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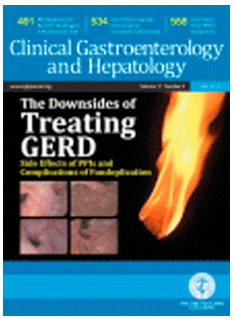

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TEGASEROD: WHAT'S OLD IS NEW AGAIN

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Abstract

Irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) are common gastrointestinal disorders imposing considerable impact on the quality of life and well-being of affected individuals. A paucity of evidence-based treatment options exist for CIC and IBS-C sufferers. Tegaserod, a 5-HT_4 agonist, has a substantial body of pre-clinical and clinical study evidence to support its beneficial role in modulating sensorimotor function of the luminal gastrointestinal tract. Tegaserod was first approved for use by the United States Food and Drug Administration (U.S. F.D.A.) for the management of IBS-C and CIC in 2002 and 2004, respectively. Tegaserod enjoyed a successful uptake in the management of these disorders during its first several years of availability in the U.S., but was later withdrawn from the market in 2007 over concerns related to adverse cardiovascular events. Since, additional safety data has been generated, and following a resubmission and review by the F.D.A., in April 2019 tegaserod was once again approved for use in IBS-C under a more restricted labeling, confining use to women under the age of 65 without heart disease or additional cardiovascular risk factors. This review summarizes the regulatory journey of tegaserod, and details the existing pharmacokinetic, physiologic, clinical, and safety data of tegaserod generated over the last two decades. The discussion also examines the future of tegaserod in the treatment of these constipation disorders, as well as its potential role in other related disorders of brain-gut interaction (DGBI).

I. Introduction: Irritable Bowel Syndrome with Constipation (IBS-C): Major Impacts and Unmet Needs

Irritable bowel syndrome (IBS) is a common disorder of gut-brain interaction (DGBI) characterized by recurrent abdominal pain associated with altered bowel habits.[1, 2] Large population-based studies estimate a worldwide IBS prevalence of 5% to 15% in developed countries, with a female predominance, and approximately one-third of IBS patients having IBS with a constipation predominant bowel pattern (IBS-C).[3-5] IBS imparts a substantial negative impact on the health related quality of life (HRQOL) of affected individuals, the average IBS patient endorsing worse HRQOL than patients with chronic liver disease.[6, 7] Previous data suggests that 12% IBS patients do not work at all because of their IBS,[8] and nearly one-quarter of IBS sufferers miss work regularly because of their IBS symptoms.[9] Accordingly, IBS is estimated to result in $1.6 billion in direct medical, and $19 billion in indirect costs annually in the United States alone.[10, 11] Given its substantial economic, societal, and individual impact, IBS is an important health care system priority.

In a 2018 American College of Gastroenterology (ACG) Monograph on the Management of IBS, there were only four prescription IBS-C treatment options given a strong recommendation for use (tricyclic antidepressants, and the secretagogues lubiprostone, linaclotide, and plecanatide).[12] However, these treatments are only effective in a portion of patients, and some are subject to potential limitations, such as the tricyclic antidepressants which may paradoxically worsen constipation via their anticholinergic effects.[13, 14] Moreover, it remains unclear whether patients who fail to experience symptom benefit with one of the secretagogue medications might still respond to another agent within this same pharmacotherapeutic class. Thus, there is still a need for additional IBS treatment options with different modes of action. Fortunately, the past few years have witnessed the U.S. Food and Drug Administration (F.D.A.) approval of three new treatments for use in this space: 1) the selective 5-HT_4 agonist prucalopride for the treatment of chronic idiopathic constipation (CIC), after more than a decade of experience with this agent in Europe and other world markets;[17] 2) tenapanor, a sodium/hydrogen exchanger 3 (NHE3) inhibitor, for the management of IBS-C;[18] and 3) tegaserod, a 5-HT_4 agonist re-approved for the treatment of women with IBS-C.[4, 19] In the most recent 2020 ACG Clinical Guideline: Management of IBS,

tegaserod was given a strong/conditional recommendation for use in women <65 years with ≤1 cardiovascular risk factor, as indicated, when response to secretagogues has been inadequate.[20]

The recent resurrection of tegaserod as a prescription option for IBS-C comes with particular interest to the neurogastroenterology community. 5-HT4 agonists are prokinetics, as they stimulate propulsive gastrointestinal motility, and have been explored as potential treatment options for several DGBIs where hypomotility is thought to be a relevant pathophysiological mechanism.[21] Originally F.D.A. approved in 2002,[22] tegaserod emerged as an extremely popular IBS-C treatment option in the early 2000s, only to be later voluntarily withdrawn from the U.S. market in 2007 over concerns primarily relating increased risk of treatment-associated cardiovascular (CV) events and ischemic colitis.[23-27] However, following a re-examination of the available data regarding CV risk associated with tegaserod, in April 2019 the F.D.A. once again approved tegaserod, with a more restricted label, now available to women under the age of 65 and without a history of cardiovascular ischemic event (unstable angina, myocardial infarction, stroke, or transient ischemic attack) and without excess cardiovascular risk (>1 of the following: active smoking, hypertension, hypercholesterolemia, diabetes mellitus, obesity, or age 55 years or older) .[28]

Moreover, as a 5-HT_4 agonist with prokinetic effects, tegaserod has gained interest for potential use in other related functional and GI motility disorders, including functional dyspepsia, gastroparesis, and disorders of esophageal hypomotility.[29-33] Indeed, over the past two decades the physiologic effects of tegaserod (initially known as SDZ HTF 919) throughout the luminal GI tract, and the corollary clinical effects of in IBS and several other motility and functional disorders have been described.[29, 31, 34-38] The purpose of this review thus is to provide the gastroenterologist a comprehensive summary of the pharmacologic, physiologic, and clinical data on tegaserod in IBS and related motility disorders. In parallel, we will detail the U.S. regulatory and marketing journey which led tegaserod from an old (but not forgotten) treatment to a newly available option for the management of IBS with constipation.

II. 5-HT_4 receptor Pharmacology

See supplementary file

III. Tegaserod Pharmacokinetics and Metabolism

See supplementary file

IV. Tegaserod Effects on Gastrointestinal Function

See supplementary file

V. "What's Old": Tegaserod from 2000-2007

A. Clinical efficacy

1. Tegaserod Phase II/III IBS-C trial summary

The initial studies evaluated a dose range of tegaserod and, based on these findings, the doses of 2 and 6 mg were selected for further evaluation.[39] Two pivotal placebo-controlled 12-week studies were conducted in IBS-C patients, one evaluating both 2 and 6 mg b.i.d. doses in males and females[40] and the other only evaluating 6 mg b.i.d. in females.[41] The primary endpoint in these studies was the subject's global assessment (SGA) of relief, assessed using a 5-point ordinal scale.[42] Table 2 summarizes the studies with tegaserod in IBS-C, the only currently approved indication for use. Additional studies were conducted in men and women with IBS without diarrhea, using satisfactory relief as an endpoint, and confirming efficacy in this group of patients as well.[19, 43, 44] The safety of tegaserod in IBS-D was also reported.[45] These studies led to the approval of tegaserod 6 mg b.i.d. for the treatment of women with IBS-C in the U.S., and many other parts of the world. In Europe, the regulatory authorities requested data on retreatment. A controlled, randomized trial evaluating two treatment cycles with tegaserod 6 mg b.i.d. in women with IBS-C confirmed similar efficacy over placebo in both treatment cycles.[46] In spite of these results, the European regulatory authority did not approve tegaserod.

