FDA Briefing Document

JOINT MEETING OF THE GASTROINTESTINAL DRUGS ADVISORY COMMITTEE AND DRUG SAFETY and RISK MANAGEMENT ADVISORY COMMITTEES

October 17, 2018

The committees will discuss supplemental new drug application (sNDA) 021200, supplement 015, for ZELNORM (tegaserod maleate) tablets for oral administration, submitted by Sloan Pharma S.a.r.l, Bertrange, Cham Branch, proposed for the treatment of women with irritable bowel syndrome with constipation who do not have a history of cardiovascular ischemic disease, such as myocardial infarction, stroke, transient ischemic attack, or angina, and who do not have more than one risk factor for cardiovascular disease.

The attached package contains background information prepared by the U.S. Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring Zelnorm (tegaserod), intended for treatment of females with Irritable Bowel Syndrome – Constipation (IBS-C) who do not have a history of cardiovascular ischemic disease, such as myocardial infarction, stroke, transient ischemic attack, or angina, and who do not have more than one risk factor for cardiovascular disease, to this Advisory Committee to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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EXECUTIVE SUMMARY

This Advisory Committee (AC) meeting was requested by the Division of Gastroenterology and Inborn Errors Products (DGIEP) for the purposes of discussing the benefit/risk assessment of tegaserod given its potential cardiovascular (CV) risk, while considering a population or subpopulation of patients in which tegaserod's benefits would be expected to outweigh the risks. The indication proposed by the current Applicant (US WorldMeds, LLC as the authorized U.S. agent for Sloan Pharma, S.a.r.l.; hereafter referred to in this document as Sloan Pharma, or the 'Applicant') is for the treatment of females with irritable bowel syndrome (IBS) with constipation (IBS-C) who are at low CV risk. If reintroduced to the U.S. market, tegaserod would join several products that are approved in the U.S. for IBS-C, and its role as a 5-HT$_4$ agonist would present a product with a different mechanism of action for this disease from those already available.

Tegaserod is a 5-HT$_4$ receptor agonist that binds with high affinity at human 5-HT$_4$ receptors, and with moderate affinity for 5-HT$_1$ receptors. The activation of 5-HT$_4$ receptors in the gastrointestinal (GI) tract stimulates the peristaltic reflex and intestinal secretion, as well as inhibits visceral sensitivity [1]. Tegaserod was approved on July 24, 2002 for the short-term treatment of women with IBS whose primary bowel symptom is constipation (IBS-C); the safety and effectiveness have not been established in men with IBS-C. On August 21, 2004, tegaserod was approved for the treatment of patients under 65 years of age with chronic idiopathic constipation (CIC); the effectiveness has not been established in patients 65 years or older. In 2007, tegaserod was removed from the U.S. market by then-Sponsor Novartis, when a pooled analysis of 29 studies revealed an imbalance in CV ischemic adverse events (AEs) associated with tegaserod use. The search for CV ischemic (CVI) events originated from a request by Swiss Medic. While an imbalance in CV safety events associated with tegaserod was noted, the strength of the signal was difficult to interpret due to limitations of the meta-analysis – for example, the trials were not designed to specifically evaluate CV safety, were of short duration, included a low CV-risk population, and involved retrospective assessment of CV information. In addition, the etiology of CVI events related to the use of tegaserod is not well understood. Additionally, the results of studies assessing potential effects of tegaserod on platelet aggregation have not been consistent. Further, it is difficult to determine potential clinical characteristics that identify patients who may be at higher risk when using tegaserod given the small number of CV AEs. Of note, tegaserod is currently marketed in foreign markets including Mexico, Brazil, and Ecuador.

In 2005, the FDA requested that Novartis provide information on Suicidal Ideation and Behavior (SI/B) events that occurred in the premarketing tegaserod clinical trials, after a routine review of Adverse Event Reporting System (AERS) reports indicated a potential postmarketing signal for suicidal behaviors with tegaserod. An imbalance in the overall frequency of SI/B events associated with tegaserod use was noted. FDA issued a letter to Novartis on February 2, 2007 recommending the inclusion of language describing this potential risk in the Warnings and Precautions section of the tegaserod prescribing information (PI). This agreed-upon language was not incorporated into labeling at the time because the drug was removed from the market for

CV safety concerns. This language is proposed for inclusion in the proposed labeling by the current Applicant as a Warning and Precaution.

Since 2007, there have been meetings between FDA and Novartis, and more recently with the current Applicant, regarding the possible reintroduction of tegaserod to the U.S. market in a population of patients in which tegaserod's benefits would be expected to outweigh the potential risks. The Applicant proposes reintroduction of this product to the market in a restricted population of females with IBS-C less than 65 years of age, with proposed contraindications to include only patients who are considered to be at low CV risk; contraindicated patients include a history of CVI disease such as myocardial infarction, stroke, transient ischemic attack, or angina, and more than one CV risk factor, where risk factors include: hypertension, tobacco use, diabetes, hypercholesterolemia, , age ≥55 years, and obesity (defined as body mass index (BMI) >30 kg/m^2). Should it be necessary to further restrict the use of tegaserod in this subpopulation to patients with severely symptomatic IBS-C for the benefit to outweigh the potential CV risk, FDA requested the Applicant conduct a post hoc efficacy analysis in a subpopulation of IBS-C patients that may be characterized as severely symptomatic.

This supplemental application includes data from a pooled analysis of 29 placebo-controlled trials across multiple indications, doses, and in trials of duration ≥4 weeks (referred to as the database 'Db15') as the primary basis to support reintroduction and labeling. The safety review also includes results from a noninterventional epidemiologic study [2] conducted to further characterize potential CV safety concerns. The FDA is not asking the Advisory Committee to reanalyze the efficacy of tegaserod for the treatment of IBS-C for which tegaserod is approved. The efficacy and safety data submitted to support the original approval of the product in IBS-C stand. All additional analyses conducted to inform benefit/risk in a potential reintroduction population are post hoc and exploratory. Given the potential for reintroduction of tegaserod in various subpopulations of interest, elucidating the benefits and risks in the presence of a potential CV and SI/B safety signal is of particular clinical importance, as patients with IBS-C may have need for additional treatment options but may also be at risk of AEs.

DRAFT POINTS TO CONSIDER

The Division requests that you consider the following points when reviewing the briefing documents for this AC meeting:

1. The strength of the CV safety signal overall, and among the patient population that is being proposed for reintroduction (females with IBS-C and low CV risk).

2. Consideration of the safety data and the potential need to further restrict the use of tegaserod to female patients with severely symptomatic IBS-C.

3. An assessment of the benefit-risk issues when considering reintroducing tegaserod to the U.S. market after being withdrawn for a CV safety concern. FDA would like to obtain the Advisory Committee's assessment of the benefits and strength of the potential risks

associated with tegaserod and whether the benefit-risk profile of tegaserod would be more favorable in a restricted population with IBS-C.

4. Consideration of the psychiatric safety AEs of completed suicide and suicidal ideation.

1. INTRODUCTION

The Applicant submitted a supplemental new drug application (NDA) 21200/S-015 for tegaserod tablets for oral use on February 26, 2018 to the Division of Gastroenterology and Inborn Errors Products (DGIEP). The proposed indication is the treatment of adult women under 65 years of age with irritable bowel syndrome (IBS) with constipation (IBS-C) in a population at low CV risk (see contraindications below).

Tegaserod was originally approved on July 24, 2002 for the short-term treatment of women with IBS-C, and on August 21, 2004 for the treatment of patients under 65 years of age with chronic idiopathic constipation (CIC). In 2007, tegaserod was withdrawn from the U.S. market due to an imbalance in CV AEs occurring with tegaserod that had not been previously identified. If reintroduced, this product would represent another treatment option for patients with IBS-C with a different mechanism of action for this disease, a serotonin type 4 (5-HT$_4$) receptor agonist.

Serotonin has been shown to be involved in regulating motility, visceral sensitivity, and intestinal secretion. Investigations suggest an important role of 5-HT$_4$ receptors in the maintenance of gastrointestinal (GI) functions in humans. 5-HT$_4$ receptor mRNA has been found throughout the human GI tract [1]. The activation of 5-HT$_4$ receptors in the GI tract stimulates the peristaltic reflex and intestinal secretion, as well as inhibits visceral sensitivity.

The Applicant's proposed labeling for tegaserod treatment of adult females under 65 years of age with IBS-C includes the following contraindications related to CV safety:
- A history of CV ischemic disease, such as myocardial infarction (MI), stroke, transient ischemic attack, or angina
- More than one CV risk factor: hypertension, tobacco use, diabetes, hypercholesterolemia, age ≥55 years, and obesity

The proposed labeling also includes a Warning and Precaution for Major Adverse CV Events (MACE), including cardiovascular death, myocardial infarction (MI), and stroke: "Evaluate cardiovascular risk factors. Monitor patients and discontinue ZELNORM for development of ischemic cardiovascular disease and discontinue ZELNORM if evidence of cardiovascular disease develops during treatment." In addition, there is a Warning and Precaution for Suicidal Ideation and Behavior (SI/B).

Given the potential for reintroduction of tegaserod in various subpopulations of interest, and in the presence of a potential CV and SI/B safety signal, DGIEP has requested this Advisory Committee (AC) meeting to aid in elucidating the benefit versus the risks of tegaserod 6 mg BID in: 1) females with IBS-C; 2) females with IBS-C at low CV risk; and/or 3) a severely symptomatic IBS-C female population regardless of underlying CV risk.

2. BACKGROUND

2.1. Condition of Interest

Irritable bowel syndrome is a functional GI disorder characterized by recurrent abdominal pain and change in bowel habits. Additionally, clinical manifestations may include cramping, bloating, abdominal distension, flatulence, mucus in stool, urgency for bowel movements, and tenesmus [3]. It is classified into four subtypes depending on the predominant change in bowel habits; IBS-C, diarrhea (IBS-D), mixed (IBS-M), or unclassified.

The worldwide prevalence of IBS is 11.2% (95% confidence interval (CI): 9.8, 12.8) based on a meta-analysis of 80 studies [4]. The prevalence varied according to country and diagnostic criteria. Among 10 North American studies, the pooled prevalence of IBS was 11.8% (95% CI: 7.4, 17.2) [4]. In this same meta-analysis, the prevalence of IBS was higher for women than men (odds ratio (OR)=1.67; 95% CI: 1.53, 1.82) and lower for individuals >50 years of age, compared with those <50 years of age (OR=0.75; 95% CI: 0.62, 0.92). The prevalence of IBS-C among the IBS subtypes was 35% [4].

The pathophysiology of IBS is not definitively known. It is multifactorial and underlying causes may vary for different patients. Traditionally, IBS was thought to be primarily due to visceral hypersensitivity and gastrointestinal motor disturbances. More recently, there is increasing evidence for the contributing factors of infection, immune activation, serotonin dysregulation, bacterial overgrowth, central dysregulation and brain-gut interaction, and genetics [5]. Studies have shown that chronic stress is associated with the onset and exacerbation of symptoms of IBS. Although findings vary among studies, IBS patients show stress-induced alterations in gastrointestinal motility, rectal perception, autonomic tone, and hypothalamic-pituitary-adrenal axis responses [6].

The diagnosis of IBS is based on the Rome IV criteria [7]. These criteria are defined as recurrent abdominal pain on average at least one day per week in the last 3 months, associated with two or more of the following criteria: 1. Related to defecation. 2. Associated with a change in frequency of stool. 3. Associated with a change in form (appearance) of stool. Criteria must be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis. Diagnostic criteria for IBS-C are > ¼ (25%) of bowel movements with Bristol stool types 1 or 2 and < ¼ (25%) of bowel movements with Bristol stool types 6 or 7.

Although clinical presentations vary, many patients with IBS have chronic symptoms with fluctuating severity and episodic flares. Some patients with IBS tolerate their symptoms well with minimal impairment in daily functioning, while other patients have symptoms that prevent them from working or participating in usual activities. IBS can impact quality of life and has both predictable and unpredictable triggers.

2.2. Key Regulatory History

Key regulatory history leading up to the tegaserod marketing withdrawal is summarized:

- In 2006, prompted by a prior FDA request to Novartis for ischemic colitis event data in tegaserod clinical trials, the Swiss regulatory authority requested Novartis to conduct a search for potential CV ischemic signals.
- On February 22, 2007, the FDA was notified by Novartis that a preliminary, retrospective analysis of pooled clinical trial data suggested an imbalance in CV ischemic adverse events with tegaserod that had not been previously identified.[1]
- On March 9, 2007, Novartis provided a comprehensive analysis "A Retrospective Initial Analysis for Coronary Ischemic Adverse Events" of 29 short-term (4 to 12 weeks' duration) placebo-controlled clinical trials involving 18,645 patients (11,614 on tegaserod versus 7,031 on placebo) with several GI disorders.
- On March 15, 2007, a Type A meeting was held with Novartis to discuss the findings from their pooled analysis.[2] At this meeting, Novartis expressed their intent to conduct additional external adjudication of the cases with more complete source information and baseline CV disease severity of patients, and their plans to conduct an epidemiological study. Novartis was notified by the FDA at this meeting that an internal center director briefing was planned on March 27, 2007, to discuss the risk assessment and a possible safety communication plan to the public. On March 23, 2007, Novartis submitted the results of the 1st external adjudication of suspect cases by a panel of experts (Mt. Sinai Medical Center, NY) via email, and subsequently as an official correspondence on April 11, 2007.
- On March 27, 2007, a center-level briefing to discuss tegaserod's CV risk assessment was held and in a follow-up meeting with Novartis on March 28, 2007, FDA asked Novartis to voluntarily remove tegaserod from the market as FDA believed that the product was unsafe for use under the conditions of use upon which it was originally approved.[3]
- On March 29, 2007, Novartis confirmed immediate suspension of tegaserod marketing and sales.
- Of note, discussions regarding a potential risk of SI/B with tegaserod treatment were held with Novartis after the FDA received and reviewed postmarketing reports of suicide and self-injurious behaviors including suicidal ideation, attempted suicide, and completed suicide in patients taking tegaserod. Information requests were sent for additional analyses and a meeting with Novartis was held on November 6, 2006.[4] Subsequently, on February 2, 2007, FDA recommended a supplement to incorporate language regarding SI/B in the Precautions section of the labeling.[5] Labeling language pertaining to SI/B was not incorporated prior to the drug being withdrawn from the market.

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[1] NDA 21-200 (SDN 189), General Correspondence dated 02/22/2007
[2] NDA 21-200, meeting minutes dated 04/13/2007
[3] Meeting minutes 07/13/2007- Emergency meeting to discuss safety concerns
[4] Type C- Post-marketing Adverse Event Reports, meeting minutes dated 11/29/2006
[5] NDA 21200- CBE-30 supplement request letter issued 02/02/2007

Key regulatory history after tegaserod withdrawal from the U.S. market is summarized:

- During an emergency safety meeting held on March 28, 2007 between FDA and Novartis, it was agreed that after the market withdrawal of tegaserod, FDA would continue to work with Novartis to identify an appropriate target population in whom the benefits of tegaserod use may outweigh the risks. FDA also noted at the time that important aspects of reintroduction, if pursued, would need to be discussed before an AC.

- Soon after withdrawal, an expanded access program began in 2007.

- A 2nd external adjudication report dated February 1, 2008 (conducted by Duke Clinical Research Institute, DCRI) was released by Novartis following the marketing withdrawal of tegaserod. This analysis included additional information in an attempt for more complete documentation of events, timing, co-administered drugs, and any significant studies to diagnose CV ischemia.

- On November 16-17, 2011, a Gastrointestinal Drugs Advisory Committee (GIDAC) meeting took place. The GIDAC discussed potential recommendations on the design and size of premarketing CV safety development programs necessary to support approval of drugs in the 5-HT$_4$ receptor agonists class for indications related to CIC, IBS-C, or other GI disorders. High level data available to the public were presented for tegaserod because Novartis was not in attendance and did not submit a background document. The panel in general voiced concerns about potential CV risks, yet most members did not feel the need for dedicated CV outcome trials as opposed to evaluating risk in adequately designed phase 3 clinical trials [8]. They could not discuss the strength of the signal from the tegaserod data presented because of the lack of detailed information. They expected to have any new NDAs in this class brought before the GIDAC to further evaluate the strength of the potential signal of CV risk, including tegaserod, if it was proposed for reintroduction to the U.S. market.

- The IND for tegaserod was transferred to Sloan Pharma effective November 24, 2015.

After the market withdrawal of tegaserod, several important meetings took place between FDA and Novartis, and more recently with US World Meds, LLC as the authorized U.S. agent for the Applicant regarding potential reintroduction of tegaserod to the U.S. market. Some of the key discussions and agreements from these meetings are summarized:

- FDA recommended that Novartis focus their reintroduction efforts on the IBS-C indication.
- FDA concurred with Novartis that the database Db15, which consists of 29 placebo-controlled trials, would be the primary database for safety evaluation. Novartis would include additional safety evidence in the form of epidemiological study findings, and in vitro and in vivo platelet aggregation studies (including the major tegaserod metabolite, 5-methoxyindole-3-carboxylic acid glucuronide, or M29).
- In response to a proposal from Novartis for identifying a subgroup with optimized benefit for IBS-C, the FDA recommended that only the 12-week preapproval trials (B301, B351,

and B358) should be used for the primary efficacy analysis using the 12-week data. Any efficacy analysis of this subgroup from the 4-week postapproval trials (A2306, A2417) should be used only to support the preapproval results.

- In subsequent meetings with the Applicant, FDA concurred that an AC meeting would be necessary, the scope of which would include presentation and evaluation of the appropriate patient populations for whom the benefits of the tegaserod are expected to outweigh the risk or residual uncertainty of risk.

- The Applicant was requested to submit additional information for the pooled clinical trial dataset Db15 including baseline/demographic characteristics including CV risk factors, subject disposition, ECGs, lab tests, and other available documentation for patients with CV events, SAEs, and/or death. The Applicant was also requested to submit adjudication datasets and methods.

- FDA noted that the appropriate population for possible reintroduction of tegaserod to the market, as well as the need for additional studies in such subgroups, would be made following the AC meeting.

- FDA also noted to the Applicant that the advice of the Advisory Committee was necessary to determine whether a risk evaluation and mitigation strategy would be necessary to ensure that the benefits of the drug outweigh the risks, and if necessary the required elements of the risk evaluation and mitigation strategy would be determined after the AC meeting.

- Some of the key agreements between FDA and the Applicant at these meetings included acceptability of the proposed safety database Db15 consisting of 29 placebo-controlled trials of ≥4 weeks' duration, and the definition of a "low CV risk" population, defined as those patients under 65 years old and with zero or one CV risk factors, where risk factors include history of CV disease, active smoking, hypertension, hyperlipidemia, diabetes mellitus, age ≥55 years, and obesity).

- The Applicant was asked to define a population of severely symptomatic IBS-C patients, where the benefit of using tegaserod outweighs the potential CV risk; efficacy analyses similar to the efficacy analyses requested for the low CV risk population, were also requested.

- The Applicant proposed several definitions of the severely symptomatic population, initially focusing primarily on abdominal pain, and later focusing on abdominal pain and abnormal bowel movement frequency. The FDA expressed concerns with the proposed severely symptomatic definitions, including the anchor-based analyses, in a General Advice Letter dated October 23, 2017. There was no final agreement on the severely symptomatic definition prior to submission of this efficacy supplement. This submission included statistical justification and response to the FDA General Advice Letter, dated October 24, 2017.

- FDA agreed that the proposed primary, secondary, and exploratory efficacy endpoints appeared acceptable in both the low CV risk and severely symptomatic subpopulations.

- FDA recommended that in addition to the individual datasets for the key efficacy studies B301, B351, B358, A2306, and A2417, the Applicant also submit efficacy datasets at subject level for study B307.

On February 26, 2018, the Applicant submitted a supplemental NDA for the reintroduction of tegaserod to the U.S. market.

2.3. Currently Approved Therapies for Irritable Bowel Syndrome - Constipation

Treatment for IBS focuses on symptom relief which may involve dietary and lifestyle modification and/or pharmacologic agents. Depending on the severity of symptoms and response, patients often try a variety of treatments alone or in combination. Nonpharmacologic treatment interventions include dietary modification to increase fiber intake, avoiding gluten, lactose, or gas-producing foods, or following a special eating plan called the low fermentable oligo-, di-, and monosaccharides and polyols (FODMAP) diet [9]. The term FODMAP refers to poorly absorbed short-chain carbohydrates that are naturally present in many foods and pass unabsorbed to the colon where they increase luminal water through osmotic activity and induce gas production due to fermentation by colonic bacteria [10]. Lifestyle modifications, including stress relief and increased exercise and sleep, can also alleviate symptoms. Other therapies include biofeedback and acupuncture.

Pharmacologic treatments are tailored to the subtype of IBS. For IBS-C, over-the-counter (OTC) fiber supplements, laxatives, or enemas may provide relief. Three treatments have been approved by FDA for IBS-C, and since the withdrawal of tegaserod from the U.S. market, summarized in Table 1 below: lubiprostone (Amitiza), linaclotide (Linzess), and plecanatide (Trulance). Lubiprostone is a chloride channel activator which increases intestinal fluid secretion, resulting in increased motility in the intestine [11]. Linaclotide is a guanylate cyclase-C agonist which results in increased intestinal fluid and accelerated transit [12]. Plecanatide is also a guanylate cyclase-C agonist, and was recently approved for use in IBS-C in 2018 [13].

Table 1: Current FDA-Approved Treatments for IBS-C

Product NDA	Relevant Indication	Mechanism of Action	Year of Approval	Dosing/Administration	Contraindications and Common AEs.
Lubiprostone (Amitiza) 021908	CIC in adults IBS-C in women ≥18 years old OIC in adults with chronic non-cancer pain	Chloride channel activator	CIC: 2006 IBS-C: 2008 OIC: 2013	Oral: CIC: 24 mcg BID OIC: 24 mcg BID IBS-C: 8 mcg BID	Contraindication: known or suspected mechanical GI obstruction Common AEs: diarrhea, nausea, and abdominal pain
Linaclotide (Linzess) 202811	CIC and IBS-C in adults	Guanylate cyclase-C agonist	2012	Oral: IBS-C: 290 mcg QD CIC: 145 mcg QD	Contraindications: pediatric patients <6 years of age due to risk of serious dehydration; patients with known or suspected mechanical GI obstruction. Common AEs: diarrhea, abdominal pain, flatulence and abdominal distension.
Plecanatide (Trulance) 208745	CIC and IBS-C in adults	Guanylate cyclase-C agonist	CIC: 2017 IBS-C: 2018	Oral: CIC: 3mg QD IBS-C: 3 mg QD	Contraindications: Patients less than 6 years of age due to the risk of serious dehydration; patients with known or suspected mechanical gastrointestinal obstruction. Common AEs: diarrhea

Source: Reviewer's Table adapted from Dr. Omolara Adewuni's clinical review of plecanatide, dated 1/15/2018, in DARRTS and [14].
Abbreviations: IBS-C, Irritable bowel syndrome with constipation; CIC, chronic idiopathic constipation, OIC, opioid-induced constipation; BID, twice a day; QD, once a day

Additional pharmacologic agents that may provide improvement in symptoms in patients with IBS include tricyclic antidepressants, selective serotonin reuptake inhibitors, and antispasmodics. These agents are not currently approved by the FDA for the treatment of IBS. Although efficacy is not definitively established, the American Gastroenterological Association (AGA) conditionally recommends using tricyclic antidepressants and antispasmodics over no drug treatment in patients with IBS based on low-quality evidence. The AGA conditionally recommends against using selective serotonin reuptake inhibitors for patients with IBS, also based on low-quality evidence in the 2014 Guideline on the Pharmacological Management [15]. IBS treatment is individualized with guidance from a physician and sometimes a dietitian.

3. EFFICACY

3.1. Review Strategy and Overview of the Clinical Development Program for IBS-C

The efficacy review focused on the data submitted to support the reintroduction of tegaserod to the U.S. market in female patients with IBS-C in various subpopulations; the review team did not reanalyze the original data that supported approval or question the original efficacy. The review team aimed to determine if the efficacy demonstrated in the original patient population that supported approval of tegaserod was comparable in a subpopulation of severely symptomatic females with IBS-C (see Section 3.2 Phase 3 Trial Designs for definition of this subpopulation). The efficacy review strategy is based on post hoc analyses of completed trials in patients with IBS-C, using the subpopulation of severely symptomatic female patients to evaluate the magnitude of benefit achievable and focus on a target population that may have a favorable benefit risk profile. The need to possibly restrict use of tegaserod to this subpopulation based on the safety profile will be discussed at the AC Meeting.

We reviewed efficacy data for all female patients in this subpopulation from the three original trials supporting approval, Trials B301, B358, and B307, as well as Trial B351, which was considered exploratory at the time of the original approval. While the three trials defined response of the overall IBS relief in Subject's Global Assessment (SGA) as the only primary endpoint, Trial B351 defined the response in SGA of abdominal discomfort/pain as an additional co-primary endpoint. Although this trial was not relied on for the determination of efficacy in the original approval, the team included Trial B351 to support the reintroduction to the market because the same endpoints are now being evaluated in a post hoc nature for all IBS-C trials and there did not appear to be any data integrity concerns that would preclude including data from Trial B351 in these analyses.

The Applicant also submitted trial data from two postmarketing requirements, Trial A2306 and Trial A2417. The data from these trials were analyzed separately for consideration of efficacy but were deemed not appropriate to be included in the analyses of the severely symptomatic subpopulation. Trial A2306 had a re-treatment design with 4 weeks of treatment, 2 to 12 weeks' treatment free until recurrence of symptoms, and then 4 weeks of re-treatment. Trial A2417 only had a 4-week treatment duration. Four-week treatment is of insufficient duration for a therapy that will likely be used long-term for IBS, which is a chronic condition. Trial A2417 did not limit enrollment to patients with IBS-C and also included patients with IBS with mixed bowel habit. Because of these unique trial designs and patient populations, Trials A2306 and A2417 were analyzed separately and considered supplemental to the focus of this efficacy review in the severely symptomatic subpopulation.

In the following sections, we discuss the primary endpoint used in the analysis and provide an overview of the results that supported the original approval. We continue with a description of the selection criteria for inclusion into the subset of severely symptomatic female IBS-C patients included in the analyses, and comment on the strengths and weakness of the various subpopulations. It is important to note that the Division's approach to the evaluation of efficacy in clinical trials of products for the treatment of IBS-C has evolved since the original tegaserod

approval; however, no new trials were conducted to support reintroduction to the market. Therefore, the review team considered the endpoints, types of data, and methods of data collection that were used in the original trials to identify the strengths and limitations of the analyses being conducted to support reintroduction to the market.

3.2. Phase 3 Trial Designs

The three phase 3 randomized, double-blind, placebo-controlled, multicenter trials to assess efficacy and safety that supported the approval of tegaserod in July 2002 were B301, B358, and B307. The trial design for all three trials was generally similar and consisted of a 4-week baseline period followed by a 12-week double-blind treatment period; Trial B358 had an additional 1-month withdrawal period to allow assessment of any change in IBS symptoms after completing the treatment period. Although there were differences in the doses evaluated in the trials, all of the trials included a 6 mg BID dose, the dose originally approved in 2002 for the treatment of IBS-C. Trial B301 evaluated tegaserod 2 mg PO BID and 6 mg PO BID in males and females, and Trial B358 evaluated tegaserod 6 mg PO BID in females only. Trial B307 evaluated 2 mg PO BID fixed dose and a dose titration regimen (2 mg PO BID for 4 weeks, titrated to 6 mg PO BID for 8 weeks, based on subject response) in males and females.[6] However, this review only discusses data for tegaserod 6 mg BID, as that was the FDA approved dose in 2002, and reintroduction to the market would include the same dose and duration as previously approved.

Trial B351 was designed similarly to trial B301 with the same treatment arms and 12-week treatment duration, but with a different primary endpoint as mentioned below.

Trials B301, B358, and B307 included 2,470 women with at least a 3-month history of IBS symptoms prior to the study baseline period that included abdominal pain, bloating and constipation who received either tegaserod 6 mg PO BID or placebo. Trial B351 included 469 women with at least a 3-month history of IBS symptoms who received either tegaserod 6 mg PO BID or placebo. In all patients, constipation was characterized by at least two of the following three symptoms, each occurring ≥25% of the time over a 3-month period: less than three bowel movements/week, hard or lumpy stools, or straining with a bowel movement [16].

3.2.1. Original Primary Endpoint

In Trials B301, B358, and B307, during each week of the 4-week baseline period and the 12-week treatment period, patients were asked the following question, known as the Subject Global Assessment (SGA) of Relief: "Please consider how you felt this past week in regard to your IBS, in particular your overall well-being, and symptoms of abdominal discomfort, pain and altered bowel habit. Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms during the past week?" The response options consisted of the

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[6] Applicant's submission, dated 2/26/2018, Summary of Clinical Efficacy, Module 2.7.3, page 8.

following five categories: completely relieved, considerably relieved, somewhat relieved, unchanged, or worse. The original primary endpoint was response in overall IBS relief in SGA using the 50%/100% rule over SGA scores at endpoint, i.e. the last 4 weeks of treatment (last 4 available weeks or all the weeks if ≤4 weeks were available).

A responder to the overall IBS relief was defined as:
   a. At least 50% of the SGAs at endpoint with complete or considerable relief OR all of the SGAs (100%) at endpoint with at least somewhat relief (i.e., complete, considerable, or somewhat) (50%/100% rule of the last 4 weeks);
   b. Number of days with laxative* use during treatment period ≤5 and no laxative* use during the last 28 days of treatment (* with the exception of bulk-forming laxatives);
   c. Duration of exposure to study medication ≥28 days;
   d. At least one post baseline SGA of relief.

The above primary endpoint was the same for Trials B301, B307, and B358, and was used as a post hoc analysis for Trial B351. Initially, Trial B351 had co-primary endpoints of the original SGA of relief (complete or considerable relief ≥50% of the time at endpoint without the option for complete, considerable, or somewhat relief for 100% of the time at endpoint) and SGA of abdominal discomfort/pain (≥20 mm and ≥40% reduction in mean visual analog scale [17]) at endpoint compared with baseline, mean of the last 4 weekly SGA values during the baseline period).

Results of the Primary Efficacy Analyses from Original Approval

As shown in Table 2 below, the treatment difference in Trial B301 between tegaserod 12 mg and placebo was 11.4% in Trial B301 and this difference was statistically significant. The treatment differences in Trial B307 and Trial B358 were 5.3% and 4.7%, respectively: and these differences were not statistically significant at a two-sided level of 0.05. Note that the results shown for Trial B351 are a reanalysis with a new primary endpoint as discussed above. Trial B351 was not included in the original label. Trials B301, B307, B351, and B358 are the same as trials A0301, A0307, A0351, and A0358, respectively.

Table 2: Proportion of Overall IBS Relief Responders During Month 3 from Trials Supporting Original Approval in Female Population

Study	Tegaserod 12 mg (N=1478) n/m (%)	Placebo (N=1461) n/m (%)	Percent Difference in Response* (95% CI)
Study B301	95 / 244 (39)	66 / 240 (28)	11.4 (3, 20)
Study B307	100 / 233 (43)	88 / 234 (38)	5.3 (-4, 14)
Study B358	334 / 767 (44)	292 / 752 (39)	4.7 (0, 10)
Study B351**	111 / 234 (47)	78 / 235 (33)	14.2 (6, 23)

Source: Adapted from Applicant's Table 5.110.2 of IR response dated 6/15/2018
Abbreviations: CI, confidence interval
* Note that the results for Studies B301, 307 and 358 are as presented in the currently approved label.
** Note that Study B351 results shown are reanalysis with new primary endpoint discussed above and not included in the original labeling for Zelnorm.

3.2.2. Defining the Severely Symptomatic IBS-C Subpopulation

During discussions between the FDA and the Applicant on reintroduction (October 4, 2016), the Applicant was asked to define a subpopulation of severely symptomatic IBS-C patients for whom the benefit of tegaserod may outweigh the potential CV risk. This subpopulation was used for reanalysis of the original efficacy data that supported approval. We are not aware of widely accepted clinical criteria, clinical guidelines, or literature to define a severely symptomatic IBS-C population. During meetings with the FDA, the Applicant proposed several definitions that have evolved with the Agency's guidance. The initial definition for severely symptomatic IBS-C focused primarily on abdominal pain. This definition evolved to include both abdominal pain and constipation symptoms (stool consistency and frequency).

Although there was extensive discussion and evolution of the proposed severely symptomatic IBS-C definition, there was no final agreement reached on the specific criteria that would define the severely symptomatic subpopulation prior to submission of this efficacy supplement. The Applicant's proposed definition for the severely symptomatic population in this efficacy supplement is as follows:

Female patients with IBS-C reporting:

- 3 or more days per week with severe or very severe abdominal pain and discomfort; AND
- 5 or more days per week with hard, very hard, or no stools.
- No history of major adverse cardiac events

In the meeting on March 15, 2017, the FDA requested that the Applicant consider limiting tegaserod use to patients with severe IBS-C who have not previously experienced a major adverse CV event. Upon further consideration during the review of this application, the team decided that CV risk should not influence the efficacy of the drug. Based on the goal of reviewing data on *all* severely symptomatic IBS-C patients, the Applicant was asked to remove

this criterion from the definition, which resulted in the following definition for the severely symptomatic population for the subsequent analyses:

Female patients with IBS-C reporting:

- 3 or more days per week with severe or very severe abdominal pain and discomfort; AND
- 5 or more days per week with hard, very hard, or no stools.

3.2.2.1. Methodology for Assessing Number of Days With Severe Symptoms

Methods to interpret the two criteria listed above can be varied because calculation of the average number of days per week does not result in an integer in most cases. The Applicant applied a ceiling method to round up the values of the two criteria for the selection of the severely symptomatic population. However, applying different rounding methods to determine which patients met the criteria resulted in subpopulations of varying severity. Therefore, the review team considered three rounding approaches: no rounding, ceiling rounding, and 0.5 rounding methods, to define the subpopulation. For example, the proposed definition of the severely symptomatic population requires 3 or more days per week with severe or very severe abdominal pain and discomfort. In the ceiling method, a patient with an average of 2.1 days per week of severe or very severe abdominal pain and discomfort would qualify because the ceiling method rounds 2.1 to 3 days per week. The ceiling rounding method is the most permissive method and allows patients with an average of more than 2 days per week with severe or very severe abdominal pain and discomfort, and an average of more than 4 days per week with hard, very hard, or no stools, to be included in the analysis set. The no rounding method requires a patient to meet the criteria exactly as defined above.

