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Drug Regulatory Affairs

Zelnorm<sup>®</sup>

for the treatment of Patients with Chronic Constipation

sNDA 21-200

**Briefing Document**

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**Table of contents**

1	Objectives .....	6
2	Executive Summary.....	6
3	Background on Constipation .....	8
3.1	Epidemiology.....	8
3.2	Defining constipation.....	9
3.3	Therapeutic options .....	10
4	Zelnorm Development Rationale .....	12
5	Zelnorm Clinical Program in Chronic Constipation .....	14
5.1	Study Design.....	14
	Dose selection rationale.....	15
5.2	Patient population .....	15
5.2.1	Rationale .....	15
5.2.2	Eligibility Criteria .....	15
5.3	Statistical Considerations.....	16
5.3.1	Sample size and Power calculation .....	16
5.3.2	Rationale for selecting the efficacy variables .....	16
5.3.3	Efficacy evaluation.....	17
6	Efficacy results in Chronic Constipation.....	18
6.1	Demographic and baseline disease characteristics .....	18
6.2	Primary Efficacy results .....	22
6.3	Other Responder Analyses (Secondary efficacy) .....	23
6.4	Early effect and durability of treatment response.....	24
6.5	Effect of Zelnorm on multiple symptoms of constipation.....	28
6.5.1	Daily Diary questions.....	28
6.5.2	Effect on bothersomeness of symptoms of constipation.....	32
6.5.3	Satisfaction with bowel habits .....	34
6.6	Relationship between primary Efficacy Variable and other efficacy variables ....	35
6.7	Responses in population subgroups.....	35
6.7.1	Influence of demographic factors.....	35
6.7.2	Influence of other factors .....	37
6.8	Laxative use during study period.....	38
6.9	Development of tolerance or withdrawal effects.....	38
6.10	Conclusions of efficacy assessments .....	39
7	Safety Evaluation in Chronic Constipation .....	39
7.1	Exposure to the drug.....	40

7.2	Patient Disposition.....	41
7.3	Adverse Events .....	43
7.3.1	Overall Adverse events .....	43
7.3.2	Adverse Event severity .....	45
7.3.3	Adverse Events of Interest .....	47
7.4	Serious Adverse Events .....	49
7.5	Clinical Laboratory and other evaluations.....	50
8	Overall Safety Evaluation.....	54
8.1	The favorable safety profile established at approval in July 2002 for IBS-C was confirmed in the Chronic Constipation clinical program .....	54
8.2	Safety topics of special interest .....	55
8.2.1	Serious Adverse Events and Fatalities .....	55
8.2.2	Clinical Significant Consequences of Diarrhea .....	55
8.2.3	Rectal bleeding.....	56
8.2.4	Ischemic colitis.....	56
8.2.5	Other forms of intestinal ischemia .....	62
8.2.6	Cholecystectomies.....	62
8.2.7	Ovarian cysts.....	63
9	Safety conclusions .....	63
10	Benefit and Risks assessment.....	64
10.1	Summary of benefits.....	64
10.2	Summary of risks.....	65
11	Overall Conclusions and Recommendation for Use .....	66
12	References .....	66
	Appendix A: Novartis Survey of Consumers Suffering from Constipation.....	68
	Appendix B: Update on Clinical Efficacy in IBS-C.....	68

**List of tables**

Table 6-1	Demographics and baseline characteristics (Studies E2301, E2302) ...	19
Table 6-2	Bowel habit and constipation symptoms during the last 14 days of baseline (daily diary data) (Studies E2301, E2302).....	21
Table 6-3	Treatment for constipation in previous 6 months .....	22
Table 6-4	Primary Efficacy Endpoint (studies E2301, E2302).....	23
Table 6-5	Other Responder Analyses.....	24
Table 6-6	Summary of mean change from baseline in daily diary data for Week 1-12 (ITT patients; Pooled Data from Studies E2301, E2302).....	28

Table 6-7	Summary of mean change from baseline in weekly diary data for Week 1-12 .....	33
Table 6-8	Summary of response rates for weekly diary data for Week 1-12 .....	33
Table 6-9	Summary of mean change from baseline in weekly diary data of Satisfaction with Bowel habits for Week 1-12 .....	34
Table 6-10	Response Rate in Satisfaction with bowel habits for Week 1-12 .....	35
Table 6-11	Relationship between primary efficacy variable and other efficacy variables .....	35
Table 6-12	Patients selected as IBS-Like (Pooled analysis-ITT population).....	37
Table 6-13	Responders (increase $\geq 1$ CSBM/week from baseline) in weeks 1-4 by feature sub-group (pooled analysis, ITT population).....	38
Table 7-1	Duration of exposure to study drug – Pivotal Studies.....	40
Table 7-2	Duration of exposure to Zelnorm –long-term extension study .....	41
Table 7-3	Participation and withdrawals by treatment – Pivotal studies .....	42
Table 7-4	Participation and withdrawals by treatment – long-term extension study .....	43
Table 7-5	Most frequent AEs ( $\geq 3\%$ patients in any group) – Pivotal studies .....	44
Table 7-6	Most frequent AEs ( $\geq 3\%$ of patients in any group) - long-term extension study.....	44
Table 7-7	Adverse events rated as severe ( $n > 5$ patients across all groups)- Pivotal studies .....	46
Table 7-8	AEs rated as severe in $>5$ patients across all treatment groups - long-term extension study .....	46
Table 7-9	Diarrhea management– Pivotal studies.....	47
Table 7-10	Diarrhea evaluation – Pivotal studies.....	48
Table 7-11	Frequent ( $\geq 2\%$ ) AEs during the withdrawal period of E2302 .....	49
Table 7-12	Number (%) of patients with notably abnormal clinical chemistry findings – Pivotal studies .....	51
Table 7-13	Summary of ECG diagnoses and parameters –Pivotal studies and Long term extension study .....	53
Table 8-1	Safety Data from CC Pivotal studies and Prescribing information (%)	54
Table 8-2	Serious Adverse Events in CC and at approval for IBS-C (%).....	54
Table 8-3	Comparison of doses and pharmacokinetic values of tegaserod following exposure to human beings (approved oral dose) and rats (high parenteral dose).....	60

**List of figures**

Figure 5-1	General study design .....	14
Figure 6-1	Weekly response rate in CSBM (ITT patients; Study E2301) .....	25
Figure 6-2	Weekly response rate in CSBM (ITT patients; Study E2302) .....	26
Figure 6-3	E2301: Time to first CSBM .....	27
Figure 6-4	Study E2302: Time to first CSBM .....	27
Figure 6-6	Spontaneous Bowel Movements (SBM) Per Week Pivotal Studies E2301, E2302 .....	30
Figure 6-7	Mean Stool Form per Week Pivotal Studies E2301, E2302 .....	31
Figure 6-8	Mean Straining per Week Pivotal Studies E2301, E2302 .....	32
Figure 6-9	Odds ratio and 95% CI of the response rate for CSBM during weeks 1-4, by subgroups (pooled ITT patients treated with Zelnorm 6mg b.i.d. and placebo) .....	36
Figure 8-1	5-HT <sub>1B</sub> receptor - mediated contractile effects on isolated coronary arteries of non-human primates. Test articles: tegaserod, sumatriptan and ergotamine .....	59

## 1 Objectives

- Novartis Pharmaceuticals Corporation (“Novartis”) submitted a supplemental New Drug Application (sNDA) in October 2003 to approve Zelnorm® for the treatment of patients with chronic constipation (CC) and relief of associated symptoms of straining, hard or lumpy stools and infrequent defecation. The dosage and administration recommendation is for 12 weeks treatment in adults using 6 mg tablets b.i.d..

The objectives of this briefing document are:

- To describe the condition of chronic constipation
- To demonstrate the efficacy of Zelnorm in the phase III clinical trials in patients with chronic constipation
- To reconfirm the overall safety of Zelnorm®
- To support a positive benefit/risk assessment for the proposed new indication of Zelnorm in the treatment of chronic constipation

## 2 Executive Summary

Zelnorm® (tegaserod maleate) is currently approved in the U.S. for the short-term treatment of women with irritable bowel syndrome with constipation (IBS-C). Zelnorm is an aminoguanidine-indole derivative which acts as a partial agonist at serotonin type 4 (5HT<sub>4</sub>) receptors present in the gastrointestinal (GI) tract. Serotonin is involved in regulating intestinal motility, intestinal secretion, and visceral sensitivity. In vivo studies have shown that Zelnorm enhances basal motor activity and normalizes impaired motility throughout the GI tract. In addition, studies demonstrated that Zelnorm moderated visceral sensitivity during colorectal distension in animals.

### **Chronic Constipation Development Program Included Duplicate Pivotal Studies**

Based on these data, Novartis undertook the investigation of Zelnorm as a treatment for CC in adults. Two well-controlled double-blind studies were conducted to evaluate the efficacy and safety of Zelnorm at doses of 6mg b.i.d. or 2mg b.i.d. during a treatment period of twelve weeks. In each study, the primary efficacy analysis yielded a statistically significant and clinically meaningful outcome for Zelnorm, and in October 2003 a supplemental NDA (sNDA) was submitted to approve Zelnorm for the treatment of adult patients with CC.

### **Patient Population Studied Supports the Indication**

Patients enrolled into these studies were considered to suffer from CC if they had experienced symptoms of constipation for a minimum of 6 months. The definition of Chronic Constipation in the phase III protocols was derived from the early definition by Drossman and the definition of the Rome II committee. This included the traditional infrequency of bowel movements, plus a number of other symptoms, including straining, sensation of incomplete evacuation and hard stools. Evaluation of baseline symptoms showed that, on average,

patients in these studies had had these symptoms of constipation for an average of 10 to 15 years prior to entering the trials. All patients enrolled met the definition of CC.

### **Primary Efficacy Variable Is Clinically Meaningful to Patients**

Previous patient surveys have shown that infrequency of bowel movement is not the most bothersome of the symptoms associated with the condition of chronic constipation (Stewart, et al., 1999). This was confirmed by the evaluation of baseline symptoms for subjects in our phase III pivotal studies with the enrolled patients complaining of multiple symptoms such as straining, hard stools and discomfort as well as infrequent bowel movements. The number of complete spontaneous bowel movements (CSBM) per week was selected as the primary efficacy endpoint in the pivotal trials. This endpoint is meaningful to patients by capturing not only the quantitative but also the qualitative aspects of their bowel habits or stool passage event. CSBM was chosen to most completely assess the impact of Zelnorm on the overall condition of constipation. This [CSBM] definition utilizes the research definition of CC developed by Rome II Committee and also evaluates the importance of other bothersome symptoms which the Committee felt characterize the condition.

Patients were considered to be responders to treatment if they achieved an increase of at least one CSBM per week compared to baseline. This meant that the bowel movement was not stimulated by a rescue medicine and was accompanied by the sensation of successful passage of stool. Hence, the event is called a complete, spontaneous bowel movement. On entering the studies, patients averaged one CSBM every other week (0.5 CSBM per week).

### **Studies Yield Statistically Significant and Clinically Meaningful Efficacy Results**

During treatment, patients receiving Zelnorm recorded a greater than three-fold increase in the mean number of CSBMs per week. Zelnorm consistently proved more efficacious than placebo throughout the active treatment phase for the primary endpoint and most secondary endpoints (bloating, abdominal discomfort, hard stools, and straining) for the overall study population. Subgroup analyses show that the response in males is similar to that in females, and the response in the elderly is less consistent than in the younger population, however, the studies were not designed nor powered to demonstrate efficacy in these subgroups.

### **Results Support 6mg b.i.d. Dose Recommendation**

As outlined above, patients in the study were treated with Zelnorm 6mg b.i.d., Zelnorm 2mg b.i.d., or placebo<sup>1</sup>. The dose selection was based on the results of the dose-finding studies for the IBS-C indication. Zelnorm was found to be safe and well tolerated in the defined study population. The safety and tolerability profile of Zelnorm in these studies was similar to that reported in the first New Drug Application (NDA) for the product, approved in July 2002. Because efficacy results show that the 6mg b.i.d. dose of Zelnorm performed consistently better than 2mg b.i.d. with a similar safety and tolerability profile to the 2mg b.i.d. dose, Novartis recommends 6mg b.i.d. as the dose for this new indication.

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<sup>1</sup> As no other products are currently indicated in the U.S. for the treatment of chronic constipation, placebo was used as the comparator.

## **Safety and Tolerability Data Support Use in CC Indication**

During the 12 week efficacy phase of the studies diarrhea was the only adverse event more frequently reported with Zelnorm than with placebo. In the majority of the reports, the diarrhea was mild to moderate, occurred within 1 week of starting treatment and generally lasted a couple of days. The drop out rate due to diarrhea was low. Long-term safety collected in a 13-month extension study confirmed the safety and tolerability of the 12-week studies. There were no cases of serious consequences of diarrhea, nor were there any cases of ischemic colitis or other forms of intestinal ischemia in the CC clinical trials. In summary, all available data in patients with CC demonstrate a favorable safety and tolerability profile for Zelnorm 6mg b.i.d..

Post-marketing experience from approximately 3 million patients treated with Zelnorm worldwide confirms the favorable safety profile of Zelnorm. Diarrhea is a known drug related event reported in clinical trials. In very rare instances in post-marketing use the resulting diarrhea has resulted in serious consequences, such as the need for re-hydration. Important to note is that serious consequences of diarrhea has not been observed in any patients in the CC pivotal trials. Very rare reported cases of suspected ischemic colitis have also been received in post-marketing use and there have been no reported cases in any Zelnorm clinical trials. The number of these reports received is consistent with the historical background incidence rate in the general population and well below the IBS population. There is no evidence to support a causal relationship between Zelnorm and ischemic colitis. The Zelnorm package insert currently includes information to physicians and patients on these two post-marketing observations. In summary, there are no safety or tolerability issues which should prevent the use of Zelnorm in the CC population.

### **Novartis Recommendation for Use**

The consistency of the efficacy data for both the primary and secondary efficacy variables in the CC program indicates that Zelnorm is effective in relieving the multiple symptoms of constipation in patients with CC. A risk/benefit evaluation of the efficacy and safety data supports the use of Zelnorm in the CC population. Novartis therefore requests a positive recommendation from the Gastrointestinal Advisory Committee and the subsequent FDA approval of the sNDA for the new indication for Zelnorm.

*Zelnorm is indicated for the treatment of patients with chronic constipation and relief of the associated symptoms of straining, hard or lumpy stools, and infrequent defecation. The recommended dose is 6mg b.i.d. for 12 weeks.*

## **3 Background on Constipation**

### **3.1 Epidemiology**

Constipation is a common problem. Estimates of prevalence in the general population have ranged from 2% (Stewart et al., 1999, Sonnenberg and Koch, 1989) to 27% (Pare et al., 2001) of the adult population, depending on the definition used. Over a decade ago (1991), the

National Health Interview Survey illuminated the chronic nature of many cases of constipation, noting that 4.5 million people in the United States reported their symptoms as being present most of or all of the time. More recently, Higgins et al. (2004) conservatively estimated that constipation affects nearly 15% of the North American population, or 42 million individuals in the United States alone. Additionally, this study reported that constipation is usually chronic, being present for more than a year in as many as 89% of those reporting constipation as a symptom (Higgins et al., 2004).

In addition to its high prevalence, constipation is also associated with a significant burden on the health care system. In 1989, it was reported that the constipation condition prompted an estimated 2.5 million physician visits per year in the U.S., including at least 100,000 referrals to gastroenterologists and 92,000 hospitalizations (Sonnenberg and Koch, 1989). More recently, surveys from the 2001 National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey showed an even greater occurrence of hospitalization resource utilization with 282,000 inpatient constipation-related hospitalizations per year. The same survey identified 5.7 million constipation-related outpatient visits which included 4.1 million physician office-based visits, 990,944 emergency room visits and 586,868 hospital outpatient visits for constipation-related problems (Data on file). Despite the high numbers of healthcare professional consultations and resource utilization (i.e office visits and prescription treatments) the majority of the patients also resort to unsupervised self medication with over-the-counter remedies, or attempt to endure symptoms that may persist for decades. Thus chronic constipation can be both debilitating and difficult to treat (Lembo and Camilleri, 2003).

Constipation occurs across age groups, including children and the elderly, and in both genders, although slightly more frequently in women. (Everhart et al., 1989; Drossman et al., 1993; Lennard-Jones, 1998; and Pare et al., 2003). An increase in prevalence with age has not been consistently demonstrated in studies, especially those using Rome criteria diagnostic (Everhart et al., 1989; Talley et al., 1993; Drossman et al., 1993; Stewart et al., 1999; and Higgins et al., 2004).

Therefore, a drug that could safely and effectively relieve these chronic symptoms would fill an important void in our current therapeutic armamentarium.

### **3.2 Defining constipation**

Constipation has traditionally been defined as infrequent stool passage. Clinical studies have determined the normal range of stool passage is between 3 and 21 stools per week (Martelli et al., 1978). However, it has become clear that patients who complain of constipation report a variety of symptoms in addition to, and sometimes, excluding the frequency of bowel movements. These symptoms include straining, hard stools, “want to but can’t,” abdominal discomfort, “haven’t finished” and “too much time on the toilet.” (Sandler et al., 1987) While commonly used criteria for constipation define decreased stool evacuation as less than three bowel movements per week. (Aichbichler et al., 1998) the study by Sandler and Drossman shows that the presence of straining, hard stools and the complaint of “want to but can’t”, all occurred more commonly than infrequent stools (Sandler et al., 1987).

When patients are questioned about their perception of constipation they frequently regard straining, passage of hard stools, or difficulty in passing stools as part of the constipation symptom complex (Pare et al., 2001). A current accepted consensus definition of constipation now includes straining, hard stools, sensation of incomplete evacuation, anorectal obstruction, or use of manual maneuvers to facilitate stool passage in addition to infrequent passage of stool as criteria for constipation (Thompson et al.; 1999; and Drossman et al., 1990). The Rome II diagnostic criteria for functional bowel disorders provide an expert consensus-based clinical measure of assessing CC (Drossman 2000). A patient diagnosed with CC according to the Rome II criteria must have experienced for at least 12 weeks during the 12 months preceding evaluation at least two of the following symptoms:

- 1) Straining in > 25% defecations,
- 2) Lumpy or hard stools in > 25% defecations,
- 3) Sensation of incomplete evacuation in > 25% defecations,
- 4) Sensation of anorectal obstruction/blockade in > 25% defecations,
- 5) Manual maneuvers to facilitate >25% defecations (e.g, digital evacuation, support of the pelvic floor); and/or
- 6) < 3 defecations per week.

Finally, the Rome criteria state that loose stools are not present, and there are insufficient criteria for IBS.

Importantly the Rome criteria note that the number of defecations per week is not a prerequisite to define constipation and the sensation of complete bowel movement is equally important. Therefore, the perception of having a complete bowel movement, in contrast to an incomplete or partial evacuation, has been suggested to be an important measure of constipation (Stewart 1999).

As noted above, constipation significantly impacts inpatient hospital utilization and outpatient care (National Hospital Discharge Survey, 2001 and National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey, 2001). Therefore, chronic constipation remains an important problem for clinical gastroenterologists and primary care physicians in the United States representing the 6<sup>th</sup> most common symptom prompting outpatient clinical visits (Russo 2004).

### **3.3 Therapeutic options**

Several different approaches are currently used to treat constipation. Laxatives including bulking agents, osmotic laxatives, and stimulants laxatives are among the most widely used products. Most of these are available over-the-counter. Recently, however, the long history of laxative use for treatment of CC has been reviewed. Two systematic reviews concluded that contrary to commonly-held beliefs, there was insufficient comparable quantitative evidence to conclude that laxatives overall are superior to placebo in CC (Tramonte et al., 1997; and Jones et al., 2002). Importantly, a majority of the reports examined were excluded (85% of the 733 reports in the Tramonte review) because these trials were of poor quality and not adequately controlled. Also in the Tramonte review, only 36 randomized clinical trials were found to be

methodologically sound and thus included for subsequent analysis, evaluating 25 different treatment regimens. The study concluded that both fiber and laxatives modestly improved bowel movement frequency in adults with CC but did not report any difference for treatment of the other symptoms associated with constipation, largely because such were not adequately evaluated. There was inadequate evidence to examine whether fiber versus other laxatives was the best approach to treatment and whether one laxative was superior to another.

