Sponsor

Novartis

Generic Drug Name

Tegaserod maleate

Therapeutic Area of Trial

Functional Dyspepsia

Approved Indication

- Short-term treatment of women with irritable bowel syndrome (IBS) whose primary bowel symptom is constipation.
- Treatment of patients less than 65 years of age with chronic idiopathic constipation.

On March 30, 2007, Novartis announced it is complying with a request from the Food and Drug Administration (FDA) to suspend US marketing and sales of tegaserod maleate, due to a recent analysis of clinical trial data identifying a small imbalance that was statistically significant in the number of cardiovascular ischemic events in patients taking tegaserod maleate. The data showed that events occurred in 13 out of 11,614 patients treated with tegaserod maleate (0.11%), compared to one case in 7,031 placebo-treated patients (0.01%). These events included heart attack, stroke and unstable angina. These cardiovascular ischemic events occurred in patients who had pre-existing cardiovascular disease and/or cardiovascular risk factors. There is no demonstrated causal relationship between tegaserod maleate and these events.

Study Number

CHTF919D2301E1

Title

A one-year, open-label, multi-center, extension study to CHTF919D2301 to assess the long term safety of tegaserod 6 mg bid given orally in female patients with symptoms of dyspepsia

Phase of Development

Phase III

Study Start/End Dates

27 September 2004 to 4 August 2006

Study Design/Methodology

Multicenter, multinational open-label, 1 year, long-term extension study of tegaserod 6 mg bid (twice daily).

Centres

113 centers in 3 countries: United States (107), United Kingdom (2), and Canada (4)

Publication

Ongoing

Objectives

Primary objective(s)

The primary objective of this study of this study was to evaluate the long term safety of tegaserod (6 mg bid) at 6 months in female patients with symptoms of dyspepsia.

Secondary objective(s)

The secondary objectives were:

- The long term safety of tegaserod (6 mg bid) at 1 year in female patients with symptoms of dyspepsia
- Efficacy on satisfactory relief of symptoms of dyspepsia
- The quality of life (QOL) using a disease specific questionnaire: Short-Form Nepean Dyspepsia Index (SF-NDI)
- Work Productivity Activity Impairment questionnaire – Dyspepsia (WPAI)
- Patient Perception of Study Medication – Dyspepsia questionnaire

Test Product (s), Dose(s), and Mode(s) of Administration

Tegaserod 6 mg tablets, BID given orally

Reference Product(s), Dose(s), and Mode(s) of Administration

None

Criteria for Evaluation

Safety and tolerability

Safety assessments consisted of monitoring and recording all AEs, including SAEs, the monitoring of hematology, blood chemistry and urine, regular monitoring of vital signs, physical condition, and body weight.

Efficacy

The efficacy variable, satisfactory relief of mid-upper abdominal discomfort, was evaluated. At all office visits during the trial, the patients were asked to answer the following question:

- "Over the past week, did you have satisfactory relief of your mid-upper abdominal discomfort which may include early fullness while eating, postmeal fullness, or bloating?" (Yes or No).
  - o "Satisfactory Relief" meant the dyspepsia symptoms were not bothersome

Additional efficacy variables were assessment of health-related Quality of Life (QoL) using a disease specific questionnaire, the Short Form Nepean Dyspepsia Index (NDI), the Work Productivity Activity Impairment (WPAI) – Dyspepsia questionnaire and the Patient Perception with Study Medication (PPSM) – Dyspepsia questionnaire.

Statistical Methods

No sample size was calculated for this extension study. As this was a single arm open-label extension, all patients' data were summarized as "Tegaserod 6mg bid" treatment group. In a few exceptional cases (like summary of diarrhea episodes and clinically relevant adverse events), the extension data are presented split by the core randomized treatment groups ("Tegaserod 6 mg bid" and "Placebo").

Two identical patient populations were used for evaluation:
Intent-to-Treat (ITT) population: All patients who received extension study drug.
Safety analyzable (SA) population: All patients who received extension study drug and had at least one safety assessment. As the statement that a patient had no AE constitutes a safety assessment, this population is identical to the ITT population. The safety analyzable population is considered as primary for all safety analyses.

All Safety analyzable/ITT patients were summarized with respect to the following demographic and background disease information collected in the context of the core study:
• Age, body weight, height, body mass index (BMI), and race
• The baseline quality of life assessed by the Nepean Dyspepsia Index (NDI) questionnaire and by the work productivity and activity impairment (WPAI QoL) questionnaire – these are summarized along with the post-baseline results.

Continuous variables were summarized (N, mean, median, standard deviation, minimum, and maximum). For binary and categorical variables, frequency counts are provided.