The following sections are also found in the supplementary file:

2. Tegaserod trials in other motility disorders

B. Tegaserod safety and tolerability

C. Seeking initial regulatory approval of tegaserod

D. Initial marketing experience with tegaserod

VI. Tegaserod: Encountering controversy and market withdrawal

A. Cisapride history

Cisapride, was introduced world-wide in the 1990's, as a serotonin 5-HT_4 agonist with 5-HT_3 antagonist activity (Table 1) and was approved by the F.D.A. for nocturnal heartburn, but was widely used for the treatment of a wide range of motility disorders.[21] However, it was eventually recognized that cisapride use could result in prolongation of the Q-T interval and thereby increase the risk of arrhythmia.[47-504] Since cisapride is metabolized by the cytochrome P450 enzyme system, it is also susceptible to drug interactions with drugs that are inhibitors of this system.[21] In 1995, a "black box" warning was issued by the F.D.A.[51] and the drug was withdrawn worldwide in July 2000.[52]

B. Alleged tegaserod relationship with serious adverse events

B.1. Cardiovascular events and arrythmia

In 2007, the F.D.A. recommended withdrawal of tegaserod from the U.S. market, and sales were voluntarily suspended in most countries over concerns relating to a signal for increased cardiovascular events based on a pooled clinical trial database review of 29 placebo-controlled trials showing an increased incidence of cardiovascular ischemic events in patients with preexisting cardiovascular disease.[51] At that time tegaserod was approved in 55 countries for the treatment of IBS-C and in more than 20 countries for chronic constipation, and it was estimated that over 6.7 million patients had taken tegaserod accounting for more than 1.4 million patient-years of treatment, thus

representing a major blow to patients benefiting from the use of this agent for management of their CIC, IBS-C or use for off-label indications, such as gastroparesis.[52,53]

The basis for this withdrawal of tegaserod was a report by the Swiss drug regulatory authority, which included a retrospective analysis of clinical studies with tegaserod involving over 18,600 patients, finding a small, statistically significant increase in the incidence of pooled cardiovascular ischemic events [13 per 11,614 (0.11%) tegaserod; 1 per 7,031 (0.01%) placebo (p=0.024)]; these events included myocardial infarction (n=4), unstable angina pectoris (n=6), and stroke (n=3) on tegaserod compared to only a single case with a transient ischemic attack with placebo.[54] Notably, no pattern relative to the time of occurrence of these events, or association with dose was detected, and most patients had pre-existent disease and cardiovascular risk factors.

Further, the early dosing studies in healthy controls went up to doses of 25 mg and with intravenous administration plasma concentrations of ≥100 times therapeutic doses were reached without clinically relevant influence on ECG parameters.[55] The event rate for major coronary ischemic events in tegaserod-treated patients [5.54 per 1000 patient years] in clinical trials is noted to be consistent with the general population 4.0 to 5.1 for women and 10.6 to 12.1 for men, per 1000 patient-years.[56] Post-marketing reports of coronary ischemic events at that time were also low with a reporting rate of 0.01 and 0.003 per 1,000 patient-years for myocardial infarctions and angina, respectively. Finally, a case-control study found no association between tegaserod and cardiovascular adverse events.[57] Indeed, a Canadian cohort showed that in patients with cardiovascular symptoms while being treated with tegaserod, symptoms worsened after stopping the treatment.[58] Moreover, in contrast to cisapride, tegaserod mechanistically lacks affinity for the HERG channel and is not extensively metabolized by CYP3A family members, and multiple studies did not suggest any arterial vasoconstrictive effect of tegaserod. Together, the risk attributed to tegaserod was viewed as non-convincing by many experts, as it lacked a mechanistic basis, was not supported by post-marketing surveillance data and required grouping together events of differing natures to reach a statistically significant difference from the placebo arm in the pooled clinical trial data set. Most recently, an independent, external adjudication of 18 cardiovascular ischemic events (CVI) among 11,614 tegaserod-treated patients found no significant increase in CVI with tegaserod compared to placebo (OR 4.24,

95% CI 0.52, 34.74, p=0.27).[59] Importantly, all of the CVI events were observed in patients with ≥1 CV risk factor, and conversely none of these events were observed in women <65 years of age without a history of CVI.

B.2. Ischemic colitis

Ischemic coltis (IC) led to the withdrawal of alosetron (a 5-HT_3 antagonist for diarrhea-predominant IBS) and indeed has been associated with several other agents in this class including cilansetron (another 5-HT_3 antagonist), E3620 (a mixed 5-HT_3 antagonist and 5-HT_4 agonist), and AZD-7371, all of which have been withdrawn from further clinical development.

The clinical trials with tegaserod, which involved over 11,600 patients using tegaserod, with a total of 3456 patient-years of exposure by 2004, reported no cases of IC. However, a number of cases were reported to the F.D.A.[61] Epidemiological evidence indicates that patients with IBS have a higher risk of developing IC than the general population, regardless of treatment. Preclinical data do not support a mechanism whereby tegaserod can cause ischemia. The cumulative worldwide reporting rate of suspected IC in tegaserod users as of 30 November 2006 was calculated as 0.058 cases per 1000 patient-years, which again is similar to the incidence of IC in the general population (0.07-0.47/1,000 patient-years) and well below the incidence in the IBS population (0.43-0.49/1,000 patient-years).[62] As a result of these reports, the precautions section of the approved labeling of Zelnorm was updated in 2004 to alert the medical community to the potential for tegaserod-associated ischemic colitis.

B.3. Abdominal surgery

In placebo-controlled trials with tegaserod, the overall incidence of abdominal and pelvic surgery was balanced across treatments, except for cholecystectomy.[61,63] The previously noted mechanistic study measuring gallbladder motility in healthy volunteers and patients with IBS-C, showed that tegaserod did not alter fasting or postprandial gallbladder motility.[63] The incidence of abdominal and pelvic surgeries is increased in IBS patients compared to a control population,[64] and a meta-analysis showed an increased incidence of abdominal surgery as not associated with tegaserod usage.

VI. "New Again": The Re-emergence of tegaserod

In light of this constellation of data dispelling concern relating to potential serious adverse events, in 2018 a supplemental new drug application (sNDA) was submitted by Sloan Pharma to U.S. F.D.A. for tegaserod use in women with IBS-C and low cardiovascular risk.[66] On October 17, 2018 an F.D.A. and Gastrointestinal Drugs Advisory Committee (G.I.D.A.C.) meeting convened to perform a complete review of the tegaserod resubmission, including the available safety data.[67] Members of that committee ultimately voted 11 to 1 in favor of re-approval of tegaserod, after finding a lack of compelling evidence of increased risk of cardiovascular events in patients taking 5-HT_4 agonists. Final approval for the new IBS-C indication ultimately was provided in March 2019. In parallel, another 5-HT_4 agonist, prucalopride, also gained F.D.A. approval for the management of chronic idiopathic constipation.[68] The new tegaserod prescribing information restricted use in adult women less than 65 years of age who do not have a history of ischemic cardiovascular disease (CVD) and who have no more than 1 CVD risk factor (e.g., smoking, hypertension, hyperlipidemia, diabetes mellitus, age ≥55 years, or obesity) and stated contraindications relating to previous history of myocardial infarction, stroke, transient ischemic attack, angina, ischemic colitis, or intestinal ischemia. A recent integrated analysis of 4 trials (3 published)[40,41,69] by Shah and colleagues examined data on tegaserod outcomes in female IBS-C patients younger than 65 years, without cardiovascular disease histories (the currently indicated treatment population)[70] In the assessment of the primary efficacy responder rate (≥30% reduction in weekly abdominal pain intensity and ≥50% increase in stool frequency (≥1/wk) for at least 6 of 12 weeks), tegaserod treatment was found to be superior to placebo (36.0% vs. 24.3%; OR 1.79, 95% CI 1.51, 2.13; $p<0.001$), nearly identical to the tegaserod response observed in the overall population of women with IBS-C. Adverse rates also were similar to placebo with tegaserod treatment, and there were no cardiovascular events observed in the indicated population. The summary outcome data in the indicated population from these studies is reported in Table 3.

VI. Conclusions and expert opinion

The efficacy of tegaserod in the management of chronic constipation disorders, including the global abdominal symptoms of IBS, has been well-established. With careful consideration of the potentially serious adverse events, in this current era the concerns relating to cardiovascular events and intestinal ischemia have been sufficiently, and convincingly, addressed to allow F.D.A. re-approval for the use of this agent in IBS-C patients. Tegaserod overall is well tolerated, with treatment -related adverse events typically being limited to diarrhea, usually transient in nature when experienced. A general consensus among neurogastroenterology experts supports the use of tegaserod in women affected by these constipation disorders, particularly with close adherence to the more restricted indications in the 2019 updated labeling.

It is clear that patients suffering from disorders of brain-gut interaction are desperately in need of additional prescription treatment options to manage their symptoms. Active bowel and abdominal symptoms exert a major toll on the quality of life and productivity of the individual,[6, 71] In addition to potential for symptom improvement, tegaserod previously has demonstrated benefit in reducing work productivity loss and daily activity impairment,[44,73] as well as decreases in GI-related resource utilization in real-world settings.[73]

IBS patients convey a willingness to accept considerable risks in exchange for the prospects of symptom relief, on average accepting a 1% risk of sudden death from a hypothetical medication in exchange for a 99% chance of cure in a standardized gamble scenario.[7, 75] Another study suggested that IBS patients would sacrifice one-quarter of their remaining life (estimated to be 15 years, on average) in order to become symptom-free.[75] These observations underscore the major blow sustained by patients when tegaserod marketing was discontinued in 2007, and seemingly conflict with the regulatory agencies' calculations of risk-benefit balance at the time, and the need for additional evidence-based therapies to offer these patients.[53]

The voluntary withdrawal of tegaserod at the request of the FDA and by Health Canada in 2007 triggered some critical comments from gastroenterologists, who perceived a bias towards irritable bowel syndrome and other functional gastrointestinal disorders in this decision.[52,53] While drugs with a known cardiac or cardiovascular risk, such as erythromycin or sildenafil, were not withdrawn, the regulatory authorities were seemingly averse to even the slightest therapeutic risk for a non-life threatening condition such as IBS. This experience echoes some of the considerations in the

withdrawal of cisapride in 2000. One could assume that well-informed physicians should be able to deal with an identifiable risk, as is the case for many drugs used in clinical practice, and that symptomatic benefit for conditions for which there are few therapeutic alternatives must also be taken into account.

