ZELNORM™

(tegaserod maleate)

For the treatment of Irritable Bowel Syndrome with Constipation (IBS-C)

FDA Joint Meeting of the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Briefing Document

Sloan Pharma, US WorldMeds

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US WorldMeds, LLC, US agent for NDA applicant, Sloan Pharma.

ADVISORY COMMITTEE BRIEFING MATERIALS

AVAILABLE FOR PUBLIC RELEASE.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
5-HT	5-hydroxytryptamine, Serotonin
5-HT_4	Serotonin type-4 receptor
AE	Adverse Event
APTC	Anti-Platelet Trialists Collaboration
BID	Bis in die (twice daily)
cAMP	Cyclic Adenosine Monophosphate
CHO	Chinese Hamster Ovary
CIC	Chronic Idiopathic Constipation
CPMP	Committee for Proprietary Medicinal Products
CSRC	Cardiac Safety Research Consortium
CV	Cardiovascular
CVIE	Cardiovascular Ischemic Events
CYP	Cytochromes P450
DSaRM	Drug Safety and Risk Management Advisory Committee
EC Cells	Enterochromaffin Cells
ECG	Electrocardiogram
eIND	Emergency IND
ESRD	End-Stage Renal Disease
FDASIA	FDA Safety and Innovation Act
FGID	Functional Gastrointestinal Disorder
GIDAC	Gastrointestinal Drugs Advisory Committee
HR	Hazard Ratio
IBS	Irritable Bowel Syndrome
IBS-C	Irritable Bowel Syndrome with Constipation
IHC	Intermountain Healthcare
IND	Investigational New Drug
M29.0	5-methoxyindole-3-carboxylic acid glucuronide
MACE	Major Adverse Cardiac Events
MI	Myocardial Infarction
MOA	Mechanism of Action
NDA	New Drug Application
NHP	Non-human Primate
NNT	Numbers Needed to Treat
NSAID	Nonsteroidal Anti-Inflammatory Drug
OR	Odds Ratio
5PD	Pharmacodynamics
PK	Pharmacokinetics
PMS	Post Marketing Surveillance
QOL	Quality of Life
SAE	Serious Adverse Event
SGA	Subjective Global Assessment
sNDA	Supplemental New Drug Application
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TIA	Transient Ischemic Attack
tIND	Treatment IND

1. EXECUTIVE SUMMARY

Patients suffering from constipation-predominant Irritable Bowel Syndrome (IBS-C) are significantly affected by their disease; and, despite advances in pharmacotherapies in recent years, many patients do not achieve a desired level of success in managing their condition. IBS-C is defined by chronic constipation accompanied by abdominal pain: these symptoms can range in severity with an impact on work capacity, social engagements, relationships and overall well-being.

Zelnorm™ (tegaserod maleate tablets, 6 mg), a serotonin (5-hydroxytryptamine, 5-HT) agonist acting at the $5HT_4$ receptor with a well-established mechanism, was the first prescription product approved for constipation conditions including IBS-C and Chronic Idiopathic Constipation (CIC). While the conditions have features in common, IBS-C patients struggle with both constipation and pain. Tegaserod may be particularly and uniquely suited to improving symptoms in these patients through its pharmacologic effects on peristalsis and pain signaling. These well characterized effects have been confirmed through meaningful symptom improvement in adequate and well controlled clinical trials of Zelnorm. Total condition improvement was reported on a subject global assessment, with effects demonstrated across studies in as early as one week and maintained throughout the 4 to 12 week primary evaluation period. Individual symptom improvement in bowel function and abdominal pain were also consistently reported across studies through symptom specific subject global assessment scales and in daily subject diaries of bowel habits (assessing both frequency and consistency) and pain showing reduced severity compared to baseline.

In 2007, an imbalance of 13 (0.11%) compared to 1 (0.01%) cardiovascular (CV) events in Zelnorm treated and placebo treated patients, respectively, was observed based on a review of a large (n>18,000) combined clinical trial database. This resulted in a voluntary withdrawal of the product from the US market so the data could be more closely evaluated and follow-up investigations conducted.

In the past decade, standards have evolved for evaluating the risk of ischemic CV events. Additionally, important new evidence is available to consider when assessing the CV safety of Zelnorm. The Sponsor, USWM, has worked with the Agency to explore patient populations where the benefit would be expected to outweigh any risk. Along with its sister company, Sloan Pharma, USWM has undertaken a re-evaluation of the totality of the available evidence and the current treatment landscape, which has culminated in the submission of a supplement which is currently under review to support product reintroduction in the US. A summary of the data supporting the reintroduction is provided in Table 1.

Table 1: Body of Data Supporting Zelnorm U.S. Reintroduction

	Efficacy Data (Individual and Pooled Study Analyses)	Safety Data (All Sources)
Clinical Evaluation	**Original Approval Program IBS-C RCTs (12-weeks):** B301, B351, and B358 (Pivotal) B307 (dose titration study) N=3,199	**4-12 Week Exposure:** Original IBS-C Approval Studies (B307, B301, B351, B358) N=3,199 Safety database comprised of 29 randomized trials (Db15, multiple indications) N= 18,645 Epidemiological study for ischemic CV outcomes N= 52,229 Zelnorm initiators and N=52,229 matched controls (Loughlin, 2010)
	Post-Marketing RCTs: A2306 (4+ 4 weeks) (Intermittent use/ retreatment study) A2417 (4 weeks) (Mixed population IBS-C) N=3,321	**>6 months Exposure**: 3 IBS-C open-label safety and extension studies up to 12 months N=821 4 open label safety trials up to 12 months (Db14, multiple indications) N=3,289 Epidemiological study for CV outcomes N=2,603 Zelnorm initiators, 15,618 matched controls, 1:6 ratio, average follow up 2.5 years (Anderson, 2009)
	Long term open-label safety studies: B209, B301E1, B307E1 N=1,235	**Expanded Access Programs:** 816 patients treated through tIND, eIND, and spIND
Nonclinical Evaluation		26 laboratory and animal studies to identify a potential mechanism for ischemic CV events.
Post-Marketing Experience		1,626,835 Patient Years of Postmarketing Experience Estimated 12 million prescriptions treating an estimated 4 million patients (2002-2017)

RCT = Randomized Controlled Trial; tIND, eIND, and spIND: treatment, emergency and single patient Investigational New Drug access programs
DB14 = database 14, Section 6.4
DB15 = database 15, Section 6.2

To ensure a favorable benefit-risk, the reintroduction proposal focuses both on a single indication (IBS-C) and a restricted patient population as follows:

- Treatment of IBS-C in females 65 and younger without a history of ischemic CV disease.

The Sponsor's proposal is supported by:

- Clinical trial data, epidemiology study findings, and mechanistic evaluations that support a favorable CV safety profile. While the available evidence supports CV safety, the data are insufficient to rule out some possibility of low risk associated with Zelnorm that was observed in the initial signal which was driven by a small number of events across controlled studies (Section 3)

- Clear demonstration of effectiveness across large, adequate and well-designed studies, with meaningful response in overall impact assessment and improvement in key symptoms (Section 5)

- Evaluations of more than 6,000 IBS-C patients, as well as data from other studied populations and postmarketing experience supporting good tolerability and a favorable safety profile (Section 6).

Because there could be residual uncertainty around the CV risk associated with Zelnorm, the Sponsor proposes its reintroduction in a restricted population based on age, gender and CV disease history. The proposed age and gender restrictions are generally consistent with patients that have inherently lower CV risk than the general population and consistent with the natural history of IBS-C, as well as the majority of the clinical trial experience, predominantly comprised of working age women. In addition, any risk will likely be further reduced by contraindicating use in individuals with pre-existing ischemic cardiac or cerebral diseases since such patients would be at greatest risk for a cardiac or ischemic event. This approach would make, Zelnorm available to many IBS-C patients who may benefit from availability of an additional effective treatment option and who are at an inherently lower risk for a CV events than the broader population.

In its supplement, the Sponsor has also presented data on a severely symptomatic population in whom a greater uncertainty of risk may be acceptable. This population is defined as having 3 or more days per week with severe abdominal pain and 5 or more days per week of hard, very hard or no stools. Results from analyses of this population enhance confidence in the robustness of the efficacy findings in the overall population and support that a reintroduction focused on the patients with the greatest disease burden could also be considered.

With acknowledgment that uncertainty may remain about the absolute absence of a CV risk, there is greater confidence today that any such risk associated with Zelnorm is very small and that the product has an overall safety profile that is very favorable. This coupled with the fact that the effectiveness has been established through multiple high quality, controlled studies providing compelling evidence that Zelnorm can be a meaningful treatment option for IBS-C patients in addressing individual symptoms and the total symptom complex which impacts

their overall well-being. If approved for reintroduction, Zelnorm would become the only serotonergic "prokinetic" agent available to manage the symptoms associated with IBS-C in the US. A reintroduction with limitations assures a greater potential benefit risk balance for patients while still addressing an unmet need.

Multiple approaches have been considered in the reintroduction evaluation for the optimization of benefit-risk. In collaboration with the Agency, the Sponsor explored population restrictions focused on risk reduction and increased tolerance for risk uncertainty (i.e., those with higher severity of disease). The Sponsor's analysis of such populations supports a favorable benefit risk assessment through either approach; and while the Sponsor has recommended a patient population based primarily on risk restriction, it supports that other explored approaches are rational, appropriate, and well supported by the data.

The remainder of the document will describe the Sponsor's efforts to characterize any potential for Zelnorm to increase CV events, review clinical efficacy and general safety, and evaluate the benefit risk considerations for Zelnorm's reintroduction in the context of the current medical landscape and proposed population restrictions.

2. REGULATORY HISTORY OF TEGASEROD

Zelnorm was approved in the U.S. in 2002 as the first available therapy to treat IBS-C. In 2004, the prior Sponsor was engaged with the Swiss Medic to evaluate ischemic-related events reported in clinical trials of Zelnorm. In 2006, the prior Sponsor presented an assessment that identified a low frequency of ischemic events; however, these results were deemed inconclusive. The prior Sponsor expanded the analyses to a larger sample size to increase sensitivity for signal detection and completed the analysis in March 2007. This retrospective analysis was performed on pooled clinical trial data of 29 placebo-controlled trials across multiple indications (e.g. IBS-C, CIC, dyspepsia) involving >18,000 patients. An imbalance in the number of CV ischemic events in patients taking Zelnorm (13 events, 0.1%) compared to placebo (1 event, 0.01%) was detected. In the interest of patient safety, the prior Sponsor voluntarily withdrew the product from the market while the data could be more closely evaluated and follow up investigations conducted.

Based on the continued patient need for Zelnorm post-withdrawal, the prior Sponsor and the Agency initiated discussion around an emergency IND (eIND) program and treatment IND (tIND) protocol. During this time the Agency also agreed that a supplemental New Drug Application (sNDA) for Zelnorm reintroduction could be submitted later that year. In April 2007, the eIND program was initiated and in October 2007, the FDA-approved tIND program began, allowing continued availability of Zelnorm, highlighting the significant interest that remained with patients and physicians for the use of Zelnorm.

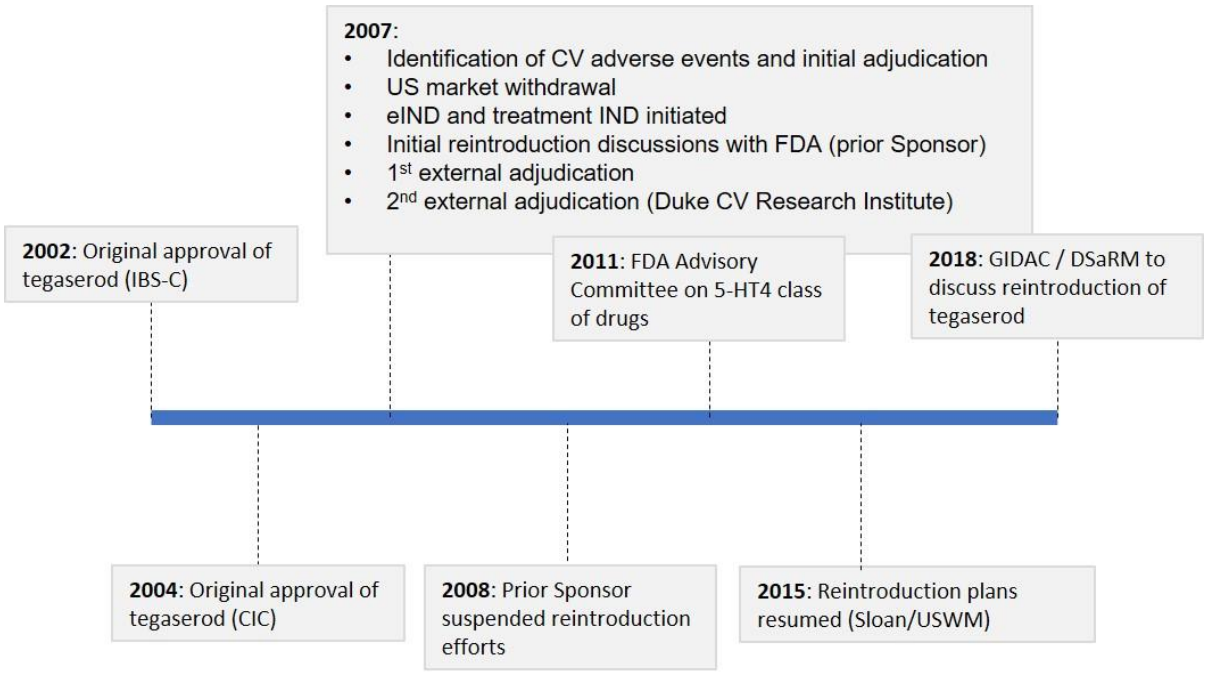
Zelnorm reintroduction discussions were initiated with the Agency immediately following market withdrawal by the prior Sponsor in April 2007. Several post-withdrawal interactions occurred between the prior Sponsor and the Agency to work towards the reintroduction of Zelnorm to the US market for both IBS-C and CIC. Per the Agency recommendations, the prior Sponsor moved forward with reintroduction efforts focused on IBS-C only. The Agency provided specific input to assess benefit-risk in specific patient populations as well as guidance on how to apply statistical programming definitions to assess benefit-risk in patients. At the same time, the prior Sponsor was performing mechanistic and epidemiological studies to better characterize the CV risk associated with the drug, as well as an additional, more robust external adjudication of the CV events by Duke Clinical Research (described in more detail in Section 3.1).

Driven in part by the 2007 withdrawal of Zelnorm, an FDA GIDAC meeting convened in 2011 to review the safety signal detected for CV ischemic events and examine the clinician's perspective on the seriousness of the risk and assess whether specific additional safety evaluations should be required for the 5-HT_4 drug class indicated for GI use (pre- and post-approval). The outcome of this meeting suggested that the original CV signal that led to Zelnorm market withdrawal was weak, and that dedicated CV safety studies were not necessary to further characterize safety profiles of 5-HT_4 products. Supporting this outcome, a recent publication from the Cardiac Safety Research Consortium (CSRC) suggests that a large cardiac outcome study would not prove valuable for a drug like Zelnorm (Sager, 2015). The authors note that a large-scale CV outcome trial would only be indicated based on a strong signal from a clinical trial(s) or one of a lesser degree with reasonable mechanistic plausibility.

Furthermore, committee members expressed the need for additional treatment options for IBS-C noting that drugs that address GI motility may address an unmet medical need.

In 2015, the rights to Zelnorm were transferred from the prior Sponsor to the current Sponsor, US WorldMeds. Reintroduction efforts were reinitiated by the current Sponsor in October 2016. The Agency stated that reintroduction may be appropriate based on currently available evidence; however, an FDA Advisory Committee meeting involving the GIDAC and DSaRM committees would be needed to guide such a decision, at which time the totality of available evidence on benefits and risks of Zelnorm will be assessed. the Agency determined a joint Advisory Committee meeting was appropriate to discuss the proposed reintroduction of Zelnorm.

Figure 1: Regulatory History of Tegaserod



3. OVERVIEW OF CARDIOVASCULAR RISK ASSESSMENT

The uncertainty around the CV risk associated with Zelnorm stems from a retrospective analysis of 29 placebo-controlled trials in over 18,000 patients, which demonstrated adverse CV ischemic events (CVIE) in 13 of 11,614 patients treated with Zelnorm (a rate of 0.11%) compared to 1 of 7,031 patients treated with placebo (a rate of 0.01%). This numerical imbalance resulted in a voluntary withdrawal of Zelnorm from the US market.

Following market withdrawal, the prior Sponsor proceeded to investigate the plausibility that the observed CVIE were due to Zelnorm. This included a second external adjudication, a large-scale epidemiological study in a routine clinical practice setting, powered to detect any association between Zelnorm and CVIE, and several nonclinical studies designed to investigate a potential mechanistic link. Additionally, USWM assessed potential ECG abnormalities and symptoms suggestive of arrhythmia from the clinical trial databases in studies where ECGs were centrally read. Key conclusions from these efforts are:

- A second external adjudication by Duke, which investigated the initial numerical imbalance of CV events observed between Zelnorm and placebo demonstrated that the frequency of confirmed CV ischemic events and MACE events in Zelnorm-treated patients was lower than previously indicated.

- An epidemiology study conducted using advanced pharmacoepidemiologic methods and powered to detect a small CV signal demonstrated no evidence of an increased risk of CV ischemic events or stroke events in Zelnorm-treated patients versus non-treated patients.

- The understanding of the role of serotonin and its receptors in the CV system has been studied thoroughly. This, coupled with several thorough pharmacological and mechanistic studies with tegaserod, do not provide any evidence that 5-HT_4 receptor agonists such as tegaserod have any action relevant to the production of CV ischemia.

- Clinical laboratory evaluations from randomized placebo controlled Zelnorm clinical trials showed no major differences between Zelnorm- and placebo-treated patients in terms of centrally- read ECG measurements (ventricular rate, PR, QRS, and QTcF), abnormal ECG findings, and systolic and diastolic blood pressure.

3.1. Adjudication History

Following the analysis request by the Swiss Medic the previous Sponsor informed the Agency of the initial findings in a brief communication on February 22, 2007 and submitted the full results on March 9, 2017. The prior Sponsor met with the Agency on March 15th, 2007 to discuss the initial findings and as a result of this meeting, additional data were requested. the prior Sponsor conducted an external adjudication of these identified cases that were consistent with ischemic event search terms on March 22, 2007. This blinded adjudication was conducted by a panel of independent physicians at Mt. Sinai Hospital (NY). The timeline was limited for the preparation of this external analysis and thus the amount of available source documents that were available for review were limited. This external adjudication showed a small, yet statistically significant imbalance of CV ischemic events in Zelnorm vs placebo: 13 (0.11%)

treated with Zelnorm vs. 1 (0.01%) treated with placebo (Table 2). While only evaluated post-hoc, there were 7 MACE events in the tegaserod group and zero in the placebo group. Because of the numerical imbalance of CV ischemic events that was observed from this external adjudication, the prior Sponsor voluntarily withdrew Zelnorm from the US market on March 30, 2007.

Table 2: CV Ischemic Events from First External Adjudication

Event	Tegaserod (N = 11,614)	Placebo (N = 7,031)
MACE[a]		
Myocardial Infarction	3 (0.03%)	0
Stroke	3 (0.03%)	0
CV Death	1 (0.03%)	0
Unstable Angina	6 (0.05%)	0
Transient Ischemic Attack	0	1 (0.01%)
Total CV Ischemic Events[b]	**13 (0.11%)**	**1 (0.01%)**
MACE Events[c]	**7 (0.06%)**	**0**

[a] MACE: Non-fatal MI, Non-fatal Stroke, and CV Death
[b] Delta proportion: 0.10%; 95% CI 0.02, 0.18; P Value 0.02
[c] Delta proportion: 0.06%; 95% CI -0.00, 0.012; P Value 0.05

To confirm the findings from the first external adjudication and to better understand the relationship between CV outcomes and baseline risk, the prior Sponsor met with the Agency on June 7, 2007 and informed them of their plans to conduct a second external adjudication. This adjudication would delineate CV ischemic events (coronary ischemic events and cerebrovascular events). Importantly, as recommended by the Agency, the adjudicators also considered Anti-Platelet Trialists Collaboration (APTC) type events (defined as non-fatal MI, stroke or vascular death), the definition of which is in line with the current standards for identifying MACE events (non-fatal MI, stroke or CV death). The adjudication was planned and conducted over approximately 6 months, which enabled collection of source documentation (i.e., cardiac lab results and hospital records) on selected cases. It utilized methodologies consistent with current adjudication practices (Seltzer, 2015) including:

- Retrieval of full source documentation
- Pre-defined search terms for case selection
- Prospective endpoint definitions and case assessments

A broadened search was performed of the clinical trial database for all possible events using 407 search terms using SMQ (Standard MedDRA queries) criteria for CV events. A blinded panel of cardiologist at Duke Clinical Research Institute, Durham, NC, reviewed all source documents, including cardiac testing reports and patient narratives and adjudicated over 10 times the number of cases as the first adjudication. A detailed summary comparing the first and second external adjudication methodologies is provided in Table 3. An executive summary of the Duke adjudication and methodologies can be found in Appendix 5.

Table 3: Summary of External Adjudications

External Adjudication Number	Patient Population	Number of Search Terms	Search Terms	Cases Adjudicated	Source Documents	Adjudication Board Members	Event Definitions
1st Adjudication (Mt. Sinai Hospital)	DB15 (18,645 patients)	166	Ischemic CV events	32 cases adjudicated by the entire committee	Narrative summaries and CRFS; limited source	2 board certified cardiologists and 1 board certified neurologist	Clinical judgement; no pre-defined definitions of CV events used
2nd Adjudication (Duke Cardiovascular Research Institute)	DB15 and DB14 (21,934 Patients)	407	Ischemic CV events Any cardiac disorders CV disorders Chest pain and chest discomfort COX2 algorithms	460 pre-screened; 304 cases adjudicated by entire committee	Full source documents including all cardiac test results; narrative summaries and CRFS	3 board certified cardiologists	Pre-defined Endpoint definitions of CV events APTC/MACE hard endpoint classifications

• Per the Agency request, the Antiplatelet Trialists' Collaboration (APTC) classification was applied during the second External Adjudication
Non-fatal myocardial infarctions, non-fatal strokes, or death from a vascular cause
MACE: non-fatal myocardial infarctions, non-fatal strokes, or CV deaths

A small numeric imbalance in the number of CV ischemic events in the tegaserod treated group vs placebo was observed [7 (0.06%) vs.1 (0.01%)]. Of these, 4 in the tegaserod group were considered Major Cardiac Adverse Events (MACE). MACE events, which include non-fatal MI, stroke or CV death and result in irreversible harm, are regarded as the events of primary importance in assessing ischemic CV risk by current standards. The other 3 events were cases of unstable angina, which are no longer considered to be highly reliable adjudication CV endpoints. (Table 4). The characteristics of those patients identified as confirmed events in the Duke Adjudication are available in Appendix 6. Importantly, all confirmed CV ischemic events occurred in patients with underlying CV risk, based on the presence of at least 1 CV risk factor in their history. Two of the patients with MACE events had a history of CV ischemic disease in addition to CV risk factors.

Table 4: CV Ischemic Events from Duke Adjudication

Event	Tegaserod (N = 11,614)	Placebo (N = 7,031)
MACE[a]		
Myocardial Infarction	1 (0.01%)	0
Stroke	2 (0.02%)	0
CV Death	1 (0.01%)	0
Unstable Angina	3 (0.03%)	0
Transient Ischemic Attack	0	1 (0.01%)
Total Events[b]	**7 (0.06%)**	**1 (0.01%)**
MACE Events[c]	**4 (0.03%)**	**0**

[a] MACE: Non-fatal MI, Non-fatal Stroke, and CV Death
[b] Delta proportion: 0.05%; 95% CI -0.03, 0.11; P Value 0.27
[c] Delta proportion: 0.03%; 95% CI -0.02, 0.09; P Value 0.30

3.1.1. Long Term Open Label Studies

CV ischemic events in the long term, open label safety database were also adjudicated by Duke adjudicators (this database was not adjudicated during the first external adjudication). This database, referred to as DB14 (Section 6.1), consists of 7 long term, open label studies between 6 and 13 months in duration in both male and female patients across multiple GI indications (Table 12). This database consists of 3289 patients. Patients received repeated treatment of Zelnorm approximately every 4 – 6 weeks and 45% of subjects received treatment for 9 months or longer. There were 165 cases identified for adjudication and the results are shown in Table 5. There was 1 MACE event (stroke) and 3 episodes of unstable angina. All four patients had two or more CV risk factors (Appendix 6).

Table 5: Number of Adjudicated Ischemic CV Events and MACE Events in DB14

Adjudicator's Assessment	Tegaserod N = 3,289 N (%)	Estimated frequencies per 1000 patient years (95% CI)
Total CV ischemic events	4 (0.12)	1.95 (0.73; 5.21)
Coronary ischemic events (unstable angina)	3 (0.09)	1.47 (0.47, 4.55)
Cerebrovascular ischemic events (stroke)	1 (0.03)	0.49 (0.07, 3.47)

3.1.2. Summary of Clinical Data Adjudications

In summary, the Duke adjudication was performed in a manner consistent with modern adjudication approaches and the CSRC recommendations. The fact that additional source documents were available to the adjudicators resulted in some previous events being determined to be non-cardiac in origin. A summary of the 6 subjects who had confirmed CV ischemic events in the first external adjudication but not in the second external adjudication conducted by Duke, can be found in Appendix 7.

Both external adjudications of CV events from the clinical trial database demonstrate a numerical imbalance. In the first, the imbalance included unstable angina, which are no longer considered to be highly reliable adjudication endpoints because of its subjective nature. Instead, MACE events (non-fatal MI, stroke or CV death) are most commonly used. A small imbalance in MACE events were observed, although the rates of events in both groups are low and within expected rates of events in the population as supported by epidemiology study control cohort rates discussed in the following sections.

3.2. Epidemiologic Data

Epidemiological studies show no difference in CV risk in patients who initiated tegaserod versus matched non-initiators. Specifically, two independent epidemiological studies have assessed CV safety by analyzing data from tegaserod-treated subjects and matched controls (from routine clinical practice) and found no evidence for an increased risk of CVIEs (Loughlin, 2010; Anderson, 2009). These studies are reviewed below.

3.2.1. Loughlin, 2010

To further characterize any potential CV risk of Zelnorm, an epidemiology study (sponsored by the prior Sponsor and conducted by i3 Drug Safety, a consulting and research analytics company affiliated with UnitedHealth) was designed and powered (>80%) specifically to detect a 1.5-fold increase in ischemic events compared to a matched control cohort. This study enabled evaluation of real-world use and was powered to confirm an increased risk even if the increased risk was a fraction of the imbalance reported in the clinical trials (0.11% vs. 0.01%, or a 10-fold difference in rates of events taking the most conservative adjudication findings). The association between tegaserod and CV ischemic events (myocardial infarction, acute coronary syndrome, coronary revascularization, or stroke) was evaluated using a matched cohort design within a large US health insurance database (Ingenix Research Data Mart). The study cohorts were followed from cohort entry for up to 6 months for the occurrence of CV

ischemic events. Outcomes were identified using insurance claims and confirmed by review of medical records. This study applied advanced pharmacoepidemiology methods, including a new-user parallel cohort design and propensity score matching to achieve close balance between the cohorts from start of follow-up. The use of both as-matched and as-treated analyses address the effect of short or repeat exposures on the outcome. These design elements address many of the potential sources of bias that may be associated with studies derived from administrative healthcare data.

This study did not confirm an imbalance in medical record-confirmed CV ischemic events between Zelnorm initiators (N=52,229) and the comparison cohort (N=52,229). Results showed that there were 107 CV events (including acute coronary syndrome, myocardial infarction (MI), coronary revascularization) confirmed among the tegaserod-initiators and 115 among the comparators (adjusted Hazard Ratio= 0.95, 95% CI 0.73 – 1.23). There were 16 strokes among the tegaserod initiators and 18 among the comparators (adjusted Hazard Ratio= 0.90, 95% CI 0.46 – 1.77). Of note, approximately half (~26,000) of the participants in both the tegaserod-treated and non-treated groups had CV risk factors at baseline (Loughlin, 2010) (Table 6).

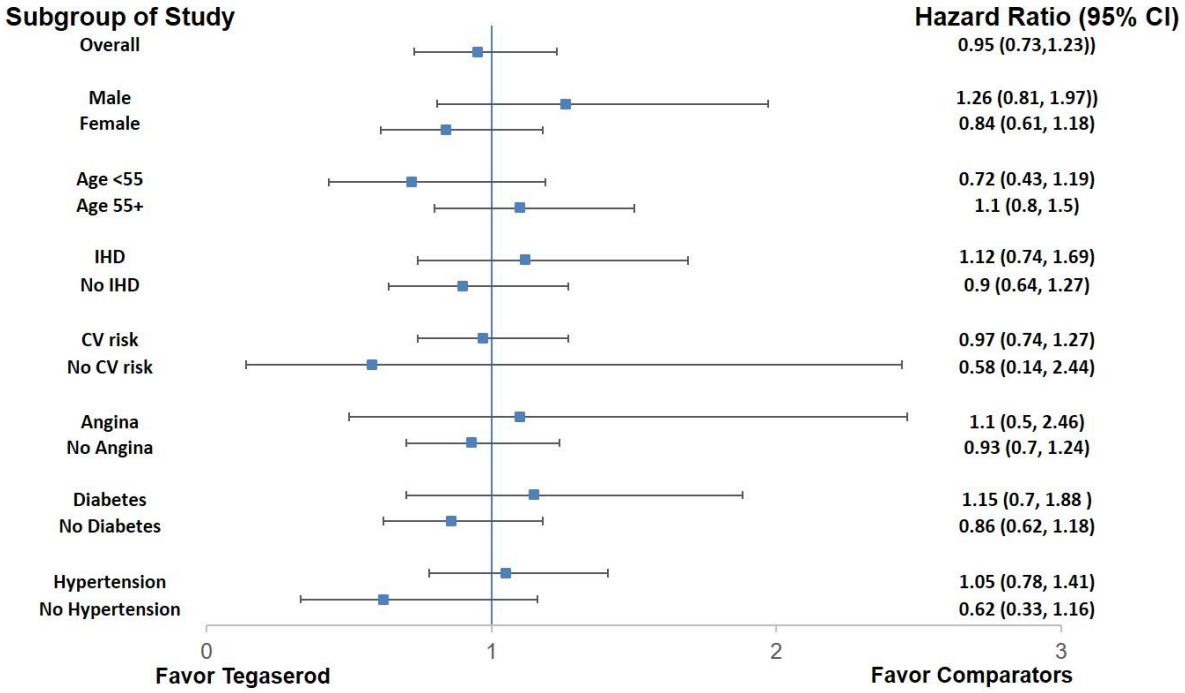
Table 6: Summary Statistics for Confirmed Cases

Group	People	CV Events[a]	Person-Years	IR[b]	HR[c]	95% CI
CV Events						
Tegaserod	52,229	107	22,160	4.83	0.95	0.73-1.23
Comparators	52,229	115	22,182	5.18		
Stroke Events						
Tegaserod	52,229	16	22,181	0.72	0.90	0.46-1.77
Comparators	52,229	18	22.205	0.81		

[a] Cardiovascular events includes acute coronary syndrome, myocardial infarction and coronary revascularization.
[b] Crude incidence rate per 1,000 person years.
[c] Adjusted for age, sex, region, calendar year, and baseline history of hypertension, treated hypertension, hyperlipidemia, statins, diabetes, treated diabetes, obesity, smoking, stroke, fibrates, angina, acute coronary syndrome, history of MI, and acute MI by Cox proportional regression.