Adverse events
Treatment emergent adverse events are listed and summarized. Two sets of summary tables

were produced:
• Treatment emergent adverse events starting during the first 6 months of the extension study, i.e. having a start day <=182
• Treatment emergent adverse events during the extension study

Adverse events that started before but continued at the first day of extension study medication were copied from the core to the extension eCRF in order to facilitate the collection of end dates. These are not considered treatment emergent in the open-label extension. However, if such an event was worsening during extension (becoming suspected to be study drug related, getting a higher severity, becoming serious, or new action(s) taken) a new record with the date of worsening as start date was to be recoded.

Efficacy evaluations
Patients assessment of satisfactory relief: During the site visits of this extension study, ie at visit 6 prior to extension treatment and at months 1, 3, 6, 9, and 12. The number and percentage of patients answering with "yes" are summarized by timepoint for all ITT patients overall and by core treatment group. Also, a percentage of assessments with answer "yes" were calculated and summarized in terms of frequency counts and percentages per category. These summaries were done overall and by satisfaction status at start of extension study.

Short-Form Nepean Dyspepsia Index (NDI): The evaluation of the NDI Short-Form focused on cluster score, i.e. summary scores . The summary score and change from baseline in summary score for each subscale are summarized descriptively (N, mean, median, standard deviation, minimum, and maximum) for the ITT population. The assessment taken prior to entering the core treatment phase was used as baseline for the open label extension.

Work productivity and activity impairment questionnaire - Dyspepsia (WPAI): Data from the WPAI-dyspepsia questionnaire developed for dyspepsia patients were used for the purpose of economic analysis. Descriptive summaries were performed. These variables are summarized descriptively at baseline and at month 6, month 12, and end of study (EOS).

Patient Perception with Study Medication – Dyspepsia (PPSM): This assessment was taken at the last study visit. PPSM data are presented as frequency counts and percentages for the ITT population.

Study Population: Inclusion/Exclusion Criteria and Demographics

Patients had to meet all of the following criteria to be included in the study:
1. Fulfilled eligibility criteria in CHTF919D2301 and successfully completed the double blind phase;
2. Demonstrated ability to communicate well with the investigator;
3. Demonstrated willingness to comply with the requirements of the long term study.

Patients were **excluded** from the study for any of the following reasons:

1. Early discontinuation from the double blind phase, CHTF919D2301.
2. History of serious consequences of diarrhea, including hypovolemia, hypotension and syncope, during the double blind phase or prior to entry into the double blind phase.
3. History of ischemic colitis confirmed by colonoscopy during the double blind phase or prior to entry into the double blind phase.
4. Severe abdominal pain or rectal bleeding not attributed only to hemorrhoids, anal fissure or other known cause

5. Were not, in the Investigator's opinion, compliant participants during the double blind phase
6. Developed a medical or surgical condition that would have excluded them from the double blind phase, CHTF919D2301.
7. Women of child bearing potential who were not continuing to use sustained contraceptive preparations (e.g., implants or intramuscular injections) or complying with an approved method of contraception. A woman was considered to be of childbearing potential unless she is post-hysterectomy, one or more years post-menopausal or one or more years posttubal ligation

Number of Subjects

	Tegaserod
Planned N	N/A
Randomized n	359
Intent-to-treat population (ITT) n (%)	359 (100%)
Completed n (%)	140 (39.0)
Withdrawn n (%)	219 (61.0)
Withdrawn due to adverse events n (%)	50 (13.9)
Withdrawn due to lack of efficacy n (%)	24 (6.7)
Withdrawn for other reasons n (%)	145 (40.4)

Demographic and Background Characteristics

	Tegaserod
N (ITT)	359
Females : males	359 : 0
Mean age, years (SD)	44.5±13.85
Mean BMI, kg/m^2 (SD)	27.7±7.0
Race	
Caucasian n (%)	277 (77.2)
Black n (%)	49 (13.6)
Asian n (%)	1 (0.3)
Other n (%)	32 (8.9)

Primary Objective Result(s)

Number (%) of patients with AEs, regardless of study drug relationship, by primary system organ class (Safety analyzable patients)

	Tegaserod 6 mg bid N=359 n (%)	
Primary system organ class	**During the first 6 months of the extension**	**During the entire extension**
Any system organ class	222 (61.8)	245 (68.2)
Gastrointestinal disorders	132 (36.8)	151 (42.1)
Infections and infestations	79 (22.0)	96 (26.7)
Nervous system disorders	42 (11.7)	49 (13.6)
Musculoskeletal and connective tissue disorders	34 (9.5)	45 (12.5)
General disorders and administration site conditions	22 (6.1)	29 (8.1)

