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**Zelnorm®  
(tegaserod maleate)**

Please note: This document is an excerpt of a larger document  
and Appendices 1 through 4 are not being provided.

**Appendix B**

**Tegaserod: Update on Clinical Efficacy Profile**

Document status: FDA Advisory Committee Briefing Document

Release date: 25-May-2004

Number of pages: 30

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## 1. Executive Summary

The pivotal clinical trials reviewed in the NDA submission were B301, B307, B351 and 0358. Since the NDA submission, three further double-blind randomized placebo-controlled trials (RCTs) with prospectively defined endpoints have demonstrated that tegaserod 6mg bid produces statistically significant improvement in global IBS symptoms compared to placebo. In addition, 9 open-label Phase IV studies have been conducted worldwide in patients with IBS-C. Details of each study with respect to study design and efficacy results can be found in Appendices 1-4.

Overall, recent clinical data supports and confirms the efficacy of tegaserod. Specifically, tegaserod showed rapid onset of action in all studies. The effect on motility was seen as early as on the first day of treatment, and effects on abdominal pain, bloating and overall relief were typically seen within a week of initiating drug therapy. Tegaserod 6mg bid treatment resulted in a significant and sustained improvement in the global endpoint (overall relief) compared with placebo over the duration of the 12 week treatment phase.

Open-label Phase IV studies have been conducted in patients with IBS-C and non-D-IBS (Appendices 3 and 4). Two studies utilized a withdrawal and re-treatment design. This may be particularly relevant for conditions such as IBS which are characterized by a cyclical pattern of symptoms. These studies support the efficacy of tegaserod and have demonstrated responder rates of 68-82% for initial treatment (weeks 1-4) with tegaserod. On discontinuing tegaserod, symptoms recurred in up to 84% of responders to initial treatment and re-treatment resulted in responder rates similar to the initial treatment group of up to 89%. Thus, there is no loss of efficacy when patients are re-treated in these open-label studies. Further details on the remaining studies can be found in Appendix 3.

## 2. Efficacy of Tegaserod in IBS

The pivotal clinical trials reviewed in the NDA submission were B301, B307, B351 and 0358. Since the NDA submission, three further randomized controlled trials (RCTs) with prospectively defined endpoints (ASG01, AFI01, A2302) have demonstrated that tegaserod produces statistically significant improvement in global IBS symptoms compared to placebo. In addition, 9 open-label Phase IV studies (AGB02, AIC01, ADE02, ACH01, ABR01, ADE01, AES01, AIA03, ANL01) have been conducted worldwide in patients with IBS-C. Details of each study with respect to study design and efficacy results can be found in Appendices 1-4.

Studies ASG01 and AFI01 had similar study designs with a 2-week baseline period, 12-week treatment period and a 4-week withdrawal phase with no medication. This design was similar to 0358 except that study patients had non-D-IBS and came from the Asia-Pacific region (ASG01) or from Nordic countries (AFI01). The non-D-IBS patient population was chosen because clinical experience has shown that the predominant bowel habit is not always stable

and often alternates between constipation and diarrhea but the alternating pattern is not necessarily equally balanced between the two. Thus, while tegaserod had been proven to be effective and safe in IBS-C, it was important to evaluate it in a wider patient population.<sup>9</sup> In addition, efficacy in different ethnic groups could be assessed.

The primary efficacy variable was the patients overall relief during the first 4 weeks of treatment. General estimating equations were used to assess global IBS symptom improvement during weeks 1-4 and weeks 1-12 of the study. These studies demonstrated significant improvement in global IBS symptoms during weeks 1-4: OR = 2.61 (95% CI:1.89-3.61) p<0.0001 for study ASG01 and OR = 1.54 (95% CI:1.14-2.08) p<0.0049 for study AFI01. In addition, the longitudinal analysis of weeks 1-12 demonstrated significant improvement in global IBS symptoms: OR = 2.39 (95% CI:1.80-3.18) p<0.0001 for study ASG01 and OR = 1.78 (95% CI:1.35-2.34) p<0.0001 for AFI01. A longitudinal analysis may be more appropriate in an episodic disorder such as IBS which is characterized by waxing and waning of symptoms. When individual IBS symptoms of abdominal pain/discomfort, bloating, straining, or frequency of bowel movements are examined in both of these randomized controlled trials, improvements in essentially all of these individual IBS symptoms are demonstrated.

Study A2302 was conducted in China and consisted of a 2-week baseline period, a 4-week treatment period and a 2-week withdrawal phase with no medication. The primary endpoint was the patient's perception of overall symptoms of IBS, assessed weekly. Compared to placebo, the weekly severity of patients perception of overall IBS symptoms was significantly lower in the tegaserod group from week 1 and throughout the treatment period.

The primary outcome results for the 4 pivotal registration studies are shown in Table 1 and for the new RCTs in tables 2 and 3.

**Table 1. Response for SGA of relief at endpoint (primary variable) in pivotal randomized double-blind placebo controlled studies**

Study	N	Female %	Response rate, %			
			Tegaserod 6mg bid	Placebo	Therapeutic gain	p
B301	881	83	38.4	30.2	8.2	0.033
B351*	799	87	45.7	33.3	12.4	0.004
0358	1519	100	43.5	38.8	4.7	0.033
B307**	845	84	42.2	37.0	5.2	0.142

\*Post-hoc analysis definition

\*\*Dose titration design

**Table 2. Responder rate for primary outcome\* in randomized double-blind placebo controlled studies ASG01 and AFI01**

Study	N	Female %	Responders for Primary Outcome, %			
			Tegaserod	Placebo	Therapeutic	p

			6mg bid		gain	
ASG01	520	88	55.8	34.8	21.0	<0.0001
AFI01	647	86	26.4	19.1	7.3	<0.0049

\*Based on GEE analysis weeks 1-4

**Table 3. Therapeutic gain (Odds Ratio) over placebo for overall satisfactory relief: Weeks 1- 4 (primary analysis) in studies ASG01, AFI01, A2302**

Study	OR	95% CI	P
ASG01	2.61	1.89-3.61	<0.0001
AFI01	1.54	1.14-2.08	<0.0049
A2302*	1.89	1.39-2.43	<0.0001

\*A2302 has different endpoint to ASG01 and AFI01

These RCTs demonstrate robust study design and have met essentially all of the study design criteria defined by ROME II: a Multi-national Consensus Document on Functional Gastrointestinal Disorders<sup>17</sup>, including use of concealed allocation, appropriate double-blinding, use of the ROME criteria to identify IBS patients, complete follow-up of patients, no placebo run-in, baseline observation of patients to assess symptoms, treatment duration of 8 to 12 weeks or longer (except study A2302), follow-up after treatment to assess symptoms, compliance with treatment is measured, sample size calculations were performed and adequate sample sizes were enrolled. The primary outcome of these trials was improvement in global IBS symptoms, in keeping with the Rome recommendations, and this was determined based on the patients' assessment of improvement of their symptoms.