The results were stratified using proportional hazards regression models by gender, age, and a wide range of baseline characteristics. None of these stratifications suggested that tegaserod has a higher risk in a particular subgroup (Figure 2) (Loughlin, 2010).

Figure 2: Adjusted Hazard Ratios for CV Ischemic Events, Tegaserod-treated vs. Non-treated Groups, Loughlin, 2010



The authors concluded that there was no evidence of an increased risk of CV ischemic events or stroke events in tegaserod-treated patients versus non-treated patients. The rate of ischemic events in tegaserod treated patients was consistent with, if not lower than that observed in matched controls. and are consistent with clinically expected associations (higher risk was observed in both cohorts with increased age and with individuals who have baseline CV risk factors such as hypertension or diabetes).

3.2.2. Anderson, 2009

An additional, smaller independent evaluation of the CV safety of tegaserod, using the Intermountain Healthcare (IHC) database was conducted by Anderson (Anderson, 2009). Tegaserod initiators (n = 2,603) were matched 1:6 with untreated (n = 15,618) patients by age, sex, and date of tegaserod initiation (within 6 months). Average age was 38.6 ± 13.5 years, and 94% were female. In this study, a search was undertaken of the entire IHC electronic database from 2002 through mid-2007, the date range of tegaserod marketing, to identify all tegaserod-treated patients. All subsequent discharge diagnoses were then searched to identify all incident CV events, including MI, cerebrovascular events (strokes or TIAs), hospitalization for unstable angina, and CV deaths. The duration of drug therapy averaged 4 months (123 days), with a median of 2 months (60 days), and ranged from 3 to 1530 days. The duration of clinical follow-up averaged 2.5 + 1.5 years. During the 2.5 average years of follow-up, a total of 66 incidents CV events occurred across both cohorts, representing a very low event rate of 0.16% per year or less than 2 per 1000 pt-year. For the primary composite CV endpoint, 54 (0.35%) untreated and 12 (0.46%) treated patients had an event (OR = 1.27, 95% CI: 0.68-2.38, P = 0.46). All 6 CV deaths occurred in the control group. The authors concluded that event rates with Zelnorm

treatment were comparable to expected event rates in this population (i.e. primarily premenopausal women), and that the results failed to confirm the reported event differential for tegaserod that was noted in the clinical trial database.

3.3. Overview of Mechanistic Evaluations

A key approach to investigating the CV safety of a drug is to examine plausible mechanisms that would increase CV risk. Following withdrawal of Zelnorm from the US market, several mechanistic studies were conducted. None have established a mechanistic link. A comprehensive summary of the efforts taken by the previous Sponsor, and the current Sponsor, to examine the potential mechanism for CV events are detailed in the following sections and are summarized below:

- No preclinical or human arrhythmia/BP effects have been observed, including:
    - No hERG liability (IC_{50}:C_{max} margin >1300x)
    - Canine CV Safety Study had no ECG/BP effects
    - Langendorff-perfused rabbit heart showed no effect on repolarization
    - No Effect on Human ECG parameters (QTcF, heart rate, PR or QRS) or BP
- No consistent statistically significant effect on in vitro platelet binding or aggregation
- No vasoactive effects on human or primate coronary arteries

3.3.1. Receptor Based Studies

Tegaserod has been shown to have high specificity and affinity for the 5-HT_4 receptor with a pKi of 8.4 in radioligand binding studies using calf and human caudate membranes. A similar pKi is reported in published literature (Beattie, 2004; Beattie, 2011; Long, 2012; Caymen Chemical, 2015). By contrast, the major metabolite, M29.0, did not show any affinity for 5-HT_4 (Appel-Dingemanse, 2002). Activation of the 5-HT4 receptor is the mechanism through which tegaserod can alleviate GI symptoms in patients with IBS-C. However, tegaserod also has binding affinity to other 5-HT receptor subtypes, including some CV-related subtypes (5-HT_{1A}, 5-HT_{1B} or 5-HT_{2A} and 5-HT2B). PK studies have indicated that plasma concentrations of tegaserod achieved at the 6 mg bid dosing (C_{max}, 10 nM; free fraction ~0.1 nM) are only sufficient for binding to the 5-HT_4 and 5-HT_{2B} subtypes, whereas the lower affinity binding at other receptors requires supratherapeutic concentrations of tegaserod for any possible receptor binding. Furthermore, 5-HT1A for which tegaserod is an agonist, is mainly located in the CNS for which tegaserod shows little penetration. At all of the other receptors tegaserod is an antagonist which would therefore result in suppression of effects mediated by endogenous 5-HT. Specifically, blockade of mitogenic signaling, valvulopathy or pulmonary hypertension in the case of 5-HT_{2B}, reversal of 5-HT_{1B} and 5-HT_{2A} vasoconstriction and a reduction of 5-H_{2A} receptor stimulation of 5-HT release from platelets resulting in attenuation of any 5-HT-dependent enhancement of platelet activation. Overall, results from these studies support the lack of a mechanistic link of tegaserod in untoward CV events.

3.3.2. Toxicology and Safety Pharmacology Studies

The toxicology/safety pharmacology program included multiple *in vitro* and *in vivo* vascular and cardiac function and platelet aggregation studies. Details of these studies are summarized in Appendix 2. Results of receptor binding studies for 5-HT subtypes other than 5-HT4 are provided in Appendix 3 and further discussed, herein, with regard to CV safety. The original NDA reviewed for the IBS-C indication and subsequent annual reports and post-approval supplements filed by the prior Sponsor, have provided data on the general pharmacokinetics (PK) and pharmacodynamic (PD) effects of tegaserod and the major metabolite (M29.0) in humans. This information is summarized in Appendix 2 .

In vitro studies on absence of effect of tegaserod on cardiac waveforms were reported in the original NDA. Studies were performed to test for action potential in isolated papillary muscles and in the perfused rabbit heart. No effects of tegaserod were seen on QT intervals or QRS duration (only papillary muscle) at concentrations of tegaserod significantly higher than the clinical C_{max} plasma levels for humans. Likewise, tegaserod inhibited hERG channels in HEK293 cells with an IC_{50} of 13.0 μM, a concentration that is > 1,000X the human free C_{max} plasma levels in humans. A similar in vitro patch clamp study using Chinese Hamster Ovary (CHO) (Beattie, 2013) showed that hERG current was only inhibited by ~25% at tegaserod concentration of 300X C_{max} plasma levels for humans. In a more recent study, tegaserod at concentrations up to 100 nM, 10X C_{max} plasma levels for humans, did not affect action potential in human atrial myocytes. Furthermore, the potential for tegaserod to cause valvular lesions was investigated due to 5-HT_{2B}-mediated effects on cardiac fibroblasts (Fitzgerald, 2000). This was not supported, as tegaserod did not produce contractions in the rat stomach fundus, a model of 5-HT_{2B} activity.

3.3.3. Arterial Contractility

Studies have been conducted to characterize any actions of tegaserod upon isolated preparations of healthy and diseased human coronary and mesenteric arteries as well as primate coronary and mesenteric arteries. These studies demonstrated that tegaserod does not produce vasoconstriction in human coronary and mesenteric arteries at clinically relevant concentrations. Furthermore, these studies showed that the vasoconstrictor effect of 5-HT_{1B} agonists were inhibited by tegaserod, suggesting that at higher concentrations tegaserod has the potential to reduce vascular tone mediated by endogenous 5-HT at this receptor. The absence of a constrictor effect on human coronary artery preparations *in vitro* was further confirmed in other published studies (Higgins, 2012; Beattie, 2013). A summary of these vascular studies conducted to investigate a potential for CV effects in humans are summarized in Appendix 2. Additionally, tegaserod was without any clinically significant effects in a series of *in vivo* studies in a rat model designed to measure macro- and microcirculatory changes in the GI tract, using either i.v. or direct intraduodenal administration. This contrasted with the 5-HT_3 agonist, alonsetron, which reduced vascular conductance. In other whole animal studies (rat and dog) reported in the original NDA tegaserod was without notable effect on multiple indices of CV function at the equivalent of clinically effective exposures.

3.3.4. Platelet Aggregation

Platelet aggregation, which can be precipitated by a wide range of factors, can increase the risk of myocardial infarction and stroke (Bampalis, 2016; Gregg, 2003). Although 5-HT itself plays a minimal direct role on platelet aggregation, it can enhance the response to other platelet aggregatory agents. Based on the known relationship between 5-HT and platelet aggregation, the Agency requested that the previous Sponsor evaluate the ability of tegaserod to bind human platelets and the *in vitro* effect of tegaserod on human platelet aggregation. An *in vitro* platelet binding study result indicated that tegaserod neither binds to human thrombocytes nor is it taken up by platelets to a significant extent. Furthermore, activation of 5-HT2A receptors could theoretically contribute to CV risk by stimulating the release of 5-HT from platelets, which by itself is a weak platelet activator but which potentiates platelet aggregation induced by other aggregatory agents. Notably, *in vitro* aggregation studies are not optimal as indicators of platelet activation *in vivo*. Four *in vitro* studies have demonstrated a lack of an association between tegaserod and platelet aggregation at concentrations equivalent to plasma levels seen with 12mg daily doses.

In the prior Sponsor study RD-2008-00298 (Serebruany, 2010), pre-incubation with tegaserod at concentrations mimicking human C_{max} values (10 nM), 3.3-times C_{max} (33 nM) and 10-times C_{max} (100 nM), respectively, resulted in minor increases in platelet aggregation induced by ADP, collagen, epinephrine, or 5-HT. exposures ($\geq$3.3X clinical C_{max} plasma levels for humans)By contrast, two other *in vitro* studies were conducted by independent investigators (Higgins, 2012; Beattie, 2013; Conlon, 2018), In these studies investigators used methods that produce a more stable platelet preparation. At concentrations of up to 100 nM tegaserod there were no differences in ability to increase platelet aggregation over that produced by vehicle, suggesting that the minor increase in platelet aggregation in the Serebruany study might not be relevant to human CV safety and was possibly a result of laboratory variables such as a heightened degree of baseline platelet activation. Based on these *in vitro* studies, it was concluded that there was no mechanistic reason to suspect a connection between tegaserod treatment and CV ischemic events. An *in vitro* platelet binding study indicated that tegaserod neither binds to human thrombocytes nor is it taken up by platelets to a significant extent.

As recommended by the Agency, a study was conducted by the current Sponsor to test for the effects of the tegaserod main metabolite, methoxyindole-3-carboxylic acid glucuronide (M29.0) on platelet aggregation. Pre-incubation with M29.0 at concentrations of 10 and 100 nM, for greater than 1 hour, appear to support the contention that M29.0 potentiated ADP (5µM) and 5-HT (5µM) + ADP (1µM)-induced platelet aggregation by a significant ~5-10%. However, it was observed that there was apparent activation of the platelets, which maximized the aggregation achievable with the agonists alone, severely limiting any conclusions and interpretations from this *in vitro* study.

3.3.5. Summary of Mechanistic Evaluations

A thorough review of tegaserod pharmacology and mechanistic evidence to assess the potential effects of tegaserod on mechanisms that could lead to CV ischemic event, including receptor binding, platelet aggregation and arterial constriction studies, provides no mechanistic basis for the observed small imbalance in ischemic CV events.

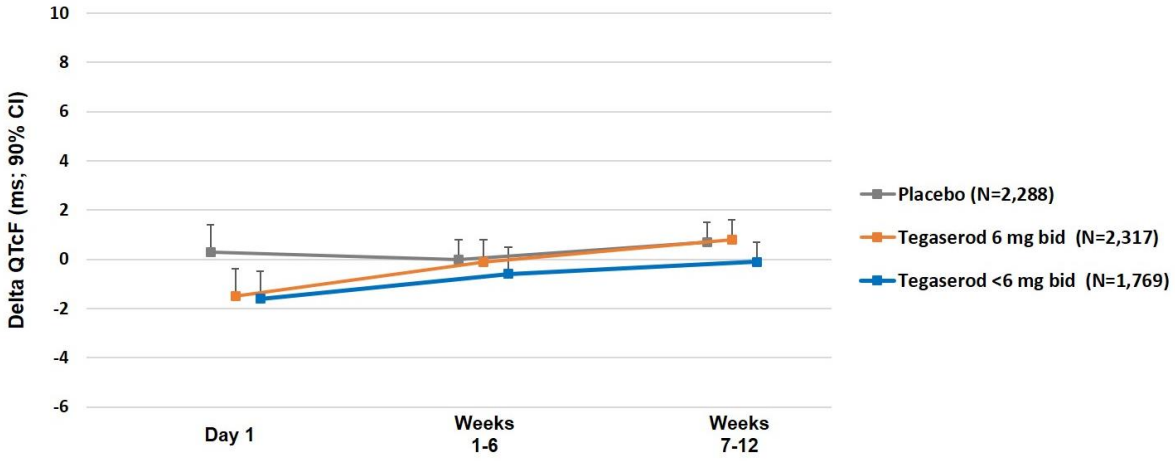
Overall, findings support that there is no consistent or conclusive connection between tegaserod's mechanism of action via agonism of 5-HT receptors, actions on platelets or arteries and the potential for adverse CV effects.

3.3.6. ECG, Blood Pressure, Heart Rate

To support reintroduction, the Sponsor assessed potential ECG abnormalities or symptoms suggestive of arrhythmia using data from DB15 and DB14 in studies where ECGs were centrally read. Overall, these analyses confirmed that tegaserod is devoid of relevant electrocardiographic effects. A more detailed summary of these findings and the methodologies used is provided in Appendix 8.

In the pooled database, using the centrally analyzed ECGs of placebo-controlled studies, there were no meaningful tegaserod-related effect on the QTcF interval which at all time points was similar to placebo and the upper 90% confidence interval for the change from baseline QTcF was always < 10 ms, the boundary of regulatory concern. There was no imbalance in the QTcF categorical analyses.

Figure 3: Change from Baseline in QTcF in DB15 Subjects whose ECGs were Centrally Read



In DB15, the BP measurements were overall uneventful and no clinically meaningful changes were observed. Likewise, there were no clinically meaningful changes in vital signs (systolic/diastolic blood pressure).

Figure 4: Change from Baseline in Supine Systolic Blood Pressure in DB15 Subjects

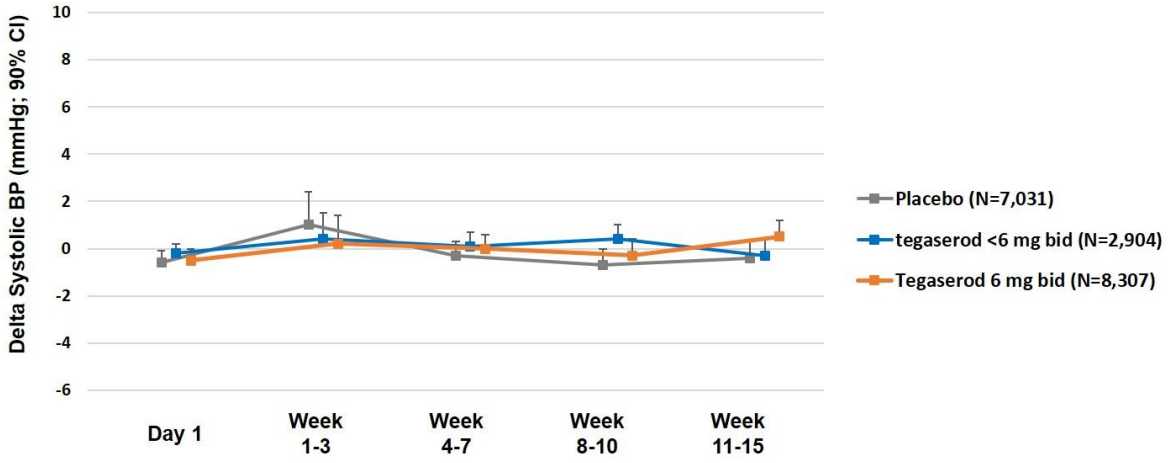
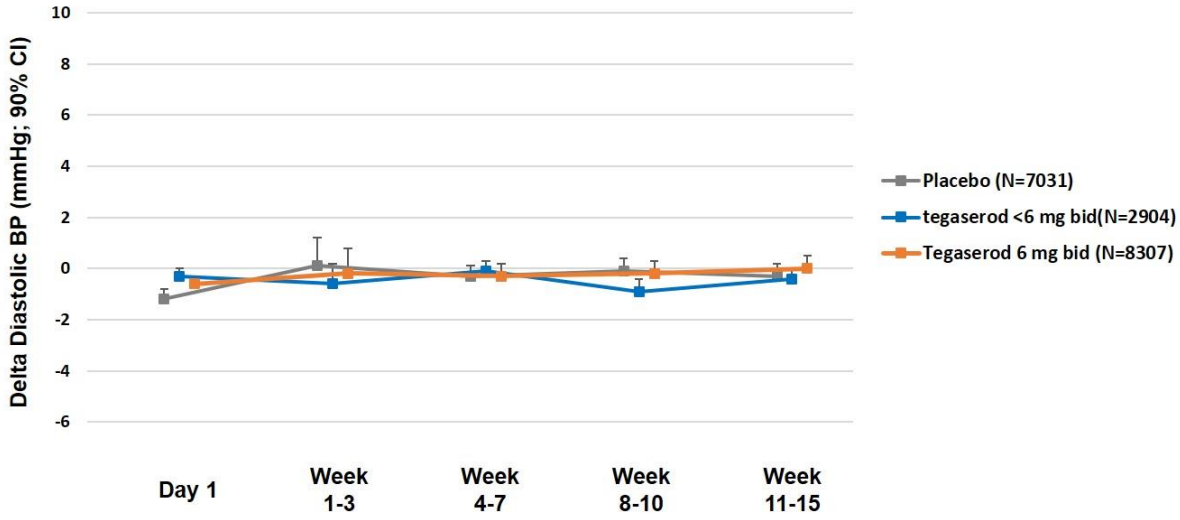
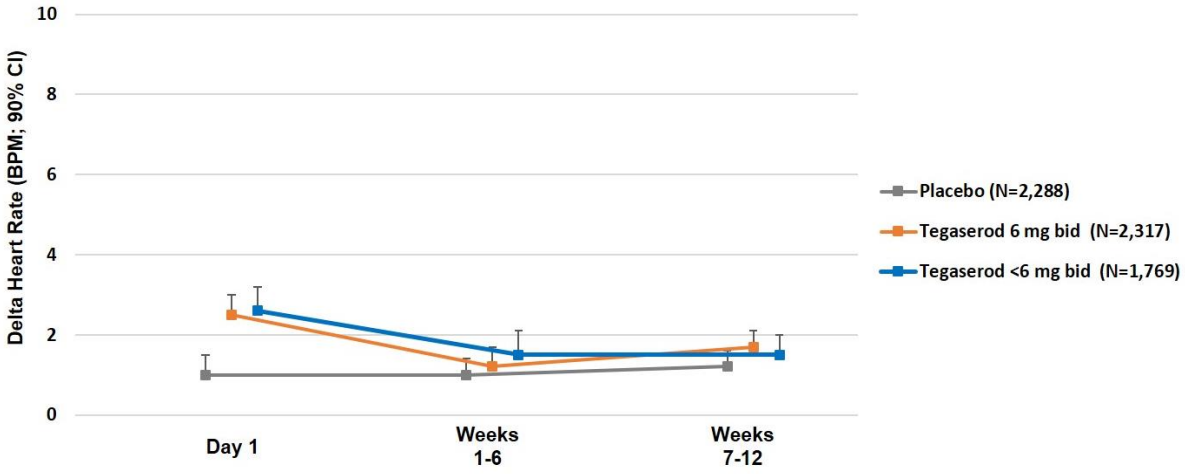


Figure 5: Change from Baseline: Diastolic Blood Pressure in DB15 Subjects



On Day 1 there was a minor increase in the ventricular rate with tegaserod 6 mg BID compared to placebo, without a dose-response, of ~1.4 BPM which was not observed at later time points. The central tendency and categorical analyses demonstrated no meaningful effects on the QRS or PR intervals.

Figure 6: Change from Baseline in Heart Rate in DB15 Subjects



In DB14, there was no meaningful effect on ECG, heart rate or blood pressure variables.

There was no meaningful difference in ventricular arrhythmia occurrence as classified by ICH E14 in the Db15 (Table 7).

Table 7: Summary of Potential Clinical Arrhythmias (ICH E14) Occurrence

	All Subjects Db15	
	Tegaserod All Doses N=11,614	**Placebo N= 7,031**
Clinical Arrhythmias- ICHE14		
At least one event	20 (0.17%)	11 (0.16%)
Syncope	14 (0.12%)	9 (0.13%)
Ventricular Fibrillation	1 (0.01%)	0
Ventricular tachycardia	0	0
Ventricular flutter	0	0
Torsade de pointes	0	0
Electrocardiogram QT prolonged	0	0
Ventricular arrhythmia	0	0
Cardiac arrest	0	0
Sudden death	0	0
Seizure	5 (0.04%)	2 (0.03%)

3.4. Cardiovascular Safety Conclusions

In summary, comprehensive investigations to evaluate the CV risk based on the original observed imbalance support a favorable CV risk profile for Zelnorm. Notably, the epidemiological studies were designed and powered specifically to detect a difference in ischemic events resulting from tegaserod treatment. This study concluded that the rate of ischemic events in tegaserod treated patients was consistent with if not lower than that observed in matched controls. These conclusions are further supported by mechanistic studies which have not established clear biological plausibility for ischemic effects. The results across these investigations can be used support a conclusion of very low CV risk. However, a small imbalance in the observed rates of CV ischemic events between the tegaserod and placebo groups in the clinical trial database cannot be ignored, which does leave some residual uncertainty.

4. MEDICAL LANDSCAPE

4.1. Disease Background

Irritable bowel syndrome (IBS) is a common and burdensome functional gastrointestinal disorder (FGID) characterized by chronic or recurrent abdominal pain or discomfort and disturbed defecation that has multiple overlapping symptoms. This condition affects 55 million people in the US (Canavan, 2014) and has a broad range of severity, covering mild symptoms to severe and intractable symptoms.

Studies have demonstrated that patients with IBS generally have lower quality of life (QOL) compared to non-sufferers (Frank, 2002). In fact, IBS suffers have lower QOL indicators than patients with diabetes and end stage renal disease (Monnikes, 2011). The impairment in quality of life is reflected in various domains of life including depression. This is particularly prominent in self-reported severe IBS (Hyun, 2011). Surprisingly, the prevalence rates of depression are similar between patients with IBS and a more serious disease, inflammatory bowel disease (IBD). Strikingly, the severity of depression and anxiety are higher in IBS patients than in IBD patients (Geng, 2018). Other measures that reflect QOL as well as the economic burden of IBS-C include lower productivity, higher hospitalization rates, more diagnostic testing even after diagnosis has been made and missed work compared to non-suffers. Annually, IBS sufferers miss 3 times as many work days as those without bowel symptoms (13.4 days vs. 4.9 days) (Drossman, 2002). The economic burden borne by patients and the healthcare system, is considerable, with annual indirect/direct cost of IBS reaching $30 billion, where annual all-cause healthcare costs associated with IBS-C can reach up to $3,856 for individual patients (Drossman, 2002; Sandler, 2002; Doshi, 2014).

Severity and frequency of pain as well as difficulty in defecation are only some of the drivers of poor quality of life in patient with IBS. Anxiety over the lack of regularity and reliability of bowel movements are unique to IBS-C as well as the concern over when a as needed laxative will act and with what urgency constrains activity in many patients. Embarrassment and sense of isolation about having a condition that lacks predictability plays a role in the diminished quality of life of IBS sufferers. The lack of mortality associated with IBS-C masks the heavy burden of this condition on individuals suffering from this condition.

Although the pathophysiology of IBS is not fully understood, it is likely a multifactorial condition with multiple identified mechanisms that cause various symptoms (Lacy, 2016). Symptoms appear to be due to disturbances in GI motility and enhanced visceral sensitivity, with psychosocial factors also potentially contributing to overall symptom expression (Lee, 2014; Kanazawa, 2008; Drossman, 2002; Camilleri, 1992). The diagnostic criteria gastroenterologists use to diagnose IBS-C is referred to as the Rome criteria. These criteria are the standard by which IBS is diagnosed and can be further differentiated into specific subtypes based on symptom assessments and durations. IBS-C is characterized by multiple symptoms (abdominal pain or discomfort, bloating, constipation), that are part of a global symptom complex (Lacy, 2016; Longstreth, 2006). IBS-C has a negative impact on patients' lives with the unmet medical need extending beyond simply treating infrequent bowel movements. It embodies a need for a therapy that, by addressing some of the pathophysiological abnormalities of the condition, can provide global symptom relief.

4.2. Current Available Therapies and the Unmet Medical Need

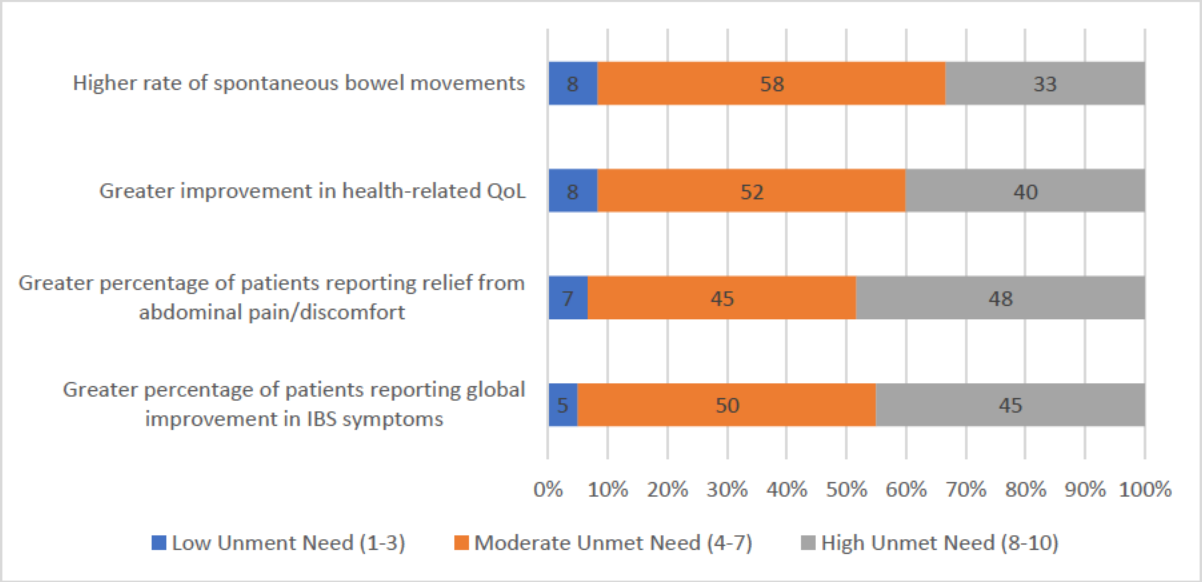
Currently, no therapy has been approved to treat the individual symptoms of IBS-C (abdominal pain or discomfort, bloating, constipation). Although over-the-counter therapies, such as stool softeners, fiber supplements, and laxatives may relieve constipation, they do not address other symptoms of IBS-C and can exacerbate bloating (Lee, 2014). Correspondingly, one study found that only 27% of IBS sufferers rated their treatment (fiber, laxatives, stool softeners, enemas, suppositories) as very or extremely effective (Whitehead, 2004).

As of August 2018, there are three FDA-approved treatments for IBS-C. In chronological order of their approval, these are lubiprostone (Amitiza™), linaclotide (Linzess™) and plecanatide (Trulance™). Lubiprostone, a bicyclic fatty acid, is a type 2 chloride channel activator. Linalcotide and plecanatide are synthetic oligopeptides that act as agonists at guanlyate cyclase-C receptors in the small intestine and colon. All promote fluid secretion into the intestine through calcium channel or guanylate cyclase activation. These three agents have been demonstrated to be superior to placebo in pivotal randomized controlled trials in IBS-C and chronic idiopathic constipation (CIC) leading to their approval. Although there were various primary endpoints used for approval of these agents, the reported therapeutic gains (difference in responder rate between treatment and placebo) from pivotal studies were in the range of 6-19.8% regardless of the agent (Amitiza® Label, 2018; Linzess® Label, 2017; Trulance™ Label, 2018). This may well relate to the fact that the pathophysiological abnormality causing IBS-C may differ in most patients and hence there is a ceiling to the potential benefit based on this mechanism.

The Sponsor's rationale for the proposed reintroduction is based on the compelling medical need for additional treatment options for IBS-C. Many health care providers (HCPs) feel current treatments do not sufficiently address symptoms associated with IBS-C. In a recent study, 55% of HCPs felt that they were not completely satisfied with current treatment options, citing inadequate efficacy. Similarly, 78% of IBS-C patients were not completely satisfied with current treatments options. (Quigley, 2018). The main reasons reported for dissatisfaction with current therapies included lack of efficacy (55%) and incidence of adverse events (39%). About one-third of IBS-C patients are completely satisfied with their current treatments (Heidelbaugh, 2015).