Respiratory, thoracic and mediastinal disorders	20 (5.6)	31 (8.6)
Injury, poisoning and procedural complications	17 (4.7)	24 (6.7)
Skin and subcutaneous tissue disorders	15 (4.2)	19 (5.3)
Metabolism and nutrition disorders	14 (3.9)	18 (5.0)
Psychiatric disorders	14 (3.9)	17 (4.7)
Investigations	12 (3.3)	15 (4.2)
Reproductive system and breast disorders	8 (2.2)	10 (2.8)
Renal and urinary disorders	8 (2.2)	11 (3.1)
Ear and labyrinth disorders	6 (1.7)	9 (2.5)
Vascular disorders	5 (1.4)	8 (2.2)
Cardiac disorders	4 (1.1)	5 (1.4)
Immune system disorders	4 (1.1)	5 (1.4)
Blood and lymphatic system disorders	2 (0.6)	3 (0.8)
Eye disorders	2 (0.6)	4 (1.1)
Hepatobiliary disorders	2 (0.6)	2 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.6)	4 (1.1)
Pregnancy, puerperium and perinatal conditions	2 (0.6)	4 (1.1)
Endocrine disorders	1 (0.3)	2 (0.6)

Number (%) of patients with adverse events (>= 2%), regardless of study drug relationship, by preferred term (Safety analyzable patients)

	Tegaserod 6 mg bid N=359 n (%)	
Preferred term	**During the first 6 months of the extension**	**During the entire extension**
Any preferred term	222 (61.8)	245 (68.2)
Diarrhea	66 (18.4)	75 (20.9)
Headache	27 (7.5)	29 (8.1)
Nausea	25 (7.0)	28 (7.8)
Abdominal pain	21 (5.8)	26 (7.2)
Vomiting	17 (4.7)	21 (5.8)
Constipation	15 (4.2)	21 (5.8)
Upper respiratory tract infection	15 (4.2)	17 (4.7)
Nasopharyngitis	12 (3.3)	16 (4.5)
Sinusitis	12 (3.3)	16 (4.5)
Abdominal pain upper	10 (2.8)	13 (3.6)
Gastroenteritis viral	10 (2.8)	15 (4.2)
Abdominal distension	9 (2.5)	12 (3.3)
Dyspepsia	9 (2.5)	14 (3.9)
Bronchitis	8 (2.2)	9 (2.5)
Urinary tract infection	8 (2.2)	11 (3.1)
Back pain	7 (1.9)	10 (2.8)
Anxiety	7 (1.9)	9 (2.5)
Dizziness	5 (1.4)	9 (2.5)
Arthralgia	6 (1.7)	8 (2.2)
Fatigue	5 (1.4)	8 (2.2)

Flatulence	7 (1.9)	8 (2.2)
Cough	5 (1.4)	7 (1.9)
Abdominal pain lower	4 (1.1)	6 (1.7)
Abdominal tenderness	4 (1.1)	6 (1.7)
GERD	2 (0.6)	6 (1.7)
Hypertension	4 (1.1)	6 (1.7)
Pain	4 (1.1)	5 (1.4)
Pharyngolaryngeal pain	4 (1.1)	5 (1.4)
Abdominal discomfort	4 (1.1)	4 (1.1)
Nasal congestions	4 (1.1)	4 (1.1)
Neck injury	4 (1.1)	4 (1.1)
Sinus congestion	4 (1.1)	4 (1.1)
Stomach discomfort	4 (1.1)	4 (1.1)
Tinea pedis	4 (1.1)	4 (1.1)
Plantar fasciitis	3 (0.8)	4 (1.1)
Rash	3 (0.8)	4 (1.1)
Tinnitus	3 (0.8)	4 (1.1)
Toothache	3 (0.8)	4 (1.1)
Muscle spasms	2 (0.6)	4 (1.1)
Pregnancy	2 (0.6)	4 (1.1)
Oedema peripheral	2 (0.6)	4 (1.1)
Arthropod bite	3 (0.8)	3 (0.8)
Candidiasis	3 (0.8)	3 (0.8)
Dermatitis contact	3 (0.8)	3 (0.8)
Diverticulitis	3 (0.8)	3 (0.8)
Dyspnoea	3 (0.8)	3 (0.8)
Hypokalaemia	3 (0.8)	3 (0.8)
Joint sprain	3 (0.8)	3 (0.8)
Osteoarthritis	3 (0.8)	3 (0.8)
Acne	2 (0.6)	3 (0.8)
Chest discomfort	2 (0.6)	3 (0.8)
Costochondritis	2 (0.6)	3 (0.8)
Ear pain	2 (0.6)	3 (0.8)
Food poisoning	2 (0.6)	3 (0.8)
Fungal infection	2 (0.6)	3 (0.8)
Influenza	2 (0.6)	3 (0.8)
Influenza like illness	2 (0.6)	3 (0.8)
Insomnia	2 (0.6)	3 (0.8)
Procedural pain	2 (0.6)	3 (0.8)
Hyperlipidemia	2 (0.6)	3 (0.8)
Rectal haemorrhage	2 (0.6)	3 (0.8)
Respiratory tract congestion	2 (0.6)	3 (0.8)
Vulvovaginal mycotic infection	2 (0.6)	3 (0.8)
Fall	1 (0.3)	3 (0.8)
Haematuria	1 (0.3)	3 (0.8)
Shoulder pain	1 (0.3)	3 (0.8)
Viral upper respiratory tract infection	0	3 (0.8)
Alanine aminotransferase increased	2 (0.6)	2 (0.6)
Anorexia	2 (0.6)	2 (0.6)
Arthropod sting	2 (0.6)	2 (0.6)
Aspartate aminotransferase increased	2 (0.6)	2 (0.6)