Table 3 below shows that the sample size for the severely symptomatic female population is almost twice as large with the ceiling rounding compared with no rounding as a method to classify a patient to severely symptomatic population.

Table 3: Sample Sizes for Severely Symptomatic Female Populations Based on Different Rounding Methods

Rounding Method	Study 301	Study 307	Study 351	Study 358
Ceiling (Applicant's method)	135	121	140	638
0.5 rounding	115	101	111	477
No rounding	74	70	87	346
Original approval sample size	484	467	469	1519

Source: Reviewer's (Dr. Ling Lan's) analysis

The sample sizes with the ceiling, 0.5 rounding, and no rounding methods were considered when interpreting the results of the exploratory efficacy analyses using each of the sample sizes, and will be discussed later in this document.

3.3. Patient Demographic and Baseline Characteristics of the Severely Symptomatic Subpopulation

To assess the appropriateness of the criteria used to define the severely symptomatic subpopulation, we reviewed the demographics and baseline disease characteristics of the severely symptomatic population. The original population had similar demographics to the severely symptomatic population, as discussed below.

Table 4 below shows the demographics of the severely symptomatic IBS-C population, females only, no rounding for data selection for the four premarket trials. The baseline demographics were generally similar among the trials for age, BMI, and race except for Trial B301 in which 97% subjects were white and no subject was of African descent. Patients in Trial B301 were predominantly from non-U.S. countries, while patients in Trials B351, B358, and B307 were predominately from the U.S. The severely symptomatic populations determined by 0.5 rounding and ceiling methods had similar results in baseline demographics as compared to the no rounding method. In general, the baseline demographics were comparable between the drug and placebo arms within the severely symptomatic population in each of the trials.

Table 4: Demographics of the Severely Symptomatic IBS-C Population, Females Only, No Rounding

Demographics	Trial B301 N=74	Trial B351 N=87	B358 N=346	Trial B307 N=70
Age, years				
Mean (SD)	41.5 (12.2)	43.7 (12.8)	40.2 (10.6)	43.3 (13.5)
Median (min, max)	41.0 (17, 67)	43.0 (20, 81)	40.0 (18, 68)	43.0 (19, 83)
Age category, n (%)				
<55 years	63 (85.1%)	70 (80.5%)	315 (91.0%)	59 (84.3%)
55 to <65 years	8 (10.8%)	10 (11.5%)	27 (7.8%)	6 (8.6%)
BMI, kg/m²				
Mean (SD)	24.2 (4.4)	25.5 (5.1)	25.5 (5.2)	25.1 (4.9)
Race, n (%)				
White	72 (97.3%)	77 (88.5%)	273 (78.9%)	60 (85.7%)
Black	0	8 (9.2%)	53 (15.3%)	5 (7.1%)
Other	2 (2.7%)	2 (2.3%)	20 (5.8%)	5 (7.1%)
Country/region				
U.S.	3 (4.1%)	85 (97.7%)	346 (100%)	61 (87.1%)
Non-U.S.	71 (95.9%)	2 (2.3%)	0	9 (12.9%)

Source: Adapted from Applicant's submission, response to Information Request received 7/9/2018
Abbreviations: BMI, body mass index; SD, standard deviation

3.3.1. Baseline Characteristics of the Severely Symptomatic Population Based on Various Rounding Methods

3.3.1.1. SGA of Severe or Very Severe Abdominal Pain/Discomfort:

All patients had ≥3 days per week with severe or very severe abdominal pain and discomfort, as per the criteria used by the Applicant to define the severely symptomatic population. However,

as shown below in Table 5, the majority of patients in all trials were reported to have ≥4 days per week with severe or very severe abdominal pain and discomfort, indicating that patients experienced abdominal pain on most days of the week. Severe or very severe abdominal pain was defined as a score of four or five on a six-point scale (0 to 5) for Trials B301, B307, and B351, and five or six on a seven-point scale (0 to 6) for Trial B358.

Table 5: Percentage of Patients With Average Number of Days Per Week With Severe or Very Severe Abdominal Pain at Baseline ≥4, n (%) (No Rounding)

Trial	Tegaserod 6 mg BID	Placebo	Total
B301	22 (64.7%)	25 (62.5%)	47 (63.5%)
B351	26 (70.3%)	36 (72.0%)	62 (71.3%)
B358	132 (73.7%)	111 (66.5%)	243 (70.2%)
B307	27 (64.3%)	19 (67.9%)	46 (65.7%)

Source: Applicant's submission, response to Information Request received 7/9/2018
Abbreviations: BID, twice daily

Figure 1 below provides a graphical representation of the distribution of number of days per week patients with severe abdominal pain at baseline in three severely symptomatic populations (no rounding, ceiling rounding, and 0.5 rounding methods). Of note, the mean number of days per week with severe abdominal pain reported by patients at baseline in the severely symptomatic population is 4 days or above, and the median is greater than approximately 3.5 days. This suggests that the patient data used to assess the clinical benefit of tegaserod in a severely symptomatic patient population likely reflected patients who have severe clinical symptoms of IBS-C, particularly for abdominal pain.

Figure 1: Number of Days Per Week with Severe Abdominal Pain/Discomfort at Baseline in Severely Symptomatic Female Populations
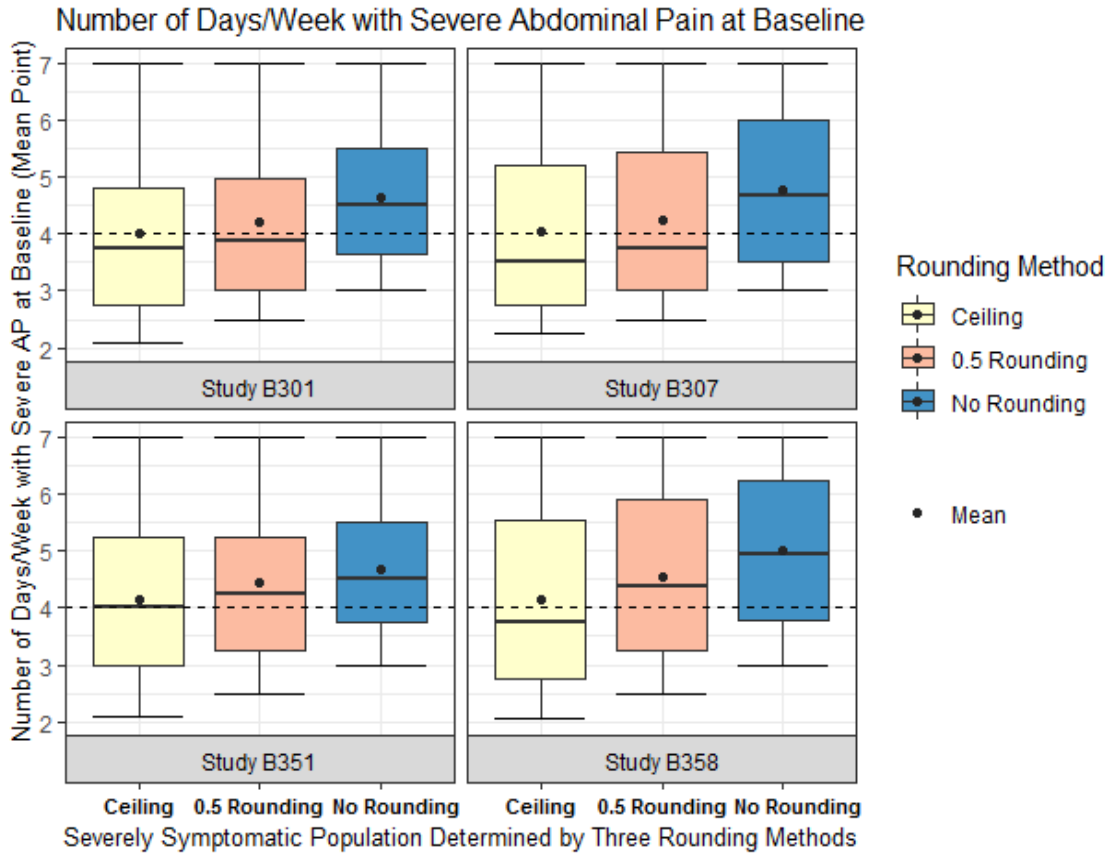
Source: Reviewer's plot, created using Applicant's data submitted on 7/9/2018 in response to Information Request.

3.3.1.2. Days with Hard, Very Hard, or No Stools:

The second component of the Applicant's proposed definition for the severely symptomatic population is 5 or more days per week with hard, very hard, or no stools. Review of the baseline characteristics shows that most patients had <3 days per week with hard or very hard stools at baseline (approximately 81.4% to 94.5% across the four trials); however, review of the data revealed that at baseline most patients reported no stools, rather than hard or very hard stools. Table 6 below shows that most patients had ≥4 days per week with no stools and some patients reported ≥5 days per week with no stools. This appears to suggest that the patient data used to assess the clinical benefit of tegaserod in a severely symptomatic patient population using the no rounding method likely reflect patients who have severe clinical symptoms of IBS-C.

Table 6: Percentage of Patients With Average Number of Days Per Week With No Stools, (No Rounding)

Trial Number of days	Tegaserod 6 mg BID n (%)	Placebo n (%)	Total n (%)
B301			
≥4	25 (73.5%)	34 (85.0%)	59 (79.7%)
≥5	13 (38.2%)	24 (60.0%)	37 (50.0%)
B351			
≥4	29 (78.4%)	38 (76.0%)	67 (77.0%)
≥5	12 (32.4%)	22 (44.0%)	34 (39.1%)
B358			
≥4	157 (87.7%)	148 (88.6%)	305 (88.2%)
≥5	116 (64.8%)	89 (53.3%)	205 (59.2%)
B307			
≥4	29 (69.0%)	12 (42.9%)	41 (58.6%)
≥5	19 (45.2%)	7 (25.0%)	26 (37.1%)

Source: Reviewer's table, adapted using the Applicant's response to Information Request received 7/9/2018
Abbreviations: BID, twice daily

3.3.1.3. Baseline Disease Severity Using 2012 IBS FDA Guidance for Industry:

The review team also considered how the baseline disease characteristics of the severely symptomatic patient data compared with the currently recommended entry criteria outlined in the 2012 IBS Guidance for Industry [18]. The guidance requires the following trial entry criteria for IBS-C:

- Abdominal Pain Intensity: weekly average of worst daily (in past 24 hours) abdominal pain score of >3.0 on a 0- to 10-point scale
  AND
- Stool Frequency: fewer than three complete spontaneous bowel movements (CSBMs) per week

The original IBS-C trials combined both abdominal pain intensity and discomfort into one scale and a single question, which is not an approach to obtain this type of data that we would recommend currently. The 2012 IBS Guidance recommends that abdominal pain intensity is the primary pain assessment and abdominal discomfort can be evaluated as a secondary endpoint. Because of these design differences, it is difficult to compare the original IBS-C trials with the current FDA recommended approach on abdominal pain entry criteria.

The team was able to compare the baseline stool frequency from the original trials with the current FDA recommendations. One limitation of data was that the collection in the original trials was related to bowel movements. The current guidance is based on CSBMs, whereas the original trials did not require the differentiation of a bowel movement (BM) from a CSBM. CSBM is defined as a BM that: (1) will be considered "spontaneous" if the BM was not preceded by the intake of a laxative agent or enema within a period of 24 hours; and (2) considered complete if the subject reported completely emptying his/her bowels in the questionnaire. The original trials did not collect the exact time of laxative usage, the exact time of a BM, or whether a BM was complete. Therefore, it is not feasible to determine whether a BM is free of rescue medication's effect or complete.

Figure 2 below shows the distribution of the number of BMs per week in the severely symptomatic populations at baseline. Therefore, some patients in the severely symptomatic population would be excluded based on today's current guidance.

Although approximately 40 to 75% of patients, depending on the trial, did not appear to meet the currently recommended definition of less than three BMs per week, the review team also took into consideration that the methods used for data collection, including the language in the question and the approach to IBS trials, evolved since the original trials were designed and conducted.

Figure 2: Number of BM/Week at Baseline in the Severely Symptomatic Populations
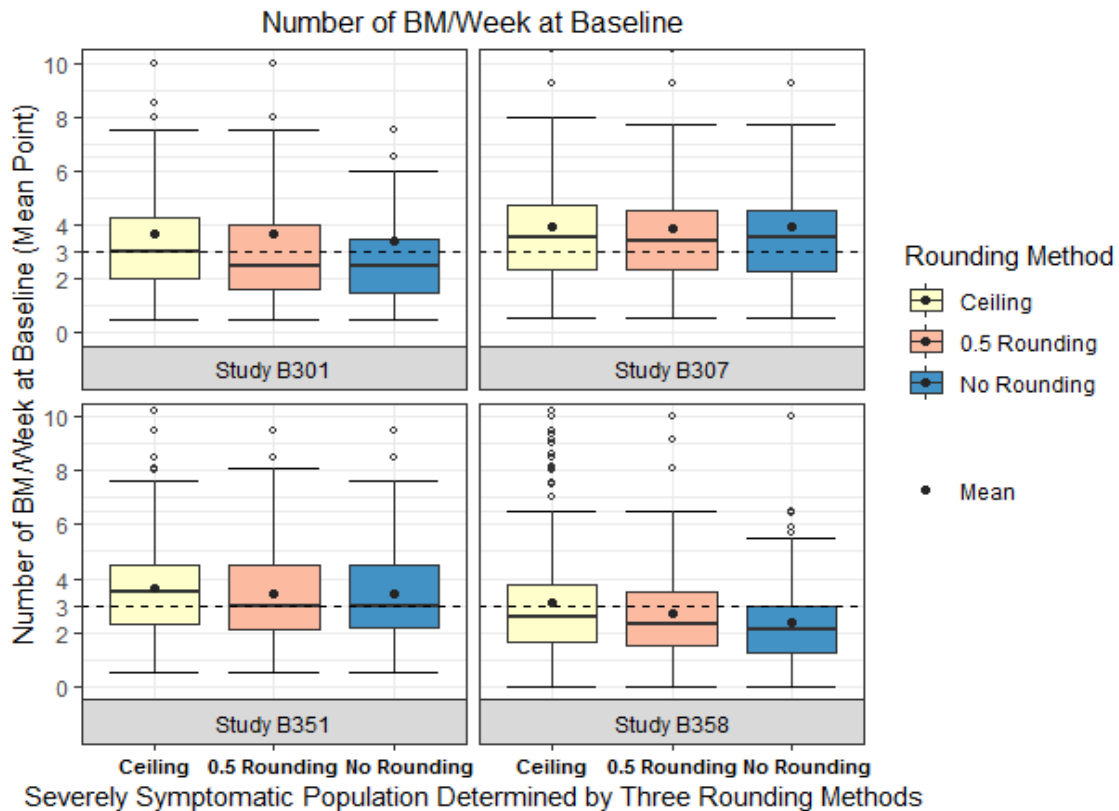
Note: Outliers not shown in the figure for Study B301: ceiling, one subj >50 BM/WK, two subj >10 BM/WK; 0.5 rounding, one subj > 50 BM/WK, two subj > 10 BM/WK; and no rounding, one subj >50 BM/WK, one subj >10 BM/WK. Outliers not shown for Study B307: ceiling, four subj >10 BM/WK; 0.5 rounding : three subj > 10 BM/WK; and no rounding, two subj >10 BM/WK. Outliers not shown for Study B351: ceiling, one subj >10 BM/WK. Outliers not shown for Study B358: ceiling, 10 subj >10 BM/WK, 0.5 rounding : four subj > 10 BM/WK; and no rounding, two subj >10 BM/WK.
Source: Reviewer's plot, based on Applicant's IR response submitted on 7/9/2018.

In summary, there are two major limitations of the Applicant-proposed definition of the severely symptomatic population. The first is the method used to select patients from the original trial populations to create the severely symptomatic population for post hoc efficacy analyses. The Applicant used the ceiling method (defined above) which is the most permissive method and includes the largest sample size compared with no rounding or rounding up at 0.5 methods.

There was no discussion on which rounding methods should be applied prior to this submission. The team explored the impact on efficacy results when various methods are used to select the patient population for efficacy analyses, discussed in Section 3.4 Summary of Efficacy Findings in the Severely Symptomatic Population below.

The second major limitation was that only some patients in the severely symptomatic population met the enrollment criteria for baseline number of BMs based on the 2012 IBS Guidance (less than three CSBMs/week). Of note, the data collected in the original trials were on BMs and not CSBMs.

Despite the two major limitations above, from a clinical perspective the Applicant's proposed severely symptomatic definition appears reasonable to define a patient population with severe IBS-C, based on the number of days with severe abdominal pain and no stools.

3.4. Summary of Efficacy Findings in the Severely Symptomatic Population

We explored three methods for patient data selection for the severely symptomatic population and how these methods change the sample size and therefore impact efficacy results. The following tables show the results of the re-analyses using the original primary endpoint in the subpopulations selected using the ceiling method and no rounding method, and 0.5 rounding method. We focused on the treatment difference between patients treated with tegaserod versus placebo to determine whether the treatment effect of tegaserod demonstrated in the original approval is numerically similar to the treatment effect in the subpopulation. The comparison of treatment effects is considered exploratory for several reasons. The extracted severely symptomatic subpopulations are post hoc selected subgroups of the original trials which no longer warrant balance between treatment arms. The sample size in the subpopulation based on the ceiling method is approximately one third of the original population across all studies. Therefore, formal statistical inference for the evaluation of treatment effect in the severely symptomatic populations can be problematic. However, these exploratory analyses are useful clinically.

As shown below, the treatment effects were notably different among the three severely symptomatic populations (determined by different rounding methods: ceiling method, 0.5 rounding method, and no rounding method) across the trials, but there were no consistent trends depending on the rounding method. With the ceiling method, the treatment differences were generally numerically similar in the severely symptomatic population compared with the original population except for Trial B307 (dose titration study). The review team conducted sensitivity analyses by applying multiple rounding methods (0.1, 0.2, 0.3, …, and 0.9 rounding) to create a set of severely symptomatic subpopulations and evaluating the primary endpoint in each of these subpopulations. In Trials 307, 351, and 358, we observed that the treatment differences generally decrease as degree of severity increases. However, the treatment differences increase as the degree of severity increases in Trial 301 (Analyses results are presented in the Appendix in Table 46).

Table 7: Primary Endpoint: Re-analysis in Female Severely Symptomatic Patients (Ceiling Method)[a]

Study	Tegaserod 12 mg n/N (%)	Placebo n/N (%)	Difference in Response 95% CI (%)	Original Approval Treatment Difference 95% CI (%)
301	25 / 67 (37.3)	16 / 68 (23.5)	13.8 (-1.6, 29.1)	11.4 (3.1, 19.8)
307	24 / 69 (34.8)	19 / 52 (36.5)	-1.8 (-19.0, 15.5)	5.3 (-3.6, 14.2)
351	33 / 64 (51.6)	29 / 76 (38.2)	13.4 (-3.0, 29.8)	14.2 (5.5, 23.0)
358	133 / 320 (41.6)	108 / 318 (34.0)	7.6 (0.1, 15.1)	4.7 (-0.2, 11.0)

Source: Applicant's IR response dated 6/15/2018, verified by Reviewer
Abbreviations: CI, confidence interval
[a] Analysis used the ceiling method (Applicant's proposed method) to select severely symptomatic patient data.

Table 8: Primary Endpoint: Reanalysis in Female Severely Symptomatic Patients (No Rounding Method)[a]

Study	Tegaserod 12 mg n/N (%)	Placebo n/N (%)	Difference in Response 95% CI (%)	Original Approval Treatment Difference 95% CI (%)
301	18 / 34 (52.9)	8 / 40 (20.0)	32.5 (8.5, 56.5)	11.4 (3.1, 19.8)
307	9 / 42 (21.4)	10 / 28 (35.7)	-14.9 (-38.2, 8.4)	5.3 (-3.6, 14.2)
351	18 / 37 (48.6)	21 / 50 (42.0)	6.6 (-14.8, 28.0)	14.2 (5.5, 23.0)
358	64 / 179 (35.8)	57 / 167 (34.1)	-0.3 (-10.5, 9.8)	4.7 (-0.2, 11.0)

Source: Applicant's IR response dated 6/15/2018, verified by Reviewer
Abbreviations: CI, confidence interval
[a] Analysis used the no rounding method to select severely symptomatic patient data.

Table 9: Primary Endpoint: Reanalysis in Female Severely Symptomatic Patients (Rounding at 0.5)[a]

Study	Tegaserod 12 mg n/N (%)	Placebo n/N (%)	Difference in Response 95% CI (%)	Original Approval Treatment Difference 95% CI (%)
301	23 / 55 (41.8)	15 / 60 (25.0)	17.8 (-0.1, 35.6)	11.4 (3.1, 19.8)
307	20 / 61 (32.8)	16 / 40 (40.0)	-10.3 (-30.5, 10.0)	5.3 (-3.6, 14.2)
351	25 / 48 (52.1)	23 / 63 (36.5)	15.5 (-3.2, 34.3)	14.2 (5.5, 23.0)
358	94 / 242 (38.8)	77 / 235 (32.8)	5.2 (-3.5, 13.8)	4.7 (-0.2, 11.0)

Source: Applicant's IR response dated 6/15/2018, verified by Reviewer
Abbreviations: CI, confidence interval
[a] Analysis used the rounding at 0.5 method to select the severely symptomatic patient data.

The review team conducted a sensitivity analysis in female severely symptomatic patients with less than three BM/week at baseline, which is analogous to the entry criteria in the 2012 IBS guidance (less than three CSBM/week). Of note, due to the small sample sizes in the subgroups, the variability of the estimates increased, which was reflected in wider confidence intervals. Table 10 below shows that the treatment difference favored patients treated with tegaserod over placebo in all trials, except for Trial B307 which favored placebo. Trial B301 had a significantly greater treatment difference in this subpopulation compared with the original approval population.

Table 10: Primary Endpoint: Reanalysis in Female Severely Symptomatic Patients With Less Than Three BM Per Week at Baseline

Study	Tegaserod 12 mg n/N (%)	Placebo n/N (%)	Difference in Response 95% Exact CI (%)	Original Approval Treatment Difference 95% CI (%)
301	10/20 (50)	6/28 (21)	29 (-0.4, 54)	11.4 (3.1, 19.8)
307	4/20 (20)	3/8 (38)	-18 (-56, 25)	5.3 (-3.6, 14.2)
351	9/17 (53)	9/19 (47)	6 (-28, 38)	14.2 (5.5, 23.0)
358	51/137 (37)	37/117 (32)	6 (-7, 18)	4.7(-0.2, 11.0)

Source: Reviewer's analyses
Abbreviations: BM, bowel movement; CI, confidence interval

Other efficacy endpoints: variation on the 2012 IBS trials guidance endpoint

The premarket trials were designed and conducted almost 20 years ago. FDA's thinking and recommendations on trial design, including clinically meaningful endpoints, has evolved. The Applicant reanalyzed the treatment effect with secondary endpoints from the original trials that were most similar to the 2012 IBS guidance as sensitivity analyses. In the 2012 IBS guidance, the FDA recommends a primary endpoint that measures the treatment effect on two major IBS signs and symptoms: abnormal defecation and abdominal pain. A patient should be categorized as an overall responder if the patient achieved the prespecified improvement in weekly or daily response for at least 50 percent of the weeks or days of treatment. The differences between one of the original tegaserod IBS-C trial secondary endpoints and the 2012 IBS guidance endpoint are highlighted below.

Table 11: Variation on the 2012 IBS Guidance Endpoint

	Original secondary endpoint of interest	2012 IBS guidance endpoint [18]
Abnormal defecation	50% Responder rates for change from baseline in **number of bowel movement** (≥1/week) over 12 weeks.	Stool frequency, as measured by the number of **complete spontaneous bowel movements (CSBMs)** per week. A weekly responder is defined as a patient who experiences an increase of at least one CSBM per week from baseline.
Abdominal pain and discomfort	**Abdominal pain and discomfort as measured by a 6- or 7-point numeric rating scale** that asks patients daily to rate their abdominal pain and discomfort over the past 24 hours. A responder is defined as a patient who experiences a decrease in the weekly average of pain and discomfort in the past 24 hours score (measured daily) of at least 30% compared with baseline weekly average for at least 50% of the weeks or days of treatment.	**Abdominal pain intensity, as measured by an 11-point (i.e., 0 to 10) numeric rating scale** that asks patients daily to rate their worst abdominal pain over the past 24-hours. A weekly responder is defined as a patient who experiences a decrease in the weekly average of worst abdominal pain in the past 24 hours score (measured daily) of at least 30% compared with baseline.

Source: Adapted from the Applicant's Summary of Clinical Efficacy, page 23, submitted 2/26/2018.
Abbreviations: CSBM, complete spontaneous bowel movement; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome – constipation

Variation on the 2012 IBS guidance endpoint applied to original trial data is defined as follows:

"Combined Responder- 50% weekly responder over 12 weeks, ≥30% reduction pain/discomfort and stool frequency increase ≥1 per week"

There are some limitations with using the combined responder endpoint with original trial data. The original trials combined abdominal pain and discomfort into one secondary endpoint. The 2012 IBS guidance suggests that abdominal pain and discomfort may be different symptoms that should be assessed by asking different questions. The guidance recommends that abdominal pain intensity as the primary pain assessment and abdominal discomfort as a secondary endpoint. Additional limitations are that the abdominal pain scales differ and the original trials did not define a bowel movement using the term complete spontaneous bowel movement. The definition of response did not account for rescue laxative usage and it used BM instead of CSBM. A similarity in endpoints between the original trials and the 2012 IBS guidance is the 50% responder rate.

Table 12: Exploratory: Variation of 2012 IBS Guidance Endpoint in Female Severely Symptomatic Subjects, Ceiling Method for Data Selection

Study	Tegaserod 12 mg n/N (%)	Placebo n/N (%)	Difference in Response 95% CI (%)
Study A0301	19 / 66 (28.8)	9 / 66 (13.6)	15.2 (1.4, 28.9)
Study A0307	19 / 68 (27.9)	11 / 51 (21.6)	6.4 (-9.2, 21.9)
Study A0351	21 / 62 (33.9)	14 / 73 (19.2)	14.7 (-0.2, 29.5)
Study A0358	144 / 319 (45.1)	105 / 312 (33.7)	11.5 (3.9, 19.1)

Source: Applicant's IR response dated 6/15/2018, verified by Reviewer
Abbreviations: CI, confidence interval; IBS, irritable bowel syndrome

Noting the limitations stated above, the treatment effect numerically favored tegaserod in all original trials, with the greatest response in patients treated with tegaserod compared to placebo in Trials B301 and B351.

3.5. Collective Evidence of Efficacy

Clinical benefit in the severely symptomatic population conclusions

Although the treatment effects for the primary endpoint were notably different for the three versions of severely symptomatic populations (determined by different rounding methods: ceiling, rounding at 0.5, and no rounding) across the trials, treatment differences were numerically in favor of tegaserod (compared with placebo) in all versions of severely symptomatic population in Trials B301, B351, and B358 except for the no rounding population in Trial B358. In Trial B307, placebo patients had numerically higher response rates for all severely symptomatic subgroups.

Figure 3 below shows the variation in the primary efficacy endpoint results for the severely symptomatic subpopulations, using the three rounding methods. When the ceiling method is used, the therapeutic gain (treatment difference between tegaserod and placebo patients) is generally similar in magnitude between the severely symptomatic and original approved populations for all three endpoints.

Figure 3: Primary Endpoint Comparison Between the Severely Symptomatic Populations, By Various Rounding Methods
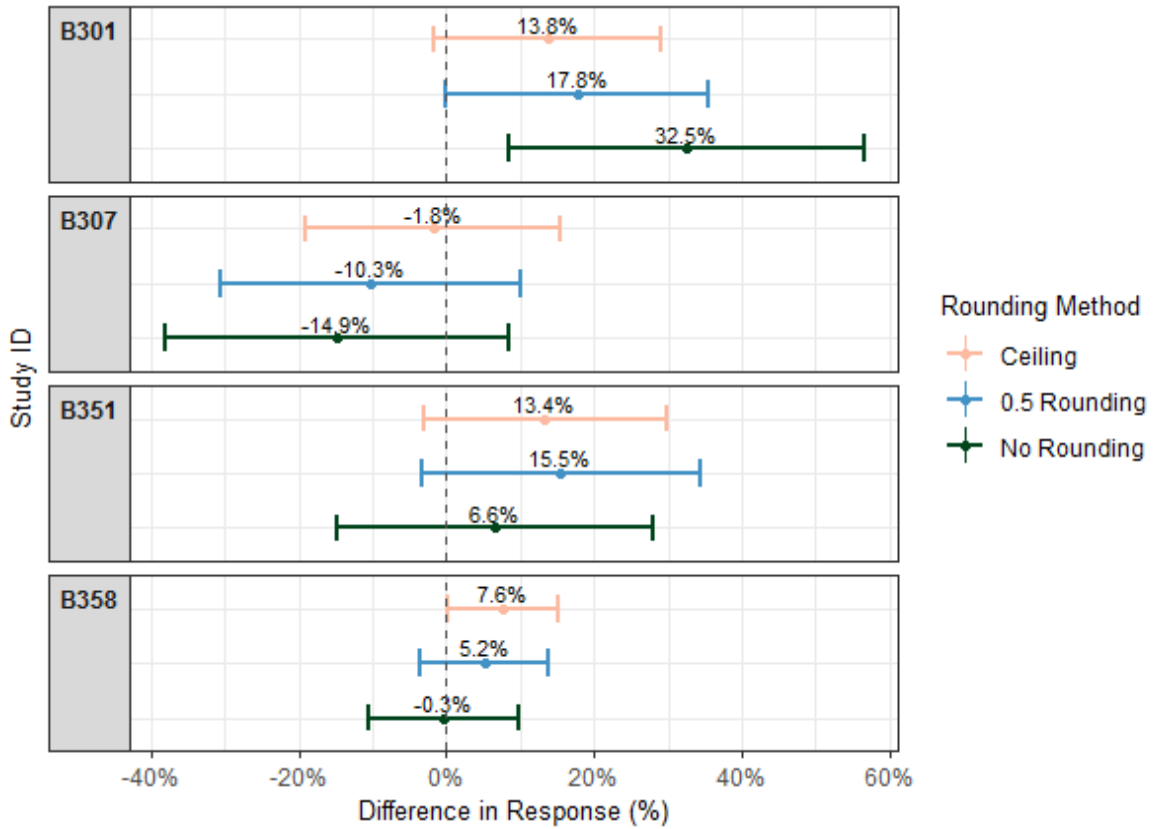
Source: Reviewer's plot, based on Applicant's IR response submitted on 7/9/2018.

4. SAFETY EVALUATIONS OF INTEREST

4.1. Cardiovascular Adverse Events of Special Interest and Associated Safety Analyses

4.1.1. Nonclinical Pharmacology/Toxicology

4.1.1.1. Summary

From a mechanistic perspective, the potential for tegaserod to cause CV ischemia is not well understood. Available 5-HT receptor affinity and functional response data for tegaserod indicate that the drug binds to 5-HT$_4$ receptors with high affinity as an agonist, and binds with moderate to high affinities for 5-HT$_1$ receptor subtypes, as an agonist. Tegaserod also has antagonistic activity at 5-HT$_2$ receptor subtypes.

The 5-HT receptor subtypes and vascular function are presented in Table 13 and Table 14.

Table 13: 5-HT Receptor Subtypes

Subtype	Location
5-HT$_1$	Blood vessels, CNS
5-HT$_2$	Blood Vessels, CNS, GI Tract, Platelets, PNS, Smooth Muscle
5-HT$_3$	CNS, GI Tract, PNS
5-HT$_4$*	CNS, GI Tract, PNS
5-HT$_5$	CNS
5-HT$_6$	CNS
5-HT$_7$	Blood Vessels, CNS, GI Tract

Source: Modified FDA Reference Document from GIDAC Meeting, 11/17/2011
Abbreviations: 5-HT, 5-hydroxytryptamine (serotonin); CNS, central nervous system; GI, gastrointestinal; GIDAC, Gastrointestinal Drugs Advisory Committee; PNS, peripheral nervous system
*Applicant's data also indicates the expression of 5-HT4 receptors on human platelets (study # RD-2008-00431).

Table 14: 5-HT Receptor Subtypes and Vascular Function

Artery		Vein	
Contraction	Relaxation	Contraction	Relaxation
5-HT$_{1B}$ 5-HT$_{2A}$	5-HT$_{1D}$ 5-HT$_7$	5-HT$_{1B}$	5-HT$_{1D}$ 5-HT$_{2B}$ 5-HT$_4$ 5-HT$_7$

Source: FDA Reference Document from GIDAC Meeting, 11/17/2011
Abbreviations: 5-HT, 5-hydroxytryptamine (serotonin)

Oral administration of up to 10 mg/kg tegaserod in dogs (approximately 113 times the recommended human dose based on C$_{max}$) had no effects on heart rate, blood pressure, or ECG parameters. Intravenous administration of 1 mg/kg in rats (1.6 times the recommended oral human dose (6 mg/dose) based on mg/m^2) produced reductions in systolic and diastolic blood pressure, with no effects observed at 0.1 mg/kg or lower. Tegaserod is a weak inhibitor of hERG potassium ionic currents, but did not induce QT prolongation in in vivo studies in dogs. Neither action potentials in isolated guinea pig ventricular papillary muscle nor QT intervals in isolated

perfused rabbit heart were affected by tegaserod at clinically relevant concentrations (i.e., human plasma concentrations). Tegaserod did not induce contractions in isolated coronary artery preparations from pigs, non-human primates, and humans, but produced a small and variable contractile response in canine coronary arteries. The major metabolite, M29, does not bind to 5-HT_{1B} or 5-HT_{1D} receptors, which are known mediators of vasoconstriction and vasodilation, respectively.

4.1.1.2. Serotonin Receptor Selectivity Studies

Tegaserod (HTF 919) is a 5-HT_4 agonist with moderate to high affinities for 5-HT_1 and 5-HT_2 receptors. Table 15 presents the binding affinities at multiple 5-HT receptor subtypes.