The gastroenterology community has advocated for additional treatment options for IBS-C. Satisfaction levels of gastroenterologists associated with currently available therapies for IBS-C is low. Survey results across several performance factors, as seen in Figure 7, demonstrate only moderate satisfaction with the performance of current IBS-C therapies.

Figure 7: Surveyed Gastroenterologists' Satisfaction with the Performance of Key Therapies for IBS-C on Efficacy, Safety and Tolerability, Convenience of Administration, and Nonclinical Factors: United States



Source: (Mackin, 2018)

Given the broad spectrum of the condition itself, IBS-C is a difficult disease to treat and requires a variety of treatment options. A significant unmet need for additional therapies in IBS-C patients currently exists. Tegaserod offers the potential to be a valuable additional option to existing therapies, due to its unique mechanism of action as the only prokinetic agent for IBS-C. Bringing a well-studied drug with a well-established mechanism of action that is distinctly different from the currently available approved or unapproved therapies back to market, gives patients another treatment option that addresses the 3 hallmark symptoms of IBS-C.

4.2.1. Efficacy and Safety Profile of Current Available Therapies

Reflective of the unmet medical need, there is a low level of clinical response seen with the available treatments in the pivotal approval trials. A responder is defined as having a limited improvement in symptoms (Amitiza® Label, 2018; Linzess® Label, 2017; Trulance™ Label, 2018). In the 2 pivotal studies for Amitiza®, Linzess®, and Trulance™ the overall therapeutic gain (i.e., improvement in response rate) over placebo was found to range between 6.0-6.4%, 7.0-19.8%, and 7-12% respectively (Table 8). Well documented and researched, high placebo rates are common in IBS-C trials due to a variety of reasons associated with the multifactorial pathophysiology of the disease (Shah, 2014; Pitz, 2005). High placebo response and multiple underlying conditions contributing to heterogeneity in the population are contributors to moderate rates of therapeutic gain; however given the stringent criteria to define a responder, treatment differences reported for these therapies are considered meaningful. However, because all available medications achieve efficacy primarily through enhanced intestinal secretion, these treatments do not provide adequate benefit to all patients.

Table 8: Summary of Current Products Approved in US for IBS-C

	Mechanism of Action (Pharmacological Effect)	Primary Endpoint	Therapeutic gain over placebo in pivotal trials (Active responder rate – Placebo responder rate)
Lubiprostone 8 µg *b.i.d.* (*Amitiza*®)	Local chloride channel activator (Change in the water/electrolyte balance in the lumen))	Responders meet the following criteria for at least 2 out of 3 months - reported "significantly relieved" for at least 2 weeks of the month; OR - reported "moderately relieved" in all 4 weeks of that month	Range from 2 studies; 6.0% to 6.4%
Linaclotide 290 µg *q.d.* (*Linzess*®)	Guanylate cycle-C (GC-C) agonist (Increased intestinal fluid; accelerated transit	Two combined responders definitions were used requiring the following criteria to be met for at least 6 out of 12 weeks OR 9 out of 12 weeks - at least 30% reduction from baseline in weekly average abdominal pain; AND, - an increase in ≥1CSBM per week, from baseline AND (only for 9 of 12 week responder definition), - at ≥ 3CSBMs; (All in the same week)	Range from 2 studies and 2 endpoint definitions: 7.0% to 19.8%
Plecanatide 3 mg *q.d.* (*Trulance*™)	Guanylate cycle-C (GC-C) agonist (Increased intestinal fluid; accelerated transit)	Responders meet the following criteria for at least 6/12 weeks - at least 30% reduction from baseline in weekly average of the worst daily abdominal pain; AND, - an increase in ≥1CSBM per week, from baseline	Range from 2 studies: 7.0% to 12.0%

CSBM: Complete spontaneous bowel movements

The principle side effects of lubiprostone (Amitiza®) 8 µg twice daily (the FDA-approved dose for IBS-C) observed in clinical trials were nausea, diarrhea and abdominal pain. Incidences of nausea, diarrhea and abdominal pain were, respectively, 8%, 7% and 5% (compared with rates on placebo of 4%, 4%, and 5%, respectively).

The principle side effects of linaclotide (Linzess®) 290 µg once daily (the FDA-approved dose for IBS-C) observed in clinical trials were diarrhea and abdominal pain. Incidence rates on linaclotide were 20% and 7%, respectively (compared with rates on placebo of 3% and 5%, respectively). In placebo-controlled trials in patients with IBS-C, 9% of patients treated with linaclotide and 3% of patients treated with placebo discontinued prematurely due to adverse reactions. In the linaclotide treatment group, the most common reasons for discontinuation due to adverse reactions were diarrhea (5%) and abdominal pain (1%). In comparison, less than 1% of patients in the placebo group withdrew due to diarrhea or abdominal pain.

The principle side effect of plecanatide (Trulance™) 3 mg once daily (the FDA-approved dose for IBS-C) observed in clinical trials in IBS-C was diarrhea; reported incidence was 4.3% with plecanatide and 1% with placebo. Although a head-to-head comparison of the safety profile of tegaserod versus other FDA-approved products have not been performed, clinical trial data suggest that tegaseord has similar and perhaps less frequent side effects including diarrhea and abdominal pain.

5. SUMMARY OF CLINICAL EFFICACY

The efficacy of Zelnorm is driven by its mechanism of action and has been demonstrated through several large placebo-controlled studies. Although the studies utilized slightly different scales and endpoint definitions, they all employed valid and reliable measures for assessing the patient's impression of treatment improvement for overall IBS-C symptoms, improvement of specific most-troubling symptoms of pain/discomfort and bowel habits, and severity and frequency of symptoms daily. These studies enable exploratory assessments across a number of subgroups to evaluate results with the overall population. The evaluations across the efficacy program support the following overall conclusions:

- Tegaserod (Zelnorm) is a selective 5-HT_4 agonist that targets receptors on specialized cells (enterocytes) in the GI tract to stimulate secretion, and nerves that control peristalsis through the release of neurotransmitters.

- Tegaserod increases fluid secretion thereby helping to soften stool (as do other approved drugs), but also reduces pain signaling, and stimulates GI contractility. These effects help to improve constipation, bloating and abdominal pain.

- The original studies that resulted in approval for IBS-C in women demonstrated significant overall and specific symptom relief between tegaserod versus placebo by week one and consistent over 12 weeks. Tegaserod has a clinically relevant benefit for overall relief and the multiple individual symptoms of IBS-C including abdominal discomfort/pain, abdominal bloating and constipation related symptoms.

- Results from post-approval studies reinforce the consistency of tegaserod's benefit in the previously approved labelled population.

- The subgroup of patients with more severe IBS-C demonstrated meaningful improvement in overall relief and symptoms with overall therapeutic gains comparable to the overall studied population.

- Analyses with a co-primary endpoint closely matching current regulatory guidance in design of IBS trials demonstrates similar if not enhanced treatment effect when compared to the original primary, SGA assessments.

- Overall, the improvements in IBS-C symptoms observed with tegaserod in comparison with placebo are within the range observed with other agents.

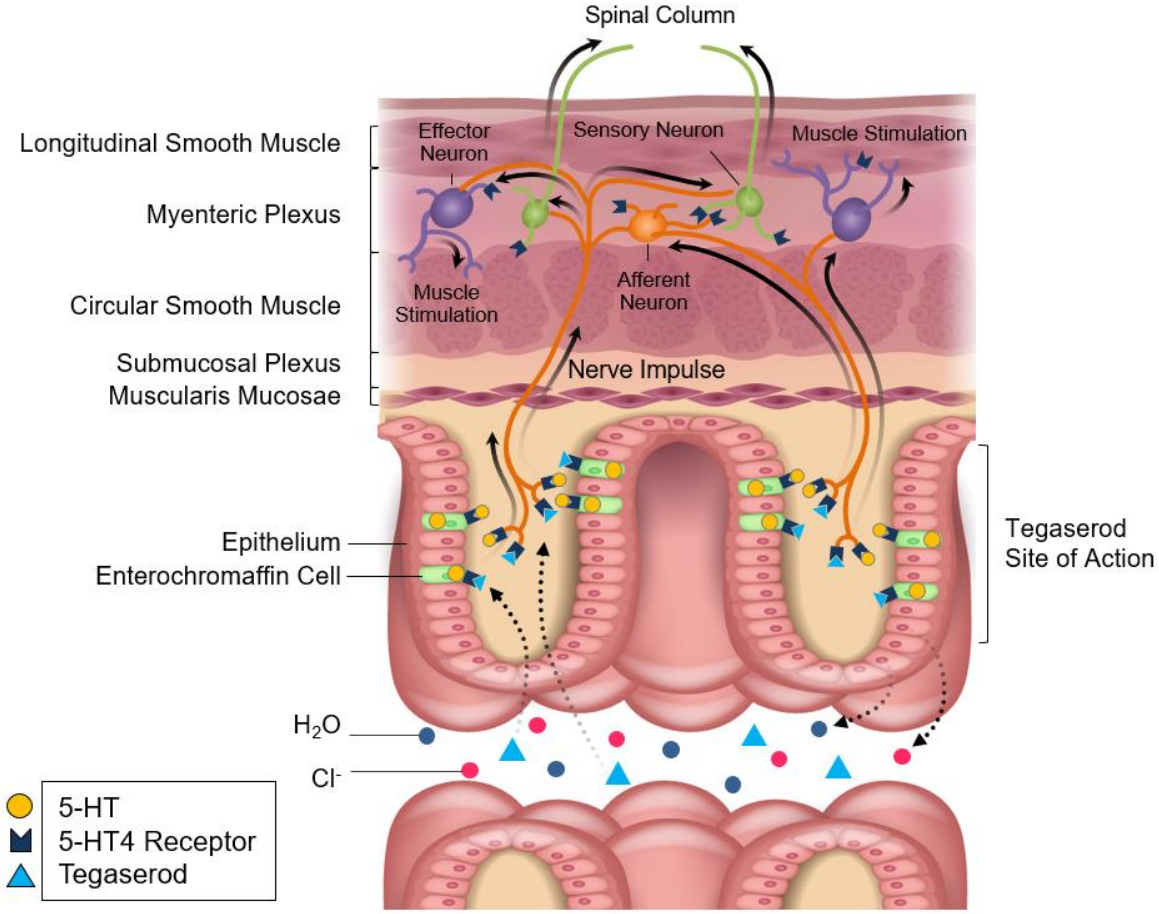
5.1. Mechanism of Action

As a 5-HT_4 receptor agonist, tegaserod offers a meaningful option in the treatment of IBS-C, based upon its distinct pharmacological mechanism of action (MOA), compared to other currently available treatments. Alterations in motility, secretion and visceral sensation in IBS-C are now thought to involve defects in signaling by 5-HT, which coordinates the activity of the enteric nervous system (Mawe, 2006). Contrary to normal individuals, patients with IBS-C have little or no rise in plasma 5-HT during a meal (Dunlop, 2005; Atkinson, 2006) and show a correlation between 5-HT levels and colonic motility or transit time (Dunlop, 2005;

Houghton, 2018), strongly suggesting impaired release from the intestinal enterochromaffin (EC) cells, which are the major source of circulating 5-HT.

Disruption of serotonergic signaling in the gastrointestinal tract can result in ineffective and uncoordinated contraction of the smooth muscle of the intestines; coordinated contractions are required for normal peristalsis to move contents through the gut. 5-HT is also involved with visceral sensation of pain and the normal regulation of the secretion of fluid into the intestinal lumen. Impairment of these mechanisms may result in constipation, bloating and abdominal pain. The 5-HT4 receptor is important in all these processes. Tegaserod is a selective agonist that targets receptors that are present on specialized cells in the GI tract to stimulate secretion, and nerves that control peristalsis through the release of neurotransmitters (Figure 8). Tegaserod has also been shown to alleviate visceral hypersensitivity, based on our current understanding, although the mechanism needs to be further elucidated. As a result, tegaserod increases fluid secretion thereby helping to soften stool (as do other approved drugs), but also reduces pain signaling, and stimulates GI contractility. These effects help to improve constipation, bloating and abdominal pain.

Figure 8: Schematic of GI Cross-Section, Sites of 5-HT$_4$ Location, and MOA



The need for an IBS-C treatment in the US has been addressed to some extent by the recent introductions of other prescription products, but their mechanism of action differs from that of tegaserod. These pharmacological treatments for IBS-C stimulate secretion into the intestinal lumen but do not interact with the serotonergic pathway. The resulting intestinal secretion and motility, as well as sensory modulation, has a positive impact on the main symptoms associated with IBS-C abdominal pain, bloating, and constipation and overall relief as is demonstrated in clinical studies of tegaserod.

5.2. Clinical Efficacy Overview

The clinical development program for tegaserod was initiated in 1994, leading to an approval in 2002 in the U.S for the treatment of females with IBS-C at a recommended dose of 6 mg bid. This approval was based on 3 placebo-controlled, 12-week clinical trials (B301, B351 and B358, see Section 5.2.1), with data from a dose titration study included (B307).

Since the approval, 2 additional randomized, placebo-controlled IBS-C studies were completed: studies A2306 and A2417 (Section 5.2.3). These studies evaluated a broader subset of patients representing different clinical patterns of IBS.

Additionally, the persistence of efficacy is further supported by open-label long term safety studies, which assessed efficacy outcomes through 12 months of treatment.

As such, the efficacy of tegaserod for IBS-C has been comprehensively investigated in 6 randomized, placebo controlled trials (4,750 exposed to tegaserod and 2,278 exposed to placebo), in addition to 3 long-term open-label studies (1,232 exposed to tegaserod) described in more detail in Section 6.

An overview of all studies included in the efficacy update are summarized in Table 9.

Table 9: Zelnorm IBS-C Efficacy Trials

Study No.	Patients randomized, Population	Medication dose/day	Primary Endpoint
Studies performed prior to US approval with 6 mg bid dose			
B301	881 Men and Women	tegas. 2 mg bid tegas. 6 mg bid placebo	SGA of relief of IBS symptoms[R] (ordinal, last 4 weeks)
B351	799 Men and Women	tegas. 2 mg bid tegas. 6 mg bid placebo	1) SGA of relief of IBS symptoms[R] (ordinal, last 4 weeks) 2) SGA of abdominal discomfort/pain[R] (VAS scale, last 4 weeks)
B358	1,519 Women	tegas. 6 mg bid placebo	SGA of relief of IBS symptoms[R] (ordinal, last 4 weeks)
B307	845 Men and Women	tegas. 2 mg bid tegas 2-6 mg bid placebo	Subjects assessment of overall symptom relief (last 4 weeks)
Studies performed subsequent to US approval			
4-week treatment and 4-week re-treatment study			
A2306	2,660 Women 18-65 years	tegas. 6 mg bid placebo	1) Relief of overall IBS symptoms[R] (binary, weeks 1-4) 2) Relief of abdominal discomfort/pain[R] (binary, weeks 1-4)
4-week study of patients with IBS-C and IBS-M			
A2417	661 Women 18-65 years	tegas. 6 mg bid placebo	Relief of overall IBS symptoms[L] (binary, weeks 1-4)

tegas. = tegaserod, SGA = Subject's Global Assessment

[R]Primary analysis using responder definition. [L]Primary longitudinal analysis of response profile for weeks 1-4.

5.2.1. Original Approval

The focus of this section is to summarize the original primary and symptom-based assessments from the previously submitted studies B301, B351, and B358. Analyses will be focused in the previously approved female patient population. These trials were the first large double-blind placebo-controlled trials to investigate efficacy of drug treatment of IBS-C utilizing the ROME criteria. Two doses of tegaserod (2mg bid and 6mg bid) were studied in B301 and B351. However, this document only presents tegaserod 6mg bid data in comparison with placebo since tegaserod 6mg bid was the FDA approved dose. In study B358, only tegaserod 6mg bid was tested.

For all studies, the demographic characteristics, baseline symptoms, and laxative use during the treatment period were similar among treatment groups. It can be noted, in study B358, more tegaserod patients (15.0%) than placebo patients (10.6%) used prohibited laxatives during the baseline period.

Studies B301, B351, and B307 recruited both male and female patients. Studies B301 and B307 required a minimum age of 18 years and study B351 had a minimum age requirement of

12 years. Patients with IBS-C associated with significant diarrhea, with diseases/conditions affecting bowel transit, or who planned to use drugs or agents that affect GI motility and/or perception, or with a history of laxative, drug or alcohol abuse, were excluded. Pregnant, lactating or fertile women not using adequate contraception, patients who were HIV positive, or patients who had previously participated in a study with tegaserod were also excluded. Patients during the baseline period with a mean VAS score <35 mm (mild abdominal pain) for the SGA of abdominal discomfort/pain, who failed to complete the daily diary cards or who used disallowed medication affecting GI motility and/or perception were excluded from the double-blind treatment period. Study B358 recruited female patients with IBS-C as defined by the Rome criteria, with patients having constipation as the predominant symptom of their altered bowel habit.

5.2.1.1. Primary Efficacy Endpoint and Results

The primary efficacy endpoint collected on a weekly basis (Weeks -4, -3, -2, -1, 1, 2, 3, etc. to 12) was Subject's Global Assessment (SGA) of relief. Patients were asked to answer the following question in their diary: "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?" Possible answers included: completely relieved, considerably relieved, somewhat relieved, unchanged, or worse.

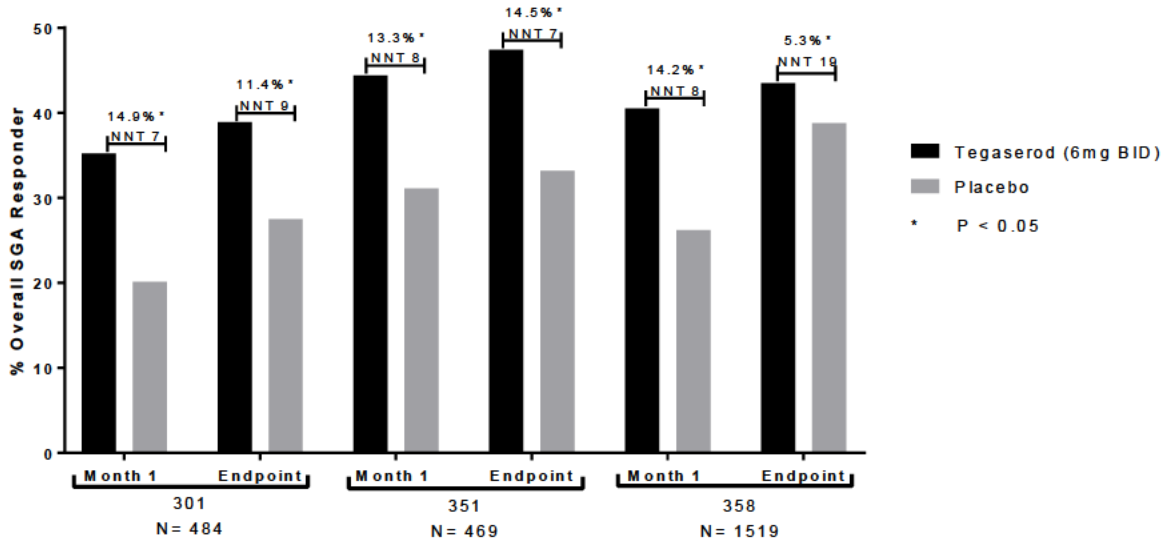
For the primary analysis, patients being "completely relieved" or "considerably relieved" for at least 50% of the last 4 available SGA assessments of relief, or "somewhat relief" for all of the last 4 available SGA of relief available during the 12 week treatment cycle were defined as "responders".

The fourth trial, Study B307, utilized a dose-titration design and evaluated the 2-mg bid dose of tegaserod and a dose-titration regimen (2 mg bid to 6 mg bid). Given the dose-titration design and lack of a fixed tegaserod 6 mg bid arm, the interpretation of these findings and comparison to the other three Phase III studies are difficult. The labeled population was restricted to females, as the benefit was not adequately demonstrated in males. Study B351 was revised half-way through the study with this responder definition. This post-hoc analysis, is considered significant, yet was deemed exploratory by the Agency reviewers. Additionally, adjusting for baseline laxative use was not pre-specified in the protocol for study B358; however, it was the only demographic variable for which there was a statistically significant imbalance at baseline and the Agency reviewer, Dr. Joseph, recommended this clinically relevant factor be accounted for in the primary analysis.

A summary of the primary efficacy results from the 3 trials (B301, B351 and B358) that led to the original approval of tegaserod for IBS-C are summarized in Figure 9. Efficacy was demonstrated using the subject's global assessment of relief (primary) and multiple key symptoms (secondary), such as abdominal discomfort/pain, abdominal bloating and bowel function as described further below. The population was restricted to females, as the benefit was not adequately demonstrated in males or in elderly patients, which represented a small proportion of the overall enrolled population (<10%).

Response rates for the subject's global assessment of relief at month 1 and endpoint (last 4 weeks of treatment) are shown in Figure 9, reflecting the recommended tegaserod dose of 6 mg bid in the originally approved population. Of importance, in the previously approved female patient population, an enhanced treatment difference ranging from 13.3% to 14.9% at month 1 were observed with high statistical significance seen across all three studies. At endpoint, a statistically significant treatment difference ranging from 5.3% to 14.2%. was also observed across all 3 studies (Figure 9).

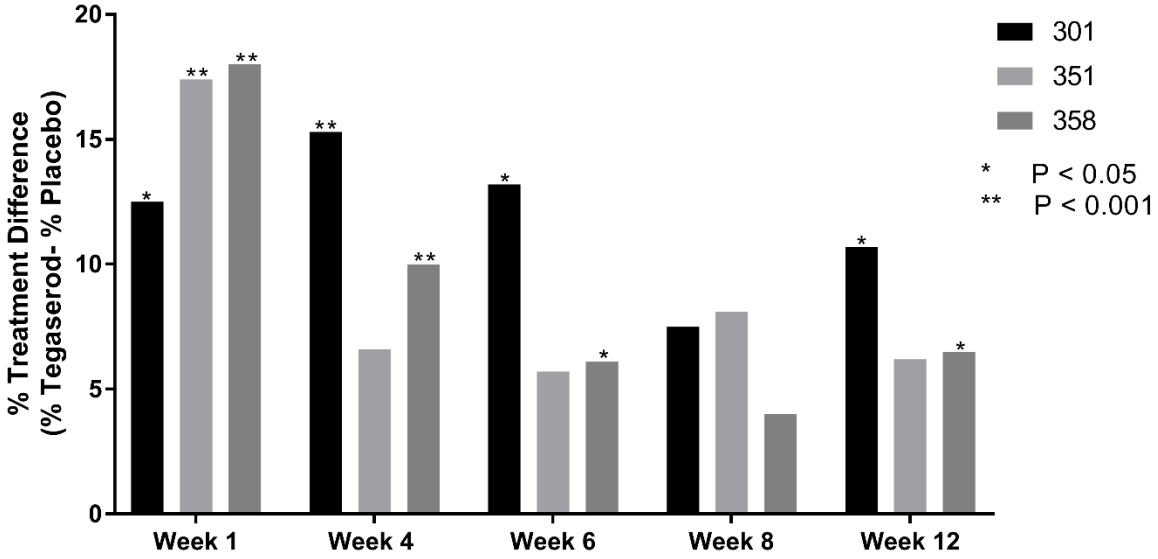
Figure 9: Between-treatment Comparisons of the Percent of Patients Responding to SGA of Relief (Primary Efficacy) During 50% of Month 1 and the Last 4 Weeks of Treatment (Endpoint) in Studies B301, B351, and B358-Females Only



These findings reflect clinically meaningful benefits, particularly in patients who have experienced symptoms for up to 13 years. Overall in studies B301, B351, and B358, tegaserod demonstrated significant improvement ($p < 0.05$) in scores for SGA of overall relief in the first month and the last 4 weeks of the 12-week treatment.

Another important therapeutic effect observed with tegaserod is its early onset of action for relieving overall IBS symptoms. Of importance, a rapid onset of action with tegaserod was observed as early as week 1 across all three studies and sustained throughout the 12-week treatment period. As shown in Figure 10, the percent of subjects in studies B301, B351, and B358 with somewhat, considerable, or complete overall symptom relief was observed as early as week 1 and sustained throughout the 12-week treatment period. These studies assessing SGA responders consistently showed higher level of response in Zelnorm treated patients compared to placebo patients. Analyses of data confirm that SGA reported improvement were consistent across the scale for Zelnorm patients compared to placebo patients, suggesting many patients experienced some level of benefit even if they did not meet the prospective responder definition.

Figure 10: Treatment Group Differences in Proportion of Subjects with Complete, Considerable, or Somewhat Relief as reported on Overall SGA over the 12-week Treatment Periods for Studies 301, 351, and 358



In addition to SGA of relief from IBS symptoms, analyses were also conducted to evaluate the effect of tegaserod on relief of multiple symptoms of IBS-C. These included relief of abdominal discomfort/pain, improvements in abdominal bloating and in stool consistency and frequency. Results from these analyses of the full ITT population can be found in Figure 11, Figure 12 and Figure 13. Using at least a 25% improvement in abdominal pain/discomfort and bloating severity scores significantly more patients experienced improvement of abdominal pain/discomfort (Figure 11) and bloating (Figure 12). Similarly, using a minimum 25% reduction in percent of days with hard, or very hard stools, patients experienced significant improvement with active treatment (Figure 13). Abdominal pain, bloating and stool consistency improvements were consistent across all studies at month 1 and at endpoint (last 4 weeks of treatment). These results were confirmed when analyses using at least 1-point improvement in abdominal pain/discomfort, bloating, and stool consistency as a cut-off. Improvement of 0.5 point on a 6-point scale are considered clinically meaningful improvement for IBS-C patients (Guyatt, 1989) . Results from studies B301, B351, and B358 saw significant improvements of at least a 1-point for abdominal pain/discomfort, bloating and stool consistency scores. These results support clinically meaningful improvements in the key symptoms affecting enrolled patients.

Figure 11: Percent of Patients with Improvement in Daily Abdominal Pain Score ≥ 25% in Studies 301, 351, and 358

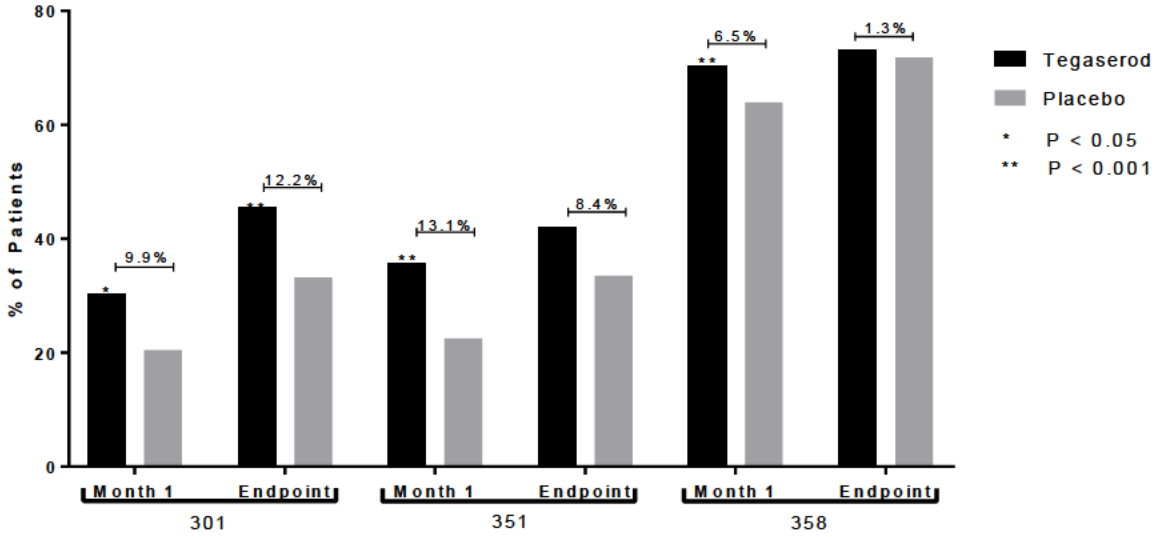


Figure 12: Percent of Patients with Improvement in Daily Abdominal Bloating Score ≥ 25% in Studies 301, 351, and 358

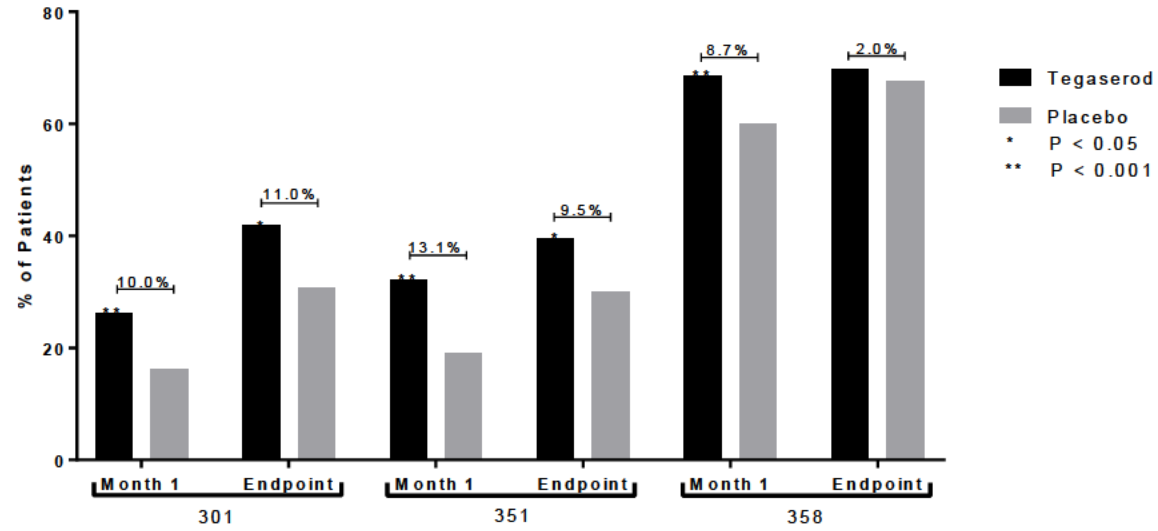
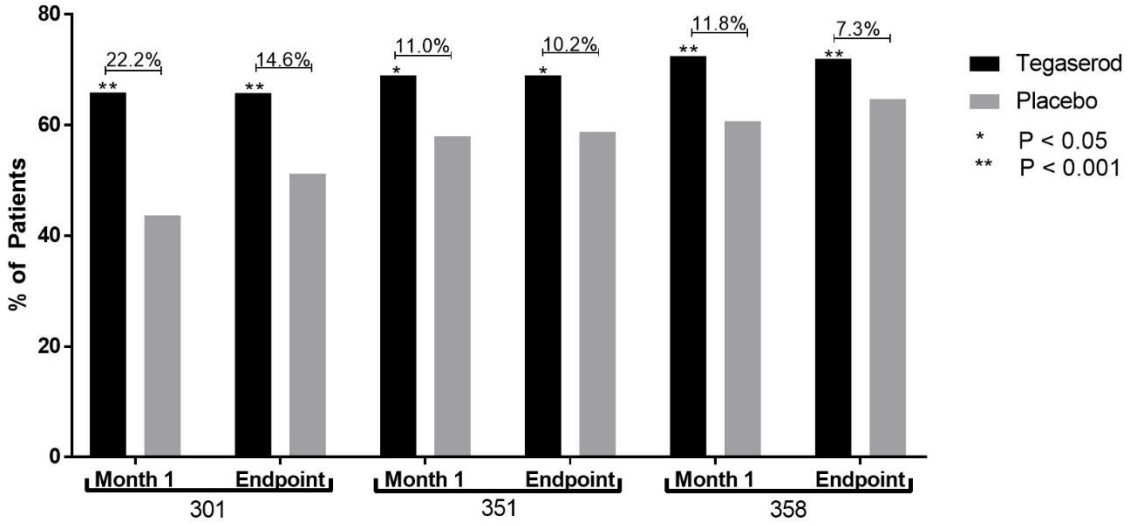


Figure 13: Percent of Patients with ≥ 25% Improvement in Percent of Days with Hard/Vary Hard Stool



Efficacy of tegaserod 6mg bid, the previously the Agency recommended approved dose, for female patients with IBS-C was clearly established from the 3 multicenter, randomized, double-blind, placebo-controlled studies. The data show the following in comparison with placebo:

- Tegaserod provided consistent, clinically relevant and statistically significant relief of overall IBS symptoms as well as relief of multiple individual symptoms associated with IBS-C such as abdominal discomfort/pain, bloating and constipation

- Tegaserod had a rapid onset of action for the relief of overall IBS symptoms with significant effect being observed as early as week 1 and sustained throughout the 12-weeks treatment period

Based on the totality of the evidence provided, the Agency recommended approval of Zelnorm 6 mg bid for the treatment of female patients with IBS-C.