The impact of the F.D.A. and Health Canada decisions was major: tegaserod entered a limited-access program worldwide and was withdrawn from most other markets in the world. The decision also helped maintain the stigma of uncertain safety that was attributed to prokinetic drugs, and especially 5-HT_4 receptor agonists, although the arrhythmogenic effect of cisapride and the presumed cardiovascular side effects of tegaserod had little to do with their 5-HT_4 receptor affinity. This unsubstantiated claim probably helps explain why prucalopride, a highly selective and safe 5-HT_4 agonist, with established efficacy in chronic constipation was only approved in the U.S. more than 10 years after its launch in Europe. It is our hope that recent decisions, such as the lifting of the risk evaluation and mitigation strategy program for alosetron, the approval of prucalopride, and the re-introduction of tegaserod, mark the end of an era wherein regulatory bodies imposed a zero-tolerance for any suggested risk, even if not really substantiated by scientific data, on drugs used for gastrointestinal function and motility disorders. Future pharmacotherapy regulatory evaluation must take into account factors such as alleviation of the burden of disease, the ability of physicians to identify and manage side effects of drugs, and importantly the willingness of patients to accept certain levels of risk when there is relevant clinical benefit.[75]

More than 20 years after the completion of the initial tegaserod clinical trials, now with the benefit of additional data yielding a more favorable assessment of its safety profile, tegaserod is once again commercially available to our IBS-C patients. Tegaserod is an attractive option for women with IBS-C who have not responded to the current standard therapies, including secretagogues. Though further clinical trials are needed, the substantial physiologic evidence indicating a positive effect of tegaserod in modulating sensorimotor functions of the foregut, namely enhanced gut motility and downregulation of visceral hypersensitivity, provide a rational basis for the potential application of tegaserod in disorders of brain-gut interaction beyond the constipation disorders, such as FD and gastroparesis, and perhaps even GERD and esophageal motor disorders.

Identification of patients who stand to benefit from the recognized 5-HT_4 agonist effects of tegaserod will rely on continued refinement of clinically relevant and objectively defined patient subgroups. For example, though the phase 3 trial program in FD generated both a positive and a negative study, these evaluations may have been hindered by the inclusion of patients with only mild symptom burden,[76] and the implementation the Rome II criteria to identify FD patients. The particular benefit of tegaserod noted among the postprandial distress syndrome (PDS) FD subtype according to the Rome IV criteria provides a new opportunity for further exploration of tegaserod efficacy in this large, clinically distinct PDS cohort. We anticipate similar candidates for treatment with tegaserod and other related 5-HT_4 agonists will be realized within the broad spectrum of gastrointestinal conditions manifesting as a result of perturbations in visceral sensitivity and dysmotility throughout the luminal gut. Despite its uncertain past, the compelling physiologic, efficacy, and safety data assembled over the past two decades forecast a brighter future for tegasterod, and the millions of patients who might benefit from its use in the management their gastrointestinal disorders.

FIGURE LEGEND

Figure 1. Observed physiologic effects and symptom responses to tegaserod in controlled, clinical trials. ↓: decrease; ↑ increase; ↔: no change; LES: lower esophageal sphincter; MMC: migrating motor complex; TLESR: transient lower esophageal sphincter relaxation, AET: acid exposure time; QOL: quality of life. Detailed information on the studies leading to this overview is found in Supplementary Table 1.

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TABLES

Table 1. Receptor binding profile of 5-HT_4 agonists for GI disorders, at therapeutic concentrations.

Drug	Receptor binding profile at therapeutic concentrations					
	5-HT_4	5-HT_3	5-HT_2	5-HT_1	D_2	hERG
Metoclopramide	+				+	
Clebopride	+	+			+	
Cisapride	+	+	+			+
Mosapride	+	+				
Cinitapride	+		+		+	
Renzapride	+	+				
Naronapride	+					
Tegaserod	+	+	+	+		
Prucalopride	+					
Velusetrag	+					

+ indicates affinity for this receptor (as either agonist or antagonist) that is likely to be clinically relevant at concentrations necessary for 5-HT_4 agonism (i.e. for therapeutic action). Information from De Maeyer et al.[131] GI, gastrointestinal

Table 2. Summary of placebo controlled tegaserod trials in IBS

Study	Study population	Patients randomized	Treatment duration	Medication dose/day	Endpoints	Responder definition	Result
Muller-Lissner et al.[79]	Efficacy/safety, and dose response in IBS-C *men & women*	881	12 wks	tegaserod 2 or 6 mg bid or placebo	Subject's Global Assessment* (SGA) of Relief SGA of Abdominal Pain and Discomfort	At least 50% of their SGA of Relief assessments either 'considerably relieved' or 'completely relieved' or 100% at least 'somewhat relieved	Responder rates for the SGA of Relief were 46.5%, 46.3% and 34.5% for the 2 mg, 6mg and placebo groups Responder rates for SGA of pain and discomfort were 29.8%, 29.9% and 22.6% respectively
Novick et al.[80]	Efficacy/safety study in IBS-C *women*	1519	12 wks	tegaserod 6 mg bid or placebo	Subject's Global Assessment (SGA) of Relief SGA of Abdominal Pain/Discomfort SGA of Satisfaction with bowel habit	At least 50% of their SGA of Relief assessments either 'considerably relieved' or 'completely relieved' or 100% at least 'somewhat relieved	Responder rates for the SGA of Relief were 43.5% and 38.8% Higher improvement of SGAs of Abdominal Pain/Discomfort, and Satisfaction with Bowel Habit with tegaserod vs. placebo.
Tack et al.[85]	Efficacy/safety, re-treatment in IBS-C *women*	2660	4 wks + 4 wks re-treatment	tegaserod 6 mg bid or placebo	Satisfactory relief of overall IBS symptoms Satisfactory relief of Abdominal Pain/Discomfort	Satisfactory relief during at least 75% of the weeks	Tegaserod was superior to placebo for relief of overall IBS symptoms and of abdominal discomfort/pain during the first (respectively) and repeated treatment
Chey et al.[19]	Efficacy/safety in IBS-C/IBS-M *women*	661	4 wks	tegaserod 6 mg bid or placebo	Satisfactory relief of overall IBS symptoms	Satisfactory relief during at least 75% of the weeks	Tegaserod showed a significantly higher response rate compared with placebo (47.5% vs 32.6%, P < 0.001)
Nyhlin et al.[83]	Efficacy/safety in non D-IBS *men & women*	647	12 wks	tegaserod 6 mg bid or placebo	Satisfactory relief of overall IBS symptoms Daily symptom diary (abdominal pain/discomfort, bloating, stool consistency and frequency)	Satisfactory relief during at least 75% of the weeks, week 1-4 Satisfactory relief during at least 75% of the weeks, week 1-12	Tegaserod showed a significantly higher response rate compared with placebo (26% vs 19%, P < 0.005) For weeks 1 to 12, percentages are 34% and 23% (p<0.001) Significantly greater reductions in the diary parameters with tegaserod

Kellow et al.[82]	Efficacy/safety in non D-IBS *men & women*	520	12 wks	tegaserod 6 mg bid or placebo	Satisfactory relief of overall IBS symptoms Daily symptom diary (abdominal pain/discomfort, bloating, stool consistency and frequency)	Satisfactory relief of overall IBS symptoms	Tegaserod showed a significantly higher response rate compared with placebo (26% vs 19%, P < 0.001) For weeks 1 to 12, percentages are 57.2% and 43% (p<0.005) Significantly greater reductions in the diary parameters with tegaserod