There are no set rules for defining the magnitude of response seen in clinical trials for IBS that constitutes a clinically meaningful benefit. Indeed clinical trial design in this field is fraught with challenges.<sup>17</sup> The condition being treated is polymorphous, there are many possible endpoints, and early trials have been difficult to evaluate because of inadequate patient definition. Furthermore, there is a strong placebo response seen in clinical trials.<sup>28</sup> A variety of reasons for this have been discussed by experts in this field and include the "care effect" meted out by health care professionals conducting the trial. The effect of placebos seems to encompass such disparate elements as anxiety, conditioning, expectation, the healer's persona, and the attachment of meaning to illness. It is also easy to confuse their effect with the natural course of the disease being treated.<sup>29</sup>

By definition, IBS is a clinical condition characterized by multiple symptoms, with no biological or morphological markers that can be used as primary outcome measures of efficacy in clinical studies.<sup>18</sup> It is thus appropriate to judge the efficacy of treatment on the basis of changes in symptoms. This is endorsed by the Rome committee guidelines which have recommended a global outcome measure.<sup>17</sup> As a result, a number of validated scales have been utilized such as The Subjects Global Assessment of Relief (SGA)<sup>30</sup>, the Global Improvement Scale (GIS)<sup>31</sup>, Adequate Relief<sup>32</sup> and Satisfactory Relief<sup>9</sup>.

In addition to assessing a global response, the effect of the drug on individual symptoms should also be determined. A clinically meaningful response is therefore one in which the patient feels benefit from an overall perspective, as well as benefit for individual symptoms.

It is important to differentiate IBS from a chronic static disorder such as hypertension, where effects of the treatment at the end of the clinical trial are most relevant to estimate the clinical benefit of the drug and therefore to estimate effect size. In contrast, IBS is a chronic relapsing disorder with fluctuating symptoms.<sup>33,34,35</sup> Thus, in order to evaluate the magnitude and consistency of drug effect in IBS, it is clinically appropriate to view results of treatment throughout the entire study period. In the case of all the pivotal randomized double-blind placebo controlled studies (B301, B307, B351 and 0358) this was 12 weeks. Of note, this was the approach used for the alosetron studies in diarrhea-predominant IBS and accepted by the FDA. In this context, based on discussions at the June 26, 2000 Gastrointestinal Drug Products Advisory Committee, Novartis proposed to the FDA that the average monthly response (i.e. longitudinal analysis) be used as the primary efficacy variable for study 0358 rather than using an endpoint analysis. However, FDA asked Novartis to retain the endpoint analysis for study 0358.

When a longitudinal analysis is conducted, this shows an 8-10% (adjusted) and 9-12% (unadjusted) therapeutic gain for tegaserod 6mg bid in studies B301 and 0358 (Table 4).

The FDA had asked Novartis to include a laxative adjustment for determining response rates (adjusted data in Table 8). Laxative adjustment meant that a single day of laxative use during the last four weeks of the study (i.e. endpoint) resulted in a non-responder classification irrespective of the magnitude of relief. Thus, response rates with the laxative adjustment do not provide a reasonable estimate of the likely clinical benefit that would be derived in clinical practice in which the occasional use of laxatives is expected.<sup>23</sup> The effectiveness of tegaserod and therefore its benefit in clinical practice, may be better evaluated by unadjusted response rates, as also shown in Table 8. Approximately 50% of patients had a positive response (unadjusted response) to tegaserod at the end of the 12-week treatment in patients on 6mg bid in the pivotal studies.

**Table 4. Placebo subtracted SGA of Relief response rates for tegaserod 6mg bid (tegaserod 4-6mg bid in study 307) in pivotal clinical trials (ITT)**

Study		Adjusted <sup>1</sup>			Unadjusted		
		Month 1	End-point	Longitudinal	Month 1	End-point	Longitudinal
B301	Response (%)	12.5%	8.3	9.6%	13.2%	11.8	12.2%
	p value	<0.001	0.033	0.001	<0.001	0.004	<0.001
0358	Response (%)	12.8%	5.3	7.9%	14.3%	6.6	9.3%
	p value	<0.001	0.033	<0.001	<0.001	0.001	<0.001

B351 <sup>2</sup>	Response (%)	10.5%	12.4	8.9%	13.8%	14.3	11.2%
	p value	0.009	0.004	0.005	0.002	0.001	0.001
B307 <sup>3</sup>	Response (%)	13.4%	6.0	6.9%	15.5%	7.3	9.4%
	p value	<0.001	0.142	0.035	<0.001	0.070	0.004

<sup>1</sup> Adjusted: Patient considered a non-responder for any laxative use. Any missing week = non-response for month 1 and longitudinal analysis; endpoint analysis = last 4 available SGA values.

<sup>2</sup> In study B351, response criterion was defined retrospectively.

<sup>3</sup> Results are for dose-titration group (4-6mg bid). ITT=intent-to-treat.

Factors to take into consideration when assessing the efficacy of a drug are:

How rapid is the onset of action?

Is there a significant benefit over placebo?

Is the effect sustained over time?

Tegaserod showed rapid onset of action in all studies. The effect on motility could be seen as early as on the first day of treatment, and effects on abdominal pain, bloating and overall relief were typically seen within a week of initiating drug therapy. Tegaserod 6mg bid treatment resulted in a significant and sustained improvement in the global endpoint (overall relief) compared with placebo over the duration of the treatment phase in these studies. This was 12 weeks in all the pivotal double blind, randomized controlled studies (B301, B307, B351 and 0358). Study 0358 included an observation period of 4 weeks following treatment discontinuation. The improvement in SGA of Relief observed during treatment decreased after drug discontinuation to similar degrees in patients randomized to tegaserod or placebo. This was consistently demonstrated in studies ASG01 and AFI01 which also included similar withdrawal periods. Thus, there was no “rebound” in IBS symptoms following withdrawal of tegaserod.

In addition, several open label studies have been conducted which continue to support the efficacy of tegaserod. AGB02 and ADE02 utilized a withdrawal and re-treatment design respectively. This may be particularly relevant for conditions such as IBS which are characterized by a cyclical pattern of symptoms. These studies have demonstrated responder rates of 68-82% for initial treatment (weeks 1-4) with tegaserod. On discontinuing tegaserod, symptoms recurred in up to 84% of responders to initial treatment and re-treatment resulted in responder rates similar to the initial treatment group of up to 89%. Thus, there is no loss of efficacy when patients are re-treated. The results of the primary efficacy variables for AGB02 and AIC01 are shown in Table 5, and those for ADE02 in Table 6.

ACH01 was an 8 week open label study with optional extension periods of 12 weeks each. Responder rates were 70% at week 4, 76% at week 8 and 86% at week 20. There are some limitations to efficacy conclusions that can be drawn from open-label studies, but the results nevertheless have been positive.

Further details of studies not discussed in this section can be found in Appendix 3.