5.2.2. Exploratory Analyses for Reintroduction

5.2.2.1. 2012 Guidance Endpoint

Since the original conduct of the study, new guidance has been issued for evaluating efficacy in functional GI disorders. The current guidance for IBS-C defines a primary endpoint assessing both improvements in abdominal pain and abnormal defecation. Exploratory analyses were conducted to test the original studies and approved population against current recommended guidelines published by the Agency to support an indication for the treatment of IBS-C (IBS Trials Guidance, 2012). Although the historical IBS-C studies were designed and conducted prior to the 2012 guidance, the Sponsor sought to confirm benefit utilizing today's recommended assessments. Using key secondary variables collected in the tegaserod 12-week trials, the following responder definition was applied: 50% weekly responder over 12

weeks, included a ≥30% reduction pain/discomfort and stool frequency increase ≥1 per week. Variations between the two endpoint definitions are outlined in Table 10.

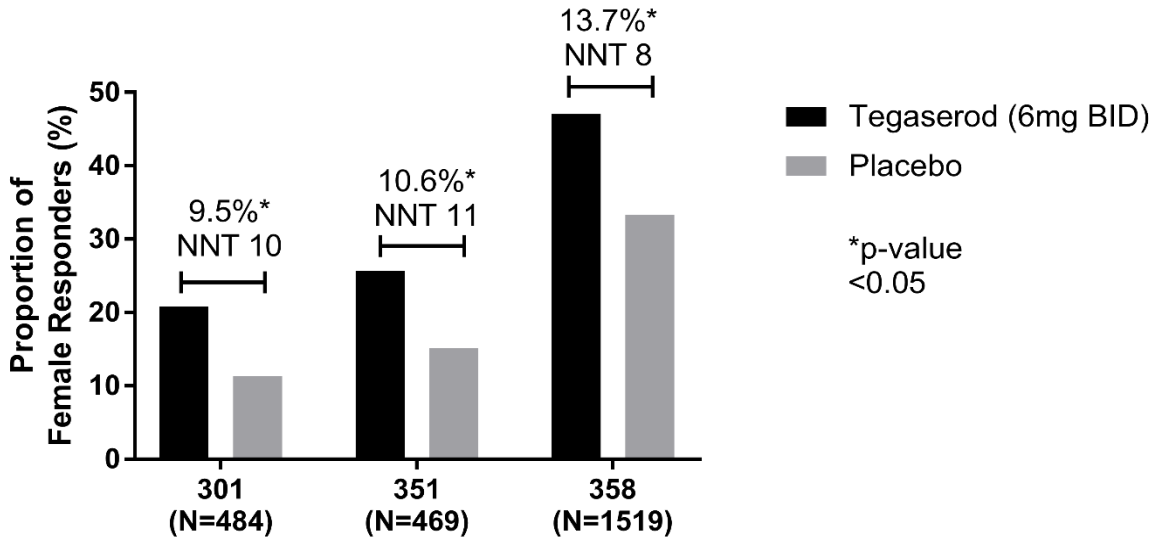
Table 10: Variations of Endpoints Utilized in Sensitivity Analyses

Endpoint Description		Endpoint Definition	Associated Entry Criteria	Variation of Endpoint Applied to Study Data in this Supplement
Abnormal Defecation	Original Zelnorm IBS-C trial endpoint	50% Responder Rates for Change from Baseline in Number of Bowel Movement (>=1/Week) over 12 Week.	Excluded: those with significant diarrhea and those who experienced at least 25% of the days with ≥ 3 bowel movements/day	"Combined Responder- 50% Weekly Responder over 12 weeks, >=30% Reduction Pain/Discomfort and Stool Frequency Increase>=1 per Week" The original IBS-C trials combined both intensity and discomfort into 1 secondary endpoint and are therefore considered a variation on the current recommended endpoint1. Additionally, the guidance recommended scale and the scale used in historical trials differ. The original IBS-C studies did not clearly define a bowel movement in terms of complete evacuation. The duration of response and % responder rate is consistent between the IBS-C trial secondary endpoint and the new guidance.
	2012 IBS Guidance Recommended Endpoint	Stool Frequency, as measured by the number of complete spontaneous bowel movements (CSBMs) per week. Weekly Responder is defined as a patient who experiences an increase of at least 1 CSBM per week from baseline for at least 50 % of the weeks or days of treatment (e.g., 6/12 weeks or 42/84 days).	Fewer than 3 CSBMs per week were included	
Abdominal Pain and Discomfort	Original Zelnorm IBS-C trial endpoint	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 percent compared with baseline weekly average for at least 50 % of the weeks or days of treatment.	The original IBS-C trials combined both pain intensity and discomfort into 1 scale/question[a].	
	2012 IBS Guidance Recommended Endpoint	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. An Abdominal Pain Intensity 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 percent compared with baseline weekly average for at least 50 % of the weeks or days of treatment (e.g., 6/12 weeks or 42/84 days)	Weekly average of worst daily (in past 24 hours) abdominal pain score of > 3.0 on a 0 to 10-point scale	
Duration of Response	Original Zelnorm IBS-C trial endpoint	A patient is an overall responder if they achieve the pre-specified improvement in weekly response for at least 50 percent of the weeks of treatment.	NA	
	2012 IBS Guidance Recommended Endpoint	A patient is an overall responder if they achieve the pre-specified improvement in weekly or daily response for at least 50 percent of the weeks or days of treatment (e.g., 6/12 weeks or 42/84 days).	NA	

[a] As discussed in the 2012 IBS Trial Guidance, recent clinical data provided to and reviewed by the Agency suggest that abdominal pain and discomfort may be different symptoms that should be assessed by different questions. Thus, the recommendation is to assess intensity as primary and discomfort as secondary

As shown in Figure 14, analyses with a co-primary endpoint as close to the new trial guidance as possible, demonstrates similar, if not enhanced treatment effect, when compared to the original primary endpoint analyses at the individual study level. For response to tegaserod vs. placebo in the pooled IBS-C Phase III studies (B301, B351, B358) limited to the females over 12 weeks, the OR was 1.84 (95% CI 1.53, 2.19; P value <0.001) with a therapeutic gain of 12.4% and NNT of 9. The results were consistent in both the pooled and individual study level analyses. These results are consistent with therapeutic gains seen with other available treatments, where therapeutic gains range from 6-19.8%.

Figure 14: Therapeutic Gain in Females with IBS-C Assessed Using the 2012 IBS Guidance Co-primary Endpoint in Studies 301, 351, and 358



5.2.2.2. Severely Symptomatic Subgroup Analyses

The Sponsor worked with the Agency to identify a subgroup that represent patients with more severe symptoms with the expectation that patients with more severe symptoms may be more willing to accept risk uncertainty based on the intensity of their disease.

There is no "gold standard" for assessing severity in IBS, and different trials used different scales and rating systems. However, all trials assessed at baseline the severity of abdominal discomfort/pain as well as the "severity" of bowel habit (bowel movement frequency and consistency), and the number of days that these symptoms persisted was also documented.

The modeling methods thus examined different combinations of severe symptoms present for different durations at baseline, to characterize the symptoms and duration shared by the patients showing the greatest impairment of quality of life at baseline (IBS-QoL). These definitions are supported both by anchoring to SGA severity ratings and guided by clinical expertise from GI specialists.

This proposed population consisted of female patients with IBS-C, who experienced at baseline:

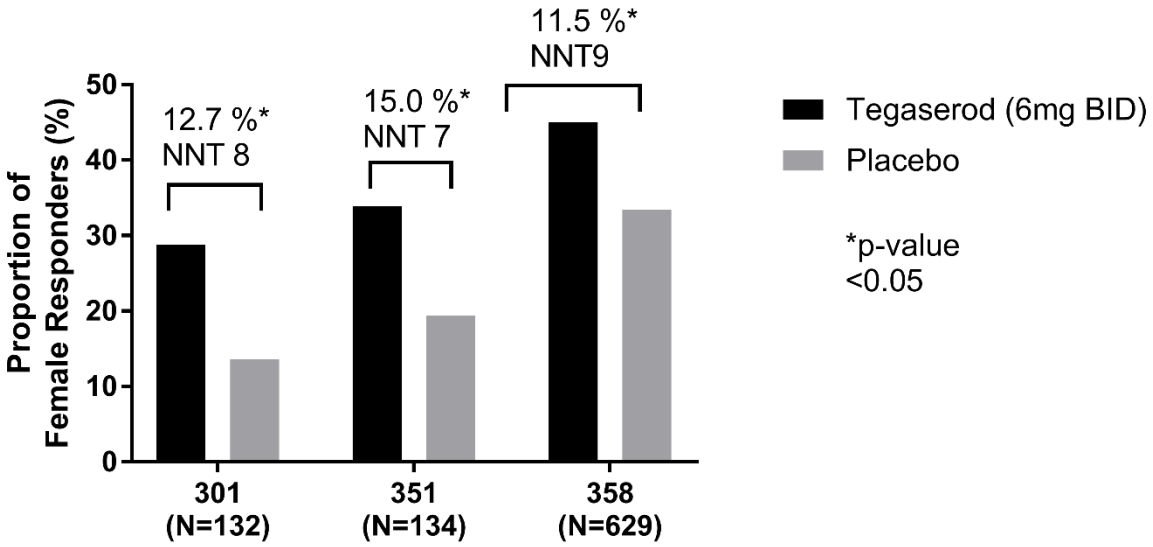
- ≥ 3 days of severe abdominal discomfort/pain on average per week before treatment (compared to the IBS-C diagnostic criteria of 1 days with any intensity of abdominal pain); AND

- ≥5 days of hard, very hard, or no stool on average per week before treatment (compared to the IBS-C diagnostic criteria of infrequent stool frequency and straining)

This definition was evaluated against the IBS Quality of Life measurement (Patrick, 1998) as this was the most extensively validated patient reported outcome measure which shows appropriate psychometric quality. Although not specific to IBS-C, these domains have been studied in IBS and are very relevant to patients with this condition. As described by Patrick et al., the IBS-QoL score becomes significantly lower as severity classification worsens (severity based on symptom frequency index and symptom bothersomeness index). Patients with the highest symptom frequency and symptom bothersomeness index had an overall IBS-QoL score ≤55 (Patrick, 1998). The Sponsor used a QOL score ≤55 as a criterion to assess QoL-anchored symptom severity. The current definition was shown to reflect a significant impairment in the QOL score (with mean baseline scores less than 55), indicating these patients suffer from the most severe disease from both a symptom and psychometric standpoint.

Figure 15 displays the degree of effect achieved in the severely symptomatic subgroup when the 2012 guidance endpoint is applied. The results demonstrate significant therapeutic gain over placebo. The benefits seen in this population may be arguably more meaningful, given that the baseline severity is significant. Improvement in both abdominal pain and stool frequency may be more meaningful to this population who have significant symptom and QoL impairment.

Figure 15: Therapeutic Gain in Females with Severe IBS-C Assessed Using the 2012 IBS Guidance Co-primary Endpoint



5.2.2.3. Efficacy in Long Term, Open-label Studies

There has been an evolution in the Agency's approach for recommending treatment courses of IBS products through product labeling, however the duration of controlled studies to evaluate the condition have consistently been 12 weeks in duration (both before and after the 2012 the Agency guidance). The pivotal studies of tegaserod meet this criterion. To further support tegaserod's continued efficacy, the longer-term studies were analyzed to assess durability of response beyond 12 weeks. As outlined below, there is support for a persistence of benefit extending to 12 months of exposure.

Study B209 was a multicenter study to assess the long-term safety and efficacy of tegaserod in a large population of patients with IBS-C. The number and proportion of patients who described their overall IBS symptoms as being either considerably or completely relieved (considered a responder) was assessed. As reported in the clinical study report, the number of responders steadily increased throughout the 12-month treatment period to reach 62.2% of those remaining after 12 months (189/304 patients). Additionally, the number of patients who self-identified as being "somewhat relieved" remained steady throughout the study through Month 12.

Study B301E1 was a multicenter study designed to evaluate the safety and tolerability of tegaserod in the long-term treatment of IBS-C in male and female subjects who completed the placebo-controlled study B301. The secondary objective was to assess the efficacy of tegaserod in the long-term treatment of IBS-C, based on the Subjects Global Assessment (SGA) of relief, abdominal discomfort/pain and bowel habits. According to the SGA of relief, overall the percentage of responders increased during the extension study. Since the responders were staying on 4 mg/d, while the non-responders were up-titrated, the percentage of responders was higher in the tegaserod 4 mg/d treatment group than in the 12 mg/d treatment group. Based

on these parameters, the percentage of responders increased overall during the extension study and the treatment groups followed a similar pattern as SGA of relief.

Study B307E1 was designed to evaluate the safety and tolerability of tegaserod in the long-term treatment of IBS-C in male and female subjects who completed the placebo-controlled study B307. The secondary objective was to assess the efficacy of tegaserod in the long-term treatment of IBS-C, based on the SGA of relief, abdominal discomfort/pain and bowel habits. The number of subjects who discontinued this study due to unsatisfactory therapeutic effect was 2 (1.3%). According to the SGA of relief, overall the percentage of responders increased during the extension study. Since the responders were staying on 4 mg/d, while the non-responders were up-titrated, the percentage of responders was higher in the tegaserod 4 mg/d treatment group than in the 12 mg/d treatment group. Based on these parameters, the percentage of responders increased overall during the extension study and the treatment groups followed a similar pattern as SGA of relief.

Overall, these collective data across the three long-term IBS-C extension studies, based on the SGA of relief, abdominal discomfort/pain, and bowel habits endpoints supports that treatment response may persist with prolonged treatment.

5.2.3. Post Approval Studies

Treatment design for IBS trials has evolved over the years. Since the approval of tegaserod for IBS-C in the USA in 2002, two additional multicenter, randomized, double-blind, placebo-controlled studies were completed: A2306 and A2417. Both studies included only female patients, the previously FDA approved patient population and used tegaserod 6mg bid, the previously FDA approved dose. These studies are unique in that they either utilized novel designs or studied novel patient populations and were designed in accordance with the ROME II criteria for IBS-C as well as with the guidelines regarding the design and analysis of IBS studies recommended by the Committee for Proprietary Medicinal Products (CPMP) of the European Health Authorities (EMA, 2003).

5.2.3.1. Studies A2306 and A2417

Study A2306 is the largest study conducted with tegaserod (>2,500 patients) designed according to the CPMP's recommendations and employed 1) a minimum treatment duration of 4 weeks, 2) two cycles of treatment, 3) the use of two primary efficacy endpoints (relief of overall IBS symptoms and of abdominal discomfort/pain, 4) responder definition as relief of IBS symptoms for at least 2 out of 4 weeks during the treatment period. The study was conducted in women 18 to 65 years of age. The efficacy results of Study A2306 are presented in Section 5.2.3.2. The results demonstrate that at the end of the first and repeated treatment periods, there was a significantly greater proportion of patients in the tegaserod group who reported satisfactory relief of overall IBS symptoms and abdominal discomfort/pain. A more pronounced treatment difference was observed in period 2 than in period 1 across all efficacy variables.

Study A2417 included a broader study population consisting of patients with either IBS-C or IBS-M (alternating diarrhea and constipation) according to the Rome II criteria. The study was conducted in women 18 to 65 years of age. Although the proposed indication for tegaserod is for patients with IBS-C, recent literature has demonstrated the close association between IBS-

C and IBS-M (Drossman 2005). Thus, demonstration of efficacy for IBS-M may provide further evidence of efficacy of tegaserod for IBS-C. The efficacy results of study A2417 are presented in Section 5.2.3.3. A2417 was the first study designed to assess the efficacy of tegaserod in patients with either IBS-C or IBS-M. Tegaserod was significantly more effective than placebo for achieving overall satisfactory relief of IBS symptoms in patients with either IBS-C or with IBS-M. However, a more pronounced effect was observed in patients with IBS-C than in those with IBS-M based on the magnitude of odds ratio.

Overall, findings from these 2 post-approval studies (A2306, A2417), detailed in this section, reinforce the consistency of tegaserod's benefit in the previously approved population.

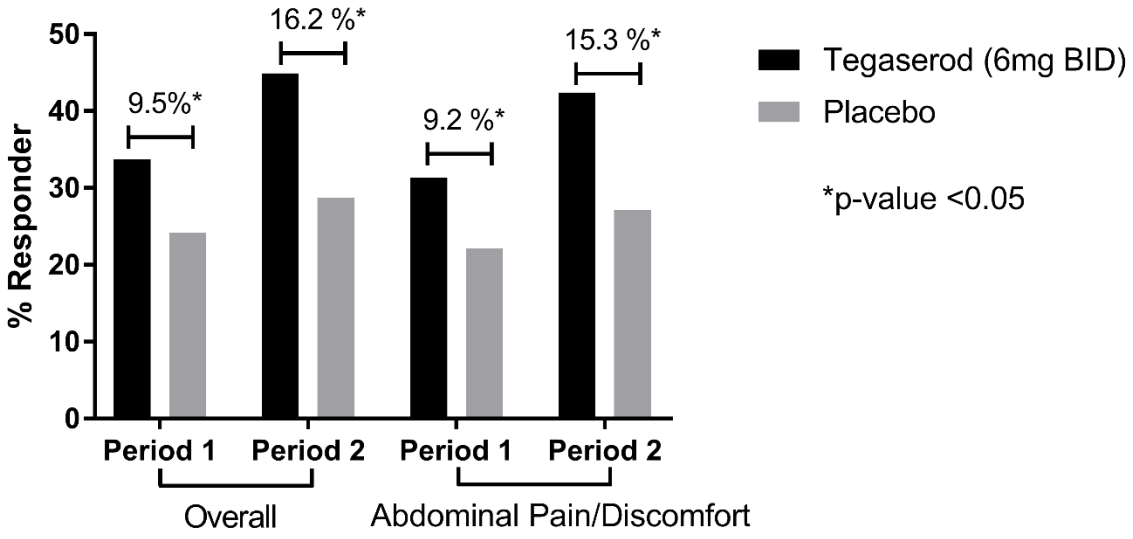
5.2.3.2. Study A2306 Endpoints and Results

Study A2306 was designed to assess the efficacy and safety of repeated treatment with tegaserod in patients with IBS-C who respond favorably to an initial 4-week treatment (Period 1) with tegaserod, and whose symptoms recur when tegaserod treatment is stopped. Given the variable symptom severity in IBS-C, an intermittent use regimen would represent a valuable option. Patients were randomized to tegaserod 6 mg bid or placebo in a 4:1 ratio for an initial 4 weeks treatment. Patients who responded in 2 out of 4 weeks for 1 of the 2 primary endpoints on tegaserod 6 mg bid were re-randomized to either receive tegaserod 6 mg bid or placebo for an additional 4 weeks of treatment if their symptoms reoccurred during the treatment-free period (2-12 weeks). Placebo responders during weeks 1-4 were randomized to tegaserod.

Study A2306 utilized a unique re-treatment design which follows the key recommendations of the draft Committee for Proprietary Medicinal Products (CPMP), 2003 points to consider in IBS, which recognizes the importance of waxing and waning of symptoms and the clinical pattern of repeat use (EMA, 2003).

Figure 16 illustrates the percent responder for tegaserod and placebo, as measured by 2 primary endpoints: abdominal discomfort/pain and overall IBS symptoms.

Figure 16: Primary Efficacy Results for Study A2306



At 1 month of treatment (period 1), overall relief was demonstrated by an OR of 1.61 (95% CI 1.29, 2.01; p value < 0.001) with a therapeutic gain of 9.2%. At the end of period 2, the OR was similar at 2.00 (95% CI 1.53, 2.61; p value < 0.001) with a therapeutic gain of 15.3%. A similar trend of effect was seen for the primary endpoint of abdominal pain and discomfort responder. This indicated that those subjects who relapsed after period 1 were at least as likely to respond to treatment as were subjects who had not previously been treated with tegaserod.

Secondary efficacy endpoints analyzed in this study included abdominal discomfort/pain intensity, bloating, number of bowel movements (change from baseline), and a Quality of Life (QoL) assessment. Specifically, IBS-QoL scores (Patrick, 1998) using a validated 34-question assessment were significantly higher in five out of the eight domains (dysphoria, body image, health worry, food avoidance, and impact on relationships, p<0.05) compared with placebo (Tack, 2005).

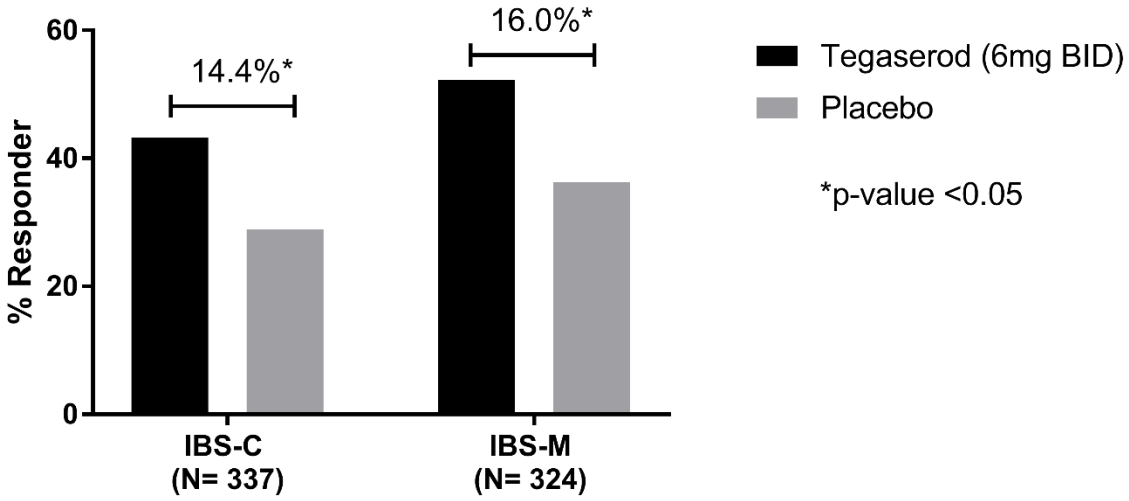
Overall, the efficacy of tegaserod for treating the multiple symptoms of female patients with IBS-C was demonstrated in study A2306.

5.2.3.3. Study A2417 Endpoints and Results

Study A2417 was conducted to obtain supplementary efficacy and safety data on a 6 mg bid dose regimen in a broader subset of female patients with IBS, stratified based on their self-reported history of IBS symptoms (IBS-C or IBS-M). The study was designed to confirm the efficacy of tegaserod versus placebo at relieving the symptoms of female patients with IBS, excluding those with diarrhea-predominant IBS (IBS-D), over the 4 weeks of treatment as measured by the weekly Patient's Overall Satisfactory Relief assessment of IBS symptoms. This was a 4-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group, study in female patients with IBS.

Figure 17 illustrates the percent responder for tegaserod and placebo, as measured by the primary endpoint: relief of overall IBS symptoms.

Figure 17: Primary Efficacy Results for Study A2417



For response to tegaserod vs. placebo in the IBS-C population at week 4, OR was 1.90 (95% CI 1.19, 3.01; P value 0.007) with a therapeutic gain of 14.4%. When considering both IBS-C and IBS-M subjects, at Week 4, the OR was 1.93 (95% CI 1.38, 2.71; P value <0.001) with a therapeutic gain of 16%.

Secondary endpoints showed benefits in favor of tegaserod. Patients treated with tegaserod had a statistically significant increase in number of bowel movements, fewer days with no bowel movements, a higher mean stool consistency score (softer stool), fewer days with straining and a relatively unchanged number of days with urgency. Of note, lower mean abdominal discomfort or pain scores and mean bloating scores were noted in tegaserod patients compared with those given placebo, but the differences were not statistically significant (Chey, 2008).

Overall, the efficacy of tegaserod for treating the multiple symptoms of patients with either IBS-C or IBS-M was demonstrated in study A2417.

5.2.4. Efficacy Conclusions

Zelnorm is a selective 5-HT_4 agonist that achieves a clinically relevant benefit for overall relief and the multiple individual symptoms of IBS-C including abdominal discomfort/pain, abdominal bloating and constipation related symptoms in the previously approved IBS-C population. This benefit is accomplished by increasing fluid secretion thereby helping to soften stool (as do other approved drugs), but also reduces pain signaling, and stimulates GI contractility. Even with differing study designs, the results of the original and post-approval studies were highly consistent in treatment response of tegaserod as compared with placebo in females with IBS-C. Studies demonstrated significant overall and specific symptom relief between tegaserod versus placebo by week one and consistent over 12 weeks. The subgroup of patients with more severe IBS-C demonstrated meaningful improvement in overall relief and symptoms with therapeutic gains comparable to the overall studied population.

Analyses with a co-primary endpoint closely matching current regulatory guidance in design of IBS trials demonstrates a similar if not enhanced treatment effect when compared to the original primary, SGA assessments. Also, the improvements in IBS-C symptoms observed with tegaserod in comparison to placebo are within the range observed with other agents. Overall the results of the extensive IBS-C database reinforce the global benefit of tegaserod across multiple symptoms and a tangible benefit that favorably impacts the daily lives of IBS-C patients.

6. SUMMARY OF CLINICAL SAFETY

The Sponsor presents analyses on various safety databases including: 29 placebo-controlled studies (DB15), a subset of this database containing the IBS-C studies only, and long-term safety studies that were between 6 and 12 months in duration (DB14). The CV safety discussed previously is comprised of several different events that when combined showed an imbalance in the clinical trial data. When analyzing individual adverse events using clinical trial data the number of events is equal to or lower in those taking Zelnorm than those taking placebo, with the exception of headache and diarrhea. Approximately 4 million patients have been treated with Zelnorm around the world. Pharmacovigilance monitoring of prescription use of Zelnorm between 2002 and 2017 shows the most common reports to be of gastrointestinal disorders, primarily diarrhea.

6.1. Databases Used for Safety Analyses

The overall safety of tegaserod was evaluated using three safety databases summarized below:

- Database 15 (DB15): 29 double-blind, placebo-controlled studies in both male and female subjects across multiple GI indications (Table 11). With the exception of one Phase II IBS-C study that was 26 weeks in duration, all other studies were between 4 and 12 weeks. This database consists of 18,645 patients: 11,614 received tegaserod and 7,031 received placebo. Most patients in this population were in the 12-week studies, with the majority of patients receiving the 6 mg bid dose (8,307 patients).

Table 11: Indications and Number of Patients Contributing to Safety Database 15

Indication	Number of studies	Number of Patients N (% contributing to overall database)
IBS-C	10	7,948 (42.6)
CIC	4	3,531 (18.9)
Functional dyspepsia	6	3,522 (18.9)
IBS-D	2	162 (0.9)
IBS-M (IBS-C + non IBS-D)	3	1,823 (9.7)
Slow transit constipation (STC)	1	12 (0.1)
GERD	2	1,526 (8.2)
Diabetic gastropathy	1	121 (0.6)

- IBS-C Studies: 6 Phase III, double-blind, placebo-controlled studies (also included in IBS-C studies of DB15): 4 pre-approval studies: B301, B351, B307, B358; and 2 post-marketing efficacy studies: A2417 (IBS-C subjects only) and A2306 (Period 1 only). The study durations ranged from 4 to 12 weeks. This database consists of 7,028 patients: 4,750 patients treated with tegaserod and 2,278 placebo patients. Most patients received the 6 mg bid dose (3,906 patients).