Study	Combined Abdominal pain/Stool frequency Responder*, 12 wks			50%/100% SGA** Responders (1 month)			50%/100% SGA**Responders (last 4 visits)		
	Tegaserod (n/N%)	Placebo (n/N%)	OR (95% CI), P value	Tegaserod (n/N%)	Placebo (n/N%)	OR (95% CI), P value	Tegaserod (n/N%)	Placebo (n/N%)	OR (95% CI), P value
301	46/212 (21.7%)	24/214 (11.2%)	2.21 (1.28,3.81); 0.004	73/219 (33.3%)	38/217 (17.5%)	2.48 (1.56, 3.92); <0.001	89/219 (40.6%)	61/217 (28.1%)	1.82 (1.21, 2.74); 0.004
307	43/203 (21.2%)	28/204 (13.7%)	1.70 (1.01, 2.88); 0.047	72/209 (34.4%)	44/212 (20.8%)	2.00 (1.29, 3.09); 0.001	91/209 (43.5%)	83/212 (39.2%)	1.21 (0.82, 1.79); 0.343
351	54/208 (26.0%)	36/209 (17.2%)	1.68 (1.05, 2.69); 0.030	78/220 (35.5%)	52/218 (23.9%)	1.75 (1.15,2.65); 0.008	107/220 (48.6%)	73/218 (33.5%)	1.90 (1.29, 2.79); 0.001
358	347/737 (47.1%)	237/713 (33.2%)	1.77 (1.43, 2.19); <0.001	256/738 (34.7%)	157/719 (21.8%)	1.88 (1.49, 2.37); <0.001	324/738 (43.9%)	282/719 (39.2%)	1.21 (0.98, 1.49); 0.072
Pooled data	490/1360 (36.0%)	325/1340 (24.3)	1.79 (1.51, 2.13); <0.001	479/1386 (34.6%)	291/1366 (21.3%)	1.95 (1.64, 2.31); <0.001	611/1386 (44.1%)	499/1366 (36.5%)	1.38 (1.18, 1.61); <0.001

*Combined Abdominal Pain/Stool Frequency Response, 12 wks defined as ≥30% reduction in weekly abdominal pain intensity and ≥50% increase in stool frequency (≥1/wk) for at least 6 of 12 weeks. ** 50%/100% SGA (Subjective Global Assessent) Responders: subjects rating themselves considerably or completely relieved ≥50% of the time or at least somewhat relieved 100% of the time.

+The indicated population was defined as women younger than 65 years with no history of CVI events who received tegaserod 6 mg b.i.d. or placebo.

b.i.d., twice daily; CI, confidence interval; CVI, cardiovascular ischemic; OR, odds ratio

Table adapted from Shah E, et al.[124]

Table 3. Integrated analysis of tegaserod for the indicated IBS-C population+ (women <65 years without a history of CVI events)

Online supplementary information

II. 5-HT$_4$ receptor Pharmacology

A. Serotonin function in the gut

Serotonin is a key signaling molecule in the gastrointestinal tract, where it is released from entero-endocrine cells in the mucosa and from neurons in the enteric nervous system[1]. Release from entero-endocrine cells can be triggered by mechanical stimulation or the presence of nutrients, tastants, bile acids or toxins, while release from enteric neurons has been implicated in the control of propulsive motility and mucosal secretion.[1-3]

Serotonin is synthesized from the essential amino acid tryptophan by tryptophan-hydroxylase-1, expressed in the gastrointestinal tract.[4] Upon its release, serotonin can exert effects through actions on 14 different identified receptors and is inactivated through the serotonin reuptake transporter system.[1,3] In the gastrointestinal tract, the 5-HT$_4$ receptor is a key target.[3,5]

B. 5-HT$_4$ receptor structure and function

5-HT$_4$ receptors are heptahelical receptors, coupled to protein G_s and activation of 3',5' cyclic adenosine monophosphate-dependent protein kinase A.[5] Several splice variants of the receptor have been described, and 5-HT$_{4(b)}$ is the dominant splice variant in human tissues. Recent animal studies suggest that the 5-HT$_4$ receptor is constitutively active,[6, 7] not requiring the release of 5-HT to modulate large intestinal motility.[8]

C. Tissue expression of 5-HT_4

5-HT_4 receptors are localized to neurons in the central nervous system, in the GI tract, bladder and heart [19]. Based on animal and a few human studies, the 5-HT_4 receptor can be expressed in the gastrointestinal tract by cell bodies and fibers of subsets of myenteric and submucous plexus neurons, by entero-endocrine cells and enterocytes, interstitial cells of Cajal and smooth muscle cells.[47, 9-11] As a major consequence of 5-HT_4 receptor activation, acetylcholine is released from interneurons and motor neurons, thus increasing propulsive motility.[5, 1]

D. 5-HT_4 agonist classes and receptor affinities

Several different classes of 5-HT_4 receptor agonists were developed for the treatment of GI disorders. Their pharmacological properties are summarized in Table 1. The molecular structure of 5-HT and of the most important *5-HT_4 receptor agonists is shown in Supplementary Figure 1.*

Substituted benzamides were the first class of 5-HT_4 agonists to be used clinically. Members of this class include metoclopramide, cisapride, renzapride, mosapride, clebopride, cinitapride and naronapride (ATI-7505).[5] Most of these molecules are not selective for the 5-HT_4 receptor. Metoclopramide and cleprobide, for instance, are also antagonists at D_2 dopamine receptors and cisapride and renzapride are antagonists at 5-HT_3 receptors. The best known agent, cisapride, also blocks the human ether-a-go-go-related gene (hERG)-encoded K^+ channel, which underlies its arrhythmogenic potential through QT prolongation, the reason for its withdrawal from markets. Naronapride is structurally similar to cisapride, but more selective, with minimal hERG channel activity as well as minimal-

to-no activity at 5-HT_3 receptors. Cinitapride is another 5-HT_4 agonist from the benzamide class, which is also an antagonist at 5-HT_2 and dopamine-2 receptors.

Indole carbazimidamides, with tegaserod and velusetrag as representative members, are the second class of 5-HT_4 agonists.[5] Tegaserod is a high affinity 5-HT_4 receptor agonist, but is also a 5-$HT_{2(a)}$ and 5-$HT_{2(b)}$ recepto antagonist and a 5-HT_1 receptor agonist. Velusetrag is a dihydroquinoline-carboxylic acid derivative that has high affinity and selectivity for 5-HT_4 receptors.[5]
Prucalopride is a high affinity and selective 5-HT_4 receptor agonist belonging to the class of *benzofurancarboxamides*. The most pronounced clinical effect of prucalopride is stimulation of colonic motility[51] Several other 5-HT_4 receptor agonists that have been evaluated in clinical trials include lintopride (STIL 2875), lirexapride (JL17454/CHF17454), PF885706 and E3620.[5]

III. Tegaserod Pharmacokinetics and Metabolism

A. Pharmacokinetics

The pharmacokinetics of tegaserod have been studied in healthy controls and in patients [12, 13]. The bioavailability of tegaserod is low, at 11%, and is further reduced when ingested with food. The drug reaches a maximum plasma peak levels 1 to 1.3 hours after intake. Tegaserod is 98% protein bound in the plasma and does not significantly cross the blood-brain barrier. The estimated plasma half-life is 11 hours. Dose-plasma level proportionality studies show that there is no accumulation of the drug with time.

B. Metabolism and elimination, contraindications with kidney/advanced liver disease

Tegaserod is metabolized by 2 distinct pathways, gastric acid catalyzed hydrolysis, followed by oxidation and conjugation, and direct gluruonidation. Two-thirds are excreted unchanged in the feces, and the remainder is excreted in the urine as inactive metabolites.

Studies in patients with severe kidney failure or haemodialysis have shown that it can be safely used in patients with mild to moderate renal failure and in patients with hepatic cirrhosis and Child-Pugh scores up to 11, without need for dose adjustment. In patients with severe hepatic or renal failure (creatinine clearance <15 mL/min) and patients on hemodialysis, tegaserod should be avoided.[14]

IV. Tegaserod Effects on Gastrointestinal Function

A. Small bowel and colonic motility

An initial in vivo report on the physiologic effects of tegaserod (known initially as SDZ HTF 919) was published in the medical literature in 1997, describing its effects on gastrointestinal and colonic transit.[15] Using radioscintigraphy and perfusion manometry in a canine model, intravenous tegaserod yielded significant in vivo increases in colonic transit of solid residue within the first hour post-administration compared to placebo. Manometry revealed prolonged post-prandial colonic contractions, but without significant changes in quantitative pressure indices (contraction amplitude or motor index) in the small intestine or colon. These positive findings led the investigators to conclude that “SDZ HTF 919 appears to be a promising agent for stimulation of mammalian colonic transit”. Another canine study found that tegaserod did enhance phase II type activity in the small bowel.[16] Shortly thereafter, the first published human study of STZ HTF 919 demonstrated significant decreases in median total colon transit times [TCTT] (4.8 hour median reduction in TCTT following tegaserod administration compared to 1.8 hour reduction with placebo) in a healthy male volunteer population.[17]