**Table 5. Effect of tegaserod and withdrawal of tegaserod on individual IBS symptoms in open-label studies GB02, AIC01**

Study	Responder Rate %	No recurrence of symptoms (%)		
		Weeks 1-4	Tegaserod arm	Withdrawal arm
AGB02	68	87	58	<0.0001
AIC01	81.6	90.2	33.1	<0.0001

**Table 6. Effect of tegaserod, tegaserod withdrawal and tegaserod re-treatment in study DE02 (ITT)**

Study	Initial treatment period Weeks 1-4 n=513	Initial treatment period Weeks 1-12 n=513	Withdrawal period n=403	Re-treatment period N=307
	Responder rate %	Responder rate %	Relapser rate %	Responder rate %
ADE02	75	85	84	89

In conclusion, tegaserod 6mg bid is clearly and consistently more efficacious than placebo for improvement in global IBS symptoms and for improvement of individual symptoms such as abdominal pain/discomfort, bloating and constipation (stool frequency, stool consistency and straining).

## American College of Gastroenterology Recommendations

A systematic review on the management of Irritable Bowel Syndrome in North America was conducted by the American College of Gastroenterology Functional Gastrointestinal Disorders Task Force.<sup>3</sup> Standard criteria for systematic reviews were met, including comprehensive literature searches, use of pre-specified study selection criteria, and use of a standardized and transparent process to extract and analyze data from studies. A North American perspective was chosen, including only treatments that are available in the United States. Evidence based recommendations were based on analyses of these data by the entire Task Force. Recommendations were graded using a formalized system that quantified the strength of evidence, which are shown in Table 7.

The Tegaserod clinical trials for the treatment for IBS with constipation received a Grade A recommendation based on Level I evidence.

**Table 7. Levels of Evidence and Grading of Recommendations**

Level I Evidence	Randomized controlled trials with p values <0.05, adequate sample sizes and appropriate methodology
Level II Evidence	Randomized controlled trials with p values >0.05, and/or inadequate sample sizes and/or inappropriate methodology
Level III Evidence	Nonrandomized trials with contemporaneous controls
Level IV Evidence	Nonrandomized trials with historical controls
Level V Evidence	Case studies
Grade A Recommendation	Recommendations supported by Level I evidence
Grade B Recommendation	Recommendations supported by Level II evidence
Grade C Recommendation	Recommendations supported by Level III-IV evidence

### 3. Individual study summaries: double-blind studies in IBS-C

#### Study B351

Study B351 was a randomized, double-blind, placebo-controlled, multicenter study to assess the safety and efficacy of tegaserod at two dose levels in subjects with IBS with constipation (IBS-C). The study was conducted in 52 centers: 3 in Canada and 49 in the USA.

**Methodology:** A 16-week, randomized, double-blind, double-dummy, prospective, parallel group, multicenter study in outpatients with IBS-C. Following the 4-week baseline period, patients were randomized, in equal allocation to receive either placebo, 2 or 6mg bid tegaserod for 12 weeks (bid regimen).

**Selection criteria:** Included were male and female patients aged 12 years or older with a diagnosis of IBS with constipation and at least mild abdominal discomfort/pain as determined by the Visual Analogue Scale (VAS) during the baseline period.

**Criteria for Efficacy evaluation:** The primary efficacy variables were the SGA of relief and the SGA of abdominal discomfort/pain. Secondary efficacy variables were the SGA of abdominal discomfort/pain, SGA of bowel habit, percentage of days with significant abdominal discomfort/pain and significant bloating, bowel movements frequency, and stool consistency. The data were retrospectively analyzed for SGA of relief with a post-hoc definition applied as described in Table 27. There has been no consensus on the primary outcome measure to be used in treatment trials of IBS. After consultation with external advisors and the FDA, the original primary outcome measures applied in this study suggested that the definition of response was too restrictive and therefore lacked the sensitivity to detect a significant treatment effect. The post-hoc definitions of response were agreed upon with the FDA and were used to prospectively define the primary variable for studies B301 and 0358.

**Table 27. SGA of relief: original and post-hoc definitions of response**

	Response criteria
Original SGA of relief	Complete or considerable relief $\geq$ 50% of the time at endpoint*
SGA of relief (post-hoc analysis)	Complete or considerable relief $\geq$ 50% of the time at endpoint* OR Complete or considerable or somewhat relief for 100% of the time at endpoint*

\* Endpoint: last 4 weeks of treatment

**Results:** 799 patients were randomized (tegaserod 2mg bid: 265, tegaserod 6mg bid: 267, placebo: 267). The population was predominantly female (87.2%), with an average age of 43 years and 87.9% Caucasian.

**Efficacy:** Both treatment groups had higher response rates compared to placebo. See Table 28.

**Table 28. Responder rates for the original SGA of relief, SGA of abdominal discomfort/pain and SGA of relief<sup>1</sup> by treatment at endpoint (ITT population)**

Efficacy variable	Responder rate (%)			P-Value <sup>2</sup>	
	2mg bid	6mg bid	Placebo	2mg bid	6mg bid
Original SGA of relief	29.4	26.2	22.1	0.049	0.266
SGA of discomfort/pain	23.4	25.1	18.7	0.184	0.074
SGA of relief <sup>1</sup>	38.9	45.7	33.3	0.157	0.004*

<sup>1</sup>Post-hoc analysis definition; <sup>2</sup> Compared with placebo; \* Indicates a statistically significant difference compared to placebo based on Hochberg's multiple comparison procedure, adjusting for two tegaserod doses, at significance level of 0.05

The primary and secondary efficacy variables showed consistent trends for a treatment effect for tegaserod compared with placebo. Statistically significant improvements in multiple symptoms of IBS, including abdominal discomfort/pain, abdominal bloating and bowel habits (stool frequency and stool consistency), were seen in the 6mg bid treatment group compared with placebo. The consistency of the data both in the weekly SGAs and the daily diary variables, as well as the effects at multiple time-points, demonstrate that the data are robust and that a treatment difference for tegaserod compared with placebo exists.

Immediately after starting treatment, all treatment groups showed improvement. At Week 1, the proportion of patients at least "somewhat relieved" was 57.9% and 62.4% for the 2mg bid and 6mg bid tegaserod groups, compared to 43.7% for the placebo group. The 6mg bid treatment group was consistently higher than placebo group, throughout the treatment period.

## Study B301

Study B301 was a randomized, double-blind, placebo-controlled, multicenter study to assess the safety and efficacy of tegaserod at two dose levels in subjects with IBS-C. This study was conducted in 92 centers: 18 in the UK, 15 in Germany, 12 in The Netherlands, 9 in Switzerland and in the USA, 7 in Italy, 6 in Turkey and in South Africa, 4 in Finland, 3 in Austria, 2 in Spain and 1 in Portugal.

**Methodology:** This was a 16-week, prospective, parallel group, double-dummy, multicenter study in patients with IBS-C. Following the 4-week baseline period, patients were randomized, in equal allocation, to receive either placebo, 4 or 6mg bid tegaserod for 12 weeks (bid regimen).

**Selection criteria:** Included were male and female patients aged 18 years or older with IBS with constipation and at least mild abdominal discomfort/pain as determined by a Visual Analogue Scale (VAS) during the baseline period.