- Database 14 (DB14): 7 long term, open label studies between 6 and 13 months in duration in both male and female patients across multiple GI indications (Table 12). This database consists of 3,289 patients. Patients received repeated treatment of tegaserod approximately every 4 – 6 weeks and 45% of subjects were exposed to tegaserod beyond 9 months.

Table 12: Indications and Number of Patients Contributing to Long Term Safety Database 14

Indication	Number of studies	Number of patients (% contributing to overall database)
IBS-C	3	1,232 (37.5)
CIC	1	840 (25.5)
Functional dyspepsia	3	1,217 (37.0)

Patient exposure for the safety databases are summarized in Table 13.Exposure was defined as the period from the date of first study drug intake to the last known date of study drug intake. Overall, exposure was similar between the tegaserod and placebo treatment groups in DB15 and IBS-C databases, with the majority of patients completing at least 30 days of treatment. To date, over 14,903 patients have been exposed to tegaserod in completed clinical trials.

Patient demographics for the safety databases are summarized in Appendix 4. Demographic characteristics were similar between the tegaserod and placebo treatment groups in DB15 and IBS-C databases. The majority of patients represented in the safety databases were under 65 years of age (~90%) and female (~85%). Patient's enrolled in the placebo-controlled trials had an average duration of symptoms at baseline of 13 months.

Table 13: Exposure in Clinical Trial Safety Databases

Database	Number of patients Tegaserod [Mean Duration of Exposure, SD]	Number of patients Placebo [Mean Duration of Exposure, SD]
DB15 Placebo-controlled trials ≥ 4 weeks duration, multiple indications	11,614 [56.8 ±29.2 days]	7,031 [57.5 ± 28.2 days]
IBS-C Placebo-controlled IBS-C studies (subset of DB15)	4,750 [54.3 ±29.8 days]	2,278 [63.7 ± 29.8 days]
DB14 Open label, long-term trials, multiple indications	3,289 [227.3 ±132.7 days]	NA

6.2. DB15 General Summary of Safety

In DB15, 8,307 male and female patients received tegaserod at 6 mg bid and 7,031 received placebo. Diarrhea and headache were the only adverse events reported in >1% of patients receiving tegaserod and more frequently (≥0.2%) than placebo (Table 14). The overall discontinuation rate was 13.3% for tegaserod and 13.3 % for placebo, with the most frequent reasons being AEs (4.8% on tegaserod and 3.6% on placebo), unsatisfactory therapeutic effect (2.6% on tegaserod and 3.0% on placebo), and withdrawal of informed consent (2.9% on tegaserod and 2.8% on placebo).

Table 14: Overall Safety Profile in DB15 and IBS-C Databases

	DB15		IBS-C	
	Tegaserod 6mg bid n (%)	Placebo n (%)	Tegaserod 6mg bid n (%)	Placebo n (%)
Total patients studied	8,307	7,031	3,906	2,278
Subjects with ≥1 TEAE	3,744 (45.1)	3,139 (44.6)	1,746 (44.7)	1,186 (52.1)
Diarrhea	857 (10.3)	285 (4.1)	240 (6.1)	71 (3.1)
Headache	647 (7.8)	537 (7.6)	341 (8.7)	224 (9.8)
Discontinued due to TEAE	417 (5.0)	261 (3.7)	155 (4.0)	93 (4.1)
SAEs	56 (0.7)	63 (0.9)	23 (0.6)	15 (0.7)
Deaths	1 (0.0)	0	0	0

6.3. IBS-C Studies General Summary of Safety

In the IBS-C studies, 3,906 male and female patients received tegaserod 6 mg twice daily and 2,278 received placebo. Diarrhea was the only adverse events reported in >1% of patients receiving tegaserod and more frequently (≥0.2%) than placebo (Table 14). The overall discontinuation rate was 12.1% for tegaserod and 14.9% for placebo, with the most frequent reason being unsatisfactory treatment effect (3.1% for tegaserod and 3.1% for placebo), withdrawal of informed consent (3.0% for tegaserod and 4.2% for placebo) and AEs (3.6% for tegaserod and 3.8% for placebo).

6.4. DB14 General Summary of Safety

In the long-term open label pooled study population, the overall discontinuation rate was 46.0% for the tegaserod 6mg bid group, with the most frequent reason being unsatisfactory treatment effect (10.6%), withdrawal of informed consent (10.7%), and AEs (10.1%). The most common TEAE leading to discontinuation was diarrhea, similar to that seen in the placebo-controlled studies. The frequency of all TEAEs was 71.6%, the most frequent being headache (17.0%), diarrhea (15.5%), abdominal pain (10.9%), nausea (6.5%), back pain (6.3%), and upper respiratory tract infection (6.0%). The overall frequency of treatment emergent SAEs was 3.8% with similar rates of GI disorder SAEs than were seen in the placebo-controlled studies (0.8% on tegaserod in Db14 vs. 0.2% on tegaserod in Db15). No deaths were reported in Db14.

6.5. Postmarketing Data

Post-marketing exposure for the treatment of IBS-C or CIC, is estimated to be 1,626,835 patient-years, reflecting the amount of substance sold or distributed between January 1, 2001 (IBD) through September 30, 2017. An overview of all post-marketing safety data including safety data on, emergency/single patient IND (eIND/spIND), US market and ex-US markets is provided in this section.

6.5.1. tIND

Of the 182 patients enrolled in the tIND program, exposure data were available on 165 patients. The mean exposure was 76.4 (SD±44.4) days with the majority of patients having more than 28 days of exposure. There were no deaths and no major CV ischemic events reported in this program. Two (1.1%) patients from the safety population experienced a SAE. One SAE occurred in a 54-year female. She experienced left posterior cerebella mass requiring surgery. The second SAE occurred in a 47-year-old female. She experienced dyspnea and peripheral edema. In both cases, the study physician assessed causality of the event as “not suspected” in relation to the t-IND program medication.

6.5.2. eIND/spIND

Of the 634 patients authorized to receive drug under the eIND/spIND program since inception in 2007 (data from FDA), there were 4 patients whose SAEs and AEs were reported to the PVG vendor. From those MedWatch forms, there were 7 unique events, 1 was non-serious; the other 6 included: 1 fatal event due to metastatic non-small cell lung cancer, disease progression (disease unknown), gastrointestinal disorder, post procedural complication due large intestine perforation, vomiting and abdominal pain.

6.5.3. US Market

A total of 8888 MedWatch reports from within the US have been submitted to date and include, as expected, a large increase in the reporting of CV events after the CV safety issue was initially made public. The rate of unique AE/SAE events (from these 8888 MedWatch reports) by system organ class per 100,000 patient years is presented in Appendix 10 (Table 21). Overall, the number of unique events per 100,000 patient years are low and are mainly gastrointestinal disorders (541.32 events per 100,000 patient years), and general disorders and administration site conditions (245.53 events per 100,000 patient years).

In addition, given the history of safety concerns with tegaserod in the past, Appendix 10 (Table 22) includes a summary of the number of unique event reports per 100,000 patient years for specific events of interest, including MACE and suicide events. Overall, the number of unique events per 100,000 patient years are low: myocardial infarction (15.00 events per 100,000 patient years), cerebrovascular accident (14.34 events per 100,000 patient years), angina pectoris (9.21 events per 100,000 patient years), acute myocardial infarction (2.24 events per 100,000 patient years), cardiac arrest (0.79 events per 100,000 patient years), attempted suicide (0.66 events per 100,000 patient years), complete suicide (0.26 events per 100,000 patient years), and sudden cardiac death (0.13 events per 100,000 patient years), despite the spike in events that occurred after market withdrawal.

6.5.4. Ex-US Markets

A total of 5319 MedWatch reports from ex-US experience have been submitted to date. Summarized in Appendix 10 (Table 23) are all unique AE/SAE events reported, per system organ class, since the first product launch in January 2001 in all ex-US markets. Overall, the number of unique events per 100,000 patient years are low, and are mainly gastrointestinal disorders (427.22 events per 100,000 patient years), and general disorders and administration site conditions (257.15 events per 100,000 patient years).

In addition, as is the case for the US market analysis, given the history of safety concerns with tegaserod in the past, Appendix 10 (Table 24) includes a summary of the number of unique event reports per 100,000 patient years for specific events of interest, including MACE and suicide events. Overall, number of unique events per 100,000 patient years are low: angina pectoris (2.39 events per 100,000 patient years), cerebrovascular accident (2.39 events per 100,000 patient years), myocardial infarction (2.27 events per 100,000 patient years), cardiac arrest (1.07 events per 100,000 patient years), acute myocardial infarction (0.83 events per 100,000 patient years), complete suicide (0.72 events per 100,000 patient years), and attempted suicide (0.48 events per 100,000 patient years).

6.5.5. FAERs Reporting Ratios

Reporting data in the pre and post-withdrawal period were used to compare reporting ratios between tegaserod and all other non-tegaserod cases in FAERS for safety topics of interest, including CV events and deaths (which would include death due to a CV event). The data are summarized in table Table 15.

Table 15: Reporting Ratios Pre- and Post- Withdrawal

	January 1, 2002 through March 30, 2007		March 31, 2007 through March 31, 2018	
Safety topic of interest	**Ratio**	**95% CI**	**Ratio**	**95% CI**
Cardiovascular				
RRR	0.12	0.02-0.86	8.6	7.89-9.38
PRR	0.12	0.02-0.86	8.61	7.90-9.39
ROR	0.11	0.02-0.81	11.54	10.24-13.01
Deaths				
RRR	0.14	0.02-0.98	0.59	0.48-0.74
PRR	0.14	0.02-0.97	0.59	0.48-0.74
ROR	0.12	0.02-0.87	0.57	0.46-0.70

RRR = relative reporting ratio; PRR = proportional reporting ratio; ROR = relative odds ratio

In the pre-withdrawal period the ratio of reports for tegaserod did not exceed the ratio of reports for all other drugs reported to FAERS in any of the safety topics of interest. Typically, a ratio of 2 denotes a safety signal. In the post-withdrawal period the ratio of reports for tegaserod exceeded the ratio of reports for all other drugs reported to FAERS for the safety topics of interest (CV events).

The ratios in the post-withdrawal period are higher than the ratios reported in the pre-withdrawal period. It should be noted that 3/4ths of cases in the post-withdrawal period were reported from April-December 2007. Clusters of reports such as these may indicate stimulated reporting, either from increased awareness or due to enhanced data gathering that may take place in situations such as drug litigation. This may have the effect of inflating the numerator of the ratio since the reporting is stimulated for a specific outcome (i.e., CV events) but not for all outcomes.

6.5.6. Other Medical Conditions

Upon request of the Agency, the previous Sponsor evaluated other safety areas of concern. These included stomach surgeries, renal impairment, suicidality and ischemic colitis.

Abdominal Surgeries, Including Cholecystectomy

Higher rates of cholecystectomy, appendectomy, and hysterectomy have been reported in IBS patients in general, unrelated to any medication use. Gallbladder contractility variables were similar for patients treated for 2 weeks with tegaserod 6 mg bid and for patients treated with placebo. These studies included healthy female patients and female patients with IBS-C. In collaboration with the Agency, the previous Sponsor updated the label to inform physicians and patients of this clinical information.

Renal or Hepatic Impairment

No dosage adjustments are required in patients with mild-to-moderate impairment. Tegaserod is not recommended to those with severe impairment.

Suicidality

An imbalance in the frequency of suicidal events was detected, although low in placebo controlled clinical trials and post-marketing database. The clinical data do not suggest that tegaserod is associated with an increase in relevant psychiatric adverse events and do not support a causal relationship between tegaserod and suicidal events in this patient population which has a high psychiatric co-morbidity. The Sponsor commits to continue to closely monitor for suicidality reports in any future tegaserod clinical trials and in the post-marketing period. In addition, the proposed label has been updated to warn of suicide risks in warnings and precautions as was recommended to the previous Sponsor in 2007. Please refer to Appendix 9 for details.

Ischemic Colitis

August 2002 and March 2004, the Agency received 20 reports of cases of ischemic colitis associated with the use of tegaserod. Due to these reports, the labeling of tegaserod was updated to alert the prescribers of the risk of tegaserod-associated ischemic colitis. Please refer to Appendix 9 for details.

6.6. Safety Conclusions

Tegaserod, at a dose of 6 mg bid, was previously deemed by the Agency to be safe and well tolerated in the original approval for IBS-C. This conclusion is confirmed by additional analyses of its safety profile in more recent placebo-controlled and open label clinical trials, as well as post-marketing studies data. Comparing the frequency of adverse and serious adverse events across all organ classes (including gastrointestinal and CV systems) in DB15 and in IBS-C studies, the frequency of events is similar between treatment groups.

Post-marketing data for tegaserod treatment of GI disorders suggested no remarkable increase in safety signals with tegaserod exposure. Postmarketing safety data represent an exposure during the cumulative period in countries in which Zelnorm has been/was approved for the treatment of IBS-C or CIC, of 1,626,835 patient-years (cutoff September 30, 2017). The reported events both pre- and post-withdrawal do not suggest a safety signal for CV and death events. In an effort to further optimize the benefit risk profile of Zelnorm, as a part of reintroduction, provisions have been made for a restricted label, considering potential concerns regarding CV safety. Safety data within all populations considered indicate a low incidence of treatment emergent adverse events, serious adverse events and adverse events bothersome enough to cause patients to withdraw from the clinical trials.

7. BENEFIT-RISK

7.1. Benefit/Risk Overview

- The original approval of Zelnorm was based on the totality of evidence that demonstrated a benefit of the product across primary and secondary endpoints in a female IBS-C population.

- Zelnorm has a clinically relevant benefit for overall relief as well as on the multiple individual symptoms of IBS-C including abdominal discomfort/pain, abdominal bloating and constipation related symptoms in the previously approved IBS-C population.

- Tegaserod has a rapid onset of action and sustained effect for relief of overall IBS symptoms, including abdominal discomfort/pain, bloating and constipation.

- Results from post-approval studies, with over 2,900 additional subjects, reinforce the consistency of tegaserod's benefit in the previously approved labelled population.

- When applying current recommended endpoint definitions from FDA IBS trial guidance (IBS Trials Guidance, 2012), treatment benefit is consistently demonstrated.

- Zelnorms benefits are consistently observed across all IBS-C population studied and can be considered effective across a wide array of disease severities. The subgroup of patients with more severe IBS have a higher burden of illness and thus, not surprisingly, the greatest potential for therapeutic gain.

- A favorable overall safety profile has been demonstrated for Zelnorm that does not appear to be influenced by age, gender or disease severity.

- An initial observation of a small imbalance in cardiovascular events from the controlled clinical trial database has been extensively evaluated. Comprehensive adjudication methods have confirmed that this finding, if real, is small.

- State-of-the art epidemiologic studies have failed to confirm an association between Zelnorm use and CV events.

- Detailed mechanistic studies do not support a CV hazard for Zelnorm

- Nonetheless, some residual uncertainty remains that makes restricted use appropriate.

- To maximize benefit while protecting against a possible small risk of CV events, the Sponsor has proposed limiting use to women under the age of 65 with no previous history of a CV event to further enhance.

The details supporting these conclusions are reviewed below.

7.2. Benefit/Risk Assessment

IBS-C is a highly prevalent, difficult disorder to treat, with major impact on a patient's quality of life. New treatment options, all of which achieve efficacy primarily through enhanced intestinal secretion, have been made available to IBS-C patients since Zelnorm's withdrawal and they are effective for some patients. In others, adequate response is not achieved, or tolerability limits their utilization. This is not unexpected given individual variability in the condition and the multiple underlying mechanisms thought to be associated with IBS-C symptoms. The reintroduction of Zelnorm would give patients and physicians access to another treatment option, which is unique in its ability to enhance motility and modulate sensory functions. The benefits of tegaserod have been comprehensively evaluated and confirmed to improve overall relief and individual hallmark symptoms of IBS-C. The value to patients has been tested in comprehensive clinical program (including treatment scenarios which are challenging) and confirmed through extensive real-world use. Given a continued need for treatment options in IBS-C and additional data and more robust analyses that have become available since Zelnorm's withdrawal, a fresh look at the total benefit risk equation is warranted.

The imbalance in CV events identified through a retrospective analysis has been scrutinized through a variety of investigations. Two external blinded adjudications (Section 3.1), of the database from which the original differences were reported both showed small event rates in both treatment groups but higher frequency in the Zelnorm group. The second adjudication is considered most consistent with current cardiovascular event adjudication practices and identified fewer confirmed cases which reduced the difference in the observed cardiovascular event rates; however both adjudications showed a difference in frequency (rate differences of 0.1% to 0.03% in Zelnorm patients compared to placebo patients, depending on the adjudication and evaluation of total CV events or MACE events).

Two independent epidemiological studies were conducted in follow up to the observed imbalance in the clinical trial database (Section 3.2). Both studies concluded that the risk of having a cardiovascular event while taking Zelnorm was not increased relative to the risk that exists in a general population of demographic similarity, and events in both treated and untreated patients occurred more frequently in patients with known risk factors. The rates of events reported in epidemiologic studies in treated and control arms (0.002% and 0.002%, respectively) were similar and were further comparable to the Zelnorm-treated patient event rates reported from the clinicaltrial database adjudications (range of 0.04 to 0.11%). The data suggest that although a difference in event rates exists in the clinical trial database, both placebo and active event rates appear to be well within the expected population event rates.

Finally, a variety of mechanistic evaluations were conducted to understand any potential pharmacologic effects that could be relevant to ischemic risk. All such investigations failed to establish biologic plausibility for a causal link between tegaserod and CV events. Zelnorm has established meaningful benefits in the treatment of IBS-C. Data from the original NDA conclusively demonstrate effectiveness of Zelnorm in the IBS-C population, including significant relief of overall IBS symptoms as well as individual symptoms of abdominal pain/discomfort, bloating, and constipation. Additionally, re-evaluation of the original NDA pivotal trials based on current knowledge and FDA recommendations (2012 IBS Guidance) supports Zelnorm's superiority over placebo in improvement of abdominal pain/discomfort

and stool frequency. The improvements in IBS symptoms observed with Zelnorm in comparison with placebo are within the range observed with other IBS-C therapies. Additional post-approval studies support the benefit of tegaserod during repeat treatment, which is important given the chronic and recurring nature of IBS symptoms, and in IBS-M patients, which are considered difficult to treat.

Zelnorm is well tolerated, as demonstrated in 12-week placebo-controlled studies and 12-month long-term and repeated treatments studies. Diarrhea, the only adverse event occurring more commonly than placebo with tegaserod therapy, was infrequently reported (5.9% compared with 3.1% placebo) and was generally mild, of short duration, and resolved without therapy. The safety of Zelnorm has been prospectively studied in over 14,000 IBS-C patients.

Overall, Zelnorm has a positive benefit risk, particularly when considering how meaningful symptom improvement is to the overall well-being of IBS-C patients and its favorable general safety profile. Due to the variety of underlying mechanisms thought to contribute to IBS-C symptomatology, and can be regarded as an appropriate treatment option from the current agents available for IBS-C.

In close collaboration with the Agency, the Sponsor has defined multiple analysis populations for exploratory benefit-risk assessment. From the clinical trial database, the Sponsor identified patients representative of those at reduced risk for cardiovascular events to assess potential variations in the safety profile and confirm preserved benefit when such patient selections are made. These populations were defined based on age, gender, history of CV ischemic disease, and number of CV risk factors. Additionally, the Sponsor identified a population of women who fit the clinical description of those who suffer from severe IBS-C and whose symptoms are severe or disabling enough that they may be willing to tolerate a higher level of uncertainty around CV risk.

The results in all identified subgroups confirm efficacy across endpoints including symptom relief. Furthermore, the incidence of TEAEs, SAEs, and discontinuations are nearly identical and show a favorable safety profile regardless of subpopulation evaluated. For details regarding efficacy and safety findings of exploratory analyses in populations with reduced cardiovascular risk and a population with severe symptoms, please refer to Appendix 1.

This suggests a discussion is warranted as to how best to select patients t maximize the benefit risk balance while allowing appropriate access to a needed drug.

Based on these considerations, the Sponsor has proposed limiting Zelnorm reintroduction to women under the age of 65 to ensure the product will be reintroduced in a population who are at a lower risk of experiencing a CV ischemic event. Further limiting to those without a history of CV ischemic disease could further reduce such risk. The proposed reintroduction considerations are similar to strategies that have been effectively employed for other drugs marketed in the US that have been associated with potential CV risk (particularly in higher risk populations), such as commonly used NSAID products (including many that are available over the counter) and prescription anti-diabetic drugs. In these cases, CV risk information has been effectively included in the Warnings and Precaution sections of the labels for these products.

7.3. Regulatory Implications to Ensure Safe and Effective Use

In addition to the proposal to reintroduce Zelnorm for a limited population (only IBS-C patients under 65), the Sponsor proposes to adopt additional measures for ensuring safe use. The Sponsor is of the view that a formal REMS program may not be indicated based on the available evidence regarding risk but welcomes the views of the Agency and Committees on this point.

All of the potential risks associated with tegaserod, as discussed in Section 3 and Section 6, appear to be acceptable and manageable. Importantly, product labeling will also be updated to include information on the clinical trial database ischemic event rates and other rare but important safety information from post-marketing reports as previously guided by the Agency. Additional precaution/warning language on CV risks in which the current PLR/PLLR format will be also adopted.

Finally, the Sponsor is committed to continued monitoring in the post-approval environment and invites guidance from the panel and Agency on the tools and methods that might be most appropriate. The Sponsor supports that any such efforts are best determined and managed through ongoing collaboration with the Agency, and may include heighted pharmacovigilance efforts on the part of the Sponsor and utilization of the Agency's Sentinel system to enable real-time signal/trend detection for any important safety issue following product reintroduction.

8. CONCLUSION

The Sponsor understands the unique situation of a drug previously removed from the market and as such has carefully evaluated the benefits and risks to supports its reintroduction, with the goal of identifying a population for whom the benefits outweigh the risks. Evaluation of the product has continued over the past eleven years following market withdrawal and there is more confidence in its overall benefit-risk based on the totality of the evidence. Nonetheless, the Sponsor appreciates that uncertainty based on the initial signal cannot be conclusively ruled out. Therefore, it has proposed a limited reintroduction for the treatment of IBS-C in female patients 65 and younger and whom are at a lower risk of a CV event than the broader population. Other approaches to population restrictions have been explored in conjunction with the Agency and also support a favorable benefit risk.

The Sponsor is appreciative of the opportunity to present the Zelnorm program data to the Committees and looks forward to participating in discussion and receiving valuable input on its proposed reintroduction.

9. APPENDICES

Appendix 1. Exploratory Analyses

Population Definitions

Females <65 years without a history of CV ischemic disease
The Sponsor presents analyses for females less than 65 without a history of CV ischemic disease as its primary proposed reintroduction population.

Females <65 years of age without a history of CV ischemic disease and no more than one CV risk factor
The Sponsor's identification of another population at low risk of developing a CV event was based on prior FDA-prior-Sponsor interactions at the time of market withdrawal and subsequent discussions. In 2007, the FDA recommended that identification of a subgroup with the optimized benefit-risk ratio should begin by excluding patients with baseline CV risk factors (i.e., history of CV disease, active smoking, history of hypertension, history of hyperlipidemia, history of diabetes mellitus, obesity, age ≥55 years). This recommendation came after assessment of the 14 events classified in the first adjudication which confirmed each subject had 1 or more CV risk factors in their history. The approach to limit based on CV risk factors was consistent with the exclusion criteria agreed upon for the tIND protocol, ending in 2008, which resulted in only 2 serious adverse event (SAE) reports, both unrelated to the CV system. Because CV ischemic disease history could predispose a patient to a major cardiac ischemic event, regardless of whether additional risk factors are present in their history, a history of CV ischemic disease was added to this definition.

For patients without a history of CV ischemic disease, the Sponsor further limited this population to those with no more than 1 CV risk factor (including a history of hypertension, history of hyperlipidemia, history of diabetes mellitus, obesity, age ≥55 years). As such, the analysis population is defined as female subjects age <65 without a history of CV ischemic disease and with no more than 1 of the following CV risk factors:

- active smoking
- history of hypertension
- history of hyperlipidemia
- history of diabetes mellitus
- obesity (BMI >30)
- age ≥55 years

Females with severe symptoms
As discussed, in section Section 5.2.2.2, the Sponsor worked with the FDA to identify a subgroup that represent patients with more severe symptoms with the expectation that patients with more severe symptoms may be more willing to accept risk uncertainty due to the intensity of their disease.

There is no "gold standard" for assessing severity in IBS, and different trials used different scales and rating systems. However, all trials assessed at baseline the severity of abdominal

discomfort/pain as well as the "severity" of bowel habit (bowel movement frequency and consistency), and the number of days that these symptoms persisted was also documented.

The modeling methods thus examined different combinations of severe symptoms present for different durations at baseline, to characterize the symptoms and duration shared by the patients showing the greatest impairment of quality of life at baseline (IBS-QoL). These definitions are supported both by anchoring to SGA severity ratings and guided by clinical expertise from GI specialists.

This proposed population is defined as female patients with IBS-C, who experienced at baseline:

- ≥ 3 days of severe abdominal discomfort/pain on average per week before treatment (compared to the IBS-C diagnostic criteria of 1 days with any intensity of abdominal pain); AND

- ≥ 5 days of hard, very hard, or no stool on average per week before treatment (compared to the IBS-C diagnostic criteria of infrequent stool frequency and straining)

This definition was evaluated against the IBS Quality of Life measurement (Patrick, 1998) as this was the most extensively validated patient reported outcome measure which shows appropriate psychometric quality. Although not specific to IBS-C, these domains have been studied in IBS and are very relevant to patients with this condition. As described by Patrick et al., the IBS-QoL score becomes significantly lower as severity classification worsens (severity based on symptom frequency index and symptom bothersomeness index). Patients with the highest symptom frequency and symptom bothersomeness index had an overall IBS-QoL score ≤55 (Patrick, 1998). The Sponsor used a QOL score ≤55 as a criterion to assess QoL-anchored symptom severity. The current definition was shown to reflect a significant impairment in the QOL score (with mean baseline scores less than 55), indicating these patients suffer from the most severe disease from both a symptom and psychometric standpoint.

Overview of safety findings in subgroups

In the post hoc analysis of the Zelnorm safety data (IBS-C studies), applying different subgroup definition of severely symptomatic and low CV risk IBS-C patients showed an additional advantage in terms of low frequencies of TEAEs, SAEs, AEs leading to discontinuation, and death. Table 16 below summarizes this information for the IBS-C studies (B301, B307, B351, B358, A2306, and A2417). These results are consistent with the findings of the larger safety database (DB15) evaluations. In the IBS-C only studies, the incidence and types of TEAEs were similar between tegaserod-treated patients and patients on placebo. Overall, a comparable and favorable safety profile is seen when in all subgroups evaluated.

Table 16: Safety Profile of Subgroups in IBS-C Studies B301, B307, B351, B358, A2306, and A2417

	Females	**Female Subjects with Age < 65 Years without History of** CV **Ischemic Disease**	**Severely Symptomatic Female Subjects**	**Female Subjects with Age < 65 Years without History of** CV **Ischemic Disease and ≤1 CV risk factor**
Total patients studied	5929	5716	2052	4521
% of overall study population	84.4%	81.3%	29.2%	64.3%
% Difference in number of events (Tegaserod 6mg BID vs. Placebo)				
Subjects with ≥1 TEAE	-7.9	-7.4	-6.9	-5.9
Diarrhea	2.8	2.90	2.5	3
Headache	-1.2	-1.00	-0.1	-0.8
Abdominal Pain	-2.3	-2.10	-2.1	-2.3
Nausea	-0.8	-0.90	0.5	-0.4
Discontinued due to TEAE	-0.3	0	-0.8	0.1
Serious AE	-0.1	0	0.1	-0.1

Overview of efficacy findings in subgroups

To support the reintroduction of tegaserod in a low CV risk patient population, analyses have been performed to support the original NDA efficacy results and demonstrate that there would be no diminution of efficacy different patient subsets. The Sponsor analyzed data in 12-week studies B301, B351, B358. These findings are particularly significant in recent discussions about the use of co-primary endpoints for characterizing therapeutic effectiveness in IBS. The recent guidance issued by FDA on IBS Trial design (2012) has recommended the use of evidence-based endpoints such as abdominal pain and stool frequency in preference to general assessment of relief based on a Subject's Global Assessment (SGA) questionnaire. As shown in Figure 18 , analyses with a co-primary endpoint as close to the new trial guidance as possible, demonstrates similar, if not enhanced treatment effect, when compared to the original primary and 2007 reintroduction primary endpoint analyses at the individual study level.

Additionally, as shown in Figure 19, the proportion of subjects who were completely, considerably, or somewhat relieved of their IBS-C symptoms are presented by week of treatment for the pooled 12-week studies and 4-week post approval studies.