Later that same year, Appel and colleagues reported on the effects of tegaserod on TCTT measurements and a healthy control sample, using a model of slow colonic transit (soluble fiber supplementation). This study similarly found significant decreases and colon transit times at the 5 and 25 mg tegaserod doses in this model.[18] Two Swiss studies of healthy volunteers were able to demonstrate enhancement of both small bowel and colonic transit on scintigraphic imaging, with significant reductions and small

bowel transit time as well as shifts to higher geometric center values, particularly at 48 hours.[19,20] In a cohort of healthy volunteers who underwent jejunal gas perfusion, a single dose of tegaserod was shown to increase gas expulsion and enhanced bolus passage of gas.[21]

In patient populations, a study by Prather and colleagues randomized 24 women with IBS-C to tegaserod, 2 mg twice daily, or placebo treatment. Scintigraphic assessment of small bowel transit, and colonic transit were determined after 1 week of treatment and revealed acceleration of orocecal transit without any significant change in gastric emptying times, suggesting an enhanced small bowel transit effect. Though mean colonic transit times were similar in both the placebo and tegaserod groups at baseline and post-treatment, emptying half-time of the proximal colon and the scintigraphic geometric center at 48 hours were accelerated by tegaserod compared with baseline, albeit not statistically greater than placebo.[22] Finally, in patients with symptoms of functional dyspepsia and dysmotility–like symptoms, a single dose of tegaserod 6 mg orally was found to enhance motor activity in the antrum, duodenum, and jejunum with development of a “fed-response” pattern, and an increase in phase III migratory motor complexes (MMCs).[23] A summary of the human studies evaluating the physiologic effects of tegaserod on the gastrointestinal tract are summarized in chronological order of completion in Supplementary Table 1. Figure 1 summarizes the physiologic and clinical trial findings by anatomic region and clinical condition, respectively.

B. Noxious colonic stimulation and rectal hypersensitivity

Tegaserod injection in rat models inhibited abdominal contractions and abdominal withdrawal reflexes, visceromotor responses reflective of pain experience, following colorectal distention using balloon model of noxious stimulation.[24-27] In a dose-dependent fashion, tegaserod inhibited rectal afferent firing following rectal distention without modulating rectal compliance, suggesting that the anti-nociceptive effect is a consequence of direct effects on the sensory afferent neurons.[25] A cat study of distention ramps measuring

the response of mechanoreceptive rectal afferents in the sacral dorsal roots found decreased rates of static afferent discharge following I.V. tegaserod administration in a dose-dependent fashion. This effect was observed without alteration of the compliance (pressure-volume relationship) of the rectum, suggesting a direct effect of tegaserod on the intramural mechanoreceptors in the cat rectum.[28]

In a rectal barostat study in healthy women, tegaserod did not alter rectal compliance and intensity ratings during phasic and slow ramp rectal balloon distention.[29] The authors also evaluated the effects of tegaserod treatment on rectal distention-induced changes of the somatic, nociceptive, cutaneo-muscular flexion reflex (also known as the RIII reflex, a polysynaptic reflex which can be elicited by cutaneous sensory nerve electrical stimulation and recorded from ipsilateral flexor muscle). At baseline, slow rectal distentions induced gradual inhibitions of this RIII reflex. After 7 days, tegaserod but not placebo pretreatment, significantly reduced these RIII inhibitions, suggesting that the drug interacts with sensory visceral signaling.[29] Similar observations were made in women with IBS-C, but no clinical relevance is established given the lack of changes in sensory ratings or compliance.[30]

C. Gastric emptying, accommodation, and sensation

Several in vivo animal studies have that tegaserod accelerates gastric emptying of solids in both rodent and canine models, including a transgenic model of diabetes mellitus.[16, 31-35] Tegaserod reversed delays in gastric emptying experimentally-induced by acoustic stress conditions in a dog model.[36] Two studies by Degen and colleagues demonstrated enhanced gastric emptying in healthy volunteers following standard 6 mg twice daily oral dosing of tegaserod, with significantly shortened gastric lag time and acceleration in rates of gastric emptying.[19, 20] In healthy volunteers tegaserod 6 mg twice daily enhanced fasting gastric compliance as well as pre-prandial and postprandial intra-balloon volumes, but sensitivity to gastric distention was snot altered.[37] The results of gastric physiologic studies in symptomatic patients have been more mixed. The previously noted study by Prather et al. failed to demonstrate

any tegaserod enhancement of gastric motility in an IBS-C cohort.[22] In a study of patients with functional dyspepsia, tegaserod had no influence on fasting gastric compliance, or thresholds to sensory perception or discomfort. However, tegaserod did enhance meal-induced accommodation in the subgroup of patients with normal gastric emptying.[38] Another group found that tegaserod increased postprandial gastric compliance in a functional dyspepsia population (though tegaserod decreased gastric compliance in a healthy volunteer comparator group in the same study).[39] The effects of omeprazole on gastric emptying, known to delay stomach emptying by as much as 40%,[40, 41] were prevented in another trial through the concomitant administration of tegaserod 6 mg three times a day in healthy volunteers.[42] Case reports also have suggested a potential utility of tegaserod for improving gastric emptying and reducing 24-hour residual volumes in critically-ill patients with impaired gastric motility.[43]

D. Esophageal motility and acid exposure

A study of low-dose tegaserod (1 mg/day and 4 mg/day) resulted in a greater than 50% decrease in postprandial esophageal acid exposure among patients with abnormal acid exposure.[44] Tegaserod also reduced the total number of gastroesophageal reflux (GERD) episodes and decreased the number of transient lower esophageal sphincter relaxations (TLESRs) postprandially, but without significant change in mean lower esophageal sphincter (LES) pressures. Another high resolution manometry study of healthy subjects again found no tegaserod effect on LES function, but did observe significant effects on peristaltic function, enhancing peristaltic velocity and promoting mid-esophageal contractility during bolus transport.[45] In patients with functional heartburn tegaserod 6 mg twice daily significantly increased experimental balloon pressure to pain and wall tension at pain (i.e., improved tolerance of noxious pressure stimulation) without alteration of sensitivity to acid perfusion in the distal esophagus. At the same time, these investigators observed a significant decrease the frequency of related heartburn/acid reflux, and regurgitation symptoms with tegaserod.[46] However, another study by the same investigators of patients with overlapping functional heartburn and functional dyspepsia

symptoms found only trends with tegaserod treatment compared to placebo in terms of the increase of balloon volume required to elicit pain or pressures leading to subjective pain (P=0.058).[47]

E. Biliary tract motility

Given the observed effects of tegaserod on peristaltic activity in the luminal intestinal tract, an investigation was undertaken to examine the influence of tegaserod on gallbladder contractility and on sphincter of Oddi function, both during the digestive and inter-digestive periods in an IBS-C and healthy female population. No significant changes in gallbladder contractility or luminal diameters of the common hepatic duct or common bile duct were observed after tegaserod compared to placebo in any study cohort.[48]

V. "What's Old": Tegaserod from 2000-2007

A. Clinical efficacy

1. Tegaserod Phase II/III IBS-C trial summary

See main document

2. Tegaserod trials in other motility disorders

The efficacy of tegaserod was also evaluated in a number of other gastrointestinal motility disorders, and summarized in Table 3. Two large randomised, controlled trials with over 2000 patients have confirmed that tegaserod is effective in the treatment of chronic constipation when administered over a period of 12 weeks.[49,50] Significant improvements in straining, distension and bloating were

also noted. In an extension study after pivotal phase 3 trials, a total of 842 patients continued treatment with 2 or 6 mg tegaserod b.i.d. for 13 months and this showed good safety and tolerance in this cohort.[51]

An extensive phase 2 study program in FD evaluated the efficacy of several doses of tegaserod in patients with normal or delayed gastric emptying. These studies suggested that tegaserod 6 mg b.i.d. can improve dysmotility-like FD symptoms in women, besides showing dose-dependent enhancement of gastric emptying in FD with delayed emptying.[52, 53] Two phase 3 studies in women with dysmotility-like FD, where a total of 2667 women with FD were treated for 6 weeks with tegaserod 6 mg b.i.d. or placebo, showed inconsistent signs of benefit.[54] The 2 primary endpoints were the percentage of days with satisfactory symptom relief, and the symptom severity on a composite average daily severity score. Statistical significance for both endpoints was obtained in one study, but not in the other, and overall therapeutic gain seemed small, although it was larger in the patients with higher baseline symptom severity. In 2 open-label follow-up studies after the controlled phase 3 trial, 780 female FD patients were treated with tegaserod 6 mg b.i.d. for 1 year. No major adverse events occurred in this cohort and perceived symptom relief, dyspepsia-related QOL and work productivity scores showed sustained improvement from baseline throughout the 1-year evaluation.[55]

A number of add-on trials of tegaserod to PPIs in rGERD were initiated, but the results of these were never published.[56-58] In addition, a mechanistic study also suggested a favorable effect of tegaserod on esophageal pain thresholds,[46] but no follow-up study in esophageal hypersensitivity conditions were published.