Currently, while the management of constipation includes lifestyle modifications, i.e., exercise, diet, particularly increased fiber in the diet, and increased fluid intake, these modifications, alone or in combination, have never been demonstrated in controlled clinical trials to have a specific beneficial effect. Bulking or hydrophylic agents are either dietary or medicinal fiber supplements which add both additional solid material and water to the stools. Patients' compliance with the use of bulking agents can be poor because of their side effects, which include flatulence, uncomfortable abdominal distension, bloating, and an unpleasant taste (Lembo and Camilleri, 2003). In fact, in many patients, increased fiber intake leads to a worsening of constipation-associated symptoms as it often increases bloating, gas, and abdominal discomfort (Mueller-Lissner 1993; and Schiller, 2001). Bulking agents such as psyllium and methylcellulose are approved in the United States for the treatment of occasional constipation. Psyllium belongs to the natural fiber category which undergoes bacterial degradation and fermentation, a process which yields gas as an end product and which may contribute to bloating and flatus. It is also recommended that psyllium should be taken with plenty of water to avoid intestinal obstruction (Lembo and Camilleri, 2003).

Patients who do not respond to fiber therapy usually try other approaches such as osmotic laxatives. Being either poorly absorbed or non-absorbed, these substances result in the secretion and persistence of water intraluminally, thereby increasing the water content of stools. The laxative effect of these agents depends on the extent to which they remain in the lumen. Because the ions contained in such laxatives can be partially absorbed, the serious adverse events related to their use are primarily from metabolic disturbances caused by excessive ion absorption in relation to subsequent excretion, for example hypermagnesemia (Xing and Soffer, 2001). Also belonging to this class are non-absorbable carbohydrates (e.g., lactulose, sorbitol), which also undergo bacterial fermentation in the colon with formation of short-chain fatty acids and gas. Their tolerance is often limited by the bloating, gas, and flatulence again consequences of excess gas produced by the colonic bacterial fermentation. Lactulose is approved in the United States for the treatment of constipation.

Recently, a powdered form of polyethylene glycol was introduced as a laxative. Polyethylene glycol (PEG) is very poorly, or not, absorbed and is not metabolized by colonic bacteria. Therefore it tends to cause less gas, bloating, and cramping than other poorly- absorbed sugars (Corazziari et al., 1996). The major disadvantage of the use of PEG, without addition of electrolytes (hypo-osmotic solutions) is the potential for excessive electrolyte and water loss into the bowel lumen causing symptomatic electrolyte depletion and contraction of the plasma volume with its associated complications. However, new PEG formulations with electrolytes (iso-osmotic) are now available and such complications are much less common. Polyethylene glycol 3350 is approved in the United States for treatment of occasional constipation. Efficacy has been shown in short term studies (2 weeks) but has not been demonstrated to date for longer periods in adults (beyond 2 weeks).

The last major category of laxatives is stimulant laxatives. These compounds produce their effect by increasing intestinal water secretion and motor activity in response to colonic irritation. They usually cause passage of stool within hours of their use, but such may be accompanied by painful abdominal cramps and diarrhea (Schiller, 2001; and Lembo and Camilleri, 2003). In patients with CC, the long-term use of stimulant laxatives is associated with a progressive loss in laxative response and thus the need to progressively increase the dose.

Rectal enemas or suppositories are another alternative for patients suffering from chronic constipation. They act to initiate evacuation of stool by actively distending the rectum, softening hard stool, and topically stimulating colonic muscle to contract. Enema use can be time-consuming, somewhat invasive, unpleasant, cause anorectal trauma and their regular use fail to address the underlying abnormalities causing the constipation. Moreover, there is no evidence that suppositories or enemas relieve symptoms of constipation other than reduced stool frequency.

Traditional therapies, which are primarily intended for acute, rescue and short-term use, do not work or cease to work, in some patients with chronic symptoms of constipation. Zelnorm would offer a valuable therapeutic option for physicians and patients in treating CC. A recent survey on CC (representative of the US population) was conducted by Knowledge Networks (See summary in Appendix A; Novartis data on file). This survey screened 40,000 consumer panelists across the United States and identified 557 qualified CC respondents to complete a random, cross-sectional survey that addressed issues relevant to CC. Overall 42% of patients surveyed were not completely satisfied with their current treatment for CC. Additionally 74% cite efficacy as the reason for their dissatisfaction. The number of dissatisfaction was found to increase as the number of associated symptoms increased.

In addition, while stool frequency may be increased by laxatives, there is little available information to show that treatment with the currently available medications, effectively provides relief for the other troublesome symptoms of CC (bloating, straining, abdominal distention and discomfort). Most patients report that to achieve satisfactory relief of constipation, not only should the frequency of defecation be increased, but other factors such as stool form and consistency, straining, abdominal discomfort, and bloating should also be improved.

Zelnorm is a serotonin type-4 (5-HT<sub>4</sub>) receptor partial agonist with GI motility-enhancing properties. It also increases intestinal secretion and attenuates painful visceral sensation in animal models. The data presented in this briefing document demonstrate that Zelnorm not only improves the frequency of stool passage in patients with CC, it also effectively treats other important symptoms associated with constipation, namely sensation of incomplete bowel evacuation, hard stools, excessive straining, and abdominal bloating.

#### **4 Zelnorm Development Rationale**

Serotonin (5-HT) has been demonstrated to be involved in the regulation of gut motility. Activation of 5-HT<sub>4</sub> receptors present on enteric nerves can stimulate coordinated GI motility (peristalsis) through facilitation of the release of neurotransmitters from nerves terminals

leading to enhanced GI transit, e.g. colon transit, as confirmed in animals (Nguyen et al., 1997) and in patients with IBS-C (Degen et al., 2001; and Prather et al., 2000).

Tegaserod is a 5-HT<sub>4</sub> receptor partial agonist with a structure similar to that of serotonin. It is a member of a novel class of compounds, the aminoguanidine indoles, designed to activate 5-HT<sub>4</sub> receptors present in the GI tract. Via activation of 5-HT<sub>4</sub> receptors, tegaserod stimulates the peristaltic reflex and inhibits visceral sensitivity; furthermore animal studies revealed a stimulation of intestinal secretion (Lacy and Yu, 2002; Beglinger, 2002; Camilleri, 2001; and Grider et al., 1998). Tegaserod does not induce perpetual propulsive or secretory activity, however, its actions only rely on natural luminal stimuli to initiate activity (Gershon, 2003). The strategic presynaptic location of 5-HT<sub>4</sub> receptors on enteric nerves enables tegaserod to improve insufficient GI motor activity in response to endogenous mucosal stimuli (Gershon, 2003).

Due to its pharmacological action in promoting GI motility, Zelnorm is a candidate for treating a variety of forms of small and/or large bowel dysfunction involving disturbed motility. Zelnorm was first evaluated in IBS-C and CC populations. Zelnorm is currently being developed in several other GI disorders in adults including dyspepsia (Dysp.), gastroesophageal reflux disease (GERD), and diabetic gastropathy (DG).

The clinical development program of Zelnorm was initiated in 1994, leading to submission of a NDA in 2000 (NDA 21-200) for the treatment of IBS-C. In 2002, Zelnorm was approved by FDA for the short term treatment of women with irritable bowel syndrome with constipation (IBS-C) at a recommended dose of 6mg b.i.d.. Zelnorm/Zelmac is also approved globally in more than 55 countries for IBS-C and in 10 countries for CC, using a dose of 6mg b.i.d.. Since the original NDA approval in 2002, additional large controlled studies in patients with IBS-C were conducted in Nordic countries (TENOR) and in the Asia-Pacific region (ZAP). The results from these additional clinical studies clearly demonstrate and confirm the sustained efficacy as well as the safety and tolerability of Zelnorm in patients with IBS-C as it was demonstrated at the time of the original IBS-C filings and approvals. An update on the clinical efficacy profile IBS-C is provided in Appendix B.

A sNDA was submitted in October, 2003 to approve Zelnorm for the treatment of patients with CC and relief of associated symptoms of straining, hard or lumpy stools, and infrequent defecation, for 12 weeks. The dosage and administration recommendation is for 12 weeks treatment in adults using 6 mg tablets b.i.d..

The clinical development of Zelnorm in CC comprises 2 placebo-controlled studies, 1 of which included a long-term extension, supplying efficacy and safety data on 2612 patients for 12 weeks and safety data on 518 treated for  $\geq 1$  year. The purpose of the long-term extension trial was to assess long term safety.

The program was designed to study a broad spectrum of patients with CC, reflecting those likely to be treated in clinical practice.

## 5 Zelnorm Clinical Program in Chronic Constipation

This section of the briefing document outlines the key features of the CC study design, highlighting the rationale for selecting dosing regimen, patient population and efficacy variables.

The primary objective of the CC program was to determine the efficacy of Zelnorm tablets 2mg b.i.d. and 6mg b.i.d., by comparing the number of complete spontaneous bowel movements (CSBM) per week during the first 4 weeks of treatment to the number of CSBM recorded by the patient during the baseline period. (“Complete” refers to a bowel movement that results in a sensation of complete evacuation, and “spontaneous” refers to a non-laxative induced stool, i.e., no laxative was taken within 24 hours preceding the bowel movement.)

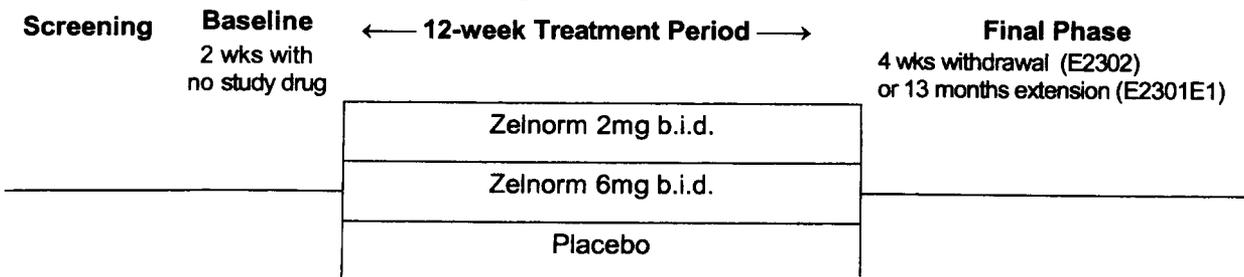
Secondary objectives were to determine the effects of Zelnorm 2mg b.i.d. and 6mg b.i.d. versus placebo on: 1) the number of CSBM/week during the 12 weeks of treatment, 2) bowel habits (stool frequency, stool form, straining, feeling of complete evacuation), 3) the patient’s assessment of bothersomeness symptoms of constipation including bothersomeness of bloating/distension and bothersomeness of abdominal discomfort/pain, 4) the patient’s satisfaction with bowel habits, 5) safety and tolerability.

### 5.1 Study Design

The CC clinical program consisted of 2 pivotal studies (Study E2301 and Study E2302), both of which were large, double-blind, randomized, placebo-controlled, 3-armed trials of similar design through the treatment phase (same entry criteria, duration, and efficacy endpoints). Each study consisted of a 2-week baseline period, followed by a 12-week treatment period. The final phase was the point of divergence between the studies, consisting of either a 4-week treatment-free follow-up period (protocol E2302) or a 13-month extension period (protocol E2301). ( figure 5-1).

Rescue medications (laxatives) were permitted when at least 96 hours had passed since the patient’s previous bowel movement, but were additionally recorded and considered in the evaluation of efficacy.

**Figure 5-1 General study design**



Each pivotal study had 3 treatment arms: Zelnorm 2mg b.i.d., Zelnorm 6mg b.i.d., and placebo.

Patients who entered the 13-month long-term extension study received either Zelnorm 2mg b.i.d. or Zelnorm 6mg b.i.d. in a double-blinded manner. Patients treated with Zelnorm in the

E2301 study were kept on their original regimen, placebo patients were switched to Zelnorm 6mg b.i.d.

## **Dose selection rationale**

Zelnorm doses ranging from 1 to 24 mg per day were assessed early in the IBS-C development program. A comprehensive phase II dose-finding clinical program in IBS-C patients showed that the low dose (i.e., 0.5mg b.i.d) and the high dose of Zelnorm (i.e., 12mg b.i.d) did not bring added benefit to the patients compared to 6mg b.i.d.. In these phase II trials in patients with IBS-C, Zelnorm doses of 2 and 6 mg b.i.d. were found to be efficacious and to have a favorable safety and tolerability profile. The Phase III trials in IBS-C patients confirmed the safety and efficacy of 2 mg and 6 mg b.i.d., while improving symptoms also present in CC patients, such as bowel frequency, stool consistency, and severity of bloating. Based on these data, Novartis decided to conduct a clinical trial program in CC evaluating the doses of 2mg b.i.d. and 6mg b.i.d..

## **5.2 Patient population**

### **5.2.1 Rationale**

The definition of CC was derived from the Rome II criteria.

As outlined above, the concept of the CSBM was introduced as an improvement over the measure of constipation as a simple count of bowel movements (BM) because CSBM takes into account both the number of stools and the patient's assessment of the quality of the bowel movements. Indeed, several reports (Sandler et al., 1990; Halet al., 1986; and Harari et al., 1997) indicate that self-reported frequency of bowel movements is poorly correlated with self-reported constipation. As noted above, it is known that profoundly constipated individuals may experience incomplete evacuation and pass hard fecal pellets multiple times per day without real relief of CC. Therefore, the simple counting of each episode of fecal productivity as a BM would only cloud the real impact of Zelnorm on the patient's CC. The tracking of CSBM, in contrast to incomplete or partial evacuation, was deemed an improved measure of constipation compared to a simple count of BM.

### **5.2.2 Eligibility Criteria**

The study population of the phase III program consisted of men and women 18 years of age or older (no upper age limit), with a history of constipation at least 6 months in duration before screening. Constipation was defined as follows:

- less than three complete spontaneous bowel movements (CSBM) per week , and
- one or more of the following:
  1. at least 25% of the stools are very hard and/or hard stools (Type 1 and/or 2 on the Bristol Stool Form scale) (O'Donnell et al., 1990);
  2. sensation of incomplete evacuation following at least 25% of the bowel movements; and/or
  3. straining on at least 25% of the defecations.

Patients excluded were those whose constipation was known to be caused by primary disease of the colon (i.e., cathartic colon, megarectum or megacolon, intestinal pseudo-obstruction, intestinal carcinoma, inflammatory bowel disease), pelvic floor dysfunction (i.e., chronic constipation resulting from bowel or gynecological surgery, with mechanical outlet obstruction, congenital anorectal malformation, or clinically significant rectocele), metabolic disturbances (i.e., hypo- or hyperthyroidism or insulin-dependent diabetes), neurologic disturbances (e.g., systemic multiple sclerosis), or concomitant medications affecting bowel habits.

Patients were excluded from the double-blind treatment phase if constipation was not confirmed by baseline diary data, if they had loose or watery stools for 3 or more days in total during the baseline period, if they were non-compliant with completing the diary assessments during the baseline period, or if they deviated from the guidelines on laxative use on more than two days during the baseline period.

### **5.3 Statistical Considerations**

#### **5.3.1 Sample size and Power calculation**

Sample size was based on the primary efficacy variable defined as the response rate for CSBM during the first 4 weeks of treatment. Responders were defined as a mean increase of 1 or more ( $\geq 1$ ) CSBM/week compared to the last 14 days of baseline.

Both pivotal studies were powered to detect 12% treatment difference over placebo assuming a placebo response rate of 30%. The sample size was adequate to achieve 90% power.

#### **5.3.2 Rationale for selecting the efficacy variables**

The primary efficacy variable was based on the number of CSBM because:

- infrequent bowel movements is a common and clinically significant symptom of CC,
- spontaneous bowel movements allow for physiologic defecation, not influenced by the use of “rescue” laxatives or enemas to be considered, and
- complete bowel movements enable the completeness of evacuations to be assessed and capture the quality of the bowel movement.

The response was evaluated on the first 4 weeks of treatment to enable the detection of early effects while reducing the impact of the short-term benefits associated with the clearing of accumulated stool.

The definition of response relied on an increase of  $\geq 1$  CSBM/week compared to baseline, which represents a clinically significant improvement for patients, who generally experience an average of only 0.5 CSBM/week.

Whereas frequency of CSBM is a useful and quantifiable objective efficacy parameter, a significant proportion of patients also complain of bloating, abdominal discomfort, hard stools, and straining. Therefore, these analyses of these parameters were included as secondary endpoints.

### **5.3.3 Efficacy evaluation**

All efficacy analyses presented in this document are from the Intent-To-treat patient population.

#### **5.3.3.1 Primary Efficacy analysis**

The primary efficacy variable was response rate for CSBM during the first 4 weeks of treatment. Responders were defined as those who had at least seven days of treatment and a mean increase of 1 or more ( $\geq 1$ ) CSBM/week compared to the last 14 days of baseline.

Patients who did not fulfill the above criteria were considered as non-responders. Patients who received less than 7 days of treatment were considered non responders.

The primary efficacy variable was analyzed using a logistic regression model which included treatment, center, and gender as factors and baseline number of CSBM/week as covariate. Each Zelnorm treatment group (2mg b.i.d and 6mg b.i.d) was compared to placebo individually. The overall significance level controlled at 0.05 using Hochberg's procedure.

#### **5.3.3.2 Secondary Efficacy Analysis**

Several secondary efficacy analyses were performed based upon the following parameters:

##### **Response rate throughout the 12 weeks of treatment**

This variable was defined and analyzed similarly to the primary efficacy variable, except for an extended time interval of 1-12 weeks.

##### **Response rate in terms of absolute number of CSBM**

Additional efficacy criteria, requested by the FDA (pre-sNDA meeting on 15-Jul-2002), also related to CSBM response rate, defined responders as those who had at least 7 days of treatment and  $\geq 3$  CSBM/week during Weeks 1-4 or Weeks 1-12. Both variables were analyzed using the same logistic regression model as the primary efficacy variable.

##### **Response rate in terms of absolute number of CSBM and increase in CSBM from baseline**

Other CSBM response rate criteria defined responders as an increase  $\geq 1$  CSBM/week from baseline and  $\geq 3$  CSBM/week during the first 4 weeks. The same definition applied for responders in the 12 week treatment interval. This variable was analyzed using the same logistic regression model as the primary efficacy variable.

##### **Evaluation of bowel habits**

To evaluate bowel habits, the following four measurements, taken from the daily assessments, were used in deriving the secondary efficacy variables: 1) Stool frequency, 2) Stool form (using the Bristol Stool Scale), 3) Straining using the ordinal 3-point scale (0=no straining, 1=acceptable straining, 2=too much straining), 4) Sensation of complete evacuation following the bowel movement (yes/no question). Weekly stool frequency, weekly mean stool form, weekly mean straining score, average number of days per week with "too" much straining, and percentage of CSBMs were all analyzed using (generalized) CMH tests stratified by center.

**Patient's assessment of symptoms of bothersomeness of symptoms of constipation (weekly question)**

A 5-point ordinal scale classified the response for each variable: bothersome constipation, bothersome abdominal distension/bloating, bothersome abdominal discomfort/pain.

The 5-point scale was: 0=not at all bothersome, 1=hardly bothersome, 2=moderately bothersome, 3=a good deal bothersome, 4= a very great deal bothersome.

**Patient's assessment of satisfaction with bowel habits (weekly question)**

A 5-point scale classified the response: 0=a very great deal satisfied, 1=a good deal satisfied, 2=moderately satisfied, 3=hardly satisfied, 4=not at all satisfied.

Treatment comparisons for these weekly assessments were again performed using generalized CMH tests stratified by center.

## **6 Efficacy results in Chronic Constipation**

The efficacy results will be displayed by study as well as combined (pooled). Pooling data from the two pivotal studies was justified because the design, objectives, patient population, dose regimen, and treatment duration were identical in the studies, which differed only in the final phase (withdrawal period or extension). The purpose of pooled analysis was:

1. to obtain more precise estimates of the treatment effect,
2. to investigate a dose-response relationship, and
3. to examine efficacy responses in subgroups.

Patient disposition (i.e., discontinuation rates) is presented in section 6.2.

A total of 2612 patients were randomized into the trials and included in the efficacy analysis, of whom 2603 patients (1742 Zelnorm-treated and 861 placebo-treated) were safety evaluable and included in the safety analysis.

### **6.1 Demographic and baseline disease characteristics**

The principal demographic and disease characteristics of the populations in studies E2301 and E2302 (table 6-1) were comparable across treatment groups. The majority of the patients were women, Caucasian, and younger than 65 years of age with a mean age of 46 years. Patients were diagnosed as chronically constipated since the majority of them had a history of constipation for approximately 10 years prior to entering into study E2301 and approximately 15 years prior to entering E2302 studies.