Table 15: Selectivity of Tegaserod for 5-HT Receptor Subtypes

Receptor Subtype	Study # RD-2004-01641	Study # PFK-1999-03473	Study # 103-167	Study # RD-2007-02133	Average Binding Affinity[a]	
	pK_i				pK_i	K_i (nM)
5-HT_{1A}	7.2	7.6	6.5		7.4	39.8
5-HT_{1B}	7.8	7.2		6	7	100
5-HT_{1D}			7.7	7.4	7.6	25.1
5-HT_{2A}	7	6.5			7.1	79.4
5-HT_{2B}	8.0				8.3	5.01
5-HT_{2C}[b]	6.8	6.5	7.2		6.9	125.9
5-HT_3	<6.0				5.5	>3162.3
5-HT_4					8.5	3.2
5-HT_6	6.7	6.5			6.6	251.2
5-HT_7	6.2				6.2	631
5-HTT	5.9	NB			<6.0	>1000

Source: Adapted from Applicant's response to Information Request dated 8/27/2018
Abbreviations: 5-HT, 5-hydroxytryptamine (serotonin); 5-HTT, Serotonin transporter (SERT), also known as the sodium-dependent serotonin transporter and solute carrier family 6 member 4; pK_i, -log10 inhibitory constant; K_i, inhibitory constant; NB, no binding.
K_i represents the concentration of drug that produces a 50% occupation of receptors
[a] Averaged values from studies and published literature cited by Applicant, including: [19-23] and , RD-2004-01641, RD-1999-03473, and 103-167, RD-2007-02133.
[b] Previously known as 5-HT_{1C}

The major tegaserod metabolite, M29, and two minor metabolites were shown to have no binding affinity for 5-HT_{1B} or 5-HT_{1D} receptors, which are known to mediate vasoconstriction and vasodilation, respectively.

4.1.1.3. In Vitro Cardiac Electrophysiology Studies

Effects on hERG potassium channel currents in HEK293 cells:

An in vitro study was conducted to assess the effects of HTF 919 on cloned hERG channels expressed in HEK293 cell. The results indicated that HTF 919 inhibited the hERG current, with IC_{50} of 13,000nM. In contrast, cisapride produced almost complete inhibition at 2,000nM, with IC_{50} of 44nM.

Effects on the action potentials of guinea pig ventricular papillary muscle:

HTF 919 had no significant effects on action potential duration, amplitude, and maximum rate of depolarization, or diastolic membrane potential recorded from isolated guinea pig ventricular papillary muscle at 10, 100, and 1000nM.

Effects on action potentials of isolated human atrial myocytes

HTF 919 had no significant effects on action potential parameters recorded from isolated human atrial myocytes collected from patients undergoing cardiac surgery at concentrations up to 100nM.

In vitro Rabbit heart Langendorff preparation:

In this study, rabbit hearts were removed and placed in a Langendorff apparatus and ECGs were recorded. The perfused isolated hearts were then treated with HTF 919 at 0, 0.5, 1, 5, 10, and 50μM. QT intervals measured from ECG recordings were 230±4, 226±2, 233±4, 233±7, 233±8, and 259±19 msec at 0, 0.5, 1, 5, 10, and 50μM, respectively. HTF 919 had no effects on QT interval at concentrations up to 10μM, and it prolonged QT interval by ~12% at a concentration of 50μM (~21±g/ml), which is much higher than the therapeutic plasma level (~6 ng/ml) following an oral dose of 12 mg/day. Metabolite M29 had no effects on QT interval at concentrations up to 50μM. In contrast, cisapride, used as a positive control, increased QT interval by 15% at concentration of 0.1μM. (This study was performed after cisapride was identified to cause cardiac electrophysiologic changes.)

4.1.1.4. Effects on Contractility of Coronary Arteries

Tegaserod had no contractile activity at concentrations up to 10 or 30μM in isolated coronary artery preparations from pigs, non-human primates, and humans. Tegaserod produced a small and variable contractile response in canine coronary arteries at 3 to 10μM [24].

Tegaserod at 1μM had no contractile effects (isometric tension) on human coronary arteries (circular strips) isolated from individuals who died of non-cardiac causes. A slight increase in contraction occurred at tegaserod concentrations of 10μM or higher.

4.1.1.5. In Vivo Nonclinical Cardiovascular Safety Pharmacology Studies

Intravenous administration of HTF 919 at doses of 0.01 and 0.1 mg/kg had no effects on blood pressure, heart rate, left ventricular dp/dt (rate of pressure rise), cardiac output, and total peripheral resistance in anesthetized rats. ECGs were not affected at these doses. However, HTF 919 at 1 mg/kg decreased systolic (~9 to 15%), diastolic (~13 to 20%), and mean arterial (~10 to 17%) blood pressures and total peripheral resistance (~16 to 19%), and produced negative dp/dt (~6 to 19%).

In anesthetized dogs, intraduodenal administration of HTF 919 had no effects on blood pressure, respiration rate, heart rate, femoral arterial blood flow, and ECG at 0.1, 1, and 10 mg/kg. In conscious dogs, single oral doses of HTF 919 had no clear treatment-related effects on heart rate,

blood pressure, and ECG at 0.3, 4, and 10 mg/kg. Plasma levels of HTF 919 were determined in this study. Maximum plasma levels of HTF 919 following 0.3, 4, and 10 mg/kg were 16.9, 138, and 401 ng/ml (males) and 3.62, 104, and 277 ng/ml (females), respectively.

HTF 919 had no effects on ECG at 0.1 and 1 mg/kg/day in the 2-week IV toxicity study in dogs, at 5, 15, and 50/60 mg/kg/day in the 26-week oral toxicity study in dogs, and at 5, 15, and 60/70 mg/kg/day in the 52-week oral toxicity study in dogs.

4.1.2. Clinical Pharmacology

4.1.2.1. Clinical Pharmacokinetics

Most of the clinical pharmacology information is stated in the previously approved label. The newly submitted study reports include in vitro platelet aggregation of tegaserod[7] and M29, and additional in vitro drug-drug interaction studies.

4.1.2.1.1. Absorption

Following oral administration, the absolute bioavailability of tegaserod when administered to fasting subjects is approximately 10%. The peak plasma concentrations are reached approximately 1 hour after oral dosing and in the range of 3 to 13nM with a single 6 mg oral dose [25; 26]. The systemic exposure to tegaserod increased dose-proportionally over the 2 mg to 12 mg range given twice daily for 5 days. There was no clinically relevant accumulation of tegaserod in plasma when a 6 mg BID dose was given for 5 days. When the drug is administered with food, the bioavailability of tegaserod is reduced by 40% to 65% and C_{max} by 20% to 40%.

4.1.2.1.2. Distribution

The protein binding of tegaserod is approximately 98%, primarily to alpha1-acid glycoprotein in the concentration range of 20 to 20000 ng/mL.

4.1.2.1.3. Metabolism and Excretion

Upon oral administration, approximately two thirds of the orally administered dose of tegaserod is excreted unchanged in the feces, with the remaining one third excreted in the urine, primarily as the main metabolite. Unchanged tegaserod was not detectable in the urine, while only unchanged tegaserod was detectable in the feces.

Tegaserod is metabolized mainly via two pathways. The first is a presystemic acid-catalyzed hydrolysis in the stomach followed by oxidation and conjugation, which produces M29. Following a single dose administration of tegaserod at 12 mg (two-fold the proposed dose), the C_{max} and AUC of M29 was 16-fold and 10-fold higher than C_{max} and AUC of tegaserod, respectively (Study W358). In vitro, M29 has negligible affinity for human 5-HT$_4$ receptors [1]. The median half-life is 8 hours for tegaserod and 5 hours for M29 (Study W358).

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[7] While the full study report was included in this NDA submission, the results from the platelet aggregation study were previously published.

The second metabolic pathway of tegaserod degradation is direct glucuronidation, which leads to generation of three isomeric N-glucuronides. [1].

The fate of the pentylaminoguianidine (PAG) side chain of tegaserod was investigated in mice following a single oral dose of labeled tegaserod. After 72 hours, 82% and 15% was excreted in feces and in urine, respectively. PAG formed condensation products with endogenous (or food-derived) keto-acids (pyruvate, alpha-keto glutarate, and others). These compounds were excreted in urine and as such seem to be absorbed systemically to some extent [15]. Information on systemic absorption of PAG in humans is not available.

4.1.2.2. Specific Populations

In patients with mild hepatic impairment, mean AUC was 31% higher and C_{max} was 16% higher compared with healthy subjects. Tegaserod has not been studied in patients with moderate and severe hepatic impairment. No dosage adjustment is recommended for patients with mild hepatic impairment. Tegaserod is not recommended in patients with moderate and severe hepatic impairment.

In patients with end-stage renal impairment requiring hemodialysis, no change in the PK of tegaserod was observed. On the other hand, C_{max} and AUC of M29 increased 2- and 10-fold in subjects with severe renal impairment compared with healthy controls, respectively. No dosage adjustment is recommended in patients with mild-to moderate renal impairment. Tegaserod is not recommended in patients with severe renal impairment.

4.1.2.3. Drug-Drug Interaction Studies

Effects of other drugs on tegaserod

In vitro, tegaserod is not a substrate of cytochrome P450 enzymes such as CYP2C8, 2C9, 2C19, 2E1, and 3A4. Tegaserod and M29 are the substrates of P-gp and BCRP, and M29 is the substrate of OAT3. Neither tegaserod nor M29 are substrates of OAT1, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K.

The in vivo interaction potential between concomitant P-gp inhibitor(s) and tegaserod was not evaluated prior to the original approval [27]. An increase in the systemic exposure of tegaserod by 74% by a concomitant P-gp inhibitor, quinidine, was later reported in the literature [27] and a short summary of the study results (A2422) was submitted in the summary of clinical pharmacology. However, the full study report of A2422 was not available to FDA.

In vitro, the solubility of tegaserod significantly decreased at neutral pH compared with acidic pH (pH 1.2), and formation of M29 is mediated by acid-hydrolysis. In a study with omeprazole and bicarbonate, the systemic exposure to tegaserod was not significantly altered, while systemic exposure to M29 was significantly decreased (~90%) when tegaserod was administered with omeprazole and bicarbonate compared with administered alone (HTF919W358).

Effects of tegaserod on other drugs

In vitro, tegaserod is neither an inhibitor nor an inducer of cytochrome P450 enzymes such as CYP2C8, 2C9, 2C19, 2E1, and 3A4. No clinically relevant effects of tegaserod were observed on the PK of dextromethorphan (CYP2D6 substrate), theophylline (CYP1A2 substrate), warfarin (CYP2C9 substrate), and oral contraceptives.

In vitro, tegaserod inhibited P-gp, BCRP, MATE1, and MATE2-K. However, significant in vivo drug-drug interaction potential via inhibition of these transporters is unlikely for the proposed dose. In addition, in vivo studies showed that there was no effect on the pharmacokinetics of digoxin (P-gp substrate).

M29 did not inhibit the activity of any of the above cytochrome P450 isoenzymes and transporters in in vitro studies [1].

4.1.2.4. Thorough QT Study

The reader is referred to Section 4.1.3.5, Other Elements of CV Safety Signal, Including Arrhythmia, Long-Term Safety, ECG (and QT Prolongation), and Blood Pressure, subsection on ECG (and QT prolongation).

4.1.2.5. Effects on Platelet Aggregation

There is conflicting information regarding tegaserod's effect on human platelet aggregation as outlined in Study RD-2008-00298, and the literature. In addition, information from Study USWM25JUN2017 regarding the effect of M29 on human platelet aggregation is incomplete.

Study RD-2008-00298 investigated the effects of in vitro addition of tegaserod on the function of platelets obtained from healthy volunteers (Table 16) and subjects with IBS-C. Preincubation with tegaserod at concentrations mimicking human C_{max} values (10nM), 3.3 times C_{max} (33nM) and 10 times C_{max} (100nM), respectively, resulted in mild but statistically significant increases (mostly at supratherapeutic concentrations) in platelet aggregation induced by ADP, collagen, epinephrine, or serotonin. The effects of tegaserod on platelet aggregation were consistent across various agonists in the study (Table 16). No differences were observed between the effects on aggregation of platelets obtained from healthy volunteers and subjects with IBS-C (data not shown).

Table 16: In Vitro Effects of Tegaserod on Platelet Aggregation in Blood Collected from Healthy Subjects (n=20, 5 males, 15 females) (Study RD-2008-00298, [28])

Agonist	Tegaserod concentration/Platelet aggregation (%)				
	Vehicle	10 nM	33 nM	100 nM	Reference range
ADP 5 μM*	64.9 ± 5.4	74.8 ± 13.4†	75.4 ± 11.2†	79.3 ± 11.0†	60–82
ADP 20 μM*	74.7 ± 5.3	77.8 ± 6.7†	81.6 ± 7.8†	87.1 ± 7.6†	68–88
Collagen 1 μg/mL*	75.1 ± 5.2	77.1 ± 6.4	82.5 ± 6.9†	90.3 ± 7.3†	68–84
Collagen 5 μg/mL*	81.3 ± 7.0	84.9 ± 7.7	88.7 ± 8.3†	90.1 ± 8.6†	79–92
TRAP 20 μM	88.3 ± 1.4	88.6 ± 1.9	89.0 ± 1.5	88.9 ± 3.2	78–93
Epinephrine 5 μM*	82.7 ± 6.9	85.6 ± 8.5	90.0 ± 6.6†	94.7 ± 7.2†	72–90
Serotonin 5 μM*	15.3 ± 4.4	21.6 ± 4.8†	22.0 ± 6.2†	26.7 ± 7.5†	10–18

Mean ± standard deviation.
*$P < 0.05$ (overall) Friedman's test.
†$P < 0.05$ (paired) sign test compared with vehicle.
ADP, adenosine diphosphate; TRAP, thrombin receptor activating peptide.

In contrast, Higgins et al. [24] reported no effects of tegaserod on platelet aggregation (Table 17). They reported that there was no statistically significant difference in the percentage platelet aggregation between control and tegaserod at concentrations 10, 33, and 100nM under experiment conditions similar to those in the previous study. When platelet aggregation was induced with 5μM ADP and platelet concentration 350,000/µL, the percentage platelet aggregation without tegaserod was similar in two reports (64.9% versus 62% by Higgins et al.), although a higher variability was observed in the Higgins study. Compared with Study RD-2008-00298, in the Higgins study, no other platelet agonists except ADP were used while various agonists were used in the study RD-2008-00298, and the sample size was smaller (n=10 versus n=20).

Table 17: In Vitro Effect of Tegaserod on Platelet Aggregation in Blood Collected from Healthy Subjects (n=10) [24]

Platelet concentration	Agonist	% Platelet Aggregation (mean±SD)				p value (Friedman's test)
		Vehicle	Tegaserod (10 nM)	Tegaserod (33 nM)	Tegaserod (100 nM)	
250,000/µL	5 μM ADP	51.5±16.9	54.4±15.4	51.3±16.8	54.1±18.2	0.9777
	1 μM ADP/5 μM 5-HT	34.1±14.8	25.7±12.3	29.7±12.0	28.4±11.8	0.3667
350,000/µL	5 μM ADP	62.0±13.9	60.2±18.0	59.3±16.4	58.6±18.4	0.9197
	1 μM ADP/5 μM 5-HT	41.5±14.3	30.1±13.0	36.9±14.6	36.8±18.5	0.0794

Abbreviations: ADP, adenosine diphosphate; 5-HT, 5-hydroxytryptamine (serotonin); SD, standard deviation.

While Study RD-2008-00298 results showed positive effects of tegaserod on platelet aggregation, inconsistent observations across studies prevent a definitive conclusion.

On the other hand, M29 at concentrations lower (100nM) than the estimated mean concentration at 6 mg tegaserod (approximately 160 nM) potentiated some of the agonists (ADP, epinephrine, and 5-HT/ADP) induced platelet aggregation by 5 to 16%, but did not reach statistical significance in the Applicant's Study USWM25JUN2017 (Table 18). In this study, the positive control thrombopoietin (500 U/mL) significantly potentiated platelet aggregation induced by the same agonists and saline. Notably, the numerically similar effect of M29 to that of thrombopoietin on epinephrine-induced (83.05% versus 88.5%) and ADP-induced platelet aggregation (86.5% versus 87.4%) was observed although it was not statistically significant

compared with the vehicle only. However, in the same study, M29 or thrombopoietin did not potentiate TRAP and collagen-induced platelet aggregation. It is unclear if this may be due to the relatively high platelet aggregation by collagen and TRAP even without a potentiator lowering the sensitivity of the assay to detect a positive effect.

Table 18: In Vitro Effect of M29 on Platelet Aggregation in Blood Collected from Healthy Subjects (n=20, 11 males, 9 females) (Study USWM25JUN2017)

Agonist (platelet activator)	Vehicle	M29 10nM	M29 100nM	Thrombopoietin (500 U/Ml)
ADP (5µM)	81.50±8.80	85.35±11.23	86.50±10.37	87.40±8.82 *
Epinephrine (10µM)	71.85±26.74	71.95±26.44	83.05±21.65	88.50±10.59 *
5-HT (5µM) + ADP (1µM)	63.65±17.26	66.65±17.26	70.70±17.50	86.20±10.53 ***
Collagen (5 µg/mL)	86.55±9.46	87.25±10.54	87.90±8.74	87.70±10.43
TRAP (5µM)	85.40±8.69	87.70±10.96	85.65±11.28	86.75±10.94
EDTA (75mM)	1.45±1.76	1.20±1.77	0.85±1.09	1.00±1.56
Saline	7.10±4.64	8.20±6.79	6.35±3.92	20.20±27.64 *

Abbreviations: 5-HT, 5-hydroxytryptamine (serotonin); ADP, adenosine diphosphate; EDTA, ethylenediaminetetraacetic acid; TRAP, thrombin receptor activator peptide
Paired t-test compared to vehicle, * $p<0.05$, ***$p<0.001$

In this study (Study USWM25JUN2017), the effect of M29 was studied at concentrations up to 100nM while mean C_{max} for M29 after 6 mg BID of tegaserod is estimated to be about 160nM[8] based on mean C_{max} of 10nM for tegaserod, assuming consistent C_{max} ratio of M29 versus Tegaserod of 16:1 with the C_{max} ratio observed at 12 mg and 25 mg (refer to studies W110 and W358). Because the concentrations of M29 used in this in vitro study are lower than the estimated mean C_{max} for M29, this study is considered inadequate to address the potential effects of M29 on platelet aggregation.

At the time of this writing, the results from an additional ex vivo study to further evaluate the effects of tegaserod/M29 on platelet activation and aggregation are pending.

4.1.3. Clinical/Statistics

4.1.3.1. Review Strategy and Overview of the Cardiovascular Signal

The safety review strategy focused on presenting the CV ischemic risk assessment in the Db15 dataset, and in patients with IBS-C. In addition, subpopulations of interest within Db15 were explored by the review team to evaluate the potential patient population which could be used in the benefit risk considerations regarding reintroduction of tegaserod. The major subgroups of interest included female patients with IBS-C (previously approved), "low CV Risk' IBS-C females (proposed), and severely symptomatic IBS-C females regardless of CV risk (an alternative subpopulation), in which benefit may outweigh the risk. The review strategy is briefly outlined below:

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[8] Actual PK of M29 was not measured in clinical studies dosed with 6 mg BID of tegaserod.

1) Characterization of the CV signal, including those CV ischemic events deemed as MACE for tegaserod from the original pooled analysis and subsequent adjudications.
   a. Description of patient progression across the three adjudications, including the reasons for a different classification, as well as strengths and limitations of each adjudication process.
2) Description of patient demographic characteristics (particularly as it relates to CV disease/risk factors) for the 24 initially identified CV ischemic cases as well as for the overall patient population in database Db15, IBS-C, and other subgroups of interest.
3) Comparison of tegaserod CV safety signal and its overall safety profile, among Db15 patients and subgroups, including low CV risk female IBS-C patients. For IBS-C, the primary safety data of interest are from the premarket Trials B301, B358, B307, and B351.
4) Review of the postmarketing safety data of tegaserod to provide:
   a. A safety update for AEs related to CV disorders.
   b. Review of overall safety including supportive data from two postmarketing trials, Trials A2306 and A2417.
   c. An assessment of the epidemiological study reports and published literature, as it relates to the CV safety of tegaserod.
   d. An expanded access program was initiated in 2007 and continues to present. In general data from this type of clinical reporting is incomplete and is not considered useful to assess a potential CV safety signal.

Description of the Safety Database

The primary safety database of interest is Db15. This database was the focus of the retrospective analysis that yielded the initial CV ischemic signal leading to the market withdrawal of tegaserod in March 2007. Db15 consisted of 11,614 patients treated with tegaserod and 7,031 placebo patients. It includes patients from several GI disorders, most of which were enrolled in the IBS-C trials, as described below[9]:

- IBS-C, N=8284 (44.43%; 10 trials),
- Chronic constipation, N=3531 (18.94%; 4 trials),
- Dyspepsia, N=3522 (18.89%; 6 trials),
- GERD, N=1526 (8.18%; 2 trials),
- non-D-IBS, N=1163 (6.24%; 2 trials),
- IBS-M, N=324 (1.74%; 1 trial),
- IBS-D, N=162 (0.87%; 2 trials),
- Diabetic gastropathy, N=121 (0.65%; 1 trial), and
- Slow-transit constipation, N=12 (0.06%; 1 trial)

Most patients in this population participated in the 12-week studies, and 8,307 tegaserod patients received 6 mg BID (12 mg per day), which is both the previously approved and the proposed dosing regimen in IBS-C. Placebo-controlled trials in IBS-C only were pooled as a subset of Db15 and include the four premarket trials, Trials B301, B358, B307, and B351, as well as 2

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[9] Source: Section 1.2.1, p.8, of Applicant's Summary of Clinical Safety (2.7.4); NDA 21200/S-015.

postapproval clinical trials. A third pooled safety database Db14 comprised of 7 open-label (uncontrolled) clinical trials of tegaserod, and was evaluated for a CVI signal specifically as it pertains to long-term use (at least 6 months to 12 months of use). A summary of the databases, clinical trials, and population sizes is presented in Table 19.

Table 19: Pooled Clinical Trial Databases Used in the CV Safety Assessment of Tegaserod

Short title	Database Code	Description	Number of patients – tegaserod [Mean Duration of Exposure]	Number of patients - placebo
Pooled placebo-controlled ≥ 4 weeks, any indication	Db15	Largest set of placebo-controlled studies that permits pooling with treatment duration of ≥4 weeks in any indication (any age, both gender): Comprised of 29 clinical studies: **B301, B351**, ASG01, AFI01, A2302, A2306 (Period 1 only), **B307, B358**, A2417, E2301, E2302, E2308, E2309, D2301, D2302, B201, B202, B207, B251, B254, B254C4, G202, D2201, D2202, D2203, D2204, B2203, G2203, AIA12.	11,614 [56.8 days]	7,031 [57.5 days]
Pooled placebo-controlled IBS-C studies [subset of Db15]	IBS-C	IBS-C placebo-controlled studies that permits pooling with treatment duration of ≥4 weeks for only the IBS-C indication (any age, both gender): Comprised of clinical studies: **B301, B351, B307, B358**, A2417 (IBS-C subjects only), A2306 (Period 1 only)	4,750 [54.3 days]	2278 [63.7 days]
Pooled uncontrolled long-term, any indication	Db14	All long-term studies in any indication with a planned treatment duration of ≥6 months (any age, both gender). Overall 7 studies: B209, B301E1, B307E1, E2301E1, D2209, D2301E1, D2302E1	3,289 [227.3 days]	NA

Pivotal IBS-C Phase III studies in **bold** font
Source: ISS-Tables 2.3.1, 2.3.3, 2.3.6
Source: Applicant's Table 1 from Summary of Clinical Safety (2.7.4); NDA 21200/S-015

4.1.3.2. Characterization of the CV Safety Signal, Including MACE

The flowchart depicted in Figure 4 provides an overview of the tegaserod CV signal detection process which involved an initial search (retrospective analysis) by then-Sponsor Novartis, of the pooled database Db15, followed with adjudication of the index cases by a Novartis internal panel of experts (internal adjudication), as well as by an external panel (1st external adjudication; Mount Sinai Medical Center, NY). Subsequently, a re-analysis of Db15 with broader search terms/algorithms was carried out, followed by an additional external adjudication of the true

positive cases identified by Duke Clinical Research Institute (DCRI; 2nd external adjudication). Additional clinical information was collected and added to the database. Please refer to 4.1.3.4 for details of the adjudication methodologies. The Novartis, Mt. Sinai, and DCRI adjudications will be referred to herein as the internal, 1st external, and 2nd external adjudications, respectively.

Figure 4: Overview of Search and Adjudication Processes of Patients with CV Events (tegaserod vs. placebo)
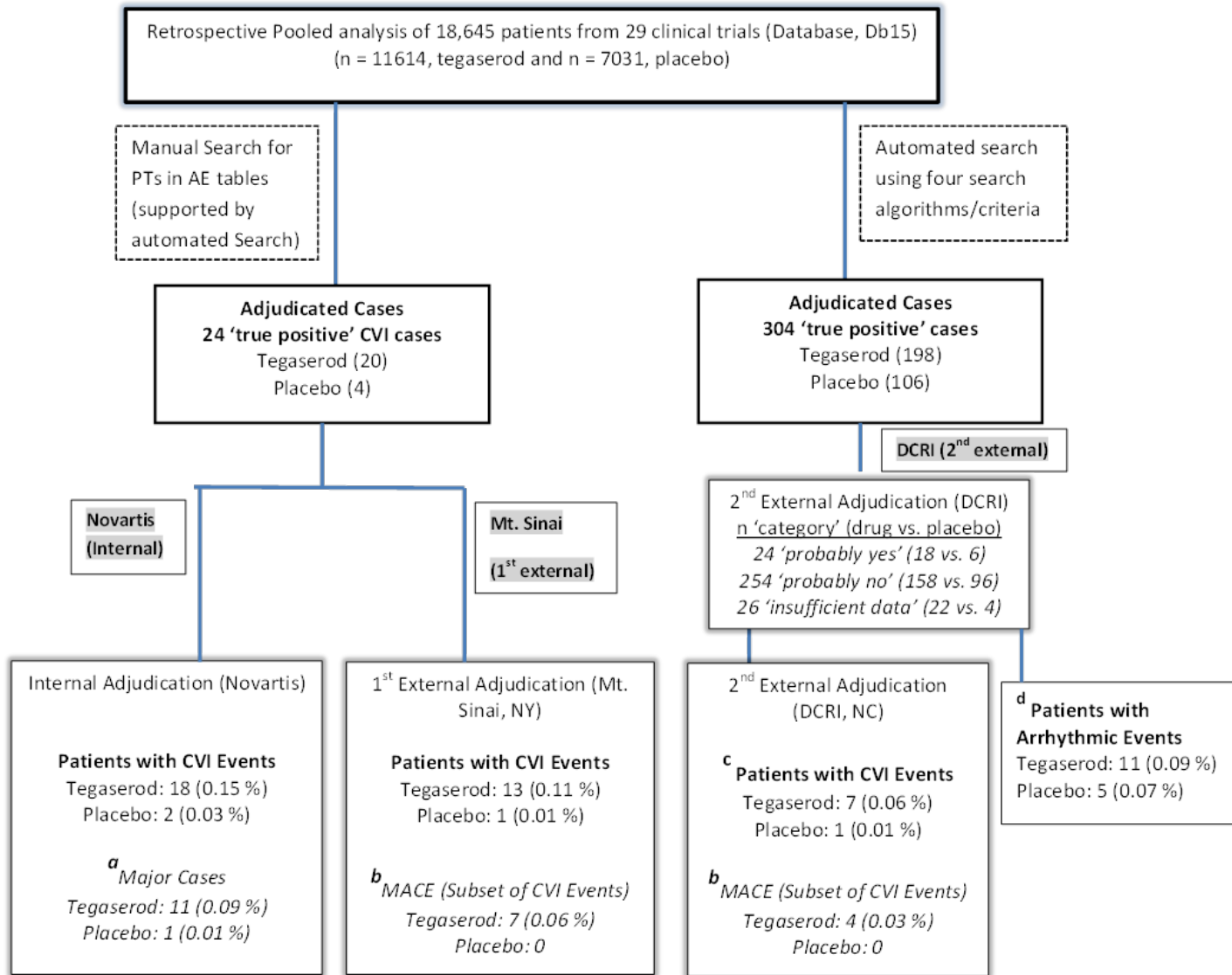
Abbreviations: AE, adverse event; CVI, cardiovascular ischemic; DCRI, Duke Clinical Research Institute; MACE, major adverse cardiovascular event; PT, preferred term
[a] Major Events included MI, unstable angina, cardiac death, cerebrovascular accident, stroke; Minor Events defined as "transient events without sequelae"
[b] MACE: Major Adverse Cardiovascular Events - defined in the 2nd external adjudication by APTC type events (Antiplatelet Trialists' Collaboration, 1994) consisting of MI, Stroke, and/or vascular death
[c] Two suspected cases of CV ischemic events from the initial search were deemed as congestive heart failure (CHF) by the 2nd external adjudication panel
[d] Two patients with arrhythmia on tegaserod also had CVI events

As shown in Figure 4, the number of confirmed cases with CV ischemic events, including the subset MACE, changed across the adjudications. The CV ischemic events confirmed in the various adjudications decreased as more patient-level clinical information was gained from data sources. However, the imbalance in CV ischemic cases for tegaserod compared to placebo remained.

During the internal adjudication by Novartis, the term "MACE" was not used; however, events were further classified as major (e.g., MI, unstable angina, cardiac death, cerebrovascular accident, stroke) or minor (transient events without sequelae). The total number of major versus minor events was based on all 24 cases, including those deemed by the Novartis panel as 'probably not' a CV event. Thus, in total, there were 11 'major' events on tegaserod (including one case internally adjudicated as 'probably not' a CV event) and 9 'minor' events (including one 'probably not'); only one out of four placebo cases was deemed as 'major' [internal adjudication deemed this case as 'probably not']. It should be noted that the 'major' classification noted here is separate from that of 'MACE'; cases deemed major by the internal adjudication included other terms such as unstable angina, thus differentiating this classification from the currently accepted definition of MACE as noted below.

It should be noted that the initial analysis and adjudications did not specifically identify events as Major Adverse Cardiovascular Events (MACE) by the current standards, defined as CV death, nonfatal MI, and nonfatal stroke. At the time of the 2nd external adjudication, Novartis included a search for Antiplatelet Trialists' Collaboration (APTC, 1994) type events, classified as vascular death, MI, and/or stroke, comparable to the MACE classification currently accepted by FDA.

Description of the CV Ischemic Safety Signal:

Of the 20 tegaserod-treated patients initially identified to have CV ischemic events, there were 8 patients with IBS-C, 8 with CIC, 1 with non-IBS-D, 2 with Functional Dyspepsia (FD), and 1 with gastroesophageal reflux disease (GERD). Fourteen out of 20 patients received the approved (and proposed) 6 mg BID dose of tegaserod, while 6 patients had received a lower dose of 2 mg BID. The placebo patients with possible CV ischemic events included two with IBS-C, one with CIC, and one with FD. Time to event in the tegaserod group relative to treatment onset was at 1 to 2 months in eight patients, at 2 to 4 weeks in six patients, and at 1 to 2 weeks in five patients. One patient had an event 30 days after treatment ended. Twelve of 20 patients discontinued treatment due to an adverse event, including 1 patient who died of MI and cardiac arrest approximately 29 days into treatment. Of the four cases on placebo, three events occurred within day 3 to day 67 of treatment initiation. One case of a cerebrovascular event (transient ischemic attack) occurred 13 days after the double-blind period ended. The number of CV ischemic events (and MACE subtype events) from the three adjudications (one internal, and two external) are summarized in Table 20 below.

Table 20: Summary of CV Ischemic (CVI) Counts – Pooled Database Db15

		Tegaserod (N=11614)	Placebo (N=7031)
Initial Search- Novartis	**Total CV Events**	**20 (0.17%)**	**4 (0.06%)**
Internal Adjudication (Novartis)	**CVI cases**	**18 (0.15%)**	**2 (0.03%)**
	Coronary	16 (0.13%)[1]	1 (0.01%)
	Cerebrovascular	3 (0.03%)[1]	1 (0.01%)
	Major cases[2]	11 (0.09%)	1 (0.01%)
	MACE (a subset of CVI)	NA	NA
1st External Adjudication (Mt. Sinai)	**CVI cases**	**13 (0.11%)**	**1 (0.01%)**
	Coronary	10 (0.09%)	0
	Cerebrovascular	3 (0.03%)	1 (0.01%)
	MACE (a subset of CVI)	7 (0.06%)	0
2nd External Adjudication (DCRI)	**CVI cases**	**7 (0.06%)**	**1 (0.01%)**
	Coronary	5 (0.04%)	0
	Cerebrovascular	2 (0.02%)	1 (0.01%)
	MACE (a subset of CVI)	4 (0.03%)	0

Abbreviations: CV, cardiovascular; CVI, cardiovascular ischemia; DCRI, Duke Clinical Research Institute; MACE, major adverse cardiovascular event; NA: not available

[1] Patient _____ (b) (6) was confirmed to have both Angina Pectoris and CVA in the internal adjudication and is therefore counted twice (one coronary and one cerebrovascular event)

[2] Major Events included myocardial infarction (MI), unstable angina, cardiac death, CVA, stroke; [Minor Events defined as "transient events without sequelae"]

Coronary events: include angina pectoris, unstable angina, coronary artery disease, coronary artery stenosis, myocardial infarction, myocardial ischemia

Cerebrovascular events: include cerebrovascular accident or stroke, transient ischemic attack, TIA, cerebrovascular disorder, cerebral artery occlusion

MACE: Though not formally referred to as MACE in these adjudications, the events were a composite of CV death, non-fatal MI and/or non-fatal stroke, which is the currently accepted definition; incidence for MACE in the table is a subset of CVI events

Source: Reviewer compilation of information from NDA 21200/S-015 summary of clinical safety, including from the three adjudication reports

The number of cases with CV ischemic events, including the subset MACE, in tegaserod-treated patients is small relative to the size of the overall safety database; however, an imbalance on tegaserod relative to placebo persisted across all adjudications. This imbalance was driven mainly by coronary ischemic events. The number of confirmed cases of CV ischemia decreased with each of the two external adjudications compared with the internal adjudication. Only 7 cases (on tegaserod) were deemed as 'confirmed' by the 2nd external adjudication, compared with the initial 18 identified by the Novartis internal adjudication and 13 by the 1st external adjudication. It is noteworthy that although the 2nd external adjudication was based on a thorough re-analysis of the database Db15 and yielded 304 'true positive' cases (i.e., those returned from applying the automated search criteria for CV events) for adjudication, no new cases of CVI, including MACE, were identified by this process compared with the two prior adjudications.

Major Adverse Cardiovascular Events:

There were seven cases from the 1st external and four cases per the 2nd external adjudications that can be deemed as MACE. No MACE cases were noted in the placebo group of database Db15. The patient IDs with an outcome of 'MACE' largely overlapped across the adjudications and no new cases of MACE were identified in the 2nd external adjudication. As summarized in the

narratives below, these cases of MACE were scattered across tegaserod clinical trials and were not identified in the registration trials, which were not designed to detect a CV risk.