**Criteria for efficacy evaluation:** The outcome for the primary analysis was based on the SGA of relief at endpoint (last 4 weeks of treatment). Secondary efficacy variables were the SGA of abdominal discomfort/pain, SGA of bowel habit, percentage of days with significant abdominal discomfort/pain and significant bloating, bowel movements frequency, and stool consistency. **Results:** 881 patients were randomized. (tegaserod 4mg/d: 299 patients, tegaserod 12/mg/d: 294 patients, placebo: 288 patients). The population was predominantly female (83.3%), with an average age of 46 years, and 98% Caucasian.

**Efficacy:** A clinically relevant and statistically significant effect was demonstrated for the primary efficacy outcome variable, SGA of relief, with both doses, 4 and 6mg bid (Table 29). The effect had an early onset and was sustained during the course of the treatment period. Furthermore tegaserod therapy was associated with a statistically significant reduction in abdominal discomfort/pain, and with an increase in the number of bowel movements. The remaining secondary variables showed a trend for a favorable treatment effect.

**Table 29. Responder rates for the SGA of relief at endpoint (ITT population)**

Primary efficacy variable		Treatment group		
		2mg bid	6mg bid	Placebo
SGA of relief	Responder rate	38.8%	38.4%	30.2%
	p-value <sup>1</sup>	0.018*	0.033*	
Unadjusted <sup>2</sup> SGA of relief	Responder rate <sup>2</sup>	46.7%	46.3%	34.5%
	p-value <sup>1</sup>	0.002*	0.004*	

<sup>1</sup> compared with placebo <sup>2</sup> responder rate not adjusted for duration of treatment, laxative intake and absence of SGA of relief assessments.

\* statistically significant (p < 0.05)

In both tegaserod treatment groups the proportion of patients with at least “somewhat relief” was consistently higher than in the placebo group during the entire treatment period.

## Study 0358

Study 0358 was a randomized, double-blind, placebo-controlled, multicenter study to assess the safety and efficacy of tegaserod 6mg bid in females with IBS-C. The study was conducted in 131 centers in the US

**Methodology:** A prospective, double-blind, randomized, parallel group, multicenter study in female patients with IBS-C. Patients were randomized to receive either placebo or tegaserod 6mg bid. The study consisted of a screening period, a 4-week baseline period (no medication), a 12-week randomized double-blind treatment period with either placebo or tegaserod 6mg bid, followed by a 4-week withdrawal period (no medication).

**Criteria for Efficacy evaluation:** The primary efficacy variable was the SGA of relief. Secondary efficacy variables included: SGA of abdominal discomfort/pain (weekly), SGA of bowel habit (weekly), SGA of satisfaction with bowel habit (weekly), and daily assessments of abdominal discomfort/pain, abdominal bloating, number of bowel movements, stool consistency and straining at defecation.

**Results:** 1519 patients with IBS-C were randomized (767 tegaserod, 752 placebo). The population was all female, with a mean age of 41 years, and 77.4% Caucasian.

**Efficacy:** Compared with placebo, the tegaserod 6mg bid group had a statistically significantly higher response rate on the SGA of relief at endpoint, the primary efficacy outcome variable (Table 30). Higher response rates were observed for tegaserod treated patients than placebo treated patients at all monthly time-points. Almost 80% of patients who were responders at Month 1 remained responders at the end of the study. The effects of tegaserod were observed as early as Week 1.

**Table 30. Responder rates for the SGA of relief at endpoint (ITT population)**

Primary efficacy variable	Tegaserod 6mg bid (N=767)	Placebo (N=752)
Responder rate	43.5%	38.8%
Treatment difference in responder rate <sup>1</sup>	5.3%	
P-value <sup>1</sup>	0.033*	

<sup>1</sup> Weighted by center size.

\* Statistically significant at the two-sided significance level of 0.05.

Furthermore, at endpoint tegaserod therapy was associated with statistically significant improvements in: SGA of abdominal discomfort/pain scores, SGA of bowel habit scores, SGA of satisfaction with bowel habit, bloating scores, number of bowel movements, stool consistency and number of days with hard stools and straining. Tegaserod treatment had an early onset of action beginning in Week 1. Results for the primary efficacy variable, the SGA of relief, were robust and consistent with the secondary efficacy variables.

## Study B307

Study B307 was a randomized, double-blind, placebo-controlled, multicenter study to assess the safety and efficacy of tegaserod at two dose regimens in subjects with constipation-predominant irritable bowel syndrome. This study was conducted in 79 centers: 41 in the United States of America, 12 in France, 11 in the United Kingdom, 6 in Germany, 4 in Belgium, 3 in Canada, and 2 in Spain.

**Methods:** This was a 16-week prospective, parallel group, double-dummy, multicenter study in patients with IBS-C. Following the 4-week baseline period, patients were randomized, in equal allocation, to receive either placebo for 12 weeks, tegaserod 2mg bid fixed regimen for 12 weeks or a dose-titration regimen. For the purpose of dose-titration only, a non-responder was defined as a patient who after 4 weeks had less than 50% of the responses to the SGA of relief question answered “considerably relieved” or “completely relieved.” Patients randomized to the dose-titration group received tegaserod 2mg bid for Weeks 1-4; patients with unsatisfactory efficacy (non-responders) at Week 4 were up-titrated to 6mg bid for the remaining 8 weeks (Weeks 5-12) of blinded therapy; those patients with a satisfactory efficacy response (responders) at Week 4 remained on the 2mg bid dose. Patients randomized to the tegaserod 2mg bid fixed regimen group or placebo group who were non-responders at Week 4 underwent mock up-titration and remained on their originally assigned treatment for Weeks 5-12.

**Selection criteria:** The study recruited male and female patients aged 18 years or older with IBS-C with at least mild abdominal discomfort/pain as determined by the Visual Analogue Scale (VAS) during the baseline period.

**Criteria for efficacy evaluation:** The primary efficacy variable was the SGA of relief. Secondary efficacy variables were the SGA of abdominal discomfort/pain, SGA of bowel habit, percentage of days with significant abdominal discomfort/pain and significant bloating, bowel movements frequency, and stool consistency.

**Results:** There were 845 patients randomized (tegaserod 2mg bid: 283, tegaserod 4-6mg bid: 277, and placebo: 285). The population was predominantly female (83.6%), with an average age of 45 years, and 90.4% Caucasian.

**Efficacy:** The responder rate for the tegaserod 2-6mg bid group at endpoint was greater than placebo, but the difference did not reach statistical significance. The responder rates at endpoint of the tegaserod 2mg bid group and placebo group were similar (Table 31).

**Table 31. SGA of Relief - responder rates at endpoint (ITT population)**

Efficacy variable	Responder rate (%)		
	Tegaserod 2mg bid N=282	Tegaserod 4-6mg bid N=275	Placebo N=284
SGA of relief	38.3	42.2	37.0
p-value <sup>1</sup>	0.837	0.142	
Unadjusted SGA of relief <sup>2</sup>	44.9	48.5	41.2
p-value <sup>1</sup>	0.447	0.070	

<sup>1</sup>compared to placebo. <sup>2</sup>responder rate not adjusted for laxative intake, treatment duration, and number of SGA of relief assessments.