**Table 6-1 Demographics and baseline characteristics (Studies E2301, E2302)**

Demographic variable	Study E2301			Study E2302		
	Zelnorm 2 mg b.i.d. N = 417	Zelnorm 6 mg b.i.d. N = 431	Placebo N = 416	Zelnorm 2 mg b.i.d. N = 450	Zelnorm 6 mg b.i.d. N = 451	Placebo N = 447
<b>Age</b> (mean years, SD)	46.5 (15.9)	46.2 (14.7)	46.0 (15.6)	46.7 (14.5)	46.7 (12.9)	47.2 (14.0)
< 65 n (%)	351 (84.2)	384 (89.1)	358 (86.1)	391 (86.9)	410 (90.9)	387 (86.6)
≥ 65 n (%)	66 (15.8)	47 (10.9)	58 (13.9)	59 (13.1)	41 (9.1)	60 (13.4)
<b>Sex</b> n (%)						
Male	58 (13.9)	62 (14.4)	53 (12.7)	50 (11.1)	45 (10.0)	40 (8.9)
Female	359 (86.1)	369 (85.6)	363 (87.3)	400 (88.9)	406 (90.0)	407 (91.1)
<b>Menopausal status (female patients only)</b> n (%)						
Pre-menopausal	201 (56.0)	201 (54.5)	219 (60.3)	212 (53.0)	211 (52.0)	209 (51.4)
Post-menopausal	158 (44.0)	168 (45.5)	143 (39.4)	178 (44.5)	186 (45.8)	184 (45.2)
<b>Race</b> n (%)						
Caucasian	410 (98.3)	423 (98.1)	409 (98.3)	381 (84.7)	385 (85.4)	376 (84.1)
Black	2 (0.5)	2 (0.5)	2 (0.5)	35 (7.8)	30 (6.7)	31 (6.9)
Oriental	1 (0.2)	4 (0.9)	1 (0.2)	2 (0.4)	3 (0.7)	1 (0.2)
Other	4 (1.0)	2 (0.5)	4 (1.0)	32 (7.1)	33 (7.3)	39 (8.7)
<b>Height</b> (mean cm)	166.0	166.5	166.0	164.8	164.6	164.4
<b>Weight</b> (mean kg)	67.5	68.4	68.6	69.6	69.9	69.9
<b>BMI</b> (mean kg/m <sup>2</sup> )	24.4	24.6	24.8	25.6	25.8	25.8
<b>BMI group</b> n (%); kg/m <sup>2</sup>						
< 18.5	12 (2.9)	11 (2.6)	15 (3.6)	9 (2.0)	9 (2.0)	4 (0.9)
18.5 - < 25	239 (57.3)	243 (56.4)	228 (54.8)	229 (50.9)	214 (47.5)	222 (49.7)
25 - < 30	117 (28.1)	137 (31.8)	115 (27.6)	137 (30.4)	144 (31.9)	147 (32.9)
30 - < 40	41 (9.8)	37 (8.6)	52 (12.5)	61 (13.6)	66 (14.6)	59 (13.2)
≥ 40	1 (0.2)	1 (0.2)	3 (0.7)	7 (1.6)	9 (2.0)	7 (1.6)
Missing	-	-	-	7 (1.6)	9 (2.0)	8 (1.8)
<b>History of Constipation Duration</b> –median (years)	10	10	10	15.5	15	16

Table 6-2 summarizes the bowel habit and constipation symptoms during the 2-week baseline period prior to randomization. The median number of CSBM/week was 0 across treatment groups in each study. The median score of satisfaction with bowel habits was 3 (=hardly satisfied).

Approximately half of the patients in each group took laxatives during the baseline period. The most frequently used medication was bisacodyl, indicated as rescue medication for

constipation per protocol. Among these patients, the median number of days/week with laxatives intake range from 1 to 1.3 days/week.

**Table 6-2 Bowel habit and constipation symptoms during the last 14 days of baseline (daily diary data) (Studies E2301, E2302)**

Assessment	Study E2301			Study E2302		
	Zelnorm 2mg b.i.d. N = 417	Zelnorm 6mg b.i.d. N = 431	Placebo N = 416	Zelnorm 2mg b.i.d. N = 450	Zelnorm 6mg b.i.d. N = 451	Placebo N = 447
<b>Number of CSBM/week</b>						
Median	0.0	0.0	0.0	0.0	0.0	0.0
Mean (SD)	0.5 (0.85)	0.5 (0.92)	0.5 (0.78)	0.5 (0.79)	0.6 (0.82)	0.6 (0.87)
<b>Number of SBM/week</b>						
Median	2.5	2.5	2.2	2.7	2.5	3.0
Mean (SD)	3.1 (2.73)	3.0 (2.85)	3.2 (3.14)	3.6 (3.31)	3.5 (3.36)	3.7 (3.26)
<b>Number of BM/week</b>						
Median	3.2	3.2	3.0	4.0	4.0	3.8
Mean (SD)	3.9 (2.54)	4.0 (2.66)	4.1 (3.04)	4.6 (3.16)	4.7 (3.18)	4.7 (3.10)
<b>Number of SBM/week with straining</b>						
Median	2.0	2.0	2.0	2.5	2.2	2.5
Mean (SD)	2.6 (2.43)	2.6 (2.62)	2.7 (2.86)	3.1 (3.05)	3.0 (3.09)	3.1 (2.94)
<b>Number of SBM/week with too much straining</b>						
Median	0.5	0.5	0.5	1.0	0.6	1.0
Mean (SD)	1.0 (1.27)	1.0 (1.56)	1.1 (1.64)	1.3 (1.59)	1.3 (1.85)	1.4 (1.71)
<b>% SBM with sensation of complete evacuation</b>						
Median	8.0	0.0	0.0	1.4	9.1	8.3
Mean (SD)	20.4 (28.13)	17.1 (24.50)	16.4 (23.50)	17.6 (24.18)	18.0 (23.90)	18.1 (23.83)
<b>Stool consistency of SBM<sup>†</sup></b>						
Median	2.5	2.3	2.5	2.9	2.8	2.6
Mean (SD)	2.7 (1.16)	2.5 (1.14)	2.7 (1.18)	2.9 (1.15)	2.9 (1.23)	2.8 (1.18)
<b>Satisfaction with bowel habits*</b>						
Median	3.0	3.0	3.0	3.0	3.0	3.0
Mean (SD)	2.9 (0.86)	2.9 (0.85)	3.0 (0.85)	3.0 (0.84)	3.1 (0.83)	3.1 (0.89)
<b>Bothersomeness of constipation*</b>						
Median	3.0	3.0	3.0	3.0	3.0	3.0
Mean (SD)	2.7 (0.89)	2.6 (0.87)	2.7 (0.87)	2.7 (0.83)	2.8 (0.92)	2.8 (0.87)
<b>Bothersomeness of abdominal distension/bloating*</b>						

Assessment	Study E2301			Study E2302		
	Zelnorm 2mg b.i.d. N = 417	Zelnorm 6mg b.i.d. N = 431	Placebo N = 416	Zelnorm 2mg b.i.d. N = 450	Zelnorm 6mg b.i.d. N = 451	Placebo N = 447
Median	2.5	2.5	3.0	3.0	3.0	3.0
Mean (SD)	2.6 (0.95)	2.5 (0.98)	2.7 (1.02)	2.7 (0.94)	2.7 (0.99)	2.7 (1.02)
<b>Bothersomeness of abdominal discomfort/pain*</b>						
Median	2.0	2.0	2.0	2.0	2.0	2.0
Mean (SD)	2.2 (1.07)	2.2 (1.06)	2.2 (1.07)	2.3 (1.01)	2.2 (1.07)	2.3 (1.03)

CSBM = Complete spontaneous bowel movement; SBM = Spontaneous bowel movement; BM = Bowel movement

† Graded on a 7-point scale (1 to 7), with lower scores indicating harder stool consistency

\* Graded on a 5-point scale (0 to 4), with lower scores indicating greater satisfaction/less Bothersomeness  
 Straining was assessed as follows (0=no straining, 1=acceptable straining, 2=too much straining)

Patients were asked to report the degree of satisfaction with treatment(s) received in the previous 6 months prior to entering into the pivotal trials. The results showed that close to 50% of patients who had received laxatives were not satisfied. Importantly, a large proportion of patients (73%) who received bulking agents expressed dissatisfaction (table 6-3).

**Table 6-3 Treatment for constipation in previous 6 months**

	Study E2301			Study E2302		
	Patients % N=1264	Mean Use/week	Treatment effect, % <sup>1</sup>	Patients % N=1348	Mean Use/week	Treatment effect, % <sup>1</sup>
Laxatives/Enemas	57.8	3	50.4	64.2	2	53.5
Diet	39.2	6.9	8.1	52.6	7	14.9
Natural remedies	26.3	4.2	26.8	43	3.5	12.8
Bulk forming agents	25.7	5.9	16.9	41.8	7	16.8
Exercise	22.4	4.2	8.1	25.5	3	40.4
Relaxation/stress management	5.4	3.6	5.9	11.5	3	14.2
Manual maneuvers	4.7	1.4	28.3	8.8	1	29.7
Other	3.7	7.6	42.6	8.2	2.5	29.7

<sup>1</sup> Percent of patients who had excellent and good therapeutic effect

## 6.2 Primary Efficacy results

The primary efficacy variable was the response rate for CSBM during Weeks 1-4. Response was defined as the mean increase of  $\geq 1$  CSBM/week for patients with at least 7 days of treatment. In both studies, the response rates for both Zelnorm doses based on the primary efficacy variable were statistically significantly higher compared to placebo group (table 6-4).

In study E2301, the response rate was dose-related, 6mg b.i.d. dose being the most effective compared to placebo.

**Table 6-4 Primary Efficacy Endpoint (studies E2301, E2302)**

	Study E2301			Study E2302		
	Zelnorm 2 mg b.i.d. N = 417	Zelnorm 6 mg b.i.d. N = 431	Placebo N = 416	Zelnorm 2 mg b.i.d. N = 450	Zelnorm 6 mg b.i.d. N = 451	Placebo N = 447
<b>Week 1-4 ( increase of <math>\geq 1</math> CSBM/week)</b>						
<b>% Responders</b>	<b>35.6</b>	<b>40.2</b>	26.7	<b>41.4</b>	<b>43.2</b>	25.1
<b>Odds Ratio<sup>1</sup></b>	<b>1.57</b>	<b>2.04</b>		<b>2.26</b>	<b>2.48</b>	
<b>95% CI for odds ratio</b>	(1.14-2.16)	(1.48-2.80)		(1.67-3.05)	(1.84-3.34)	
<b>p-value<sup>2</sup></b>	<b>0.0059</b>	<b>&lt;0.0001</b>		<b>&lt;0.0001</b>	<b>&lt;0.0001</b>	

CSBM = complete spontaneous bowel movements

<sup>1</sup> An odds ratio > 1 favors Zelnorm over placebo

<sup>2</sup> The significance of the treatment difference is determined by the Hochberg procedure

### 6.3 Other Responder Analyses (Secondary efficacy)

Zelnorm 6mg b.i.d. showed a significantly higher response rate ( $p < 0.05$ ) compared to placebo for all definitions of responder at both time periods (Weeks 1 to 4 and Weeks 1 to 12). Results from the key secondary efficacy variable (increase of  $\geq 1$  CSBM/week, Weeks 1-12) were comparable to the primary efficacy variable for the 6mg b.i.d. dose (Table 6-5).

Additional efficacy analyses also related to CSBM response rate were performed. These analyses defined responders as those with  $\geq 3$  CSBM/week during Weeks 1-4 or Weeks 1-12, for those patients with  $\geq 7$  days of active treatment. The difference did not always reach statistical significance with Zelnorm 2mg b.i.d.

**Table 6-5 Other Responder Analyses**

	Study E2301			Study E2302		
	Zelnorm 2 mg b.i.d. N = 417	Zelnorm 6 mg b.i.d. N = 431	Placebo N = 416	Zelnorm 2 mg b.i.d. N = 450	Zelnorm 6 mg b.i.d. N = 451	Placebo N = 447
<b>% Responders: increase of <math>\geq 1</math> CSBM/week</b>						
<b>Weeks 1-12</b>	35.9	<b>43.2*</b>	30.6	<b>40.3*</b>	<b>44.8*</b>	26.9
<b>% Responders: <math>\geq 3</math> CSBM/week</b>						
<b>Weeks 1-4</b>	<b>18.8*</b>	<b>22.2*</b>	12.9	<b>23.0*</b>	<b>21.8*</b>	12.9
<b>Weeks 1-12</b>	17.1	<b>25.2*</b>	14.3	<b>22.7*</b>	<b>22.0*</b>	13.1
<b>% Responders: increase of <math>\geq 1</math> CSBM/week plus <math>\geq 3</math> CSBM/week</b>						
<b>Weeks 1-4</b>	<b>17.6*</b>	<b>21.0*</b>	11.9	<b>22.7*</b>	<b>21.4*</b>	11.3
<b>Weeks 1-12</b>	15.9	<b>24.1*</b>	13.3	<b>22.3*</b>	<b>21.4*</b>	12.0

CSBM = complete spontaneous bowel movements

\* Statistically significant versus placebo ( $p < 0.05$ ) determined by applying the Hochberg procedure

Various supportive and sensitivity analyses were performed to show the robustness of the primary efficacy results. A few patients did not contribute to the logistic regression because of missing covariates. To assess their impact a CMH test stratified by center was performed to all patients. This test yielded similar p-values as the primary analysis.

The analysis of the primary and key secondary variables (CSBM response rates) in the pooled data from the two efficacy studies confirmed the results of the individual trials. Zelnorm 6 mg b.i.d. showed a consistently higher response rate than 2 mg b.i.d., and superiority which reached statistical significance for the variable “increase of  $\geq 1$  CSBM/week over Weeks 1-12”.

Thus, the CSBM response rate data (*primary and key secondary*) from both studies pooled confirms Zelnorm 6mg b.i.d. to be generally superior to Zelnorm 2mg b.i.d. This indicates that Zelnorm 6mg b.i.d. is the preferred dose for achieving efficacy, since its superiority over placebo was more consistent than that of Zelnorm 2mg b.i.d.

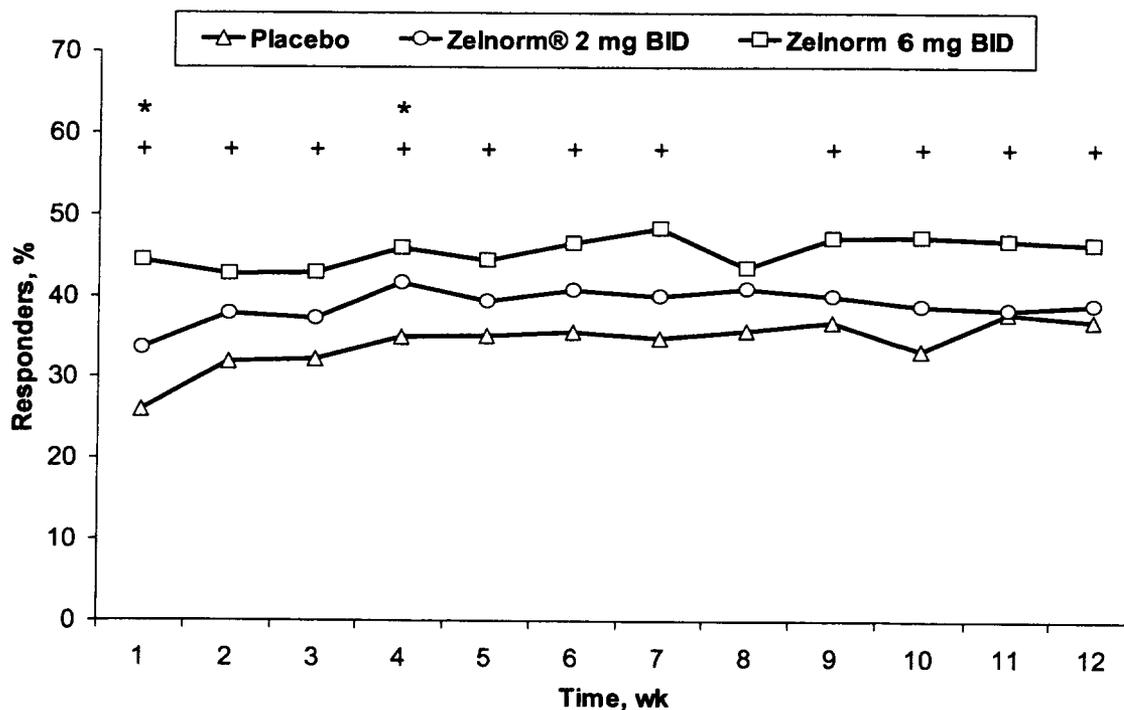
## 6.4 Early effect and durability of treatment response

### Weekly response rate in CSBM

The weekly percentage of patients who achieved an increase of  $\geq 1$  CSBM/week compared to baseline is shown graphically in figures 6-1 and 6-2. The early effect of Zelnorm within 1 week of treatment was demonstrated in each study. The percent of patients with an increase of  $\geq 1$  CSBM/week compared to baseline was statistically significantly greater with Zelnorm 2mg b.i.d. and 6mg b.i.d. than with placebo (Figures 6-1 and 6-2).

The weekly percentage of patients who achieved an increase of  $\geq 1$  CSBM/week compared to baseline is shown graphically in Figures 6-1 and 6-2. The early response at 1 week was sustained throughout the entire duration of treatment. The treatment effect in favor of Zelnorm was maintained during the treatment period in spite of the increase in placebo responder rate over time. Both treatment groups showed significant differences compared to placebo in the E2302 study, while the 6mg b.i.d. showed clear superiority compared to 2mg b.i.d. and placebo in the E2301 study.

Figure 6-1 Weekly response rate in CSBM (ITT patients; Study E2301)



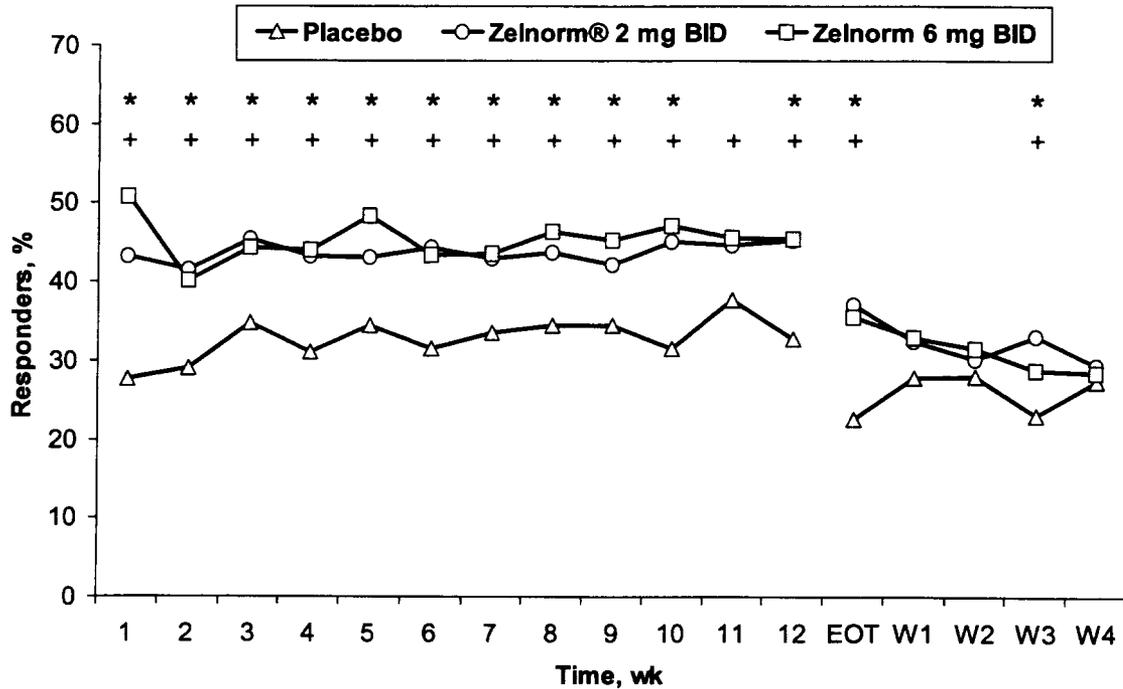
\* $P < .05$ , Zelnorm 2 mg b.i.d. vs placebo; \* $P < .05$ , Zelnorm 6 mg b.i.d. vs placebo.

P values based on CMH tests

Responder = increase of  $\geq 1$  CSBM/wk and  $\geq 7$  days of treatment.

CSBM = Complete spontaneous bowel movement.