- The seven cases of MACE noted in the 1st external adjudication included one CV death, three MI, and three strokes.
- The 2nd external adjudication confirmed four cases of MACE, which included one CV death, one MI, and two strokes. In addition, patient   (b) (6) had a confirmed MI, but was adjudicated to have unstable angina (deemed a 'leading event' by DCRI panel). Thus, the actual number of MACE outcomes in the 2nd external adjudication would be five.
- Of the two patients that had a different outcome in the 2nd external adjudication relative to the 1st external adjudication, one patient with an outcome of stroke in the 1st external adjudication was deemed to have insufficient data to adjudicate by the panel, and another patient with asymptomatic ECG changes and deemed to have an MI in the 1st external adjudication was concluded to have 'probably no CV event' by the panel. As noted above, a third patient with MI in the 1st external adjudication was deemed to have 'Unstable angina' (a leading event) by the 2nd external adjudication, although an MI was also confirmed in this patient.

Narratives for seven patients with a MACE outcome in one or both external adjudications are provided in the table below.

Table 21: Narratives for Seven Patients With a MACE Outcome

1	(b) (6) **Acute MI (internal adjudication), CV death (1st external), MI and CV Death (2nd external)** **Characteristics**: 64 y/o, white female, with non-IBS-D, on tegaserod 6 mg BID in trial AFI01; patient had no reported history of CV ischemic (CVI) disease but had two CV risk factors (age ≥55, smoking) at baseline. Isolated high BP with no formal diagnosis or treatment; hypothyroidism, stress; on concomitant Estraderm; **Event**: SAE of 'acute myocardial infarction' occurred on day 29 of treatment; patient was traveling in the car with her fiancé when she complained of chest pains and lost consciousness. When she arrived at the hospital ER by ambulance, she was unconscious her pupils were large and unreactive, the blood pressure was 70/40, and "nothing found in neurological examination". She progressed to develop asystole, was intubated and given cardiopulmonary resuscitation and rescue medications (adrenalin (13 mg), atropine (5 mg), cordarone (150 mg), and tribonate (300 ml)). An ECG was performed during this time. The tracing is not available, but the emergency room note states: "Most likely a large lateral infarct. Appears basically as a hemiblock in aVF (augmented vector foot) and reciprocal ST reductions in II, aVF and III. Varies between a number of different rhythms, such a systolic, ventricular fibrillation and ventricular tachycardia." The resuscitation procedures were not successful, and the patient was pronounced dead. No autopsy was performed. According to the hospital records, "the cause of death is acute heart infarct on the basis of chest pains and serious ECG changes". *__FDA Comments:__ This patient has no history of CV disease and has several CV risk factors: age over 55 years of age, smoking, and possible untreated hypertension (no formal diagnosis). Other risk factors (obesity, diabetes, and hyperlipidemia) are unknown. An ECG was not obtained at baseline and it is unclear whether a previous ECG from 1997 (~5 years prior to study entry) has been reviewed. Available information supports the adjudication findings of MI and CV death. Given the patient's unremarkable PMH, including prior CV symptoms, absence of significant findings on physical examination at screening, and the acute onset of event while on study drug, a relationship between the study drug and the event (MI and subsequent death) may not be definitively ruled out.*
2	(b) (6) **MI (internal adjudication), MI (1st external), MI (2nd external); SAE** **Characteristics:** 53 y/o, white female with IBS-C on tegaserod 6 mg BID (trial A2306); patient had a history of CVI disease (cardiovascular disease, peripheral vascular disease with aortic-femoral bypass, tingling of left arm) and two CV risk factors (smoking, hyperlipidemia); patient has a family history of significant heart disease. Pretreatment ECG was marked as abnormal for age, with a short PR interval (0.10 sec), minor ST depression, sinus rhythm, accelerated AV conduction, and non-specific ST abnormality. **Event**: On day 7 of treatment, the patient was admitted to the hospital due to the onset of left neck, left arm and chest pain associated with nausea, dizziness, and diaphoresis which occurred while driving vehicle and was diagnosed with an MI and underwent cardiac catheterization which revealed occlusion and inferior and apical hypokinesis. Nitrates and intravenous eptifibatide were administered. A chest X-ray on day 8 showed multiple miliary granuloma and a normal heart size. On day 9, the patient underwent a percutaneous transluminal coronary angioplasty together with stent placement. The procedure was well tolerated and the patient was discharged on day 10. Discharge medication included clopidogrel and nadolol. Atorvastatin dose was also increased and acetylsalicylic acid continued. The patient was considered completely recovered by day 27. The study medication was temporarily interrupted due to this event from day 7 to day 10. Hospital records document that cardiac enzymes were elevated in a range diagnostic for acute MI. *__FDA Comments:__ This patient has relevant PMH and CV risk factors (smoking and hyperlipidemia), and laboratory and clinical findings support the adjudication findings of MI, with occlusive coronary disease requiring stent placement. Although the patient reported also experiencing 'less intense' CV symptoms approximately 1 week prior to study entry, the documentation is not consistent in the medical records; overall the role of study drug in the development of a new onset MI may not be definitively ruled out.*

3	(b) (6) **Stroke (Internal), Stroke (1st External), Stroke (2nd External); SAE** **Characteristics**: 57 y/o, white female with functional dyspepsia on tegaserod 2 mg BID; patient had a history of cerebrovascular disease (cerebral artery occlusion) and 2 risk factors (age ≥55, hyperlipidemia) at baseline. Dyspepsia, drug hypersensitivity and herpes simplex active at entry; on acyclovir at study entry and run-in. Patient has been a heavy smoker and probably had untreated hypertension. **Event**: On day 25, the patient presented to the emergency room with impaired vision in the left eye, and memory "problems". The patient was hospitalized. MRI of the brain and MRI angiography of the head (day 26) revealed an acute right posterior cerebral artery territory infarct, with no evidence of hemorrhage, no focal hemodynamically significant stenosis. The patient's visual impairment consisted of tunnel vision. The study medication was permanently discontinued on day 24. She was treated with Coumadin from day 25 and she was discharged on day 29. After discharge from the initial hospitalization, the patient went back to the ER because of weakness of her right upper arm. By the time of the physical exam the weakness had resolved and a follow up MRI did not show any acute changes. The patient was started on heparin IV and Coumadin (on Plavix at admission). She was discharged with a diagnosis of transient ischemic attack and was on Coumadin. *FDA Comments: This patient had CV-related risk factors including a very long history of hypertension and heavy smoking; patient had cerebrovascular disease history, supported at the time of the adverse event by brain MRI findings of sequelae of chronic microvascular ischemic changes / severe chronic intracranial atherosclerosis. The time of diagnosis of cerebral artery occlusion in relation to study entry is however unclear. Physical findings and diagnostic data support the adjudication findings of stroke. However, the role of study drug in the acute onset of the AE is unclear.*
4	(b) (6) **Stroke, Angina Pectoris (Internal), Stroke (1st External), Stroke (2nd External); SAE** **Characteristics**: 78 y/o, white male with chronic constipation on tegaserod 2 mg BID; patient had a history of CVI disease (two strokes, one MI), history of bilateral carotid endarterectomies and two CV risk factors (age ≥55, hypertension) at baseline and a family history of MI; patient was on aspirin and antihypertensives. **Event**: On day 57, the patient visited the emergency department because of an irregular heartbeat. Medical history upon admission revealed cardiac catheterization done two months prior to study entry. An ECG on day 57 showed sinus rhythm with a rate of 72 beats per minute and frequent premature ventricular contractions, sometimes in bigeminal pattern. The patient had first degree AV block, left axis deviation, and some inferior nonspecific ST-T wave changes. The patient was placed on a cardiac monitor, pulse oximetry, and oxygen therapy. Chest X-ray and lab work was unremarkable, cardiac enzymes were normal. He was treated with atenolol, isosorbide dinitrate, aspirin, and vitamin B12, and then released with a diagnosis of angina. On day 70 the patient visited the cardiologist and that same day the patient had a cardiac catheterization that showed diffuse coronary artery disease (70 to 80% block). His cardiac catheter was complicated by a small stroke that led to his admission, characterized as weakness on the right side of his body. The patient had a neurological evaluation. CAT (computerized axial tomography) scan of the head showed no acute changes. Treatment of this postcatheterization event included heparin, clopidogrel, warfarin, metoprolol, and atorvastatin. Discharge from the hospital was on day 74. Patient completed the study. The patient had a quintuple coronary artery bypass graft on day 110 and was improving. *FDA Comments: This patient has several relevant CV risk factors, as well as a history of two strokes and MI prior to initiating the study. The patient's initial complaint was that of irregular heartbeat and occasional chest pain brought on by exertion, and he was found to have occlusive coronary artery disease at the time of AE. The AE of stroke that occurred as a complication of cardiac catheterization was confirmed in all three adjudications.*

5	(b) (6) **MI, V-fib (Internal), MI (1ˢᵗ External), Unstable Angina (leading), MI, V-fib (2 External); SAE** **Characteristics**: 45 y/o, white male with IBS-C on tegaserod 2 mg BID; patient had symptomatic left leg claudication and left hip pain at baseline and two CV risk factors (hyperlipidemia, smoking); patient had a family history of CAD, long history of tobacco abuse with questionable bronchitis; the claudication started one year prior to study entry without trauma or injury, and pain increased with walking; **Event**: On day 61, the patient was diagnosed with arterial blockage in the left leg and discontinued study drug. He was hospitalized on day 63 for chest pain due to a myocardial infarction. The patient underwent a triple bypass for two occluded coronary arteries. A postoperative complication of ventricular fibrillation required CPR (cardiopulmonary resuscitation) and electrical defibrillation and the patient was discharged 9 days after hospitalization. *FDA Comments: This young male patient had prior symptoms of peripheral vascular disease (leg claudication) and had several CV risk factors. He was found to have occlusive coronary artery disease at the time of the event; chest pain, MI and ventricular fibrillation appear to be of new onset while the patient was on the study drug. Therefore, a likelihood of new/worsening CVI AEs in the presence of the drug may not be ruled out.*
6	(b) (6) **Probably not an MI (Internal), MI (1ˢᵗ External), No CV event (2ⁿᵈ External); non-SAE cardiac event** **Characteristics**: 47 y/o, black female with functional dyspepsia on tegaserod 6 mg BID; patient had a history of CVI disease (prior stroke) and two CV risk factors (hypertension, obesity) at baseline; At Baseline, ECG finding showed "Clinically significant abnormality; prolonged QT interval, possibly old anteroseptal injury or infarct". **Event**: Based on an ECG finding on day 56, an asymptomatic "undiagnosed anteroseptal infarct (QRST contour)" was reported. At day 61 the ECG finding was "clinically significant abnormality: QRS (T) contour consistent with an anteroseptal infarct, age undetermined. Change from baseline: now absent R wave on V1-3, No injury current. Could reflect extension of previous injury or change in ECG techniques, i.e. lead placement." Patient completed study as planned on day 56. *FDA Comments: This was an ECG-only finding on the last study visit in the absence of any symptoms; given the absence of new symptoms, and a baseline ECG abnormality suggestive of an old infarct similar to the one on the study drug, it does not appear that the patient experienced a new or worsening CV event on the drug.*
7	(b) (6) **Cerebrovascular disorder (Internal), Stroke (1ˢᵗ external), Insufficient Data (2ⁿᵈ external); SAE- cardiac event** **Characteristics:** 50 y/o, black female with IBS-C on tegaserod 6 mg BID; patient had no reported history of CVI disease but had two CV risk factors (smoking, hypertension) at baseline. **Event**: At screening visit, the sitting vital signs were BP 160/108 mm Hg, HR 80 bpm. There were no clinically significant ECG abnormalities. The last dose of study medication was on day 15 of the double-blind treatment period. On day 1 of the withdrawal period (day 16 from first dose of study medication), the patient was hospitalized due to a stroke. The patient did not answer the four attempts that were made to contact her via certified mail sent to her home. The patient was considered an adverse event dropout due to hospitalization for a stroke, and lost to follow-up. *FDA Comments: The reported AE of stroke is significant both as it relates to the onset relative to study drug intake (after 15 days of dosing) and absence of prior CV disease in the patient. However, there were no source documents that describe the event further, and the patient was lost to follow up after the AE, thus explaining the 2ⁿᵈ external adjudication of 'insufficient data' as per their methodology.*

Abbreviations: AE, adverse event; AV, atrioventricular; BID, twice daily; BP, blood pressure; CAT, computerized axial tomography; CPR, cardiopulmonary resuscitation; CV, cardiovascular; CVI, cardiovascular ischemic; DCRI, Duke Clinical Research Institute; ECG, electrocardiogram; IBS-D, irritable bowel syndrome – diarrhea; IV, intravenous; MACE, major adverse cardiovascular event; MI, myocardial infarction; MRI, magnetic resonance imaging; PMH, past medical history; SAE, serious adverse event; y/o, year-old

Source: Updated Patient Narratives; NDA 21-200/S-015 [Module 5.3.5.4.]

Please refer to Table 39 in the appendix for the narratives of remaining CVI cases (non-MACE) that were confirmed in one or more adjudications.

4.1.3.3. Statistical Perspective

To evaluate the CV risk among subjects exposed to tegaserod compared with placebo, a meta-analysis of all 29 randomized placebo-controlled clinical trials was conducted. The meta-analysis preserves the within-study randomization and includes information from trials without any CV events.

Most of the trials had short durations with 28 of the 29 trials having treatment durations between 4 to 12 weeks, and were for multiple indications. The trials were not designed to specifically evaluate CV safety or to assess CV information. A summary of the 29 trials is provided in Table 42 in the Appendix.

The analysis population is the safety analyzable population defined as all patients exposed to the study treatment who had at least one postbaseline safety evaluation. The outcomes of interest are ischemic events and MACE cases.

The Mantel-Haenszel (MH) risk difference [29] stratified by trial was used to estimate the expected excess number of CV events per 10,000 patients in the tegaserod arm compared with placebo and the corresponding 95% CI. The size of the test (alpha-level) was not adjusted for multiple testing.

In total, the assessment of CV safety was based on 18,645 subjects: 11,614 on tegaserod and 7,031 on placebo. The majority of subjects were female, <55 years of age, and white (Table 22). Sex, age, race, history of ischemic disease, and CV risk factors are approximately balanced between tegaserod and placebo.

Table 22: Patient Demographics

Characteristic		Tegaserod N=11,614 n (%)	Placebo N=7,031 n (%)
Sex	Male	1447 (12)	877 (12)
	Female	10,167 (88)	6,154 (88)
Age (yrs)	Mean (SD)	43 (13)	43 (14)
	Range (min-max)	13-89	17-87
Race	White	8,972 (77)	5,065 (72)
	Black	745 (6)	484 (7)
	Asian	670 (6)	669 (9)
	Other	1,227 (11)	813 (12)
History of Ischemic Disease		287 (2)	168 (2)
Cardiovascular Risk Factors	Active smoking[1]	1,355 (12)	603 (9)
	Hypertension	2,045 (18)	1,248 (18)
	Hyperlipidemia	2,070 (18)	1,164 (17)
	Diabetes mellitus	439 (4)	284 (4)
	Age ≥55 years	2,337 (20)	1,513 (22)
	Obesity (BMI >30)[1]	1,836 (16)	1,166 (17)

Abbreviations: BMI, body mass index; SD, standard deviation
[1] Patients without the condition are not distinguished from patients missing data for the condition in calculating percentages

The risk difference estimates from the meta-analysis are shown in Table 23. For the ischemic events, all three adjudications show an increased number of events per 10,000 patients in the tegaserod arm compared with placebo. For MACE, the tegaserod arm has an increase of 5.4 events per 10,000 patients (95% CI: 1.1, 9.7) in the 1st external adjudication, and an increase of 3.1 events per 10,000 patients (95% CI: -0.2, 6.3) in the 2nd external adjudication.

In conclusion, the meta-analysis of 29 placebo-controlled trials indicates an increased number of ischemic events in all three adjudications, and MACE associated with tegaserod exposure compared with placebo in the 1st and 2nd external adjudications. This analysis does not overcome limitations related to short trial durations, low CV-risk population, and retrospective assessment of CV information that should be factored into the interpretation of the risk estimates.

Table 23: Cardiovascular Risk by Adjudication and Endpoint

Adjudication	Endpoint	Tegaserod N=11,614	Placebo N=7,031	Risk Difference[1] (95% CI)
Internal adjudication by Novartis (December 2006)	Major cases: Any ischemic event[2]	11	1	7.6 (1.6, 13.7)
1st external adjudication by Mt. Sinai (March 2007)	Confirmed ischemic event	13	1	10.1 (3.2, 17.0)
	MACE	7	0	5.4 (1.1, 9.7)
2nd external adjudication by Duke (May-October 2007)	Confirmed ischemic event[3]	7	1	3.8 (-0.8, 8.4)
	MACE	4	0	3.1 (-0.2, 6.3)

Abbreviations: CI, confidence interval; CVA, cerebrovascular accident; MACE, major adverse cardiovascular event; MI, myocardial infarction

[1] Expected excess or reduction (depending on the sign of the estimate) in the number of cardiovascular events per 10,000 patients in the tegaserod arm compared to placebo

[2] Comprised of confirmed, unconfirmed, or probably not

[3] Patient (b) (6) classified as having unstable angina as the leading event even though patient also had myocardial infarction

Major cases included MI, unstable angina, cardiac death, CVA, stroke

MACE consists of non-fatal stroke, non-fatal myocardial infarction, and cardiovascular death

4.1.3.4. Adjudications

An important goal of this NDA supplement review was to understand how the CV ischemic (and MACE) cases were adjudicated, including a description of the available data that supported each adjudicated outcome. While all three adjudications were conducted in a blinded fashion by experts, they differed in the source data available to support the decision at the time of adjudication, used different CV event classification systems, and involved either a re-adjudication of the 24 initially identified cases (internal and 1st external adjudications) or included a re-analysis of Db15 with broader search terms for CV signal detection (2nd external adjudication by DCRI). Given the time elapsed since the study conduct, the pooled analysis, and adjudications and the recent change of ownership, not all information required to conclude adequacy of adjudication outcomes appears to be available.

It should be noted at the outset that the interpretation of findings from all three adjudications is limited due to the following considerations. This was a retrospective analysis of pooled data, which may not allow complete capture of baseline information including that of CV ischemic disease and risk factors. Additionally, objective measures to confirm ischemic events were unavailable in many cases. Terminology for coronary ischemic events was inconsistent across studies. Several patients with CV ischemic events appeared to have baseline CV symptoms without an established diagnosis. Information was also limited on the severity of CV diseases at baseline. For many trials, the time elapsed between the initial study conduct and the time of pooled analysis was too long to ensure complete source data recovery. The type of data available at the time of adjudication has been summarized within the description of the adjudication methodologies below. Patients with diabetes were under-represented in these trials as most trials excluded patients with diabetes (except for one study specifically conducted in 81 gastropathy patients with diabetes), and active smoking status was captured in only 15 of 29 trials. In the 2nd external adjudication report, details and rationale for designating a case as 'probably no CV event' were also limited.

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The search and adjudication methods utilized are discussed in more detail below, along with their outcomes.

Initial search of the pooled database:

Database Db15 was screened for cases of coronary, cerebrovascular, and other ischemic events. Search terms for ischemic events were identified manually based on the summary tables of any AE and of SAEs (in line with the CIOMS Standard Medical Queries (SMQs) for ischemic heart disease). A search in the list of adverse events of Db15 was also run using the comprehensive list of 166 search terms in the categories of coronary, cerebrovascular and other ischemic events. This approach was unable to identify any additional ischemic events beyond those identified manually.

- Results: After reviewing the totality of clinical information, and excluding miscoded cases, 24 cases of ischemic events were identified. Patients with an ischemic event (MedDRA Preferred Terms) were identified and classified by treatment and type of event. While the number of CV ischemic cases was small relative to the overall patients in the pooled database, this initial analysis suggested that the frequency of CV events was higher in patients receiving tegaserod (n=20) compared with patients receiving placebo (n=4) (OR=3.03, 95% CI: 1.04, 8.87; p-value=0.035).

Internal Adjudication (December 2006):

All 24 "true positive" cases identified in the initial search underwent adjudication by a panel of six Novartis internal experts, including two cardiologists, in a blinded fashion. Narratives of cases included information derived primarily from SAE reports, CRFs and source document information obtained from queries. The Applicant noted that as many of the cases were from investigative sites from up to 10 years ago, source documentation was not obtained for many of these cases. The expert panel classified whether the case was a newly occurring or worsening ischemic event, with the potential responses of confirmed (based on definite clinical diagnosis supported by symptoms or treatment or objective measures), unconfirmed (based on a typical medical history but without objective measures to support the diagnosis), or probably not (atypical or preexisting without clear worsening and/or objective measures support an alternative diagnosis or were negative). In addition, cases were classified as major (e.g., MI, unstable angina pectoris, cardiac death, cerebrovascular accident/stroke) or minor (transient events without sequelae, e.g., angina pectoris, transient numbness). In patients with more than one ischemic event, the classification was made based on the 'leading' adverse event. Both confirmed (12) and unconfirmed (6) cases were reported as CVI events. CV risk factors, preexisting CV disease at baseline, and concomitant medication use was also included in assessing event rates. The risk factors assessed in this adjudication were consistent with the other two, and included history of CV disease, active smoking, history of hypertension, history of hyperlipidemia, history of diabetes mellitus, age ≥55 years, or obesity.

- Results: The overall frequency of cases with ischemic events following the internal adjudication was 18 (0.15%) on tegaserod and 2 (0.03%) on placebo (p<0.05). Four

cases (2 on drug, 2 on placebo) were classified by the adjudicators as "probably not" for reasons provided below:

1. Patient   (b) (6) (initially described as having an MI) on tegaserod had an asymptomatic ECG finding which was likely preexisting at baseline.
2. Patient   (b) (6) (Angina) reported angina pectoris at 30 days into the withdrawal period after treatment with tegaserod and subsequently had an uneventful re-challenge with active drug.
3. Patient   (b) (6) Intermittent Claudication) on placebo, which was likely o   d unrelated to the peripheral circulation.
4. Patient   (b) (6) (Chest Pain) a 35-year old female on placebo. Investigations in the Emergency Room were "negative for a cardiac event" although ECG could not rule out an infarction. Patient had no CV risk factors and completed the study without discontinuation of study medication.

Of note, both the placebo cases described above were also deemed as 'not a CV event' by the two external adjudications; of the two tegaserod cases, patient   (b) (6) was classified as 'probable MI' by the 1st external adjudication, but as no 'probably no CV event' by the 2nd external adjudication. This AE occurred 30 days after 4 weeks of tegaserod treatment, and an updated narrative indicates that MI was ruled out based on a normal ECG and normal cardiac enzymes.

1st External Adjudication (March 2007):

Additional efforts were undertaken to obtain source documents from the sites for all 24 cases. The source data were reviewed by four physicians at Novartis and any new relevant information obtained from this review was added to the case narratives before providing it to the adjudicators, with special mention that this additional information was retrieved post hoc from source data review. The original case description remained untouched. In addition to the original narratives that included information from SAE forms and CRFs, relevant medical information regarding the patient (e.g., hospital records, discharge summary, diagnostic or surgical procedures, laboratory results, ECG reports/tracings) were available at the time of this adjudication for the majority of cases. Per the 1st external adjudication report dated March 23, 2007, a review of these additional data confirmed that, in the majority of cases, patients had a history of CV disease at baseline. A panel of independent physicians from Mount Sinai Hospital, NY (including two cardiologists and one neurologist) reviewed the 24 cases identified in the internal analysis, along with the additional available source documentation. Adjudicators were blinded to the treatment and determined whether the events were major or minor, and classified the events into five categories: Definite, Probable, Possible, Definitely Not, or Unable to Adjudicate (due to insufficient information). Definite and Probable events were interpreted as 'confirmed' events.

- Results: Overall, 14 cases were 'confirmed' (9 definite, 5 probable), with 13 (0.11%) on tegaserod and 1 (0.01%) on placebo. Of the 13 cases in tegaserod, 10 were cases with coronary ischemic events including 3 MIs, 1 death, and 6 cases of unstable angina. Three other cases were stroke. The one case in placebo was a TIA. Of the 10 cases that were not confirmed, 9 cases were deemed as 'definitely not an event' and 1 case deemed as a 'possible' event (overall, 7 on drug and 3 on placebo) relative to the initially identified 24

cases. These cases were primarily related to angina/chest pain, coronary artery disease, and congestive heart failure. There was one case of MI that was deemed not an event in this adjudication, with no further explanation in the narrative section of the case assessment form.

2nd External Adjudication (February 2008):

This adjudication used a prespecified methodology for both case selection and case assessment. The search algorithm was developed by Novartis, while the adjudication methodology was developed and conducted by physicians associated with DCRI. The process sought to identify, evaluate, and classify cases of CV ischemic events (coronary and cerebrovascular) in tegaserod clinical studies based on a broader search compared to the initial search, which included MedDRA search terms for 'cardiac disorders', utilized a search algorithm used in conjunction with a Cox-2 inhibitor compound, and included a search of cases for the terms 'chest pain' and 'chest discomfort.' Individual case descriptions were updated with additional source data to provide a dataset for each patient that was as comprehensive as possible. Per the 2nd adjudication report dated February 1, 2008, additional source data retrieval included all source documents pertinent to the patient, including any pretrial or post-trial medical history that was relevant to cardiovascular status, and any newly identified information relevant to the event. Not all patients had this additional information. Case narratives were written to include all relevant information. An independent Contract Research Organization (CRO), "MD Evidence" (Orange, California, USA), was used to organize the adjudication. The Adjudication Committee consisted of three board certified cardiologists (two associated with DCRI and one from Johns Hopkins University Medical Center). The final adjudication results were provided to Novartis for analysis.

This adjudication also sought to identify, evaluate, and classify cases of congestive heart failure, arrhythmias, and conduction disorders. Based on available medical history, concurrent medication at the time of study enrollment, and baseline assessments, patient records were screened for a patient's CV risk and number of risk factors (range zero to seven: history of CV disease, active smoking, history of hypertension, history of hyperlipidemia, history of diabetes mellitus, age ≥55 years, or obesity). In case of missing data needed for the derivation of individual CV risk factors, a patient was regarded as not having the respective risk factor. Events were classified as 'probable CV event', 'probably no CV event', 'undetermined- source documents pending', or 'insufficient data to classify.' A 'probable CV event' was defined as a newly occurring or worsening event, where the case description was consistent with a CV event, and source documents (e.g., ECG tracings, cardiac enzymes, cardiac catheterization reports, cardiac imaging reports, etc.) supported the endpoint definition for a particular CV event. No evidence for anther more likely diagnosis was identifiable. Patients with more than one CV ischemic event were classified per the 'leading event' as identified by the Adjudication Committee. CV ischemic events assessed as 'probable CV event' were also categorized as 'Antiplatelet Trialists Collaboration' events, which is a classification which includes vascular death, nonfatal myocardial infarction, and stroke (which is comparable to the current standard for identifying MACE]. An event was deemed as 'probably not a CV event' when the case description might not be consistent with a CV event, and source documents (as described above) either did not meet endpoint definitions for a CV event or available source documents supported a different diagnosis. An event was deemed to have 'insufficient data' for adjudication where the case description may be consistent with CV event, but no or insufficient source documents

were available. Finally, an event was classified as 'undetermined/pending' if the case description was consistent with a CV event, but source data were pending such that the case adjudication could not be concluded.

The 2nd external adjudication methodology had prespecified criteria for identifying cases of MI, unstable angina, stroke or transient ischemic attack, arrhythmia/conduction abnormality, and congestive heart failure exacerbation. Prescreening of individual cases was conducted against these criteria to exclude cases prior to full panel adjudication. If a patient had a stable pattern of angina prior to study entry, recurrent angina during the study was classified as "stable angina" if none of the objective criteria for "unstable angina" were met.[10]

A patient was counted as having an APTC ("MACE") type event if he/she
- o had an MI confirmed by adjudication and indicated as leading event OR
- o had a stroke confirmed by adjudication and indicated as leading event AND/OR
- o died from any (serious) adverse event that is covered by any of the search algorithms applied to identify cases for adjudication (grouped as "vascular death")

If a patient had a confirmed leading event of MI or stroke and subsequently died, that patient was classified as "vascular death" only, i.e., NOT as MI or stroke within the APTC subcategories.

- Results: It should be noted that due to the re-analysis of the Db15 database for a CV signal for the 2nd external adjudication, a different mix of patients were adjudicated and confirmed, compared with the internal and 1st external adjudications. However, all 24 index cases initially identified by the Novartis search (20 on drug, 4 on placebo) were also part of the 304 'true positive' cases identified during the re-analysis of Db15 prior to the 2nd external adjudication. Of the 304 cases adjudicated, 24 (7.9%) cases (18 on tegaserod and 6 on placebo) were classified by the panel as 'probably yes' for a newly occurring or worsening CV event, while a majority 254 (83.6%) were deemed as 'probably no CV event', and 26 (8.2%) as having 'insufficient data' to classify.
- The 254 patients [158/11,614 (1.36 %) on tegaserod, 96/7031 (1.36 %) on placebo] who were classified as 'probably no CV event' by the 2nd external adjudication panel had a total of 320 AEs (127 placebo, 193 tegaserod). The AEs in these patients were listed under the following SOCs: Cardiac Disorders [palpitations, angina, arrhythmias, conduction, and valvular disorders], General Disorders and Administration Site Conditions [chest discomfort and chest pain], Nervous System Disorders [syncope], other SOCs gastrointestinal, vascular, infections, infestations], or few events for which a SOC was unassigned AEs of angina, ventricular tachycardia, chest pain, and non-cardiac AEs].

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[10] Worsening or recurrent severe or repetitive angina symptoms lasting at least 10 minutes in duration with at least two of the following,
• Associated dynamic ST-segment changes (≥1 mm ST depression or ST elevation)
• Leading to inpatient hospitalization
• Leading to an unplanned cardiac catheterization, with or without revascularization, that shows evidence of hemodynamically significant stenosis (>70%)
If a patient has a stable pattern of angina and has recurrent angina symptoms during the trial, then the patient will be classified as "stable" angina if they do not meet above criteria for "unstable angina".

- Overall, 26 events in 24 patients were confirmed (i.e., deemed 'probably yes'), including 10 CV events (9 on drug and 1 on placebo) and 16 arrhythmias (11 on tegaserod and 5 on placebo). It should be noted that the 11 cases of arrhythmias on tegaserod included 2 patients who also had a CVI event. These two patients ((b) (6) and   (b) (6)) were classified as having both CV ischemic events and arrhythmias by the 2nd external adjudication.

The following is a description of the 24 confirmed cases:

  o The 24 cases that were ultimately confirmed by the 2nd external adjudication included 10 cases (9 on tegaserod and 1 on placebo) that were initially identified in the Novartis search.
  o Of these 10 cases, 8 were confirmed as CV ischemic events (7 on tegaserod, 1 on placebo) and 2 were deemed as non-ischemic congestive heart failures, both on tegaserod. Of the seven CV ischemic cases on tegaserod, two were strokes and five were coronary ischemic events including one MI, one sudden death (secondary to an MI), and three events of unstable angina.
  o The remaining 14 cases confirmed by the 2nd external adjudication panel were new cases of arrhythmia (9 on tegaserod and 5 on placebo).
  o Eleven CV ischemia cases on tegaserod and three on placebo that were initially identified in the Novartis search were deemed as either 'probably no CV event' (n=8) or as having 'insufficient data' (n=3) by the 2nd external adjudication panel. Details could not be obtained from the available information for the reasoning behind the 2nd external adjudication outcome for these 11 initially identified cases. Based on the available AE descriptions and patient narratives, it appears that the cases deemed as 'probably no CV event' by the panel had either underlying coronary artery disease (CAD), stable angina, asymptomatic ECG findings, or absence of objective measures and/or diagnosis in presence of symptoms (e.g., negative ECG, normal cardiac enzymes).

Of note, there were additional cases that could not be adjudicated due to insufficient source documentation and showed an imbalance with tegaserod versus placebo (22 versus 4) during the 2nd external adjudication process: these AEs included chest pain (9 versus 2), angina (1 versus 0), cerebrovascular disorder (1 versus 0), chest discomfort (1 versus 0), and by-pass procedure (1 versus 0). The additional events occurred more in the tegaserod group than in placebo and raise questions about the number of missed CV events due to missing data.

4.1.3.5. Other Elements of CV Safety Signal, Including Arrhythmia, Long-Term Safety, ECG (and QT Prolongation), and Blood Pressure

4.1.3.5.1. Arrhythmic Events

A secondary objective of the 2nd external adjudication process was to identify cases of arrhythmia. Of the 26 events in 24 confirmed ('probably yes') cases in drug and placebo groups that were identified in this re-analysis by the full adjudication panel, an imbalance in arrhythmic events was noted for tegaserod versus placebo (11 on tegaserod versus 5 on placebo) in database Db15. Of these arrhythmia cases, 9 of 11 patients on tegaserod and all 5 on placebo were newly

identified by the 2nd external adjudication and were not part of the initial 24 cases identified by
the Novartis search for a CV signal. Most patients experiencing arrhythmias either had a prior
history of those arrhythmias and/or had multiple CV risk factors or CV disease at study entry.
The types and counts of arrhythmic events in drug versus placebo treatments of database Db15
are tabulated in Table 24.

Table 24: Arrhythmic Events [n (% n/N)] in Drug vs. Placebo- All Patients (Db15)

AE	Atrial Fibrillation	Supra-Ventricular Tachycardia	Ventricular Fibrillation	Ventricular Tachycardia	AV Block	Other (Arrhythmia, Palpitations, Tachycardia)	Bradycardia
Drug; 11 (0.09%)	5	2	2^	1^	0	2	0
Placebo 5 (0.07%)	1	0	0	0	1	2	1

N= total number of patients in the pooled database Db15 exposed to either tegaserod (N=11,614) or placebo (N=7031)
n= number of arrhythmic events
Abbreviations: AE, adverse event; AV, atrioventricular; Fib, fibrillation; Tach, tachycardia
^ Patient ID ____(b) (6), whose ECG showed several cardiac arrhythmias including ventricular fibrillation and ventricular
tachycardia after experiencing a fatal MI, is counted twice under both AE terms

Although an imbalance of 11 cases on tegaserod versus 5 on placebo was noted, the difference
was not statistically significant. In addition, two cases of ventricular fibrillation occurred along
with, and were perhaps caused by, an ischemic event.

