**Table 1, Supplemental Digital Content 1.** Study design details

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| **Study** | **Inclusion/Exclusion Criteria** | **Study Design** | **Treatment** | **Primary Efficacy Endpoint(s)** | **Secondary/Other Efficacy Endpoints** | **Safety Assessments** |
| 301(21) | Inclusion criteria:* Men and women aged ≥18 years
* 3-month history of IBS symptoms
	+ Lower abdominal pain or discomfort either relieved by a bowel movement or associated with a change in frequency of bowel movements
	+ ≥2 of 3 constipation symptoms ≥25% of the time during 3 months prior to study entry: <3 bowel movements/week, hard/lumpy stools, straining
* Normal colonic anatomy confirmed by colonoscopy, sigmoidoscopy or barium enema within past 5 years and after symptom onset
* At least mild abdominal pain and discomfort and ≥3 weekly assessments during baseline period required to be randomized

Exclusion criteria:* History of diarrhea on ≥25% of days
* Planned or concomitant use of drugs affecting GI motility and/or perception\*†
* Female patients, if they were pregnant, breastfeeding, or did not use an adequate method of contraception
* Condition affecting gastric, small bowel, or colonic transit
* History of drug, alcohol, or laxative abuse
* Patients with >10 missing days of data from baseline were excluded from randomization
 | 12-week, randomized, double-blind, placebo-controlled multicenter studyTreatment was preceded by a 4-week treatment-free baseline period  | * Tegaserod 2 mg b.i.d.
* Tegaserod 6 mg b.i.d.
* Placebo b.i.d.
 | SGA of Relief of IBS symptoms (last 4 weeks) | * SGA relief of Abdominal Pain and Discomfort (VAS)
* Daily assessment of intensity of bloating, stool frequency, stool consistency, and straining during bowel movement
 | * AE monitoring
* Physical examination
* Vital signs
* Pregnancy screening
* Standard laboratory safety tests
* ECG evaluation
 |
| 307(24) | Inclusion criteria:* Men and women aged ≥18 years
* 3-month history of IBS symptoms
	+ Continuous or repeated lower abdominal pain or discomfort either relieved by a bowel movement or associated with a change in frequency of bowel movements or associated with a change in stool consistency
	+ ≥2 of 3 constipation symptoms ≥25% of the time during 3 months prior to study entry: <3 bowel movements/week, hard/lumpy stools, straining
* Inadequate symptoms improvement despite ≥2 months of treatment with nonpharmacological therapies due to ineffectiveness or intolerance
* Organic disease ruled out by colonoscopy, sigmoidoscopy, or, in patients >50 years of age and those with guaiac-positive stool or occult blood not due to hemorrhoidal bleeding who did not have procedures performed within the past year, colonoscopy plus sigmoidoscopy with double-contrast barium enema, performed within past 5 years and after symptom onset
* At least mild abdominal pain and discomfort and ≥3 weekly assessments during baseline period required to be randomized

