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MONOGRAPH

VELUSETRAG

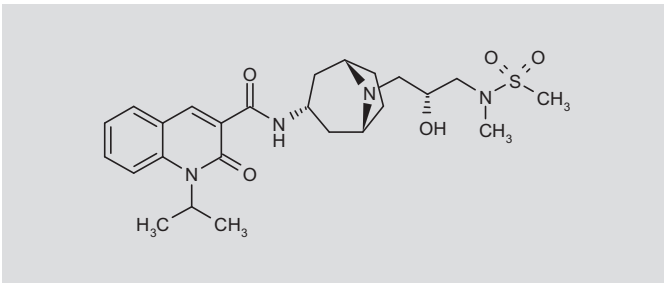
Rec INN; USAN

5-HT$_4$ Receptor Agonist
Treatment of Chronic Constipation

TD-5108

N-[(1*R*,3*R*,5*S*)-8-[2(*R*)-Hydroxy-3-[*N*-methyl-*N*-(methylsulfonyl)amino]propyl]-8-azabicyclo[3.2.1]oct-3-yl]-1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxamide

InChI: 1S/C25H36N4O5S/c1-16(2)29-23-8-6-5-7-17(23)11-22(25(29)32)24(31)26-18-12-19-9-10-20(13-18)28(19)15-21(30)14-27(3)35(4,33)34/h5-8,11,16,18-21,30H,9-10,12-15H2,1-4H3,(H,26,31)/t18-,19+,20-,21-/m0/s1



$C_{25}H_{36}N_4O_5S$

Mol wt: 504.642

CAS: 866933-46-2 (free base)

CAS: 866933-51-9 (hydrochloride)

EN: 415701

SUMMARY

Chronic constipation and irritable bowel syndrome (IBS) with constipation affect patient quality of life and are associated with a high healthcare expenditure. Conventional therapies for chronic constipation have limited effectiveness. New-generation, selective 5-HT$_4$ receptor agonists are effective for chronic constipation, but none are currently approved in the U.S.; prucalopride is approved for the treatment of chronic constipation in Europe. The 5-HT$_4$ receptor agonist velusetrag is being developed for chronic constipation and IBS with constipation; it has high selectivity and affinity for the 5-HT$_4$ receptor. Velusetrag accelerates colonic transit in a dose-related manner, with a dose of 30 mg daily being the most effective over 9 days of treatment in healthy controls. In patients with chronic constipation, velusetrag increased spontaneous bowel movements after 4 weeks of therapy, with no serious cardiac events reported. Velusetrag has shown great promise, and further studies in chronic constipation and IBS with constipation are warranted.

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*Synthesis prepared by R. Pandian, C. Estivill, N. Díaz. Thomson Reuters, Provença 398, 08025 Barcelona, Spain.