Asthenia	2 (0.6)	2 (0.6)
Bowel sounds abnormal	2 (0.6)	2 (0.6)
Breast mass	2 (0.6)	2 (0.6)
Chest pain	2 (0.6)	2 (0.6)
Depressed level of consciousness	2 (0.6)	2 (0.6)
Early satiety	2 (0.6)	2 (0.6)
Eructation	2 (0.6)	2 (0.6)
Gastritis	2 (0.6)	2 (0.6)
Herpes simplex	2 (0.6)	2 (0.6)
Hypertonic bladder	2 (0.6)	2 (0.6)
Lethargy	2 (0.6)	2 (0.6)
Muscle strain	2 (0.6)	2 (0.6)
Muscoskeletal discomfort	2 (0.6)	2 (0.6)
Neck pain	2 (0.6)	2 (0.6)
Otitis media	2 (0.6)	2 (0.6)
Pain in extremity	2 (0.6)	2 (0.6)
Pharyngitis streptococcal	2 (0.6)	2 (0.6)
Pollakiurua	2 (0.6)	2 (0.6)
Sinus headache	2 (0.6)	2 (0.6)
Stress	2 (0.6)	2 (0.6)
Vaginitis bacterial	2 (0.6)	2 (0.6)
Vertigo	2 (0.6)	2 (0.6)
Weight decreased	2 (0.6)	2 (0.6)
Palpitations	1 (0.3)	2 (0.6)
Pyrexia	1 (0.3)	2 (0.6)
Pleurisy	1 (0.3)	2 (0.6)
Tooth infection	1 (0.3)	2 (0.6)
Upper limb fracture	1 (0.3)	2 (0.6)
Viral infection	1 (0.3)	2 (0.6)
Weight increased	1 (0.3)	2 (0.6)
Blood glucose increased	1 (0.3)	2 (0.6)
Bursitis	1 (0.3)	2 (0.6)
Chills	1 (0.3)	2 (0.6)
Depression	1 (0.3)	2 (0.6)
Ear infection	1 (0.3)	2 (0.6)
Haematochezia	1 (0.3)	2 (0.6)
Hypothyroidism	1 (0.3)	2 (0.6)
Migraine	1 (0.3)	2 (0.6)
Mood swings	1 (0.3)	2 (0.6)
Asthma	0	2 (0.6)
Foot fracture	0	2 (0.6)
Abscess	1 (0.3)	1 (0.3)
Allergy to arthropod sting	1 (0.3)	1 (0.3)
Alopecia	1 (0.3)	1 (0.3)
Atrial fibrillation	1 (0.3)	1 (0.3)
Blood alkaline phosphatase increased	1 (0.3)	1 (0.3)
Body temperature increased	1 (0.3)	1 (0.3)
Bradycardia	1 (0.3)	1 (0.3)
Breast cancer	1 (0.3)	1 (0.3)
Breast cyst	1 (0.3)	1 (0.3)
Carotid bruit	1 (0.3)	1 (0.3)
Carpal tunnel syndrome	1 (0.3)	1 (0.3)
Cerebrovascular accident	1 (0.3)	1 (0.3)

