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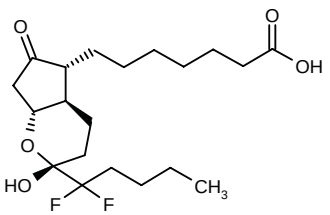
Lubiprostone

Prop INN; USAN

Treatment of Constipation
Treatment of Irritable Bowel Syndrome
Treatment of Postoperative Ileus
CIC-2 Channel Activator

RU-0211
SPI-0211

7-[(2*R*,4a*R*,5*R*,7a*R*)-2-(1,1-Difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[*b*]pyran-5-yl]heptanoic acid



$C_{20}H_{32}F_2O_5$

Mol wt: 390,4638

CAS: 333963-40-9

CAS: 136790-76-6 (as the monocyclic tautomer)

EN: 320088

Abstract

Constipation is defined as infrequent and/or unsatisfactory defecation and it is estimated that 4-5 million Americans (about 2% of the population) are affected, making it one of the most common disorders. Constipation is considered secondary in the presence of a recognizable cause, or idiopathic or functional when no cause can be identified. Conventional therapeutic approaches for the treatment of constipation include dietary and lifestyle modifications and exercise, and if all else fails, administration of laxatives. Unfortunately, constipation, and chronic idiopathic constipation in particular, is often refractory to standard treatment and current therapies are frequently poorly tolerated. Thus, there is a need for new agents with novel mechanisms of action. Lubiprostone has emerged as a novel agent with considerable promise as a treatment for constipation. Lubiprostone is a bicyclic fatty acid that potently activates intestinal Cl^- channels and increases intestinal water secretion and intestinal fluid Cl^- concentrations without altering Na^+ or K^+ concentrations. Lubiprostone is in phase III development for the treatment of constipation and phase II development for constipation associated with irritable bowel syndrome and postoperative ileus.

Synthesis

Lubiprostone can be obtained by two related ways:

1) Desilylation of commercial Corey's lactone (I) with TBAF in THF gives carbinol (II), which is oxidized by means of $(COCl)_2$ and DMSO in dichloromethane to yield the carbaldehyde (III). Condensation of compound (III) with phosphonate (IV) by means of thallium ethoxide in dichloromethane affords the unsaturated difluoroketone (V), which is reduced with H_2 over Pd/C in ethyl acetate to afford the saturated ketone (VI). Reduction of ketone (VI) with $NaBH_4$ in methanol provides the secondary alcohol (VII), which is further reduced with diisobutylaluminum hydride in toluene to give the lactol (VIII). Condensation of lactol (VIII) with 4-carboxybutyl triphenylphosphonium bromide (IX) by means of *t*-BuOK in THF yields the prostaglandin $F_{2\alpha}$ derivative (X), which is esterified by means of benzyl bromide and DBU in dichloromethane to afford the benzyl ester (XI). Oxidation of ester (XI) with CrO_3 and pyridine in dichloromethane provides the THP-protected prostaglandin E_2 derivative (XII), which is treated with AcOH in THF/water to give the prostaglandin E_2 benzyl ester derivative (XIII). Finally, this compound is submitted to simultaneous benzyl ester group cleavage and double bond reduction by means of H_2 over Pd/C in ethyl acetate (1, 2). Scheme 1.

2) Oxidation of the (–)-Corey's lactone (XIV) with Collins reagent (CrO_3 and pyridine) gives aldehyde (XV), which is condensed with phosphonate (IV) by means of thallium ethoxide in benzene to yield the unsaturated difluoroketolactone (XVI). Hydrogenation of compound (XVI) with H_2 over Pd/C in ethyl acetate affords the saturated analogue (XVII), which is reduced with $NaBH_4$ in methanol/THF to provide the hydroxylactone (XVIII), which is then protected at the hydroxy group with TBDMS-Cl and imidazole to give the silyl ether (XIX).