Exclusion criteria:* Significant diarrhea on ≥25% of days
* Condition affecting bowel transit
* Planned use of drugs affecting GI motility and/or perception\*†
* Evidence of a cathartic colon
* History of laxative, drug, or alcohol abuse
* Clinical evidence of significant disease that may interfere with successful study completion
* Symptoms of significant illness in preceding 2 weeks
* Major psychiatric illness requiring psychiatric treatment, except well-compensated depression
* Surgical/medical conditions interfering with absorption, distribution, metabolism, or excretion of study medication
* HIV-positive
* Female patients, if they were pregnant, breastfeeding, or did not use an adequate method of contraception
* Patients with >10 missing days of data from baseline, and those who used disallowed medications affecting GI motility and/or perception on >4 days or met any other exclusion criteria during baseline were excluded from randomization
 | 12-week, randomized, double-blind, placebo-controlled multicenter studyTreatment was preceded by a 4-week treatment-free baseline period | * Tegaserod 2 mg b.i.d.
* Tegaserod dose titration (2 mg b.i.d. first 4 weeks, titrated to 6 mg b.i.d. for last 8 weeks based on response at 4 weeks)
* Placebo b.i.d.
 | SGA of Relief of IBS symptoms (last 4 weeks) | * Proportion of patients “completely relieved” or “considerably relieved” ≥50% of time (last 4 weeks)
* Proportion of patients at least “somewhat relieved” 100% of time (last 4 weeks)
* SGA relief of Abdominal Pain and Discomfort (VAS)
* SGA of Bowel Habit (VAS)
* Daily assessment of stool frequency, stool consistency, severity of abdominal pain, and severity of bloating
* Quality of Life survey (tertiary endpoint)
 | * AE monitoring
* Physical examination
* Vital signs
* Pregnancy screening
* Standard laboratory safety tests
* ECG evaluation
 |
| 351 (unpublished data) | Inclusion criteria:* Male and female patients aged ≥12 years
* 3-month history of IBS symptoms
	+ Continuous or repeated lower abdominal pain or discomfort either relieved by a bowel movement or associated with a change in frequency of bowel movements or associated with a change in stool consistency
	+ ≥2 of 3 constipation symptoms ≥25% of the time during 3 months prior to study entry: <3 bowel movements/week, hard/lumpy stools, straining
* Inadequate symptoms improvement despite ≥2 months of treatment with nonpharmacological therapies due to ineffectiveness or intolerance
* Organic disease ruled out by colonoscopy, sigmoidoscopy, or, in patients >50 years of age and those with guaiac-positive stool or occult blood not due to hemorrhoidal bleeding who did not have procedures performed within the past year, colonoscopy plus sigmoidoscopy with double-contrast barium enema, performed within past 5 years and after symptom onset
* At least mild abdominal pain and discomfort and ≥3 weekly assessments during baseline period required to be randomized

Exclusion criteria:* Significant diarrhea on ≥25% of days
* Condition affecting bowel transit
* Planned use of drugs affecting GI motility and/or perception\*†
* Evidence of a cathartic colon
* History of laxative, drug, or alcohol abuse
* Clinical evidence of significant disease that may interfere with successful study completion
* Symptoms of significant illness in preceding 2 weeks
* Major psychiatric illness requiring psychiatric treatment, except well-compensated depression
* Surgical/medical conditions interfering with absorption, distribution, metabolism, or excretion of study medication
* HIV-positive
* Female patients, if they were pregnant, breastfeeding, or did not use an adequate method of contraception
* For patients undergoing pharmacokinetic sampling:
	+ Weight below 30 kg
	+ Donated or lost ≥500 mL blood ≤2 months prior to dosing
* Patients with >10 missing days of data from baseline, and those who used disallowed medications affecting GI motility and/or perception on >4 days or met any other exclusion criteria during baseline were excluded from randomization
 | 12-week, randomized, double-blind, placebo-controlled multicenter studyTreatment was preceded by a 4-week treatment-free baseline period | * Tegaserod 2 mg b.i.d.
* Tegaserod 6 mg b.i.d.
* Placebo b.i.d.
 | * SGA relief of IBS symptoms (last 4 weeks)
* SGA relief of abdominal discomfort/pain (VAS, last 4 weeks)
 | * Daily assessment of stool frequency, stool consistency, severity of abdominal pain, and severity of bloating
* Quality of Life survey (tertiary endpoint)
 | * AE monitoring
* Physical examination
* Vital signs
* Pregnancy screening
* Standard laboratory safety tests
* ECG evaluation
 |
| 358(22) | Inclusion criteria:* Women aged ≥18 years
* ≥3-month history of IBS symptoms
	+ Lower abdominal pain or discomfort
	+ ≥2 of 3 constipation symptoms ≥25% of the time that had not improved despite ≥2 months of treatment with nonpharmacological therapies: <3 bowel movements/week, hard/lumpy stools, straining
* Organic disease ruled out by colonoscopy, sigmoidoscopy with double-contrast barium enema in patients >50 years of age, performed within past 5 years and after symptom onset
* At least mild pain and at least normal stool consistency required to be randomized

