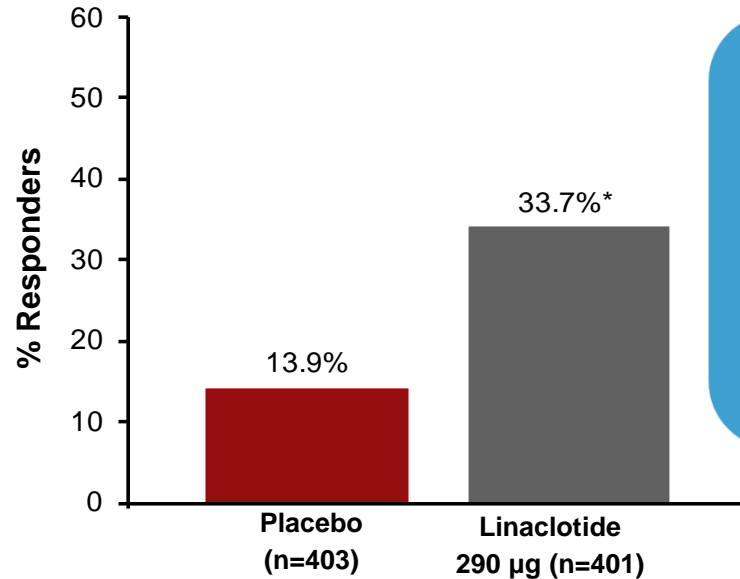
- Linaclotide
- Plecanatide
- Lubiprostone
- Tenapanor
- Tegaserod

CIC

- Linaclotide
- Plecanatide
- Lubiprostone
- Prucalopride

Linaclootide for IBS-C

- Guanylate-C receptor agonist
- 4 RCT, 2867 patients
- IBS-C dose:290 mcg daily
- NNT=6

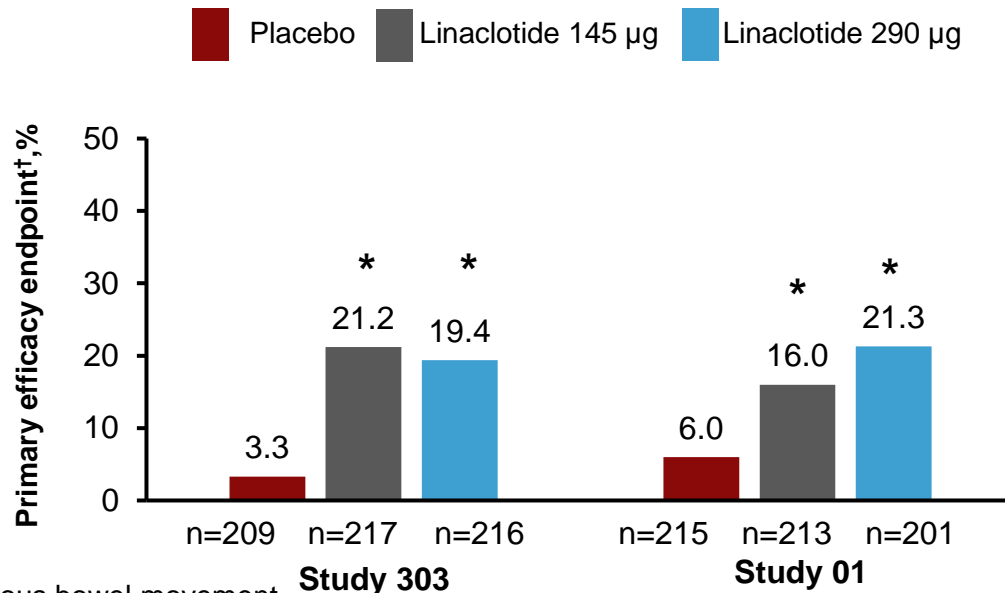


FDA Primary Endpoint: $\geq 30\%$ reduction worst abdominal pain and increase ≥ 1 CSBM, both for $\geq 6/12$ weeks

* $P < 0.0001$ for all analyses of linaclootide vs placebo groups, using Cochran-Mantel-Haenszel test.
Rao S et al. *Am J Gastroenterol.* 2012;107(11):1714-1724.