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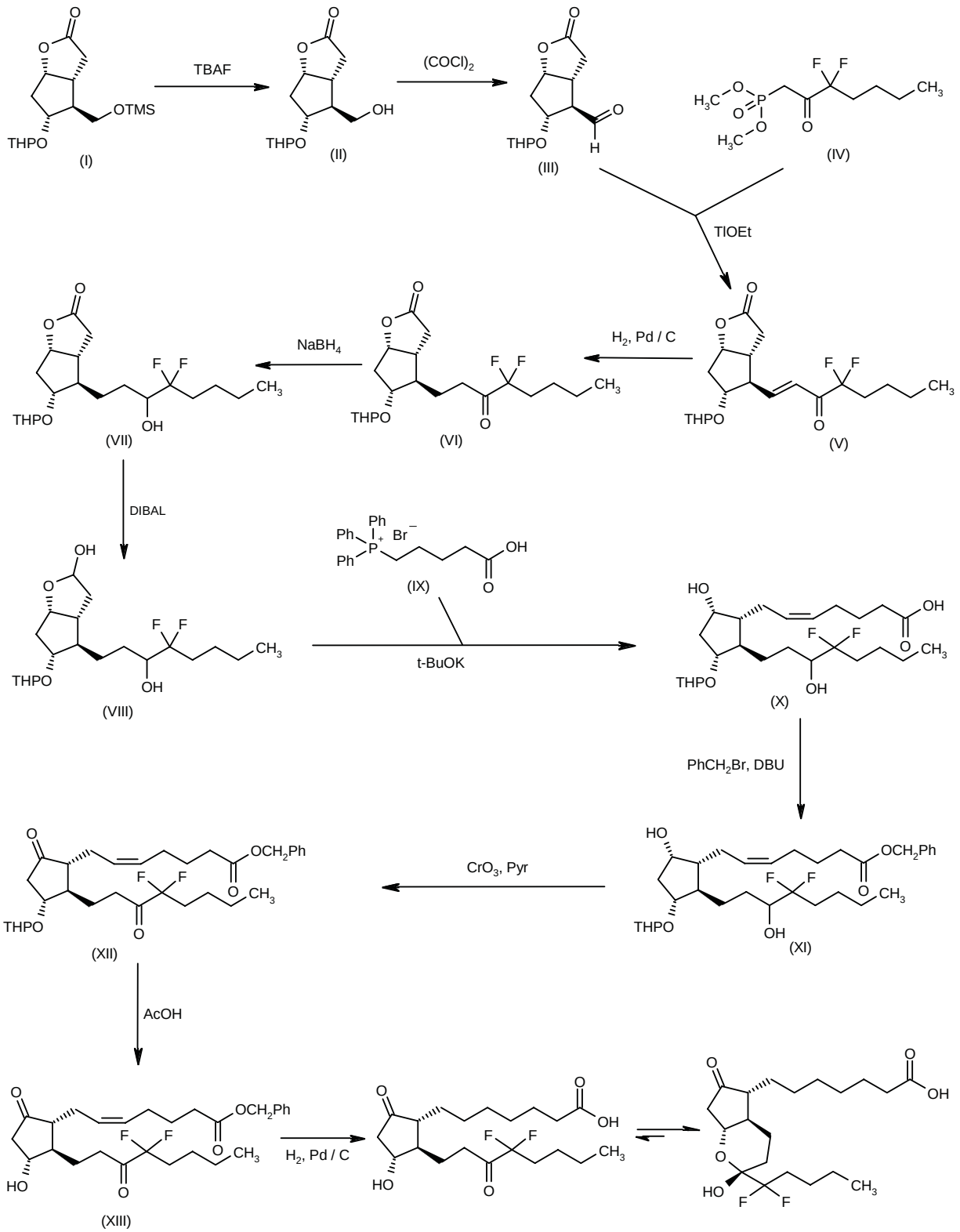