A brief overview of cases by arrhythmic event type is presented below. Refer to Table 40 in the
appendix for narratives of patients with arrhythmic events in the tegaserod and placebo groups.

Ventricular Tachycardia/Fibrillation:

Both ventricular tachycardia and ventricular fibrillation occurred as part of a cluster of symptoms
in a patient who had an acute MI and suffered a cardiac arrest (ID ____(b) (6); a 64-year
old, white, non-IBS-D female patient on 6 mg BID tegaserod). Another case of ventricular
fibrillation occurred as a complication of coronary bypass surgery in a patient with an MI (ID
____(b) (6); a 45-year old, white, male IBS-C patient on 2 mg BID tegaserod). These two
cases of arrhythmias were confirmed as CVI/MACE events by all adjudications.

Supraventricular Tachycardia (SVT):

Two patients with SVT events had prior history (a 42-year-old, white, female IBS-C patient on 6
mg BID tegaserod and a 45-year old, white, female, functional dyspepsia patient on 2 mg BID
tegaserod). Neither patient was >65 years, had other significant CV disease, or had more than
one CV risk factor at baseline. Both patients completed the study.

Atrial Fibrillation:

An imbalance in atrial fibrillation (5 vs. 1) events in the pooled patient population from the meta-
analysis is noted. The age range of patients with a finding of atrial fibrillation was from 61 to 75

years old. Of these, two were females with IBS-C or GERD on 2 mg BID tegaserod, and three
were males with chronic constipation on 6 mg BID tegaserod; two of five patients in the
tegaserod group with atrial fibrillation had prior history of this arrhythmia (one male and one
female). Both patients also had multiple CV risk factors at baseline. Two other patients with
atrial fibrillation had no prior history of arrhythmia: however, they had multiple CV ischemic
risk factors at baseline, including hypertension and history of CV disease. All four patients
continued the study (one later withdrew consent). The fifth patient had a history of
hospitalization for palpitations, orthopnea, hemoptysis, weight loss, stomach pain, tachycardia
with irregular rhythm, and had a history of CAD with multiple risk factors, including
hypertension [ID   (b) (6)]. This patient died 28 days after study start date (drug
discontinued at day 7). The primary cause of death was attributed to progressive pulmonary
insufficiency attributed to stage IV adenocarcinoma of the lung and secondarily to an obstructive
superior vena cava syndrome.

For the overall population (Db15), the incidence of new or recurrent AF in the tegaserod group
was 276/100,000 patient-years (5/1806 patient-years) vs. 90/100,000 patient-years (1/1106
patient-years) in the placebo group. Historically, age-adjusted rates of AF incidence (North
America, 2010) have been reported as 264.5/100,000 for men and 196.3/100,000 for women
[30]. Historical global incidence rates are about 77.5/100,000 for men and 59.5/100,000 for
women. In addition, rates of AF increase with increasing age. Overall, the rate of AF in Db-15 is
low and not inconsistent with historical rates. When the population is limited to the "low CV
risk" group, all events are excluded.

Other arrhythmic events:

A 63-year old IBS-C female on 6 mg BID tegaserod [(b) (6)] with a history of
premature beats/extrasystole at baseline was reported to have an unspecified arrhythmia. Both
age and hyperlipidemia were considered as CV risk factors. She experienced palpitations,
fainting spell, and tiredness. Holter monitoring revealed intermittent left bundle branch block.
The patient discontinued the study. A 28-year-old female IBS-C patient on tegaserod 6 mg BID
[(b) (6)] reported having tachycardia and palpitations. There was no prior history
of arrhythmias, CV disease, or risk factors. However, she reported a 10-year history of fainting
spells. This patient completed the study.

Overall, while the incidence is small, there was an imbalance between drug versus placebo for
arrhythmias that was not statistically significant. In general, the small numbers of events in the
placebo group may denote a population at lower arrhythmic risk at baseline. In the tegaserod
group, two cases also had an ischemic event, and events such as atrial fibrillation and SVT
occurred in patients who had a prior history of the experienced arrhythmia and/or other risk
factors. The outcome of arrhythmic events was not severe, except in three cases where
arrhythmia occurred in presence of more serious comorbidities and was not the primary cause of
serious outcome, including death. Patients with arrhythmia in general had one or more of the CV
risk factors as well as history of arrhythmia (except for the two cases of SVT). When assessing
arrhythmic events by subpopulation, the overall females of Db15 database reflected a less
pronounced imbalance (seven tegaserod versus five placebo), and patients with AEs had one or
more CV risk factors, including baseline history of arrhythmia or cardiovascular disease. In the

female IBS-C population, the incidence of arrhythmic events was smaller (four tegaserod versus two placebo).

In addition, evaluation of central read ECG data including QT interval information from the placebo-controlled clinical trials of Db15 did not suggest evidence of significant changes in tegaserod treated patients (refer to Section 4.1.3.5.3 below on ECG findings including QT).

4.1.3.5.2. Long-Term (Open-label) Use

Four different automated searches were also conducted in the pooled open label clinical trial database Db14 using established criteria. Db14 included seven uncontrolled long-term studies of at least 6 months' duration, across GI disorders of IBS, CIC and dyspepsia (trials A0209, A0301E1, A0307E1, E2301E1, D2209, D2301E1, D2302E1) with a total of 3289 tegaserod-treated patients. The mean exposure in open label studies was over 6 months (227.3 days versus 56.8 days in placebo-controlled trials). One hundred twenty-eight cases were adjudicated by the 2nd external adjudication panel of which 10 (7.8%) were classified as "probably yes" for a newly occurring or worsening CV event. These included four cardiovascular ischemic events (three coronary events of 'unstable angina,' one cerebrovascular event of 'stroke') and six arrhythmic events (five events of atrial fibrillation and one sinus bradycardia). Of the 10 confirmed cases, 8 patients had more than one CV risk factor at baseline. All four patients with "ischemic" events had two or more CV risk factors at baseline. The three coronary ischemic events occurred 122 days, 197 days, and 322 days into the open-label study, while the single cerebrovascular event occurred on day 168 of the open-label phase. The arrhythmic events occurred between 47 to 295 days into the open-label study.

Overall, the frequency and pattern of CV events (ischemic and arrhythmic) in the open-label, long-term use database Db14 were comparable with those from the placebo-controlled clinical trial database, Db15. It does not appear that prolonged exposure to tegaserod was associated with an increased frequency of CV events. Based on the observed time to event within the placebo-controlled trials of 4 to 12 weeks' duration in Db15 and within the longer-use open-label trials (6 to 12 months) in Db14, the CV ischemic events following tegaserod use did not show a trend for a greater frequency of occurrence with a longer duration of use.

4.1.3.5.3. ECG Findings (Including QT)

The Applicant has provided a summary of all centrally analyzed ECG data available from Db15, IBS-C trials, and Db14. Data are presented for the overall and relevant subpopulations of interest. In the centrally analyzed studies, 12-lead ECGs were generally obtained at baseline, and at 2±0.5 hours post-dose on days 1, 29, and 85 or end-of-study. Duplicate ECG recordings with mean interval measurements from three consecutive complexes were analyzed and interpreted in a blinded fashion. ECG data analyses included a central tendency descriptive statistical summary, including two-sided 90% confidence intervals of values and changes from baseline by treatment, and categorical analyses.

In general, the analyses of trials with centrally analyzed ECG data from the pooled database Db15, IBS-C trials of Db15 (B301, B307 and B351), and relevant subpopulations of interest (low CV risk, low CV risk IBS-C, and severely symptomatic IBS-C) suggested no meaningful

effects on the QTcF, QRS, or PR intervals based on central tendency and categorical analyses. Across populations and subgroups, the tegaserod group had a slightly higher incidence of ECG abnormalities, although in general overall there was little difference between tegaserod and placebo.

Overall, the frequency of ST segment depression was 1.8% (tegaserod) vs. 1.6% (placebo). In an elderly subgroup (≥65 years, n = 296), ST segment depression was 10.7% (tegaserod) vs. 8.3% (placebo).   The frequency of T-wave flattening was 2.2% (tegaserod) vs. 2.0% (placebo). In the elderly subgroup, T-wave flattening was 7.0% (tegaserod) vs. 3.7% (placebo). Although ST segment changes and T-wave flattening can indicate myocardial ischemia, overall there is little difference between the two groups. Although the difference between the groups is more pronounced in a small elderly subgroup, the clinical meaningfulness of this finding is uncertain.

In addition, an analysis using the proposed indicated population (low CV risk female with IBS-C, n = 4239) was performed. The frequency of ST segment depression was 0.8% (tegaserod) vs. 1.0% (placebo). The frequency of T-waves flattening was 1.4% (tegaserod) vs. 1.3% (placebo).

These changes appear to represent nonspecific changes from intrinsic variation and are unlikely of clinical relevance. According to Novartis, re-analyses of these ECGs by presence/absence of CV risk factors confirmed the earlier assessment.[11]

In the tegaserod group of Db15, there were five MIs identified by ECG and one in placebo. Per Novartis, none of these MIs were confirmed after re-evaluation of the ECGs by an electrophysiology expert. Of note, none of these five patients was identified in the initial search of Db15 (24 initial cases).

- A summary of these case assessments was presented in the internal adjudication report (appendix 3). In two cases, the baseline (day -28) ECG showed an anteroseptal infarct pattern in leads V1-V4 (a lack of proper R wave progression), a pattern that was also seen in subsequent ECGs on day 1, day 29, and day 85 and was therefore not considered by the expert as a case of a new finding [(b) (6)].
- For patient   (b) (6) , the expert noted that the baseline (day -28), day 29, and day 85 patterns were similar, and normal. On day 1, an ECG change compatible with an inferior infarction pattern was noted; however, the expert stated that this change is commonly seen with low voltage in the inferior leads and expressed uncertainty in whether this patient had already experienced an inferior infarction (scar). He concluded that changes suggesting a new event occurring on day 1 were not seen.   The 2 remaining cases of MI on ECG were attributed to a change in the lead placement   (b) (6) , and   (b) (6)].

In general, trials with centrally analyzed ECG data from the long-term, open-label, pooled database Db14 suggested ECG findings similar to those observed in the placebo-controlled trials

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[11] DCRP consult review by Dr. Thomas Marciniak, 03/23/2007

of Db15. The most frequent ECG abnormality included flat T waves (1.2%) of uncertain clinical significance.

The 2nd external adjudication report included a narrative for a patient who was adjudicated to have an MI in Db14. This patient was not included as part of the ten confirmed CV cases occurring in the long-term, open-label trials, as the patient did not have an AE covered by the pre-specified selection criteria. This 55 y/o, white female IBS-C patient received placebo during the core trial and was receiving tegaserod 4 mg to 12 mg titration regimen during the extension phase. She had three CV risk factors (age ≥ 55 years, obesity and hypertension). ECG taken at the end of the extension study (day 170) showed changes of an inferior MI, which were reportedly not seen in previous tracings. No clinical manifestations of MI were reported. The investigator did not record this AE in the CRF.

It should be noted that a thorough QT (TQT) study was not conducted for tegaserod. At the time of approval, Novartis performed a pooled analysis of ECG data from phase 3 and long-term trials and did not observe differences in QTc prolongation between the treatment and placebo groups. However, ECG assessments from phase 3 trials are typically not obtained with the same rigor as in TQT studies (e.g., central reading may not occur, lack of an exposure margin above therapeutic exposures, lack of a positive control for assay sensitivity, limited sampling times). In addition, the exposure-response relationship for QTc effects for tegaserod is not known. In 2002 Morganroth et al. [31] reported no increase in the change from baseline in the QTc interval with an increase in tegaserod plasma concentration up to 100 times those measured after therapeutic doses (6 mg BID oral) after administration of tegaserod (0.8, 3.2, 5, 8, 14, and 20 mg; each dose, n=6) and placebo as a constant rate IV infusion of 40 min. However, the study did not include a positive control. The results in the publication were not verified by the FDA. It should be noted that the ICH E14 guidance was published in 2005. Available data were deemed not sufficient to exclude small mean QTc effects (10 msec) for the drug.

In clinical studies conducted across several indications (including IBS-C and CIC), centrally analyzed ECGs were recorded in 4,605 male and female patients receiving tegaserod 6mg orally every 12 hours or placebo. An absolute QTcF >480 msec to 500 msec was observed in no subjects receiving tegaserod and 1 subject receiving placebo; no subject had a QTcF >500ms. An increase in QTcF >30 to 60 msec was observed in 7.3% of subjects receiving tegaserod and 8.0% receiving placebo; an increase in QTcF >60 msec was observed in 0.3% and 0.2% of subjects, respectively.

4.1.3.5.4. Vital Signs Data (Including Blood Pressure)

In the majority of tegaserod clinical trials (Db15), resting blood pressure (BP) and heart rate measurements were obtained in sitting, supine, and standing positions. In addition, orthostatic measurements were obtained. For the IBS-C trials B251, B301, B307, and B351, a 3-hour profile was obtained following intake of the first dose that included measurements of BP and heart rate around the time of peak tegaserod plasma concentrations which occurred at approximately 1 h post-dose. BP and heart rates were evaluated at various time points postdose, and changes relative to baseline were evaluated for central tendency and categorical analyses.

The Applicant reports that for the safety population (placebo-controlled, 29 trial pooled database Db15), no consistent meaningful increases from baseline systolic BP were seen in the 12 mg/day tegaserod cohort compared with the placebo cohort (supine, sitting, 3-minute standing, immediate standing, orthostatic). In the safety population, at >12 mg/day tegaserod an increase in supine systolic BP of 1.0 to 1.9 mm Hg was reported (tegaserod versus placebo) at weeks 4 to 15 of tegaserod treatment. Similar increases were reported in sitting systolic BP, immediate standing systolic BP, and 3-minute standing systolic BP. For diastolic BP, a greater reduction of 3-minute standing diastolic BP in placebo versus 12 mg/day tegaserod at day 1 (differences in change from baseline of 0.6 to 1.3 mm Hg) was noted.

As noted in the Draft Guidance for Industry titled Assessment of Pressor Effects of Drugs, [32] published in May 2018, elevated systolic and diastolic BPs can increase CV risk. Epidemiologic evidence demonstrates that even a 2- to 3-millimeter of mercury (mm Hg) increase in existing high BP increases rates of stroke, heart attack, and death. The effect of a drug on BP can therefore be an important consideration in benefit-risk assessment.

To assess the clinical impact of ~2 mm Hg changes in systolic BP over time, CV risk was estimated using the Applicant's reported data, and based on Atherosclerotic Cardiovascular Disease risk algorithm published in 2013 American College of Cardiology and American Heart Association Guideline [33; 34]. An increase in systolic BP of 2 mm Hg had a minimal (undetectable) effect on the 10-year CV risk in the lower CV risk patient (i.e., the proposed indicated population). The baseline estimated 10-year risk was low, ~0.4%, and a small increase in systolic BP would be expected to have minimal clinical impact in this population. The same increase in systolic BP increased the 10-year risk in the relatively higher CV risk patients from 5.4% to 5.6 % (0.2 per 1000 patient-years) for patients with medium CV risk and 25.2% to 25.8% (0.6 per 1000 patient-years) for patients with high CV risk. This example shows that the increase in CV risk, caused by 2 mm Hg rise in systolic BP, was small in all patients, but was of greater magnitude in patients with a higher baseline CV risk.

The Guidance also notes that the precision of BP measurement differs widely, such that small increases in BP that could be relevant for the overall assessment of the risks of a drug may not be reliably detected in some drug development programs. Controlled blood pressure data for tegaserod was assessed in trials 4-12 weeks in duration; however long-term CV events were not studied. In addition, these trials were not designed to assess BP changes over time (e.g., ambulatory blood pressure monitoring data were not collected, ~80% of patients had missing cuff BP data). However, despite the limitations, it seems reasonable to deduce that the proposed indicated population of female patients with IBS-C and at low CV risk, in general has very low CV risk at baseline. Hence, the absolute CV risk in this relatively young and healthy female patient population is trivially affected by any small to moderate BP increase. We also turned to the clinical review of MACE from Db15, as discussed in Section 4.1.3.1.

4.1.3.6. Patient Demographic and Baseline CV Risk Characteristics

The Applicant proposes to limit tegaserod use in an IBS-C subpopulation with "low CV risk". In this regard, the Applicant has proposed to contraindicate use in patients with any of the following criteria: (1) patients with a history CVI disease, (2) patients with more than one CV risk factor,

defined as age ≥55 years, hypertension, hyperlipidemia, active smoking, diabetes, or obesity. In addition, the proposed indication is restricted to female IBS-C patients under 65 years of age. In considering the proposed restrictions to the target patient population, the review team characterized the baseline demographic factors, including the presence of ischemic disease or CV risk factors, in the cases of patients who had CV outcomes to discern if a potential pattern or combination of CV risk factors might increase CV risk. For context, the baseline CV risk characteristics of patients within the broader Db15 populations/subgroups were also evaluated.

Demographic and baseline CV risk factors in the initially identified CV ischemic cases:

To further understand how these factors may have impacted CV risk for an individual patient, a review of baseline characteristics was conducted in all 24 patients with CV ischemic signal who were identified in the initial search. In addition, case counts by demographic characteristics, particularly CV risk factors, are summarized in Table 25 for these initial 24 patients.

Table 25: Summary Tabulation of Demographic Characteristics of Patients With CV Ischemic Events (Tegaserod vs. Placebo); N=24 [Initial Cases]

		All patients (Db15)		All females		Female IBS-C	
		Drug (N=20)	Placebo (N=4)	Drug (N=12)	Placebo (N=3)	Drug (N=7)	Placebo (N=2)
Age Group	18 to <55	8	1	7	1	4	0
	55 to <65	5	1	4	1	2	1
	>65 years	7	2	1	1	1	1
History	CVI disease[a]	12[b]	1	6	0	4	0
CV Risk Factors (RFs)	Patients with >1 CV RFs[a]	17	2	10	1	6	1
Type of CV RF	Active smoking[c]	7	0	5	0	3	0
	Hypertension	11	1	6	1	4	1
	Hyperlipidemia	11	2	6	1	4	1
	Diabetes[d]	1	0	1	0	0	0
	Age ≥55 years	12	3	5	2	3	2
	Obesity	5	1	3	0	1	0

Source: Reviewer compilation from updated patient narratives and patient listings (NDA 21200/S-015)

Abbreviations: CV, cardiovascular; CVI, cardiovascular ischemic; ECG, electrocardiogram; IBS-C, irritable bowel syndrome – constipation; RF, risk factor

[a] Applicant-proposed contraindications for the "reintroduction population [i.e. low CV Risk]

[b] Does not include six patients in whom either retrospective chart analysis could not rule out abnormal ECG at baseline that was suggestive of ischemia, and/or had symptoms at baseline without a formal diagnosis of CVI disease

[c] Information on active smoking status was not collected in all trials

[d] Clinical trials generally excluded patients with diabetes

The demographic summary in Table 25 suggests that CVI events occurred in both males and females, and across all age cohorts in the randomized clinical trials of tegaserod versus placebo. The numbers of patients are small, and counts are descriptively presented. Most patients in the tegaserod group were white, except for three black females and two Asian males. All four placebo patients were white. Many tegaserod-treated patients had a history of CVI disease at baseline (12 of 20 cases) and had more than one CV risk factor (17 of 20) and therefore would likely be excluded from receiving tegaserod per the proposed contraindications. Six of seven patients aged >65 years were male. Most had CVI disease and/or more than one CV risk factor at baseline. The risk factors of age ≥55 years, hypertension, hyperlipidemia, active smoking and

obesity occurred in decreasing order of frequency; diabetics were generally excluded in these clinical trials. This trend continued in all subgroups of interest, including female IBS-C patients.

Similarly, the demographics of patients who were adjudicated to have a MACE event were examined more closely to understand how baseline risk factors may have impacted MACE risk in an individual patient, as well as to descriptively present case counts by demographic characteristics, and in particular, CV risk factors.

Table 26: Demographic Characteristics of Patients With MACE Events (per the 2nd External Adjudication Outcome)[a]

Patients With 'MACE' Type Event [DCRI]	Baseline Characteristics	All patients (Db15) Drug (N=4)	All Females Drug (N=3)	Female IBS-C Drug (N=1)
Age group	18 to <55	1	1	1
	55 to <65	2	2	0
	≥65 years	1	0	0
History	CVI disease	3	2	1
CV risk factors (RFs)	Patients with >1 CV RFs	4[b]	3	1
Type of CV RF	Active smoking[c]	2	2	1
	Hypertension[d]	1	0	0
	Hyperlipidemia	3	2	1
	Diabetes[e]	0	0	0
	Age ≥55 years	3	2	0
	Obesity	0	0	0

Source: Reviewer compilation from updated patient narratives and patient listings (NDA 21200/S-015)
Abbreviations: AE, adverse event; CV, cardiovascular; CVI, cardiovascular ischemic; DCRI, Duke Clinical Research Institute; MACE, major adverse cardiovascular event; MI, myocardial infarction; RF, risk factor
[a] There were no cases of MACE in the placebo group so that column is not displayed
[b] The count of overall MACE events is 5. However, patient ID _____ (b) (6), who had an MI, was adjudicated as a case of 'unstable angina' by DCRI (deemed to be a 'leading event'). This patient was also confirmed to have MI by the other two adjudications.
[c] Active smoking was not captured in all clinical trials
[d] Two female patients with MACE type AEs had possible untreated hypertension, but no formal diagnosis
[e] Diabetics were generally excluded from the clinical trials

Table 26 summarizes the risk factors at baseline for the MACE cases. The MACE counts are presented per the 2nd external adjudication, which was the only adjudication that prospectively included evaluation for APTC events (Antiplatelet Trialists' Collaboration: Vascular death, MI, stroke) and are similar to the current standard of Major Adverse Cardiovascular Events or MACE (CV death, nonfatal MI, or nonfatal stroke). There were 4 MACE cases confirmed by the 2nd external adjudication in the tegaserod-treated patients of Db15 and none in the placebo-treated patients. All four patients with MACE type event had more than one CV risk factor, with hyperlipidemia and age ≥55 years occurring most commonly. Three patients had a prior CV history (including CV disease, stroke/MI, cerebrovascular occlusion). The numbers of patients are very small, such that a definitive pattern or combination of specific risk factors could not be identified.

It should be noted that while MI was confirmed for patient ID _____ (b) (6) in all three adjudications (deemed as primary outcome in the internal and 1st internal adjudications), the 2nd

external adjudication outcome for this patient was 'unstable angina' (deemed as a leading event). This was a male IBS-C patient with left leg claudication and left hip pain, and two CV risk factors (hyperlipidemia and active smoking) at baseline. Thus, although per the 2nd external adjudication, the number of APTC (MACE) type events was four, including patient _____ (b) (6) would change the total number of events to five.

Demographic and CV risk characteristics of Db15 and subpopulations:

Selected demographic characteristics from over 18,000 patients across indications such as IBS-C, CIC, FD, GERD, non-IBS-D, and by subgroups of interest are compiled in Table 27 below. Considering the Applicant's proposed restrictions of a 'low CV risk' target population (i.e., females under 65 years and contraindication of high CV risk patients), it was of interest to evaluate the demographics of the overall patient pool as well as specific subgroups of interest, including IBS-C females in Db15, for their baseline CV risk characteristics. No definitive conclusions may be drawn as the Db15 database may not be reflective of the actual population that would receive the drug if approved.

A breakdown of database Db15 and subgroups by various CV risk factors is presented in Table 27, and includes the proposed restrictions/contraindications (i.e., age ≥65, history of CVI disease, or more than one CV risk factor), as well as risk combinations of interest.

Table 27: Demographic Characteristics in Db15 by Subgroup and CV Risk Factors

	All Patients (Db15)		All Females from Db15		Female IBS-C Patients	
Treatment	Tegaserod	Placebo	Tegaserod	Placebo	Tegaserod	Placebo
Characteristic	N=11614	N=7031	N=10167	N=6154	N=4490	N=2148
Gender (n %)						
Female	10167 (88%)	6154 (88%)	10167 (100%)	6154 (100%)	4490 (100%)	2148 (100%)
Male	1447 (12%)	877 (12%)	0	0	0	0
Age group (n %)						
≥65 years[a]	690 (6%)	475 (7%)	484 (5%)	337 (5%)	164 (4%)	93 (4%)
18 to <65 years	10919 (94%)	6554 (93%)	9678 (95%)	5815 (95%)	4322 (96%)	2055 (96%)
History of Ischemic CV Disease (n %)[a]	287 (2%)	168 (2%)	201 (2%)	113 (2%)	63 (1%)	37 (2%)
CV Risk Factors (n %)						
Active smoking[b]	1355 (12%)	603 (9%)	1192 (12%)	534 (9%)	922 (21%)	422 (20%)
Hypertension	2045 (18%)	1248 (18%)	1641 (16%)	995 (16%)	663 (15%)	314 (15%)
Hyperlipidemia	2070 (18%)	1164 (17%)	1745 (17%)	984 (16%)	868 (19%)	413 (19%)
Diabetes mellitus	439 (4%)	284 (4%)	352 (3%)	233 (4%)	110 (2%)	69 (3%)
Age ≥55 years	2337 (20%)	1513 (22%)	1869 (18%)	1225 (20%)	728 (16%)	382 (18%)
Obesity (BMI >30)[b]	1836 (16%)	1166 (17%)	1610 (16%)	1033 (17%)	684 (15%)	349 (16%)
No. of CV Risk Factors (n %)						
CV Risk Factor =0	5501 (47%)	3432 (49%)	4983 (49%)	3103 (50%)	1968 (44%)	935 (44%)
CV Risk Factor =1	3300 (28%)	1917 (27%)	2891 (28%)	1660 (27%)	1461 (333%)	675 (31%)
CV Risk Factor >1[a]	2813 (24%)	1682 (24%)	2293 (23%)	1391 (23%)	1061 (24%)	538 (25%)
CV Risk Factor >2[a]	1139 (10%)	680 (10%)	900 (9%)	545 (9%)	385 (9%)	207 (10%)
CV Risk Factor >3[a]	393 (3%)	224 (3%)	305 (3%)	172 (3%)	114 (3%)	52 (2%)
CV Risk Factor >4[a]	89 (1%)	56 (1%)	66 (1%)	40 (1%)	24 (1%)	14 (1%)
CV Risk Factor >5[a]	13 (<1%)	9 (<1%)	9 (<1%)	6 (<1%)	2 (<1%)	2 (<1%)
Age ≥65 + History of Ischemic CV Disease + CV Risk factor >1[b, c]	104 (1%)	75 (1%)	64 (1%)	44 (1%)	15 (<1%)	16 (1%)
Age <65 + No History of Ischemic CV Disease + CV Risk factor ≤1[b, d]	8639 (74%)	5217 (74%)	7756 (76%)	4664 (76%)	3398 (76%)	1588 (74%)

Source: Safety statistical reviewer compilation from database Db15
Abbreviations: BMI, body mass index; CV, cardiovascular; IBS-C, irritable bowel syndrome — constipation; N, sample size for the populations; n, sample size fort the subgroups
[a] Proposed population exclusion/contraindication
[b] Patients without the condition are not distinguished from patients missing data for the condition in calculating percentages
[c] Risk combination of interest, highest CV risk, population with all three contraindications
[d] Risk combination of interest, lowest CV risk, population without contraindications

The majority of the patients in the 29-trial pooled database were females (88%) in both drug and placebo groups. Approximately 95% patients were between ages of 18 to <65 years. The trend remained consistent for DB15 females-only and female IBS-C subpopulations. Of note, the frequency of patients with concomitant cardioprotective medication, such as beta-blockers or platelet aggregation inhibitors, and antihypertensives or lipid-lowering drugs appeared balanced across treatment groups (refer to Table 43 in the Appendix). There was a slightly higher frequency of nonsteroidal use in the patients taking tegaserod versus placebo (a difference between groups of about 1%). Approximately 1 to 2% of patients in Db15 had a history of CVI disease at baseline, with a consistent trend noted in the subgroups of interest. In general, the Db15 patients' baseline demographic and CVI disease/risk characteristics were comparable across drug and placebo. Approximately 75 to 77% of patients in Db15 and subgroups had zero

or one CV risk factors and the predominant risk factors were hypertension, hyperlipidemia, obesity or age ≥55 years (occurring in 15 to 20% of patients).

For IBS-C patients who were deemed to have one CV risk factor at baseline (and thus would be eligible to receive tegaserod in the absence of CVI disease history), the breakdown by type of risk factor is presented to characterize the CV risk profile in the proposed target population in Table 28.

Table 28: Types and Incidence of CV Risk Factors in IBS-C Females with One Risk Factor at Baseline

	Female IBSC Patients with 1 Risk Factor			
Treatment	Tegaserod		Placebo	
N	1461		675	
	n	%	n	%
Smoking	575	39	245	36
Hypertension	137	9	59	9
Hyperlipidemia	262	18	123	18
Diabetes	9	1	6	1
Age	201	14	100	15
Obesity	246	17	125	19

Source: Division of Biostatistics VII (DB7) compilation from database Db15
Patients without the condition are not distinguished from 23 patients missing data for the condition in calculating percentages
N, sample size for the subpopulations; n, sample size for the subgroups

The above breakdown suggests that smoking (36 to 39%), hyperlipidemia (18%), and obesity (17 to 19%), followed by age >55 years (14 to 15%) were the most common risk factors in IBS-C females in the clinical trial database. Patients with diabetes were generally excluded from trials and therefore may not be accurately represented. Smoking status was obtained at screening in the IBS-C trials and therefore the overall incidence of this risk factor appears greater compared with that in the broader Db15 population, where smoking data were available in only 15 of 29 trials.

Approximately 75% of female IBS-C patients in Db15 fit the criteria for the proposed 'low CV risk' subpopulation i.e., under 65 years of age, with no CVI disease history, and with no more than one CV risk factor. Thus, about 25% of patients in Db15 and subgroups would not have been able to receive tegaserod if limited by the proposed criteria. It is reassuring to note that within the safety database from clinical trials, most females with IBS-C would still be able to receive the drug, with the caveat that this would not necessarily be reflective of the actual population that might receive the drug if approved.

4.1.3.7. CVI Signal by Subpopulations – Assessment of Reintroduction Population

The Applicant proposes a reintroduction population defined as female IBS-C patients under 65 years of age, and with a 'low CV Risk' at baseline defined by the following contraindications:

- A history of CV ischemic disease such as MI, stroke, TIA, or angina
- More than one CV risk factor: hypertension, tobacco use, diabetes, hypercholesterolemia, age ≥55 years, obesity

These characteristics are accepted as the major risk factors for developing CV disease [17].

As presented in Table 29, the number of confirmed CVI/MACE events is reduced when patients with high CV risk at baseline are excluded (MACE incidence is shown in the table for the two external adjudications):

Table 29: CVI Events by Various Subgroups

Adjudication	Event Type	All Patients, Db15 Drug (N=11614)	All Patients, Db15 Placebo (N=7031)	Females, Db15 Drug (N=10167)	Females, Db15 Placebo (N=6154)	Low CV Risk Females, Db15 Drug (N=7815)	Low CV Risk Females, Db15 Placebo (N=4701)
Internal (Novartis)	CVI Events	18 (0.15%)	2 (0.03%)	10 (0.1%)	1 (0.02%)	2 (0.03%)	0
1st External (Mt. Sinai)	CVI Events	13 (0.11%)	1 (0.01%)	8 (0.08%)	1 (0.02%)	1 (0.01%)	0
	MACE	7 (0.06%)	0	5 (0.05%)	0	0	0
2nd External (DCRI)	CVI Events	7 (0.06%)	1 (0.01%)	4 (0.04%)	1 (0.02%)	1 (0.01%)	0
	MACE	4 (0.03%)	0	3 (0.03%)	0	0	0

Source: Reviewer's compilation of case counts and incidence rates from summary of clinical safety, and adjudication reports.
Abbreviations: CV, cardiovascular; CVI, cardiovascular ischemic; DCRI, Duke Clinical Research Institute; MACE, major adverse cardiovascular event

This reduction in cases is consistent when applied to the results from the two external adjudications; the number of CVI and MACE events on tegaserod reduce to one and zero, respectively, and hence supports CV safety in a narrow reintroduction population (i.e., female IBS-C patients with low CV risk). However, it should also be noted here that approximately 99% of patients in Db15 that had one or more CV risk factors at baseline (i.e., proposed contraindications) did not go on to experience a cardiovascular event.

The review of index cases suggests that ischemic events occurred mostly in patients with cardiac risk factors or with a history of CV disease (i.e., population at increased baseline risk for ischemic events). As can be expected from the small number of CVI/MACE cases, the majority of patients in Db15 did not experience a CVI event while on tegaserod. However, baseline CVI disease/risk characteristics were comparable in Db15 across drug and placebo. Given the size of the safety database and its randomized nature, one would expect CV events to also be balanced between treatment groups.

Severely Symptomatic IBS-C

The review team additionally explored both the safety and efficacy of this product in patients with severely symptomatic IBS-C (refer to Section 3 Efficacy for further discussion regarding efficacy). Seven IBS-C patients who were identified in the internal adjudication had a CVI signal, and symptom severity information was available for six patients. Of these, only one patient [ID _____ (b) (6)] was determined to have "severely symptomatic" IBS-C as per

the FDA recommended definition. This female patient had symptoms described as worsening of exercise-induced angina during a routine stress test, and was adjudicated as having a case of unconfirmed, minor Angina Pectoris in the internal adjudication. The first external adjudication deemed this patient's case as 'definitely not an event', and it was deemed as 'probably no CV event' in the 2nd external adjudication, but noted to have 'stable angina.' This patient had multiple prior angioplasties and was diagnosed with atherosclerosis-related carotid stenosis. She was reported to have a normal baseline ECG. While it may be of interest to know the number of patients (of the initial 24 cases) who had a CV event and severely symptomatic IBS-C (an alternative target subpopulation), we would not expect severity of GI symptoms to impact a patient's CV risk profile.

4.1.3.8. CV Signal: Conclusions

The number of cases with CV ischemic events, including the subset MACE, in tegaserod-treated patients is small relative to the size of the overall safety database; however, an imbalance on tegaserod relative to placebo persisted across all adjudications.