B. Tegaserod safety and tolerability

The clinical trials with tegaserod in IBS-C, chronic constipation and functional dyspepsia showed good to excellent safety and tolerability.[44,46, 49-56] In this extensive trial data set, the frequency of adverse events was similar between treatment groups except for diarrhea, which was more frequent on tegaserod. This treatment associated diarrhea has been extensively evaluated and well

characterized and is expected based on the known promotility effect of tegaserod. In clinical trials, diarrhea was generally mild and transient, and tended to occur mainly at the beginning of treatment. Importantly a study performed in patients with IBS with diarrhea showed that tegaserod at doses of 2 and 6 mgs b.i.d. was safe and not associated with complications of diarrhea or serious adverse events.[59] The frequency of adverse events by system organ class was also similar between treatments with the exception of the gastrointestinal system organ class.

C. Seeking initial regulatory approval of tegaserod

Tegaserod encountered some substantial early hurdles in its regulatory approval process. In 2000, the US Food and Drug Administration issued an approvable letter for tegaserod under the trade name Zelnorm, (Novartis AG, Basel, Switzerland) but stipulated the need for an additional confirmatory trial given inconsistent results in the initial three trials submitted for review, and requested abdominal surgery data. Though initially F.D.A. approval was sought for tegaserod use in both men and women, guidance directed indications to women only in light of a female (84%) predominance in the clinical trials. In 2001, Novartis and Bristol-Myers Squibb Company voluntarily withdrew their marketing application for tegaserod (Zelmac) to treat IBS-C from the European Medicines Evaluation Agency (EMEA) after concerns were raised by the EMEA with regard to the relevance of some of the observed tegaserod effects, and concerns surrounding the methodological approach employed in some of the tegaserod preclinical studies. Early evidence of potential cardiovascular issues were also raised, including more frequent electrocardiogram (ECG) detection of ST depression with tegaserod, particularly among older patients, and a signal of greater cardiac ischemic events on tegaserod, despite a relatively young (mean age 45) healthy study population.[60] Ultimately, the F.D.A. did however approve tegaserod in July, 2002 for the treatment of IBS-C in women.

D. Initial marketing experience with tegaserod

Tegaserod marketing in the United States for women with IBS-C began in 2002, and later was F.D.A. approved and marketed for the treatment of chronic idiopathic constipation in 2004. Tegaserod enjoyed a very successful uptake in the management of these disorders, in part due to a paucity of prescription treatment options for the management of chronic constipation and IBS-C (at the time, only alosetron was available on a restricted use basis for IBS with diarrhea, and lubiprostone did not receive F.D.A. approval for IBS-C until later in 2006). By 2007. it was estimated that close to 500,000 Americans were taking the drug.[61] While the majority of tegaserod prescriptions were believed to be for on-label indications, some patients with foregut conditions such as FD and gastroparesis were also using this medication off-label for established prokinetic effects, though this practice largely was limited by restrictions in third-party insurance coverage for such indications.

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66.

Supplementary figure 1:

Molecular structure of 5-HT and of several 5-HT4 receptor agonists, illustrating the chemical heterogeneity of the different classes of agents. Tegaserod's molecular structure is closely related to that of 5-HT.

Supplementary Table 1. A summary of controlled, human studies of the physiologic effects in healthy volunteer and patient populations.

Author (Reference)	Subjects/ demographics	Study Arms	Study Design	Study Duration	Physiologic testing performed	Key findings	Additional comments
Appel et al 1997[17]	40 HV (all M); 36 completed protocol, 19-37 y.o.	TEG 25mg, 50, mg, or 100 mg; matched PBO	DB, PC, RCT (8TEG:4PBO per group); 3 study groups	15d (single dose d1, BID dosing on d2-d15)	Colon transit: TCTT; ROM Q 12 h x 6 at baseline, d2-6, d10-14. Testing performed on subset of 6 subjects per group (4 TEG, 2PBO)	Colon: ↓TCTT in pooled TEG vs PBO after 1w and 2w; P<0.05 for each	Pharmacokinetics testing also performed; Loose stool experienced in 21/24 (87.5%) TEG participants
Appel et al 1997[18]	60 M HV, 18-39 y.o.	TEG 1, 25mg, 50, mg, 100 mg, matched PBO BID	DB, PC, RCT (12 subjects per dose)	3 study periods of 7d (Period 1:self-selected diet, Period 2: liquid formula + soluble fiber supplement, Period 3: diet + fiber supplement + TEG)	Colon transit: TCCT and SCTT at end of each study period (ROM admin Q24h x6d, abdominal X-ray day 7,15,24)	Colon: ↓TCTT in 5 mg, 25 mg BID TEG vs PBO in Period 3(median difference of -22 and -26h , respectively, vs Period 2, P<0.05 for each); enhanced motility in left and sigmoid colon (data not shown)	Fiber supplemented diet prolonged TCCT (from median 30-34 h to 59-89 h) with an increase in all segmental colon transit times; No significant change in TCTT at 1 mg and 100 mg doses
Prather et al 2000[22]	24 IBS-C patients (Rome I, all F), baseline TCCT >40 h on ROM	TEG 2 mg or matched PBO BID	DB, PC, RCT	7d	GE/Small bowel transit: 99m Tc-sulfur colloid egg meal (baseline and 7d Rx); Colon transit: Mean TCCT at baseline (ROM Q 24h x 4d, abdominal X-ray day 5); Scintigraphy (111 InCl3 labelled methylacrylate coated capsule; baseline and after 7d Rx)	Stomach: ↔ no change in GE for any time period; Small bowel: ↑ OCT (proximal colon filling at 6h)accelerated by TEG vs PBO (70.4% ±1.3% vs 46.4 % ±1.9% p=0.015); Colon: ↑proximal colon emptying t 1/2 and GC48 with TEG vs baseline (but not PBO); ↔ mean TCTT (TEG 59.5 ±2.1h vs 62.1 2±2.1h	

Kahrilas et al 2000[38]	19 patients with mild/moderate GERD (61%M, 39%F, mean 35 y.o., mean 7.5 years disease)	TEG 1mg, 2mg, 12mg, 24mg, matched PBO BID	DB, PC, RCT, XO	14d per treatment	Esophageal manometry and pH testing at last dose of each 14d period	Esophagus:↓TLESRs vs PBO in post-prandial period (1-4 hrs after meal) ; ↓ postprandial AET (of those with AET >5% on PBO, >50% decrease in AET with TEG 1 mg/day (8/11 subjects) and 4 mg/day (10/11 subjects); ↔ TLESRs every 30 min, mean LES pressure, distal peristaltic amplitude	Both 1mg and 4 mg TEG decreased mean number of reflux episodes, only 1 mg/day resulted n a statistically significant reduction in postprandial AET
Degen L et al 2001[19]	12 M HV (39 ±7 y.o.)	Regimen 1: TEG 6 mg BID x3d, TEG 0.6 mg IV/PBO d4; Regimen 2: TEG 6 mg BID x3d, TEG 6mg PO/IV saline d4; Regimen 3: TEG 6 mg BID, PBO/IV saline d4	DB,PC, DD, 3-way XO	4d regimens x3, 1 week washout	GE: Scinitgraphy (99mTC-labelled egg meal); Colon transit: Scinitgraphy (111InCl3 labelled methylacrylate coated capsule)	Stomach: ↓Mean gastric lag time statistically shortened by 27% with PO TEG (P<0.05 vs PBO) and 38% with IV TEG (P<0.01 vs PBO); significant ↑ of rates of gastric emptying (P<0.001 vs. PBO); Small bowel: ↑Statistically significant effect on SBTT (PO TEG: 30% reduction; IV TEG: 37% reduction, P<0.05 vs PBO); significant acceleration of proximal colonic filling with PO TEG (P<0.01) and IV TEG (P<0.001); Colon: ↑GC shift to higher value after 24h, significant at 48h with PO TEG (P<0.01) and IV TEG (P<0.05) vs. PBO	
Coffin et al 2003[29]	20 F HV, 19-46 y.o.	TEG 6 mg BID or matched PBO	DB, PC, RCT	7d	Rectal balloon distention (slow ramp and rapid distentions-10, 20, 30, 40 mm Hg in randomized order), RIII reflex measurement 3 min before distention (control), during continuous rectal distention, and 4-min post-distention	Rectal sensitivity: ↓ inhibitory effects on RIII reflex elicited by slow ramp distension significantly lower in TEG group (72.8 ±11.4% of control at maximal volume of distention vs. 54.8 ±5.7% in PBO, ANOVA p<0.0001); ↔ Rapid distention RIII response similar to baseline, TEG ≈ PBO	Post-Rx maximal volumes of distention were similar to baseline. Intensity of visceral sensations (verbal questionnaire) similar in both TEG and PBO pre- and post-Rx. Compliance curves during slow ramp and rapid phasic distentions similar in both groups, not affected by TEG