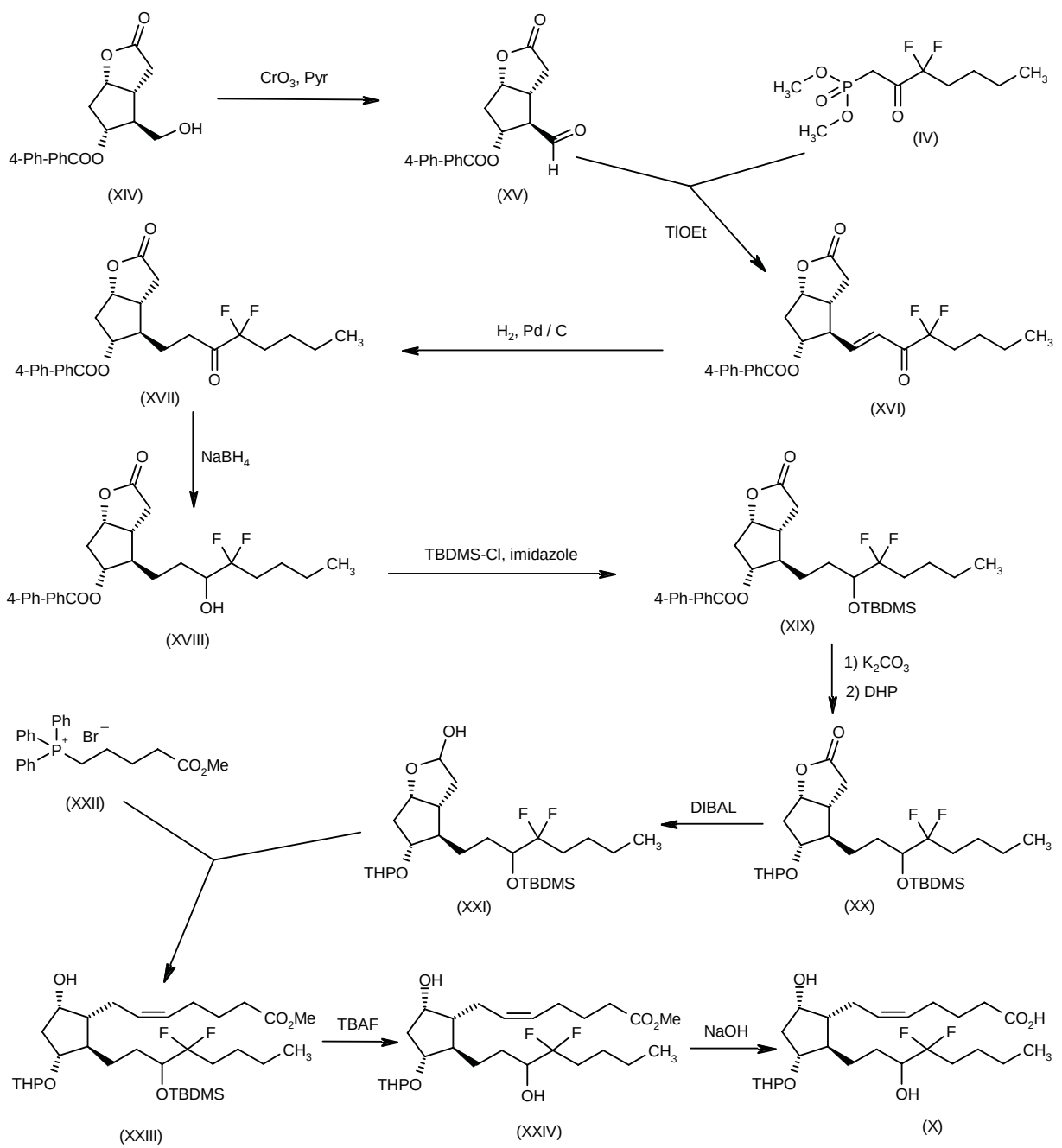
Scheme 1: Synthesis of Lubiprostone