The Applicant's definition of low CV risk appears reasonable, and further exploration of CV risk factor combinations did not represent a specific pattern that could characterize a population at higher CV risk. Because of the retrospective nature of the analysis, the documentation of accurate CV medical history, including severity at baseline, may not have been thorough for all patients. Patients with diabetes were generally excluded from clinical trials and therefore may not be a true representation of patients who are seen in clinical practice. In addition, active smoking status was not captured in 14 trials and therefore the incidence provided may not be precise. However, with the caveat of missing data, the frequency of CV risk factors appeared otherwise balanced across treatment groups. It should also be noted the analysis used the following approach to control for missing data, such that if any CV risk factors were missing from the patient's record the analysis was performed by treating missing values as not having the CV risk factor. Therefore, subjects who actually may have had more than one CV risk factor could have been included in the low CV risk subpopulation safety analyses, and thus could have been at risk for CV events.[12] The reduced number of confirmed CVI/MACE events in the low CV risk female population therefore may provide some reassurance that the benefit-risk profile is favorable in this subpopulation.

The review of index cases suggests that ischemic events occurred mostly in patients with CV risk factors or with a history of CV disease (i.e., a population at increased baseline risk for ischemic events). Therefore, it may be reasonable to narrow the indication to females with IBS-C who are at low CV risk. An exploratory analysis of female IBS-C patients within Db15 showed that approximately 75% of female IBS-C patients in Db15 would fit the low CV risk criteria, with the caveat that this would not necessarily be reflective of the actual population that might receive the drug if approved. Alternatively, a severe IBS-C population in whom the benefits of tegaserod treatment could be expected to outweigh the potential risks could be considered. An additional restriction of the drug to patients who are at low CV risk AND severely symptomatic female IBS-C patients would narrow the population further such that many patients with IBS-C might

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[12] DCRP consult review by Drs' Garnett and Stockbridge (June 2, 2017)

not be eligible; however, several other products for IBS-C have been approved in the U.S. since tegaserod was withdrawn from the market, and represent available treatment options for patients with this disease, albeit via different mechanisms of action. An overall benefit-risk evaluation is critical in considering the appropriate reintroduction population for this product.

4.1.4. Postmarketing/Epidemiologic Study

4.1.4.1. Division of Pharmacovigilance Analysis of Postmarketing Cardiac and Cerebrovascular Events

The Division of Pharmacovigilance (DPV) completed a review of the FDA Adverse Event Reporting System (FAERS) database for postmarketing cases of coronary and cerebrovascular adverse events[13] reported with tegaserod use from July 24, 2002 (U.S. approval date for tegaserod) to March 31, 2018. The Applicant proposed a restricted population of low CV risk for tegaserod reintroduction (i.e., females under 65 years of age with no history of major CVI disease (myocardial infarction, stroke, transient ischemic attack, or angina) or no more than one cardiovascular risk factor (hypertension, tobacco use, diabetes, hypercholesterolemia, age ≥55 years, or obesity). Spontaneous postmarketing reports in the FAERS database are not a reliable source to allow determination of causality between a drug and adverse event that has a high background rate in the underlying population (e.g., MI in patients with high CV risk). Therefore, we evaluated the FAERS cases to determine whether the coronary or cerebrovascular events occurred among the Applicant's proposed low CV risk population for reintroduction. These cases would be of interest because they may suggest a potential role for a drug-induced adverse event (e.g., stroke in a young patient with low CV risk).

The search of the FAERS database retrieved 67 cases of coronary (n=39) and cerebrovascular (n=28) events associated with tegaserod use that contained sufficient information to assess the patient's baseline CV risk. Table 30 below contains the descriptive characteristics of the 67 cases. We did not include male patients in our assessment because the proposed indication for tegaserod is in females. The majority of patients (60 out of 67) did not have low CV risk at baseline, and would not fit the Applicant's proposed criteria for reintroduction; 35 had a history of CVI disease, and 55 had two of more cardiovascular risk factors.[14] Six (coronary, n=2; cerebrovascular, n=4) of 67 cases met the Applicant's proposed criteria for tegaserod use of no or low CV risk (i.e., no CVI disease and zero or one CV risk factor). However, five of the six cases did not report the presence or absence of all CV risk factors; the remaining case of MI had a family history of MI. It is possible that some of the cases would be ineligible for tegaserod based on the criteria if all CV risk factors were reported. Of the four cases of cerebrovascular

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[13] We included the following Preferred Terms (PTs) in our search, which are consistent with the sponsor's database adjudications described in Table 21: Summary of CV Ischemic (CVI) Counts – Pooled Database Db15: Angina pectoris, Angina unstable, Cerebral artery occlusion, Cerebrovascular accident, Cerebrovascular disorder, Coronary artery disease, Coronary artery stenosis, Myocardial infarction, Myocardial ischaemia, Sudden cardiac death, and Transient ischaemic attack.

[14] Note that CVI disease and the presence of two or more cardiovascular risk factors are not mutually exclusive.

events that met the Applicant's proposed population, three received concomitant estrogen or hormone replacement therapy.[15]

Table 30: Characteristics and CV Risk Factors of Coronary and Cerebrovascular Event Cases Associated With Tegaserod in FAERS, N=67[a]

Characteristic	Coronary Events (n=39)			Cerebrovascular Events (n=28)		
Sex						
Female	39			28		
Male	0			0		
Age (years)						
18 to 55	12			10		
55 to 65	10			9		
≥65	17			6		
Not reported	0			3		
Country						
United States	32			24		
Foreign	7			4		
Serious Outcomes						
Death	5			2		
Hospitalization	30			21		
Life-threatening	14			1		
Disability	1			3		
Other serious	22			20		
Indication						
IBS	18			13		
Constipation	10			8		
Other	3			4		
Not reported	8			3		
History of CVI disease[b]						
Yes	21			14		
No	4			2		
Not reported	14			12		
CV risk factors	Yes	No	NR	Yes	No	NR
Tobacco Use	14	8	17	3	3	22
Hypertension	23	5	11	19	3	6
Hyperlipidemia	20	4	15	17	1	10
Diabetes mellitus	13	6	20	10	1	17
Obesity	4	7	28	4	1	23
Age ≥55 years	27	12	0	15	10	3
Number of confirmed cardiovascular risk factors[c]	Zero (1) One (3) Two (17) Three (9) Four (6) Five (3)			Zero (1) One (7) Two (4) Three (11) Four (5) Five (0)		

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[15] Estrogen and other hormone replacement therapy product labeling contains a boxed warning for increased risk of stroke.

Characteristic	Coronary Events (n=39)	Cerebrovascular Events (n=28)
Patients without CVI disease or ≤1 CV risk factor	2[d]	4[e]

Abbreviations: CAD, coronary artery disease; CV, cardiovascular; CVI, cardiovascular ischemic; FAERS, FDA Adverse Event Reporting System; IBS, irritable bowel syndrome; NR, not reported
[a] Cases received by FDA from July 24, 2002 to March 31, 2018
[b] CVI disease included myocardial infarction, stroke, or CAD.
[c] Cases may have additional risk factors that were not stated in the report.
[d] There was one case of myocardial infarction and one case of unstable angina.
[e] All four of these patients experienced a stroke; three of the four were on concomitant estrogen or hormone replacement therapy.

We did not identify a specific pattern of cases of coronary or cerebrovascular events occurring in patients receiving tegaserod who otherwise had no or low CV risk for such events. Only one case of MI confirmed the patient's absence of all CV risk factors (per the Applicant's criteria), but did have a family history of CVI disease.

We are mindful of the fact that the absence of reporting does not necessarily mean the absence of a signal and that FAERS data have limitations. A limitation to FAERS data includes under-reporting to the FAERS database. FDA does not receive all adverse event reports that may potentially occur with a product. Many factors can influence the reporting of an event, including the length of time a product has been marketed. Spontaneous adverse event reports are frequently missing complete information necessary for determining whether there is a causal relationship between a product and an adverse event; in this review, missing information may not have allowed us to accurately categorize the CV risk status for each patient. Also, spontaneous adverse event reports are rarely reliable to determine a causal association between a drug and adverse event with delayed time to onset or high background rate in the underlying population. Because of these limitations, FAERS data alone cannot be relied upon to definitively rule out a risk of use of tegaserod in the Applicant's proposed population for reintroduction.

4.1.4.2. Division of Epidemiology Review of Observational Study

To support the CV safety of tegaserod, the Applicant submitted a final report from an observational (non-randomized) study funded by Novartis and completed in 2007 by i3 Drug Safety, with main results subsequently published by Loughlin, *et al.*, in 2010 [2]. With the analytic datasets used by i3 Drug Safety not available, FDA assessed not only the 2010 manuscript by Loughlin but also the study protocols and study reports prepared in 2007 by i3 Drug Safety for Novartis.

Using a U.S. database (Ingenix Research Data Mart) of insurance claims submitted to UnitedHealthcare, i3 Drug Safety constructed two propensity-score-matched cohorts representing patient-time associated with either the initiation or non-initiation of tegaserod between September 2002 and December 2006.

The exposed cohort contained 52,229 patients (11.8% men, 23.6% age ≥55 years) with an index pharmacy claim for tegaserod and no claims for tegaserod during the preceding six months. With index date chosen at random, the unexposed cohort contained 52,229, 1:1 propensity-score-

matched patients sampled from a large comparator pool of patients with medical claims containing a diagnosis code frequently seen in the exposed cohort. Cohort matching occurred within 1-year blocks of calendar time. As shown in Table 31, the exposed and unexposed cohorts appeared well matched on baseline risk factors for CV disease.

Table 31: Baseline Risk Factors for Matched Pairs, by Exposure Cohort, N=52,229

Demographic characteristic	Exposed, %		Std. Diff.[a]
	Yes	No	
Male sex	11.8	12.1	0.01
Age ≥55 years	23.6	25.0	0.03
Medical diagnosis[b]			
Hypertensive diseases	16.9	17.9	0.03
Disorders of lipid metabolism	16.0	17.1	0.03
Diabetes mellitus and complications	5.9	6.7	0.03
Drug treatment[c]			
Anti-hypertensives and diuretics	26.5	28.1	0.04
Statins	12.2	12.8	0.02
Insulin and other anti-diabetics	5.6	6.1	0.02
Composite risk factor			
Coronary ischemic disease or coronary revascularization[b]	3.1	3.6	0.03
Any cardiovascular disease risk[d]	46.9	49.5	0.05

REFERENCE: Table 1g in Final Study Report from i3 Drug Safety.
[a] Std. Diff., Standardized Difference.
[b] As defined by diagnosis or procedure codes attached to health insurance claims for inpatient or outpatient care received during a 6-month preindex baseline period.
[c] As defined by drug codes attached to pharmacy claims for drugs dispensed during a 6-month preindex baseline period.
[d] Composite formed from 11 baseline risk factors, representing age ≥55 years, medical diagnosis of hypertensive disease, diabetes mellitus, disorder of lipid metabolism, obesity, or tobacco use disorder, prescription for anti-hypertensive, antidiabetic, statin, or fibrate, and coronary ischemic disease or coronary revascularization.

Using ICD-9 diagnosis and CPT-4 procedure codes on hospital claims, i3 Drug Safety identified CV events occurring during the 6 months after each patient's index date, as follows.

- Acute Myocardial Infarction (AMI): ICD-9 410.x (Acute myocardial infarction) or ICD-9 798.x (Sudden death, cause unknown).

- Acute Coronary Syndrome (ACS): ICD-9 411.1 (Intermediate coronary syndrome).

- Coronary Revascularization (CR): CPT-4 codes for coronary artery bypass, coronary endarterectomy, percutaneous transluminal coronary angioplasty (PTCA), or coronary revascularization.

- Stroke: ICD-9 432.x (Other and unspecified intracranial hemorrhage), ICD-9 433.x (Occlusion and stenosis of precerebral arteries), ICD-9 434.x (Occlusion of cerebral arteries), ICD-9 435.x (Transient cerebral ischemia), ICD-9 436.x (Acute, but ill-defined, cerebrovascular disease), or ICD-9 437.x (Other and ill-defined cerebrovascular disease).

To validate these events, i3 Drug Safety obtained patient charts for 85% and 84% events occurring in exposed and unexposed patients, respectively. A study clinician blinded to study exposure reviewed each chart abstract prepared by research nurses. For chart validation purposes:

- AMI required an event date specified by physician diagnosis in the patient's chart or a "likely clinical scenario" supported by other evidence, such as abnormal electrocardiogram with elevated blood creatine kinase.

- ACS required an event date specified by physician diagnosis in the patient's chart or a "likely clinical scenario" associated with an appropriate diagnostic procedure, such as coronary catheterization.

- CR required procedure-date-documented coronary artery bypass graft surgery, percutaneous coronary intervention, or thrombolysis by intravenous infusion.

- Stroke (exclusive of transient ischemic attack) required an event specified by physician diagnosis in the patient's chart or diagnosis supported by appropriate diagnostic test (*e.g.*, computed tomography of brain) or therapeutic intervention (*e.g.*, intravenous streptokinase).

Charts confirmed: 1) Cardiovascular Ischemic Event (CVIE, a composite of AMI, ACS, or CR) in 232 of 378 (61%) patients with CVIE on claims; and 2) Stroke in 35 of 205 (17%) patients with Stroke on claims (Table 32).

Table 32: Outcomes Identified by Claims and Confirmed by Medical Records[a]

Outcome	Claims	Confirmed	PPV[b]
Cardiovascular Ischemic Event (CVIE)	378	232	0.72
Myocardial Infarction (MI)	141	68	0.57
Acute Coronary Syndrome (ACS)	127	69	0.64
Coronary Revascularization (CR)	237	182	0.90
Stroke	205	35	0.20

Reference: Table 2a and Table 2b in Final Study Report from i3 Drug Safety.
Abbreviations: PPV, positive predictive value
[a] Including unmatched patients in tegaserod-exposed group.
[b] Positive predictive value, calculated as confirmed/f·claims, where f=0.85, the fraction of events with medical records available.

In the 6 months after an index prescription for tegaserod, hospital claims identified 170 patients with one or more CVIE, including 60, 58, and 107 patients with diagnosis codes for AMI, ACS, and CR, respectively (Table 33).

Table 33: Incidence and Hazard Ratios for Claims-Based Outcomes (52,229 Matched Pairs), Before Patient-Chart Confirmation[a]

Outcome	EXP	Event, N	Incidence per 1000 patient-years		Crude Hazard Ratio		Adjusted Hazard Ratio[b]	
			Rate	95% CI	HR	95% CI	HR	95% CI
Cardiovascular ischemic event	Yes	170	7.67	6.56, 8.92	0.88	0.72, 1.08	0.90	0.73, 1.10
	No	193	8.70	7.52, 10.0				
Acute myocardial infarction	Yes	60	2.71	2.06, 3.48	0.82	0.58, 1.16	0.84	0.60, 1.19
	No	73	3.29	2.58, 4.13				
Acute coronary syndrome	Yes	58	2.62	1.99, 3.38	0.91	0.64, 1.29	0.91	0.64, 1.31
	No	64	2.88	2.22, 3.68				
Coronary revas-cularization	Yes	107	4.83	3.96, 5.83	0.89	0.69, 1.16	0.91	0.70, 1.18
	No	120	5.41	4.48, 6.47				
Stroke	Yes	80	3.61	2.86, 4.49	0.66	0.49, 0.87	0.67	0.51, 0.89
	No	122	5.50	4.57, 6.57				

Reference: Tables 3a-e in Final Study Report from i3 Drug Safety.
Abbreviations: CI, confidence interval; EXP, tegaserod exposure; HR, hazard ratio
[a] Outcomes observed over 6-month window, ≈22,200 total patient-years per exposure group (≈5.1 months per patient, on average). Data based on Cox proportional hazards regression.
[b] Adjusted for age, sex, year, geographic region, and 14 baseline covariates.

Table 34 shows the main results from i3 Drug Safety for the chart-confirmed outcomes of CVIE and stroke:

- With 107 and 115 exposed and unexposed patients with one or more events, respectively, i3 Drug Safety estimated CVIE risk during the 6 months after tegaserod exposure at adjusted hazard ratio (HR)=0.95 (95% CI: 0.73, 1.23).

- With 16 and 18 exposed and unexposed patients with one or more events, respectively, i3 Drug Safety estimated Stroke risk during the 6 months after tegaserod exposure at HR=0.90 (95% CI: 0.46, 1.77).

Table 34: Incidence and Hazard Ratios for Chart-Confirmed Outcomes (52,229 Matched Pairs), by Tegaserod Exposure[a]

Outcome	EXP	Event, N	Incidence per 1000 patient-years		Crude Hazard Ratio		Adjusted Hazard Ratio[b]	
			Rate	95% CI	HR	95% CI	HR	95% CI
Cardiovascular Ischemic Event	YES	107	4.83	3.96, 5.83	0.93	0.72, 1.21	0.95	0.73, 1.23
	NO	115	5.18	4.28, 6.22				
Stroke	YES	16	0.72	0.41, 1.17	0.89	0.45, 1.75	0.90	0.46, 1.77
	NO	18	0.81	0.48, 1.28				

Reference: Tables 6a-b in Final Study Report from i3 Drug Safety.
Abbreviations: CI, confidence interval; EXP, tegaserod exposure; HR, hazard ratio
[a] Outcomes observed over 6-month window, ≈22,200 total patient-years per exposure group (≈5.1 months per patient, on average). Data based on Cox proportional hazards regression.
[b] Adjusted for age, sex, year, geographic region, and 14 baseline covariates.

A subset analysis showed strong risk stratification by baseline presence or absence of a cardiovascular disease risk factor (Table 35).

Table 35: Claims-Based and Chart-Confirmed Cardiovascular Ischemic Events (CVIE)[a] by Any Baseline Risk Factor

CVIE Outcome	Any baseline CV risk factor[b]	Event, N	Incidence per 1000 patient-years	
			Rate	95% CI
Claims-based	No	33	1.44	0.99, 2.02
	Yes	330	15.44	13.8, 17.2
Chart-confirmed	No	8	0.35	0.15, 0.69
	Yes	214	10.01	8.71, 11.4

Reference: Tables 4a and 7a in Final Study Report from i3 Drug Safety.
Abbreviations: CI, confidence interval; CV, cardiovascular; CVIE, cardiovascular ischemic event
[a] Data from matched tegaserod-exposed and unexposed patients.
[b] Age ≥55 years, medical diagnosis of hypertensive disease, diabetes mellitus, disorder of lipid metabolism, obesity, or tobacco use disorder, prescription for anti-hypertensive, antidiabetic, statin, or fibrate, coronary ischemic disease, or coronary revascularization.

In addition to analyses conducted over fixed 6-month exposure windows, i3 Drug Safety also presented results from an as-treated analysis. With average duration of tegaserod use during the 6-month study timeframe estimated at 2.4 months per patient, this as-treated analysis estimated risk for chart-confirmed CVIE during current tegaserod use (59 events over 10,359 patient-years) relative to nonuse (114 events over 21,848 patient-years) at adjusted rate ratio (RR)=1.14 (95% CI: 0.83, 1.56). The as-treated analysis estimated risk for chart-confirmed Stroke during current use (9 events over 10,365 patient-years) relative to nonuse (18 events over 21,870 patient-years) at adjusted RR=1.09 (95% CI: 0.49, 2.42).

In summary, i3 Drug Safety used a U.S. database of medical insurance claims to construct two propensity-score-matched cohorts representing patient-time associated with either the initiation or non-initiation of tegaserod between September 2002 and December 2006. In 52,229 matched patient pairs, study-defined endpoints for cardiovascular outcomes occurred no more frequently during 6-month postindex follow-up in tegaserod exposed than unexposed patients. For example, a Cox proportional hazards regression analysis estimated relative risk for first chart-confirmed Cardiovascular Ischemic Event (CVIE) at adjusted HR=0.95 (95% CI: 0.73, 1.23), and first chart-confirmed Stroke at HR=0.90 (95% CI: 0.46, 1.77).

FDA found no evidence for selective reporting based on the overall consistency of information in a study protocol, final study report, and published manuscript, in addition to the responses of the Applicant to several requests for additional information. A formal analysis for the internal validity of results found moderate risk of bias due to confounding. Therefore, these results, though a product of an observational study that used sound methods overall, are regarded by FDA as <u>not</u> comparable to the results from a well-performed randomized trial. The CVIE composite included Coronary Revascularization, without distinction between intervention for acute (emergent) or chronic (elective) indications. Concerned primarily about tegaserod's acute effects, FDA regarded elective intervention for stable CV disease as poorly suited for the CVIE composite outcome. If frequent relative to emergent interventions, elective interventions might weaken the CVIE outcome as a measure for possible CV risk from tegaserod. Finally, a small number of events limited the potential meaningfulness of the result reported for Stroke.

4.2. Neuropsychiatric Adverse Events of Interest

4.2.1. Clinical/Statistics

In 2005, the FDA requested that Novartis provide information on Suicidal Ideation and Behavior (SI/B) events that occurred in the premarketing tegaserod clinical trials, after a routine review of spontaneous postmarketing reports submitted to FAERS indicated a potential postmarketing signal for suicidal behaviors with tegaserod. Subsequently, FDA evaluated the Novartis's analysis of all placebo-controlled studies comprised of 10,951 patients treated with tegaserod and 6,236 patients treated with placebo (as of March 2006), including an exposure-adjusted relative risk analysis. The overall frequency of SI/B events (based on MedDRA classification) was 8 patients out of 10,951 (0.07%) in the tegaserod group versus one patient out of 6,236 (0.02%) in the placebo group. In premarketing clinical trials, 2 tegaserod-treated patients completed suicide (1 in a placebo-controlled study and 1 during an open-label tegaserod study). During a placebo-controlled trial, a female patient treated with tegaserod for IBS and predominant constipation completed suicide on day 36 of treatment. She had a 14-year history of depression and was treated with amitriptyline. The investigator concluded that the suicide was not related to tegaserod. No additional information was provided in the case report. During an open-label study of tegaserod, a female patient with a history of psychiatric disorder and psychosomatic disorder (both unspecified) completed suicide on day 30 of tegaserod treatment. The investigator concluded that the suicide was not related to tegaserod. No additional information was provided in the case report.

Suicidal ideation in clinical trials was proportionately more frequent among patients receiving antidepressant medication but was not limited to such patients. The eight cases in the tegaserod-treated patients included one completed suicide, two suicide attempts, four self-injurious behavior (with unknown suicidal intent), and one suicidal ideation, as compared with one suicide attempt in the placebo group. Accordingly, based on the Columbia Classification Algorithm of Suicide Assessment (C-CASA) criteria[16] [35], a higher incidence of SI/B events in tegaserod treated patients was noted compared with placebo-treated patients. Table 36 summarizes the pooled clinical trial data:

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[16] FDA's current guidance is to recommend prospective SI/B screening using a C-CASA based questionnaire at all clinical trial in-person visits for any drugs with psychiatric indications or biologically plausible psychiatric effects or a subject population with elevated psychiatric risk. For more information, see Center for Drug Evaluation and Research, 2012a, Guidance for Industry Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials, Food and Drug Administration, accessed 2018, https://www.fda.gov/downloads/drugs/guidances/ucm225130.pdf.

Table 36: Summary of SI/B events in Tegaserod Placebo-Controlled Trials, Pooled Data

Treatment	Tegaserod	Placebo
N[*]	12,281	7,564
Person-years	1881.5	1154.4
SI/B adverse events (total)	8	1
Rate/1000 person-years	4.3	0.9
Suicidal adverse events by category (n)[**]		
Completed suicide	1	0
Suicide attempt	2	1
Self-injurious behavior, intent unknown	4	0
Suicidal ideation	1	0
Total	*8*	*1*

Source: Modified from Dr. Andrew Mosholder's DEPI Consult Review, 10/24/2006, and include data from 2 subsequent short-term clinical trials which had no SI/B events.
Abbreviations: SI/B, suicidal ideation and behavior
[*] 544 patients from crossover studies are counted in both groups
[**] Classification by Dr. K. Posner and colleagues, Columbia University

Of the 8 patients on tegaserod who experienced SI/B events, 3 had IBS-C (including the completed suicide), 2 were reported to have IBS-C and/or GERD, 2 had chronic constipation, and 1 had diabetic gastropathy. The patient on placebo also had IBS-C.[17] It is important to note that patients with IBS have an extremely high rate of psychiatric morbidity compared with the general population and many other patient populations. Studies consistently demonstrate that IBS patients have a high prevalence of primary psychiatric disorders. Approximately 54 to 94% of IBS patients meet criteria for at least one primary psychiatric disorder, depending on the specific type of patient population [36]. Approximately 50% of community-based IBS patients meet criteria for one or more psychiatric disorder. The prevalence of psychiatric disorders among IBS patients seeking care at tertiary care hospitals is greater than 90%. The most common psychiatric disorders among IBS patients are: major depressive disorder, generalized anxiety disorder, panic disorder, and somatoform disorders (somatization disorder, hypochondriasis, somatoform pain disorder, conversion disorder, and other somatoform disorders). All these disorders are risk factors for SI/B. A meta-analysis from 2014 indicated that IBS patients have a significantly increased risk for anxiety and depressive disorders, compared with healthy controls [37]. In another review, investigators noted that prevalence rates of anxiety and depression ranged from 40 to 100% in IBS patients [38].

Furthermore, patients with IBS appear to have an increased risk of suicidal ideation and behavior, independent of comorbid depression, anxiety, or other psychiatric conditions. Spiegel et al. performed a systematic review of relevant medical literature regarding suicidal behavior in patients with abdominal pain and IBS [39]. Patients with IBS appeared to have a 2- to 4-fold risk of suicidal behavior compared with various comparator populations. The SI/B events included completed suicide, suicide attempts, intentional self-harm (without suicidal intent), and suicidal ideation. Chronic abdominal pain was an independent predictor of suicidal behavior after adjusting for comorbid psychiatric disorders (primarily depression and anxiety). However, the authors acknowledged that the studies had variable designs, study quality, patient

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[17] Dr. Andrew Mosholder's DEPI Consult Review, dated 10/24/2006

populations, control groups (healthy subjects and non-abdominal chronic pain), and there were methodological limitations.

Although there is a high baseline frequency of psychiatric disorders among IBS patients, this would not explain the imbalance in SI/B events between the tegaserod and placebo groups. Therefore, FDA issued a letter to Novartis on February 2, 2007 recommending the inclusion of language describing this potential risk in the Warnings and Precautions section of the PI. This agreed-upon language was not incorporated into labeling at the time because the drug was removed from the market for CV safety concerns. This language is currently proposed for inclusion in the proposed labeling as a Warning and Precaution.

The incidence of psychiatric events in general from the Psychiatric Disorders SOC in database Db15 was also evaluated, and the clinical trial data for all indications indicated a slightly higher incidence rate of psychiatric AEs on all doses of tegaserod (3.1%) versus placebo (2.5%). The most common psychiatric AEs on the tegaserod group (all doses) included insomnia (1.1%), anxiety (0.7%), depression (0.6%), and nervousness (0.2%). These events occurred at a similar rate in the placebo group of Db15 (refer to Table 44 in Appendix).

4.2.2. Postmarketing/Epidemiology

4.2.2.1. Division of Pharmacovigilance Analysis of Postmarketing SI/B Events

DPV performed an analysis of spontaneous postmarketing reports of suicidal ideation and behavior (SI/B) and related psychiatric AEs submitted to the FAERS database during use of tegaserod (from product launch in 2002 through March 31, 2018). DPV also reviewed postmarketing cases of SI/B submitted by the Applicant in response to an FDA information request. Throughout postmarketing use of tegaserod, a very small number of confirmed completed suicides have been reported (n=5). These involved three female and two male patients. Four patients had a diagnosis of IBS. One patient was treated with tegaserod for a diagnosis of chronic constipation, chronic abdominal pain, and long-term opioid use. All five patients who completed suicide had a previous psychiatric history and at least one additional risk factor for suicide. Psychiatric diagnoses included major depressive disorder, chronic/recurrent depressive disorder, bipolar disorder, probable somatoform disorder, alcohol use disorder, and opioid dependence. Additional risk factors for suicide in these cases included: nonadherence to antidepressant treatment, lack of psychiatric or psychotropic treatment, chronic severe pain, chronic serious medical disorders (e.g., diabetes mellitus, multiple amputations, intractable urinary incontinence, neoplasms), and concomitant use of medications known to pose a risk of suicide (antidepressants, varenicline, and gabapentin). In all cases, the reporters (including clinicians and family members) stated they did not think that the suicide was related to treatment with tegaserod. In most cases, the temporal relationship between tegaserod treatment and the psychiatric events were not suggestive of a causal relationship, or specific information about dates of treatment or the adverse event onset were lacking.

In the postmarketing cases of suicidal ideation, the clinical features were similar to those in the completed suicide cases. DPV reviewed all cases reporting adverse event terms consistent with SI/B; however, we report here on the six specific cases that contained enough information to

allow an attempt at causality analysis. All six patients with suicidal ideation (in the subset of informative cases) had a previous history of psychiatric disorder, including depressive disorders, bipolar disorder, panic disorder, or other anxiety disorders, all of which are risk factors for SI/B. One patient had a previous history of SI/B. None of the suicidal ideation cases involved suicidal behavior or other dangerous behavior, and none of the events resulted in hospitalization, initiation of psychiatric medications, or changes in current psychiatric medications. In the suicidal ideation cases, four patients discontinued tegaserod treatment, and two patients continued tegaserod but decreased their dose; suicidal ideation resolved in all cases. The temporal relationships between tegaserod treatment and the onset of suicidal ideation were not strongly suggestive of a contributory role for tegaserod. In several cases, information was lacking regarding dates of tegaserod treatment and adverse event onset.

Overall, DPV concludes that the postmarketing cases of SI/B reported with tegaserod use in the FAERS database, in themselves, do not provide clear evidence of a causal relationship between tegaserod treatment and the psychiatric adverse events. The IBS patient population has an extremely high background rate of psychiatric morbidity including SI/B. All patients in these cases had previous histories of psychiatric disorders that are risk factors for SI/B, and most patients had at least 1 additional risk factor for SI/B. Furthermore, most cases did not have suggestive temporal relationships between tegaserod treatment and the onset of the psychiatric events. Generally, the cases had limited information for fully assessing potential causal relationships between the AEs, tegaserod, or other factors. The cases had few details about important variables such as: (1) patients' previous psychiatric history and responses to treatment; (2) the presence or absence of potentially relevant life events or psychosocial stressors; (3) medical history; and (4) and concomitant medication history.

It is not clear that there is a biologically plausible mechanism for tegaserod to increase the risk of SI/B; however, it is not possible to rule out an effect, given its serotonergic mechanisms. There appears to be limited clinical literature regarding a potential role for 5-HT$_4$ receptors or 5-HT$_4$ agonists in the pathophysiology or regulation of mood or behavior. Nonclinical literature suggests that 5-HT$_4$ receptors have roles in memory, cognition, learning, and regulation of some behaviors, such as feeding [40]. Some authors postulate that 5-HT$_4$ agonists could have antidepressant effects [41]. In addition, nonclinical studies indicate that tegaserod has minimal penetration across the blood-brain barrier (BBB) [42]. A rodent study demonstrated that only ~2% of radiolabeled tegaserod was absorbed across the BBB after injection in the carotid artery.[18]

4.2.2.2. Division of Epidemiology Review of Observational Study

To address a concern about suicide-related events possibly associated with tegaserod, the Applicant submitted a final report from an observational (non-randomized) study funded by Novartis and completed in 2007 by i3 Drug Safety, with main results subsequently published as a meeting abstract by Loughlin, et al., in 2009 [43]. In the same patient cohorts used to study cardiovascular events, i3 Drug Safety changed the outcome variables of interest to self-injury and death due to any cause.

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[18] Dr. Ke Zhang, Division of Gastroenterology and Inborn Errors Products, Pharmacology review dated 7/14/2000

As described earlier, i3 Drug Safety used a U.S. database of medical insurance claims to construct two propensity-score-matched cohorts representing patient-time associated with either the initiation or non-initiation of tegaserod between September 2002 and December 2006. In 52,229 matched patient pairs, self-injury events, ascertained by ICD-9 E-code and confirmed by chart review, occurred no more frequently during 6-month post-index follow-up in tegaserod exposed than unexposed patients. In lieu of death-certificate match, the insensitive method used by i3 Drug Safety to ascertain death due to suicide required patient contact with an emergency department or admission to a hospital. Specifically, a Cox proportional hazards regression analysis estimated the relative risk for first chart-confirmed self-injury event at adjusted HR 0.74, 95% CI 0.44-1.25. i3 Drug Safety identified two suicides, one each in tegaserod exposed and unexposed patients. A separate as-treated analysis estimated risk for chart-confirmed self-injury during current tegaserod use (11 events over 10,366 patient-years), relative to nonuse (25 events over 21,872 patient-years), at an adjusted Rate Ratio (RR) 0.92, 95% CI 0.45-1.87.

FDA found no evidence for selective reporting in a study that found no statistically significant association between tegaserod and self-injury. FDA assessed the observational study methods as sound overall. Sensitive to the potential for confounding in observational (non-randomized) studies, FDA considered the self-injury result as not comparable to the results from a well-performed randomized trial. Because of the small number of events and the insensitive method used to ascertain suicide, i3 Drug Safety added little information specifically about possible suicide from tegaserod.

4.3. Overall Safety

The general safety profile of tegaserod was established in 2 prior NDA applications for IBS-C (2002) and CIC (2004). In the current reintroduction NDA, the focus is on CV safety. The overall safety of tegaserod relative to placebo was also evaluated in the current NDA for the pooled database (Db15), as well as in relevant subpopulations of interest, including female IBS-C patients, low CV risk populations, and severely symptomatic IBS-C populations. The goal of this assessment was to understand whether the overall safety profile remains generally comparable to that established at the time of drug approvals, and if there are any differences in safety profile among subgroups.

Table 37 summarizes the safety profile of tegaserod from the currently approved label relative to placebo in 2,632 male and female patients who participated in IBS-C phase 3 trials and received tegaserod 6 mg BID or placebo. Although not explicitly stated in previous NDA submissions and/or FDA reviews, it appears that the labeled safety data were derived from Trials B301, B351, and B358. Data from Trial B307 appears to have been excluded from this table, potentially because the design of that trial was titration-based, and it would be difficult to specifically retrieve data at the intended dosing regimen.

Table 37: Adverse Events Occurring in ≥1% of IBS-C Patients and More Frequently on Zelnorm (tegaserod maleate) Than Placebo

System/ Adverse Experience	Zelnorm® 6 mg b.i.d. (n=1,327)	Placebo (n=1,305)
Gastrointestinal System Disorders		
Abdominal Pain	12%	11%
Diarrhea	9%	4%
Nausea	8%	7%
Flatulence	6%	5%
Central and Peripheral Nervous System		
Headache	15%	12%
Dizziness	4%	3%
Migraine	2%	1%
Body as a Whole - General Disorders		
Accidental Trauma	3%	2%
Leg Pain	1%	< 1%
Musculoskeletal System Disorders		
Back Pain	5%	4%
Arthropathy	2%	1%

Source: Zelnorm prescribing information [1]
Abbreviations: b.i.d., twice daily; IBS, irritable bowel syndrome

Male and female patients from IBS-C trials experienced GI and nervous system AEs most commonly. Of the events noted to occur at a higher rate on tegaserod relative to placebo, diarrhea and headache were notably higher on tegaserod than on placebo.