Linaclotide for CIC: CSBM Frequency

Primary Responder Endpoint at 12 Weeks
(≥ 3 CSBMs/week and increase of ≥ 1 CSBM/week for $\geq 9/12$ weeks)



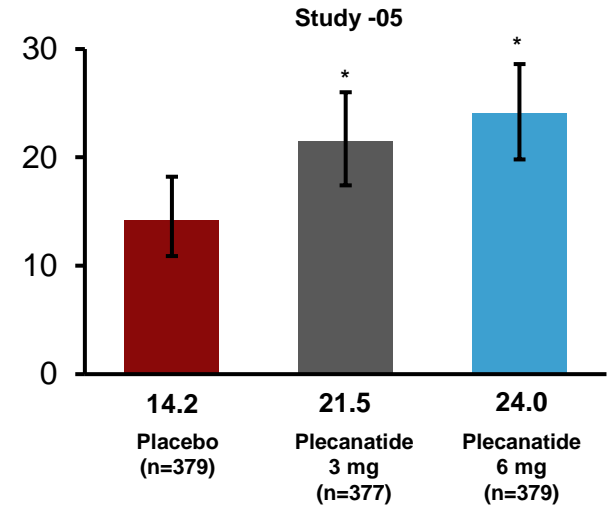
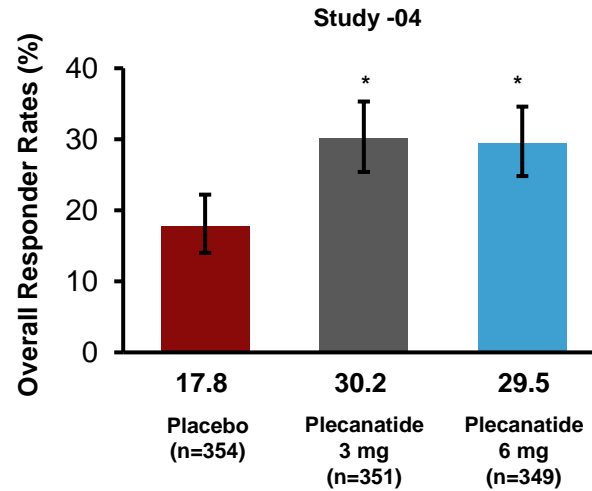
CSBM, Complete spontaneous bowel movement.

* $P < 0.001$ vs placebo. ** $P \leq 0.01$ vs placebo.

Lembo AJ et al. *N Engl J Med.* 2011;365:527-536.

Plecanatide for IBS-C

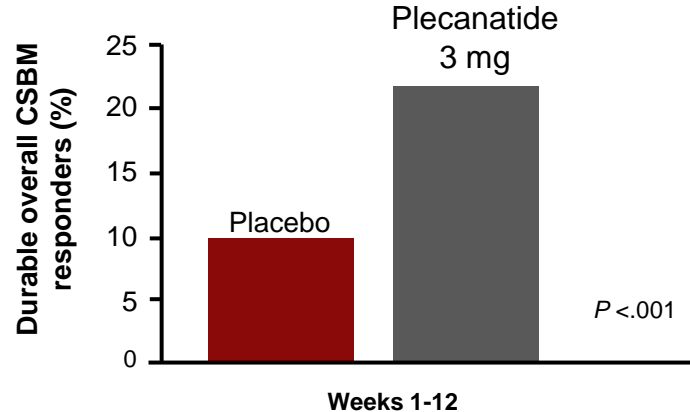
- Guanylate-C receptor agonist
 - 8x greater binding affinity at GC-C receptors at pH <7
- 3 RCT, n=2612
- IBS-C dose: 3mg daily
- NNT=10



* $P < 0.001$ vs placebo.

Brenner D et al. *Am J Gastroenterol*. 2018.