Cervical cyst	1 (0.3)	1 (0.3)
Cervical dysplasia	1 (0.3)	1 (0.3)
Cholecystitis	1 (0.3)	1 (0.3)
Cystitis	1 (0.3)	1 (0.3)
Decreased appetite	1 (0.3)	1 (0.3)
Dehydration	1 (0.3)	1 (0.3)
Dermatitis allergic	1 (0.3)	1 (0.3)
Diabetes mellitus	1 (0.3)	1 (0.3)
Diarrhoea haemorrhagic	1 (0.3)	1 (0.3)
Diarrhoea infectious	1 (0.3)	1 (0.3)
Drug hypersensitivity	1 (0.3)	1 (0.3)
Dry eye	1 (0.3)	1 (0.3)
Dry mouth	1 (0.3)	1 (0.3)
Dyslipidaemia	1 (0.3)	1 (0.3)
Dysmenorrhoea	1 (0.3)	1 (0.3)
Eczema	1 (0.3)	1 (0.3)
Epicondylitis	1 (0.3)	1 (0.3)
Epistaxis	1 (0.3)	1 (0.3)
Exostosis	1 (0.3)	1 (0.3)
Eye injury	1 (0.3)	1 (0.3)
Faeces discolored	1 (0.3)	1 (0.3)
Flank pain	1 (0.3)	1 (0.3)
Food allergy	1 (0.3)	1 (0.3)
Frequent bowel movements	1 (0.3)	1 (0.3)
Gastroenteritis	1 (0.3)	1 (0.3)
Genital abscess	1 (0.3)	1 (0.3)
Gingival infection	1 (0.3)	1 (0.3)
Haematemesis	1 (0.3)	1 (0.3)
Haemoglobin decreased	1 (0.3)	1 (0.3)
Haemorrhoidal haemorrhage	1 (0.3)	1 (0.3)
Haemorrhoids	1 (0.3)	1 (0.3)
Hepatic steatosis	1 (0.3)	1 (0.3)
Herpes zoster	1 (0.3)	1 (0.3)
Hiatus hernia	1 (0.3)	1 (0.3)
Hypercalcaemia	1 (0.3)	1 (0.3
Hyperventilation	1 (0.3)	1 (0.3)
Hypoaesthesia	1 (0.3)	1 (0.3)
Hypogeusia	1 (0.3)	1 (0.3)
Hypoglyceamia	1 (0.3)	1 (0.3)
Hypopharyngeal neoplasm benign	1 (0.3)	1 (0.3)
Hyposmia	1 (0.3)	1 (0.3)
Hypotrichosis	1 (0.3)	1 (0.3)
Intervertebral disc protrusion	1 (0.3)	1 (0.3)
Irritability	1 (0.3)	1 (0.3)
Joint injury	1 (0.3)	1 (0.3)
Labyrinthitis	1 (0.3)	1 (0.3)
Lacrimation increased	1 (0.3)	1 (0.3)
Leukopenia	1 (0.3)	1 (0.3)
Liver function test abnormal	1 (0.3)	1 (0.3)
Localised infection	1 (0.3)	1 (0.3)
Major depression	1 (0.3)	1 (0.3)
Menopausal symptoms	1 (0.3)	1 (0.3)
Micturition urgency	1 (0.3)	1 (0.3)
Muscular weakness	1 (0.3)	1 (0.3)

Musculoskeletal chest pain	1 (0.3)	1 (0.3)
Musculoskeletal stiffness	1 (0.3)	1 (0.3)
Myalgia	1 (0.3)	1 (0.3)
Myelitis	1 (0.3)	1 (0.3)
Myositis	1 (0.3)	1 (0.3)
Nephrolithiasis	1 (0.3)	1 (0.3)
Obesity	1 (0.3)	1 (0.3)
Oesophageal pain	1 (0.3)	1 (0.3)
Osteochondrosis	1 (0.3)	1 (0.3)
Otitis externa	1 (0.3)	1 (0.3)
Platelet count increased	1 (0.3)	1 (0.3)
Premenstrual syndrome	1 (0.3)	1 (0.3)
Productive cough	1 (0.3)	1 (0.3)
Pruritis	1 (0.3)	1 (0.3)
Pruritis generalized	1 (0.3)	1 (0.3)
Pyuria	1 (0.3)	1 (0.3)
Renal pain	1 (0.3)	1 (0.3)
Restless legs syndrome	1 (0.3)	1 (0.3)
Rhinitis	1 (0.3)	1 (0.3)
Seasonal allergy	1 (0.3)	1 (0.3)
Skeletal injury	1 (0.3)	1 (0.3)
Smear cervix abnormal	1 (0.3)	1 (0.3)
Spinal compression fracture	1 (0.3)	1 (0.3)
Syncope	1 (0.3)	1 (0.3)
Tachycardia	1 (0.3)	1 (0.3)
Tenosynovitis stenosans	1 (0.3)	1 (0.3)
Throat irritation	1 (0.3)	1 (0.3)
Thrombocytopenia	1 (0.3)	1 (0.3)
Tinea infection	1 (0.3)	1 (0.3)
Toe deformity	1 (0.3)	1 (0.3)
Tongue disorder	1 (0.3)	1 (0.3)
Tonsillitis	1 (0.3)	1 (0.3)
Tooth abscess	1 (0.3)	1 (0.3)
Tooth impacted	1 (0.3)	1 (0.3)
Urticaria	1 (0.3)	1 (0.3)
Vaginal haemorrhage	1 (0.3)	1 (0.3)
Varicose vein	1 (0.3)	1 (0.3)
Anemia	0	1 (0.3)
Appendicitis	0	1 (0.3)
Arthritis	0	1 (0.3)
Bladder spasm	0	1 (0.3)
Blepharospasm	0	1 (0.3)
Bronchial hyperactivity	0	1 (0.3)
Bronchiectasis	0	1 (0.3)
Bunion	0	1 (0.3)
Burning sensation	0	1 (0.3)
Change of bowel habit	0	1 (0.3)
Conjunctivitis	0	1 (0.3)
Defeacation urgency	0	1 (0.3)
Dyspnoea exertional	0	1 (0.3)
Ear discomfort	0	1 (0.3)
Faecal incontinence	0	1 (0.3)
Fluid retention	0	1 (0.3)
Fungal test positive	0	1 (0.3)