Tegaserod provided early relief of overall IBS-C symptoms. The onset of relief from IBS-C symptoms I as early as Week 1 and Month 1 of therapy. Although not statistically significant, trends favoring tegaserod were sustained throughout the entire treatment period. A greater relief from C-IBS symptoms was not observed following dose-titration. The lack of statistically meaningful differences observed at study endpoint between tegaserod and placebo was probably related to the dose-titration study design.

## Study A2302

Study A2302 was a randomized, double-blind, placebo-controlled, multicenter study to assess the safety and efficacy of tegaserod 6 mg b.i.d. in Chinese patients with IBS-C and was conducted in 12 centers in China.

**Methodology:** An 8-week, double-blind, randomized, parallel group, placebo-controlled, multicenter study with a 2-week baseline period (no medication), a 4-week randomized, double-blind treatment period with either tegaserod 6 mg bid or placebo (1:1), followed by a 2-week withdrawal period (no medication).

**Criteria for Efficacy evaluation:** The primary efficacy variable was the patient's perception of overall symptoms of IBS during the previous week and was assessed weekly. This primary efficacy variable was analyzed longitudinally by means of a generalized linear model, using generalized estimating equations (GEE) to estimate the parameters. The model included treatment, center and week (Weeks 1 to 4) as main factors.

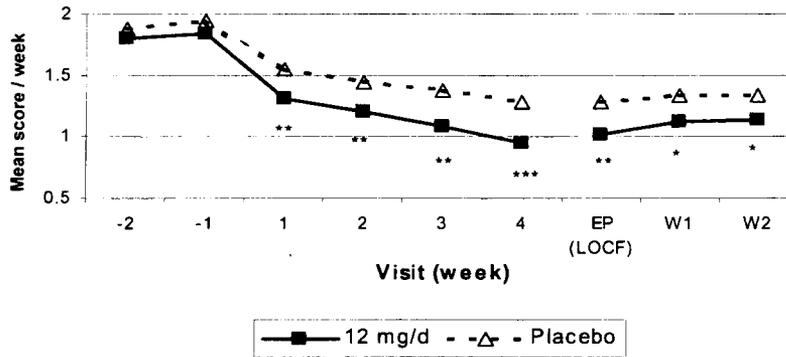
Secondary efficacy variables were severity of the patient's constipation (weekly assessment) and patient's assessment of their individual IBS symptoms (daily assessments).

**Selection criteria:** Included were male and female out-patients  $\geq$  18 years of age who met the Rome II criteria for IBS-C

**Results:** 510 patients were randomized (254 tegaserod and 256 placebo). 481 patients entered the withdrawal phase (236 tegaserod, 245 placebo). The patients entered into the study were all Oriental, were predominantly female (82%), and had a mean age of 39 years.

**Efficacy:** Compared to placebo, the weekly severity of patients perception of overall IBS symptoms, the primary efficacy parameter, was significantly lower (Weeks 1 – 4,  $p < 0.0001$ ) in the tegaserod group from Week 1 onwards and throughout the treatment period. All subgroups on tegaserod had approximately 25% better scores than similar subgroups on placebo. The effects of tegaserod on secondary IBS efficacy parameters showed consistently higher scores in the tegaserod group starting in Week 1 and lasting throughout the treatment period. During the withdrawal period, a trend toward reversal was seen, but both groups showed better scores relative to baseline with tegaserod retaining a significant treatment advantage over placebo ( $p = < 0.05$  Odds Ratio OR = 1.84) group (Figure 1).

Figure 1. Patients' perception of overall IBS symptoms



\*  $p \leq 0.021$  \*\*  $p \leq 0.002$  \*\*\*  $p \leq 0.0001$

Scores: 0 not at all, 1 somewhat, 2 moderately, 3 a good deal, 4 a very great deal

## Other studies

Other completed double-blind, placebo controlled studies in IBS-C are studies AIA04 and AIA12.

**Study AIA04** was a single center placebo-controlled parallel group study in patients with C-IBS to assess the effect on small bowel motility. Treatment duration was 4 weeks with tegaserod 6mg bid or placebo. A total of 13 patients (9 on tegaserod, 4 on placebo) participated. No significant effect on small bowel motility, especially on the motility index was observed.

**Study AIA12** was a randomized, double-blind, placebo-controlled, multicenter, multinational study to assess the effect of tegaserod on response to colonic distension in female C IBS patients, followed by an 8-week open label extension study. 54 were randomized into the double-blind phase of the study (24 on tegaserod 6 mg b.i.d. and 25 on placebo). Of the patients who completed the double-blind period, 48 entered and 41 completed the open label. The study showed no statistically significant difference between the treatment groups in terms of the primary efficacy variables (pressure eliciting pain threshold during the ascending procedure; pressure eliciting discomfort threshold during the tracking procedure, or slope and intercept of the intensity VD-VAS scale stimulus response curve during the fixed stimulus procedure). All treatment related adverse events were mild or moderate.

#### 4. Individual study summaries: double-blind studies in non-diarrhea IBS

##### Study ASG01

Study ASG01 was a multi-center, double-blind, placebo-controlled, randomized, parallel-group, fixed dose study to evaluate the efficacy, safety and tolerability of tegaserod in patients with Non-Diarrhea IBS (non-D IBS). This study was conducted in 57 centers in Asia Pacific: 15 in Korea; 6 in Taiwan; 10 in Australia; 6 in Thailand; 5 in the Philippines; 3 in Hong Kong; 4 in Malaysia; 3 in Singapore; 3 in New Zealand; and 2 in Indonesia.

**Methods:** This was a multicenter, double-blind, placebo-controlled, randomized, parallel-group, fixed dose study in patients with non-D IBS (as defined by the Rome II criteria). Following a 2-week baseline period (no medication or placebo), patients were randomized to receive either placebo or tegaserod 6mg bid for 12 weeks followed by a 4-week withdrawal period (no medication or placebo).

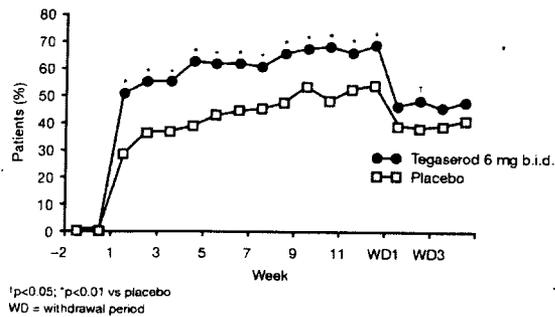
**Selection criteria:** Included were male or female patients aged 18 to 65 years, with a diagnosis of IBS not satisfactory relieved during baseline, with discomfort/pain > 1.0 on the 4-point scale (0 to 3) during the baseline period, and at least one of the following during the baseline period: one episode of < 3 bowel movements per 7 days; or/and one defecation of hard or very hard stools; or/and one defecation/attempted defecation connected with straining.