Tack J et al 2003[37]	19 HV (10F, 9M, mean 23.9 y.o.)	TEG 2 mg, 6mg or PBO BID	DB, PC, RCT, 3-way XO	7 ±3d x3	Gastric barostat protocol assessing MDP, stepwise sequential ramp distentions +2mm Hg increments to discomfort/pain; mixed liquid meal (200 ml) and intragastric balloon measurements	Stomach: Gastric compliance: ↑intra-balloon volume at 6 mm Hg with TEG vs PBO (P<0.05), trend toward enhancing compliance with all pressure-volume data points (P=0.09); ↔ gastric perception, ↔ intra-balloon pressures or volumes inducing first perception or discomfort; ↑ gastric volumes with meal: TEG ↑ intra-balloon volumes before- and after meal (P=0.04, P=0.03, respectively),↔ gastric accommodation with meal	
Fisher et al 2004[48]	40 IBS-C patients, 13 HV (all F)	TEG 6 mg BID, TEG 12 mg BID (n=20 IBS-C)	DB, PC, RCT	14d x 2, 1 week washout	Real-time high resolution ultrasonography of gallbladder at baseline and following liquid meal	Gallbladder: ↔ Gallbladder contractility (ejection fraction, rate, period; fasting and residual volume, maximal emptying; Bile ducts: ↔ CBD and CHD luminal diameter, no significant dilation of CBD or CHD during gallbladder emptying in any cohort	
Tougas et al 2005[42]	40 healthy M volunteers; 18-40 y.o.	open label omeprazole 20 mg + TEG 6 mg or matched PBO TID	DB, PC, RCT	14d	GE: Scintigraphy (99mTC-labelled egg meal) at baseline and post-Rx	Stomach: TEG reversed omeprazole-induced delay gastric emptying (22.7% prolongation, T1/2 from 75.1 ±6.3 to 92.0 ±5.7 min, P<0.003, ↑ gastric retention 9.3 ±4.0% at 120 min, P<0.04); omeprazole effect reversed by TEG (P>0.2 for each)	
Degen et al 2005[20]	40 HV, 23M, 17 F	TEG 6 mg, matched PBO BID	DB, PC, RCT, XO	3.5 d	GE: Scintigraphy (99mTC-labelled egg meal); Colon transit: Scintigraphy (111InCl3 labelled methylacrylate coated capsule)	Stomach: ↑(lag phase, emptying rate, t1/2, and AUC); significant vs. PBO; Small intestine: ↑(30% in M, 37% in F); significant vs. PBO; Colon: ↑((geometric center shift at 24h, 48h); significant vs. PBO, except M at 24h (P=0.06)	M>F baseline gastric and colonic transit indices; tegaserod M>F ↑gastric emptying
Coleski R et al 2006[21]	16 HV (12M, 4F), mean 30 ±3 (19-49) y.o.	TEG 6 mg PO x1	XO, random order	single dose, studies x2 ≥7d apart	Jejunal gas perfusion, quantification of evacuated gas, intestinal gas dynamic parameters	Subjects (n=10) with physiologic gas retention in control studies: TEG ↑ expulsion (1768 ± 73 to 1973 ± 37 mL), ↓retention (p < 0.05); TEG ↑total volumes expelled as boluses (1708 ±73 vs 1846 ± 59 mL, p < 0.05);↑ bolus numbers (n=4), ↑ bolus volumes (n=7).	

Rodriguez-Stanley 2006[46]	42 FH patients (15M, 27W, 20-68 y.o.)	TEG 6 mg or PBO x 14d	DB, PC, RCT, XO	14d x 2, 7-10d washout	Esophageal balloon distention (5 cm proximal to LES) and Bernstein sensory testing	Esophagus: TEG significantly ↑ balloon pressure to pain (P=0.004) and the mean (P=0.002) and maximal wall tension at threshold of pain (P=0.0004). ↔TEG affect pain with acid infusion	TEG also decreased frequency of heartburn/acid reflux (P=0.004), regurgitation (P=0.039), and regurgitation distress (P=0.048); global preference was 63.4% for TEG vs. 12.2% PBO
Fox et al 2006[45]	17 HV (8M, 9F), mean 30 (22-40) y.o.	TEG 6mg BID or matched PBO	DB,PC, XO	7d per treatment, 5-14d washout	High resolution esophageal manometry and pH testing before and after test meal	TEG ↔ had no effect on LES pressure vs. PBO; ↑ peristaltic velocity ($P < 0.001$) and ↓distal contractile pressure ($P < 0.05$). During the studies of bolus transport, TEG ↑ mid-esophageal contractility($P < 0.02$) and ↓ the 'proximal transition zone' ($P < 0.05$).	↔ liquid bolus transport; trend to improved solid bolus transport was observed (66% vs. 31%;P=0.07).
Tutuian R et al 2006[62]	20 HV (12F, mean 32.7 y.o)	TEG mg BID or matched PBO	DB, PC, XO	2d per period, 7-14d washout	Multichannel intraluminal impedance-esophageal manometry and multi-channel intraluminal impedance-pH monitoring 2h post-prandially	No change in esophageal peristaltic amplitude, bolus transit time, or acid/non-acid reflux events	
Thumshirn et al 2007[39]	16 FD patients, 12 HV	TEG 6 mg or matched PBO BID	DB, PC, RCT, XO	7±3d per treatment, 7-14d washout	Gastric barostat protocol assessing MDP, gastric compliance and sensation using stepwise sequential distentions + 2 mm Hg until pain, gastric tone before/after duodenal lipid infusion	Stomach: TEG ↑post-prandial gastric compliance in FD patients (67.8±5.8 vs 59.7± 5.3 ml/mm Hg in PBO, P=0.04), ↓gastric compliance in HV (58.8 ±10.8 vs 70.3 ±11.1 ml/mm Hg in PBO. P=0.034) and ↑ gastric accommodation in healthy volunteers (237 ±127 vs. 190 ±99 ml with PBO, P=0.04); ↔gastric sensation in both groups	
Foxx-Orenstein et al 2007[63]	46 F IBS-C patients (mean 41.5 y.o.)	TEG 6mg BID, Naltrexone 50mg QD, combination, PBO`	DB,PC,RCT	6d	GE: Scintigraphy (99mTC-labelled egg meal); Colon transit: Scintigraphy (111InCl3 labelled methylacrylate coated capsule); Small bowel, ascending colon t1/2, and colonic geometric center (8, 24, 48 h)	TEG ↑ small bowel ($P < 0.01$) and colon transit ($P < 0.01$); GC24 significant with TEG alone (P=0.006 vs PBO) and AC t1/2 (P=0.043 vs PBO); TEG + naltrexone ↔ TEG alone.	Naltrexone ↔ colonic transit vs PBO

Harish K et al 2007[64]	44 M IBS-C patients	TEG 6 mg or PBO	DB, PC, RCT	12w	20 uniform radiopaque marker capsule ingestion at 0, 12 and 24 h (12 h intervals) abdominal X-ray at 36 h. If more than 80% of markers were retained, additional X-rays were obtained at 12-h interval until at least 80% markers passed or maximum of four X-rays	mean ± SD for the total colonic, right colonic, left colonic and rectosigmoid transit time (in hours) were 19.0 ± 3.9, 7.7 ± 1.6, 5.64 ± 1.5 and 5.6 ± 2.2 with TEG compared to 22.5 ± 3.7, 9.7 ± 2.3, 6.6 ± 1.3 and 6.2 ± 2.2 in PBO group at the end of 12 weeks (P<0.05 for each)	
Di Stefano M et al 2007[65]	22 F IBS-C patients (	TEG 6 mg BID or PBO	DB, PC, RCT	4w	Minimal distending pressure (MDP) determination, intra-balloon pressure set MDP+2 and fasting rectal tone was measured for a 30-min period; the liquid caloric meal given orally. Rectal tone measurement continued for a further 60 min to evaluate meal induced modifications of rectal tone and phasic contractility	Mean postprandial recto-sigmoid volume significantly reduced (101 ± 33 mL) with TEG; PBO did not affect (139 ± 79 mL) (P = 0.036). Mean percent postprandial modification was –23 ±22 (range from 2 to –77) with TEG and 1 ± 20 (range from 36 to –26) in PBO; significantly different (P = 0.0106)	
Miner et al 2008[47]	25 patients, overlapping FH and FD	TEG 6 mg or PBO x 14d	DB, PC, RCT, XO	14d x 2, 14d washout	Esophageal and gastric balloon distention sensory testing	Esophagus: ↔ volume to pain (P=0.106); ↔ ramp distention pressure to pain (P=0.77) or step distention (P=0.058); ↔esophageal compliance (P=0.97) ; Stomach: ↔ volume to pain (P=0.144 step, P=0.31 ramp); ↑mean ramp distention pressure to pain with TEG (15.8 vs. 11.3 with PBO, P=0.044); ↔gastric compliance (P=0.22)	Gastric balloon volume to pain was 48% higher with TEG (265 ml vs. 179 ml, but P=0.31); no effect of TEG on gastric step distention pressure to pain (P=0.81); possible carry-over effect in study design