Plecanatide for CIC: CSBM Frequency



Primary efficacy end point: % of durable overall CSBM responders over 12 weeks

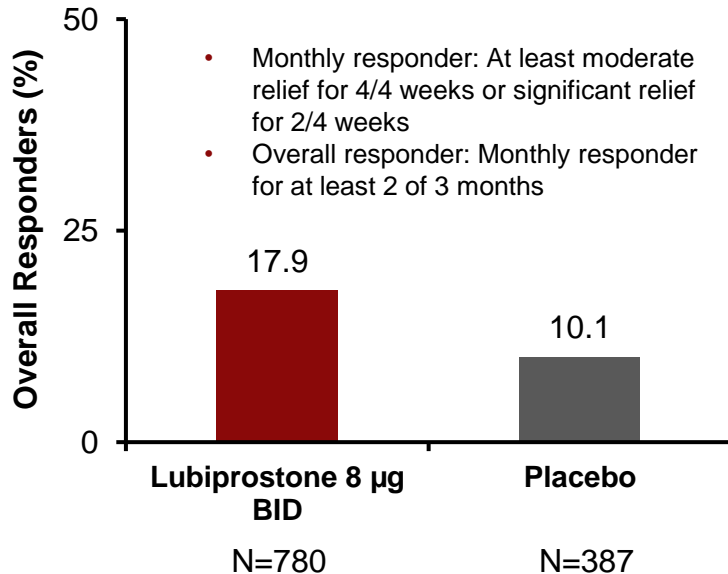
Durable overall CSBM responders: ≥ 3 CSBMs per week

AND

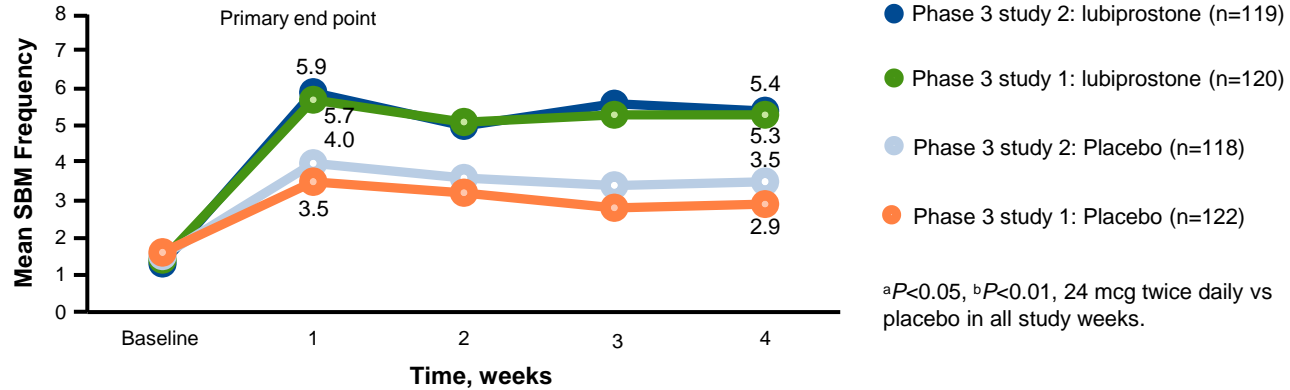
Increase of ≥ 1 CSBM per week from baseline for at least 9 of 12 weeks and at least 3 of the last 4 weeks

Lubiprostone for IBS-C

- Type 2 chloride channel activator
- 3 RCT, 1366 patients
- IBS-C dose: 8 mcg BID in adult women
- NNT=12.5