**Criteria for efficacy evaluation:** The primary efficacy variable was the patient's overall relief during the first 4 weeks of treatment (overall satisfactory relief was measured weekly); this measurement was collected in the patient diary on a weekly basis. Overall relief was measured during the short-term (first 4 weeks of the double-blind treatment period), and long-term (entire 12 weeks of the double-blind treatment period). Secondary efficacy variables included self-assessment on a daily basis in the patient diary for: abdominal discomfort/pain, bloating, stool frequency, stool consistency, sensation of complete bowel evacuation, urgency and straining, during the short-term (4 weeks) and long-term (12 weeks) period.

**Results:** 520 patients were randomized (259 tegaserod 6mg bid, 261 placebo).

**Efficacy:** Increases in the number of patients with satisfactory relief were observed from Week 1 in both groups, most notably in the tegaserod 6mg bid group. This effect was observed at all time-points from Week 1 to Week 12, with the degree of therapeutic gain being consistent throughout (Figure 2). At Weeks 1 to 4 (primary endpoint;  $P < 0.0001$ ) and Weeks 1 to 12 ( $P < 0.0001$ ), the proportion of patients with satisfactory relief was significantly greater in the tegaserod 6mg bid group, regardless of the inclusion of covariates. The therapeutic gain over placebo was demonstrated by odds ratios of 2.61 at Weeks 1 to 4, and 2.39 at Weeks 1 to 12.

Figure 2: Patients with overall satisfactory relief from IBS symptoms in study ASG01 (ITT population; N = 520)



In general, reductions in abdominal discomfort/pain, bloating, stool consistency, and the number of days with no bowel movements were significantly greater in the tegaserod 6mg bid group than in the placebo group at all endpoints analyzed and were significantly greater in the tegaserod 6mg bid group than placebo at most weeks during the treatment period. Increases in the number of bowel movements (at Weeks 1 to 4) and decreases in hard/lumpy stools (Weeks 1 to 12) were also significantly greater in the tegaserod 6mg bid group than in the placebo group. Few significant differences were observed for changes in urgency, the number of days with a sensation of incomplete evacuation or normal stools, and straining.

## Study AFI01

Study AFI01 was a multi-center, multinational, double-blind, placebo-controlled, randomized, parallel-group, fixed dose study to evaluate the efficacy, safety and tolerability of tegaserod in patients with Non-D IBS. This study was conducted in 91 centers: 23 in Denmark, 21 in Finland, 1 in Iceland, 23 in Norway and 23 in Sweden.

Methods and Selection criteria were the same as in study ASG01.

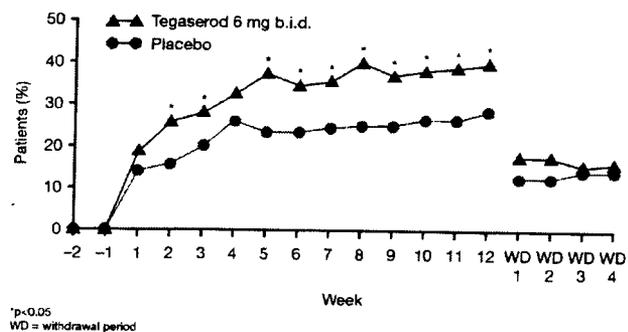
**Results:** 647 patients were randomized (327 tegaserod 6 mg bid , 320 placebo).

**Efficacy:** Increases in the number of patients with satisfactory relief were observed from Week 1 in both groups, most notably in the tegaserod 6 mg bid group. This effect was observed at 10 of 12 time-points from Week 1 to Week 12, with the degree of therapeutic gain being consistent throughout. At Weeks 1 to 4 (primary endpoint;  $P < 0.006$ ) and Weeks 1 to 12 ( $P < 0.003$ ), the proportion of patients with satisfactory relief was significantly greater in the tegaserod 6 mg bid group, regardless of the inclusion of covariates. The therapeutic gain over placebo was demonstrated by odds ratios of 1.54 at Weeks 1 to 4, and 1.78 at Weeks 1 to 12.

There were no statistically significant differences between the treatment groups during the first 4 weeks of treatment and in the last 4 weeks of treatment in abdominal pain/discomfort and abdominal bloating. However, the number of days with “no bowel movements” and “hard/very hard stools” during the first 4 weeks of treatment were 1.7 and 3.3 days less in the tegaserod group than in the placebo group (95% CI [1.0,2.4],  $p < 0.0001$  and [2.0,4.6],  $p < 0.0001$ ). In addition, the reductions from baseline were also statistically significantly greater in the tegaserod group than in the placebo group for the number of days with straining and sensation of incomplete evacuation during the first 4 weeks of treatment and the last 4 weeks of treatment. Increases were seen in the number of days with more than three bowel movements, loose/watery stools, and urgency, with these increases being significantly greater in the tegaserod group than in the placebo group during the first 4 weeks of treatment and the last 4 weeks of treatment, except for urgency (significant during the first 4 weeks only).

It is concluded that tegaserod 6 mg bid is effective in the treatment of patients from the Nordic area suffering from IBS without diarrhea as primary bowel symptoms

Figure 3 Patients with overall satisfactory relief from IBS symptoms in study AFI01 (ITT population; N = 644)



## 5. Individual study summaries: open-label studies in IBS-C

### Study AGB02

Study AGB02 investigated the recurrence of symptoms after withdrawal of treatment, in comparison to continuation of treatment, in patients with IBS-C responding favorably to treatment with tegaserod. This was carried out in 67 centers in the United Kingdom.

**Methodology:** This was a randomized, open-label, parallel group, multi-centre trial in patients with IBS-C receiving tegaserod 6mg bid. Following the 4-week screening period, patients received 4 weeks of treatment with tegaserod to determine whether the patient responded to treatment. Patients who responded to treatment were randomized (equal allocation) to either continue on tegaserod or to withdraw from treatment for 8 weeks. In the withdrawal arm, if they had a relapse of symptoms during the 8-week period, 4 weeks of treatment was given, and then they completed the study. In the treatment arm, if they relapsed during the 8-week period they were withdrawn from the study. If they completed the 8-week treatment period without a relapse of symptoms, treatment was stopped for 8 weeks and they completed the study. If during this 8-week period they had a relapse they were offered a further 4 weeks of treatment.

**Selection criteria:** Included were male and female patients 18 years of age and over with IBS whose main symptoms were abdominal pain or discomfort and constipation.

**Criteria for efficacy evaluation:** The primary efficacy variable was the proportion of patients who had a recurrence of symptoms at the end of the randomized comparative period, as derived from their weekly Overall Relief Assessment (ORA). Secondary efficacy variables were the percentage of responders in the group of patients who completed the initial treatment phase, as derived from their weekly ORA and the recurrence or not of symptoms at the end of the randomized comparative period, as derived from the weekly scores of symptoms of pain and bloating, frequency of bowel movements, and stool consistency.