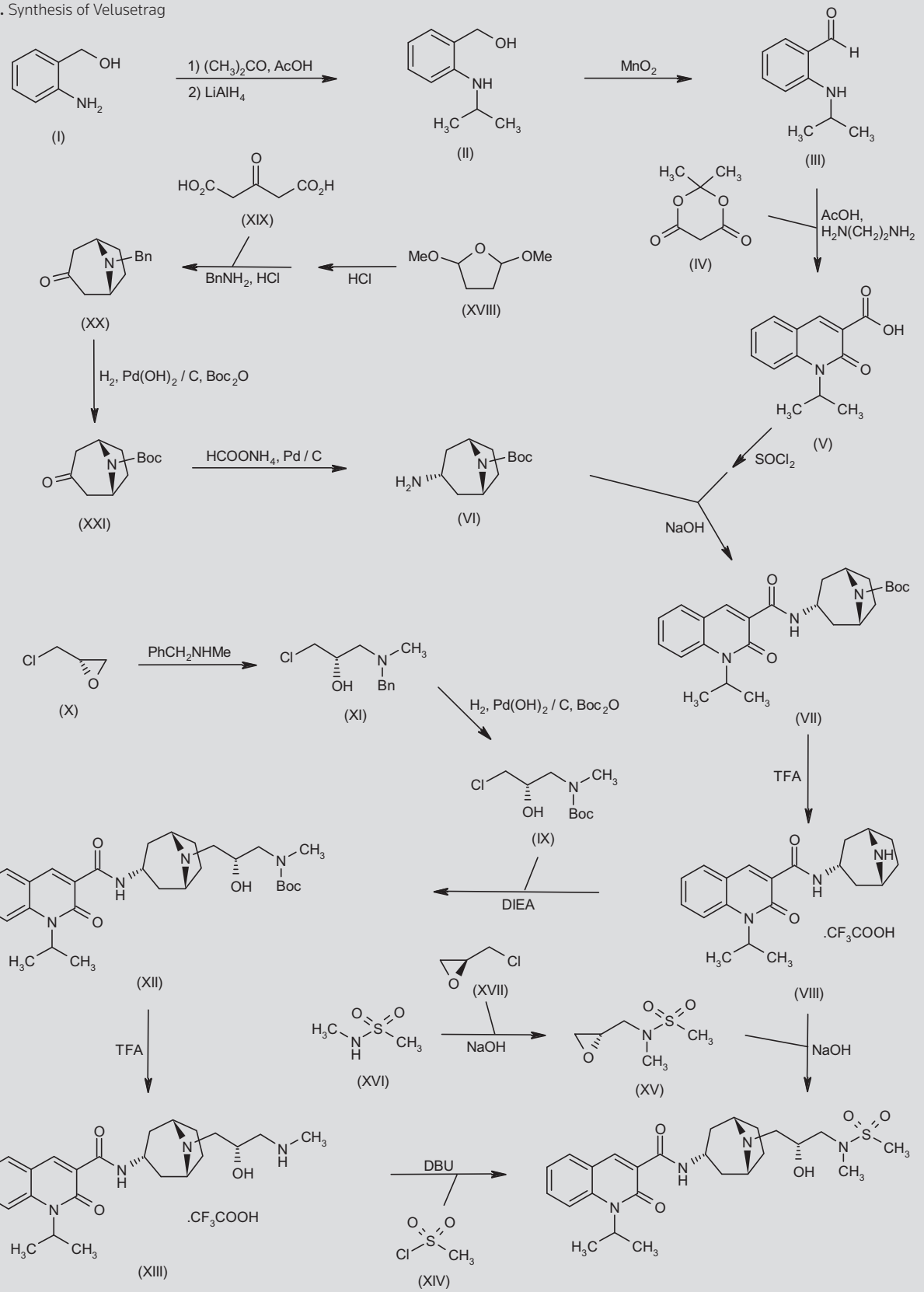
SYNTHESIS*

Velusetrag is prepared using the following strategy:

Reaction of 2-aminobenzyl alcohol (I) with acetone in aqueous AcOH affords 2,2-dimethyl-1,4-dihydro-2*H*-3,1-benzoxazine, which is reduced with $LiAlH_4$ in THF, producing 2-(isopropylamino)benzyl alcohol (II). After oxidation of alcohol (II) to the corresponding benzaldehyde (III) by means of MnO_2 in toluene at 117 °C, Knoevenagel condensation with Meldrum's acid (IV) in the presence of AcOH and ethylenediamine in MeOH gives 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (V) (1-8). Chlorination of acid (V) with $SOCl_2$ in toluene at 95 °C and subsequent coupling of the resulting acid chloride with *N*-Boc-*endo*-3-aminotropane (VI) in the presence of NaOH in toluene/water affords the corresponding amide (VII). Deprotection of the *N*-Boc-tropane derivative (VII) by means of TFA in CH_2Cl_2 furnishes the corresponding amine TFA salt (VIII) (1-9), which is then *N*-alkylated with 1-chloro-3-(*N*-Boc-*N*-methylamino)propan-2(*S*)-ol (IX) [prepared by condensation of (*S*)-epichlorohydrin (X) with *N*-methylbenzylamine in hexane and subsequent hydrogenolysis of the obtained benzylamine derivative (XI) in the presence of $Pd(OH)_2$/C and Boc_2O in EtOAc] in the presence of DIEA in MeOH at 80 °C to give the *N*-Boc-methylamine derivative (XII). Deprotection of this compound by means of TFA in CH_2Cl_2 and *N*-sulfonylation of the obtained free amine (XIII) with methanesulfonyl chloride (XIV) in the presence of DBU in CH_2Cl_2 then affords velusetrag. Alternatively, reaction of amine (VIII) with *N*-[(*S*)-glycidyl]-*N*-methylmethanesulfonamide (XV) [prepared by alkylation of *N*-methylmethanesulfonamide (XVI) with (*S*)-epichlorohydrin (XVII) using aqueous NaOH (8, 10)] in the presence of NaOH in MeOH yields velusetrag (1-3, 5, 6, 8).

N-Boc-*endo*-3-aminotropane (VI) is prepared by hydrolysis of 2,5-dimethoxytetrahydrofuran (XVIII) with aqueous HCl, followed by Mannich reaction of the resulting succinaldehyde with $BnNH_2$ and 1,3-acetonedicarboxylic acid (XIX) in the presence of HCl in H_2O to give *N*-benzyl-8-azabicyclo[3.2.1]octan-3-one (XX). Treatment of this compound with H_2 over $Pd(OH)_2$/C and Boc_2O in EtOAc yields *N*-Boc-8-azabicyclo[3.2.1]octan-3-one (XXI), which is then converted to the desired amine (VI) by reductive amination with $HCOONH_4$ in the presence of Pd/C in MeOH/H_2O (1-8). Scheme 1.