Figure 18: Subgroup Analyses Using the 2012 Guidance Endpoint

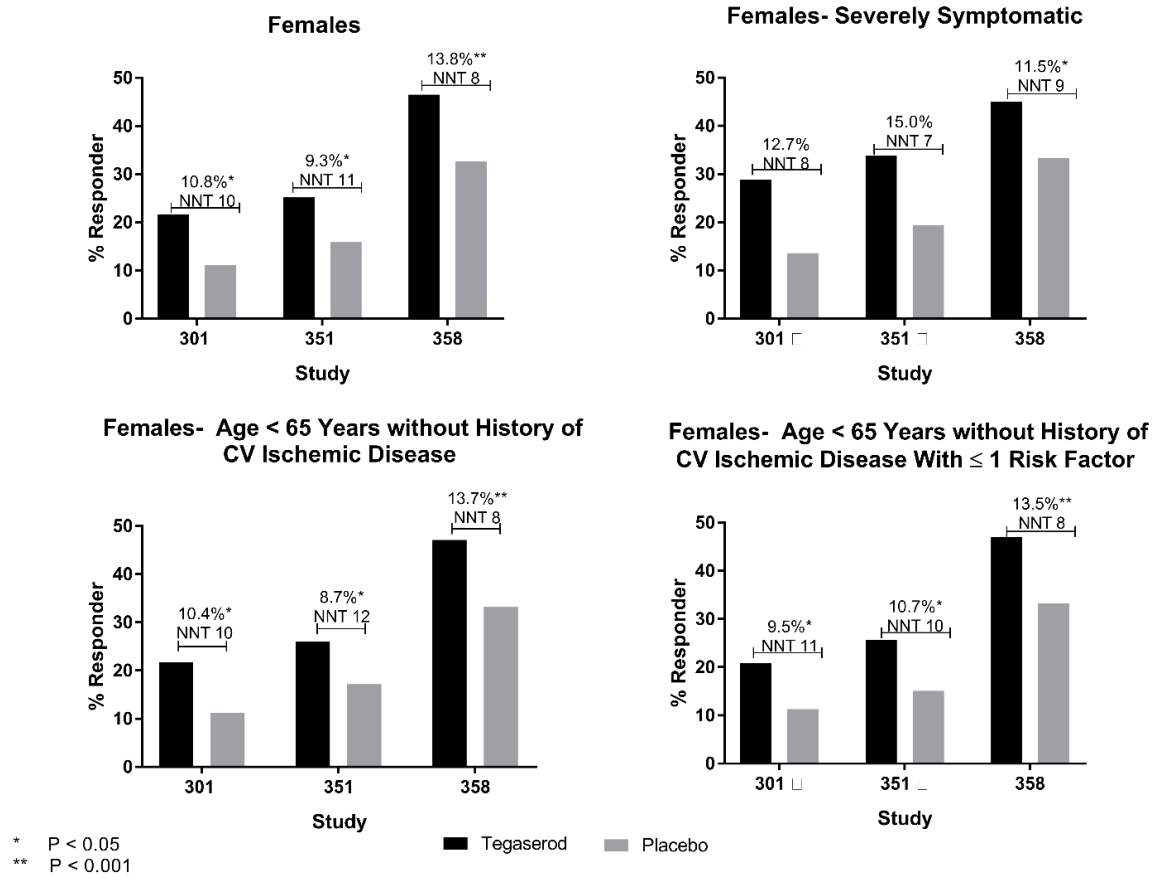
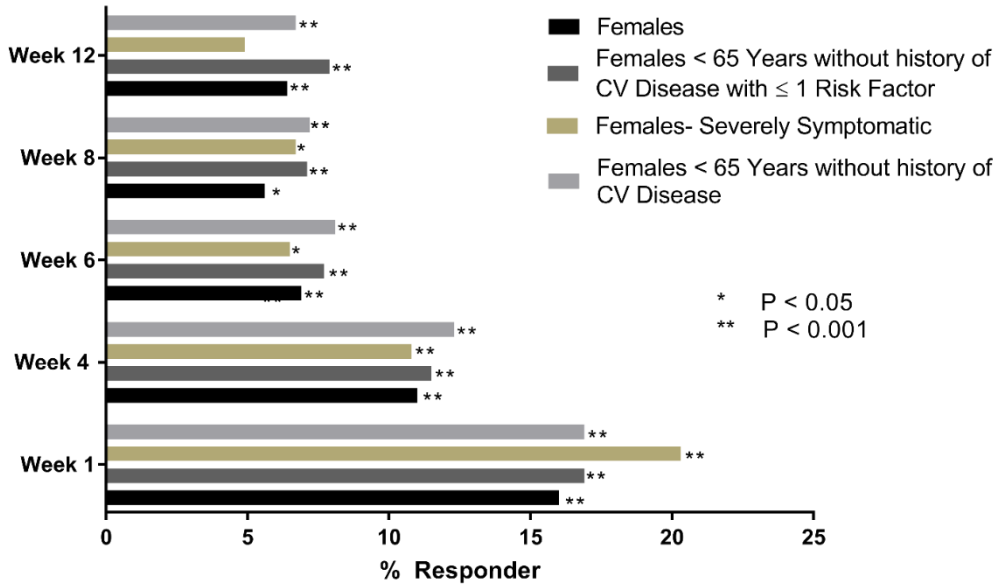


Figure 19: Proportion of Subjects with Complete Relief, Considerable Relief, and Somewhat Relief at Weeks 1, 4, 6, 8, and 12 - Subgroups



Appendix 2. Summary of Clinical Pharmacology and Vascular Studies

The original NDA for the IBS-C indication and subsequent annual reports and post-approval supplements filed by the prior Sponsor, have provided data on the pharmacokinetics (PK) and pharmacodynamic (PD) effects of tegaserod in humans.

General Clinical Pharmacokinetics

Tegaserod is rapidly absorbed following oral administration where Cmax is achieved approximately 1 hour after initial exposure. The bioavailability of tegaserod is equivalent to about 10% in the fasted state, which is reduced 40%-65% with food (the fed state reduces Cmax 20%-40%). The PK of tegaserod in patients with IBS are comparable to PK in healthy individuals and similar between males and females. Lastly, no clinically relevant drug-drug interactions have been identified (Appel-Dingemanse, 2002).

PK studies have indicated that plasma concentrations of tegaserod achieved at the 6 mg bid dosing (C_{max}, 10 nM) were only sufficient for activating the 5-HT_4 and not subtypes 1A, 1B, 2A or 2B receptors. These findings are the results of several studies conducted by the prior Sponsor to evaluate the binding affinities, functional activities, and potencies for tegaserod at human 5-HT receptors. Tegaserod PK are not altered to a clinically significant extent by renal insufficiency. However, Cmax for the major metabolite, M29.0, approximately doubled its $AUC_{0-\infty}$ increased approximately 11-fold after a single tegaserod dose in subjects with end-stage renal disease (ESRD) undergoing dialysis. Tegaserod PK is not altered to a clinically significant extent by mild hepatic impairment. However, the trend for markers of hepatic impairment in cirrhotic subjects was such that elevated exposures to tegaserod and its major metabolite M29.0 might occur in patients with moderate to severe hepatic impairment. Therefore, tegaserod should not be used in patients with severe renal or hepatic impairment.

Additional studies were conducted investigating drug transporter, inhibitor and induction studies of cytochromes P450 (CYP) enzymes, drug-drug interactions, and investigation of the possible significance of P-gp and brain penetration were conducted to further develop the drug profile of tegaserod (see details in this section).

Human Metabolism and Metabolites

Tegaserod is metabolized mainly via 2 pathways. The first is a pre-systemic acid-catalyzed hydrolysis in the stomach followed by oxidation or O-demethylation and glucuronide conjugation, resulting in the major metabolite M29.0 and the less prevalent metabolite M7.0. Radioligand binding studies demonstrated that M29.0 had negligible affinity for 5-HT4 receptors (Appel-Dingemanse, 2002). The second metabolic pathway for tegaserod is direct glucuronidation of the guanidine group of the molecule, leading to generation of 3 isomeric N-glucuronides (M43.2, M43.8, and M45.3).

Specific investigations were carried out to supplement the previously performed radioligand binding studies investigating the main human metabolite, M29.0. Study concluded that M29.0 lacks significant pharmacodynamic activities at plasma concentrations associated with tegaserod treatment at the recommended therapeutic doses.

Vascular Studies (Studies RD-2003-02798, RD-2008-00299, RD-2004-01345, RD-2008-00299, RD-2004-01345, and 203-227)

Activation of 5-HT_{1B} and 5-HT_{2A} (Nilsson, 1999) and 5-HT_{2B} (Borman, 2002) receptors has been shown to produce arterial vasoconstriction, including that of coronary arteries (Kaumann 1994). Studies using isolated primate coronary arteries (Studies RD-2003-02798 and RD-2008-00299) showed that tegaserod concentrations of up to 10 µM (1000X C_{max} plasma levels in humans) had no constrictor effect, in contrast to constriction produced by 5 HT1B agonists sumatriptan and ergotamine or 5-HT itself. On the contrary, tegaserod competitively inhibited the vasoconstrictor effects of 5-HT or sumatriptan with a pA2 = 7. In a second NHP study using coronary tissue (Study RD-2004-01345) and mesenteric arteries (see below), tegaserod was once again without any vasoconstrictor effect at concentrations up to 10 µM, while reference compounds sumatriptan and ergotamine produced contractions. In studies with human tissue, tegaserod did not elicit constriction of proximal and distal right coronary artery strips except at supratherapeutic concentrations. Responses were not different in diseased or healthy arteries, as defined by impaired endothelial-dependent responses (Study RD-2008-00299). In this series of experiments antagonist activity against the 5-$HT_{1B/1D}$ receptor agonist sumatriptan was not evident.

Vascular responses of NHP and human mesenteric arteries were also tested (Study RD-2004-01345). Tegaserod at up to 10 µM (1000X C_{max} plasma levels in humans) was without any vasoconstrictor effect in contrast to the positive controls 5-HT and sumatriptan. However, as with coronary vessels, tegaserod acted as a competitive inhibitor of 5-HT and sumatriptan-induced vasoconstriction with a potency that was consistent with the pKi of 7.2 measured for the binding of tegaserod at the 5-HT_{1B} receptor. Thus, coronary and mesenteric arteries from both NHP and humans tegaserod showed no clinically meaningful vasoconstrictor response but exhibited functional 5-HT_{1B} antagonism.

Vascular effects using rat thoracic aortic rings were investigated previously in the original NDA. Neither tegaserod nor M29.0 alone at concentrations up to 10 µM induced contraction. Furthermore, precontracted tissue was relaxed in the presence of tegaserod, whereas M29.0 was without effect (Study 203-227).

Cardiac Function *In Vitro* (Studies 992005, RD-1999-03133, 998169, RD-2008-00430, and RD 2004 01729)

In vitro studies showing the absence of effect of tegaserod on cardiac waveforms were reported in the original NDA. Studies were performed to test for action potential in isolated papillary muscles (Study 992005) and in the perfused rabbit heart (Study RD-1999-03133). No effects of tegaserod were seen on QT intervals or QRS duration (only papillary muscle) at concentrations of tegaserod that exceeded the C_{max} for human dose. Likewise, tegaserod inhibited hERG channels in HEK293 cells with an IC50 of 13.0 µ M, a concentration that is > 1,000X the human C_{max} plasma levels in humans (Study 998169). A similar *in vitro* patch clamp study using Chinese Hamster Ovary (CHO) (Beattie, 2013) showed that hERG current was only inhibited by ~25% at tegaserod concentration of 300X the human exposure. In a more recent study, tegaserod at concentrations up to 100 nM did not affect the action potential in human atrial myocytes (Study RD-2008-00430). The potential for tegaserod to cause valvular

lesions because of 5-HT2B mediated effects on cardiac fibroblasts (Fitzgerald, 2000) was excluded based on demonstration that tegaserod did not produce contractions in the rat stomach fundus (Study RD 2004 01729) a model of 5-HT_{2B} activity. Beattie 2004 reached similar conclusions, showing that tegaserod produced a concentration-dependent inhibition of 5-HT_{2B}-induced contractions in the rat stomach fundus (pA2 = 8.3). There was no histopathological evidence of cardiac lesions or low-level platelet aggregation,

Collectively, these *in vitro* studies discussed in the sNDA Section 2.6.2 Pharmacology Written Summary show that tegaserod is devoid of any arrhythmogenic potential and does not show any evidence for cardiac pathology.

Platelet Aggregation Studies (Studies DMPK(CH)-R0100770, RD-2008-00298, and USWM25JUN2017)

Agents that potentiate platelet aggregation increase the risk of coronary artery disease and stroke. The first of 6 studies presented in the sNDA Section 2.6.2 Pharmacology Written Summary that examine the potential for tegaserod to interact with platelets was reported in the original NDA and showed that tegaserod did not bind to platelets (Study DMPK(CH)-R0100770) even though immunoreactive bands specific for 5-HT_4 receptor protein were found (Study RD-2008-00298). Of 3 studies on the effect of tegaserod on platelet aggregation, the first of these (Study RD-2008-00298) used preincubation of whole blood with tegaserod and subsequent platelet preparation at an unusually high centrifugation speed and platelet concentration. A mild additive aggregatory effect was observed with ADP or 5-HT + ADP, but not with other aggregating agents at the highest concentration (100 nM, 10X C_{max} plasma levels in humans). Two other published studies conducted by independent investigators (Higgins 2012 and Beattie 2013) each failed to observe any effects of tegaserod on platelet aggregation at up to 100 nM tegaserod. In an additional study designed to test the effect of preincubation with M29.0 the results showed very high basal platelet aggregation in the vehicle control and minimal additive effects of a variety of aggregating agents as well as high PF4 levels, which is an index of platelet activation (Study USWM25JUN2017). The study was deemed inconclusive and therefore unable to demonstrate reliably whether M29.0 affected platelet aggregation. In conclusion, thus far, no effects of tegaserod or its metabolites have been seen on platelet aggregation at levels well in excess of the expected human exposure.

***In Vivo* Safety Pharmacology** (Studies 99-00526, RD-1999-03636, 991112, RD-2003-02616, RD-2004-01341, RD-2004-01343, RD-2004-01344)

Tegaserod was tested for cardiovascular effects in several *in vivo* animal models, including 3 in the original NDA. i.v. administration in the anaesthetized rat (Study 99-00526), intraduodenal dosing in the anaesthetized dog (Study RD-1999-03636), and oral dosing in the non-instrumented conscious dog (Study 991112). Various cardiovascular parameters were assessed including the electrocardiogram, blood pressures, vital respiratory capacity and heart rate as well as local blood flow. Since then a series of additional studies was conducted in the anesthetized rat to examine local blood flow in the GI tract using 2 different routes of administration of tegaserod (i.v. and intraduodenal), with and without fasting (Studies RD-2003-02616, RD-2004-01341, RD-2004-01343, and RD-2004-01344).

In the standard sodium pentobarbital-anaesthetized rat model, sequential tegaserod infusion (0.01, 0.1, and 1 mg/kg); exposure of up to ~10X the human blood levels (Study 99-00526) effects were considered marginal in this model. The reduction in blood pressure and systemic vascular resistance (15%) at the mid-dose was further increased at 1 mg/kg and overall cardiac and vascular indices returned to vehicle control levels within the observation period.

A series of 5 studies (Studies RD-2001-01109, RD-2003-02616, RD-2004-01341, RD-2004-01343, and RD-2004-01344) were conducted in an anesthetized rat model designed to measure macro- and micro-circulation of the colon. A full discussion of these studies has been presented and accepted previously (Preclinical Expert Report 2004). In the first of these studies, hemodynamic changes measured over 3 consecutive time periods (0-5, 5-20 and 35-50 minutes post-injection were minimally affected, apart from a transient decrease (< 5 minutes), in blood pressure and mesenteric artery blood flow. Tegaserod (0.1 to 3.0 mg/kg) did not cause changes in mesenteric or mucosal vascular conductance (Study RD-2001-01109). In subsequent studies comparing the effect of tegaserod to the 5 HT3 agonists, alonsetron and cilansetron in fasted and non-fasted rat, tegaserod at all doses (0.3, 1.0, and 3.0 mg/kg i.v.) did not affect mesenteric blood flow and the increase in colonic vascular conductance returned to control values rapidly, in contrast to the decrease in mesenteric circulation with the 2 5 HT3 agonists (Study RD-2003-02616). Intraduodenal administration of 30 mg/kg tegaserod, which resulted in an exposure of 24-fold HED of 6 mg bid therapeutic dose, also showed that tegaserod did not impair mesenteric or colonic circulation (RD-2004-01341, RD-2004-01343, and RD-2004-01344).

As reported in the original NDA, in anesthetized dogs, intraduodenal doses of 0.1, 1.0. and 10 mg/kg tegaserod (0.28 - 28-fold HED of 6mg bid therapeutic dose), had no effects on blood pressure (systolic, mean, diastolic), respiration rate, heart rate, and femoral arterial blood flow or ECG were evident over the 3-hour observation period (Study RD-1999-03636). Likewise, in conscious dogs, oral doses of up to 10 mg/kg tegaserod (C_{max} 150X higher compared to the human C_{max} ~ 3 ng/ml observed following the 6 mg bid dosing) did not cause any changes in cardiovascular parameters in comparison to the controls (Study 991112).

Appendix 3. Summary of Tegaserod Binding Affinity for Other 5-HT Receptors and Possible Functional Cardiovascular Significance

Table 17 shows the 5-HT receptor binding affinity of tegaserod and summarizes the expected main CV actions at multiples of human exposure. Of those receptors that did show some affinity for tegaserod, only effects at 5 HT_{2B} need be considered at therapeutic doses. Agonism at the 5-HT_{2B} receptor mediates mitogenic signaling and may be involved in pulmonary hypertension and causes valvulopathy (Fitzgerald, 2000). However, in the rat fundus assay, tegaserod showed functional antagonism at the 5-HT_{2B} receptor both *in vitro* and *in vivo* as also confirmed by independent investigation (Beattie, 2004) and therefore any risk of cardiac valvopathy can be excluded. This was also supported by the absence of any histopathological evidence in toxicology studies.

Table 17. Affinity and Effects of Tegaserod Receptor Binding to Various 5-HT Subtypes

5-HT Receptor	General Locations	Proposed Tegaserod Cardiovascular Effects	Agonist (+)/ Antagonist (-)	pKi	Human C_{max} Relative Binding Threshold (10 nM)
5-HT_4	ANS	Tachycardia	+	8.5	0.3
5-HT_{2B}	ANS, Blood Vessels	Hypotension, Vasorelaxation	-	8.3	0.5
5-HT_{1D}	Blood Vessels	Tachycardia, Vasorelaxation	-	7.6	2.5
5-HT_{1A}	Blood Vessels	Bradycardia, Hypotension	+	7.4	4.0
5-HT_{2A}	ANS, Blood Vessels, Platelets	Hypotension, Prevention of Platelet Aggregation, Bradycardia, Vasorelaxation	-	7.1	7.9
5-HT_{1B}	Blood Vessels	Tachycardia, Vasorelaxation	-	7	10.0
5-HT_{2C}	ANS, Blood Vessels, Platelets	Hypotension	-	6.9	12.6
5-HT_6	Unknown	No Involvement	Unk	6.6	25.1
5-HT_7	Blood Vessels	Unk	Unk	6.2	63.1
5-HTT	Blood Vessels, Platelets	Unk	Unk	<6.0	100.0
5-HT_3	ANS	Unk	Unk	5.5	316.2

ANS = Autonomic Nervous System; NB = no binding; pKi = -log dissociation constant, 5-HTT = Serotonin transporter (SERT), also known as the sodium-dependent serotonin transporter and solute carrier family 6 member 4, Unk = unknown

With respect to the other receptors 5-HT_{1A} shows moderate affinity for tegaserod, but cardiovascular effects are centrally mediated and therefore binding is not relevant since tegaserod does not cross the blood brain barrier to any appreciable extent. With respect to the role of 5-HT_{1D}, which also shows moderate affinity for tegaserod and higher affinity compared to 5-HT_{1B}, in the cardiovascular system, it has not been decisively defined and any effects are indirect and believed to be neuronally mediated. The 5-HT_{2C} receptor is not present in the cardiovascular system (Villalon, 2007).

Cardiovascular effects of tegaserod at 5-HT_{1B} and 5-HT_{2A} are conceivable but only at even higher doses as any activity would only be apparent at concentrations that are at least 15 times that of tegaserod therapeutic exposure levels. 5-HT_{1B} is found on endothelial cells and on vascular smooth muscle cells where it can mediate both vasoconstriction and vasodilation. The possibility that tegaserod could activate 5-HT_{1B} receptors, a mechanism which has been associated with angina pectoris-like symptoms, myocardial ischemia mediated via coronary vasoconstriction (Longmore, 2000) and ischemic colitis (Knudsen, 1998) was convincingly excluded based on results of vascular studies. Notably, tegaserod was without any direct vasoconstrictor effect on coronary or mesenteric arteries from NHP and human, apart from a mild constrictor effect on human proximal coronary arteries at ~1000X the therapeutic exposure. On the contrary, at high levels of exposure, vasorelaxation would be expected in conditions of heightened vascular tone that are dependent on endogenous 5-HT, in view of the antagonism exhibited by tegaserod at the 5-HT_{1B} receptor. Furthermore, in rat aorta, tegaserod did not show any vasoconstrictor effects, but produced a minimal relaxation at supratherapeutic concentrations.

5-HT_{2A} is present in platelets where it facilitates auto-release of 5-HT from platelets and mild platelet aggregation. Furthermore, possible platelet effects were unlikely since tegaserod neither binds to nor is it taken up by platelets and although monomer and dimer protein fragments of 5-HT_4 have been reported no function in platelet aggregation has been ascribed to this finding. More significantly, receptor binding studies showed that tegaserod is an antagonist at this receptor. Therefore, any interaction at this receptor which results in 5-HT release would be expected to be inhibitory. Two platelet aggregation studies confirmed that tegaserod, at concentrations up to 0.1 µM (10X the clinical C_{max} of 0.01 µM), did not significantly enhance the sensitivity of the platelets to activation and aggregation (Higgins, 2012; Beattie, 2013). Mild effects were observed in the third *in vitro* study with tegaserod, and only at high concentrations. This result may have been artifacts of technical differences in centrifugation speed, which is known to impact platelet activation and which was outside of the current recommendations (Merolla, 2012). The findings were a laboratory test phenomenon of no clinical significance. Findings in a study with M29.0 were regarded as inconclusive based on evidence of significant platelet aggregation even without the addition of aggregating agents and evidence of high levels of PF4 in PRP signifying platelet activation as well as values of aggregation of over 100% which is not biologically possible.

Appendix 4. Patient Demographics of Safety Databases

	DB15 All Subjects		IBS-C Studies All Subjects			DB14 All Subjects	
	Tegaserod All doses (N=11,614)	**Placebo (N=7031)**	**Tegaserod 6mg bid (N=3906)**	**Tegaserod All doses (N=4750)**	**Placebo (N=2278)**	**Tegaserod 6mg bid (N=2800)**	**Tegaserod All doses (N=3289)**
Age (years)							
Mean (SD)	43.3 (13.25)	43.2 (13.67)	42.5 (12.01)	42.8 (12.29)	42.9 (12.48)	45.2 (13.90)	45.4 (14.06)
Age Category							
<12 y	0	0	0	0	0	0	0
12- < 18 y	5 (0.0%)	2 (0.0%)	3 (0.1%)	4 (0.1%)	0	0	0
18- < 65 y	10919 (94.0%)	6554 (93.2%)	3782 (96.8%)	4546 (95.7%)	2161 (94.9%)	2535 (90.5%)	2958 (89.9%)
65- < 75 y	539 (4.6%)	393 (5.6%)	97 (2.5%)	164 (3.5%)	101 (4.4%)	221 (7.9%)	275 (8.4%)
>= 75 y	151 (1.3%)	82 (1.2%)	24 (0.6%)	36 (0.8%)	16 (0.7%)	44 (1.6%)	56 (1.7%)
Sex							
Male	1447 (12.5%)	877 (12.5%)	125 (3.2%)	260 (5.5%)	130 (5.7%)	299 (10.7%)	393 (11.9%)
Female	10167 (87.5%)	6154 (87.5%)	3781 (96.8%)	4490 (94.5%)	2148 (94.3%)	2501 (89.3%)	2896 (88.1%)
Race							
Caucasian	8972 (77.3%)	5065 (72.0%)	3228 (82.6%)	4002 (84.3%)	1895 (83.2%)	2547 (91.0%)	2978 (90.5%)
Black	745 (6.4%)	484 (6.9%)	243 (6.2%)	286 (6.0%)	189 (8.3%)	152 (5.4%)	182 (5.5%)
Other	1897 (16.3%)	1482 (21.1%)	435 (11.1%)	462 (9.7%)	194 (8.5%)	101 (3.6%)	129 (3.9%)
CV Risk Factor							
At least one CV Risk Factor	6039 (52.0%)	3556 (50.6%)	2160 (55.3%)	2684 (56.5%)	1290 (56.6%)	(NA)	(NA)
Active smoking	1355 (11.7%)	603 (8.6%)	778 (19.9%)	993 (20.9%)	449 (19.7%)	(NA)	(NA)

	DB15 All Subjects		IBS-C Studies All Subjects			DB14 All Subjects	
	Tegaserod All doses (N=11,614)	**Placebo (N=7031)**	**Tegaserod 6mg bid (N=3906)**	**Tegaserod All doses (N=4750)**	**Placebo (N=2278)**	**Tegaserod 6mg bid (N=2800)**	**Tegaserod All doses (N=3289)**
History of Hypertension	2045 (17.6%)	1248 (17.7%)	569 (14.6%)	740 (15.6%)	364 (16.0%)	(NA)	(NA)
History of Hyperlipidemia	2070 (17.8%)	1164 (16.6%)	758 (19.4%)	937 (19.7%)	452 (19.8%)	(NA)	(NA)
History of Diabetes Mellitus	439 (3.8%)	284 (4.0%)	96 (2.5%)	118 (2.5%)	76 (3.3%)	(NA)	(NA)
Age >=55 years	2337 (20.1%)	1513 (21.5%)	623 (15.9%)	804 (16.9%)	429 (18.8%)	(NA)	(NA)
Obesity (BMI >30)	1836 (15.8%)	1166 (16.6%)	601 (15.4%)	721 (15.2%)	368 (16.2%)	(NA)	(NA)
History of CV Ischemic Disease	287 (2.5%)	168 (2.4%)	50 (1.3%)	80 (1.7%)	44 (1.9%)	89 (3.2%)	119 (3.6%)
Duration of IBS symptoms (months)							
N	4895	2432	3901	4742	2272	(NA)	(NA)
Mean (SD)	163.3 (143.29)	168.9 (148.79)	165.8 (142.91)	165.4 (144.09)	172.6 (151.03)	(NA)	(NA)
Median	120.0	120.0	120.0	120.0	120.0		
Min, Max	1, 816	2, 876	2, 816	2, 816	2, 876		

Db14 baseline CV risk factors and duration of IBS symptoms were not captured in this database as many of these studies were extensions of 12-week placebo-controlled studies, of which this data is represented in Db15.

Appendix 5. Second External Adjudication of CV Events (Duke Adjudication) – Executive Summary

Executive Summary

Earlier investigations on the tegaserod database had shown an imbalance in the frequency of cardiovascular (CV) ischemic events in the placebo controlled clinical trial database, which was confirmed by 2 adjudications, one conducted internally in Dec 2006 by Novartis, and an external adjudication in March 2007.

As these earlier adjudications were done without complete source document retrieval and limited in scope to search terms that were suggestive of ischaemia, a further external adjudication utilizing search terms more broadly encompassing cardiovascular events was deemed appropriate. This 2nd external adjudication used a comprehensive pre-specified methodology regarding both case selection and case assessment.

The analysis was conducted in a large placebo controlled database of 18,645 patients from 29 studies, and identified potential events by a broad search covering all events related to cardiovascular (encompassing coronary and cerebrovascular) ischemia, all terms related to cardiac disorders, terms used by the sponsor to identify events related to Cox-2 inhibitors and terms that may additionally capture CV ischemic events with clinical manifestation such as chest pain/discomfort. Individual case descriptions were subsequently complemented by extensive source data to provide as comprehensive as possible dataset for each patient. Cases were then assessed by an external panel blinded with respect to treatment. While the methodology of case selection (search algorithm) was developed by Novartis, the adjudication methodology was developed by the external adjudication panel independently of the sponsor.

Out of the 390 cases identified by the automated search in the placebo controlled trials, there were 8 cases with an ischemic CV event, 7 (0.06%) on tegaserod, 1 (0.01%) on placebo (OR 4.24, p = 0.273), the majority of which were coronary events. If the Antiplatelet Trialists' Collaboration (APTC) classification is applied, then the number of cases was 4 (0.03%) vs. 0 (p = 0.304). Seven of the 8 patients with CV ischemic events had 2 or more CV risk factors, and one patient had one CV risk factor (age >=55 years of age). The number of patients which did not allow a classification by the panel due to insufficient data, tended to be higher on tegaserod (11.1% of 198 cases) than on placebo (3.8% of 106 cases).

A direct comparison of this outcome with that of the earlier adjudications is difficult as the methodology used was different. Nonetheless, the present data are consistent with the earlier adjudications where 11 vs. 1 (major events; internal adjudication), and 13 vs. 1 cases (1st external) on tegaserod vs. placebo, respectively were reported. However, the total number of cardiovascular ischemic events in this 2nd external adjudication was lower and the difference in event rate did not reach statistical significance.

As a secondary objective, the clinically relevant arrhythmias and cardiac conduction disorders were assessed in the 2nd external adjudication. While the overall frequency of arrhythmias and cardiac conduction disorders was similar across treatments, the number of cases with clinically relevant atrial fibrillation was higher on tegaserod 5 (0.04%) than on placebo 1 (0.01%) (p = 0.420).

The frequency and pattern of CV events in the open label database (n=3289) which included trials of a duration from 6 months up to one year was assessed compared to the double-blind placebo controlled trials for which trials had a treatment duration of 4-12 weeks. If exposure

duration is taken into account, the number of cases by 1000 patient years was similar to that seen in the placebo controlled trials, suggesting that prolonged exposure to tegaserod is not associated with an increased frequency of CV ischemic events.

In conclusion, this retrospective analysis of a large clinical trial database shows, based on a low incidence of cases, an imbalance in the frequency of CV ischaemic events on tegaserod in comparison to placebo. The CV events were primarily coronary in nature. In all but one patient who had only age as risk factor, the coronary ischaemic events occurred exclusively in patients with two or more CV risk factors prior to treatment with study medication. This second external adjudication has shown a reduced numeric imbalance for CV ischemic events between tegaserod and placebo compared to earlier adjudications and did not reach statistical significance. Relative to cardiac arrhythmias and cardiac conduction disorders, there was a small imbalance in the frequency of clinically relevant events of atrial fibrillation that did not reach statistical significance.

1 Background: earlier searches and adjudications

1.1 Initial search followed by Novartis internal adjudication

The pooled database of 29 placebo-controlled clinical studies with tegaserod comprising 18,654 patients (Database 15) was screened for cases of ischaemic events. Adverse event frequency tables were manually reviewed and any patients with a preferred term suggestive for an ischaemic event were identified. In these patients the available clinical information was reviewed and obviously false positive cases (e.g. due to miscoding) were excluded. Overall 24 "true positive" cases were identified. As a quality control, in addition an automated search was conducted on the same database using 166 preferred terms related to ischaemic disorders. This automated search did not reveal any additional cases. Individual case reports blinded regarding treatment (narrative summaries) were adjudicated by a panel of 6 Novartis experts including 2 cardiologists based on predefined criteria. The narratives were predominantly based on case report form and SAE report information without retrieval of additional documents relevant to the adverse event. The evaluation was done independently by each expert in a blinded fashion. Upon review of classification by each adjudicator, consensus was obtained in case of discrepancy. Cases were classified as to whether the case was a newly occurring or worsening ischaemic event, with the potential answers: confirmed, unconfirmed, or probably not. In addition cases were classified as either a major or a minor ischaemic event. The results of this analysis have been reported (FDA Briefing Book March 7, 2007).