Hand fracture	0	1 (0.3)
Hot flush	0	1 (0.3)
Hypercholesterolaemia	0	1 (0.3)
Kidney infection	0	1 (0.3)
Laryngitis	0	1 (0.3)
Limb crushing injury	0	1 (0.3)
Lower respiratory tract infection	0	1 (0.3)
Malaise	0	1 (0.3)
Malignant melanoma	0	1 (0.3)
Melaena	0	1 (0.3)
Melanocytic naevus	0	1 (0.3)
Metrorrhagia	0	1 (0.3)
Multiple allergies	0	1 (0.3)
Nerve compression	0	1 (0.3)
Oesophageal spasm	0	1 (0.3)
Oesophageal stenosis	0	1 (0.3)
Osteoporosis	0	1 (0.3)
Panic attack	0	1 (0.3)
Pelvic discomfort	0	1 (0.3)
Pelvic inflammatory disease	0	1 (0.3)
Rash erythematous	0	1 (0.3)
Rash generalized	0	1 (0.3)
Rectocele	0	1 (0.3)
Rhinitis allergic	0	1 (0.3)
Rib fracture	0	1 (0.3)
Skin infection	0	1 (0.3)
Sleep apnoea syndrome	0	1 (0.3)
Tendonitis	0	1 (0.3)
Thyroid neoplasm	0	1 (0.3)
Tonsillar hypertrophy	0	1 (0.3)
Vitamin D deficiency	0	1 (0.3)
Wheezing	0	1 (0.3)

Secondary Objective Result(s)

Number (%) of patients with satisfactory relief of mid-upper abdominal discomfort during extension, overall and by core treatment group (ITT patients)**

	Tegaserod 6mg bid/ Tegaserod 6mg bid N = 174 n / N*(%)	Placebo/ Tegaserod 6mg bid N = 185 n / N*(%)	Any treatment/ Tegaserod 6mg bid N = 359 n / N*(%)
Over the past week, did you have satisfactory relief of your mid-upper abdominal discomfort which may include early fullness while eating, postmeal fullness, or bloating?			
No of patients answering yes at			
Day 1	80 / 170 (47.1)	72 / 181 (39.8)	152 / 351 (43.3)
Month 1	120 / 156 (76.9)	114 / 172 (66.3)	234 / 328 (71.3)
Month 3	107 / 132 (81.1)	116 / 139 (83.5)	223 / 271 (82.3)
Month 6	90 / 117 (76.9)	96 / 123 (78.0)	186 / 240 (77.5)
Month 9	65 / 86 (75.6)	66 / 93 (71.0)	131 / 179 (73.2)
Month 12	47 / 68 (69.1)	54 / 73 (74.0)	101 / 141 (71.6)
End of study (Day = 2)	90 / 171 (52.6)	103 / 180 (57.2)	193 / 351 (55.0)

* Denominator used: No of patients within a subgroup having satisfactory relief assessment at the timepoint
** Treatment group refer to Core Study Treatment Group/ Extension Study Treatment Group combination.