**Figure 6-2 Weekly response rate in CSBM (ITT patients; Study E2302)**

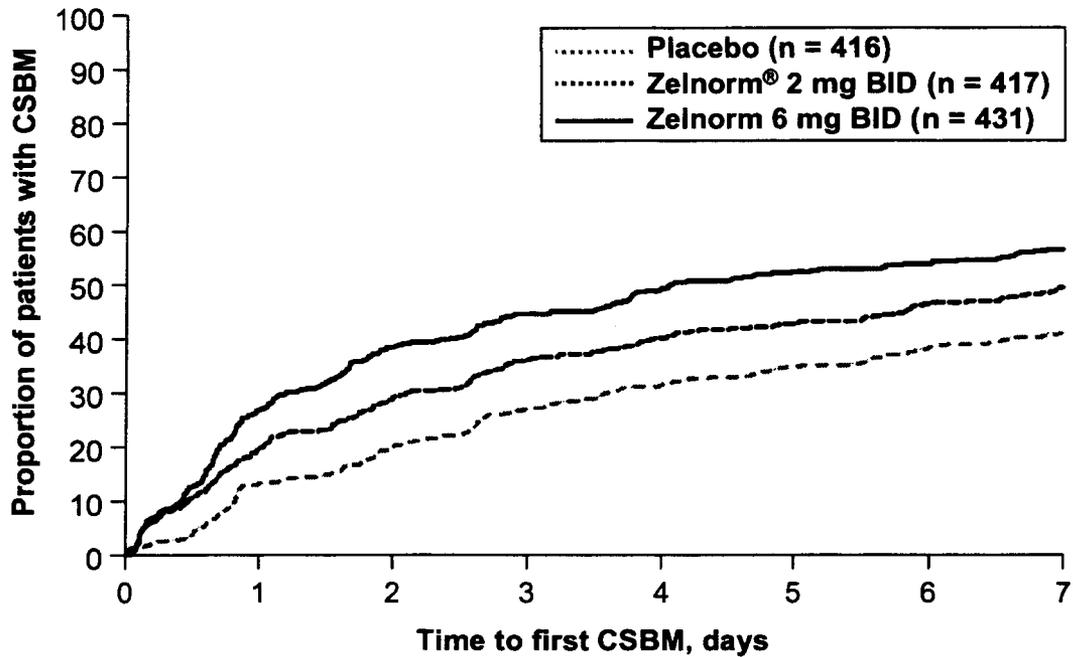


\* $P < .05$ , Zelnorm 2 mg b.i.d. vs placebo; \* $P < .05$ , Zelnorm 6 mg b.i.d. vs placebo.  
 P values based on CMH test  
 Responder = increase of  $\geq 1$  CSBM/wk and  $\geq 7$  days of treatment.  
 CSBM = Complete spontaneous bowel movement.

**Time to first CSBM**

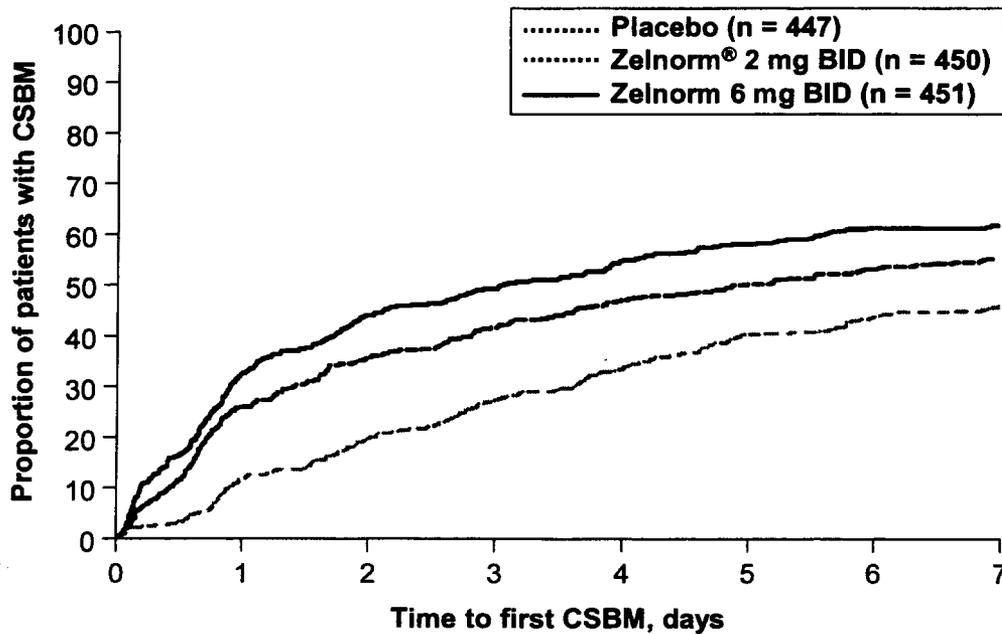
In both studies, patients treated with Zelnorm experienced their first CSBM significantly earlier than those receiving placebo and the dose of 6mg b.i.d. provided faster results. (Figures 6-3, 6-4)

Figure 6-3 E2301: Time to first CSBM



CSBM = Complete spontaneous bowel movement.

Figure 6-4 Study E2302: Time to first CSBM



CSBM = Complete spontaneous bowel movement.

Importantly, the median time to first SBM (spontaneous bowel movement) was much faster with Zelnorm compared to placebo (18.14 hours with Zelnorm 6mg b.i.d., 19.30 hours with Zelnorm 2mg b.i.d., versus 33 hours with placebo).

## 6.5 Effect of Zelnorm on multiple symptoms of constipation

### 6.5.1 Daily Diary questions

To evaluate bowel habits, patients were asked to assess the following on a daily basis:

- Stool frequency,
- Stool form (on a 7-point scale, with lower scores indicating harder consistency),
- Straining (no straining, acceptable straining, too much straining), and
- Feeling of complete evacuation (yes/no) following bowel movement.

These data were used to derive the secondary efficacy variables summarized in the Table 6-6 below, followed by brief description of the individual variables.

**Table 6-6 Summary of mean change from baseline in daily diary data for Week 1-12 (ITT patients; Pooled Data from Studies E2301, E2302)**

	Study E2301			Study E2302		
	Zelnorm 2 mg b.i.d. N = 417	Zelnorm 6 mg b.i.d. N = 431	Placebo N = 416	Zelnorm 2 mg b.i.d. N=450	Zelnorm 6 mg b.i.d. N=451	Placebo N=447
<b>Data from daily diary (mean change from baseline)</b>						
Number of CSBM/week	1.0 p=0.0766	1.3 p<0.0001	0.8	1.4 p<0.0001	1.3 p<0.0001	0.7
Number of SBM/week	1.6 p<0.0001	2.0 p<0.0001	0.9	2.0 p<0.0001	1.9 p<0.0001	1.0
Number of BM/week	1.4 p=0.0002	1.7 p<0.0001	0.8	1.6 p<0.0001	1.5 p<0.0001	0.7
Stool form score for SBM*	0.7 p<0.0001	1.0 p<0.0001	0.4	0.6 p=0.0012	0.8 p<0.0001	0.4
Straining score for SBM	-0.3 p=0.2215	-0.3 p<0.0001	-0.2	-0.3 p<0.0001	-0.4 p<0.0001	-0.2
Number of days/week with "too much straining"	-0.1 p=0.0400	-0.3 p=0.7677	-0.3	-0.4 p=0.1233	-0.4 p=0.1209	-0.2
Percentage of SBMs with a sensation of complete evacuation	12.5 p=0.8706	18.4 p=0.0854	14.3	17.0 p=0.0011	17.6 p=0.0003	10.4

CSBM = Complete spontaneous bowel movement; SBM = Spontaneous bowel movement; BM = Bowel movement

\*Graded by patients on a 7-point scale, with lower scores indicating harder stool

p-values based on CMH tests

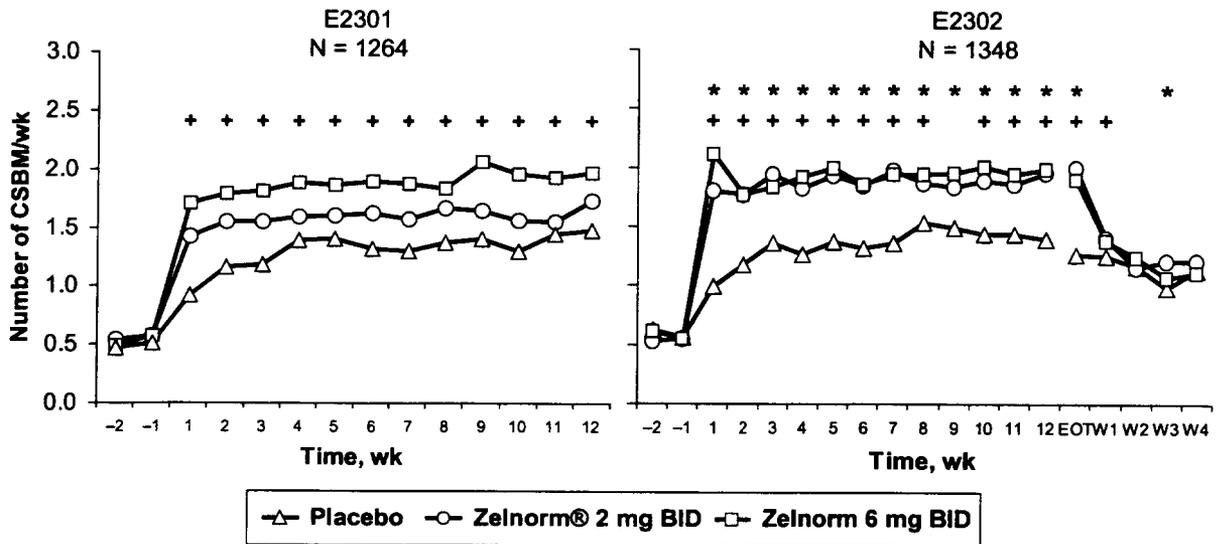
### Complete spontaneous bowel movements: Number per week

For both studies, the number of CSBM/week increased 3- to 4-fold after the start of treatment with Zelnorm (figure 6-5).

In Study E2301, the largest increase was observed in the 6mg b.i.d. group. In this group, the difference from placebo was statistically significant during the first week and maintained through the 12 weeks of treatment. The Zelnorm 2mg b.i.d. group was consistently greater than the placebo group, but the magnitude was lower, and did not reach statistical significance compared to placebo.

In Study E2302, both Zelnorm groups were statistically superior to placebo through the 12 weeks of treatment, but there was no clear superiority of either Zelnorm dose over the other dose.

**Figure 6-5 Number of Complete Spontaneous Bowel Movements per Week (Pivotal Studies E2301, E2302)**



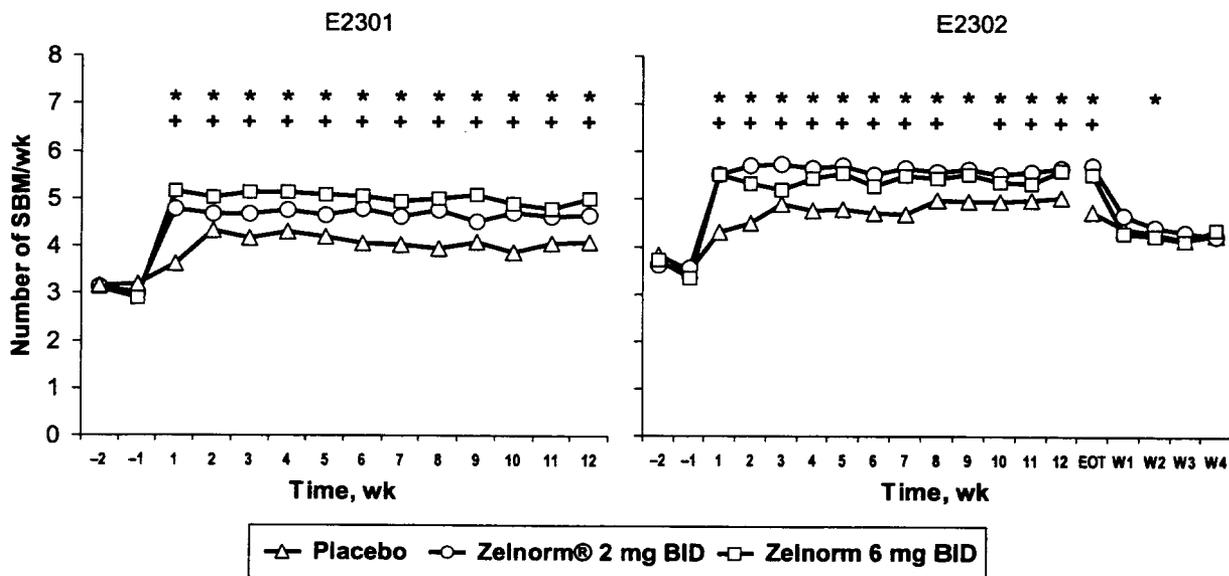
\* $P < .05$ , Zelnorm 2 mg b.i.d. vs placebo.  
 + $P < .05$ , Zelnorm 6 mg b.i.d. vs placebo, van Elteren test adjusted for center.  
 Mean data.  
 EOT = End of treatment; W = Withdrawal.

**Spontaneous bowel movements: Number per week**

Figures 6-6 presents the number of SBM/week for both studies E2301 and E2302.

In both studies, patients experienced a rapid, sustained, and statistically significant increase in the number of spontaneous bowel movements following initiation of treatment. While Study E2302 indicated similar results for both Zelnorm doses, Study E2301 indicated a clear superiority of 6mg b.i.d. over placebo and 2mg b.i.d.

**Figure 6-6 Spontaneous Bowel Movements (SBM) Per Week Pivotal Studies E2301, E2302**



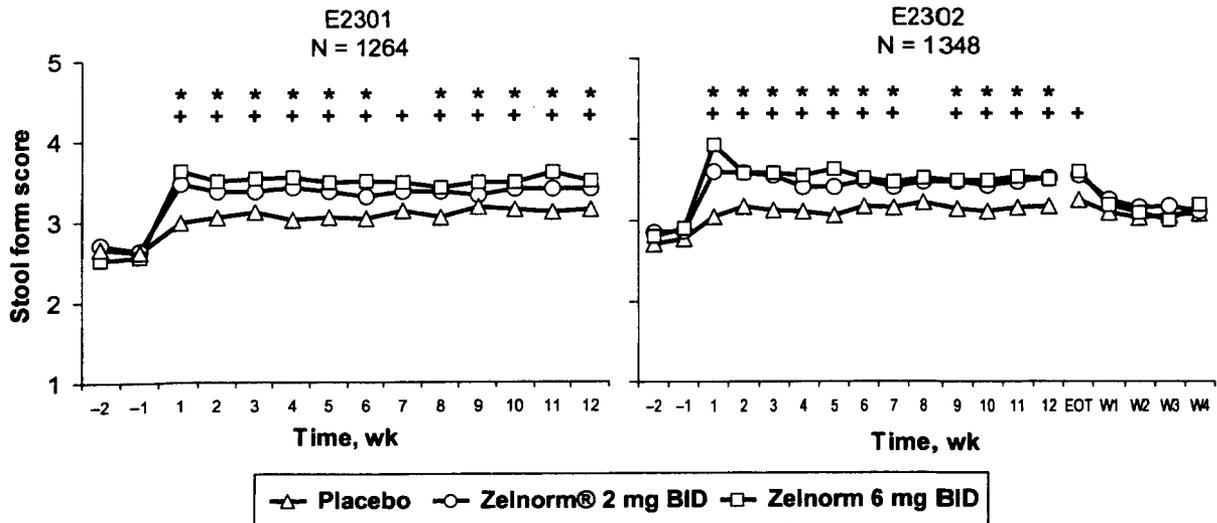
\* $P < .05$ , Zelnorm 2 mg b.i.d. vs placebo; + $P < .05$ , Zelnorm 6 mg b.i.d. vs placebo. Van Elteren test adjusted for center. SBM = Spontaneous bowel movement; EOT = End of treatment; W = Withdrawal

**Stool form**

For each bowel movement, patients were asked to rate the stool form using a 7-point scale (the Bristol stool scale), where 1 corresponds to hard lumps and 7 to watery stools.

The evaluation of the mean weekly stool form score of SBM revealed that both doses of Zelnorm were clinically and statistically significantly superior to placebo in rendering softer stool score for most weeks of double-blind treatment. A strong trend in favor of Zelnorm was observed. The improvement in stool form was dose-dependent in both trials (Figure 6-7).

**Figure 6-7 Mean Stool Form per Week Pivotal Studies E2301, E2302**



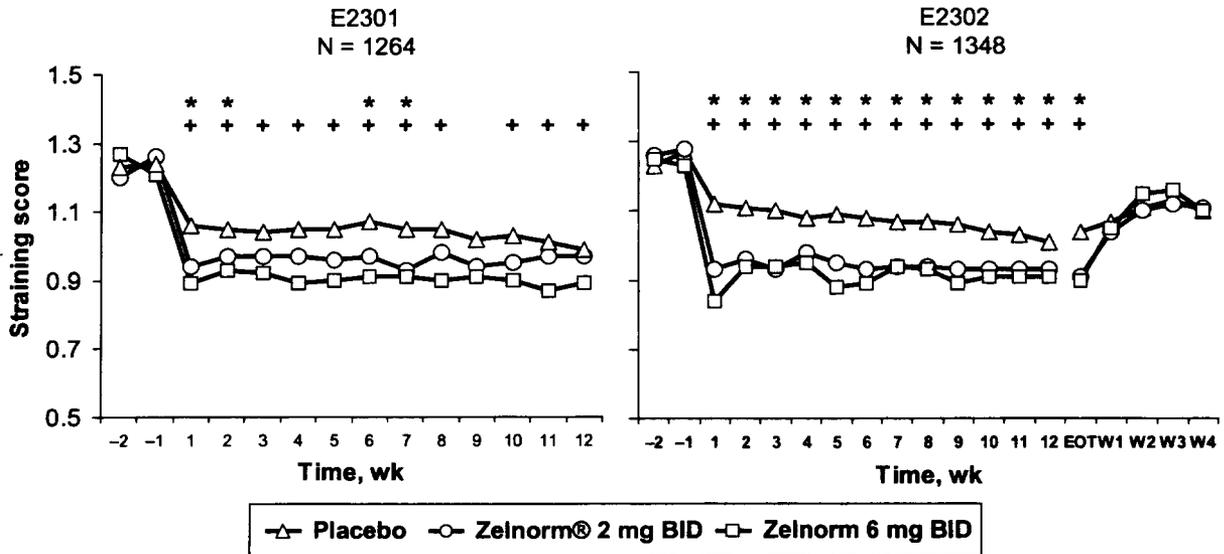
\* $P < .05$ , Zelnorm 2 mg b.i.d. vs placebo.  
 + $P < .05$ , Zelnorm 6 mg b.i.d. vs placebo, van Elteren test adjusted for center.  
 Mean data.  
 Scale 1 - 7, 1 = hard, 7 = watery.  
 EOT = End of treatment; W = Withdrawal.

**Straining**

Patients evaluated the straining associated with spontaneous bowel movements (SBM) using a 3 point scale: no straining (0), acceptable straining (1), and too much straining (2). Results presented here represent straining associated with spontaneous bowel movements and therefore were independent of the influence of laxative use.

Figure 6-8 presents the mean weekly straining score of spontaneous bowel movements.

**Figure 6-8 Mean Straining per Week  
 Pivotal Studies E2301, E2302**



\**P* < .05, Zelnorm 2 mg b.i.d. vs placebo.  
 +*P* < .05, Zelnorm 6 mg b.i.d. vs placebo, van Elteren test adjusted for center.  
 Scale 0 - 2, 0 = no straining, 1 = acceptable straining, 2 = too much straining.  
 EOT = End of treatment; W = Withdrawal.

In both studies, patients treated with 6mg b.i.d. experienced a significant reduction of the straining associated with spontaneous bowel movements. The effect was noted at the first week of treatment and sustained over the entire 12 weeks.

### 6.5.2 Effect on bothersomeness of symptoms of constipation

Patients were asked to rate, on a weekly basis, several symptoms associated with constipation using a 5-point scale (0 to 4 where lower scores indicate greater satisfaction/less bothersomeness). Responders were defined as patients who had a mean decrease from baseline of  $\geq 1$  point on the 5-point scale. The mean changes from baseline and response rates are summarized in Tables 6-7 and 6-8, followed by brief discussion of the individual variables.