1.2 Adjudication by first external board

In preparation for adjudication by an external board, efforts were undertaken to obtain source documents and any other available relevant medical information about the patient, from the sites in all cases with "true positive" events and cases with "false positive" events in order to complete the information on individual case reports. The source data and other medical information were reviewed by qualified personnel at Novartis (4 MDs who were blinded to treatment assignment) and any new relevant information obtained from this review was added post-hoc from source documents to the case narratives. It should be noted that source data were able to be obtained for the majority of cases but not for all the cases.

The first external adjudication was conducted by an independent committee comprised of 2 board certified cardiologists and 1 board certified neurologist (Michael E. Farkouh MD, MSc, FACC (chair), Mary Ann McLaughlin MD, MPH, FACC, Jesse Weinberger, MD from Mt. Sinai Medical Center, New York). The adjudication process did not involve Novartis personnel in any way.

Case narratives of the 24 "true positive" and 8 "false positive" with additional information from the document retrieval were provided to the panel of experts. Narratives were blinded with respect to the study medication. The expert panel was also blinded to the status of each case of being either "true" or "false positive". In addition panelists had access to individual Case Report Forms and all available relevant medical information regarding the patient. Events adjudicated were classified into 1 of 5 categories for cardiovascular ischemic events: definite event, probable event, possible event, definitely not an event and unable to adjudicate due to insufficient evidence. Definite and probable events were interpreted as confirmed events. Overall 14 of the 32 cases were classified as confirmed. The results of this analysis have been reported (FDA Briefing Book 23-Mar-2007).

2 Overall objectives of second external adjudication

The objective of this second external adjudication was to obtain the most comprehensive and objective assessment of the cardiovascular safety of tegaserod based upon source data, any other available relevant medical information about the patient, and an evaluation by an independent expert panel.

- identify, evaluate and classify cases of CV ischaemic events (coronary ischemic and cebrovascular ischemic events) in tegaserod clinical studies based on a) a broader search including MedDRA search terms for "cardiac disorders", b) an established search algorithm used in conjunction with Coxib compounds, and c) a search of cases for "chest pain" and "chest discomfort";
- utilize the search methodology delineated in this document to identify, evaluate and classify cases of congestive heart failure, arrythmias and conduction disorders.

3 Methods

3.1 Identification of index cases in clinical trial database

Four different, searches on the reported adverse events (Section 3.1.2) were conducted in the pooled double-blind placebo-controlled database and in the pooled open label trial database, using established search criteria. In addition, the data were reconciled with the ARGUS database, to capture and resolve any discrepancies between the data sources, should they occur.

3.1.1 Definition of databases

Database Db14 included 7 uncontrolled long-term studies of at least 6 months planned duration, across three functional GI disorders, i.e. irritable bowel syndrome (IBS), chronic idiopathic constipation (CIC) and dyspepsia.

Database Db15 reflects the largest database which allowed pooling of placebo controlled studies. It included patients from 29 studies in several functional GI disorders, including IBS, CIC, dyspepsia, GERD, and diabetic gastropathy (Table 3-1).

Table 3-1 Clinical trial databases

Data-base (Code)	Short title	Definition	# of safety analyzable patients	
			Teg n	Plac n
Db 14	Pooled uncontrolled long-term, any indication	All long-term studies in any indication with a planned treatment duration of ≥6 months (any age, both gender). Overall 7 studies: A0209, A0301E1, A0307E1, E2301E1, D2209, D2301E1, D2302E1	3,289	NA
Db15	Pooled placebo controlled short term, any indications	Largest set of placebo controlled studies that permits pooling with treatment duration of ≥4 weeks in any indication (any age, both gender): studies A0301, A0351, ASG01, AFI01, A2302, A2306 (period 1 only), A0307, A0358, A2417, E2301, E2302, E2308, E2309. D2301, D2302, A0201, A0202, A0207, A0251, A0254, A0254C4, B0202, D2201-4, B2203, G2203, AIA12 (D-B part).	11,614	7,031

ARGUS is a comprehensive pharmacovigilance software system providing advanced tools to ensure regulatory compliance on a global basis. Apart from safety databases on spontaneous reports and postmarketing reports it includes all serious adverse event reports from clinical trials which are reported by the trial investigators to Novartis. This latter database was used for reconciliation with the clinical trial database (see Section 3.1.2).

Information regarding clinical trial database was not provided to the adjudication panel in order to maintain the scientific integrity of the adjudication process.

3.1.2 Search for index terms in clinical trial database

Databases Db14 and Db15 were screened for patients with adverse events with matching Preferred Terms (PT in MedDRA 9.0). Four different, partially overlapping, automated searches were made and are presented separately:

- *Ischaemic coronary and cerebrovascular events*, using the Standard MedDRA Query (MedDRA 9.0) search algorithms for "Myocardial ischaemia" and for "Cerebrovascular ischaemic conditions". The search algorithm includes overall 89 PTs (Section 8.1-Appendix 1, Adjudication Methodology).
- *Any cardiac disorders*, using all terms classified under the MedDRA Primary System Organ Class (SOC, MedDRA 9.0) of Cardiac Disorders. The search algorithm includes overall 259 PTs (Section 8.1-Appendix 1, Adjudication Methodology).
- *Cardiovascular disorders*, based on a search algorithm used in conjunction with a Coxib compound (COX189A Summary of Clinical Safety-Appendix 2), including overall 57 PTs.
- *Chest pain and chest discomfort*, using the PTs chest pain and chest discomfort (MedDRA 9.0): 2 PTs only. (Section 8.1-Appendix 1, Adjudication Methodology).

3.1.3 Reconciliation with ARGUS database

Since coding of an individual adverse event report may differ slightly between the clinical and the ARGUS database and lead to inconsistencies, a reconciliation between the databases was undertaken. The same searches were run on the ARGUS database and any cases identified in ARGUS were added to the list of index cases, using the PT from ARGUS. The total number of individual patients identified by the four searches was 390 and 149 for databases D15 and Db14, respectively (Section 8.3-PT-table1E and PT-table 1D). For the sources of the retrieval see Table 3-2

Table 3-2 Synopsis of searches performed

Search		Database	Number of hits		
Algorithm	# Preferred Terms		Clinical Trial Database	Add'l cases from ARGUS*	Total
SMQ for ischaemia	89	Db 14	20	2	22
		Db 15	31	2	32
Cardiac disorders primary SOC	259	Db 14	89	1	90
		Db 15	214	3	217
Coxib	72	Db 14	30	2	32
		Db 15	54	4	58
Chest pain/chest discomfort	2	Db 14	51	2	53
		Db 15	153	0	153

* cases may have been counted by more than one search algorithm
Source: Section 8.3-PT-table 1D and PT-table 1E

PTs and identifiers of the additional 12 cases retrieved by ARGUS search are provided in Table 3-3. All but one were captured with the search; case PHHO2005US08556 was included as it was coded inaccurately as ischaemia (no search SMQ search term) instead of myocardial ischaemia. By definition, none of the PT that identified cases in the ARGUS database matched the search criteria used in the CT database. Overall 4 cases were identified exclusively by ARGUS search.

Table 3-3 Reconciliation of clinical trial databases

Type of search	Clinical Trial Database		ARGUS database	
	PID	PT of main event in CT database	PID	Preferred term
SMQ on coronary and cerebrovasc ischaemia	(b) (6)	Vasoconstriction	(b) (6)	Coronary artery bypass
		Atrial fibrillation		Coronary artery disease
		Atrial fibrillation		Coronary artery disease
		Chest pain		Ischaemia (myocardial)
Cardiac Disorders (SOC)		Urosepsis		Tachycardia
		Pregnancy		Fetal tachycardia
		Adenocarcinomy of lung		Palpitations
Coxib		Arrhythmia		Syncope, supraventricular extrasystoles
		Coronary artery disease		Angina pectoris, coronary artery disease
		Cerebrovascular disorder		Cerebrovascular accident
Chest pain/discomfort		Atrial fibrillation		Chest pain
		Bradycardia, hypoglycaemia		Chest discomfort

* exclusively identified by ARGUS search

Following reconciliation, patient identifiers and data summaries (demography, background history, concomitant medication, adverse events, and investigator's comment) and CRFs of the index cases were provided as basis for the narrative preparation and to compile the documentation for adjudication.

3.1.4 Characterization of population regarding CV risk factors and morbidity at baseline (only for Db15)

Based on their medical history, co-medication at the time of enrollment into the study, and their baseline assessments, patients were screened for their CV risk. Risk factors included the following 7 categories: History of CV disease, active smoking, history of hypertension, history of hyperlipidemia, history of diabetes mellitus, age ≥55 yrs, or obesity (BMI >30 kg/m2). The number of risk factors (range 0 to 7) was determined for each patient.

Cardiovascular disease: All conditions that were documented as relevant medical history or current medical condition in this database were checked by a medical reviewer based on MedDRA preferred term level. Based on this review a list of about 90 preferred terms, e.g. angina pectoris, myocardial infarction, cerebrovascular accident, etc. were identified and patients with a pre-existing cardiovascular disease were defined as patients for which one or more of these conditions was documented.

Active smoking: Patients were defined as being active smokers based on screening prior to entering the study. This information was only recorded in 15 of the 29 studies, as it was not requested by the study protocol (CRF) in 14 studies.

Hypertension: Patients were defined as fulfilling the risk factor hypertension if any of the following applied:

- Elevated blood pressure at baseline (systolic >140 mmHg, or diastolic >90 mmHg)
- Medical history or current medical condition at baseline included any of the following terms: Essential hypertension, hypertension, labile hypertension, blood pressure increased, or blood pressure systolic increased, renal hypertension, diastolic hypertension, systolic hypertension (based on MedDRA preferred term).
- Prior treatment with antihypertensive drugs, these were identified based on the following criteria whereby all 3 had to be fulfilled: 1) Medication was given prior to the first intake of study medication; 2) Medication falls into one of the following ATC classes: antihypertensives, diuretics, beta blocking agents, calcium channel blockers, or agents acting on the renin-angiotensin system; 3) The "reason" for the medication contained the string "hyperten" but not "ocular".

Hyperlipidemia: Patients were defined as fulfilling the risk factor hyperlipidaemia if any of the following applied:

- Baseline total cholesterol > 6.21 mmol/L (> 240 mg/dL). This was not measured in 7 of 29 studies
- Medical history or current medical condition at baseline included any of the following terms: Blood cholesterol increased, blood triglycerides increased, dyslipidaemia, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, lipid metabolism disorder, lipids abnormal, lipids increased, (based on MedDRA preferred terms).
- Prior treatment with lipid lowering drugs (all three must be fulfilled): 1) Medication was given prior to the first intake of study medication; 2) Medication belonged to one of the following ATC classes: serum lipid reducing agents, or nicotinic acid and derivatives; 3) The "reason" for medication contained any of the text strings: "lipid", "cholest", "colest", "glycer".

Diabetes mellitus: Patients were defined as fulfilling the risk factor diabetes mellitus if any of the following terms was mentioned as relevant medical history or current medical condition: Cataract diabetic, diabetic foot, diabetic gastroparesis, diabetic ketoacidosis, diabetes mellitus, diabetes mellitus insulin-dependent, diabetes mellitus non-insulin-dependent, diabetic microangiopathy, diabetic neuropathy, diabetic nephropathy, diabetic neuropathic ulcer, diabetic retinal oedema, diabetic retinopathy, neocrobiosis lipoidica diabeticorum, obesity, and overweight based on MedDRA preferred terms or if they were enrolled into the diabetic gastropathy [Study G2203].

Elderly: Patients were defined as fulfilling the risk factor elderly if the age was ≥55 years at baseline.

Obesity: Patients were defined as fulfilling the risk factor obesity if the body mass index at baseline was above 30 kg/m^2. Body mass index could not be calculated for 3 of 29 studies, because the height was not collected.

In case of missing data needed for the derivation of individual risk factors, a patient was regarded as not having the respective risk factor.

3.2 Preparing documentation for adjudication

3.2.1 Document Retrieval

For the purposes of this adjudication, document retrieval was not limited to "source documents" pertaining to the trial itself. Any pre- or post- study medical history relevant to cardiovascular status, or relevant to the event, were also retrieved. These supplemental documents were not available in all cases.

Upon the receipt of the lists of patients generated through different search strategies, the following procedures took place:

- The new patient list was cross-checked versus existing lists for removal of duplicate cases
- A spreadsheet was created that contains key patient information such as patient ID, DOB, initials, country, event, treatment period etc
- Individual case folders were created for each patient
- CRFs were retrieved from storage
- Instructions were provided to all personnel involved with document retrieval to obtain:
  - All source documents pertinent to the patient regardless of apparent relevance to the event
  - Any pre- or post- study medical history relevant to cardiovascular status, or relevant to the event, was also be retrieved. These supplemental documents may have not been available in all cases.
- Non-English documents were translated by certified medical translators.

To protect patient identification during the retrieval of documents, a clear instruction was provided to all Novartis personnel involved in document retrieval to strictly follow their current local privacy laws. If a new patient informed consent form was required, the new form was sent to local Novartis personnel to obtain consent from the investigative site.

Retrieval of source data from trial centers yielded new clinical information in the majority of the patients with a hit during the initial search in Db15 and Db14.

3.2.2 Writing Case Narratives

Once the CRFs, source documents and additional medical information were in place, case narratives were written by either Novartis medical doctors or trained medical writers. The narrative included: 1) History of or current diagnosis of any underlying cardiovascular/cerebrovascular diseases or symptoms suggestive of a underlying CV disease (data relating to the time-period preceding the event); 2) Risk factors according to the NIH guideline (National Heart, Lung and Blood Institute, 2001) for CV ischaemic disease such as hypertension, hyperlipidemia, diabetes, smoking, obesity and family history of CV disease were also be described (data relating to the time-period preceding the event); 3) A detailed description of the CV event including timing of the event, clinical presentation, diagnostic procedures, diagnosis, treatment and follow-up medical information; 4) A table summarizing

the key relevant information. (template, see Adjudication Methodology, Section 8.1-Appendix 2).

In case medical information was assessed as incomplete such as missing procedure report, hospital discharge summary etc, a request for further medical information was made.
Medical review of each case narrative was performed by an MD to ensure consistent methodology was applied for all narratives and to assess that all relevant information has been captured in the generation of the narrative as well as clarifying any potential inaccuracies with the medical writer and ensuring that there was blinding of treatment allocation for subsequent external adjudication. This MD was then to provide the approval for the narrative to be sent for external adjudication.

3.2.3 Adjudication package

An individual adjudication package was prepared for each case. The package contained a case narrative, one paper copy of all source documents and supplemental medical information including translation where applicable, a checklist (see Adjudication Methodology, Section 8.1-Appendix 3) and one CD-ROM containing all paper documents. To maintain the integrity of the adjudication process and eliminate any potential bias, the following procedures were implemented:

- Treatment allocation was blinded to the external adjudicators, the word "Zelnorm/Zelmac or Tegaserod" was not used. Instead, the term "study drug" was used in case narratives
- False positive cases due to coding errors were included in the adjudication and serve as dummy cases

Brief narrative summaries and source documents (e.g., EKG tracings, cardiac enzyme results, original history and physical exam reports, cardiac catheterization reports, and reports from other cardiac imaging studies) were provided by the sponsor for all cases.

3.3 Adjudication

An independent CRO, "MD Evidence" (Orange, California, USA), was used to organize the adjudication. The adjudication was conducted by physicians associated with the Duke Clinical Research Institute. The final adjudication results were provided to Novartis for analysis.

3.3.1 Prescreening

Prior to review by the full adjudication panel, individual cases that obviously did not meet the criteria for myocardial infarction, unstable angina, arrhythmia/conduction abnormality, congestive heart failure exacerbation, stroke or transient ischemic attack, and cases which were miscoded (e.g. tonsillitis miscoded as angina) and other events specified (e.g. superficial phlebitis due to venous puncture) were reviewed by a single member of the panel using pre-specified criteria (see Adjudication Methodology, Section 8.1-Appendix 4). If the single panel member decided that a case meets pre-specified criteria, then that case was excluded from review by the full adjudication panel.

During the pre-screening process, the adjudication team added an additional criterion to exclude cases. Although the criteria were not appended to the original "Pre-Screening Review of Cases" document. The additional criterion for excluding cases was: "Miscellaneous

Complaint": Any disorder or complaint that was not associated with any documented EKG changes, documented new radiologic defects, or documented changes in CV function or morphology (e.g., abnormal exercise stress test, abnormal echocardiogram, abnormal Holter) monitor) AND the totality of the medical history is not consistent with a CV event. (Mahaffey, et al., 2008).

3.3.2 Adjudication Procedure

- Each adjudication panel member received a workbook containing a narrative summary and source documents for each case.
- Panel members were to review the cases in advance of the adjudication meeting.
- During the meeting, each narrative summary was reviewed. Members of the panel were not told if patient was taking tegaserod or placebo. All references to use of study medication were deleted in order to insure that blinding is maintained. Ample time was provided for discussion and questions.

3.3.3 Classification of cases by adjudication panel

- After discussion, each panel member independently completed a score sheet about the "classification" of the possible CV event. "Classification" categories include: "probable CV event"; "probably no CV event"; "undetermined-source documents pending"; or, "insufficient data to classify". Final classification of event was determined by majority vote. (Definitions, see Adjudication Methodology, Section 8.1-Appendix 6)
- For all cases that are classified as "probable CV event" or "probably no CV event", each panel member stated if "adequate source documents are available for this decision" or "limited source documents" are available for this decision. This decision was a judgment which was made by each panel member based upon their experience.
- A "probable CV event" was by definition a newly occurring or worsening event.
- For each case that is classified as "probable CV event", panel members determined the type of the CV event.
- For each case that was classified as "probable CV event", panel members also determined if each patient had a history of cardio-vascular disease prior to entering the trial.
- If the "probable CV event" was myocardial infarction, unstable angina, stroke or transient ischaemic attack, panel members identified the date of the CV event.
- In patients in which the "probable CV events" were classified into more than one of the following categories: *myocardial infarction, unstable angina, stroke or transient ischaemic attack*, panel members identified the leading CV event and its date of onset.
- If the "probable CV event" was a new cardiac arrhythmia or conduction abnormality, then the panel members classified the type of arrhythmia/conduction abnormality.
- If a patient had a stable pattern of angina prior to entry into the study and if the patient had recurrent angina during the study, then the patient was classified as "stable angina" if they did not meet any of the objective criteria for "unstable angina".

3.3.4 Recording and reporting of adjudication results

- Individual results (by patient) of the adjudication were collected in a questionnaire (see Adjudication Methodology, Section 8.1-Appendix 2). Across patient results were tabulated and compiled in an executive summary. The completed questionnaires were the basis for the data processing by the sponsor.
- A formal query process was established between the sponsor and the panel to resolve any inconsistent answers, should they occur.
- The single member of the panel conducting the prescreening, provided a line listing with the cases classified as non-CV cases with the reason for the classification.
- Following the completion of the adjudication, MD Evidence provided an executive summary of the blinded adjudication results to Novartis (available upon request).
- Panel members signed a form confirming their participation in the adjudication process, which was included in the executive summary.

3.4 Analysis plan

Un-blinding was conducted by Novartis prior to conducting statistical analyses. The analyses relative to the adjudication outcome are described in the overall submission analysis plan.

3.4.1 Statistical analysis

The post-hoc analysis included all patients classified as safety analyzable. The analysis population "Safety analyzable" was typically defined as all patients receiving at least one dose of study medication and having had post-baseline safety assessment.

The coding of Adverse Events and Medical Histories/Current Medical Conditions was revised prior to this analysis to be in line with version 9.0 of the MedDRA dictionary. This may have resulted in slight changes of terms when comparing these analyses with the individual study reports.

Only treatment-emergent adverse events were included in the automated database search to identify patients to undergo adjudication. Treatment emergent events are defined as events with an onset date on or after the start of study treatment. In principle adverse events were reported even if they occurred after the stop of study medication.

For Db15 (placebo controlled trials) exceptions were made as follows:

- The majority of study did not have a scheduled withdrawal period after end of treatment, i.e. with the exception of serious adverse events, no data was collected after end of treatment. In order to keep consistency with these studies in the pooled database, no follow up period data was used for studies that had a withdrawal period [Study A0358, Study AFI01, Study ASG01, Study E2302, and Study A2302].
- For [Study A2306], only data from treatment period 1 was included (i.e. adverse event start date on or before end of period 1) in Db15.
- For [Study AIA12], only data up to study day 28 (core study) was included.
- For other studies with an extension period, only data assigned to the core study was used. When start dates or end dates were not available, visit dates at baseline/randomization or end of study were imputed.

The above mentioned exceptions were only used for non-serious adverse events, serious adverse events with an onset date during treatment-free interval or withdrawal period were included.

Cases to undergo external adjudication were selected based on different types of automated MedDRA preferred-term based searches on the adverse event and the serious adverse event databases as described above. The proportion of patients with events identified overall and by search type were summarized overall and by treatment group for Db15 and Db14. For the double-blind database Db15, between-treatment comparisons (tegaserod vs. placebo) were performed using Fisher's exact test and the 2-sided p-values were displayed as were the odds ratios for tegaserod vs. placebo together with the asymptotic 95% CI around the odds ratio.

Adjudication outcome (probably a CV event, probably not a CV event, unable to determine/insufficient data/not enough documents available, case excluded after pre-screening) was summarized by treatment.

CV ischaemic events assessed as 'probably a CV event' were categorized as follows in the 2nd external adjudication:

- Coronary ischaemic event (defined as unstable angina or myocardial infarction)
- Cerebral ischaemic event (defined as stroke or transient ischaemic attack)
- APTC (Antiplatelet Trialists' Collaboration ,1994) type event, i.e. myocardial infarction, stroke, and/or vascular deaths

Patients having more than one CV ischaemic event were classified into the above categories according to the event identified as "leading event" by the adjudication panel. Only patients that were adjudicated for one or more of the search criteria mentioned above were included in the summary tables. Patients adjudicated even though their reported adverse events were not covered in any of the specified automated searches were listed only.

A patient was counted as having an APTC type event if he/she

- had a myocardial infarction confirmed by adjudication and indicated as leading event *OR*
- had a stroke confirmed by adjudication and indicated as leading event *AND/OR*
- 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").

In case a patient had a confirmed leading event of myocardial infarction or stroke and died subsequently, that patient was displayed as "vascular death" only, i.e. NOT as myocardial infarction or stroke within the APTC sub-categories.

For all types of events confirmed by the 2nd external adjudication, the number and proportion of patients experiencing the event was reported for Db14 and Db15. For Db15 between-treatment comparisons (tegaserod vs. placebo) for the proportion of patients experiencing the event was performed using Fisher's exact test and the 2-sided p-value was displayed. If the odds ratio for tegaserod vs. placebo could be computed, it was displayed together with the asymptotic 95% CI around the odds ratio.

For all patients with a myocardial infarction, unstable angina, cardiac arrhythmias/conduction abnormalities, CHF exacerbation, stroke, or transient ischaemic attack the adjudicators also

assessed the patient's history of cardiovascular disease prior to entering the trial. As the data were only collected for this subset of patients it will only be summarized by type of history for these patients. This information is considered supplementary and was used to derive the CV risk factors for the by risk factor analyses conducted.

Meta-analyses using 3 alternative methods were conducted for CV ischeamic events as a sensitivity analysis to the results from the analyses without adjusting for study.

1. Exact analysis
2. Logistic regression with study as a fixed effect
3. Logistic regression with indication as a fixed effect

Studies with zero observed events for tegaserod and placebo were excluded from the analyses using methods (1) and (2), since the odds ratio for studies with zero event cannot be defined and will not add any information to the overall estimate of the treatment effect.

In order to provide an analysis which takes into account some study variation and also includes all of the data in the analyses (i.e. studies with a zero total event count are included in the analysis) method (3) was applied.

The time from start of study drug to the occurrence of the leading CV ischemic event was calculated (in days) to perform a Kaplan-Meier time-to-event analysis. If a patient did not experience an event (i.e. they are a censored observation), the time to end of treatment exposure was used.

The Kaplan-Meier estimate for the failure function = 1 – survival function versus time (days) was displayed graphically by treatment.

Time to event data (days) were analyzed using a Cox proportional hazards model with treatment fitted as a factor. The hazard ratio (tegaserod vs. placebo) and associated 95% confidence interval were presented together with the 2-sided p-value from the likelihood ratio test.

The estimated incidence rate per 1000 patient-years was provided for CV ischaemia in Db14 and Db15.

For Db15, the relative risk adjusted for exposure (tegaserod vs. placebo) was computed by modeling the incidence rate (per patient year) of a patient experiencing any ischaemic adverse event, using a log-linear model with treatment as a factor. From this analysis, the following was presented: The estimated frequency of events per 1000 patient years for each treatment group (with Wald 95% confidence interval), the relative risk for tegaserod vs. placebo (with Wald 95% confidence interval), and the 2-sided Wald p-value (to test the hypothesis that the relative risk = 1), (SAS Institute Inc 1999).

The proportion of patients who experienced a CV ischaemic event was modeled using logistic regression including treatment as a fixed effect for Db15. The following covariates were fitted and the automatic stepwise selection procedure was used in SAS in order to select the final model (see below for more details).

1. Sex: Female vs. Male
2. History of cardiovascular disease: Yes vs. No
3. History of hypertension: Yes vs. No

4. History of hyperlipidemia: Yes vs. No
5. Diabetes mellitus medical history: Yes vs. No
6. Age group: >= 55 vs. < 55 years

The risk factors smoking and obesity are missing for many patients, thus these covariates were not included in the analysis.

The stepwise selection procedure works as follows:

The procedure estimates parameters for each of the risk factors. Each risk factor is added to the model alone with the intercept. Next, the procedure computes the adjusted chi-square statistics for each risk factor not in the model and examines the largest of these statistics. If it is significant at the 10% significance level, the corresponding variable is added to the model. Variables are entered into and removed from the model in such a way that each forward selection step can be followed by one or more backward elimination steps. The stepwise selection process terminates if no further variable can be added to the model or if the variable just entered into the model is the only variable removed in the subsequent backward elimination.

The odds ratios of the treatment comparison (tegaserod vs. placebo) and of the remaining factors in the model were presented together with associated 95% confidence intervals (Wald) and 2-sided p-values (Wald), (SAS Institute Inc 1999).

3.4.2 Limitations of Methodology

The interpretation of this data is limited due to the following: This was a retrospective analysis in studies of functional GI disorders without prospective identification and collection of cardiovascular history and symptoms. Baseline characteristics relevant to the assessment of the risk for/history of coronary ischaemia were therefore incompletely captured in some patients. Furthermore, the database included several older studies some of which were conducted more than 10 years ago. There was a lack of objective information that was able to be obtained for the ischaemic events in many cases. Additionally, several patients with CV ischemic events seemed to have baseline CV symptoms without an as yet established cardiovascular diagnosis. As there was no baseline assessment of CV symptoms in patients as yet undiagnosed, the assessment of balance between CV risk at baseline is limited between treatment groups

The criteria to exclude patients at pre-screening allowed room for interpretation as to which cases have/have not to be excluded from full-panel adjudication, and were therefore overlapping with those defining the classification “probably no CV event”.

4 Results

Overall 578 cases have been adjudicated out of the double-blind placebo controlled studies (Db15) and the open label studies (Db14). Of these 578 cases, 539 were identified by automated search (selection criteria Section 3.1.2) and an additional 39 (Db15: n = 23; Db 14: n= 16) which did not fulfill the pre-specified selection criteria and were inadvertently included. The adjudication results of these 39 cases are reported in (Section 8.3-PT listing 6D and PT listing 6E). None of them were classified by the panel as a “probable” CV event, with

Appendix 6. Characteristics of Subjects with Adjudicated CV Ischemic or MACE Events in DB15 and DB14

Characteristics of Subjects with Adjudicated CV Ischemic or MACE events in DB15

PID, dose	Age/Sex	Adverse event Classification by adjudicators	Day of treatment in 12-week studies (leading event)	CV risk factors identified	Study Indication	Source Data
(b) (6) **12 mg/d**	53/F	Myocardial infarction	5	Hyperlipidemia History of CV disease Active smoking	IBS-C	Adequate
(b) (6) **12mg/day**	64/F	CV Death	30	Age ≥ 55 Hypertension	IBS-C and IBS-M	Limited
(b) (6) **4 mg/d**	57/F	Stroke	26	Hyperlipidemia Age ≥ 55	FD	Adequate
(b) (6) **4 mg/d**	78/M	Stroke	69	History of CV disease Hypertension Age ≥ 55	CIC	Adequate
(b) (6) **4 mg/d**	69/M	Unstable angina	44	Age ≥ 55	IBS-C	Adequate
(b) (6) **4 mg/d**	69/M	Unstable angina	63	Hyperlipidemia Active Smoking*	IBS-C	Adequate
(b) (6) **12 mg/d**	47/F	Unstable angina	4	Hyperlipidemia Active Smoking	CIC	Adequate
(b) (6) **Placebo**	70/F	TIA	98	Hypertension Hyperlipidemia Age ≥ 55	IBS-C	Adequate

Characteristics of Subjects with Adjudicated CV Ischemic or MACE events in DB14

PID*	AE Classification	Day of Trt.	CV Risk Factors Identified
(b) (6)	Unstable angina	197 (6.5 months)	Hypertension, hypercholesterolemia atrial fibrillation, LV hypertrophy, age ≥55 yrs
	Stroke	168 (5.6 months)	Obesity, ex-smoker
	Unstable angina	323 (10.7 months)	Coronary artery disease, age ≥55 yrs
	Unstable angina	122 (4 months)	Hypertension, hypercholesterolemia, mitral valve prolapse, age ≥55 yrs

Appendix 7. Subjects with CV Events in the First Adjudication Of DB15 Who Weren't Confirmed in the Second Adjudication

Subject_ID	Treatment	Sex	Age	Number of risk factors	CV event from 1st adjudicatoin	2nd adjudicatoin	Start day of event relative to treatment start	Indication
(b) (6)	Tegaserod 12 mg	F	50	2	Probable stroke	Insufficient data	16 (first day of withdrawal period)	IBS-C
	Tegaserod 12 mg	F	47	2	Probable myocardial infarction	Probably no CV event	56	FD
	Tegaserod 12 mg	M	69	4	Probable unstable angina	Insufficient data	2	CIC
	Tegaserod 12 mg	M	72	1	Definite unstable angina	Probably no CV event	56	CIC
	Tegaserod 4 mg	F	75	5	Probable unstable angina	Probably no CV event	38	IBS-C
	Tegaserod 12 mg	F	50	2	Definite unstable angina	Probably no CV event	12	IBS-C

Appendix 8. ECG Analyses

Method

In clinical studies conducted in the later part of the development, ECGs were generally recorded at baseline and the end of the study while on study drug. More frequent recordings/evaluations were not considered necessary since an extensive analysis was done previously (see below, 12-week data in IBS).