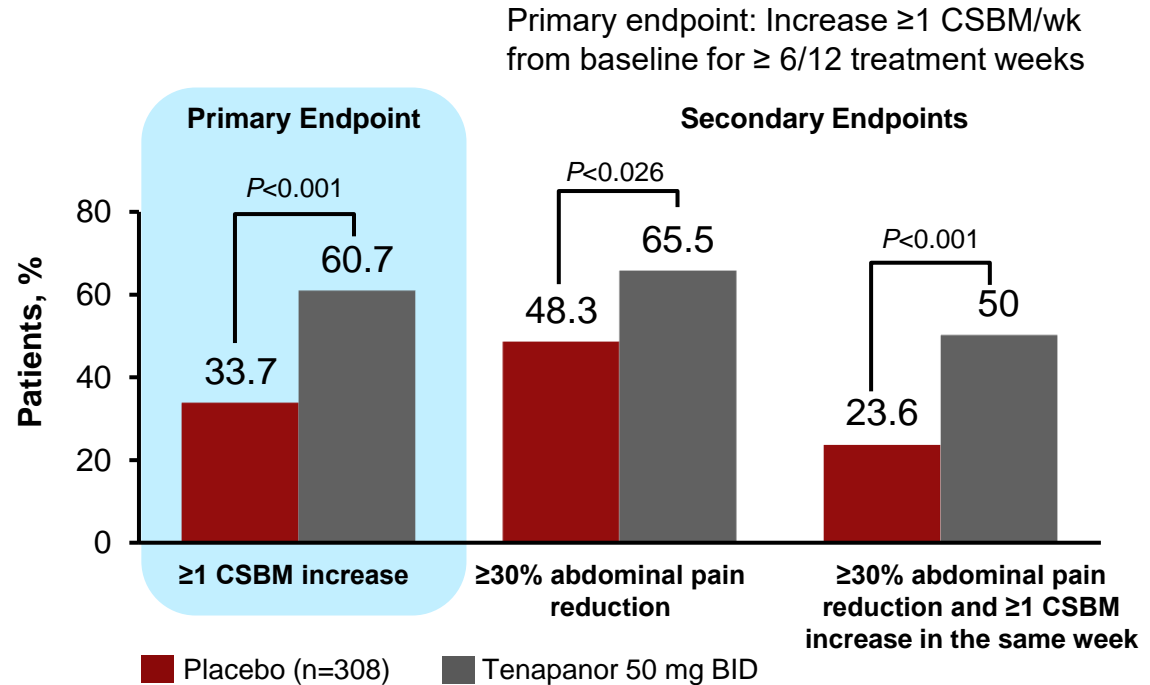
Lubiprostone for CIC: SBM Frequency



- 24 mcg BID significantly increased SBMs over baseline and placebo within 1 week
- Efficacy maintained for all study weeks

Tenapanor for IBS-C

- NHE3 Inhibitor: traps water and phosphate in GI lumen; pain modulation via TRPV-1
- 50 mg BID: significantly higher CSBM responder rate vs placebo
- FDA approved: IBS-C 9/2019
- Most frequent AEs: diarrhea, headache, nausea, abdominal pain



Tegaserod for IBS-C

- Mixed 5-HT (serotonin) agonist (prokinetic); 6 mg PO BID
- Approved for women < 65 yo with ≤ 1 CV risk factor

Pooled, post hoc analysis patients with low CV risk

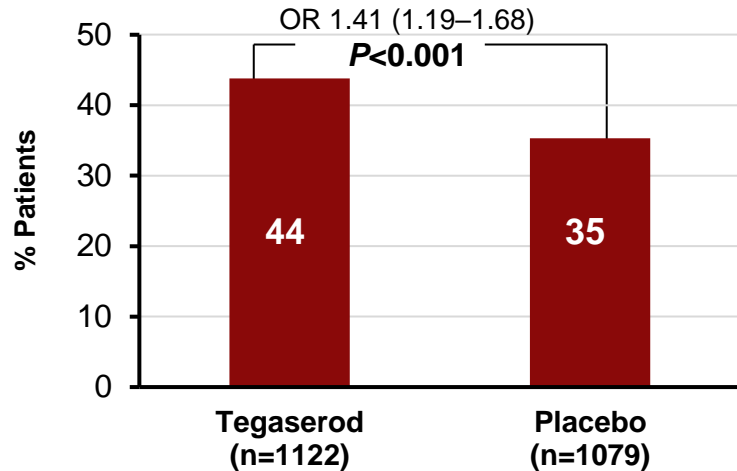
Study B301 (n=325)

Study B358 (n=1181)

Study B307 (n=336)

Study B351 (n=359)

(N=2201)