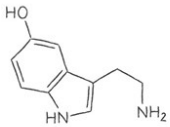
Nasr et al 2009[23]	22 patients with upper gut dysmotility (4M/18F, mean 37 ±12y.o.)	TEG 12 mg or erythromycin 125 mg I.V.	Open-label, XO	Single dose	Ambulatory 24-h antroduodenal manometry with 6-sensor solid state probe, quantification of pressure wave activity and motor patterns	TEG ↑motor activity in all 3 segments of upper gut (antrum, duodenum, jejunum vs. baseline, P<0.04 for each; TEG effect extended to 3rd hour of recording, peak between 120-180 min; motor pattern of "fed-response" with intermittent Type II, Phase III MMCs in 12 (55%) subjects	Motor response also increased with erythromycin; response higher in jejunum with TEG, occurred withing 2nd/3rd hr, higher in antrum (with 30 m) with erythromycin
Sabaté et al. 2008[30]	30 F IBS-C, 18-60 y.o.	TEG 6 mg BID or matched PBO	DB, PC, RCT	7d	Rectal balloon distention, RIII reflex measurement 3 min before distention (control), during continuous rectal distention, and 3-min post-distention	Rectal sensitivity: ↓ inhibitory effects on RIII reflex elicited by distentions significantly lower in TEG group (ANOVA p<0.0001)	No significant changes in volume-sensation or differences in compliance with TEG
Tack et al 2011[38]	30 FD patients (7M, 23F, 41.8 ±2.3 y.o.)	TEG 6 mg BID or matched PBO	DB, PC, RCT	5d	GE: 13C octanoic gastric emptying breath test with egg meal; Gastric barostat protocol assessing MDP, stepwise sequential ramp distentions +2mm Hg increments to discomfort/pain; mixed liquid meal (200 ml) and intragastric balloon measurements	Stomach: ↔ TEG effect on MDP (7.9 ±0.4 vs. 7.4 ±0.4 mm Hg), ↔ fasting gastric compliance (44 ± 10 vs 61 ± 6 mL mm Hg-1), ↔fasting thresholds for first perception (3.6 ± 0.4 vs 4.2 ± 0.2 mmHg above MDP), ↔ discomfort (9.9 ± 0.7 vs 10.5 ± 0.5 mmHg above MDP). ↔ intra-balloon volumes before and after the meal (respectively 146 ±14 vs 120 ± 11 and 297 ± 28 vs 283 ± 29 mL, each NS), ↔ amplitude of meal-induced gastric relaxation (151 ± 23 vs 162 ± 23 mL, NS).	In the subgroup with normal gastric emptying (n=22), TEG ↑meal-induced accommodation (126 ± 23 vs 175 ± 29 mL, P<0.001)

TEG: tegaserod; DB: double-blinded; DD: double dummy; PBO: placebo; PC: placebo-controlled, RCT: randomized controlled trial; XO: crossover design; HV: Healthy volunteer; Q: every; BID: twice a day; TCTT: total colon transit time; SCTT: segmental colon transit time; SBTT: small bowel transit time; IBS-C: Irritable bowel syndrome with constipation; F: female; M:male; ROM: radiopaque marker; GE: gastric emptying; OCT: orocecal transit; GC: geometric center; TLESRs: transient lower esophageal sphincter relaxations; LES: lower esophageal sphincter; AET: acid exposure time; RIII reflex: somatic, nociceptive, cutaneo-muscular flexion reflex; CBD: common bile duct; CHD: common hepatic duct; FD: functional dyspepsia; FH: functional heartburn; MDP: minimal intra-balloon distending pressure; NS: not significant; MMC: migrating motor complex; ↑: increased ↔: no change; ↓decreased; h: hour; d: day; w: week

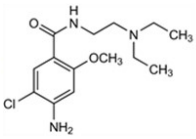
Supplementary table 2. Summary of placebo controlled tegaserod trials in conditions other than IBS

Study	Study population	Patients randomized	Treatment duration	Medication dose/day	Endpoints	Responder definition	Result
Johanson et al.[49]	Women and men with constipation	1384	12 wks	tegaserod 2 or 6 mg bid or placebo	Complete spontaneous bowel movements (CSBM) during the first 4 weeks CSBM response over 12 weeks	Increase of ≥1 CSBM/week compared with baseline	Responder rates week 1-4 were 43.2%, 41.2% 25.1% for the 6mg, 2mg and placebo groups Responder rates for week 1-12 were 44.8%, 40 and 26.9% respectively
Kamm et al.[50]	Women and men with constipation	1264	12 wks	tegaserod 2 or 6 mg bid or placebo	Complete spontaneous bowel movements (CSBM) during the first 4 weeks CSBM response over 12 weeks	Increase of ≥1 CSBM/week compared with baseline	Responder rates week 1-4 were 40.2%, 35.6% 26.7% for the 6mg, 2mg and placebo groups Responder rates for week 1-12 were 43.2%, 35 and 30.6% respectively
Tack et al.[52]	Functional dyspepsia with normal gastric emptying	271 (b.i.d; study) 247 (t.i.d. study)	6 wks	tegaserod 0.5, 2 or 6 mg or placebo b.i.d. or t.i.d.	Satisfactory relief of meal-related stomach symptoms, weekly binary question Daily diary of dyspeptic symptoms	Satisfactory relief of meal-related stomach symptoms during at least 50% of the weeks	No significant differences were observed The highest response rates were seen with tegaserod 6 mg b.i.d. and with tegaserod 2 mg t in female patients.
Tougas et al.[53]	Functional dyspepsia with delayed gastric emptying	163	6 wks	tegaserod 6 bid or 6 mg t.i.d. or 12 mg b.i.d. or placebo	Gastric retention at 4 hours of a scintigraphy emptying scan	Retention less than 6.3% at 4 hours	Tegaserod 6 mg t.i.d. was associated with 80% responder rate compared to 50% with placebo (statistically significant)
Vakil et al.[54]	Women with functional dyspepsia	Trial 1: 1360	6 wks	tegaserod 6 mg bid or placebo	Percentage of days with satisfactory relief of dyspepsia symptoms Composite average daily severity score for three cardinal dyspepsia symptoms	≥50% of days with satisfactory relief ≥1-point improvement from baseline for composite daily diary score	For satisfactory relief, Tegaserod was superior t placebo (32.2%vs 26.6%, P=0.0002) For composite daily diary score, tegaserod was superior to placebo (49.9%vs 41.9.6%, P=0.002
Vakil et al.[54]	Women with functional dyspepsia	Trial 2: 1307	6 wks	tegaserod 6 mg bid or placebo	Percentage of days with satisfactory relief of dyspepsia symptoms Composite average daily severity score for three cardinal dyspepsia symptoms	≥50% of days with satisfactory relief ≥1-point improvement from baseline for composite daily diary score	For satisfactory relief, Tegaserod was not super placebo (31.9% vs 29.4%, P=0.066). For composite daily diary score, tegaserod was superior to placebo (50.3% vs 45.8%, P=0.092)

5-Hydroxytryptamine



Metoclopramide



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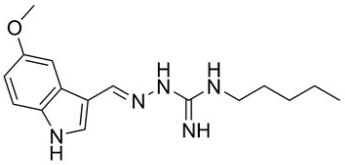

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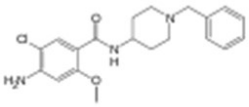

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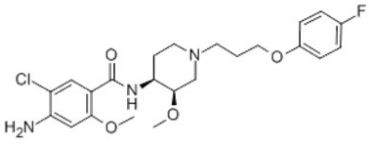

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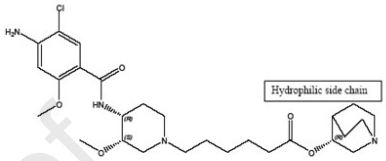

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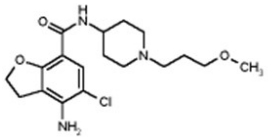

Velusetrag