In the studies summarized in Table 18, all ECG recordings collected throughout the trials were analyzed and interpreted by central laboratories. Based on information available to the Sponsor (for studies B307, B209, B301, B351, and E2301), the general methodology for the central read ECG assessments is presented below. The Sponsor assumed this methodology was generally consistent across all central read studies.

- Twelve-lead ECGs were obtained at baseline, on Day 1 after the first day dosing (tegaserod peak plasma concentrations occur approximately 1 hour after oral dosing), on day 29 and day 85 or end of study at 2±0.5 hours after the last dose, or any unscheduled visit if the patient reported symptoms of fainting or unusual dizziness.

- Sites used their existing ECG machines to generate ECGs (2 identical originals) or 1 original and 1 first generation copy. Instructions were provided to the central laboratory, for the proper collection and handling of ECGs.

- Each original 12-Lead ECG strip and Lead II rhythm strip had a study-specific patient identification label affixed by the investigator personnel.

- The recordings were analyzed and interpreted by a central reader detailing each abnormality and overall ECG evaluation in a blinded fashion.

- Each ECG report usually included heart rate and mean interval measurements from 3 consecutive complexes. Findings were provided in hardcopy text.

- Measurements of the intervals listed below were performed for each ECG tracing by trained technicians on calibrated Jandel Scientific SigmaScan® digitizing tablets.

    - 3 PR measured (mean PR interval reported)

    - 3 QRS measured (mean QRS width reported)

    - 3 R-R measured (mean Heart Rate reported

    - 3 QT measured (mean QT interval reported)

    - 3 Qtc calculated (mean QTc reported)

- The Digitizing System was accurate within ± 3ms and was more precise then calipers or rate rulers. ECG nuances, such as U-waves and T-wave artifacts that provided

difficult for automated analysis, were distinguished by experienced technicians and cardiologists using the American College of Cardiology guidelines. All 12-lead ECGs were interpreted by a Premier Research Worldwide cardiologist for: rhythm, conduction, infarction, morphology, ST waves, T waves, and U waves. A single, US-based board-certified cardiologist blinded to treatment provided interpretations for all ECGs; additional cardiologists were available as back-up.

- ECG analysis was subject to strict quality control protocols. The program included over-reading of 100% of the 12-Lead ECG reports and in addition, the prior Sponsor required that 2% of all study-specific ECGs be reprocessed in a blinded fashion.

- Individual ECG abnormalities at each time point were assessed and compared with baseline (categories: no change, worsened, improved, or not available), and an "overall" ECG assessment was made for each ECG independent of the baseline (categories: normal, abnormal, and unable to evaluate).

Table 18: Studies with Central Laboratory Read ECG

Study Number	Indication	Central Laboratory
Placebo controlled studies (DB15)		
B301	IBS-C	Premier Research Worldwide
B307	IBS-C	Premier Research Worldwide
B351	IBS-C	Premier Research Worldwide
A2302	IBS-C	eResearch Technology (eRT)
B254 (Cohorts 1-4)	IBS-D	Premier Research Worldwide
E2301	CIC	eResearch Technology (eRT)
E2302	CIC	eResearch Technology (eRT)
E2308	CIC	eResearch Technology (eRT)
Long term safety studies (DB14)		
B209	IBS-C	Premier Research Worldwide
B301E1	IBS-C	Premier Research Worldwide
B307E1	IBS-C	Premier Research Worldwide
E2301E1	CIC	Premier Research Worldwide

Studies without central read data in DB15 included B201, B202, B251, B207, B358, A2306, D2201, D2202, D2203, D2204
Studies in DB15 which did not include an ECG assessment were AIA12, ASG01, AFI01, G202, G2203, E2309, D2301, D2302, and B2203

Results

ECG data are available in overall 6,374 safety analyzable patients from DB15 studies and 2516 patients in the IBS-C studies only with central read ECGs and an additional 2,072 patients from long term safety studies (DB14).

The following ECG data analyses were originally presented in the ISS for IBS-C and are herein presented for studies apart of DB15, IBS-C studies, and DB14:

- Central tendency descriptive statistical summary, including 90% confidence intervals) of values and changes from baseline for ventricular rate, PR, QRS, and QTcF intervals by treatment. For the QTcF interval, prolongations from baseline are summarized and categorized. For this analysis QTcF (Fridericia heart rate correction) was used since it is more accurate than the Bazett's correction (reference ICH E14).

- Categorical actual analyses (treatment emergent only) for Day 1 and Overall

    - QTcF >450 ms to 480 ms
    - QTcF >480 ms to 500 ms
    - QTcF >500 ms
    - QTcF change from baseline >30-60 ms
    - QTcF change from baseline >60 ms
    - Increase in PR interval from predose baseline >25% to a PR >220 msec;
    - Increase in QRS interval from predose baseline >25% to a QRS >120 msec;
    - Decrease in HR from predose baseline >25% to a HR <50 bpm; and
    - Increase in HR from predose baseline >25% to a HR >100 bpm

- Overall ECG assessment of new or worsening abnormalities

In the following subsections data are presented for the following populations:

- All Subjects with Central Read ECG in DB15 (B254, B301, B307, B351, A2302, E2301, E2302, and E2308)
- All Subjects with Central Read ECG IBS-C Studies (B301, B307, B351)
- Long Term Safety Studies with Central Read ECG DB14 (B209, B301E01, B307E01, E2301E1)

ECG Results in All Subjects (DB15) and Those in IBS-C studies with Centrally Analyzed ECGs

<u>ECG results in all subjects (DB15)</u>

In the pooled database, using the centrally analyzed ECGs, of placebo controlled studies (DB15), there were no meaningful tegaserod-related effect on the QTcF interval which at all time points was similar to placebo and the upper 90% confidence interval for the change from baseline QTcF was always < 10 ms, the boundary of regulatory concern. There was no imbalance in the QTcF categorical analyses. On day 1 there was a minor increase in the

ventricular rate with tegaserod 12 mg compared to placebo, without a dose-response, of ~1.4 BPM which was not observed at later time points. The central tendency and categorical analyses demonstrated no meaningful effects on the QRS or PR intervals (Table 19).

The ECG intervals measured on days 1, weeks 1-6 and weeks 7-12 showed that the time course of the QTcF interval was uneventful. The frequency of ECGs that were considered as newly abnormal or worsened ECG abnormalities, assessed in all subjects from central read ECG studies, was overall similar in the tegaserod and placebo groups (Table 19). The tegaserod group had a slightly higher number of subjects with new or worsening observations under ectopic atrial rhythms (0.24% vs 0.13%) and the non-specific biomarker of flat T waves (2.72% vs 1.62%). Overall, there was not a meaningful increase at higher doses and was not clinically significant (of note biphasic T waves and inverted T waves were observed with generally similar proportions).

In the tegaserod cohort there were 5 new myocardial infarctions identified by ECG and 1 in the placebo cohort. The ECGs from these 5 subjects were carefully re-evaluated by Dr. Joel Morganroth, an established electrophysiology expert. Based on a re-reading of the tracings on April 21, 2000 by Dr. Morganroth, none of these new myocardial infarctions were confirmed. 3 of the 5 had a change in a previous myocardial infarction pattern present at baseline and were not suggestive for a new finding. Two were attributed to a change in the lead placement. Of these patients, none had angina pectoris; 2 [(b) (6)] had reported severe and mild chest pain, on Days 1 and 19, respectively. It is also noted that the Second Adjudication performed by Duke identified only 1 clinical myocardial infarction in the DB15 database.

ECG results in subjects with IBS-C (DB15)

In the pooled IBS-C database (studies A0301, A0307 and A0351) with centrally analyzed ECGs, there were no meaningful tegaserod-related effect on the QTcF interval which at all time points was similar to placebo and the upper 90% confidence interval for the change from baseline QTcF was always < 10 ms, the boundary of regulatory concern. There was no imbalance in the QTcF categorical analyses. On day 1 there was a minor increase in the ventricular rate with tegaserod 12 mg compared to placebo, without a dose-response, of ~1.5 BPM which was not observed at later time points. The central tendency and categorical analyses demonstrated no meaningful effects on the QRS or PR intervals or ventricular rate (categorical analysis). The ECG intervals measured on days 1, weeks 1-6 and weeks 7-12 showed that the time course of the QTcF interval was uneventful. There was a slight increase in the number of subjects with new or worsening observations under non-specific biomarker of flat T waves (4.29%% vs 3.46%), comparing tegaserod and placebo groups respectively. Although, this trend is not clinically significant (of note biphasic T waves and inverted T waves were observed with generally similar proportions). Five MI's, later determined to not be new infarctions, are discussed above.

Table 19: Summary of ECG Diagnoses and Parameters – DB15 Studies with Central Laboratory Read ECG)

	All Subjects DB15		All Subjects IBS-C Studies	
	Tegaserod All Doses N=4,086	**Placebo** N= 2,288	**Tegaserod All Doses** N= 1,679	**Placebo** N= 837
Ventricular Rate (Central Read)				
Baseline: mean ±SD (bpm)	67.4 ±10.58	67.9 ± 10.52	66.6 ± 10.48	66.6 ± 10.48
Day1 change from baseline: mean (90% CI) (bpm)	2.6 (2.1, 3.0)	1.0 (0.4, 1.5)	-1.6(-2.7,-0.5)	-1.8(-2.5,-1.0)
Change from baseline Weeks 1-6 : mean, (90% CI) (bpm)	1.4 (1.0, 1.7)	1.0 (0.6,1.4)	1.4 (1.0,1.8)	1.0 (0.4,1.6)
Change from baseline Weeks 7-12: mean, (90% CI) (bpm)	1.6 (1.3, 1.9)	1.2 (0.8, 1.6)	2.7 (2.3, 3.2)	2.5 (1.9, 3.1)
QTcF interval (Central Read)				
Baseline: mean ±SD (ms)	392.7 ± 21.04	392.1 ± 20.45	394.1 ± 21.15	392.2 ± 19.67
Day1 change from baseline: mean (90% CI) (bpm)	-1.5(-2.2, -0.8)	0.3 (-0.7, 1.4)	-1.8(-2.5,-1.0)	0.6(-0.5,1.7)
Change from baseline Weeks 1-6 : mean, (90% CI) (bpm)	-0.3 (-0.9,0.4)	0.0 (-0.9,0.8)	-0.6(-1.4, 0.2)	0.4(-0.7,1.4)
Change from baseline Weeks 7-12: mean, (90% CI) (bpm)	0.3 (-0.2, 0.9)	0.3 (-0.5, 1.1)	-0.3(-1.5, 0.5)	-0.2 (-0.2, 2.2)
QTcF categorical (Central Read)				
Overall >450 to 480 ms: n (%)	25 / 3822 (0.7)	8 / 2148 (0.4)	12 / 1638 (0.7)	4 / 823 (0.5)
Overall >480 to 500 ms: n (%)	1 / 3848 (0.0)	1 / 2160 (0.0)	1 / 1653 (0.1)	0 / 827
Overall >500 ms: n (%)	0 / 3848	0 / 2160	0 / 1653	0 / 827
>30 to 60 ms from baseline: n (%)	280 / 3849 (7.3)	173 / 2160 (8.0)	144 / 1654 (8.7)	87 / 827 (10.5)
> 60 ms from baseline: n (%)	10/ 3849 (0.3)	4/ 2160 (0.2)	5/ 1654 (0.3)	3 / 827 (0.4)
ECG Abnormalities (Central Read)				
Conduction: Left Bundle Branch Block	1 (0.02%)	0	1 (0.06)	0
Conduction: Right Bundle Branch Block	4 (0.10%)	1 (0.04%)	3 (0.18)	1 (0.12)
Intra-Ventricular Conduction Defect	0	0	0	0
MI: Antero Septal V1-V4	4 (0.10%)	1 (0.04)	4 (0.24)	0
MI:INFERIOR (2), 3, F	1 (0.02%)	0	1 (0.06)	0

	All Subjects DB15		All Subjects IBS-C Studies	
	Tegaserod All Doses N=4,086	**Placebo** N= 2,288	**Tegaserod All Doses** N= 1,679	**Placebo** N= 837
Rhythm: Atrial Fibrillation	1 (0.02%)	2 (0.09%)	0	2 (0.24)
Rhythm: Atrial Flutter	1 (0.02)	1 (0.04)	0	1 (0.12)
Rhythm: Ectopic Atrial Rhythm	10 (0.24)	3 (0.13)	6 (0.36)	3 (0.36)
Rhythm: Junctional Escape BE	1 (0.02)	0	1 (0.06)	0
T waves: Biphasic	4 (0.10)	0	2 (0.12)	0
T waves: Flat	111 (2.72)	37 (1.62)	72 (4.29)	29 (3.46)
T waves: Inverted	29 (0.71)	15 (0.66)	22 (1.31)	9 (1.08)
U Waves: Abnormal	1 (0.02)	0	1 (0.06)	0

ECG Results in Long Term Safety Studies

The QTcF interval analysis was conducted in the pooled long-term trials (B209, B301E1 and B307E1). During 26 to 52 weeks of treatment with tegaserod, the incidence of clinically relevant QTc changes was low and similar to that found in the shorter 12-week studies. QTcF upper 90% CI for the change from baseline are all < 10 ms for the tegaserod 12 mg and All cohorts. At the time points with meaningful numbers of subjects (i.e., > 20 subjects; weeks 7-12 and 13-52), for the Tegaserod 12mg/day and All cohorts the QTcF was reduced from baseline by 0.2 to 1.1 ms, indicating no meaningful QTcF prolongation effect. As would be expected, for the comparisons that include only a few subjects, the confidence intervals are wide and clinically meaningless. There were only a small number of subjects reaching an overall treatment emergent increase in QTcF: >450 to 480 ms (1 in the Tegaserod <12 mg and 8 in the Tegaserod 12 mg cohort), while no subject experienced a QTcF >480 ms. The proportions having an increase from baseline of 30 ms- 60 ms (Tegaserod 12 mg cohort: 8.5%) is similar to the same cohort as well as placebo group in the double-blind studies. The proportion of subjects having an increase from baseline QTcF>60 ms is small (0.4%) and similar to that observed in the double-blind studies. Thus the frequency of these categorical outliers is what would be expected in this patient population. The long-term open label studies showed frequencies of new or worsening ECG abnormalities comparable to frequencies in placebo-controlled studies. The most frequent ECG abnormality included flat T waves (1.2%). Overall, these results were consistent with what was observed in the placebo-controlled studies. Three MI's were identified in subjects from the long-term studies, 1 event of which differed from those events identified in the 12 week placebo-controlled studies. This 1 subject represented 0.05% of subjects in the long-term database.

Adverse Event Treatment Emergent Occurrence of Arrhythmias

The Adverse Event Occurrence in the clinical database of arrhythmias was examined 2 ways:

- For ventricular arrhythmias using the paradigm detailed in ICH E14 which includes the non-arrhythmia terms of syncope and seizure

- For all other Treatment Emergent arrhythmias identified in the database and tabulated

Arrhythmias in All Subjects (DB15) and IBS-C (DB15) Cohorts

There was no meaningful difference in ventricular arrhythmia occurrence as classified by ICH E14 in the DB15) and IBS-C (DB15) Cohorts. The frequency of arrhythmias not defined under the ICH E14 guidelines, were similar across treatment groups and subpopulations analyzed. A summary is provided in Table 20.

Table 20: Summary of Clinical Arrhythmias Occurrence

	All Subjects DB15		**All Subjects IBS-C Studies**	
	Tegaserod All Doses N=11,614	**Placebo** N= 7,031	**Tegaserod All Doses** N=4,750	**Placebo** N=2,278
Clinical Arrhythmias- ICH e14				
At least 1 event	20 (0.17%)	11 (0.16%)	14 (0.29%)	5 (0.22%)
Syncope	14 (0.12%)	9 (0.13%)	11 (0.19%)	3 (0.14%)
Ventricular Fibrillation	1 (0.01%)	0	0	0
Ventricular tachycardia	0	0	0	0
Ventricular flutter	0	0	0	0
Torsade de pointes	0	0	0	0
Electrocardiogram QT prolonged	0	0	0	0
Ventricular arrhythmia	0	0	0	0
Cardiac arrest	0	0	0	0
Sudden death	0	0	0	0
Seizure	5 (0.04%)	2 (0.03%)	3 (0.06%)	2 (0.9%)
Non-ICH E14 Arrhythmias	N=11614	N=7031	N=4750	N=2278
At least 1 event	14 (0.12%)	5 (0.07%)	6 (0.13%)	3 (0.13%)
Arrhythmias	6 (0.05%)	4 (0.06%)	3 (0.06%)	3 (0.13%)
Atrial Fibrillation	8 (0.07%)	0	3 (0.06%)	0
Arrhythmia neonatal	0	0	0	0
Arrhythmia prophylaxis	0	0	0	0
Arrhythmia supraventricular	0	0	0	0
Bradyarrhythmia	0	0	0	0
Foetal arrhythmia	0	0	0	0

	All Subjects DB15		**All Subjects IBS-C Studies**	
	Tegaserod All Doses N=11,614	**Placebo** N= 7,031	**Tegaserod All Doses** N=4,750	**Placebo** N=2,278
Foetal tachyarrhythmia	0	0	0	0
Nodal arrhythmia	0	0	0	0
Pacemaker generated arrhythmia	0	0	0	0
Paroxysmal arrhythmia	0	0	0	0
Reperfusion arrhythmia	0	0	0	0
Sinus arrhythmia	0	0	0	0
Supraventricular tachyarrhythmia	0	0	0	0
Tachyarrhythmia	0	0	0	0
Withdrawal arrhythmia	0	0	0	0

Appendix 9. Additional Safety Considerations

Suicidal Events

Clinical Trial Data

In 2005, the Agency requested that the prior Sponsor provide information on suicidal events derived from tegaserod clinical trials. In the placebo controlled clinical trial database comprising 10,951 patients treated with tegaserod and 6236 patients treated with placebo (as of March 2006), the overall frequency of suicidal events and behavior (according to MedDRA classification) was very rare with 0.034% on tegaserod versus 0.017% on placebo. There was one completed suicide on tegaserod, with the patient records indicating a 14-year history of depression.

As further requested by the Agency, the previous Sponsor performed an analysis using the classification developed by Columbia University (Columbia Classification Algorithm of Suicide Assessment, C-CASA), there was small not statistically significant greater incidence of suicide in tegaserod treated patients compared to that seen in placebo patients the frequency of suicidal behavior was 0.07% on tegaserod versus 0.02% on placebo (P value 0.212). This apparent increased incidence of suicide in tegaserod treated patients was based on very small numbers and did not reach statistical significance. Among the 8 cases identified in the tegaserod group, four were classified as completed suicide (n=1), suicide attempts (n=2) and suicide ideation (n=1) and four cases were classified as "self injurious behaviors, intent unknown". These cases of self-injurious behaviors (intent unknown) included: panic attack (n=1), acute alcoholic intoxication (n=1) and depression suicidal (n=2). Importantly none of these patients discontinued tegaserod and they did not report any recurrence of self-injurious behaviors during treatment. Most of the patients had at least 1 risk factor for suicide prior to starting tegaserod including earlier suicidality, medical history of depression, anxiety or other psychiatric disorders. There did not appear to be a pattern of suicidal behaviors associated with patient's age, dose or time to occurrence. In summary, clinical data do not suggest that tegaserod has an impact on psychiatric adverse events and do not support any causal relationship between tegaserod and suicidal events.

At a meeting of the Agency on November 6, 2006, the Agency and Sponsor agreed to update the Adverse Reactions section of the label regarding the risk of suicidality. In a letter dated February 2, 2007, the Agency provided recommended updates to the label. Those updates were not incorporated as the product was removed from the market shortly thereafter. The current label, proposed for reintroduction, has been updated to reflect the Agency recommended language regarding psychiatric risk in the Warnings and Precautions section.

Epidemiological Data

In order to further address the question of suicidality events, a large claims-based retrospective matched cohort study was performed on patients who initiated tegaserod (n=52,229) from September 2002 until December 2006 compared with a well –propensity score matched cohort of patients who did not initiate tegaserod (n=52,229) during this timeframe. This study is utilized the Ingenix Research Data Mart, a health insurance claims database. Patients were

followed for hospital admission, emergency department visit or professional visit with 1) Diagnosis code for suicide attempt and self-inflicted poisoning/injury and no death outcome during the stay, or 2) Diagnosis code for suicide attempt and self-inflicted poisoning/injury and discharge status of death. Data from this analysis show similar cumulative number of potential events in the two cohorts: Suicide attempt and self-inflicted poisoning/injury was reported in 25 (0.048%) tegaserod users and in 32 (0.065%) in non-users, and suicide attempt and self-inflicted poisoning/injury with outcome death in one (0.002%) tegaserod users and in no non-user.

Preclinical Data

Two Safety Pharmacology studies have been performed in mice to specifically address the potential of tegaserod to trigger side effects in the central nervous system. The first CNS safety pharmacology study revealed slightly more in-place motor activity and locomotion following administration of high doses (32 and 100 mg/kg p.o.) of tegaserod to mice. Increased defecation in each treatment group was the main difference to control mice. The second study showed transient, however, consistent signals for potential CNS effects (alertness, spontaneous activity, startle response) in mice at an oral dose of 10 mg/kg tegaserod. The therapeutically relevant pharmacodynamic activity of tegaserod in the gastrointestinal tract is exhibited at an oral dose of 0.1 mg/kg in mice (and humans). It cannot be ruled out that the behavioral changes observed were due to exaggerated gastrointestinal actions of tegaserod applied at high dosages to the mice.

Further investigation of blood-brain barrier permeability and/or exposure in the CNS was conducted in six *in vivo* non-clinical studies as part of the original NDA and sNDA. These studies utilized oral, intravenous, and intracarotid administration methods in mice and rats. Three of the 6 studies using radioautography showed no or below limit of detection for tegaserod in the brain. In the other three studies which used brain extraction methods which have a higher sensitivity, but do not specifically exclude contamination with red blood cells, tegaserod was detected at very low, non-clinically relevant concentrations.

Postmarketing Experience

In post marketing database, there have been reports of 2 completed suicides (US only), 4 suicide attempts (3 in US, 1 Ex-US), 18 reports of suicidal ideation (16 in US, 3 Ex-US), 1 suicidal depression (US only), and 3 intentional overdoses (Ex-US only). This number of cases corresponds to an incidence rate of 28/ 1,626,835 patient-years = 1.72 per 100,000 patient-years. Furthermore, epidemiological data suggest that suicide attempts (outcomes unknown) and self-inflicted injuries occurred more frequently in individuals with known IBS and/or constipation diagnoses than in a control group drawn from the same population (Spiegel, 2007). Based on the totality of the evidence, the Sponsor has concluded that the frequency of suicidal events for patients that had been administered tegaserod is low. Furthermore, the clinical data do not suggest that tegaserod is associated with any increase in relevant psychiatric AEs. As such, the data do not support a conclusion of a causal relationship between tegaserod and suicidal events in this patient population which has a high psychiatric co-morbidity.

Overall Conclusion

According to the re-classification by Columbia, there is a low incidence and a numerical imbalance in the frequency of suicidality events on tegaserod in placebo controlled clinical trials which does not reach statistical significance (at the 2-sided 5% significance level).

- Clinical trial data do not suggest that any specific psychiatric AEs are more frequent on tegaserod, nor do post-marketing data suggest that tegaserod treatment is associated with an increased risk for suicidal events.

- The medical history of the clinical trial population indicates that there is, in line with the literature, a high prevalence of psychiatric co-morbidity associated with these functional GI disorders, especially depression and anxiety, which are known risk factors for suicidality.

- The post-marketing reporting rate of events associated with suicide in tegaserod-treated patients is substantially lower than that estimated and published for patients with IBS and/or constipation.

- Preclinical data do not suggest that tegaserod at therapeutically relevant doses has a potential for CNS effects. Single dose experiments showed a mild-moderate blood brain penetration of tegaserod in animal models, however, its predictability for humans is unknown.

Based on the totality of the data to date, the frequency of suicidal events is low in placebo controlled clinical trials and post-marketing. Furthermore, the clinical data do not suggest that tegaserod is associated with an increase in relevant psychiatric adverse events and do not support a causal relationship between tegaserod and suicidal events in this patient population which has a high psychiatric co-morbidity. The Sponsor commits to continue to closely monitor for suicidality reports in any future tegaserod clinical trials and in the post-marketing period. In addition, the proposed label has been updated to warn of suicide risks in warnings and precautions.

Ischemic Colitis

No cases of ischemic colitis were reported in clinical trials prior to 2002. However, between August 2002 and March 2004, the Agency received 20 reports of cases of ischemic colitis associated with the use of tegaserod. Due to these reports, the labeling of tegaserod was updated to alert the prescribers of the risk of tegaserod-associated ischemic colitis.

With a cutoff of April 30, 2007, a search was conducted in the ARGUS database for spontaneous and Post Marketing Surveillance (PMS) reports using nine MedDRA 9.1 preferred terms related to ischemic colitis. Overall 107 reports were identified in 103 patients, the vast majority were SRs. The patients age ranged between 20 – 89 yrs (median 54 yrs). Of the 76 reports of IC in which duration of therapy prior to onset of IC was reported, 51% occurred within the first 2 months of treatment and 37% from 8 weeks to over one year of treatment, and 11% after one year of treatment. The outcome of the events was complete

recovery (39), improved (17), unchanged (4), death (9), and unknown (24). These data correspond to an incidence rate of 103/1,597,000 patient-years = 0.064 per 1000 patient-years, which is similar to the incidence of ischemic colitis in the general population (0.07-0.47/1,000 patient-years). The reported incidence of ischemic colitis in the IBS population is 0.43-0.49/1,000 patient-years (Cole, 2018).

Appendix 10. Postmarketing Data

Table 21: Unique AE/SAE Post-Marketing Events from MedWatch Reports from the US Market

System Organ Class	Number of Unique Events per 100,000 patient years
Gastrointestinal disorders	578.42
General disorders and administration site conditions	541.32
Nervous system disorders	245.53
Investigations	157.89
Musculoskeletal and connective tissue disorders	111.32
Cardiac disorders	117.50
Respiratory, thoracic and mediastinal disorders	104.74
Psychiatric disorders	86.84
Skin and subcutaneous tissue disorders	85.66
Injury, poisoning and procedural complications	57.89
Vascular disorders	52.76
Surgical and medical procedures	58.95
Metabolism and nutrition disorders	38.95
Infections and infestations	40.79
Renal and urinary disorders	29.87
Eye disorders	24.47
Reproductive system and breast disorders	24.61
Hepatobiliary disorders	15.13
Ear and labyrinth disorders	10.66
Blood and lymphatic system disorders	9.47
Neoplasms benign, malignant and unspecified (including cysts and polyps)	10.92
Immune system disorders	7.50
Social circumstances	6.05
Endocrine disorders	2.76
Pregnancy, puerperium and perinatal conditions	5.53
Congenital, familial and genetic disorders	1.58
Product issues	0.00

Table 22: Unique Post-Marketing Events of Interest from MedWatch Reports from the US Market

Preferred Term	Number of Unique Events per 100,000 patient years
Diarrhea	197.37
Myocardial Infarction	15.00
Cerebrovascular Accident	14.34
Angina Pectoris	9.21
Acute Myocardial infarction	2.24
Cardiac Arrest	0.79
Attempted Suicide	0.66
Completed Suicide	0.26
Sudden Cardiac Death	0.13

Table 23: Unique AE/SAE Post-Marketing Events from MedWatch Reports from ex-US Markets

System Organ Class	Number of Unique Events per 100,000 patient years
Gastrointestinal disorders	427.22
General disorders and administration site conditions	257.15
Nervous system disorders	118.32
Skin and subcutaneous tissue disorders	36.26
Musculoskeletal and connective tissue disorders	39.24
Psychiatric disorders	37.21
Investigations	35.30
Cardiac disorders	31.01
Infections and infestations	34.71
Injury, poisoning and procedural complications	33.75
Respiratory, thoracic and mediastinal disorders	24.33
Vascular disorders	22.30
Metabolism and nutrition disorders	16.10
Eye disorders	10.26
Renal and urinary disorders	14.19
Surgical and medical procedures	35.54

System Organ Class	Number of Unique Events per 100,000 patient years
Immune system disorders	8.23
Reproductive system and breast disorders	9.30
Ear and labyrinth disorders	4.77
Hepatobiliary disorders	8.47
Pregnancy, puerperium and perinatal conditions	5.61
Neoplasms benign, malignant and unspecified (including cysts and polyps)	11.69
Social circumstances	2.50
Blood and lymphatic system disorders	2.62
Endocrine disorders	1.67
Congenital, familial and genetic disorders	0.95
Product issues	0.12

Table 24: Unique Post-Marketing Events of Interest from MedWatch Reports from ex-US Markets

Preferred Term	Number of Unique Events per 100,000 patient years
Diarrhea	178.55
Angina Pectoris	2.39
Cerebrovascular Accident	2.39
Myocardial Infarction	2.27
Cardiac Arrest	1.07
Acute Myocardial infarction	0.83
Completed Suicide	0.72
Suicide Attempt	0.48

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