Scheme 2: Synthesis of Intermediate (X)



Hydrolysis of the ester group of compound (XIX) in basic medium, followed by reaction with dihydropyran yields the tetrahydropyranyl ether (XX), which is reduced with DIBAL to afford the lactol (XXI). Condensation of lactol (XXI) with 4-(methoxycarbonyl)butyl triphenylphosphonium bromide (XXII) provides the unsaturated methyl ester (XXIII), which is desilylated by means of TBAF in THF to give the diol (XXIV). Finally, hydrolysis of the ester group of compound (XXIV) with NaOH in methanol yields the already described intermediate prostaglandin $F_{2\alpha}$ derivative (X) (3). Scheme 2.

The [^{13}C]-spectrum of lubiprostone confirms that in the absence of water, the compound exists predominantly in the form of the bicyclic hemiacetal (4, 5).

Introduction

Constipation, defined as infrequent and/or unsatisfactory defecation, is estimated to occur in 4-5 million Americans (about 2% of the population), making it one of the most common disorders. An individual is diagnosed with constipation if he/she experiences 1 or more of the following symptoms for 3 or more months while not taking laxatives: straining at defecation more than 25% of the time; lumpy and/or hard stools more than 25% of the time; sensation of incomplete evacuation more than 25% of the time; and 2 or fewer bowel movements per week (6-8).

Constipation is considered secondary in the presence of a recognizable, usually multifactorial cause. Causes include inadequate amounts of dietary fiber and/or liquids, lack of exercise, medications (*e.g.*, opioids, antidepressants, calcium channel blockers, NSAIDs), problems with colonic, rectal or intestinal function, anatomical problems (anal fissures, thrombosed hemorrhoids, strictures, tumors), endocrinopathic and metabolic conditions (*e.g.*, pregnancy, hypercalcemia, hypokalemia, hypothyroidism, diabetes mellitus), neurological disorders (*e.g.*, stroke, Hirschsprung's disease, Parkinson's disease, multiple sclerosis, Chagas' disease), connective tissue disorders (*e.g.*, scleroderma, amyloidosis), changes in life or routine (*e.g.*, older age, travel), depression and abuse of laxatives. When there is no cause that can be identified, constipation is defined as chronic idiopathic or functional, including bowel disorders such as constipation-dominant irritable bowel syndrome (IBS). The symptoms associated with idiopathic constipation may or may not be the result of abnormal colonic motility which can delay the transit of intestinal contents and impede the evacuation of rectal contents. Thus, a patient can be classified as having slow-transit or normal-transit constipation (6-9).

Conventional therapeutic approaches for the treatment of constipation include dietary and lifestyle modifications and exercise, and if all else fails, administration of laxatives. Several types of laxative are currently available: bulk-forming agents, also known as fiber supplements, which are taken with water and cause the absorption of water in the intestine and soften stools; stimulants, which cause rhythmic intestinal contractions; stool softeners, which provide moisture to the stool and prevent dehydration; lubricants, which lubricate the stool, enabling it to move through the intestine; and saline laxatives, which draw water into the colon for easier passage of stools. Unfortunately, constipation, particularly chronic idiopathic constipation, is often refractory to standard treatment and current therapies are often poorly tolerated (6).

Thus, there is a need for new agents with novel mechanisms of action, including full or partial 5-HT_4 receptor agonism, opioid receptor antagonism and opening of chloride channels. The few agents currently available or under active development for the treatment of constipation are presented in Table I. Of these, Sucampo's lubiprostone (RU-0211, SPI-0211) has shown considerable promise as a treatment for constipation. Lubiprostone is a bicyclic fatty acid (prostaglandin E_1) and Cl^- channel opener that increases intestinal water secretion and intestinal fluid Cl^- concentration without altering Na^+ or K^+ concentrations. It was chosen for further development as a treatment for constipation.