As appropriate patient populations for whom the benefits of tegaserod are expected to outweigh the potential risks are evaluated, it was of interest to assess the overall safety profile in subpopulations of interest, and to compare with the currently labeled safety of tegaserod in the IBS-C population. The safety profile was in general comparable for the labeled population (Trials B301, B351, and B358) versus all four premarket trials (i.e., B301, B351, B358, and B307). The latter information is presented here as it encompasses a larger sample size.

Table 38: Treatment Emergent Adverse Events Reported in ≥1% of Patients – IBS-C Studies 301, 351, 307 and 358

Preferred Term	Females		Low CV risk		Severely Symptomatic		Low CV risk and Severely Symptomatic	
	Tegaserod N=1477 n (%)	Placebo N=1459 n (%)	Tegaserod N=1122 n (%)	Placebo N=1077 n (%)	Tegaserod N=540 n (%)	Placebo N=531 n (%)	Tegaserod N= 406 n (%)	Placebo N= 395 n (%)
Diarrhea	128 (8.7)	59 (4.0)	102 (9.1)	43 (4.0)	42 (7.8)	17 (3.2)	33 (8.1)	14 (3.5)
Headache	203 (13.7)	178 (12.2)	167 (14.9)	136 (12.6)	61 (11.3)	47 (8.9)	53 (13.1)	39 (9.9)
Abdominal pain	185 (12.5)	168 (11.5)	142 (12.7)	124 (11.5)	62 (11.5)	56 (10.5)	N/A	N/A
Nausea	118 (8.0)	99 (6.8)	97 (8.6)	75 (7.0)	49 (9.1)	32 (6.0)	37 (9.1)	20 (5.1)
Flatulence	99 (6.7)	77 (5.3)	85 (7.6)	54 (5.0)	40 (7.4)	27 (5.1)	32 (7.9)	20 (5.1)
Dizziness	55 (3.7)	49 (3.4)	N/A	N/A	23 (4.3)	13 (2.4)	16 (3.9)	9 (2.3)
Dyspepsia	66 (4.5)	51 (3.5)	57 (5.1)	41 (3.8)	23 (4.3)	19 (3.6)	19 (4.7)	15 (3.8)

Source: Applicant's Table 11 in response to FDA information request (07/27/2018; SN 0075)
Abbreviations: CV, cardiovascular; IBS-C, irritable bowel syndrome – constipation
Note: Subjects from Study 307 received 2 mg BID from weeks 1-4 and were switched to 6 mg BID from weeks 5-12 due to lack of response. TEAEs shown are for all 12 weeks of the study, and thus include data at the 2mg BID initial dose.

Table 38 suggests that the type and incidence of AEs occurring in at least 1% of patients and more frequently on tegaserod (6 mg BID) than placebo (i.e., GI and nervous system) were generally comparable to the labeled AEs. Headache, abdominal pain, diarrhea, nausea, and flatulence were the most frequent AEs in the overall tegaserod group in all populations evaluated. In addition, the frequency of AEs was generally comparable across the IBS-C subpopulations of interest, including low CV risk[19] and severely symptomatic[20] populations. For nausea, the difference between tegaserod and placebo appears greatest in the subgroup of patients with low CV risk and severely symptomatic IBS-C (4%) as compared with females with IBS-C (1%) and currently approved labeling (1%). However, given the relatively small sample size in this restricted population, the increased incidence rate is difficult to interpret.

The overall safety profile of tegaserod in the female IBS-C population and subpopulations of interest appears to be comparable to the established safety profile of the drug.

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[19] Low CV risk female IBS-C patients are under 65 years of age, no history of CV ischemic disease and zero or one CV risk factors.
[20] Severely symptomatic female IBS-C patients (regardless of their CV disease history) are defined to have: (1) 3 or more days per week with severe or very severe abdominal pain and discomfort; AND (2) 5 or more days per week with hard, very hard, or no stools.

5. APPENDIX

Table 39: CVI Events Confirmed in One or More Adjudications (Other Than MACE Events)

Tegaserod	
	(b) (6) **Angina Pectoris, CAD (internal adjudication), Unstable Angina (1st external), and Unstable Angina (2nd external)**
1	**Characteristics:** 47 y/o, white female with chronic constipation, on tegaserod 6 mg BID in trial E2302; patient has no formal diagnosis of CVI disease at baseline but reported intermittent (over one year) occurrence of pharyngeal tightness and discomfort on exertion that was relieved by rest; patient has one CV risk factor (smoking; '1 pack/day for 25 years').
	Event: On day 4 of study drug, the patient presented to the emergency room with throat tightness and discomfort after some physical exertion. She was also reported to have substernal deep pain radiating to the mid-anterior neck lasting for 1 to 5 minutes relieved by lying down. At the ER, she had ECG, blood work and x-rays that turned out to be all negative. A cardiologist discharged her with a diagnosis of angina pectoris, and prescription for aspirin 81 mg and nitroglycerin 0.4 mg under tongue every 5 minutes up to three times/day for relief of chest pain. A cardiac stress test was recommended. A stress test was performed on day 8 accompanied by symptoms of chest pressure radiating to left neck, multiple premature ventricular contractions. Results were reported as follows: Resting heart rate 74, stress heart rate 146; Resting blood pressure (BP) 104/70, stress BP 102/80. Resting ECG: normal sinus rhythm, early repolarization, non-specific ST changes in V3. Stress ECG: Frequent premature ventricular contractions, 1 mm ST segment depression inferiorly and laterally. On day 33, the patient was hospitalized after presenting with sore throat, shortness of breath, and fatigue. On day 47 the patient underwent a thallium stress test that was positive for occlusive coronary artery disease. SPECT results showed decreased radiotracer activity involving the anterior, apical, septa walls with normalization of this activity with rest. Finding was considered consistent with ischemia of the anterior, apical and septal walls. Ventricular dilatation was noted at stress and the ejection fraction was approximately 29%. An angiogram with stent placement was done on day 51. The patient interrupted study medication on day 51 and day 52. The patient was completely recovered and discharged from the hospital on day 52. Discharge medications included carvedilol, lisinopril, clopidogrel, simvastatin, spironolactone, and aspirin. The patient completed the double-blind treatment period on day 85 and completed the withdrawal portion of the study on day 106. The investigator did not suspect a relationship between the event and the study medication.
	FDA Comments: This patient is a younger aged female, with active smoking as the only known CV risk factor. The occurrence and worsening for at least one year of 'pharyngeal tightness and discomfort on exertion and relieved by rest' was not associated with a formal diagnosis. However, symptoms of shortness of breath and fatigue on day 33 appear to be of new onset. The patient had a positive stress test and SPECT, and underwent angiogram and stent placement and appears to have previously undiagnosed occlusive coronary artery disease.
2	(b) (6)**: Coronary Artery Stenosis (internal), no CV event (1st and 2nd external)**
	Characteristics: 52 y/o, black female patient with chronic constipation on tegaserod 6 mg BID; patient had at baseline a history of chest pain/tightness, LV hypertrophy, congenital heart defect (enlarged heart)] and four CV risk factors (diabetes, hypertension, hyperlipidemia, obesity). Other relevant medical history includes leg claudication, persistent headache; concomitant medications include Premarin, Glucophage, simvastatin, insulin,
	Event: On day 24 of study drug, a coronary angiography was performed because of chest pain. No anti-angina drugs recorded. No mentioning of a hospitalization. Neither before nor after the investigation was angina, chest pain or other cardiac symptoms reported as an AE during the study period. The angiography revealed a stenosis of the circumflex and right coronary arteries. A posttreatment hematocrit obtained on (day 85) was low hematocrit at 0.30 (from 0.33). The only other adverse event reported during the study was upper body rash. Patient completed the study as planned. The investigator did not suspect a relationship between the event and the study medication.

	Additional source data obtained at the time of 1st external adjudication noted findings from an 'invasive cardiovascular report': "there is hemodynamically significant stenosis in the right coronary artery but noncritical. No significant demonstrable peripheral vascular disease. The patient was discharged with an aggressive management plan with lipid lowering agents for coronary atherosclerosis. Consideration should be given with to increasing antianginal meds and further evaluation if the patient's chest pain continues". There are no records of any medications prescribed postintervention. *FDA comments: Patient had CV risk factors, and had evidence of coronary artery stenosis. There was no record of surgical or other interventions related to the stenosis. Chest pain did not re-occur after the initial event, although the patient continued on the study drug. There may not be a relationship of the study drug to the event, which may be related to a pre-existing condition.*
3	(b) (6): **Angina Pectoris (internal), no CV event (1st and 2nd external)** **Characteristics:** 60 y/o, white female IBS-C patient on tegaserod 6 mg BID, with baseline CV ischemic disease history (multiple prior angioplasties due to unstable angina; atherosclerosis-related carotid stenosis); baseline ECG was normal. Patient had two CV risk factors (age ≥55 years, smoking) **Event**: On day 28, the patient was admitted to the hospital due to a worsening of exercise-induced angina experienced during a routine stress test. During hospitalization, the patient underwent coronarography which was "negative for significant stenosis". No change was made to current medication dose and no new medications were given for the event. The patient was considered recovered on day 29 and discharged from the hospital. The underlying cause of angina was determined to be arteriolosclerosis. No additional treatment was administered for arteriolosclerosis. The patient discontinued from the study due to hyperkalemia (baseline potassium was 3.9 mmol/L, versus 6.0 mmol/l on day 55, with ULN 5.3). An ECG at study discontinuation was not performed. The investigator did not suspect a relationship between the event and the study medication. *FDA Comments: Patient has pre-existing angina and multiple prior angioplasties; the event in case appears to be exercise induced angina and may be unrelated to the study drug.*
4	(b) (6): **Angina Pectoris, probably not (internal), No CV event (1st and 2nd external)** **Characteristics:** 57 y/o, white, female IBS-C patient with baseline CV ischemic disease history (angina pectoris), three CV risk factors (age ≥55 years, hypertension, hyperlipidemia); family history of CV disease **Event**: On day 56 (day 30 of the treatment-free interval, TFI), the patient was hospitalized due to severe chest pain. Myocardial infarction was ruled out following a normal electrocardiogram and cardiac enzymes. The patient was subsequently diagnosed with angina. Acetylsalicylic acid and heparin-fraction sodium salt were administered as treatment. The patient was discharged after 24 hours and was considered as completely recovered on day 57. The study medication was neither interrupted nor discontinued for this event. The patient completed study participation on day 120 (day 31 of Period 2) as planned. Investigator assessment of causality: The investigator did not suspect a relationship between the event and the study medication. *FDA Comments: Patient has CVI history at baseline. The chest pain occurred on day 30 after stopping the study drug, during the treatment free interval. Angina appears not to be drug related.*

5	(b) (6): CAD, ventricular tachycardia (Internal), unstable angina (1st external), no CV event (2nd external)
	Characteristics: 50 y/o, white, female IBS-C patient on tegaserod 6 mg BID with a history tachycardia, cough of unknown etiology, migraine at baseline, and presence of three CV risk factors (hypertension, hyperlipidemia, obesity).
	Event: On day 12 of the double-blind treatment period, the patient complained of dizziness, cough, dyspnea, and severe headache. On the same day, she was hospitalized for a questionable myocardial infarction which was not confirmed. She had severe hypertension and recurrent episodes of bronchospasm which had been ongoing for approximately three months. Study medication was stopped on day 16 of the double-blind treatment period when and she underwent right and left heart catheterization. The patient was found to have severe coronary artery disease of the left main, circumflex and right coronary arteries. The patient had coronary artery bypass surgery on day 17 of the double-blind treatment period. Her postoperative course was complicated by one episode of ventricular tachycardia. She was discharged eight days later in good condition. A final ECG had no clinically significant abnormality. The Investigator considered the relationship of study medication to these events as not suspected.
	FDA Comments: The patient had no prior record of significant CV events, but had multiple risk factors including obesity, hypertension, and hyperlipidemia. Tachycardia, headache and cough were pre-existing symptoms, though dizziness and dyspnea appear to be of new onset while on study drug. Patient was found to have occlusive coronary artery disease.
6	(b) (6): **Angina Pectoris (internal), unstable angina (1st external), no CV event (2nd external)**
	Characteristics: 75 y/o, white, female IBS-C patient on tegaserod 2 mg BID; patient has CVI history including coronary artery disease; she is noted to have arrhythmia and abnormal ECG at baseline; concomitant medications include conjugated estrogens; risk factors were age ≥55, hypertension, hyperlipidemia
	Event: On day 38, she was hospitalized with unstable angina pectoris. She was treated upon admission with nitrates, analgesics, and heparin. Study medication was not interrupted. As her condition improved, she was stabilized on medication and discharged on day 54. Her discharge medications included furosemide, simvastatin, molsidomine, metoprolol, sarotene and Dona 200. She completed the study. The investigator considered this event not related to study medication, but due to a coexisting medical condition.
	FDA Comments: The patient's narrative describes the AE as 'unstable Angina' but source documents are unavailable to further corroborate this finding. Based on the information in the 2nd external adjudication report, this patient was assessed by DCRI to have 'stable angina' (as opposed to newly occurring or worsening unstable angina). This case was deemed as 'Probably No CV event', as the primary focus of the DCRI adjudication was to identify cases of unstable angina, MI, stroke, cardiac arrhythmia, congestive heart failure or TIA.
7	(b) (6): **Coronary artery disease (internal), not an event (1st external), congestive heart failure (CHF; non-ischemic; 2nd external)**
	Characteristics: 84 y/o, white, male with chronic constipation, on tegaserod 6 mg BID; He has ischemic heart disease, exertional angina, cerebral atherosclerosis, atrial fibrillation, and pre-existing chronic heart failure at baseline; risk factors include age ≥55 y/o, hypertension, obesity.
	Event: On day 40 of study drug, the patient experienced increased edema of the lower extremities and dyspnea. Hospital records note that the patient was hospitalized for treatment of (chronic) ischemic heart disease; (chronic) exertional angina pectoris, (chronic) atrial fib, and grade III heart failure (recurring problem). The study medication was interrupted on days 41 and 42 due to moderate diarrhea, which resolved on day 41, and the study medication was subsequently continued as instructed until he completed the study on day 85. The diarrhea was considered related to study medication but non-serious. The patient was discharged from hospital on day 93 and had fully recovered at time of discharge. The investigator assessed that this event was not related to the study medication but did consider it to be related to a lack of efficacy and progression of an underlying illness.
	FDA Comments: Elderly patient has multiple medical problems, prior CVI history, and appears to have had an exacerbation of congestive heart failure based on available information. CHF event resolved despite study medication.

8	(b) (6): **Angina Pectoris (internal), unstable angina (1st external), no CV event (2nd external)** **Characteristics:** 72 y/o, Asian male patient with chronic constipation on tegaserod 6 mg BID; patient's CVI history includes stroke, chest pain and black out; patient also had conduction abnormality (Wolf-Parkinson-White) and atrial fibrillation. Ex heavy-smoker (three packs per day); CV risk factors include age ≥ 55 years and hypertension **Event:** On day 57 of study drug, the patient experienced severe cardiac chest pain and was hospitalized the next day. Normal angiogram on day 60. Chest pain was treated with bisoprolol. Physical exams documented by emergency room and admitting physicians recorded no positive cardiopulmonary findings or chest abnormality. Two ECGs showed atrial fibrillation and poor R wave progression (both long standing). Cardiac Cath study was done immediately and demonstrated mild to moderate non-obstructive atherosclerotic disease. Aggressive risk modification was recommended. The patient completely recovered on day 61 and was discharged from hospital the same day. Other AEs reported included diarrhea and a cervical syndrome. Comedication was eperisone HCl. The patient discontinued the study on day 57 due to a withdrawal of consent. The investigator did not suspect a relationship between the event and the study medication. *FDA Comments: This elderly male patient had a history of cerebrovascular event (Stroke), cardiac conduction abnormality, and developed chest pain while on study drug. After the cardiac event, patient was newly diagnosed by cardiac catheterization to have mild to moderate non-obstructive atherosclerotic disease. DCRI deemed the event as 'probably no CV event', with no additional details provided.*
9	(b) (6): **CAD (internal), not an event (1st external), CHF (2nd external)** **Characteristics:** 75 y/o, white male patient with chronic constipation, on tegaserod 6 mg BID; patient's baseline CVI history includes CAD, angioplasty, cardiomyopathy, deep vein thrombosis, dizziness, back pain, migraine and congestive heart failure. His risk factors include age ≥55 y/o, high cholesterol, smoking and obesity. Patient has a family history of cardiac disease and death. **Event:** On day 85, the patient experienced shortness of breath when lying down, episodes of cough and chest pain which radiated to his left arm which worsened on exertion. Cardiac ECHO done as outpatient shortly before hospitalization showed EF of 55%. Admission history and physical examination describes sinus bradycardia, negative cardio-pulmonary findings and 1-2+ pretibial edema with nontender calves. Course in hospital apparently unremarkable. No evidence for acute myocardial injury by enzymes or ECG change. Serum D-dimer weakly positive raising possibility of pulmonary embolus. Testing focused on defining status of coronary circulation and excluding acute MI. The study medication was discontinued on day 85. The patient was discharged from the hospital on day 88 with stable vital signs. At the time of reporting the outcome of this event was unknown. The investigator did not suspect a relationship between these events and the study medication. *FDA Comments: Patient had multiple medical issues, including prior cardiac disease history; available information supports exacerbation of congestive heart failure.*
10	(b) (6): **Angina Pectoris (internal), unstable angina (1st external), insufficient data (2nd external)** **Characteristics:** 69 y/o, Asian male patient with chronic constipation, on tegaserod 6 mg BID; patient has ischemic heart disease at baseline and had stents placed; his risk factors included age ≥55 years, dyslipidemia, and hypertension; he also has chronic obstructive pulmonary disease. **Event:** On day 2 of the study drug the patient experienced cardiac chest pain of moderate severity, which was considered drug- related by the investigator. Chest pain was treated with isosorbide dinitrate. Due to this event, the patient discontinued treatment on day 37. Other adverse events reported during the active treatment period included abdominal pain, and back pain. Investigator's evaluation of the causality of the event to study drug: suspected. *FDA comments: DCRI deemed the case to have 'insufficient data' as the source data was limited and/or not 'readable'. In addition, there were no ECGs performed at the baseline, and at the onset of chest pain, nor after the event. Available information reveals that the patient had prior history of cardiac ischemic disease, stents and had an acute onset of chest pain on day 2 of study drug.*
11	(b) (6): **Vasoconstriction (internal), not an event (1st external), insufficient data**

	(2nd external) **Characteristics:** 61 y/o, white male patient with chronic constipation on tegaserod 6 mg BID; patient's baseline CVI history includes myocardial infarction, CAD, peripheral artery disease, headaches, circulatory collapse; baseline ECG was abnormal (atypical right bundle branch block); patient had three CV risk factors (age ≥55 years, hypertension, hyperlipidemia) **Event:** On day 40, the patient was admitted to hospital after a catheterization showed coronary vasoconstrictions. The study medication was permanently discontinued on day 40 and the patient withdrew from the study that day. On day 56, the patient underwent four coronary artery bypass grafts. On day 66, the patient was discharged. On the same day, the patient collapsed at home and was readmitted to hospital. The patient was diagnosed with anemia and was transfused with packed red blood cells. The patient had recovered from anemia on day 82 and was discharged on day 84. On day 132, the patient underwent an ECG, which showed a normal sinus rhythm, possible left atrial enlargement, non-specific intra-ventricular block and possible inferior infarct. The investigator did not suspect a relationship between the event and the study medication, indicating concomitant heart-disease progression as event causality. **FDA Comments:** Patient has a prior history of heart disease and MI; the role of drug in the finding of 'vasoconstrictions' on catheterization is unclear.
12	(b) (6)**: Angina Pectoris, myocardial ischemia (internal), unstable angina (1st external), unstable angina (2nd external)** **Characteristics:**69 y/o, white male patient with GERD on tegaserod 2 mg BID; patient's baseline history includes dyspnea, back pain, shortness of breath, palpitations, chest pain/pressure, baseline ECG- sinus bradycardia; borderline first-degree AV block; 'borderline abnormal changes possibly due to myocardial ischemia'; CV risk factor is age ≥55 years. **Event:** On day 30 on drug, the patient complained of being tired at the study visit, but refused the offer of an evaluation by a staff physician. At the day 44 visit the patient described having shortness of breath on exertion and the investigator noted a systolic murmur which had not been present at the baseline physical exam. The patient was referred to a cardiologist the same day who obtained a treadmill test and a stress ECHO on day 47. The examinations concluded on an anterior apical ischemia and chest pain consistent with angina, and this was confirmed by an angiogram on day 49 which revealed severe coronary artery disease. An angioplasty on day 49 was unsuccessful, and bypass surgery was performed the following day. The patient had an uneventful recovery and was discharged on day 53. He did not complete the study, taking with the last dose of study medication administered on day 49. The patient returned for the final visit on day 69 and is was noted to be completely recovered. The investigator judged the event as unrelated to tegaserod. *FDA Comments: Patient had shortness of breath and chest pain/pressure on exertion prior to study entry and had a baseline (borderline) abnormal ECG. Clinical findings and myocardial ischemia noted on stress echo support the diagnosis of angina that was noted across all three adjudications, and appears to be related to underlying occlusive coronary artery disease.*
13	(b) (6)**: MI (Internal), Fatigue (1st External), No CV event (2nd External)** **Characteristics:** 38 y/o, Caucasian female with IBS-C on tegaserod 2 mg BID; patient has no reported history of CVI disease and no CV risk factors at baseline. Past Medical History includes endometriosis and hysterectomy. Concomitant medications were calcium, premarin, and aspirin (for CV prophylaxis); patient has a family history of Marfan's syndrome; Retrospective baseline ECG assessment after the completion of study showed 'Sinus bradycardia, primary AV block' and concluded 'cannot rule out anteroseptal myocardial infarct'. **Event**: On Day 1, a few hours after 1st dose of study medication, ECG showed unchanged sinus bradycardia, new/worsened "primary" AV block and "septal ischemia". On Day 6, the subject complained of fatigue. On Day 7, one day after study drug was discontinued, patient reported heavy limbs. On Day 8, final evaluation visit "severe" systolic murmur was noted. Treatment with study medication was discontinued on day 6 due to AEs; ECG findings on Day 14 showed unchanged sinus bradycardia and "primary" AV block; new/worsened vs baseline T-wave inversion in septal leads and septal ischemia. *FDA Comments: Patient was a young female without CV disease history or known CV risk factors, but was on hormones (Premarin) and had a family history of Marfan's (known CV manifestations in that disease). Baseline abnormal ECG and a history of aspirin for CV*

	prophylaxis for approximately 9 years prior to study start is suggestive of prior history; Per CRF file, the three ECGs (baseline, day 1 and day 14) are noted to be "practically identical", suggesting that there may not have been a new/worsening CV event.
Placebo	
1	(b) (6) **Cerebrovascular disorder (internal), Transient Ischemic Attack, TIA (1st external), TIA (2nd external)** **Characteristics:** 71 y/o, white, female IBS-C patient on placebo; patient had no CVI disease history but had 3 CV risk factors (age ≥ 55 years, hypertension, hyperlipidemia) at baseline. Concomitant medications include estrogen/progesterone; PMH include chronic bronchitis, and hypothyroidism. Baseline ECG showed sinus bradycardia, incomplete right bundle branch block and interpreted as clinically insignificant, borderline abnormal. **Event:** On Day 13 of the withdrawal period (Day 98 from the first dose of study medication), the patient experienced numbness and tingling on the right side of her face, the right side of the body and the right arm. The patient was admitted to the hospital on the following day. CT scan of the head and a carotid artery ultrasound were performed with no findings. The tingling and numbness in both the face and arm resolved spontaneously within 45 minutes to one hour, but patient had another episode while she was in the Emergency Room which lasted for a few minutes. At no time has she had any speech deficit, difficulty with walking, or any problems with her strength other than a prior episode when she dropped a bowl of hot porridge on her foot. While in the Emergency Room, the patient had recurrent paresthesia and clumsiness of her right hand to the point that it was felt to be unsafe to pick up a cup of coffee. It was thus decided to admit her. Over a three to four hour period the clumsiness and incoordination resolved but the paresthesia persisted. The patient was admitted, placed on heparin overnight and then switched to aspirin. Her symptoms had resolved by the next day and she was discharged. Diagnostic Impression at the time was intermittent paresthesia, possible transient ischemic attack. **FDA Comments:** *Patient's symptoms are consistent with that of a TIA. She does not have a reported prior CVI history, but has risk factors including use of hormone replacement therapy, age, hypertension, and hyperlipidemia.*

Source: Reviewer's compilation of information from adjudication study reports and updated patient narratives
Abbreviations: AE, adverse event; BID, twice daily; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; CVI, cardiovascular ischemic; DCRI, Duke Clinical Research Institute; ECG, electrocardiogram; ECHO, echocardiogram; ER; emergency room; GERD, gastroesophageal reflux disease; IBS-C, irritable bowel syndrome – constipation; MI, myocardial infarction; SPECT, single photon emission computed tomography; TIA, transient ischemic attack; y/o, year-old

Table 40: Patient Narratives: Arrhythmic Events in Tegaserod-Treated Patients

1.	(b) (6) **Atrial fibrillation; paroxysmal absolute tachyarrhythmia; compensated cardiac insufficiency (SAE)** **Characteristics:** 69 y/o, white, female IBS-C patient on tegaserod 2 mg BID; baseline history includes atrial fibrillation, recurrent tachyarrhythmia, coronary artery disease, angina pectoris, recurrent carotid artery stenosis, cardiac insufficiency; Patient has three CV risk factors (age ≥55 years, hypertension, hyperlipidemia); screening and baseline ECGs were noted to be abnormal (flat T waves), but with normal sinus rhythm and no MI. **Event:** On day 24 of study drug, patient was hospitalized for paroxysmal sudden occurrence of palpitations and pain in her left arm and dizziness when standing up with probable orthostatic hypotension (BP 110/60 mm Hg while supine) and fast pulse rates of 140 to 170/min after exposure to stress related to celebration of her birthday. An ECG reportedly confirmed the tachyarrhythmia as atrial fibrillation accompanied by repolarization disorder (per the available information, ECG report and tracing from hospital could not be obtained but official summary reportedly notes these changes). Atrial fibrillation and compensated cardiac insufficiency were diagnosed, and all were recorded as SAEs since the patient required hospitalization. Treatment included oxygen, Cordichin (quinidine plus verapamil), heparin, clonidine, β-acetyldigoxin, pravastatin, cibadrex, aspirin, methyldigoxin, and hypericum extract. After uncomplicated

	cardioversion on the next day, the patient had normal sinus rhythm and a normal heart rate. The study ECG on day 30 also showed a normal sinus rhythm and continued repolarization disorder. She was discharged on day 31 with stable blood pressure and a sustained normal sinus rhythm. The investigator stated that the tachyarrhythmia was probably caused by preexisting stenosis of a coronary vessel. The patient was continued into the extension phase of the study, but later withdrew consent. Screening and baseline ECGs were abnormal (flat T waves) but with normal sinus rhythm and no MI. A study ECG performed on the day of discharge from the hospital and again at 2, 3, 4 months after, were interpreted as "worsened" (depressed ST segment and inverted T waves), but all showed normal sinus rhythm and absence of MI. Atrial fibrillation was not documented on any study tracings but was only reported in the summary of hospital events. *FDA Comments: Patient was elderly with arrhythmic and CVI disease history; the paroxysmal onset of palpitations was reported as atrial fibrillation and did not appear to recur after re-challenge when patient was continued on the study drug; underlying history may explain the adverse events; the reason for patient's withdrawal of consent was not provided; poststudy information available for this patient (for up to 8 years after study) suggest symptoms, hospitalizations, diagnostic procedures and investigations related to cardiovascular AEs, including a diagnosis of incipient hypertrophic obstructive cardiomyopathy, arterial hypertension, hypercalcemia, atypical angina pectoris, low-grade carotid arteriosclerotic plaques*
2	^{(b) (6)} **; Palpitations/Paroxysmal Supraventricular Tachycardia** **Characteristics:** 42 y/o, white, female IBS-C patient on tegaserod 6 mg BID; patient has a history of supraventricular tachycardia (SVT) for 6 years prior to study dates, and palpitations; at study entry she was not on her prescribed medication Sotalol (discontinued due to side effects). She had no other CV risk factors. Baseline and study ECGs were normal and did not demonstrate the arrhythmia **Event:** Intermittent, severe palpitations occurred on day 3 of study drug and continued intermittently through the end of the study. The investigator did not consider this to be a serious adverse event and noted that the patient had suffered them before entering the trial. The patient was referred to a consultant cardiologist for evaluation of the palpitations on day 7 of study drug. Sotalol was again prescribed and continued through study end. Patient continued the core and extension studies. *FDA Comments: Patient had a prior history of palpitations/SVT and was no longer on the prescribed Sotalol for approximately 3 years prior to study entry (due to fatigue). The recurrence of palpitations/SVT temporally close to the start of the study drug and the report of palpitations 'continuing intermittently' throughout the study do not allow ruling out the role of the study drug in the adverse event. Medical history is available for approximately 7 years after the end of study and includes additional episodes of SVT, findings of mitral valve regurgitation, left ventricular hypertrophy and tricuspid regurgitations; percutaneous transluminal ablation of AV node was done and was deemed as successful with a normal exercise ECG a month after the ablation.*
3	^{(b) (6)} **; Tachycardia/Palpitations** **Characteristics:** 28 y/o, white female IBS-C patient on tegaserod 6 mg BID; patient has no history of cardiac arrhythmias or CV disease and no CV risk factors at baseline; patient was premenopausal (endometriosis with infrequent menstrual bleeding since age ~26); she was on medroxyprogesterone acetate (Provera) starting ~3 months prior to study entry. **Event:** On day 6 of study drug, patient had an AE of "tachycardia" (per Applicant narrative, 'the clinical details suggested that this event was palpitations). At the time of the initial report of tachycardia, there was no clinical or ECG confirmation of the finding. The tachycardia was considered to be of "moderate" severity and a causal relationship to study drug was not suspected. It was initially treated with aspirin therapy. Approximately one week later, patient went to the ER due to continued tachycardia. Other symptoms included fatigue, dizziness, sensation of heart palpitations, and pain on the left side of her chest (without radiation of the pain). She gave a history of cold-like symptoms, fatigue and "heart palpitations" for one month (i.e., beginning about 2 weeks before beginning the study). She underwent telemetry in the emergency room, and an initial ECG showed ventricular bigeminy but reportedly no ST/T changes. Other findings were: no dyspnea, cyanosis or signs of peripheral decompensation; normal heart sounds with no murmurs; heart rate 95 bpm; blood pressure 129/64 mm Hg. The patient was given aspirin

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(Magnecyl) two 500-mg tablets.

Because the patient did not improve, she was admitted to cardiology where "no rising infarct markers" were found and there was no clinical evidence of increased central venous pressure. Approximately 7 hours after coming to the emergency room, the ventricular bigeminy had been replaced by ventricular extra beats about every 5th beat. At this time, the patient recalled that she had been having fainting spells for 10 years with no apparent triggering cause (she did not consult a physician regarding these symptoms). Two echocardiograms found no cardiac dilatation and no pericardial fluid. There was normal "movement in the left chamber", and blood samples showed no signs of bacterial infection. No viral studies were reported. There were no signs of myocardial infarction. The patient was given metoprolol succinate 50 mg QD and felt better, with no sweats and decreased palpitations and was discharged home with a tentative diagnosis of myocarditis.

A follow-up ECG done on showed sinus bradycardia and a ventricular extra beat. The ECG done at screening was reported to be normal with no ventricular ectopic activity and with a heart rate of 59 bpm. The end-of-study ECG showed a heart rate of 54 bpm (on metoprolol) with no ventricular ectopic activity.

The same adverse event ("tachycardia") was again reported at the beginning of the extension study; again it was reported to be moderate in severity and not causally related to study drug therapy. Blood pressure was normal at baseline (111/67 mm Hg) but mild hypotension was noted on two occasions approximately one month apart (95/70 mm Hg and 98/57 mm Hg). No adjustment was made to the study drug dose and the patient continued in the trial. At the end of the extension study, the patient was still reported to be experiencing "tachycardia" and remained on metoprolol 25 mg QD. The patient was followed up at ~3 months after completion of the extension study at which time she was still taking metoprolol 25 mg QD and experiencing an occasional heart palpitation.

FDA Comments: Patient has no significant prior CV history; she experienced moderate tachycardia (heart rate at the time of the initial AE was not reported) while on study drug, which responded to metoprolol; the AE continued throughout the study and was present at 3 months after study completion. The symptoms described could be attributed to myocarditis; role of the study drug in the AE may be ruled out based on symptoms that persisted at 3 months after study completion.

4	(b) (6); **Arrhythmia**

Characteristics: 63 y/o, white, female non-IBS-D patient on tegaserod 6 mg BID; patient did not have a significant prior history of arrhythmias or CVI disease except for 'few premature beats/extrasystole reported prior to treatment and at baseline'; patient had two CV risk factors (age ≥55 y/o and hyperlipidemia)

Event: After approximately 27 days on study drug, the patient experienced an episode of palpitations deemed by investigator as moderate severity. This was 'probably associated with a fainting spell'. As a result, she was admitted to a hospital and a Holter monitor was done. As detailed in the SAE from hospital records, the Holter monitor revealed a few ventricular and supraventricular extrasystoles with only two very short supraventricular bursts consisting of three or four elements. There was no tachycardia or tachyarrhythmia. There was also an intermittent left bundle branch block. It was deemed that the most likely diagnosis was that patient had palpitations rather than a true arrhythmia. She was treated with flecanide. Owing to the hospitalization, this was recorded as a serious adverse event. The study drug was stopped and not restarted as the patient discontinued the study. The patient also experienced tiredness and colic on the same day as the palpitations. An ECG was conducted two weeks prior to start of study drug (tracing not available) showed extra beats and bigeminy. Extrasystole was thus diagnosed as an active problem at the start of the clinical trial before study medication was given. Per CRF 'no significant arrhythmia was documented during the period of hospitalization'. The AE was recorded as not present at the final examination.