Summary of Nepean Dyspepsia Index (SF-NDI) sub-scales and changes from baseline during extension study, by visit (ITT patients)

Treatment: Tegaserod 6mg bid (N=359)

Sub-scale		Baseline*		Endpoint		? from Baseline
Visit	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
Tension						
Baseline*	354	5.2 (2.12)				
Month 1	328	5.1 (2.12)	328	3.5 (1.75)	323	-1.7 (2.30)
Month 3	274	5.2 (2.13)	271	3.4 (1.77)	269	-1.8 (2.46)
Month 6	239	5.1 (2.14)	239	3.4 (1.74)	237	-1.8 (2.44)
Month 9	181	5.1 (2.14)	179	3.4 (1.90)	177	-1.8 (2.44)
Month 12	142	5.1 (2.07)	138	3.2 (1.55)	137	-1.8 (2.32)
EOS	354	5.1 (2.12)	285	3.8 (2.07)	281	-1.3 (2.55)
Interference with daily activities						
Baseline*	354	4.8 (2.25)				
Month 1	328	4.8 (2.26)	327	3.1 (1.66)	322	-1.7 (2.43)
Month 3	274	4.8 (2.25)	271	3.0 (1.56)	269	-1.7 (2.58)
Month 6	239	4.7 (2.25)	239	3.1 (1.60)	237	-1.6 (2.42)
Month 9	181	4.7 (2.25)	179	3.1 (1.67)	177	-1.7 (2.45)
Month 12	142	4.6 (2.17)	138	3.0 (1.52)	137	-1.6 (2.43)
EOS	354	4.8 (2.25)	285	3.5 (1.98)	281	-1.1 (2.59)
Eating/Drinking						
Baseline*	354	6.8 (2.06)				

Month 3	274	6.8 (2.07)	271	3.9 (1.79)	269	-2.9 (2.54)
Month 6	239	6.8 (2.09)	239	3.9 (1.77)	237	-2.8 (2.65)
Month 9	181	6.8 (2.03)	179	3.6 (1.82)	177	-3.1 (2.70)
Month 12	142	6.6 (2.03)	138	3.7 (1.79)	137	-2.8 (2.69)
EOS	354	6.8 (2.06)	285	4.3 (2.28)	281	-2.3 (2.93)
Knowledge/Control						
Baseline*	354	5.4 (2.01)				
Month 1	328	5.4 (2.01)	328	3.6 (1.88)	323	-1.8 (2.28)
Month 3	274	5.4 (2.02)	271	3.4 (1.78)	269	-2.0 (2.41)
Month 6	239	5.4 (2.04)	239	3.5 (1.87)	237	-1.8 (2.37)
Month 9	181	5.3 (2.00)	179	3.4 (1.71)	177	-1.9 (2.32)
Month 12	142	5.3 (1.98)	138	3.4 (1.68)	137	-1.9 (2.21)
EOS	354	5.4 (2.01)	285	3.9 (2.07)	281	-1.5 (2.36)
Work/Study						
Baseline*	354	4.6 (2.23)				
Month 1	328	4.6 (2.26)	327	3.0 (1.57)	322	-1.66 (2.45)
Month 3	274	4.6 (2.29)	271	2.9 (1.51)	269	-1.7 (2.44)
Month 6	239	4.6 (2.31)	239	3.0 (1.59)	237	-1.6 (2.48)
Month 9	181	4.6 (2.28)	179	2.9 (1.55)	177	-1.7 (2.36)
Month 12	142	4.5 (2.19)	138	2.8 (1.31)	137	-1.6 (2.40)
EOS	354	4.6 (2.23)	285	3.3 (1.82)	281	-1.3 (2.56)

* Baseline is the last measurement prior to or including the day of randomization
? = Change from baseline: endpoint - baseline
EOS = End of Study is the latest post-baseline measurement during extension.

Summary of Work productivity and activity impairment (WPAI) questionnaire (ITT patients who were employed at baseline)

Treatment: Tegaserod 6 mg bid (N=244)		**Baseline***		**Timepoint**		**Change**
Timepoint	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N†**	**Mean (SD)**
Percentage work time missed due to dyspepsia symptoms in the week prior to assessment						
Month 6	163	5.5 (15.70)	143	2.1 (9.75)	138	-3.3 (13.98)
Month 12	96	6.3 (16.54)	79	0.9 (3.51)	77	-4.2 (12.90)
EOS	233	5.2 (14.14)	164	2.5 (10.49)	156	-1.9 (13.970
Percentage work time impaired due to dyspepsia symptoms in the week prior to assessment						
Month 6	160	37.4 (24.98(	142	16.7 (21.15)	135	-20.3 (27.48)
Month 12	94	38.7 (25.72)	79	15.1 (20.07)	76	-24.5 (24.78)
EOS	230	38.7 (25.65)	163	18.2 (22.77)	155	-19.4 (28.56)
Percentage work time missed or impaired due to dyspepsia symptoms in the week prior to assess-ment						
Month 6	165	35.0 (24.76)	156	15.3 (19.62)	151	-20.5 (27.32)
Month 12	96	36.0 (25.44)	82	14.3 (19.31)	81	-22.7 (26.32)
EOS	238	36.3 (25.28)	170	16.5 (22.65)	167	-18.5 (28.74)
Percentage daily activity impaired due to dyspepsia symptoms in the week prior to assessment						
Month 6	171	44.4 (24.18)	165	16.4 (18.84)	165	-27.9 (26.14)
Month 12	98	44.8 (24.42)	93	15.7 (20.13)	93	-29.9 (26.27)