**Table 6-7 Summary of mean change from baseline in weekly diary data for Week 1-12**

	Study E2301			Study E2302		
	Zelnorm 2 mg b.i.d. N = 417	Zelnorm 6 mg b.i.d. N = 431	Placebo N = 416	Zelnorm 2 mg b.i.d. N=450	Zelnorm 6 mg b.i.d. N=451	Placebo N=447
Bothersomeness of constipation	-0.6 p=0.0009	-0.7 p<0.0001	-0.5	-0.6 p<0.0001	-0.7 p<0.0001	-0.4
Bothersomeness of abdominal distension/bloating	-0.5 p=0.0074	-0.5 p=0.0006	-0.4	-0.7 p<0.0001	-0.6 p=0.0003	-0.4
Bothersomeness of abdominal discomfort/pain	-0.4 p=0.0062	-0.4 p=0.0002	-0.3	-0.5 p<0.0001	-0.4 p=0.0001	-0.2

Graded by patients using a 5-point scale, with lower scores indicating increased satisfaction/less bothersome symptoms

The p-values are from the repeated measures analysis of the whole 12 week treatment period

**Table 6-8 Summary of response rates for weekly diary data for Week 1-12**

	Study E2301			Study E2302		
	Zelnorm 2 mg b.i.d. N = 417	Zelnorm 6 mg b.i.d. N = 431	Placebo N = 416	Zelnorm 2 mg b.i.d. N=450	Zelnorm 6 mg b.i.d. N=451	Placebo N=447
Bothersomeness of constipation	34.6 p=0.0169	40.9 p<0.0001	27.7	35.1 p=0.0019	37.5 p=0.0003	25.7
Bothersomeness of abdominal distension/bloating	30.8 p=0.2553	32.3 p=0.1096	27.1	36.0 p=0.0069	35.4 p=0.0264	27.6
Bothersomeness of abdominal discomfort/pain	27.8 p=0.0697	28.3 p=0.0506	22.5	31.8 p=0.0005	30.5 p=0.0047	21.4

Patients who have a mean decrease of  $\geq 1$  point on a 5-point ordinal scale compared to baseline.

P values based on CMH tests

### Bothersomeness of constipation

In both studies, patients from all treatment groups experienced improvements compared to baseline in the bothersomeness of constipation, but the improvements were larger in both Zelnorm groups compared to placebo (Table 6-7).

The results for the responder rates (patients who had a decrease from baseline of at least one point on the 5-point scale) over the 12 week period were consistent with the results for change from baseline for each individual study. The results were statistically significant (Table 6-8).

### Bothersomeness of abdominal distension/bloating

Zelnorm-treated patients experienced a greater decrease in bothersomeness of abdominal distension/bloating compared to baseline than the placebo group.

The analysis, considering the whole 12-week treatment period, showed overall statistically significant differences between each dose of Zelnorm and placebo in both studies.

The responder rate over the 12 weeks of treatment showed a trend in favor of each Zelnorm group which was statistically significant in E2302 but not in E2301.

**Bothersomeness of abdominal discomfort/pain**

In both trials, Zelnorm-treated patients experienced a greater decrease in abdominal discomfort/pain compared to baseline than the placebo group, with both doses showing a similar magnitude of effect over the whole 12-week treatment period.

Again the analysis, considering the whole 12-week treatment period showed overall statistically significant differences between each dose of Zelnorm and placebo in both studies.

The responder rate was similar for both Zelnorm doses and superior to placebo in both studies; however, statistical significance was reached only in E2302.

**6.5.3 Satisfaction with bowel habits**

Satisfaction with bowel habits was measured on a 5-point scale (0= a very great deal satisfied, 1=a good deal satisfied, 2= moderately satisfied, 3=hardly satisfied, 4=not at all satisfied). Patients who have a mean decrease  $\geq 1$  point were designated as responders.

Both trials showed very similar results in the evaluation of satisfaction with bowel habits. Patient’s satisfaction with bowel habits was consistently better in each Zelnorm group compared to the placebo group. Statistical significance for each dose compared to placebo was reached for most weeks in both trials, as well as when considering the whole 12-week treatment period in the repeated measures analysis. For this variable, there was no Zelnorm dose clearly superior to the other in either study (Tables 6-9 and 6-10).

**Table 6-9 Summary of mean change from baseline in weekly diary data of Satisfaction with Bowel habits for Week 1-12**

	Study E2301			Study E2302		
	Zelnorm 2 mg b.i.d. N = 417	Zelnorm 6 mg b.i.d. N = 431	Placebo N = 416	Zelnorm 2 mg b.i.d. N=450	Zelnorm 6 mg b.i.d. N=451	Placebo N=447
Satisfaction with bowel habits	-0.7 p=0.0002	-0.7 p<0.0001	-0.5	-0.8 p<0.0001	-0.8 p<0.0001	-0.5

Graded by patients using a 5-point scale, with lower scores indicating increased satisfaction

The p-values are from the repeated measures analysis of the whole 12 week treatment period

**Table 6-10 Response Rate in Satisfaction with bowel habits for Week 1-12**

	Study E2301			Study E2302		
	Zelnorm 2 mg b.i.d. N = 417	Zelnorm 6 mg b.i.d. N = 431	Placebo N = 416	Zelnorm 2 mg b.i.d. N=450	Zelnorm 6 mg b.i.d. N=451	Placebo N=447
Satisfaction with bowel habits	39.4 p=0.0116	40.6 p=0.0025	31.7	43.5 p=0.0002	42.9 p=0.0003	30.6

Responder: Patients who have a mean decrease of  $\geq 1$  point on a 5-point ordinal scale compared to baseline.  
 P values based on CMH tests

## 6.6 Relationship between primary Efficacy Variable and other efficacy variables

Importantly there was a strong relationship between the primary efficacy variable and other efficacy variables. The degree of improvement of stool form and straining as well as satisfaction with bowel habits was significantly more pronounced in Zelnorm responders as defined as  $\geq 1$  CSBM increase/week compared to placebo responders (Table 6-11).

**Table 6-11 Relationship between primary efficacy variable and other efficacy variables**

	Responders			Non responders		
	Zelnorm 2mg b.i.d	Zelnorm 6mg b.i.d	Placebo	Zelnorm 2mg b.i.d	Zelnorm 6mg b.i.d	Placebo
Stool form <sup>1</sup>	1.05 (n=316)	1.33 (n=336)	0.79 (n=214)	0.47 (n=425)	0.61 (n=403)	0.20 (n=523)
Straining <sup>2</sup>	-0.49 (n=315)	-0.54 (n=336)	-0.39 (n=214)	-0.16 (n=428)	-0.17 (n=402)	-0.08 (n=522)
Satisfaction with Bowel Habits <sup>3</sup>	-1.16 (n=326)	-1.19 (n=358)	-1.03 (n=214)	-0.29 (n=489)	-0.31 (n=468)	-0.20 (n=599)

Responders defined as the primary efficacy variable

<sup>1</sup> Mean change (week 1-4) from baseline in stool form score, <sup>2</sup> Mean change (week 1-4) from baseline in straining score, <sup>3</sup> Mean change (week 1-4) from baseline in satisfaction with bowel habits.

P values based on CMH tests . p< 0.001 apply to each treatment comparison

## 6.7 Responses in population subgroups

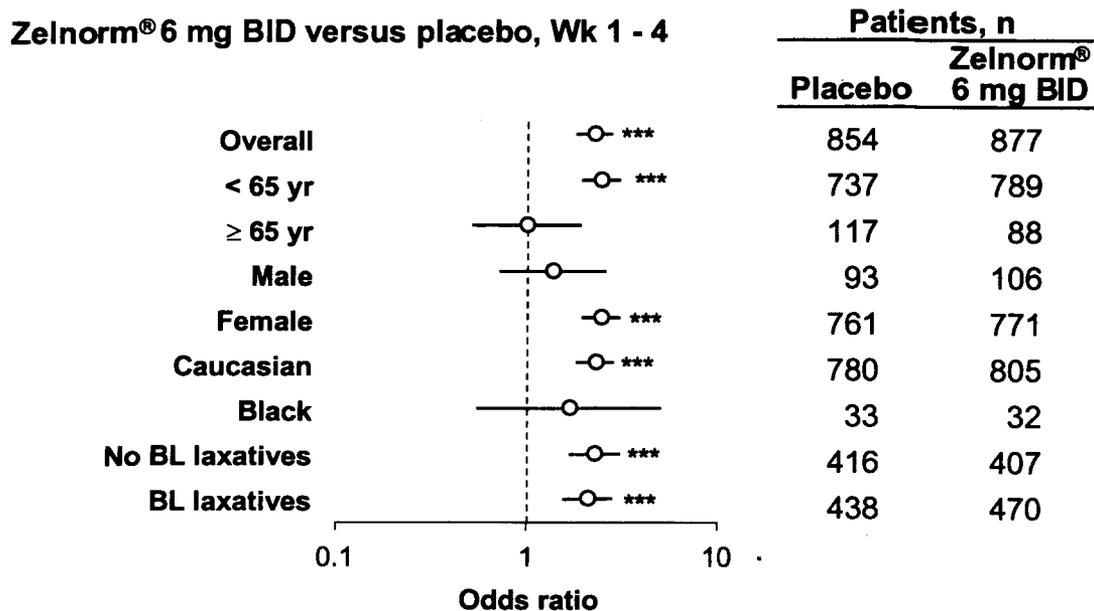
### 6.7.1 Influence of demographic factors

Data from the two efficacy studies were pooled to provide a larger dataset for examining efficacy in subgroups (gender, race, age, baseline use of laxatives).

This type of analysis was planned prospectively but the protocols did not require the enrollment of a minimum number of patients in any of these subgroups. Although no

demographic groups except children and adolescents ( $\leq 18$  years) were excluded from study, several subgroups were under-represented. Thus, only 10-14% of those studied were elderly ( $\geq 65$  years) or male. In addition,  $< 10\%$  of patients were non-Caucasian. The large confidence intervals reflect the smaller sample size in some of these subgroups (Figure 6-9).

**Figure 6-9 Odds ratio and 95% CI of the response rate for CSBM during weeks 1-4, by subgroups (pooled ITT patients treated with Zelnorm 6mg b.i.d. and placebo)**



\*\*\* $P < .0001$  vs placebo. Logistic regression.

CSBM = Complete spontaneous bowel movement; Responder = increase of  $\geq 1$  CSBM/wk.

**Age:**

Because of the relatively small numbers of patients older than 65 years, it is difficult to draw conclusions on the efficacy in this subgroup. There was no difference in the response rates between Zelnorm and placebo, however for patients on Zelnorm the response rates were similar to those in patients less than 65 years. The placebo response is higher in patients  $\geq 65$  years compared to patients  $< 65$  years. Thus the lack of apparent treatment effect in  $\geq 65$  years patients (Figure 6-9).

**Gender:**

In male patients, the response rate was higher for Zelnorm 6mg b.i.d than placebo. However because of the small number of male patients ( $< 12\%$ ), statistical significance was not reached in this comparison (Figure 6-9).

**Race**

The number of non-Caucasian patients was small (<9%). However, the Zelnorm 6mg b.i.d. versus placebo comparisons favored Zelnorm (Figure 6-9).

**6.7.2 Influence of other factors**

All patients selected for the pivotal trials met entry criteria for chronic constipation. However, patients with a history of current IBS were not specifically excluded from the trials. Therefore, Novartis performed an analysis to assess the response rate of Zelnorm in a subgroup of patients with features consistent with a diagnosis of IBS (i.e., IBS-like). To carry out this analysis, Novartis retrospectively identified patients with such IBS features. This identification was deemed most conservative because it targeted all patients who present with abdominal pain/discomfort as their main complaint or most bothersome symptom. Although abdominal pain/discomfort is one of the symptoms that may occur in patients with constipation (Stewart et al., 1999), patients reporting abdominal pain/discomfort as their predominant symptom (i.e., main complaint) may be considered more likely to be suffering from IBS.

Patients with IBS-like features were required to meet at least one of the following criteria: 1) Medical history of IBS, 2) Reported abdominal discomfort as their predominant complaint (historical data), 3) presence of abdominal pain/discomfort and diarrhea during baseline (diary data).

This IBS-like population represented approximately 22% of patients enrolled in the pivotal trials (Table 6-12).

**Table 6-12 Patients selected as IBS-Like (Pooled analysis-ITT population)**

	Zelnorm 2 mg b.i.d. N=867 n(%)	Zelnorm 6 mg b.i.d. N=882 n(%)	Placebo N=863 n(%)
a. Diagnosis of IBS in medical history	29 (3)	39 (4)	21 (2)
b. Abdominal discomfort as main complaint	108 (12)	109 (12)	102 (12)
c. Abdominal discomfort/pain bothersomeness score > 0 and diarrhea <sup>1</sup>	86 (10)	72 (8)	80 (9)
IBS-like: Meets any of the above criteria	201 (23)	197 (22)	185 (21)

<sup>1</sup> Patients with ≥ 25% of SBM loose or watery or > 3 SBM/d for ≥ 25 % of days

The subgroup analysis by disease feature type (IBS-like, reminder CC) confirmed the robustness of the efficacy of Zelnorm in patients suffering from CC with a treatment difference of 18% between Zelnorm 6mg b.i.d. and placebo (Table 6-13).

**Table 6-13 Responders (increase  $\geq$  1 CSBM/week from baseline) in weeks 1-4 by feature sub-group (pooled analysis, ITT population)**

Sub-populations	Zelnorm 2 mg b.i.d. N=867	Zelnorm 6 mg b.i.d. N=882	Placebo N=863
<b>Patients with IBS-type features</b>			
n	200	196	185
Number of responders (%)	69 (34.5)	67 (34.2)	47 (25.4)
Odds ratio <sup>1</sup>	1.82	1.76	
95% CI for odds ratio	1.11, 2.99	1.06, 2.90	
p-value	0.0186	0.0280	
<b>Remaining ITT patients</b>			
n	654	681	669
Number of responders (%)	261 (39.9)	297 (43.9)	174 (26.0)
Odds ratio <sup>1</sup>	2.00	2.48	
95% CI for odds ratio	1.56, 2.56	1.94, 3.17	
p-value	<0.0001	<0.0001	

<sup>1</sup> An odds ratio >1 favors Zelnorm over placebo

## 6.8 Laxative use during study period

The protocols specified that patients without a bowel movement for at least 96 hours were allowed to take bisacodyl tablets as rescue medication to a maximum of 15 mg/day. In both studies, laxative intake was comparable between treatment groups during the baseline period.

In study E2301, the mean number of days of laxatives use (normalized to 7 days) at baseline was 0.65, 0.71 and 0.69 in Zelnorm 2mg b.i.d, 6mg b.i.d and placebo respectively. During the treatment period, the mean number of days of laxatives use was lowest in both Zelnorm groups (0.46 and 0.43 days/week) and highest in the placebo group (0.59 days/week). In study E2301, the difference from placebo was statistically significant for both Zelnorm groups (p=0.0147 and p=0.0118 for Zelnorm 2and 6mg b.i.d., compared to placebo, respectively).

In study E2302, the mean number of days of laxatives use (normalized to 7 days) at baseline was 0.56, 0.62 and 0.56 in Zelnorm 2mg b.i.d, 6mg b.i.d and placebo respectively. During the treatment period, the mean number of days of laxatives use was 0.34, 0.40 and 0.41 in Zelnorm 2mg b.i.d , 6mg b.i.d and placebo respectively. No statistically significant between-group differences were observed in study E2302.

## 6.9 Development of tolerance or withdrawal effects

No tolerance was observed during the 12 weeks of treatment in either study, nor in the 13 months of the extension study.

No withdrawal or rebound effects were observed in the 4 weeks after ending therapy (Figures 6-5 to 6-8).

## 6.10 Conclusions of efficacy assessments

- **The primary efficacy endpoint was met:** Data from two adequate and well-controlled trials show that the primary efficacy variable (defined as the response rate to increase  $\geq 1$  CSBM/week at weeks 1-4) to be clinically and statistically significantly different from placebo for Zelnorm 2mg b.i.d. and 6mg b.i.d.
- **Dose-response effect:** Although 2mg b.i.d. and 6mg b.i.d. doses of Zelnorm both were found to be effective in reducing symptoms of chronic constipation, higher response rates were achieved with the 6mg b.i.d. dose. This was true for the primary and key secondary analyses of CSBM, as well as the more stringent alternative response definition agreed upon with the FDA. The magnitude of effect reached 13.5% and 18.1% for Zelnorm 6 mg b.i.d. compared to placebo for studies E2301 and E2302, respectively.
- **Early effect and sustained effect throughout the 12-week treatment duration:** The beneficial effect was observed in both studies after the first week of treatment with Zelnorm, when the percentage of patients with an increase of  $\geq 1$  CSBM/week compared to baseline was statistically significantly greater with Zelnorm 2mg b.i.d. and 6mg b.i.d. than with placebo. Both studies showed sustained treatment effect, using all responder definitions, throughout the 12-week treatment period, without any indication for the development of tolerance, supporting the recommended treatment duration of 12 weeks.
- **Positive effect on multiple symptoms of constipation as well as satisfaction with bowel habits:** Additional efficacy variables, which describe individual constipation symptoms and overall assessment of constipation (other secondary efficacy variables), and which are of particular importance to the patient, were improved in both studies by Zelnorm 6 mg b.i.d.
- **There was a strong relationship between the primary efficacy variable and the other efficacy measures .** The degree of improvement of stool form and straining as well as satisfaction with bowel habits was significantly more pronounced in Zelnorm responders compared to placebo responders
- **Efficacy in gender and age subgroups.** Consistent efficacy in favor of Zelnorm was seen in females and males, though the treatment difference was numerically lower in males. In the younger patients (< 65 years old), a strong effect was demonstrated. This effect was not seen in the small number of elderly (> 65) patients in these studies.

## 7 Safety Evaluation in Chronic Constipation

This section of the briefing document provides a comprehensive summary of the safety data in chronic constipation including:

- pooled safety analysis from the two pivotal double-blind, placebo-controlled studies in chronic constipation (E2301, E2302); and
- safety data from the 13-month long-term extension study in which patients received open label drug either at the dose of 2mg b.i.d. or 6mg b.i.d. (E2301E1).

## 7.1 Exposure to the drug

Exposure to Zelnorm in clinical studies was based on the number of patients given at least one dose of study drug.

### Pivotal studies

In the two pivotal studies, exposure to study medication was comparable across all treatment groups. The median duration of exposure was 86 days (Table 7-1).

**Table 7-1 Duration of exposure to study drug – Pivotal Studies**

	Zelnorm 2 mg b.i.d. (N = 861)	Zelnorm 6 mg b.i.d. (N = 881)	Placebo (N = 861)	Zelnorm any dose (N = 1742)	Total (N = 2603)
<b>Duration of exposure</b> (cumulative number (%) of patients)					
≥ 28 days	822 (95.5%)	820 (93.1%)	807 (93.7%)	1642 (94.3%)	2449 (94.1%)
≥ 56 days	768 (89.2%)	782 (88.8%)	747 (86.8%)	1550 (89.0%)	2297 (88.2%)
≥ 85 days	604 (70.2%)	585 (66.4%)	603 (70.0%)	1189 (68.3%)	1792 (68.8%)
<b>Summary statistics</b> (days)					
Mean ± SD	81.1 ± 20.8	79.8 ± 22.6	79.3 ± 23.3	80.4 ± 21.8	80.0 ± 22.3
Median	86.0	86.0	86.0	86.0	86.0
Range	1 - 117	1 - 122	1 - 128	1 - 122	1 - 128

Studies: E2301 (excluding extension data), E2302

### Long term extension study

The 13-month long-term extension study employed two Zelnorm dose levels (2 mg b.i.d. and 6 mg b.i.d.). Exposure to Zelnorm in this patient population across the pivotal study (E2301) and the extension phase (E2301E1) is summarized in Table 7-2. Since patients who received placebo in the pivotal study (E2301) were switched to Zelnorm 6mg b.i.d. in the extension study, the total number of patients receiving Zelnorm 6mg b.i.d. is nearly twice as high as the number of patients receiving Zelnorm 2mg b.i.d.. The median duration of exposure was 370 days.

**Table 7-2 Duration of exposure to Zelnorm –long-term extension study**

Duration of exposure	Zelnorm 2 mg b.i.d. - 2 mg b.i.d. N=283	Zelnorm 6 mg b.i.d. - 6 mg b.i.d. N=283	Placebo - Zelnorm 6 mg b.i.d. N=274	Zelnorm any dose N=840
<b>Duration of exposure to Zelnorm (cumulative number (%) of patients)</b>				
≥ 4 months	274 (96.5)	270 (95.7)	199 (72.6)	743 (88.5)
≥ 8 months	207 (72.9)	212 (75.2)	176 (64.2)	595 (70.8)
≥ 12 months	182 (64.1)	191 (67.7)	145 (52.9)	518 (61.7)
≥ 16 months	130 (48.5)	145 (51.4)	1 (0.4)	276 (32.9)
<b>Summary statistics (days)</b>				
Mean duration ± SD	350.3 ± 138.7	358.9 ± 137.3	255.8 ± 144.5	322.4 ± 147.5
Median duration	442	448	350	370
Range	36 – 532	29 – 530	10 – 461	10 – 532

Months = lunar months (28 days).

The Placebo - Zelnorm 6 mg b.i.d. group refers to patients who crossed over from placebo treatment at entry into the extension. Duration of exposure for all other patients includes exposure to active drug during the core study.