Scheme 1. Synthesis of Velusetrag



Velusetrag can be converted to its salts, including hydrochloride, citrate, adipate, phosphate, sulfate, tartrate, malate, hydrobromide and mesylate, by treatment with the respective acids (1-3, 5, 6, 8).

BACKGROUND

Chronic constipation is a common gastrointestinal (GI) disorder that affects 10-20% of the American population (11, 12). The economic impact of chronic constipation is significant, with an estimated 7.95 million physician visits annually (13), with increased medical care use and expenses in women in the U.S. (14). Constipation also has a negative impact on the health-related quality of life of individuals, with psychological and social consequences (15, 16). Irritable bowel syndrome (IBS) with constipation is associated with altered bowel function, as well as abdominal discomfort and/or pain and bloating, which are relieved with defecation. IBS with constipation also leads to impaired quality of life.

Current treatments for chronic constipation include stool softeners, fiber supplements, osmotic and stimulant laxatives. Overall, these have varying degrees of efficacy. Therapies with distinct mechanisms of action have been developed in an attempt to enhance treatment efficacy. These newer therapies are directed at stimulating fluid secretion into the intestinal lumen (osmotic laxatives), chloride secretion (secretory agents) and colonic motor function (prokinetics and stimulant laxatives). Among the latter group of drugs, some have limited effectiveness or have been withdrawn from the U.S. market because of reported adverse effects (e.g., tegaserod).

Chloride secretagogues

Chloride channels in the apical membrane of the enterocytes lead to chloride and fluid secretion into the intestinal lumen by activating the chloride type 2 channel (CLC-2) and the cystic fibrosis transmembrane regulator (CFTR) (15, 16). Thus, lubiprostone was initially reported to be a selective CLC-2 activator (17), although recent studies suggest it also activates CFTR (18, 19). It is the only currently available chloride secretagogue drug approved for chronic constipation (24 μg b.i.d.) and IBS with constipation (8 μg b.i.d.). Clinical trials (20, 21) have demonstrated its efficacy in chronic constipation and IBS with constipation, but the side effect of nausea seen in approximately 20% of patients limits its long-term tolerability (22) or reduces patient compliance. Other chloride secretagogues in development are linaclotide and plecanatide.

5-HT_4 receptor agonists

5-HT_4 receptor agonists stimulate colonic motor function by activating gastrointestinal motor neurons and interneurons, releasing excitatory neurotransmitters such as acetylcholine and substance P, and resulting in propulsion of contents along the gastrointestinal tract (23). Older-generation 5-HT_4 receptor agonists include cisapride and tegaserod. Cisapride accelerated colonic transit (24) and relieved constipation in patients with chronic constipation. Cisapride blocked the human voltage-gated potassium channel K_V11.1 (hERG1), leading to QT_c prolongation and ventricular arrhythmias. This led to withdrawal from the U.S. market. Tegaserod, a 5-HT_4 receptor partial agonist, accelerated small bowel and colonic transit (25) and was effective in patients with chronic constipation (26) and IBS with constipation (27). Tegaserod had modest clinical efficacy (25), but has also been withdrawn from the market because of an alleged increased risk of cardiovascular events. Tegaserod interacted with multiple 5-HT receptor agonists; this nonselective pharmacology and its limited oral bioavailability (10%) are believed to have contributed to its limited efficacy (28-30).

New-generation 5-HT_4 receptor agonists have high selectivity and affinity for intestinal 5-HT_4 receptors, leading to improved efficacy. They also have reduced effects on the hERG channel, leading to fewer adverse cardiovascular events. The newer agents include prucalopride, naronapride and velusetrag.

Prucalopride, a dihydrobenzofurancarboxamide derivative, is a highly selective, high-affinity 5-HT_4 receptor agonist that stimulates gastrointestinal and colonic transit (31). In three similarly-designed, well-powered, randomized, placebo-controlled, parallel-group clinical trials of 12 weeks' duration, doses of prucalopride of 2 and 4 mg were effective in the relief of constipation relative to placebo. The primary efficacy endpoint was the proportion of patients having three or more complete spontaneous bowel movements (SBMs) per week. After 12 weeks of treatment, the therapeutic benefit of prucalopride over placebo was 18% (32). Overall, prucalopride was well tolerated, and the most common side effects were headache, nausea, abdominal pain and diarrhea, occurring in 10% or more of treated participants (32-34). No clinically significant cardiovascular adverse effects have been documented in clinical trials. Patient satisfaction with prucalopride treatment based on a validated quality-of-life instrument (Patients' Assessment of Constipation Quality of Life, PAC-QOL) showed significant benefit in favor of prucalopride over placebo (32, 35). Prucalopride is currently approved in Europe as daily doses of 1 mg in the elderly (over 65 years of age) and 2 mg in adults.