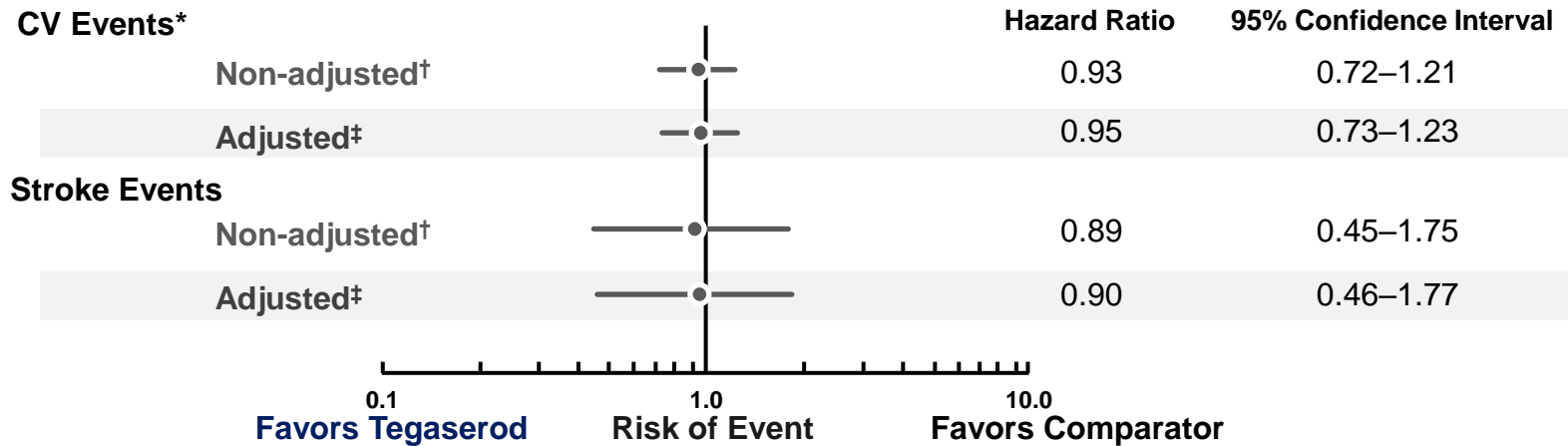


Considerable or complete relief at least 50% of last 4 weeks in 12-week study,
or at least somewhat relieved 100% of the last 4 weeks.

*Defined as patients who do not have a history of ischemic cardiovascular disease and who have no more than one cardiovascular disease risk factor.

MACE Events With Tegaserod

Risk of CV and stroke events with tegaserod vs comparators



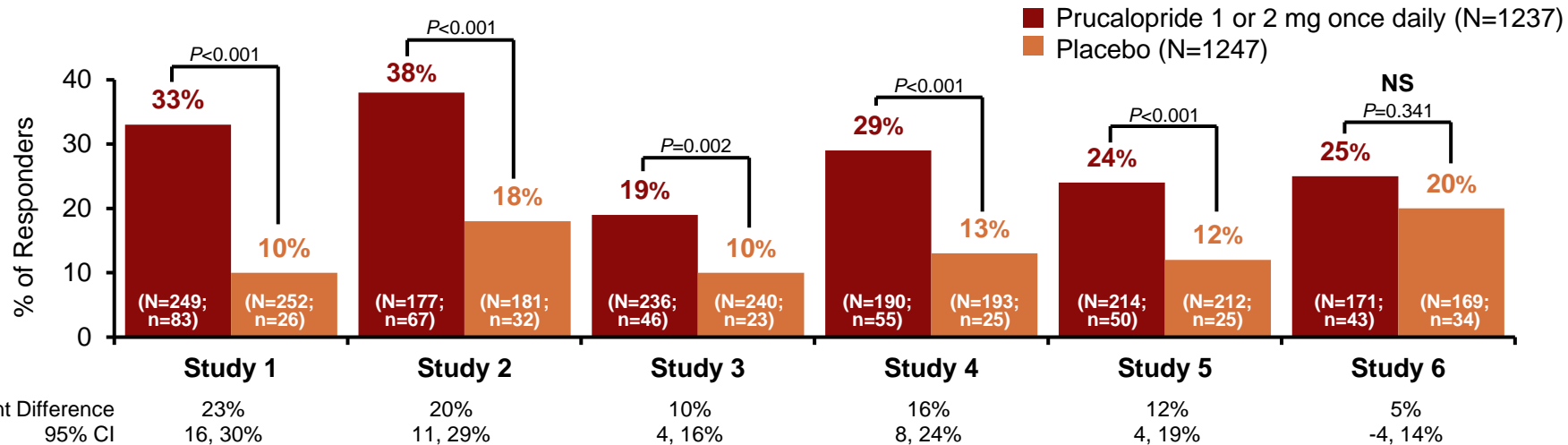
*CV events include acute coronary syndrome, MI, coronary revascularization; †Unadjusted by Cox proportional hazards regression;

‡Adjusted for age, sex, region, calendar year, and baseline history of hypertension, treated hypertension, hyperlipidemia, statins, diabetes, treated diabetes, obesity, smoking, stroke, fibrates, angina, acute coronary syndrome, history of MI, and acute MI by Cox proportional regression.