Pharmacological Actions

An *in vitro* study demonstrated that intestinal Cl^- channels are the specific target of lubiprostone. The agent concentration-dependently and hyperbolically increased short-circuit current in basolateral membrane-permeabilized T84 gastrointestinal epithelial cells under Cl^- gradient conditions (EC_{50} ~ 20 nM). In addition, specific, concentration-dependent and hyperbolic activation of the human CIC-2 Cl^- channel was demonstrated in experiments using whole-cell clamped HEK cells stably expressing transfected human CIC-2 (EC_{50} ~ 30 nM). Lubiprostone had no effect on endogenous Cl^- currents in mock-transfected or nontransfected HEK cells. In studies using other epithelial cell types, lubiprostone-induced activation of Cl^- channels was unaffected by inhibition of protein kinase A or Ca^{2+} chelators, suggesting that the agent does not target CFTR (cystic fibrosis transmembrane conductance regulator) or Ca^{2+}-activated Cl^- channels. Together these results suggest that lubiprostone specifically targets CIC-2 Cl^- channels in the apical membrane of T84 cells (10, 11). In fasted rats administered doses of 1, 10 or 100 μg/kg p.o. lubiprostone, dose-dependent increases in the concentration of chloride ions in the bowel were detected, indicating that the compound opens chloride channels and promotes chloride ion transport *in vivo* (11).

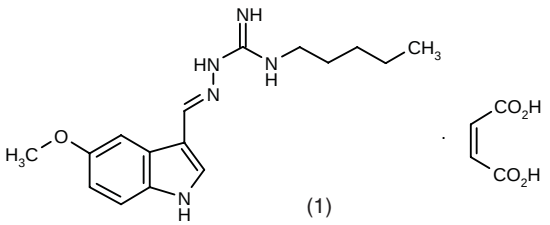
Clinical Studies

Single- and multiple-dose phase I studies were conducted in healthy volunteers to investigate primarily the safety of oral lubiprostone. In the single-dose studies, 16 subjects were administered doses of 6-96 μg and in the multiple-dose studies, 24 volunteers received doses of 24, 30 and 36 μg t.i.d. for 6 days. The dose-limiting toxicity in these studies was nausea, with a maximum tolerated dose (MTD) of 96 μg as a single dose and of 36 μg t.i.d. Following single doses, a trend for increased bowel movements was seen in volunteers given lubiprostone, particularly at the highest dose, where all 6 subjects had bowel movements (BMs). The highest dose of lubiprostone also tripled the average number of BMs per subject compared to placebo. In the multiple-dose study, 24 μg t.i.d. was determined to be optimal in terms of pharmacodynamic and adverse effects. Bowel movement frequency also increased on multiple-dose lubiprostone compared to placebo (12).

The safety and efficacy of lubiprostone (24, 48 or 72 μg/day for 3 weeks starting after a 2-week drug-free

Table I: Drugs recently launched or in active development for constipation (Prous Science Integrity®).

Drug	Mechanism of action	Source	Indication	Phase
1. Tegaserod maleate (Zelmac®, Zelnorm®)	5-HT_4 partial agonist	Novartis	Constipation-predominant IBS	L-2001
2. Alvimopan hydrate (Entereg™)	Mu opioid antagonist	Adolor/GlaxoSmithKline	Postoperative ileus	III
			Opioid-induced bowel dysfunction	II
			Chronic constipation	II
			IBS	I
3. Lubiprostone	Chloride channel activator	Sucampo	Constipation	III
			Constipation-predominant IBS	II
			Postoperative ileus	II
4. Methylnaltrexone bromide	Opioid antagonist	Progenics	Opioid-induced bowel dysfunction	III
			Postoperative ileus	II
5. Visicol® (INKP-100)*		InKine	Constipation	III
6. ABT-224	5-HT_4 agonist	Abbott	Constipation	II



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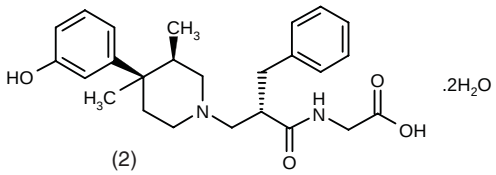
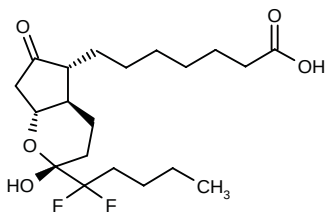