Exclusion criteria:* Significant diarrhea on ≥25% of days
* Structural abnormalities of the GI tract
* Disease/condition affecting bowel transit
* Evidence of a cathartic colon
* History of laxative, drug, or alcohol abuse
* Concomitant use of drugs affecting GI motility and/or perception†
* Pregnant, breastfeeding, or did not use an adequate method of contraception
* Condition affecting gastric, small bowel, or colonic transit
* History of drug, alcohol, or laxative abuse
 | 12-week, randomized, double-blind, placebo-controlled multicenter studyTreatment was preceded by a 4-week treatment-free baseline period and followed by a 4-week withdrawal period | * Tegaserod 6 mg b.i.d.
* Placebo b.i.d.
 | SGA relief of IBS symptoms (ordinal, last 4 weeks) | * SGA relief of Abdominal Pain and Discomfort
* SGA of Satisfaction with Bowel Habit
* Daily assessment of intensity of bloating, stool frequency, stool consistency, and straining during bowel movement
 | * AE monitoring
* Physical examination
* Vital signs
* Pregnancy screening
* Standard laboratory safety tests
* ECG evaluation
 |

AE, adverse event; b.i.d., twice daily; ECG, electrocardiogram; GI, gastrointestinal; HIV, human immunodeficiency virus; IBS, irritable bowel syndrome; SGA, subjective global assessment; VAS, visual analog scale.

\*Patients experiencing severe constipation were allowed to use predefined laxatives as rescue medication, and patients with bothersome diarrhea were permitted loperamide in addition to study medication.

†Patients taking chronic stable doses of bulking agents could continue to do so.

**Table 2, Supplemental Digital Content 2.** Components of the responder rate for SGA of relief at endpoint from individual studies (ITT population)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Tegaserod 12 mg/d****n/N (%)** | **Placebo****n/N (%)** | **Treatment difference****%** | ***P*-value** |
| **Patients “completely relieved” or “considerably relieved” ≥50% at endpoint** |
| Study 301 | 77/294 (26.2%) | 59/288 (20.5%) | 5.5% | 0.116 |
| Study 307\* | 73/275 (26.5%) | 80/284 (28.2%) | -1.4% | 0.703 |
| Study 351† | 78/250 (31.2%) | 67/257 (26.1%) | 5.5% | 0.179 |
| Study 358 | n‡/767 (27.0%) | n‡/752 (23.4%) | NA | 0.080 |
| **Patients at least “somewhat relieved” 100% of the time at endpoint** |
| Study 301 | 108/294 (36.7%) | 79/288 (27.4%) | 9.4% | 0.013 |
| Study 307\* | 110/275 (40.0%) | 96/284 (33.8%) | 7.0% | 0.084 |
| Study 351 | 112/267 (41.9%) | 80/267 (30.0%) | 12.3% | 0.003 |
| Study 358 | NA | NA | NA | NA |

ITT, intent-to-treat; NA, not available; SGA, Subjective Global Assessment.

\*Includes patients receiving tegaserod 4–12 mg/d; †Based on unadjusted analysis; ‡n-value not available.

**Table 3, Supplemental Digital Content 3.** Confirmed adjudicated cardiovascular and MACE cases identified during adjudication: 29 placebo-controlled studies in any indication with duration ≥4 weeks (safety population)

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| --- | --- | --- | --- |
|  | **All Patients** | **Women Only** | **Low CV Risk Patients Aged <65 Years** |
| **Parameter** | **Tegaserod (N=11614)****n (%)** | **Placebo (N=7031)****n (%)** | **Tegaserod (N=10167)****n (%)** | **Placebo (N=6154)****n (%)** | **Tegaserod (N=7786)****n (%)** | **Placebo (N=4686)****n (%)** |
| Number of confirmed CV events from first adjudication | 13 (0.11) | 1 (0.01) | 8 (0.08) | 1 (0.02) | 1 (0.01) | 0 |
| Number of MACE from first adjudication | 7 (0.06) | 0 | 5 (0.05) | 0 | 0 | 0 |
| Number of confirmed CV events from second adjudication | 7 (0.06) | 1 (0.01) | 4 (0.04) | 1 (0.02) | 1 (0.01) | 0 |
| Number of MACE from second adjudication | 4 (0.03) | 0 | 3 (0.03) | 0 | 0 | 0 |

# CV, cardiovascular; MACE, major adverse cardiac events.