**Results:** 519 patients were screened and 500 were enrolled onto treatment. Patients were mainly female (88%), and 98% were Caucasian. Of the 274 responders, 271 were randomized to either continue on tegaserod (n=130), or to withdraw from treatment (n=141), for 8 weeks. 214 patients completed the study, 98 patients in the treatment-continuation arm, and 116 patients in the treatment-withdrawal arm.

**Efficacy:** A significant percentage of patients responded to treatment in the initial treatment phase. Of the 410 patients who completed the initial 4 weeks of treatment with tegaserod 6mg bid, 274 (68%) experienced satisfactory relief of symptoms. At the end of the 8-week comparative phase, the proportion of patients who had a recurrence of symptoms, was significantly lower in the treatment-continuation arm, as compared with the treatment-withdrawal arm ( $p < 0.0001$ ). 87% (90/104) of patients maintained on tegaserod for 12 weeks had no recurrence of symptoms. This compares with the treatment-withdrawal arm, in which 58% (61/105) of patients had no recurrence of symptoms at the same time-point. The results of the recurrence of symptoms, as derived from the ORA, are summarized in Table 32.

**Table 32. Recurrence of symptoms: Intent to Treat population**

		All Patients		P-value
		Yes N(%)	No N(%)	
Comparative Phase Week 4	Continuation Arm	10(7.7%)	111(85.4%)	
	Withdrawal Arm	93(66.0%)	37(26.2%)	
Comparative Phase Week 8	Continuation Arm	14(10.8%)	90(69.2%)	<0.0001
	Withdrawal Arm	44(31.2%)	61(43.3%)	

There was a statistically significant effect of treatment on the individual scores for symptoms of bloating and pain at the end of the 8-week comparative phase (bloating:  $p < 0.0225$ ; pain:  $p < 0.0322$ ). There was no significant effect of treatment on the individual scores for stool frequency ( $p < 0.2624$ ).

### Study AIC01

Study AIC01 investigated the recurrence of symptoms after withdrawal of treatment, in comparison to continuation of treatment, in patients with IBS-C responding favorably to treatment with tegaserod. This study was conducted in 90 centers in Latin America: Argentina: 19, Brazil 5, CAC 3, Chile 4, Colombia 16, Ecuador 4, Mexico 16, Peru 4, Venezuela 17, Uruguay 1

**Methodology:** A randomized, open-label, parallel group, multi-centre trial in patients with IBS-C receiving tegaserod 6mg bid. A 2-week screening period without treatment provided the baseline measure of symptoms and was followed by a 4 week initial treatment period. At the end of that period, the patients who responded favorably were randomized to either continue or discontinue tegaserod in the comparative period. Patients were assessed for persistence of response or relapse after four weeks and eight weeks.

**Selection criteria :** Included were male and female patients aged at least 18 years with a diagnosis of IBS whose main symptoms are abdominal pain or discomfort and constipation (Rome II criteria) .

**Criteria for efficacy evaluation:** The primary efficacy assessment was the Overall Relief Assessment to define responders and recurrence of symptoms.

**Responder:** A patient was considered as responder when satisfactory relief was obtained for at least two of the four weeks.

**Recurrence:** A patient who had responded, was considered as having recurrence when satisfactory relief was not obtained for at least three out of the four weeks.

Secondary efficacy variables included evaluation of pain and bloating, daily symptoms of stool frequency, and weekly overall relief assessment.

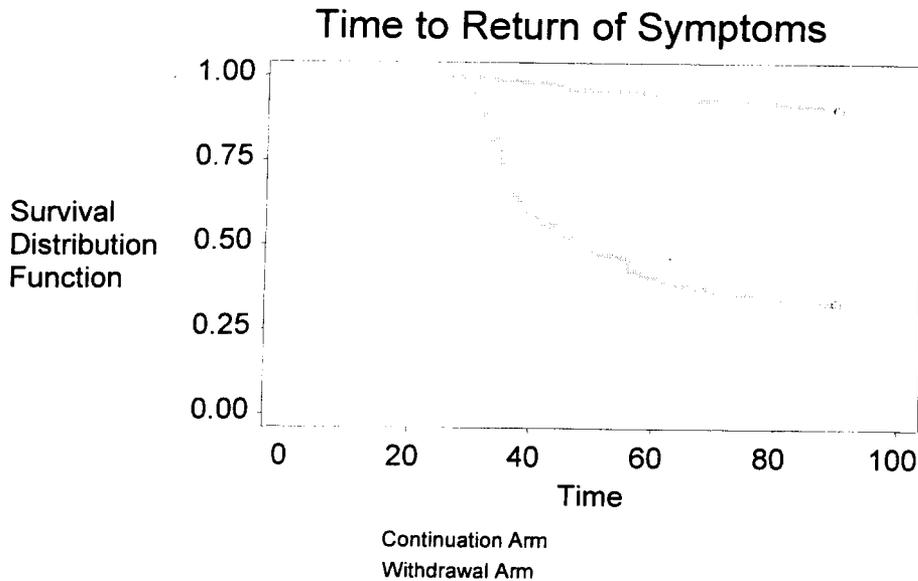
**Results:** 718 patients were screened and 678 were enrolled in the study. There were 544 responders who were randomly allocated to one of the groups: 276 to continuation arm and 268 to withdrawal arm. 449 patients completed the study. Demographic characteristics and

baseline symptoms were similar in all patients. The population was 91.9% female and 8.1% male, and 49.9% was Caucasian and 47.6% were classified as pertaining to other race (Hispanic). The mean age of the patients was 49.24 years.

**Efficacy:** 553 out of 678 enrolled patients (81.6%) were responsive to four weeks of tegaserod treatment. Patients were then assigned to either the continuation arm (n=276) or the withdrawal arm (n=268). 66.9% of the withdrawal arm patients experienced a recurrence of the symptoms during the study and only 9.8% of the continuation arm patients experienced recurrence ( $p < 0.0001$ ). The odds ratio for recurrence of symptoms in the withdrawal group was 18.7. The median time to symptom recurrence was 21 days for patients in this withdrawal group.

There were no significant differences in all efficacy assessments during baseline and month 1 when all patients received tegaserod. During months 2 and 3, there were significant differences between the groups ( $p < 0.0004$ ). Once tegaserod was withdrawn over two thirds of patients relapsed within 3 weeks. There were significant differences between the groups for pain, bloating, daily symptoms of stool frequency and weekly overall relief assessment in Months 2 and 3 ( $p < 0.0004$ ).

**Figure 7.** Time to symptom recurrence: maintenance arm versus withdrawal arm



## Study ADE02

Study ADE02 was an open, multicenter study with tegaserod 6mg bid for two treatment intervals of different length interrupted by a withdrawal period in patients with irritable bowel syndrome with constipation in a primary care setting. This was conducted in 89 centers in Germany.