(2)

Sodium phosphate monobasic monohydrate, USP, and sodium phosphate dibasic anhydrous, USP



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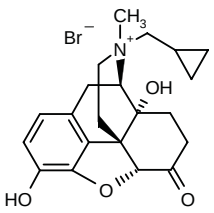

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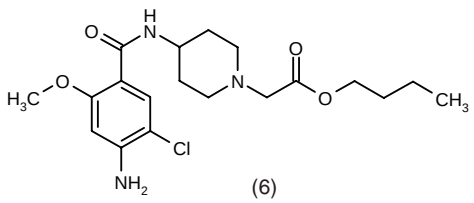

(6)

*Launched in 2001 for cleansing of the colon prior to colonoscopy

period) were examined in a randomized, placebo-controlled study involving 129 constipated (< 3 BMs/week and a 6-month history of at least 1 other Rome II criteria symptom for functional constipation) subjects (mostly Caucasian females). Lubiprostone was well tolerated. The most common adverse events were nausea, headache, diarrhea and bloating. The incidence of most adverse events was similar in both placebo- and lubiprostone-treated groups. A higher incidence of nausea was reported in patients receiving lubiprostone, with incidence increasing in a dose-dependent manner. However, only 4 patients evenly distributed throughout the dose groups withdrew due to nausea. Withdrawal due to lack of efficacy occurred only on placebo. A significant increase in the average daily and weekly number of spontaneous BMs as compared to placebo was observed in an intent-to-treat analysis at lubiprostone doses of 48 and 72 μg/day. In addition, significantly more patients receiving the 2 higher doses had a BM on the first day of treatment. Treatment with lubiprostone was also associated with significant improvements in stool consistency, bloating and global assessment of constipation severity (12, 13).

The safety and efficacy of lubiprostone (24 μg b.i.d. for 4 weeks starting after a 2-week drug-free period and followed by a 2-week drug-free follow-up) were demonstrated in a multicenter, randomized, placebo-controlled phase III trial in 242 constipated (as in the above study) subjects (90% female; 86% Caucasian). Lubiprostone was well tolerated, the most common adverse events reported being nausea, diarrhea and headache. Nine subjects withdrew due to adverse events. A significant increase in spontaneous BMs was observed in all weeks of the treatment period in the group receiving lubiprostone as compared to placebo (frequency: 5.1-5.7 *vs.* 2.8-3.5 on placebo). Significantly more lubiprostone-treated patients had a BM within 24 h of the first dose as compared to placebo (57% *vs.* 37%). Lubiprostone-treated patients also had significant improvements in stool consistency and straining and in global assessment of treatment effectiveness as compared to placebo during the 4-week treatment period (14).

The efficacy and safety of lubiprostone as a treatment for constipation are being examined in several phase III studies. The second of 3 phase III safety trials was recently completed and confirmed the findings of the first 6-month study, *i.e.*, long-term safety and sustained efficacy in treating constipation. This 48-week open-label trial enrolled 299 patients with documented constipation at sites in the U.S. The first 6-month study involved 308 constipated subjects, including follow-up subjects from the first pivotal efficacy study, and showed that lubiprostone (24 μg b.i.d.) was significantly better for all constipation variables tested as compared to placebo. The final open-label 12-month safety study is ongoing, with results expected in the fourth quarter of this year. The second of two phase III pivotal efficacy studies for lubiprostone was also recently completed and confirmed the significant results of the first pivotal efficacy study. Two multicenter phase II studies have also been initiated to examine the efficacy and safety of lubiprostone as a treatment for constipation-predominant IBS and postoperative ileus (15-18).

Source

Sucampo Pharmaceuticals, Inc. (US).

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