Loughlin J et al. *J Cardiovasc Pharmacol Ther.* 2010;15(2):151-157.

Prucalopride for CIC: CSBM Frequency

Percentage of Patients With an Average of ≥ 3 CSBMs/Week Over the 12-Week Treatment Period



P-values based on a Cochran-Mantel-Haenszel test. N=number of patients per treatment group. n=number of responders.

CI=confidence interval; NS=not significant.

Prucalopride Prescribing Information. Lexington, MA: Shire LLC.

Prescription Agents for IBS-C*: Summary

| Name | MOA | Dose | Contraindications | Common AEs | Take with food? | May Also Improve |
|---------------------|---|-----------------------|--|---|-----------------------------|---|
| Lubiprostone | CIC-2 activator Increases intestinal fluid secretion | 8 mcg BID in women | Bowel obstruction | Nausea, diarrhea | With (may reduce nausea) | Bloating, abdominal discomfort, straining, stool consistency, constipation severity |
| Linaclotide | GC-C agonist Increases intestinal fluid secretion | 290 mcg qD | <18 years old Bowel obstruction | Diarrhea | >30 min before first meal | Stool consistency, straining, bloating |
| Plecanatide | GC-C agonist Increases intestinal fluid secretion | 3 mg qD | <18 years old Bowel obstruction | Diarrhea | With or without | Stool consistency, straining, bloating |
| Tegaserod | 5-HT _{3,4} agonist Stimulates colonic peristalsis | 6 mg BID | Intestinal perforation or obstruction | Headache, abdominal pain, nausea, diarrhea | With or without | Stool consistency, straining, bloating |

NOTE: These agents have NOT been directly compared in clinical trials.

* Currently marketed in US.

CIC-2 = type-2 chloride channel; GC-C = guanylate cyclase-C.

Prescription Agents for CIC: Summary

| Name | MOA | Dose | Contraindications | Common AEs | Take with food? | May Also Improve |
|---------------------|---|------------------|---|--|-----------------------------|---|
| Lubiprostone | CIC-2 activator Increases intestinal fluid secretion | 24 mcg BID | Bowel obstruction | Nausea, diarrhea, headache | With (may reduce nausea) | Bloating, abdominal discomfort, straining, stool consistency, constipation severity |
| Linaclotide | GC-C agonist Increases intestinal fluid secretion | 72 or 145 mcg qD | <18 years old Bowel obstruction | Diarrhea, abdominal pain, flatulence | >30 min before first meal | Stool consistency, straining, bloating |
| Plecanatide | GC-C agonist Increases intestinal fluid secretion | 3 mg qD | <18 years old Bowel obstruction | Diarrhea | With or without | Stool consistency, straining, bloating |
| Prucalopride | 5-HT ₄ agonist Stimulates colonic peristalsis | 2 mg qD | Intestinal perforation or obstruction Hypersensitivity | Headache, abdominal pain, nausea, diarrhea | With or without | Stool consistency, straining, bloating |

NOTE: These agents have NOT been directly compared in clinical trials.

CIC-2 = type-2 chloride channel; GC-C = guanylate cyclase-C.

Conclusions

- Chronic constipation is common and costly
- IBS-C and CIC have significant symptom overlap
 - Continuum differentiated by pain (IBS); similar treatment approaches
- OTC laxatives are widely used by patients and HCPs for IBS-C/CIC
 - Limited evidence basis of efficacy for multiple symptoms
 - Significant patient dissatisfaction
- Multiple prescription therapies are available for IBS-C/CIC
 - Level 1 evidence for efficacy for multiple symptoms
 - Lack of comparison to OTCs limits superiority conclusions
 - Large cost/access differential vs OTC therapies