**Methodology:** A multicenter, open-label, single-arm study. A 2-week screening period without treatment was followed by a 12-week initial treatment period, recording symptoms and weekly assessment of overall satisfaction. All patients then discontinued treatment. Non-responders discontinued the study. Responders were assessed for relapse at 4 and then at 8 weeks; in addition, patients were instructed to report to the investigator immediately in case of occurring relapse. Patients without relapse within these 8 weeks discontinued the study. Patients who relapsed during the withdrawal period received another 4-week course of treatment.

**Selection criteria:** Included were male and female patients with IBS with constipation (Rome II criteria).

**Results:** A total number of 543 patients was screened. A total of 532 patients (97.97%) was enrolled in the study at visit 2. 513 patients (94.4%) were exposed to the study medication. The majority of patients were women (73%) and Caucasian (99%). The mean age was 52 years. 383 of 543 patients (70.5%) completed the study.

403 of the 436 patients were eligible for the withdrawal period (ITT) as they were responders in the initial treatment period. 307 of the 338 patients (ITT) were eligible for the re-treatment period as they were relapsers during the withdrawal period.

**Efficacy:** Responder rates, defined as patients with satisfactory relief from IBS symptoms, were high in the initial treatment period as well as in the re-treatment period.

A total of 386 (75.24%) out of 513 patients was considered as responders and 127 (24.76%) as non-responders to the study medication on day 29.

On day 85 a total of 391 (76.22%) out of 513 patients was considered as responders and 122 patients (23.78%) as non-responders to the study medication.

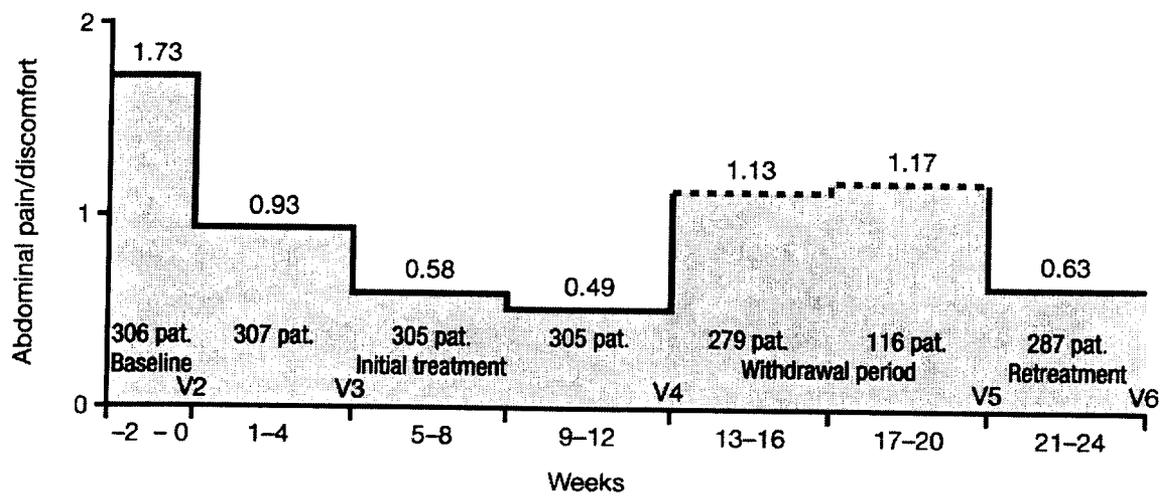
A total of 436 (84.99%) out of 513 patients were considered as responders on day 29 and/or on day 85.

In the withdrawal period, 83.87% of patients were relapsers and in the re-treatment period, 89.25% of patients were considered responders. (ITT)

In the per-protocol analysis, 95.11% of patients were considered as responders on day 29 and/or on day 85. In the withdrawal phase, 86.52% patients were relapsers and in the re-treatment phase 96.19% of patients was considered responders.

In the initial tegaserod treatment phase, and in the re-treatment phase, improvements in abdominal pain/discomfort and bloating were reported. In addition, stool frequency and consistency improved and this was accompanied by a decrease in straining.

Figure 5 Mean abdominal pain/discomfort score in patients enrolled in retreatment phase



## **6. Individual study summaries: Other open-label studies in IBS-C**

The following open-label studies in IBS-C have also been completed, but conclusions that can be drawn from them are limited either due to pending data analysis or poor quality: ABR01, ADE01, AES01, AIA03, ANL01.

ABR01 was a three month open label study in IBS-C patients with unsatisfactory response to other therapies for IBS-C conducted at a single center in Brazil. However, only 18 patients were enrolled. 88.2% of patients were considered responders at endpoint, but the small numbers preclude any meaningful conclusions.

ADE01 was a three month open-label study with IBS-C patients who had previously been successfully treated with cisapride or responding unsatisfactorily to other previous therapies. The study was conducted in 35 sites in Germany. Tegaserod 6 mg b.i.d. was administered for 12 weeks. Daily recording of pain and bloating, and weekly assessment of overall satisfaction by diary. 212 patients were enrolled, 166 completed the study and 46 were prematurely withdrawn. Patients with satisfactory relief from IBS symptoms were 64% after 4 and 70% after 12 weeks of treatment. During the duration of the study there was a decrease in abdominal pain/discomfort and in bloating. The mean stool frequency increased and the mean stool consistency softened, accompanied by an increase in urgency for defecation and a decrease in straining. Sense of incomplete evacuation remained nearly unchanged during treatment.

AES01 was a three month open label study in IBS-C patients in 30 centers in Spain. 210 patients were enrolled. The results of this study are in the process of being analyzed.

AIA03 was a double-blind, randomized, parallel group, placebo-controlled multicenter, study in female IBS-C patients, conducted in Mexico, Brazil, and Argentina. The study consisted of a 2-week baseline period (no placebo, no medication), a 2-week randomized double-blind treatment period with either placebo or tegaserod 6 mg b.i.d. followed by a 10-week tegaserod 6 mg b.i.d. open label treatment period. Objective was to investigate the effect of tegaserod on the distension pressure required to elicit moderate abdominal pain during the fasting and post-prandial periods in constipation predominant IBS (IBS-C) female patients. Fifty-eight patients were evaluable (29 in each group) for the safety analysis and 23 and 24 were evaluable for the primary efficacy analysis in the tegaserod and placebo groups, respectively. There was no statistically significant difference between tegaserod 6 mg b.i.d. and placebo in the relative pressure change for moderate abdominal pain, the relative volume change for moderate abdominal pain, the relative pressure change for first sensation or rectal compliance. Tegaserod was well tolerated for up to 10 weeks.

ANL01 was a multicenter, open-label, randomized, parallel group study in IBS-C patients using a withdrawal design. The study was conducted in 112 sites in the Netherlands. After 1 month initial treatment with tegaserod, responders were randomized to either continue or discontinue tegaserod. Patients were assessed for persistence of response after 1 and 2 months. At the final visit in the comparative period, pts were allowed to remain on treatment

for as long as he/she continued to benefit from the treatment. 506 were enrolled and 340 randomized (167 in continuation group, 173 in withdrawal group). The results of this study are in the process of being analyzed.

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