Studies: E2301 and E2301E1

## 7.2 Patient Disposition

### Pivotal studies

Patient participation and withdrawals in the pivotal studies are summarized in Table 7-3. The overall discontinuation rate was higher in the placebo group (18.4%) than in the Zelnorm groups (16%). The discontinuation rate due to adverse events was comparable in the placebo group (3.7%) and the Zelnorm 2 mg b.i.d. group (3.3%), and somewhat higher in the Zelnorm 6mg b.i.d. group (5.3%). Most frequent AEs leading to discontinuation included abdominal pain, diarrhea, abdominal distension, and nausea.

**Table 7-3 Participation and withdrawals by treatment – Pivotal studies**

	<b>Zelnorm 2 mg b.i.d.</b>	<b>Zelnorm 6 mg b.i.d.</b>	<b>Placebo</b>	<b>Zelnorm any dose</b>	<b>Total</b>
	n (%)	n (%)	n (%)	n (%)	n (%)
<b>Total no. of patients exposed to study drug</b>	861 (100)	881 (100)	861 (100)	1742 (100)	2603 (100)
No. (%) completed	730 (84.8)	733 (83.2)	703 (81.6)	1463 (84.0)	2166 (83.2)
No. (%) discontinued	131 (15.2)	148 (16.8)	158 (18.4)	279 (16.0)	437 (16.8)
<b>Main reason for discontinuation</b>					
Adverse event(s)	28 (3.3)	47 (5.3)	32 (3.7)	75 (4.3)	107 (4.1)
Unsatisfact. therapeutic effect	38 (4.4)	33 (3.7)	62 (7.2)	71 (4.1)	133 (5.1)
Subject withdrew consent	25 (2.9)	38 (4.3)	25 (2.9)	63 (3.6)	88 (3.4)
Lost to follow-up	28 (3.3)	22 (2.5)	21 (2.4)	50 (2.9)	71 (2.7)
Protocol violation	10 (1.2)	7 (0.8)	15 (1.7)	17 (1.0)	32 (1.2)
Administrative problems	1 (0.1)	0 (0.0)	3 (0.3)	1 (0.1)	4 (0.2)
Abnormal laboratory value(s)	1 (0.1)	1 (0.1)	0 (0.0)	2 (0.1)	2 (0.1)

Studies: E2301, E2302

### Long term extension study

Patient participation and withdrawals during the long-term extension study are summarized in Table 7-4. More than 50% of the patients completed 13 months' treatment and 46.2% of patients discontinued treatment for various reasons. No marked difference was seen between treatment groups for discontinuations overall or by primary reason for withdrawal. The most frequent reason for discontinuation was unsatisfactory therapeutic effect, followed by withdrawal of consent. Adverse events led to withdrawal in only 6% of patients.

**Table 7-4 Participation and withdrawals by treatment – long-term extension study**

	Zelnorm 2 mg b.i.d. - 2 mg b.i.d.	Zelnorm 6 mg b.i.d. - 6 mg b.i.d.	Placebo - Zelnorm 6 mg b.i.d.	Zelnorm any dose (total)
Eligible for participation in extension study (completed E2301)	347	359	342	1048
Entered the extension study *	284 (100)	283 (100)	275 (100)	842 (100)
Exposed in the extension study	284 (100)	282 (99.6)	274 (99.6)	840 (99.8)
no. (%) completed	154 (54.2)	158 (55.8)	139 (50.5)	451 (53.6)
no. (%) discontinued	130 (45.8)	124 (43.8)	135 (49.1)	389 (46.2)
<b>Main reason for discontinuation</b>				
Unsatisfactory therapeutic effect	56 (19.7)	51 (18.0)	55 (20.0)	162 (19.2)
Subject withdrew consent	31 (10.9)	30 (10.6)	31 (11.3)	92 (10.9)
Adverse event(s)	20 (7.0)	14 (4.9)	19 (6.9)	53 (6.3)
Lost to follow-up	7 (2.5)	16 (5.7)	9 (3.3)	32 (3.8)
Administrative problems	7 (2.5)	7 (2.5)	13 (4.7)	27 (3.2)
Protocol violation	6 (2.1)	3 (1.1)	6 (2.2)	15 (1.8)
Condition no longer requiring study drug	2 (0.7)	4 (1.4)	1 (0.4)	7 (0.8)
Abnormal laboratory value(s)	1 (0.4)	0 (0)	2 (0.7)	3 (0.4)

\* includes 9 patients who entered the extension study without participating in E2301

Studies: E2301, E2301E1

## 7.3 Adverse Events

### 7.3.1 Overall Adverse events

#### Pivotal Studies

Approximately 56 to 60% of the patients enrolled in the pivotal studies experienced at least one adverse event (AE). The frequency of AEs was slightly higher in the placebo group (59.6%) compared to the Zelnorm groups (56.7%). Not unexpectedly, gastrointestinal disorders were the most frequently reported events and were equally reported with placebo (24.6%) and with Zelnorm (24.2%). There was no imbalance across treatment groups for any system organ classes.

Among the most frequently-observed AEs (incidence  $\geq$  3% in any group), the incidence of diarrhea appeared to be higher with any Zelnorm dose than with placebo. Other AEs were well balanced between treatment groups. (Table 7-5).

**Table 7-5 Most frequent AEs (≥ 3% patients in any group) – Pivotal studies**

	Zelnorm 2 mg b.i.d. N = 861 n (%)	Zelnorm 6 mg b.i.d. N = 881 n (%)	Placebo N = 861 n (%)	Zelnorm any dose N = 1742 n (%)
<b>Patients</b>				
Total number (%) of patients with AE(s)	485 (56.3)	503 (57.1)	513 (59.6)	988 (56.7)
<b>Adverse event preferred term</b>				
Headache NOS	87 (10.1)	97 (11.0)	114 (13.2)	184 (10.6)
Nasopharyngitis	44 (5.1)	63 (7.2)	62 (7.2)	107 (6.1)
Diarrhea NOS	36 (4.2)	58 (6.6)	26 (3.0)	94 (5.4)
Abdominal pain NOS	52 (6.0)	41 (4.7)	45 (5.2)	93 (5.3)
Nausea	41 (4.8)	41 (4.7)	32 (3.7)	82 (4.7)
Upper respiratory tract infection NOS	30 (3.5)	31 (3.5)	17 (2.0)	61 (3.5)
Abdominal distension	28 (3.3)	32 (3.6)	30 (3.5)	60 (3.4)
Sinusitis NOS	27 (3.1)	30 (3.4)	20 (2.3)	57 (3.3)
Flatulence	27 (3.1)	25 (2.8)	30 (3.5)	52 (3.0)
Dyspepsia	24 (2.8)	25 (2.8)	26 (3.0)	49 (2.8)

NOS: not otherwise specified

Studies : E2301 (without the extension), E2302

**Long term extension study**

The AE pattern observed in the long-term extension study was similar to that seen in the pivotal studies. Although frequencies of AEs were generally higher in the extension study due to the longer exposure, no relevant differences were seen between patients exposed to 2mg b.i.d. and those exposed to 6mg b.i.d. for the same length of exposure (Table 7-6). The most frequently observed AEs included: headache, abdominal pain and diarrhea.

**Table 7-6 Most frequent AEs (≥ 3% of patients in any group) - long-term extension study**

	Zelnorm 2 mg b.i.d. - 2 mg b.i.d. N = 283	Zelnorm 6 mg b.i.d. - 6 mg b.i.d. N = 283	Placebo - Zelnorm 6 mg b.i.d. N = 274	Zelnorm any dose (total) N = 840
Total number (%) of patients with AE(s)	226 (79.9)	215 (76.0)	180 (65.7)	621 (73.9)
Adverse Event preferred term	n (%)	n (%)	n (%)	n (%)
Headache	68 (24.0)	60 (21.2)	44 (16.1)	172 (20.5)
Abdominal pain NOS	42 (14.8)	32 (11.3)	30 (10.9)	104 (12.4)
Diarrhea NOS	23 (8.1)	28 (9.9)	29 (10.6)	80 (9.5)
Nasopharyngitis	27 (9.5)	31 (11.0)	19 (6.9)	77 (9.2)
Nausea	35 (12.4)	26 (9.2)	12 (4.4)	73 (8.7)
Influenza	19 (6.7)	29 (10.2)	16 (5.8)	64 (7.6)
Back pain	17 (6.0)	20 (7.1)	14 (5.1)	51 (6.1)

Abdominal distension	16 (5.7)	22 (7.8)	11 (4.0)	49 (5.8)
Abdominal pain upper	18 (6.4)	19 (6.7)	12 (4.4)	49 (5.8)
Constipation	13 (4.6)	18 (6.4)	11 (4.0)	42 (5.0)
Dyspepsia	21 (7.4)	11 (3.9)	9 (3.3)	41 (4.9)
Flatulence	11 (3.9)	14 (4.9)	16 (5.8)	41 (4.9)
Sinusitis NOS	16 (5.7)	14 (4.9)	6 (2.2)	36 (4.3)
Arthralgia	12 (4.2)	12 (4.2)	7 (2.6)	31 (3.7)
Dizziness	12 (4.2)	15 (5.3)	4 (1.5)	31 (3.7)
Bronchitis NOS	16 (5.7)	8 (2.8)	5 (1.8)	29 (3.5)
Insomnia	7 (2.5)	13 (4.6)	8 (2.9)	28 (3.3)
Cough	10 (3.5)	7 (2.5)	7 (2.6)	24 (2.9)
Respiratory tract infection NOS	10 (3.5)	6 (2.1)	8 (2.9)	24 (2.9)
Pharyngolaryngeal pain	9 (3.2)	6 (2.1)	8 (2.9)	23 (2.7)
Urinary tract infection NOS	8 (2.8)	9 (3.2)	6 (2.2)	23 (2.7)
Depression	5 (1.8)	6 (2.1)	9 (3.3)	20 (2.4)
Migraine NOS	9 (3.2)	7 (2.5)	4 (1.5)	20 (2.4)
Fatigue	5 (1.8)	9 (3.2)	5 (1.8)	19 (2.3)
Pharyngitis	4 (1.4)	10 (3.5)	5 (1.8)	19 (2.3)
Chest pain	10 (3.5)	5 (1.8)	3 (1.1)	18 (2.1)
Vomiting NOS	7 (2.5)	10 (3.5)	1 (0.4)	18 (2.1)
Vertigo	9 (3.2)	5 (1.8)	3 (1.1)	17 (2.0)

Adverse events are sorted by descending order of incidence in the combined Zelnorm groups.

Studies : E2301E1 (including periods of Zelnorm exposure during E2301). The placebo-Zelnorm group had a shorter exposure to Zelnorm compared to other groups.

### 7.3.2 Adverse Event severity

Adverse event severity was rated by the investigator as either mild, moderate, or severe. The study protocol did not provide a specific definition of severity.

#### Pivotal studies

Incidence rates of severe AEs were generally low (Table 7-7). In pivotal studies, the most frequently reported severe AE was abdominal pain occurring in 2% of patients at equal frequencies across treatment groups. Diarrhea incidence and severity displayed a dose-dependent pattern.

**Table 7-7 Adverse events rated as severe (n> 5 patients across all groups)-  
 Pivotal studies**

	<b>Zelnorm 2 mg b.i.d. N = 861 n(%)</b>	<b>Zelnorm 6 mg b.i.d. N = 881 n(%)</b>	<b>Placebo N = 861 n(%)</b>	<b>Zelnorm any dose N = 1742 n (%)</b>
Abdominal pain NOS	11(1.3)	12(1.4)	12(1.4)	23(1.3)
Headache NOS	4(0.5)	9(1.0)	8(0.9)	13(0.7)
Diarrhea NOS	3(0.3)	7(0.8)	2(0.2)	10(0.6)
Abdominal distension	3(0.3)	6(0.7)	4(0.5)	9(0.5)

Studies: E2301 and E2302

**Long term extension study**

In the long-term extension study, headache and abdominal pain were the only severe AEs occurring in >2% of the patients (Table 7-8).

**Table 7-8 AEs rated as severe in >5 patients across all treatment groups - long-  
 term extension study**

	<b>Zelnorm 2 mg b.i.d. - 2 mg b.i.d. N = 283</b>	<b>Zelnorm 6 mg b.i.d. - 6 mg b.i.d. N = 283</b>	<b>Placebo - Zelnorm 6 mg b.i.d. N = 274</b>	<b>Zelnorm any dose (total) N = 840</b>
Headache	13 ( 4.6)	9 ( 3.2)	8 ( 2.9)	30( 3.6)
Abdominal pain NOS	7 (2.5)	12 (4.2)	11 (4.0)	30 (3.6)
Abdominal pain upper	6 (2.1)	4 (1.4)	5 (1.8)	15 (1.8)
Nausea	5 (1.8)	5 (1.8)	2 (0.7)	12 (1.4)
Back pain	3 (1.1)	5 (1.8)	4 (1.5)	12 (1.4)
Diarrhea NOS	4 (1.4)	2 (0.7)	4 (1.5)	10 (1.2)
Influenza	3 (1.1)	3 (1.1)	3 (1.1)	9 (1.1)
Abdominal distension	2 (0.7)	5 (1.8)	1 (0.4)	8 (1.0)
Constipation	2 (0.7)	3 (1.1)	2 (0.7)	7 (0.8)
Migraine NOS	4 (1.4)	2 (0.7)	1 (0.4)	7 (0.8)

Study E2302E1

### 7.3.3 Adverse Events of Interest

#### Diarrhea

Diarrhea is known to be a dose-dependent, drug-related event and, therefore, is considered an adverse event that warrants further analysis to better understand its clinical implications in patients with CC.

In the pivotal trials, diarrhea was reported as severe in  $\leq 0.5\%$  of patients (Table 7-7). None of the severe diarrhea cases from the pivotal studies met the definition of Serious Adverse Event (SAE), or resulted in any clinically significant consequences of diarrhea such as hypokalemia, hypovolemia, need for i.v. fluids, or medically significant consequences of hypovolemia such as syncope, hypotension, or cardiac effects.

In the majority of cases, no action was taken in response to the diarrhea and it rarely led to dose interruptions or the use of concomitant medication. Rates of discontinuation due to diarrhea were comparable in the Zelnorm 2mg b.i.d. and placebo groups. The rate was higher in the Zelnorm 6mg b.i.d. group (Table 7-9) but still low in absolute terms (less than 1% of patients in the higher dose group). Also, in the majority of the cases diarrhea did not require treatment.

**Table 7-9 Diarrhea management– Pivotal studies**

	Zelnorm 2 mg b.i.d. N = 861	Zelnorm 6 mg b.i.d. N = 881	Placebo N = 861	Zelnorm any dose N = 1742
<b>Actions taken</b>	n (%)	n (%)	n (%)	n (%)
Diarrhea NOS	36 (4.2)	58 (6.6)	26 (3.0)	94 (5.4)
No action taken	24 (2.8)	30 (3.4)	19 (2.2)	54 (3.1)
Concomitant medication taken	5 (0.6)	6 (0.7)	3 (0.3)	11 (0.6)
Dose adjusted / interrupted	6 (0.7)	21 (2.4)	3 (0.3)	27 (1.5)
Dose permanently discontinued	3 (0.3)	8 (0.9)	2 (0.2)	11 (0.6)

Patient numbers for actions taken may add up to more than the total number of patients with an event because each AE occurrence was counted and more than one action was possible.

Studies: E2301 and E2302

The incidence, time of onset, relation to dose, duration, and severity of diarrhea are summarized in Table 7-10. Onset was at a similar time for Zelnorm 2mg b.i.d. and placebo, but was earlier with Zelnorm 6mg b.i.d. (median 5.5 days). Duration was short and similar in all groups. Although more patients on Zelnorm experienced diarrhea, the recurrence rate was comparable between Zelnorm and placebo.

**Table 7-10 Diarrhea evaluation – Pivotal studies**

	Zelnorm 2 mg b.i.d.	Zelnorm 6 mg b.i.d.	Placebo	Zelnorm any dose
Patients without diarrhea - n (%)	825 (95.8%)	823 (93.4%)	835 (97.0%)	1648 (94.6%)
<b>Patients with diarrhea - n (%)</b>	<b>36 (4.2%)</b>	<b>58 (6.6%)</b>	<b>26 (3.0%)</b>	<b>94 (5.4%)</b>
not using antipropulsants	34 (3.9%)	55 (6.2%)	25 (2.9%)	89 (5.1%)
using antipropulsants	2 (0.2%)	3 (0.3%)	1 (0.1%)	5 (0.3%)
<b>Days to onset of first episode</b>	n = 36	n = 58	n = 26	n = 94
Mean (days) ± SD	33.6 ± 30.99	21.8 ± 26.57	39.5 ± 24.76	26.3 ± 28.76
Median (range)	30.5 (1 - 90)	5.5 (1 - 80)	41 (1 - 79)	11.5 (1 - 90)
Onset on day 1	9	19	2	28
Onset on days 2 to 7	4	12	2	16
Onset on days 8 to 29	5	10	5	15
Onset on days 30 to 59	9	8	10	17
Onset on days 60 to 89	8	9	7	17
Onset on day 90 or later	1	0	0	1
<b>Duration of first episode (days)</b>	n = 34	n = 56	n = 25	n = 90
Mean ± SD	4.2 ± 5.44	8.8 ± 18.18	2.7 ± 2.32	7.1 ± 14.84
Median (range)	2 (1 - 29)	2.5 (1 - 85)	2 (1 - 9)	2 (1 - 85)
<b>Diarrhea episodes per patient</b>				
1 episode	29 (3.4%)	48 (5.4%)	22 (2.6%)	77 (4.4%)
2 episodes	3 (0.3%)	9 (1.0%)	3 (0.3%)	12 (0.7%)
> 2 episodes	4 (0.5%)	1 (0.1%)	1 (0.1%)	5 (0.3%)
<b>Patients who experienced diarrhea who had multiple episodes</b>	7/36 (19.4%)	10/58 (17.2%)	4/26 (15.4%)	17/94 (18%)

Studies: E2301 and E2302

The incidence of diarrhea observed in the long-term extension study was comparable in patients who switched from placebo to Zelnorm (10.5%) and in patients who remained on Zelnorm (9.5%). The characteristics of diarrhea were comparable to those reported in the pivotal studies. Importantly, none of the diarrhea cases reported in the long-term extension study resulted in clinically significant consequences.

#### Withdrawal Data

In one of the two pivotal chronic constipation studies (E2302), primary and secondary efficacy results obtained during treatment and during a subsequent four-week withdrawal period were analyzed for potential rebound effects. No evidence of a rebound effect on gastrointestinal function after discontinuation of Zelnorm was observed. No treatment group difference in constipation-related symptoms remained after one to two weeks, and constipation symptom severity approached but did not reach pre-treatment baselines. This gradual reversal without any indication of any rebound effect was the same as that observed in previous Zelnorm studies.

Relatively few patients (211 patients; 18.9% overall) had adverse events during the four-week withdrawal period of Study E2302, and the three most frequent events occurred more frequently in the placebo group than in the Zelnorm groups (Table 7-11).

**Table 7-11 Frequent (≥ 2%) AEs during the withdrawal period of E2302**

	Zelnorm 2 mg b.i.d. N = 380	Zelnorm 6 mg b.i.d. N = 375	Placebo N = 361
Total number (%) of patients with AE(s)	60 (15.8)	78 (20.8)	73 (20.2)
Headache NOS	6 (1.6)	7 (1.9)	10 (2.8)
Nasopharyngitis	3 (0.8)	5 (1.3)	8 (2.2)
Upper respiratory tract infection NOS	0	4 (1.1)	8 (2.2)

In the 30-day post-treatment follow-up period stipulated in all study protocols for the reporting of SAEs, no event was reported which might suggest CNS-mediated withdrawal effects.

## 7.4 Serious Adverse Events

### Pivotal studies

Non-fatal serious adverse events occurred in 44 patients (1.7%). Incidence rates were comparable across all treatment groups, with 11 patients on Zelnorm 2mg b.i.d., 16 patients on Zelnorm 6mg b.i.d., and 17 patients on placebo experiencing at least one SAE. Only one event (severe abdominal and stomach pain in a patient on Zelnorm 2mg b.i.d. which led to hospitalization and permanent discontinuation from the study) was considered by the investigator as suspected to be related to study drug. Three patients each in the Zelnorm 6 mg b.i.d. and placebo groups and 4 patients in the Zelnorm 2mg b.i.d. group discontinued due to SAEs.