EOS	244	44.6 (24.09)	190	19.1 (22.65)	190	-25.0 (28.56)

* Baseline is the last measurement prior to or including the day of randomization to the core study.
†N = the number of patients with data at baseline and each timepoint
EOS - End of Study is the latest post-baseline measurement during extension.

Summary of Patient's perception of study medication (PPSM) questionnaire applied at end of study (ITT patients)

Question	**Tegaserod 6 mg bid**
Response	**N=359 n (%)**
Regarding your expectations of treatment, how has the medication that you received since you entered this trial provided relief of your dyspepsia symptoms?	
Number of patients answering the question	n=275
Far above your expectations	63 (22.9)
Above your expectations	71 (25.8)
Met your expectations	67 (24.4)
Far below your expectations	17 (6.2)
Overall, how satisfied are you with the medication that you received since you entered this trial?	
Number of patients answering the question	n=275
Extremely satisfied	91 (33.1)
Satisfied	97 (35.3)
Neither satisfied nor dissatisfied	38 (13.8)
Dissatisfied	35 (12.7)
Extremely dissatisfied	14 (5.1)
Before enrolling in this clinical trial, did you ever receive medication treatment for your dyspepsia symptoms?	
Number of patients answering the question	n=275
Yes	86 (31.3)
No	189 (68.7)
If yes to previous question: Overall, do you prefer the medication that you received since you entered this trial to the treatment you received before this clinical trial?	
Number of patients answering the question	n=164
Yes, I definitely prefer the medication that I am receiving now	89 (54.3)
I have a slight preference for the medication that I am receiving now	14 (8.5)
I have no preference either way	4 (26.8)
I have a slight preference for my previous treatment	7 (4.3)
No, I definitely prefer my previous treatment	10 (6.1)
In the future, would you be willing to use the same medication that you received since you entered this trial for your dyspepsia symptoms?	
Number of patients answering the question	n=275
Yes, I would definitely want to use the same medication again	145 (52.7)
I might want to use the same medication again	45 (16.4)
I am not sure	32 (11.6)
I might not want to use the same medication again	18 (6.5)
No, I definitely would not want to use the same medication again	35 (12.7)
Would you recommend the medication that you have received since you entered this trial to family or friends with dyspepsia?	

Number of patients answers the question	n=275
No	39 (14.2)
Yes	236 (85.8)

Serious Adverse Events and Deaths

	Tegaserod N=359 n (%)	
	During the first 6 months of the extension	**During the entire extension**
No. (%) of subjects studied	359	359
No. (%) of subjects included in safety population	359	359
No. (%) of subjects with AE(s)	222 (61.8)	245 (68.2)
Number (%) of subjects with serious or other significant events	n (%)	
Death	0 (0.0)	0 (0.0)
SAE(s)	8 (2.2)	13 (3.6)
Discontinued due to SAE(s)		9 (2.5)

Summary of SAEs during the entire extension

SAE (preferred term)	Drug related? (Y/N)	Discontinued? (Y/N)	Hospitalized? (Y/N)
Cerebrovascular accident	N	Y	Y
Abdominal pain	N	N	Y
Chest pain	N	Y	Y
Chest discomfort	N	Y	Y
Intervertebral disc protrusion	N	N	Y
Abdominal pain	N	Y	N
Malignant melanoma	N	Y	N
Panic attack	N	N	Y
Costochondritis	N	N	Y
Diverticulitis	N	Y	Y
Nephrolithiasis	N	N	N
Appendicitis	N	N	Y
Upper abdominal pain	N	Y	Y
Costochondritis	N	Y	Y
Diarrhea	N	Y	Y
Dizziness	N	Y	Y
Vomiting	N	Y	Y
Bradycardia	Y	Y	Y
Dizzines	Y	N	Y
Hypoglycemia	Y	N	Y
Breast cancer	N	Y	Y

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