FDA Comments: It is not clear whether patient had experienced palpitations associated with the finding of extrasystole prior to study entry. Thus, it is unclear whether the symptoms while on study drug were of new onset. There was no positive re-challenge as patient discontinued the study.

5	(b) (6); **Acute MI; ventricular fibrillation, ventricular tachycardia; death**

	Characteristics: 64 y/o, white, female non-IBS-D patient on tegaserod 6 mg BID; patient had no history of cardiac arrhythmias or CV disease but had CV risk factors (age ≥55 y/o, hypertension); possible smoking (unclear); [patient is discussed in detail in MACE cases] **Event:** Patient suffered an MI and found to be in cardiac arrest on day 29 of study treatment. ECGs taken at the time of AE showed various arrhythmic patterns including ventricular tachycardia, ventricular fibrillation. The cause of death was deemed due to an acute heart infarct. *FDA Comments: Given the patient's unremarkable medical history, including absence of prior CV symptoms, absence of significant findings on physical examination at screening, and the acute onset of event while on study drug, a relationship between the study drug and the AEs may not be definitively ruled out.*
6	(b) (6)**; Atrial fibrillation, chest pressure, hypertension** **Characteristics:** 63 y/o, white female GERD patient on tegaserod 2 mg BID; patient has no significant prior history of arrhythmias or CVI disease at baseline, other than 'positional vertigo; patient is on hormone replacement therapy (estrogen patch) and is alcoholic; her baseline ECG was normal; patient had four CV risk factors at baseline (Age ≥55 y/o, hypertension, hyperlipidemia, obesity – BMI 40.2); she had prior hysterectomy and is on estrogen patch for hormone replacement therapy; she is on medications for positional vertigo, and hypertension. **Event:** Approximately after 44 days of study drug, patient presented to the emergency room complaining of rapid heart rate, epigastric pain, shortness of breath and chest pressure. She denied diaphoresis or radiation of pain. She was heavily intoxicated at the time. Initial assessment was heat exhaustion, acute alcohol intoxication and rule out myocardial infarction. The patient was found to be in atrial fibrillation with rapid ventricular response (156 bpm). She was converted to normal sinus rhythm with Cardizem, digoxin, and Adenocard and reported that the chest pressure resolved immediately. In the ER she had suicidal thoughts of stabbing herself and was transferred to a local psychiatric hospital. She was treated for dysthymia (mild depression) associated with acute alcohol intoxication, alcoholism and withdrawal syndrome. She was given no psychotropic medications. She was started on atenolol 25mg by mouth daily and was discharged to home. *FDA Comments: Patient has no prior history of arrhythmias or other CV disease; Patient's last dose was 12 hours prior to the AE. Atrial fibrillation appears to be a new diagnosis, but may be explained by heavy alcohol intoxication.*
7	(b) (6)**; Worsening of supraventricular tachycardia with shortness of breath and presyncope** **Characteristics:** 45 y/o, white female patient with functional dyspepsia, on tegaserod 2 mg BID; patient has a history of cardiac arrhythmias (supraventricular tachycardia, SVT), and had mitral valve prolapse; she had one CV risk factor (hyperlipidemia); on verapamil for SVT for one year prior to study entry; **Event:** Patient with history of sinus tachycardia reported worsening of tachycardia, shortness of breath and presyncope on day 34 of study drug (the event was reported as mild in the CRF). Patient was referred to and subsequently scheduled to have radiofrequency ablation. The procedure was successful; patient was discharged the following day. No significant changes were noted on her lab values and ECG performed at 3 weeks after ablation. Patient continued on and completed the study. *FDA Comments: Patient with a prior history of SVT had a recurring episode and was successfully treated with cardiac ablation; the role of the study drug is unclear.*
8	(b) (6)**; Myocardial Infarction and ventricular fibrillation** **Characteristics:** 45 y/o, white, male IBS-C patient on tegaserod 2 mg BID; patient has a history of peripheral artery disease and left hip pain at baseline; she had two CV risk factors (hyperlipidemia, active smoking) **Event:** On day 61, the patient was diagnosed with arterial blockage in the left leg and discontinued study drug. He was hospitalized on day 63 for chest pain due to a myocardial infarction. The patient underwent a triple bypass for two occluded coronary arteries. A complication of ventricular fibrillation occurred, and the patient was discharged 9 days after hospitalization. The patient completed the final evaluation visit on day 91. At this time the patient appeared pale and thin, his red blood cells were low, alkaline phosphatase high and hemoglobin low but not significant. The investigator considered the myocardial infarction as a

	co-existent disease and not related to study drug. (Patient was also discussed in the CVI case narratives) **FDA Comments:** *Patient with occlusive coronary disease had ventricular fibrillation as a complication of his triple bypass graft surgery. He recovered and was discharged. The postoperative complication does not appear to be related to the study drug.*
9	(b) (6) **Atrial fibrillation, palpitations, orthostatic dizziness** **Characteristics:** 61 y/o, white, male CIC patient on tegaserod 6 mg BID; patient has atrial fibrillation at baseline and has three CV risk factors (age ≥55 years, hypertension, obesity); **Event:** The AE is worsening or reoccurrence of atrial fibrillation of moderate severity, which occurred on day 35 of study drug. The patient then spent approximately 2 hours in a hospital ambulatory care emergency department for this problem and was successfully treated by electrical cardioversion (i.e. returned to normal sinus rhythm) and then allowed to return home. No SAE was reported. The emergency room records could not be obtained. Follow-up information on this specific event is not available. Paroxysmal atrial fibrillation was listed as an active condition present at baseline. Patient has been on amiodarone HCl (Cordarone) and digoxin since 1990 (14 years prior to study). **FDA Comments:** *Patient had long history of atrial fibrillation; the relationship with study drug is unclear.*
10	(b) (6) **atrial fibrillation** **Characteristics:** 75 y/o, white, male CIC patient on tegaserod 6 mg BID; patient was noted to have coronary heart disease 'not active at the start of the study' and had two CV risk factors (age ≥55 years and hypertension); patient was on aspirin at study entry **Event:** On day 11 of study drug, atrial fibrillation (AF) of moderate severity was reported and noted to be continuing at the end of the study. ECGs were not performed as part of this study. The physician notes that the occurrence of AF was not related to study drug, but is a complication of known coronary heart disease. Concomitant medication to treat the AF was prescribed. Subsequently, the patient was hospitalized 12 days later for further examination and treatment. Upon admission, the patient did not complain of chest discomfort or palpitations, and laboratory results revealed normal serum glutamic oxaloacetic transaminase, glutamate pyruvate transaminase, lactic acid dehydrogenase and creatine phosphokinase levels. Discrete leg edemas receded following administration of low-dose diuretics, and successful cardioversion was then performed. The subsequent ECG revealed sinus bradycardia (heart rate of 45 to 60 bpm), which improved following treatment with ipratropium bromide (heart rate of 50 bpm). Marcoumar was also prescribed and the patient was discharged from hospital in good health. The physician recommended long-term ECG checks and coronary angiography to determine the cause of the AF, given the patient has risk factors for CV disease (hyperlipidemia and hypertension). Patient completed the study. **FDA Comments:** *Patient has relevant risk factors of coronary disease and hypertension; however, since atrial fibrillation seems to be of new onset, the role of study medication is unclear.*
11	(b) (6) **; palpitations; atrial fibrillation** **Characteristics:** 75 y/o, male (race noted as 'other') with CIC and on tegaserod 6 mg BID; patient has a history of atherosclerotic CAD, was a past-smoker; his CV risk factors included age and hypertension; he had a 3-month history of palpitations, hemoptysis, and stomach pain; he had a history of hospitalization due to palpitations, orthopnea, weight loss, tachycardia with irregular rhythm with 'undiagnosed CV disease'; **Event:** Patient was initially hospitalized few days after the screening visit with a chief complaint of weight loss; other complaints were palpitations and orthopnea; BP was 140/90, heart rate was 120 bpm and deemed irregular and a respiratory rate of 20/min; duodenal and gastric ulcers, abnormal findings on chest X-rays were noted as well as multiple fluid filled densities in the liver in left kidney during an ultrasound; ECG was normal; patient was tested for tuberculosis (negative) and discharged as stable with metoprolol and diazepam. Patient appears to have initiated the study despite this initial hospitalization. Patient was re-hospitalized 6 days after the start of study drug with complaints of persisting palpitations, and worsening dyspnea plus cough for 3 months and intermittent hemoptysis. A chest CT (computed tomography) scan revealed a mass in the right upper lung and other findings suggesting chronic disease; a mass was detected in the right lobe of the liver considered probable

	metastasis from a suspected lung cancer; a cervical lymph node biopsy demonstrated metastatic adenocarcinoma; ECG at the time of this second hospital admission is reported as showing sinus rhythm with premature atrial complexes, left atrial enlargement and left ventricular hypertrophy. An ECG done 2 days later demonstrated atrial fibrillation with a heart rate of 130/minute. Digoxin had apparently been started at the time of hospitalization. A repeat ECG showed atrial fibrillation with a ventricular response of 150/minute, plus new ST-T wave changes suggestive of left lateral wall ischemia. Medications for cardiac symptoms such as angina pectoris and atrial fibrillation were given after hospitalization, but per the investigator's records, the reason for the drug for angina pectoris was "preventative". The patient developed progressive pulmonary insufficiency which was attributed to a stage IV adenocarcinoma of the lung and an obstructive superior vena cava syndrome. He died before the planned radiation therapy could be initiated. The cause of death is listed as complications of the stage IV adenocarcinoma of the lung. Secondary causes listed include coronary artery disease and superior vena cava obstruction. *FDA Comments: Patient's symptoms of palpitations and dyspnea were present prior to the study drug, leading to the first hospitalization*

Source: Reviewer's compilation of information from 2nd external adjudication study report
Abbreviations: AE, adverse event; AF, atrial fibrillation; AV, atrioventricular; BID, twice daily; BP, blood pressure; bpm, beats per minute; CAD, coronary artery disease; CIC, chronic idiopathic constipation; CRF, case report form; CV, cardiovascular; CVI, cardiovascular ischemic; ECG, electrocardiogram; ER, emergency room; GERD, gastroesophageal reflux disease; IBS-C, irritable bowel syndrome – constipation; IBS-D, irritable bowel syndrome – diarrhea; MACE, major adverse cardiovascular event; MI, myocardial infarction; QD, daily; SAE, serious adverse event; SVT, supraventricular tachycardia; y/o, year-old

Table 41: Patient Narratives: Arrhythmic Events in Placebo-Treated Patients

Placebo 1	(b) (6) **Profound Bradycardia**
	Characteristics: 31 y/o, white female IBS-C patient on placebo; patient is an ex-smoker with no CVI or arrhythmic history, and no CV risk factors at baseline; baseline ECG was normal with rate of 60 bpm
	Event: On day 84 of study drug (last day) patient showed "profound bradycardia", (local Internal Medicine interpretation was "Mobitz I Block" with a rate of 36-40 bpm). There was no indication that the patient was symptomatic. The Adverse Events Assessment page of the CRF indicates that this was the first day that the AE was noted. Severity was indicated to be mild and a relationship to study medication was suspected. No action was taken.
	A memo from the site states that the patient returned 18 days later for another ECG. A note on that date states that her ECG still showed profound bradycardia and an appointment was made for her to see a cardiologist. The patient was seen by a cardiologist on (b) (6). An ECG showed normal sinus rhythm and an exercise treadmill test was done and was normal. The patient's heart rate response to exercise was appropriate. The cardiologist stated that the profound bradycardia noted while on study medication could represent an effect of the study drug, but the effect was transient and there was no residual effect.
	FDA Comments: Bradycardia developed while on placebo. No CV issues were noted during cardiologist examinations; further follow up information is unavailable.

2	(b) (6) ; **Palpitations**
	Characteristics: 52 y/o, white female IBS-C patient on placebo; Patient has no reported history of CVI disease or arrhythmias; and no CV risk factors at baseline;
	Event: The adverse event (AE) is listed as palpitations but investigator showed concern about ectopic cardiac activity demonstrated by ECG. The investigator's comments from CRF note that the patient developed intermittent palpitations. Because of the palpitations, she had an unscheduled visit the next day. At that time, her vital signs included a blood pressure (BP) of 100/80 and pulse of 78 bpm. An ECG was performed and read by the investigator as showing sporadic "VPS" (ventricular premature systoles). Her dose of study drug was reduced and she was started on metoprolol as prophylaxis to prevent "VT" (ventricular tachycardia). Metoprolol was continued though the end of the study. Her palpitation symptoms are recorded to have resolved the next day.
	Of note, the Baseline ECG demonstrated "VPC" (ventricular premature contraction) and such is also present on the ECG obtained on day 1 which was recorded about 90 minutes after the first dose of study drug. The investigator office notes of day 1 state, "After she took the pills (1 hour later) she experienced palpitations and ECG showed one VPS. During the examination, she had three extra beats/min". All the study required ECG's were interpreted by eRT as being "normal".
	FDA Comments: Ventricular premature contractions were seen at baseline and after study drug per the narrative; the relationship to the drug (in this case, placebo) is unclear.
3	(b) (6) ; **Atrial Fibrillation**
	Characteristics: 63 y/o, white, female patient with CIC on Placebo; patient has a history of atrial fibrillation, identified during a prior abdominal surgery for which cardioversion was done and treated with verapamil; she has two risk factors (age ≥55 years and hyperlipidemia)
	Event: On day 89 patient referred to emergency room, complaining of acute onset of irregular and fast heart rate associated with some mild chest discomfort as well as pounding in the ear. She denied dizziness, light-headedness, nausea, vomiting or shortness of breath. She mentioned that she has had 2 prior episodes similar to this in the past. One just before an abdominal operation about 1999 (she had cardioversion) and one approximately 2 years before the current, for which she was hospitalized 2 to 3 days. The emergency room ECG showed atrial fibrillation with rapid ventricular response rate of 154 bpm. There was no evidence of acute coronary syndrome or ischemia, which may have precipitated the atrial fibrillation and thyroid-stimulating hormone is, was within normal range. The patient was diagnosed with atrial fibrillation with rapid ventricular response status post cardioversion. She was cardioverted and started on metoprolol 25mg a day and was discharged. She continued the study medication. A subsequent ECG showed sinus rhythm, possible left atrial enlargement (-0.1 MV P wave in V1/V2); RSR (QR) in V1/V2 consistent with right ventricular conduction delay: overall, Borderline ECG. However, this ECG was interpreted as normal and no change from baseline ECG on a final report. All lab values outside range were considered not clinically significant.
	FDA Comments: Patient has significant prior history of arrhythmia (atrial fibrillation). The recurrence of AF after 12 weeks on placebo does not suggest a relationship to the treatment.
4	(b) (6) **Mobitz II second degree block; pacemaker implantation; chest pressure; palpitations; shortness of breath**
	Characteristics: 59 y/o, white female CIC patient on Placebo; patient has a history of cardiomyopathy, endocarditis and left bundle branch block; she is an ex-smoker; and is on hormone replacement therapy; she has three CV risk factors at baseline (hyperlipidemia, age ≥55 years, and obesity)
	Event: A cardiologist report notes that on day 9 into the withdrawal period the patient presented to the cardiology clinic with a complaint of increasing exertional fatigue and shortness of breath. At the time, she was noted to be in second degree AV block. Because of these symptoms, the patient underwent a pacemaker implantation. Given the patient's history of cardiomyopathy, she was also given an angiogram, which demonstrated nonsignificant coronary artery disease. The events were not considered related to study medication and the patient completed the study trial.
	FDA Comments: The events appear related to her underlying medical conditions.

5	(b) (6); **Arrhythmia**
	Characteristics: 62 y/o, white, female CIC patient on Placebo; patient has history of cardiac arrhythmias (paroxysmal tachycardia once or twice per year associated with anxiety); sensation of cardiac pressure but no effect on daily life (per consulting cardiologist letter); her CV risk factors include age ≥55 years and hyperlipidemia.
	Event: Two episodes reported as "arrhythmia" of moderate severity occurred during the core study. Following these episodes, Tromcardin (tablets containing potassium and magnesium) and treatment with verapamil was initiated and continued until the end of the study. A cardiology consult was obtained. The cardiologist's judgment about the event was: "Patient suffers from paroxysmal supraventricular tachycardia, probably AV nodal". An ECHO and a subsequent stress test were normal. A Holter monitor recording is reported as showed sinus rhythm throughout with no tachycardia but some ventricular and supraventricular extrasystoles. The cardiologist concluded that the patient "is stable under treatment with verapamil" but that Tromcardin therapy is given because the patient "senses extrasystoles occasionally". Heart rates on the ECGs varied from 54-56 bpm. No ECGs were available during the arrhythmia/tachycardia episodes.
	FDA Comments: Patient experienced recurrence of prior episodes of cardiac arrhythmias.

Source: Reviewer's compilation of information from 2nd external adjudication study report

Abbreviations: AE, adverse event; AV, atrioventricular; BP, blood pressure; bpm, beats per minute; CIC, chronic idiopathic constipation; CRF, case report form; CV, cardiovascular; CVI, cardiovascular ischemic; ECG, electrocardiogram; ECHO, echocardiogram; IBS-C, irritable bowel syndrome – constipation; y/o, year-old

Table 42: Summary of Trials Included in the Meta-Analysis

Study	Population	Study Design	Dosage Regimen	Tegaserod (N)[a]	Placebo (N)[a]	Treatment Duration
A2302	Subjects with IBS-C	R, DB, MC, PG	12 mg/d (6 mg BID)	241	246	4 weeks
A2306	Women with IBS-C	R, DB, MC, PG	12 mg/d (6 mg BID)	2132	525	Two 4-week DB periods separated by a 2 to 12 week treatment-free interval
AIA12	Women with IBS-C receiving colonic distension procedure	R, MC, PG, DB then open-label extension	12 mg/d (6 mg BID)	27	27	4 weeks DB; 8 weeks open label
A0201	Subjects with IBS-C	R, DB, MC, PG	50 mg/d (25 mg BID)	24	21	4 weeks
A0202	Subjects with IBS-C	R, DB, MC, PG	1 mg/d (0.5 mg BID) for 4 weeks, ascending at 4-week intervals to 4 mg/d (2 mg BID), 12 mg/d (6 mg BID), and 24 mg/d (12 mg BID)	85	38	20 weeks
A0251	Subjects with IBS-C	R, DB, MC, PG	1 mg/d (0.5 mg BID) or 4 mg/d (2 mg BID) or 12 mg/d (6 mg BID) or 24 mg/d (12 mg BID)	434	113	12 weeks
A0301	Subjects with IBS-C	R, DB, MC, PG	4 mg/d (2 mg BID) or 12 mg/d (6 mg BID)	590	286	12 weeks
A0307	Subjects with IBS-C	R, DB, MC, PG	4 mg/d (2 mg BID) or for non-responders in the dose titration group 4 mg/d (2 mg BID) for Weeks 1-4 and 12 mg/d (6 mg BID) for Weeks 5-12	557	284	12 weeks
A0351	Subjects with IBS-C	R, DB, MC, PG	4 mg/d (2 mg BID) or 12 mg/d (6 mg BID)	532	267	12 weeks
A0358	Women with IBS-C	R, DB, MC, PG	12 mg/d (6 mg BID)	767	752	12 weeks
E2301	Subjects with chronic constipation	R, DB, MC, PG	4 mg/d (2 mg BID) or 12 mg/d (6 mg BID)	844	415	12 weeks

Study	Population	Study Design	Dosage Regimen	Tegaserod (N)[a]	Placebo (N)[a]	Treatment Duration
E2302	Subjects with chronic constipation	R, DB, MC, PG	4 mg/d (2 mg BID) or 12 mg/d (6 mg BID)	898	446	12 weeks
E2308	Subjects with chronic constipation	R, DB, MC, PG	12 mg/d (6 mg BID)	303	303	4 weeks
E2309	Men with chronic constipation	R, DB, MC, PG	12 mg/d (6 mg BID)	158	164	12 weeks
G2203	Subjects with diabetic gastropathy	R, DB, MC	6 mg/d (2 mg TID) or 18 mg/d (6 mg TID)	81	40	6 weeks
D2201	Subjects with FD and delayed gastric emptying	R, DB, MC, PG	4 mg/d (2 mg BID) or 12 mg/d (6 mg BID) or 24 mg/d (12 mg BID)	163	55	8 weeks
D2202	Subjects with FD and normal gastric emptying	R, DB, MC, PG	1 mg/d (0.5 mg BID) or 4 mg/d (2 mg BID) or 12 mg/d (6 mg BID)	201	70	8 weeks
D2203	Subjects with FD and delayed gastric emptying	R, DB, MC, PG	1.5 mg/d (0.5 mg TID) or 6 mg/d (2 mg TID) or 18 mg/d (6 mg TID)	95	33	8 weeks
D2204	Subjects with FD and normal gastric emptying	R, DB, MC, PG	1.5 mg/d (0.5 mg TID) or 6 mg/d (2 mg TID) or 18 mg/d (6 mg TID)	184	63	8 weeks
D2301	Women with FD	R, DB, MC	12 mg/d (6 mg BID)	681	674	6 weeks
D2302	Women with FD	R, DB, MC	12 mg/d (6 mg BID)	649	654	6 weeks
B2203	Subjects with GERD	R, DB, MC, PG	Tegaserod 12 mg/d (6 mg BID) or in combination with 20 mg/d omeprazole or 20 mg/d omeprazole alone	426	429	4 weeks
B0202	Subjects with GERD	R, DB, MC, PG	0.4 mg/d (0.2 mg BID) or 1 mg/d (0.5 mg BID) or 4 mg/d (2 mg BID)	500	171	8 weeks
A0254	Subjects with IBS-D	R, DB, MC, PG	1 mg/d (0.5 mg BID) or 4 mg/d (2 mg BID) or 12 mg/d (6 mg BID)	52	24	4 weeks

Study	Population	Study Design	Dosage Regimen	Tegaserod (N)[a]	Placebo (N)[a]	Treatment Duration
A0254C	Subjects with IBS-D	R, DB, MC, PG	1 mg/d (0.5 mg BID) or 4 mg/d (2 mg BID) or 12 mg/d (6 mg BID)	69	17	4 weeks
A2417	Women with non-diarrhea IBS	R, DB, MC, PG	12 mg/d (6 mg BID)	329	331	4 weeks
AFI01	Subjects with non-diarrhea IBS	R, DB, MC, PG	12 mg/d (6 mg BID)	327	316	12 weeks
ASG01	Subjects with non-diarrhea IBS	R, DB, MC, PG	12 mg/d (6 mg BID)	259	261	12 weeks
A0207	Subjects with slow transit constipation	R, DB, PG	12 mg QD on day 1 and days 4 to 29	6	6	4 weeks

Abbreviations: IBS-C, irritable bowel syndrome (IBS) with constipation; FD, functional dyspepsia; GERD, gastroesophageal reflux disease; IBS-D, irritable bowel syndrome (IBS) with diarrhea; R, randomized; DB, double-blind; PG, parallel-group; MC, multi-center; BID, twice a day; TID, three times a day; QD, once a day
[a] Patients from the safety analyzable population

Table 43: Frequency of Potentially Relevant Concomitant Medications Taken Prior to the Start of Study Drug

Class	ATC class	Tegaserod any dose N=11614 (%)	Placebo N=7031 (%)
NSAIDs	Anti-inflammatory agents, non-steroids	204 (1.8)	94 (1.3)
	Anti-inflammatory prep., non-steroids for topical use	1691 (14.6)	945 (13.4)
	Anti-inflammatory products for vaginal administration	1516 (13.1)	843 (12.0)
	Cox-2 inhibitors	241 (2.1)	146 (2.1)
Antimigraine	Antimigraine preparations	9 (0.1)	12 (0.2)
Products	Selective serotonin 5HT1 agonists	222 (1.9)	125 (1.8)
Antihypertensive drugs[1]	Antihypertensives, diuretics, beta blocking agents, calcium channel blockers, agents acting on renin-angiotensin system.	1009 (8.7)	650 (9.2)
Lipid lowering drugs[2]	Serum lipid reducing agents, and nicotinic acid and derivatives.	538 (4.6)	376 (5.3)
Betablocking	Betablocking agents	37 (0.3)	24 (0.3)
Agents	Betablocking agents, non-selective	138 (1.2)	65 (0.9)
	Betablocking agents, selective	353 (3.0)	241 (3.4)
Platelet aggregation inhib.	Platelet aggregation inhibitors, excl. heparin	790 (6.8)	477 (6.8)

1) ATC codes: CO2**, CO3**, CO7**, CO8**, CO9**; 2) ATC codes: C10**, CO4AC.
Source: Applicant's Table 4-2; NDA 21200/S-015; Second external adjudication study report
Abbreviations: 5HT, 5-hydroxytryptamine (serotonin); NSAID, non-steroidal anti-inflammatory drug

Table 44: Psychiatric Adverse Events in Pooled Patients of Db15 and IBS-C Patients Only

Preferred Term	All Patients, Db15			IBS-C Patients		
	Tegaserod 12 mg/day N = 8307	Tegaserod All doses N = 11614	Placebo N = 7031	Tegaserod 12 mg/day N = 3906	Tegaserod All doses N = 4750	Placebo N = 2278
Total psych events	194 (2.3 %)	364 (3.1 %)	175 (2.5 %)	109 (2.8 %)	163 (3.4 %)	79 (3.5 %)
Insomnia	71 (0.9 %)	128 (1.1 %)	71 (1 %)	46 (1.2 %)	69 (1.5 %)	34 (1.5 %)
Anxiety	40 (0.5 %)	78 (0.7 %)	34 (0.5 %)	26 (0.7 %)	40 (0.8 %)	22 (1 %)
Depression	31 (0.4 %)	70 (0.6 %)	46 (0.7 %)	18 (0.5 %)	29 (0.6 %)	23 (1 %)
Nervousness	8 (0.1 %)	21 (0.2 %)	10 (0.1 %)	4 (0.1 %)	7 (0.1 %)	4 (0.2 %)
Depressed mood	2 (0.02 %)	4 (0.03 %)	1 (0.01 %)	2 (0.1 %)	2 (0.04 %)	0
Libido decreased	3 (0.04 %)	4 (0.03 %)	1 (0.01 %)	2 (0.1 %)	2 (0.04 %)	0
Suicide Attempt	0	2 (0.02 %)	1 (0.01 %)	0	1 (0.02 %)	1 (0.04 %)
Bipolar disorder	2 (0.02 %)	2 (0.02 %)	0	2 (0.1 %)	2 (0.04 %)	0
Depersonalization	1 (0.01 %)	2 (0.02 %)	0			
Depression: suicidal	1 (0.01 %)	2 (0.02 %)	0			
Panic Attack	0	2 (0.02 %)	0			

Source: Reviewer's compilation from Applicant tables in the Integrated Summary of Safety, NDA 21200/S-015
Abbreviations: IBS-C, irritable bowel syndrome – constipation

Table 45. Sensitivity Analyses on the Primary Endpoint in Severely Symptomatic Subpopulations Based on Multiple Rounding Methods for Each Efficacy Trial

Round-ing*	N	Placebo	Tegaserod 12 mg	Difference in Response 95%CI (%)	Round-ing	N	Placebo	Tegaserod 12 mg	Difference in Response 95%CI (%)
Trial 301					**Trial 307**				
Ceiling	135	23.5 (16/68)	37.3 (25/67)	13.8 (-2, 29)	Ceiling	121	36.5 (19/52)	34.8 (24/69)	-1.7 (-19, 15)
[2.1,4.1]	133	24.2 (16/66)	37.3 (25/67)	13.1 (-2, 29)	[2.1,4.1]	121	36.5 (19/52)	34.8 (24/69)	-1.7 (-19, 15)
[2.2,4.2]	132	24.2 (16/66)	36.4 (24/66)	12.2 (-3, 28)	[2.2,4.2]	121	36.5 (19/52)	34.8 (24/69)	-1.7 (-19, 15)
[2.3,4.3]	120	24.6 (15/61)	40.7 (24/59)	16.1 (0, 33)	[2.3,4.3]	106	42.9 (18/42)	34.4 (22/64)	-8.5 (-27, 10)
[2.4,4.4]	117	24.6 (15/61)	42.9 (24/56)	18.3 (1, 35)	[2.4,4.4]	103	41.5 (17/41)	32.3 (20/62)	-9.2 (-28, 10)
[2.5,4.5]	115	25 (15/60)	41.8 (23/55)	16.8 (0, 34)	[2.5,4.5]	101	40 (16/40)	32.8 (20/61)	-7.2 (-26, 12)
[2.6,4.6]	98	22 (11/50)	45.8 (22/48)	23.8 (6, 42)	[2.6,4.6]	87	35.3 (12/34)	28.3 (15/53)	-7 (-27, 13)
[2.7,4.7]	98	22 (11/50)	45.8 (22/48)	23.8 (6, 42)	[2.7,4.7]	83	33.3 (11/33)	28 (14/50)	-5.3 (-26, 15)
[2.8,4.8]	80	24.4 (11/45)	51.4 (18/35)	27 (6, 48)	[2.8,4.8]	74	35.7 (10/28)	26.1 (12/46)	-9.6 (-31, 12)
[2.9,4.9]	77	23.8 (10/42)	51.4 (18/35)	27.6 (7, 49)	[2.9,4.9]	73	35.7 (10/28)	24.4 (11/45)	-11.3 (-33, 10)
[3,5]	74	20 (8/40)	52.9 (18/34)	32.9 (12, 54)	[3,5]	70	35.7 (10/28)	21.4 (9/42)	-14.3 (-36, 7)
Trial 351					**Trial 358**				
Ceiling	140	38.2 (29/76)	51.6 (33/64)	13.4 (-3, 30)	Ceiling	638	34 (108/318)	41.6 (133/320)	7.6 (0, 15)
[2.1,4.1]	137	38.2 (29/76)	50.8 (31/61)	12.6 (-4, 29)	[2.1,4.1]	612	33.8 (104/308)	40.8 (124/304)	7 (-1, 15)
[2.2,4.2]	137	38.2 (29/76)	50.8 (31/61)	12.6 (-4, 29)	[2.2,4.2]	581	32.9 (97/295)	40.6 (116/286)	7.7 (0, 15)
[2.3,4.3]	115	35.4 (23/65)	52 (26/50)	16.6 (-1, 35)	[2.3,4.3]	537	32.6 (89/273)	39.8 (105/264)	7.2 (-1, 15)
[2.4,4.4]	112	35.9 (23/64)	52.1 (25/48)	16.2 (-2, 35)	[2.4,4.4]	505	32.4 (81/250)	39.2 (100/255)	6.8 (-2, 15)
[2.5,4.5]	111	36.5 (23/63)	52.1 (25/48)	15.6 (-3, 34)	[2.5,4.5]	477	32.8 (77/235)	38.8 (94/242)	6 (-3, 15)
[2.6,4.6]	101	37.5 (21/56)	48.9 (22/45)	11.4 (-8, 31)	[2.6,4.6]	433	32.7 (69/211)	36.5 (81/222)	3.8 (-5, 13)
[2.7,4.7]	101	37.5 (21/56)	48.9 (22/45)	11.4 (-8, 31)	[2.7,4.7]	405	33.2 (65/196)	36.4 (76/209)	3.2 (-6, 12)
[2.8,4.8]	91	41.2 (21/51)	47.5 (19/40)	6.3 (-14, 27)	[2.8,4.8]	388	32.6 (62/190)	35.9 (71/198)	3.3 (-6, 13)
[2.9,4.9]	89	42 (21/50)	48.7 (19/39)	6.7 (-14, 28)	[2.9,4.9]	363	32.6 (58/178)	36.2 (67/185)	3.6 (-6, 13)
[3,5]	87	42 (21/50)	48.6 (18/37)	6.6 (-14, 28)	[3,5]	346	34.1 (57/167)	35.8 (64/179)	1.7 (-8, 12)

* Rounding methods are defined as: (1) Ceiling method used the cutoffs: severe or very severe abdominal pain >2 days/week, and hard or very hard or no stools >4 days/week; (2) the other rounding methods used the following cutoffs: the first component inside "[ ]" represents ≥ number of days/week with severe or very severe abdominal pain, and the second component represents ≥number of days/week with hard or very hard or no stools. For example, 0.1 rounding (which correspond to [2.1, 4.1] cutoffs) defines severely symptomatic subpopulation with severe or very severe abdominal pain ≥2.1 days/week, and hard or very hard or no stools ≥4.1 days/week. Similarly, 0.2 rounding corresponds to [2.2, 4.2] cutoffs, etc.
Source: Reviewer's analyses based on submitted dataset

6. GLOSSARY

AC   advisory committee
ACS   acute coronary syndrome
ADP   adenosine diphosphate
AE   adverse event
AERS   Adverse Event Reporting System
AF   atrial fibrillation
AMI   acute myocardial infarction
APTC   Antiplatelet Trialists' Collaboration
AUC   area under the curve
AV   atrioventricular
BID   twice daily
BM   bowel movement
BMI   body mass index
BP   blood pressure
bpm   beats per minute
CAD   coronary artery disease
CDER   Center for Drug Evaluation and Research
CHF   congestive heart failure
CI   confidence interval
CIC   chronic idiopathic constipation
CR   coronary revascularization
CRF   case report form
CSBM   complete spontaneous bowel movement
CV   cardiovascular
CVI   cardiovascular ischemic
CVIE   cardiovascular ischemic event
DCRI   Duke Clinical Research Institute
DGIEP   Division of Gastroenterology and Inborn Errors Products
DPV   Division of Pharmacovigilance
ECG   electrocardiogram
ECHO   echocardiogram
FAERS   FDA Adverse Event Reporting System
FD   functional dyspepsia
FDA   Food and Drug Administration
GERD   gastroesophageal reflux disease
GI   gastrointestinal
GIDAC   Gastrointestinal Drugs Advisory Committee
HR   hazard ratio
5-HT   5-hydroxytryptamine (serotonin)
5-HT_4 serotonin type 4
IBS-C   irritable bowel syndrome – constipation
IBS-D   irritable bowel syndrome – diarrhea
IBS-M   irritable bowel syndrome – mixed
IV   intravenous

MACE   major adverse cardiovascular event
MedDRA Medical Dictionary for Regulatory Activities
MI   myocardial infarction
MRI   magnetic resonance imaging
NDA   new drug application
OIC   opioid-induced constipation
OR   odds ratio
PD   pharmacodynamic
PK   pharmacokinetic
QD   daily
RF   risk factor
SAE   serious adverse event
SD   standard deviation
SGA   Subject's Global Assessment
SI/B   suicidal ideation and behavior
SVT   supraventricular tachycardia
TIA   transient ischemic attack

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