Except for the gastrointestinal system, no body system was affected in more than 2 patients in any treatment group. The gastrointestinal SAEs affected 5 patients (one case each with colitis, gastrointestinal hemorrhage, aggravated hemorrhoids, abdominal pain, and abdominal pain with upper abdominal pain) in the Zelnorm 2mg b.i.d. group, 3 patients (one case each with an anal fissure and subsequent rectal lesion, gastroparesis, and abdominal pain) in the Zelnorm 6mg b.i.d. group, and 2mg b.i.d. patients (one case each of inguinal hernia and of hemorrhoids) in the placebo group.

### Long-term extension study

Overall, 37 patients in the key long-term extension study experienced SAEs: 15 (5.3%) in Zelnorm 2mg-2mg group, 12 (4.2%) in the Zelnorm 6mg-6mg group and 10 (3.6%) in the placebo-Zelnorm 6mg b.i.d. Importantly, few patients discontinued study medication due to SAEs. The SAEs leading to study drug discontinuation were 5 patients in the Zelnorm 2 mg b.i.d. group (fecal abnormality, dyspepsia, acute pyelonephritis, bone neoplasm, breast fibroadenoma), 2 in the Zelnorm 6mg b.i.d. group (anal fistula excision and suicidal ideation, encephalopathy) and 2 in the placebo-Zelnorm 6mg b.i.d. group (ovarian cyst, basal cell carcinoma).

## **7.5 Clinical Laboratory and other evaluations**

### **Clinical chemistry**

Blood chemistry variables included serum calcium, uric acid, glucose, total protein, albumin, urea, total bilirubin, total cholesterol, alkaline phosphatase, ALT, AST, sodium, potassium, chloride, creatinine, and total creatine kinase.

### **Pivotal studies**

No notable abnormalities were reported in any patient for total protein, albumin, urea, chloride, ALT and AST. The majority of the laboratory parameters for which notable abnormalities were reported (Table 7-12), were comparable across treatment groups. No significant trend was observed in favor of malabsorption, renal, or liver toxicity.

**Table 7-12 Number (%) of patients with notably abnormal clinical chemistry findings – Pivotal studies**

Variable	Time point	Zelnorm 2 mg b.i.d.	Zelnorm 6 mg b.i.d.	Placebo
		N = 861	N = 881	N = 861
		n (%)	n (%)	n (%)
Alkaline phosphatase high	Baseline	0	0	0
	End of study	0	0	1 (0.1)
Calcium high	Baseline	0	0	0
	End of study	1 (0.1)	0	0
Total creatine kinase high	Baseline	2 (0.3)	1 (0.1)	0
	End of study	2 (0.3)	2 (0.3)	0
Creatinine high	Baseline	1 (0.1)	0	0
	End of study	2 (0.3)	0	0
Glucose low	Baseline	1 (0.1)	2 (0.3)	2 (0.3)
	End of study	4 (0.5)	3 (0.4)	2 (0.3)
Glucose high	Baseline	2 (0.3)	1 (0.1)	1 (0.1)
	End of study	3 (0.4)	1 (0.1)	2 (0.3)
Potassium low	Baseline	0	1 (0.1)	1 (0.1)
	End of study	0	0	0
Potassium high	Baseline	0	0	1 (0.1)
	End of study	3 (0.4)	3 (0.4)	3 (0.4)
Sodium high	Baseline	1 (0.1)	1 (0.1)	1 (0.1)
	End of study	0	0	0
Bilirubin (total) high	Baseline	1 (0.1)	3 (0.4)	2 (0.3)
	End of study	0	3 (0.4)	2 (0.3)
Cholesterol high	Baseline	4 (0.5)	3 (0.4)	2 (0.3)
	End of study	0	3 (0.4)	2 (0.3)
Uric acid high	Baseline	1 (0.1)	0	0
	End of study	0	0	0

The denominator for the percentages given is the number of patients with data available.

### Long-term extension study

No relevant systematic changes from baseline were found for most parameters during treatment with Zelnorm 2 mg or 6 mg b.i.d. One patient was withdrawn due to elevated serum total creatine kinase levels (approximately 20 times upper limit of normal).

### Hematology

The number of patients with notably abnormal hematology findings was similar across treatments groups in the pivotal studies, except for a marginal increase in the number of patients with high eosinophils in the Zelnorm 2mg b.i.d. group (1.7%), but not in the Zelnorm 6mg b.i.d. (0.9%) or placebo groups (1%). In the long-term extension study, the percent of

patients with newly occurring eosinophil count increases to  $\geq 500/\text{mm}^3$  was similar between treatment groups and ranged from 3.3% to 4.5%.

## **ECG**

The percentage of patients with new or worsened ECG abnormalities at any time during the study was comparable across treatment groups (Table 7-13). Similar characteristics were observed when all ECG abnormalities (including anomalies existing at baseline) were considered. Ectopic atrial rhythm occurred in one patient on Zelnorm 2mg b.i.d. and 2 patients on Zelnorm 6mg b.i.d.; and one case each of atrial flutter and fibrillation were reported in the Zelnorm 2mg b.i.d. group. No ventricular tachycardia or fibrillation was seen on the ECGs. In addition to the rhythm abnormalities presented in Table 7-13, conduction and morphology abnormalities, evidence of myocardial infarction, and abnormal ST segments, T waves and U waves could all lead to ECGs being classed as abnormal. No clinically relevant changes from baseline were observed for mean ventricular rate (Table 7-13).

In all, there was no evidence of any consistent effect of Zelnorm 2mg b.i.d. and 6mg b.i.d. on QTc duration. QTc outliers defined as changes from baseline of  $\geq 30\text{ms}$  to  $< 60\text{ms}$  and the number and percent of patients with at least one post-first dose prolongation were similar across treatment groups and comparable to placebo. No patient had a QTc measurement  $\geq 500\text{ms}$  at any time during the study.

**Table 7-13 Summary of ECG diagnoses and parameters –Pivotal studies and Long term extension study**

	Pivotal Studies (E2301 + E2302)			Long-term extension population <sup>1</sup>	
	Zelnorm 2 mg b.i.d. N = 861	Zelnorm 6 mg b.i.d. N = 881	Placebo N = 861	Zelnorm 2 mg b.i.d. N = 283	Zelnorm 6 mg b.i.d. N = 557
<b>ECG abnormalities</b>	n (%)	n (%)	n (%)	n (%)	n (%)
Any new or worsened abnormality <sup>2</sup>	37 (4.3)	34 (3.9)	31 (3.6)	31 (11.4)	35 (7.3)
<b>Rhythm abnormalities</b>					
Sinus bradycardia	1 (0.1)	2 (0.2)	5 (0.6)	1 (0.4)	4 (0.8)
Ectopic atrial rhythm	1 (0.1)	2 (0.2)	0	2 (0.7)	1 (0.2)
Atrial flutter	1 (0.1)	0	0	-	-
Atrial fibrillation	1 (0.1)	0	0	1 (0.4)	0
<b>ECG interval summaries</b>					
<b>Ventricular rate (bpm)</b>					
Baseline mean ± SD	67.9 ± 10.7	66.8 ± 10.7	67.5 ± 10.5	na	na
Change from baseline	0.1 ± 9.2	0.8 ± 9.2	-0.2 ± 9.4	na	na
<b>QTc interval (ms)</b>					
Baseline mean ± SD	400.5 ± 22.5	399.2 ± 23.1	400.5 ± 22.4	na	na
Change from baseline	1.2 ± 21.7	2.1 ± 21.4	0.3 ± 21.7	na	na
max % increase	0.5 ± 5.45	0.7 ± 5.42	0.2 ± 5.50	na	na
n (%) increase ≥ 30ms to < 60 ms	58 (6.7%)	77 (8.7%)	67 (7.8%)	na	na
n (%) increase ≥ 60 ms	5 (0.6%)	4 (0.5%)	2 (0.2%)	na	na
At least 1 post-first dose prolonged QTc <sup>3</sup>	2 (0.3%)	4 (0.5%)	4 (0.5%)	2 (0.7%)	2 (0.4%)

ECG interval data are shown for all patients with baseline and at least one post-baseline measurement (key safety population: n = 760 for Zelnorm 2mg b.i.d. and placebo, and n = 781 for Zelnorm 6mg b.i.d.; key long-term safety population: n = 268 for Zelnorm 2mg b.i.d., n = 473 for Zelnorm 6mg b.i.d.)

<sup>1</sup> Includes findings from the Zelnorm treatment periods during the core study E2301

<sup>2</sup> Including rhythm, conduction, and morphology abnormalities, myocardial infarction, and abnormal ST segments, T waves and U waves.

<sup>3</sup> Prolonged QTc is > 450ms for males and > 470ms for females.

na = not applicable

### Vital signs and weight

Mean systolic and diastolic blood pressure decreased very slightly across all treatment groups in the pivotal studies.

Mean body weight remained unchanged in all treatment groups. In the long-term extension study, weight changes by ≥10% occurred in 2-6% of the patients across treatment groups with no clear relationship to dose.

## 8 Overall Safety Evaluation

### 8.1 The favorable safety profile established at approval in July 2002 for IBS-C was confirmed in the Chronic Constipation clinical program

The safety profile in the CC clinical program confirmed the positive safety profile established at approval for IBS-C in July 2002 (Table 8-1).

**Table 8-1 Safety Data from CC Pivotal studies and Prescribing information (%)**

	Pivotal Studies (E2301 + E2302)		Prescribing Information for IBS-C	
	Placebo N = 861	Zelnorm 6 mg b.i.d. N = 881	Placebo N = 1305	Zelnorm 6 mg b.i.d. N = 1327
Headache	13	11	12	15
Abdominal Pain	5	5	11	12
Diarrhea	3	7	4	9
AEs leading to discontinuation	4	5	5	7

The most frequently reported adverse events were headache, abdominal pain, and diarrhea. The reporting rates of headache and diarrhea in the CC program were similar to, but slightly lower than, the rates documented in the IBS-C program. However, the reporting rate of abdominal pain was substantially lower in CC than in IBS-C, illustrating the fact that abdominal pain is a feature mainly of IBS-C.

**Table 8-2 Serious Adverse Events in CC and at approval for IBS-C (%)**

Percent	Pivotal Studies (E2301 + E2302)		Data at NDA approval July 2002	
	Placebo N = 861	Zelnorm 6 mg b.i.d. N = 881	Placebo N = 1589	Zelnorm 6 mg b.i.d. N = 2446
SAEs	1.6	1.4	1.1	1.6
SAEs leading to discontinuation	0.3	0.3	0.6	0.7

The pattern of serious adverse events was similar in the CC studies as compared to the data at approval of Zelnorm in July 2002 (Table 8-2).

One issue raised at the July 2002 approval was the incidence of cholecystectomies that appeared to be higher with Zelnorm (0.17% vs. 0.06% on placebo). In the CC clinical trials there was only one patient with cholecystectomy (Zelnorm, 0.06%).

It is important to note that the incidence of abdominal and pelvic surgeries including cholecystectomies appeared to be lower with Zelnorm compared to placebo in the CC clinical program, which suggests that there is no causal relationship between Zelnorm and

abdominal/pelvic surgeries, and that Zelnorm does not have a deleterious effect on gallbladder function.

## **8.2 Safety topics of special interest**

Novartis has agreed with the FDA to focus the safety overview on topics of special interest:

- serious adverse events including fatalities,
- serious consequences of diarrhea,
- rectal bleeding,
- ischemic colitis and other forms of intestinal ischemia,
- cholecystectomies, and
- ovarian disease.

In order to address these topics appropriately, Novartis has performed a comprehensive safety database review of Zelnorm clinical trials and post-marketing experience data. The post-marketing experience data cutoff was May 14, 2004.

The clinical trials encompassed more than 11,600 patients on Zelnorm. Of these, 8641 patients participated in randomized clinical trials. The overall clinical experience with Zelnorm corresponded to 3456 patient-years of treatment.

Zelnorm is currently marketed in more than 30 countries. It has been on the market for 3 years, in the U.S. for 2 years. It is estimated that 3 million patients have taken Zelnorm world-wide, corresponding to more than 300,000 patient years of treatment.

### **8.2.1 Serious Adverse Events and Fatalities**

In clinical trials, SAEs were well balanced between Zelnorm (107/6864, 1.56%) and placebo (64/3915, 1.63%). The estimated frequency per 100 patient-years was 7.95 on Zelnorm and 8.21 on placebo. There were 6 fatalities reported in clinical trials: 3 cancers, 2 suicides and 1 acute myocardial infarction. None of the fatalities was considered related to Zelnorm treatment by the investigators. Ages ranged from 57 to 88 years. During post-marketing experience in 3 million patients treated with Zelnorm, 38 fatalities were reported: 7 cardiovascular, 6 cancer, 4 gastrointestinal, 3 psychiatric, 10 other, and 8 from unknown causes. Patients' ages ranged from 32 to 94 years old, with a median age of 77 years.

### **8.2.2 Clinical Significant Consequences of Diarrhea**

As expected with a promotility agent like Zelnorm, in controlled clinical trials severe diarrhea occurred more frequently with Zelnorm (3.0%) than placebo (0.8%). Most of these cases were self-limiting and only 6 cases led to clinically significant consequences of diarrhea (CSC-diarrhea) defined as one or more of the following events:

- Hospitalization, life threatening, death,
- Hypokalemia (< 3.3 mmol/l),
- Hypovolemia,

- Need for i.v. (intravenous) fluids,
- Medically significant events such as hypotension, syncope or cardiac effects.

Out of the 6 CSC-diarrhea cases identified in clinical trials, 2 could have been related to other causes (antibiotic induced diarrhea and gastroenteritis). Four patients were hospitalized and 2 needed i.v fluids. The outcome of all cases was favorable. Importantly, 4 patients who experienced CSC-diarrhea did not experience a recurrence of diarrhea at re-challenge. The other 2 patients were not re-challenged.

In post-marketing experience, CSC-diarrhea was reported to have occurred in 30 patients. Sixteen of these patients were hospitalized, 11 needed i.v. fluids, 8 reported hypotension, 4 experienced concurrent syncope, 4 were considered life-threatening, and 1 had hypokalemia. One fatality was reported from unrelated causes (acute pancreatitis with aspiration pneumonia).

The age range of these patients was 18-82 years with a median of 49 years. Nine patients were over 65 years of age. Twenty-eight were women, and the treatment duration before the event occurred ranged from 1-5 days with a median of 1 day.

### **8.2.3 Rectal bleeding**

The following terms were used to search the databases of completed clinical trials for rectal bleeding adverse events: Hemorrhage rectum, Gastrointestinal hemorrhage NOS, Hematochezia, Rectal hemorrhage, Anal hemorrhage, Melena, and Blood in stool.

Reported cases of rectal bleeding were well balanced in clinical trials. Overall, in completed controlled clinical trials, rectal bleeding was recorded as an adverse event in 1.2% of patients on Zelnorm, and in 1.3% of patients on placebo. The severity of rectal bleeding episodes was reported as mild and self-limiting. No patient underwent blood transfusion.

In post-marketing experience, 82 cases of rectal bleeding were reported as of May 14, 2004: 21 of these were reported in patients with suspected ischemic colitis, 1 in another form of intestinal ischemia, 3 in "other colitis", 23 with hemorrhoids as the possible source of bleeding, 1 anal fissure, 1 anal rectal disorder, and in 32 cases the bleeding source was undetermined. All cases resolved uneventfully.

### **8.2.4 Ischemic colitis**

#### **Ischemic colitis**

Ischemic colitis is a rare condition that is potentially serious, but generally mild and transient. The clinical manifestations are dominated by rectal bleeding and abdominal pain. The diagnosis is usually established on colonoscopy demonstrating typical mucosal erosions in the colon. In most cases no specific treatment is needed.

#### **Epidemiology data in support of background incidence of ischemic colitis**

Several studies indicate that there is a low background incidence of ischemic colitis in the general population (5-10 per 100,000 patient-years) and that patients with IBS have a 4-5 times higher incidence. Data from the Medi-Cal (1995-2002) claims database indicate an

incidence of 47 cases of ischemic colitis per 100,000 patient years in non-IBS subjects, and 179 cases per 100,000 in patients with IBS (Singh et al., DDW 2004). In a study from United HealthCare (1995-1999), the corresponding numbers were 7 per 100,000 patient years in non-IBS subjects, and 43 per 100,000 patient years in IBS patients (Cole et al., 2004). A report from Olmsted County (1976-1998) indicates an incidence of 10 per 100,000 patient years in the general population (Loftus et al., 2002).

#### **Evaluation of clinical databases for potential reports of potential ischemic colitis**

Novartis established a process to identify and evaluate reports of potential ischemic colitis in clinical trials and post-marketing surveillance.

Clinical trial and post-marketing databases were reviewed up through March 31 and June 1 2004, respectively, and the following screening criteria were applied to identify all potential reported cases for review:

##### **A. For patients with reports of rectal bleeding:**

The terms rectal bleeding, rectal hemorrhage, hematochezia, lower GI bleeding or melena were explicitly used in the AE report, and the bleeding led to performance of diagnostic tests such as sigmoidoscopy, colonoscopy, angiography, barium enema, CT scan or abdominal surgery.

##### **B. For patients with reports of (ischemic) colitis:**

The term “ischemic colitis, colonic ischemia, intestinal ischemia, ischemic bowel disease, abdominal ischemia”, or “colitis” was explicitly used in the AERS report as a possible diagnosis, or presence of any endoscopic or histological evidence of intestinal ischemic change or necrosis.

#### **No cases of ischemic colitis in Zelnorm clinical trials**

Novartis very carefully reviewed all cases of rectal bleeding in clinical trials (n > 11,600), and no case of ischemic colitis were found. Therefore the reported incidence of ischemic colitis in clinical trials is 0 per 3,456 person years.

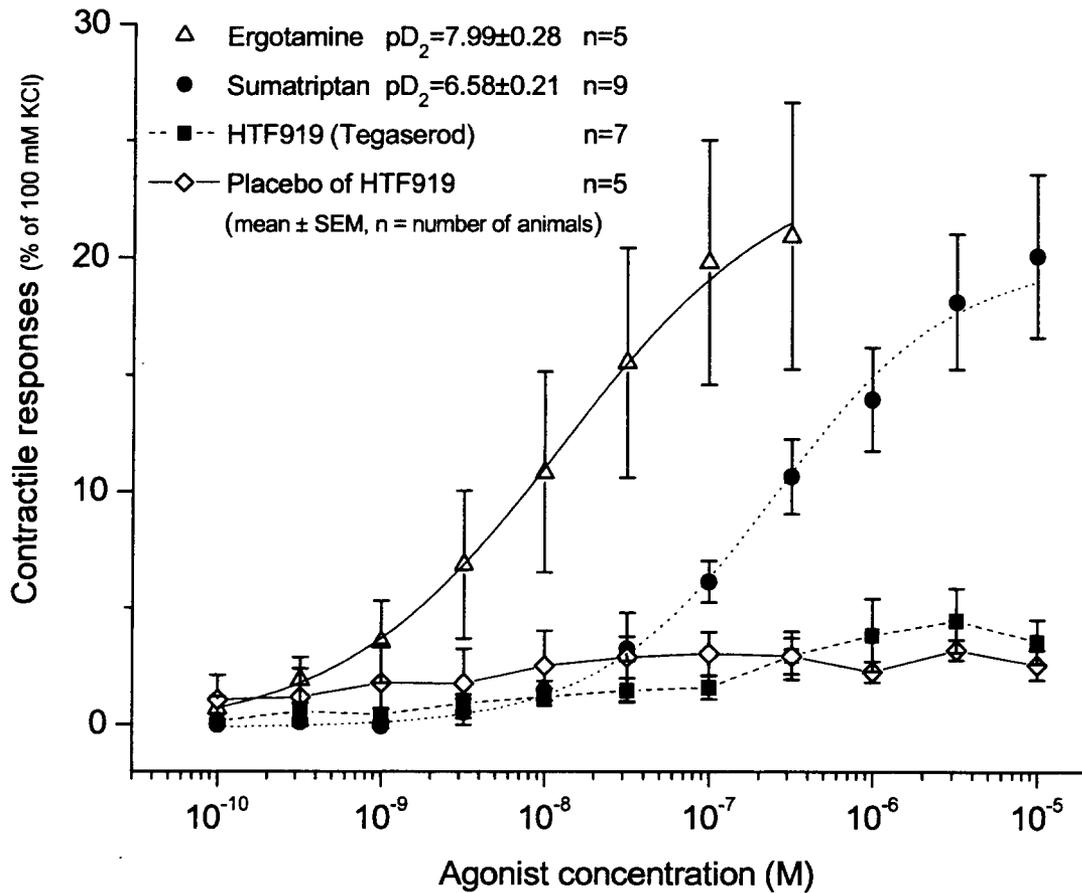
#### **Reported cases of ischemic colitis in post-marketing experience**

As of June 1, 2004, Novartis has received 29 reports of suspected ischemic colitis. This represents a reporting rate of 8.0 per 100,000 patient years, which is consistent with the background incidence in the general population. (NB - Due to a late request by FDA to use a June 1, 2004 cut-off for post-marketing reports of ischemic colitis, the patient years for June 1 was extrapolated from previous data points. There is a lag of 2 weeks to obtain drug distribution data required for these calculations. The reporting rate will be updated for the July 14<sup>th</sup> Advisory Committee Meeting.) These cases have been generally transient and self-limiting and only led to surgery and colon resection in one patient with lung fibrosis. The one death reported was an elderly woman with Alzheimer’s disease, who developed central I.V. line sepsis and expired after antibiotic treatment was withdrawn.

**Preclinical investigations indicate no involvement of tegaserod in mesenteric or colonic ischemia**

In order to elucidate whether Zelnorm has the potential to cause ischemic colitis, several specific preclinical investigations have been performed. Tegaserod acts as an agonist at 5-HT<sub>4</sub> receptors in the GI tract and does not have appreciable affinity for 5-HT<sub>3</sub> receptors; however, it has moderate affinity for 5-HT<sub>1B</sub> receptors known to be expressed in the vascular system (including the GI tract, where it is also located in neurons). Therefore, specific pharmacological investigations were performed to determine whether tegaserod could trigger 5-HT<sub>1B</sub> receptor-induced vasospastic reactions exemplified by contractions of coronary arteries obtained from non-human primates. The reference compounds, sumatriptan and ergotamine, elicited substantial contractions of coronary arteries, whereas the vasomotor effects of tegaserod (0.1 nM–10 μM) were not different from those of vehicle controls (Figure 8-1). Moreover, thorough investigations revealed a 5-HT<sub>1B</sub> receptor antagonist activity of tegaserod (to be contrasted with the 5-HT<sub>1B</sub> agonist effects of sumatriptan and ergotamine). These studies clearly demonstrated that tegaserod has no potential to cause vasoconstriction through 5-HT<sub>1B</sub> receptors. Moreover, given the functional integrity and responsiveness of the artery preparation (relaxation upon exposure to substance P; contraction upon exposure to PGF<sub>2α</sub> and serotonin), it is concluded that tegaserod even at very high concentrations (10 μM) has no direct vasoconstrictory potential.

**Figure 8-1** 5-HT<sub>1B</sub> receptor - mediated contractile effects on isolated coronary arteries of non-human primates. Test articles: tegaserod, sumatriptan and ergotamine.



Supplementary studies were carried out recently in order to investigate the effects of tegaserod and the reference compound, sumatriptan, on isolated human and non-human primate mesenteric arteries. In accordance with the findings from isolated coronary arteries tegaserod exhibited no contractile activity on mesenteric arteries, whereas sumatriptan caused vasoconstrictions with  $pEC_{50}$  values of 6.5 (human) and 6.8 (monkey) and intrinsic activities of about 25 % (compared to serotonin – induced contractions). Again, tegaserod acted as a 5-HT<sub>1B</sub> receptor antagonist in both human and monkey mesenteric arteries. These results indicate that tegaserod is devoid of any vasoconstrictory potential affecting coronary or mesenteric arteries.

In order to examine whether tegaserod exhibited any acute hemodynamic effects *in vivo*, particularly on visceral micro-circulation, a model using anaesthetized rats was established and validated which allowed for simultaneous measurements of blood flow in the superior mesenteric artery and within the wall of the transverse colon (micro-circulation) Importantly,

all changes in hemodynamics were expressed as changes in vascular conductance (mucosal VC, mesenteric VC), which was calculated as blood flow divided by mean arterial pressure (MAP). Since compounds that affect the heart cause changes in cardiac output and blood pressure, and thereby, could alter visceral blood flow; the determination of vascular conductance is the appropriate mechanism to investigate whether or not a drug specifically elicits colonic and/or mesenteric vasoconstriction or vasodilatation. Alterations of vascular conductance and vascular resistance (inverse of VC) provide a more accurate depiction of the local effects of agents under investigation for potential vasoconstriction or vasodilatation.

Following validation of the methodology using N-nitro-L-arginine methylester (L-NAME, a nitric oxide synthase inhibitor), and calcitonin gene-related peptide (CGRP, a vasodilatory agent), multiple doses of tegaserod were administered intravenously and mesenteric and colonic blood flow and vascular conductance (VC) were measured. In the Validation Study, tegaserod, at doses of 1 and 3 mg/kg (intravenously), caused a transient fall in mean arterial pressure, mirrored by a simultaneous increase in vascular conductance of the mesenteric artery. Apart from this transient effect. Tegaserod at doses from 0.1 to 3.0 mg/kg i.v. (30-fold greater than the exposure to a patient receiving the approved/recommended dose of 6mg b.i.d.; Table 8-3) had no effect on the micro-circulation of the rat transverse colon. No effect of Zelnorm was found on mesenteric or mucosal vascular conductance.

**Table 8-3 Comparison of doses and pharmacokinetic values of tegaserod following exposure to human beings (approved oral dose) and rats (high parenteral dose)**

Species	Dose	Dose (normalized*)	C <sub>max</sub>	AUC
Human	6 mg p.o.	0.1 mg/kg p.o	2.7 ± 1.2 ng/mL	8.9 ± 4.2 ng·h/mL
Rat	3 mg/kg i.v.	3 mg/kg i.v.	-	377 ng·h/mL

\* 60 kg body weight

Since it has been shown that treatment of patients suffering from diarrhea-predominant irritable bowel syndrome with alosetron, a 5-HT<sub>3</sub> receptor antagonist, can be associated with ischemic colitis, a comparative study with tegaserod was performed particularly addressing the potential effects of 5-HT<sub>3</sub> antagonists (alosetron and cilansetron) on visceral hemodynamics in anaesthetized rats.

In this second investigation (Comparative Study), the effects of intravenous administration of alosetron (30 to 300 µg/kg) and cilansetron (100 and 300 µg/kg) were studied. Colonic motor activity as reflected by the intraluminal pressure was not modified by these two test articles at any dose. However, both alosetron and cilansetron caused a time-dependent decrease in mesenteric blood flow and mesenteric vascular conductance. This study demonstrated that both alosetron and cilansetron elicited mesenteric vasoconstriction and may represent a class effect for the 5-HT<sub>3</sub> receptor antagonists.

Zelnorm was tested in this *in vivo* model at intravenous doses of 0.3, 1.0, and 3.0 mg/kg (30-fold greater than the exposure to a patient receiving the approved/recommended dose of 6 mg b.i.d. ; see Table 8-3) . Consistent with data from the Validation Study, tegaserod did not affect mesenteric or colonic vascular conductance indicating lack of vasoconstriction or

vasodilatation activity. Statistically significant reductions in mesenteric and colonic mucosal blood flow observed following administration of the highest dose of tegaserod (3.0 mg/kg i.v.) appeared to be caused by reductions in cardiac function (decrease in heart rate). This decrease in heart rate was likely the result of the extremely high tegaserod exposure which was administered intravenously (30 times the recommended dose). In addition, high baseline (pre-treatment) values of mesenteric and colonic blood flow in this particular treatment group (3.0 mg/kg i.v.) led to an apparent decrease in mesenteric and colonic flow rate in animals treated with tegaserod. Most importantly, even at this unusually high intravenous exposure, mesenteric and colonic vascular conductance was comparable to control values providing further support for the lack of effect of tegaserod on the micro-circulation.

Based on the initial findings that both alosetron and cilansetron caused a time-dependent decrease in mesenteric blood flow and vascular conductance (period of 50 min post-injection) a follow-up study was performed with a prolonged observation period (170 min) in order to reject/confirm the initial findings and to assess the reversibility of the apparent vasoconstrictor effects of 5-HT<sub>3</sub> receptor antagonists *in vivo*. These experiments were carried out with tegaserod (1 mg/kg i.v.), alosetron (0.03 mg/kg i.v.), cilansetron (0.1 mg/kg i.v.) and renzapride (1 and 3 mg/kg i.v.), a mixed 5-HT<sub>3</sub> antagonist/5-HT<sub>4</sub> agonist. During the extended observation period tegaserod did not affect mesenteric or colonic BF or VC. Hence, it follows that tegaserod administered i.v. at a dose of 1 mg/kg did not compromise the splanchnic circulation during the observation period of nearly 3 hours. Alosetron, however, decreased both mesenteric BF and VC during the initial observation period of 5 - 20 min post-injection. This observation confirms previous findings and suggests that alosetron's small vasomotor effects on the superior mesenteric artery is transient and reversible. Both cilansetron and renzapride were devoid of statistically significant effects on mesenteric or colonic BF or VC in rat model. The findings suggest that mesenteric vasoconstrictions triggered by 5-HT<sub>3</sub> receptor antagonists is not a robust effect.

Supplementary experiments were performed to examine the effects of tegaserod and alosetron, relative to vehicle, on BF/VC in the superior mesenteric artery of anaesthetized non-fasted rats. A secondary objective was to test whether baseline values of mesenteric blood flow / conductance differed between fasted and non-fasted anaesthetized rats. Tegaserod did not change mesenteric BF or VC in non-fasted anaesthetized rats, whereas alosetron tended to decrease both parameters. Comparisons with previous data obtained in fasted rats (cf. above) revealed that the baseline values of mesenteric blood flow and vascular conductance in anaesthetized non-fasted rats ( $17.42 \pm 1.00$  ml/min,  $208.75 \pm 16.19$   $\mu$ l/min per mmHg, n = 22) were significantly ( $P < 0.01$ , Student's t test) larger than those recorded in anaesthetized fasted rats ( $12.23 \pm 0.40$  ml/min,  $150.08 \pm 6.65$   $\mu$ l/min per mmHg, n = 31). It follows that the lack of effect of tegaserod on mesenteric BF and VC is independent of the postprandial and interdigestive phase of gut activity. The same is true for the slight inhibitory effects of alosetron.

In order to mimic the per os administration of tegaserod additional acute experiments were carried out in the anaesthetized rat model with drug (30 mg/kg) administered via the intraduodenal (i.d.) route to examine vascular effects. Alosetron (5-HT<sub>3</sub> antagonist; 0.3 mg/kg i.d.) and clonidine (alpha<sub>2</sub> adrenoceptor agonist; 0.03 mg/kg i.d.) were applied as reference

compounds. Tegaserod was without significant effects on the cardiovascular parameters under examination. Alosetron caused a small but statistically significant decrease in mesenteric BF; mesenteric VC tended to be reduced by alosetron, however, was not significantly different from control values. Intraduodenal administration of clonidine led to a decrease in MAP, HR, mesenteric and colonic BF and to an increase in colonic VC and (to some extent) mesenteric VC. These results indicate that particularly the colonic vascular bed of the rat was dilated by clonidine. Finally, the data demonstrate the importance of measuring both blood flow and vascular conductance.

In summary, the pharmacological data available to date demonstrate no visceral vasoconstrictory action of tegaserod. Even very high *in vitro* concentrations (coronary artery preparation) and very high *in vivo* exposure (anesthetized rats) do not trigger vasomotor effects. These findings indicate that there is no vascular mechanism that could lead to mesenteric or colonic ischemia with Zelnorm.

### Conclusions

The following conclusions were drawn by Novartis and have been supported by a panel of external gastrointestinal experts (Lawrence Brandt, MD, Michael Gershon, MD, Walter L. Peterson MD, and Philip Schoenfeld, MD):

- there are no reports of ischemic colitis or other forms of intestinal ischemia in clinical trials involving more than 11,600 treated patients,
- no such findings of IC were identified in pre-clinical toxicology studies,
- pre-clinical research studies indicate that there is no effect on mesenteric or colonic blood flow,
- the post-marketing reports of suspected IC have no specific demographic pattern,
- the post-marketing reporting rate is consistent with the general population and well below the IBS population.

#### 8.2.5 Other forms of intestinal ischemia

Three fatal cases of other intestinal ischemia have been reported. One 66 year old female patient with 2-3 years history of abdominal angina received samples of Zelnorm because of worsening abdominal pain. According to her husband who handled her medication he can not recall her taking Zelnorm. The patient expired following an exploratory laparotomy revealing small bowel infarction. One 41 year old female with hypothyroidism died following surgery for severe bowel impaction, toxic megacolon and colon necrosis. There is no documentation that she ever took her prescribed Zelnorm. A 67 year old patient experienced multi-organ failure for unknown reason. One possible cause was intestinal ischemia, but the diagnosis was never established since no endoscopy, surgery or autopsy were performed.

#### 8.2.6 Cholecystectomies

There is an imbalance between Zelnorm and placebo in clinical trials with regard to cholecystectomies. In placebo-controlled trials, the incidence of cholecystectomies in patients receiving Zelnorm is 0.12%; for patients receiving placebo, it is 0.03%. Data from a national

Hospital Survey (1999) put these findings in perspective. In the age group 25-44 years, the incidence of cholecystectomies is 0.19 per 100 patient years, and, in the age group 45-64 years, the corresponding number is 0.29 per 100 patient years. In IBS patients, the prevalence is 2- to 3-fold higher, which is comparable to the incidence in Zelnorm trials: 0.59 per 100 patient years.

In post-marketing experience, 30 biliary tract events have been reported. Eighteen were cholecystectomies, 3 reported cholelithiasis, and 9 “other”. There were no severe complications reported.

As part of its original post-approval commitments, Novartis conducted a mechanistic trial to assess the effect of Zelnorm on gallbladder motility in healthy volunteers and patients with IBS-C. This trial demonstrated that Zelnorm does not stimulate gallbladder contraction during the interdigestive period and does not alter meal-induced gallbladder contraction dynamics or concomitant bile duct diameter during the digestive period assessed by serial ultrasound measures.

### **8.2.7 Ovarian cysts**

In clinical trials, 4 patients on Zelnorm and 3 patients on placebo had ovarian cysts. In post-marketing experience there are 5 reports of ovarian cysts and 2 Fallopian tube cysts as of May 14.

## **9 Safety conclusions**

The experience from clinical trials involving more than 11,000 patients and approximately 3 million patients in post-marketing experience indicates that Zelnorm is a safe and well tolerated drug.

- Serious adverse events are well balanced between placebo and Zelnorm in clinical trials.
- Diarrhea occurs more frequently in Zelnorm-treated subjects than in placebo. It is generally mild and self-limiting. Clinically serious consequences of diarrhea are very rare in clinical studies and are rarely reported in post-marketing use. Diarrhea did not cause any fatalities.
- The occurrence of rectal bleeding is well balanced in clinical trials between Zelnorm- and placebo-treated patients. In post-marketing experience, rectal bleeding is rarely reported.
- No cases of ischemic colitis were found among > 11,600 patients receiving Zelnorm in clinical trials. In post-marketing experience, the reporting rate of suspected cases of ischemic colitis was low, and consistent with the background incidence. Pharmacological studies indicate no mechanism by which Zelnorm can cause vasoconstriction.
- Four fatalities have been reported in patients with different forms of intestinal ischemia. These were very complicated cases with many confounding factors likely to cause the conditions. In addition, two of the patients probably did not take the drug.

- In clinical trials, there were more cholecystectomies in patients receiving Zelnorm than those receiving placebo, but the rate of cholecystectomies is consistent with the background incidence in IBS. Reports from post-marketing experience were rare and uncomplicated. A thorough pharmacodynamic study showed no effect of Zelnorm on gallbladder motility.
- Occurrence of ovarian cysts is well-balanced in clinical trials between Zelnorm and placebo. Reports from post-marketing experience are very rare.

## 10 Benefit and Risks assessment

### 10.1 Summary of benefits

Chronic constipation is a common GI disorder. It is characterized not only by infrequent bowel movements but also by the presence of straining, the passage of hard, lumpy stools, and, at times, by abdominal discomfort. First-line therapy with increased dietary fiber and/or fluid intake and exercise may provide relief, however, compliance is often difficult and benefit is limited. Moreover, fiber may actually increase bloating and discomfort. Enemas and rectal lavage are time-consuming, somewhat invasive and, to some patients, embarrassing and culturally unacceptable. Stimulant, cathartic, and osmotic laxatives are commonly used and effective for occasional or intermittent constipation, but can worsen abdominal cramping, pain, or discomfort and can also lead to soiling associated with liquid, watery stools and frequent stools or incontinence. Moreover, laxatives are only approved for short-term relief of constipation and are not indicated for long-term therapy as their safety and efficacy have not been established in this setting. Therefore, at the present time, none of the currently available therapies has been found to be safe and effective in the management of patients with chronic constipation. A drug that could safely and effectively relieve these chronic symptoms would fill an important void in our current therapeutic armamentarium.

Using a composite variable (increase of CSBM/week compared to baseline) to integrate the evaluation of two key symptoms (infrequent bowel movements, sensation of incomplete evacuation), Zelnorm was shown to be clinically and significantly more effective than placebo in patients with symptoms associated with chronic constipation over the entire 12-week study period. Furthermore, Zelnorm consistently improved all key symptoms associated with chronic constipation, including straining, frequency of defecation, hard or lumpy stools, abdominal discomfort/pain, and distension/bloating. This effect was evident beginning in the first week of therapy and was maintained throughout the 12-week treatment period. This positive overall effect was reflected by the significantly higher scores for satisfaction with bowel habit in the group treated with tegaserod.

For patients with chronic constipation, the benefits of Zelnorm include its rapid onset of action, its reliable and sustained symptomatic relief and the safety and tolerability evidenced by:

1. more frequent and softer stools which are easier to pass,
2. a predictable and consistent onset of action, with a low incidence of side effects (mild diarrhea), and,

3. symptomatic improvement of distension/bloating and abdominal discomfort and pain.

Additionally, Zelnorm is convenient to use, as it is taken in tablet form, and can be used safely and effectively for a longer period (12 weeks) than is recommended for currently available treatments (2 weeks).

The population studied in this development program presented with persistent symptoms that have been present for an average of 10 to 15 years duration. Of note is the enduring dissatisfaction of these patients with their treatment options (evidence of which was obtained via questionnaire rating their satisfaction with current or previous treatments). Thus, successful relief of these symptoms would fill a glaring, unmet medical need in these patients.

For patients and physicians alike, the benefits of Zelnorm also include the avoidance of the potential side effects of the commonly-used alternative therapies, including gas, flatulence, bloating, cramping and pain, as well as melanosis coli and the liquid, watery stools often seen with osmotic and cathartic laxatives and the risk of hypermagnesemia (Gattuso and Kamm, 1994; and Schiller 2001).

Thus the benefits of Zelnorm are a safe, well tolerated, effective and convenient therapy for a common chronic condition which impairs quality of life and is often difficult to treat.

## 10.2 Summary of risks

The safety and tolerability data, obtained from 2603 patients overall, including 518 treated for  $\geq 1$  year (13 months), indicate that Zelnorm is safe and well tolerated without specific organ toxicity.

Apart from an initial increase in diarrhea, the AE profile of Zelnorm is similar to that of placebo.

Diarrhea is the only relevant drug-related side effect. This effect mainly occurs during the first week of treatment and rarely leads to discontinuation of treatment. Clinically significant consequences of diarrhea have not been reported in testing in chronic constipation, but have been reported in patients with IBS-C.

Hematological, biochemical, and cardiovascular parameters did not show any signs of specific toxicity.

In view of the known cardiac side-effects of the non-selective 5-HT<sub>4</sub> receptor agonist cisapride, careful ECG evaluations were made in all studies involving Zelnorm. Healthy subjects taking single and multiple oral doses or single i.v. doses showed no correlation between plasma concentrations of Zelnorm and QTc intervals. In earlier, phase III studies of IBS-C, there was no influence of Zelnorm on any ECG intervals, nor on QTc duration, indicating that Zelnorm has no relevant electrocardiographic action (Morganroth 2002). These results were confirmed in the CC studies.

For the physician and for Health Authorities, the risk of additional abdominal surgery in a population which frequently reports abdominal discomfort and pain is a valid concern. Abdominal and pelvic surgeries were reported with similar frequencies for Zelnorm and placebo, indicating no increased risk associated with Zelnorm treatment. Although data from

the pooled indications do not allow a small increase in the risk of cholecystectomies to be excluded, they show the risk to be extremely small.

## 11 Overall Conclusions and Recommendation for Use

The consistency of the data for both the primary and the secondary efficacy variables obtained at multiple endpoints in the CC clinical program, indicates that Zelnorm is effective in relieving the multiple and varied symptoms reported by patients with chronic constipation. Moreover, the safety profile in the chronic constipation clinical program was similar to that reported at the time of IBS-C approval in July 2002.

Therefore, the data strongly support approval of the use of Zelnorm for the treatment of patients with chronic constipation and relief of the associated symptoms of straining, hard or lumpy stools, and infrequent defecation. The recommended dose is 6mg b.i.d. for 12 weeks.

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