Naronapride (ATI-7505) is a 5-HT_4 receptor agonist that is structurally related to cisapride but lacks cytochrome P450 CYP3A4 metabolism, reducing the risk of drug interactions with medications that inhibit CYP3A4 metabolism and the consequent cardiovascular side effects seen with cisapride when given concomitantly with inhibitors of CYP3A4. A phase IIa clinical trial in 48 healthy volunteers, predominantly females (> 60%), with a mean age of 33.3 ± 0.9 years evaluated the effects of multiple doses of naronapride (3, 10 and 20 mg or placebo orally t.i.d.) on gastric, small bowel and colonic transit using scintigraphy after a 9-day treatment phase (36). Naronapride at 10 mg t.i.d. accelerated colonic transit at 24 hours and ascending colonic emptying, and stool consistency was improved at the doses of 10 and 20 mg t.i.d.

A phase IIb trial evaluated multiple doses of naronapride of 20, 40, 80 or 120 mg b.i.d. orally and placebo in 214 patients with chronic constipation for 4 weeks (37). The primary efficacy endpoint was the total number of SBMs during the first week of treatment compared to placebo. Patients treated with naronapride had a greater number of SBMs during week 1 of treatment compared to placebo: 5.7, 5.0, 6.7 and 5.2, respectively, for naronapride doses of 20, 40, 80 and 120 mg, and 3.9 for placebo. Naronapride was well tolerated, and adverse events included headache, diarrhea, nausea and vomiting (36, 37), which were similar to placebo. In the Thorough QT Study (38), naronapride 40 or 200 mg every 6 hours for 8 days had no effect on cardiac repolarization or other ECG parameters.

PRECLINICAL PHARMACOLOGY

Velusetrag (TD-5108) is a potent agonist with high intrinsic activity at human 5-HT_4 receptors and ≥ 500-fold selectivity over all other 5-HT receptor subtypes (39). To date, two clinical trials have been conducted to assess efficacy using well-validated pharmacodynamic and clinical effects, and these are described in detail below.

5-HT is produced and stored in the enteroendocrine cells, and large amounts are secreted into the lamina propria after a meal. The main effects of 5-HT, which are mediated through one of the seven 5-HT receptor agonist subtypes, are gastrointestinal secretion, sensation and motility (40, 41). 5-HT receptor agonists are abundantly available throughout the gastrointestinal tract, and the pharmacological effects of activating serotonergic mechanisms are most prominently demonstrated by the effects of 5-HT_4 receptor agonists on gastrointestinal and colonic motility and transit (42).

The in vitro pharmacological profile of velusetrag was compared with other 5-HT_4 agonists: tegaserod, mosapride and cisapride (43). Velusetrag showed preferential binding to the 5-HT_4 receptor and selectivity of > 500-fold relative to all other 5-HT receptor subtypes. At a concentration of 3 μM velusetrag had no effect on the hERG channel. Using in vitro 5-HT_4 receptor agonist models, velusetrag produced a concentration-dependent increase in cAMP (pEC = 8.3) contraction of the longitudinal muscle–myenteric plexus preparations of the guinea pig colon and relaxation of the rat isolated esophagus precontracted with carbachol (44).

In vivo studies have been published and demonstrate typical 5-HT_4 agonist effects for velusetrag. Subcutaneous velusetrag (0.003-3 mg/kg), tegaserod, cisapride and mosapride increased colonic transit, measured by the passage of carmine red dye in guinea pig colon, compared to vehicle. The effect of velusetrag was dose-dependent (45), with the highest dose (3 mg/kg) increasing intestinal transit by 40%. Intravenous velusetrag (0.003-1 mg/kg) produced dose-dependent relaxation (measured by sonomicrometry) of the rat esophagus; however, it is unclear whether this may lead to pathological esophageal reflux disease. Velusetrag produced a dose-related increase in the contractility of the antrum, fundus, duodenum and jejunum of dogs after oral (0.1 and 0.3 mg/kg) and i.v. (3, 10 and 30 μg/kg) doses. This contractile activity was demonstrated within the initial 30 minutes after the dose and continued for a 3-hour period.

PHARMACOKINETICS AND METABOLISM

Velusetrag is metabolized through the cytochrome P450 CYP3A4 system. The average percent binding of velusetrag to plasma proteins is 31.6% in human samples (Theravance data on file). A study of 48 healthy volunteers evaluated the pharmacokinetics of single ascending doses of velusetrag of 0.1-90 mg and multiple doses of 50 mg/day for 14 days (46). Serial plasma samples were collected and analyzed using a sensitive liquid chromatography/tandem mass spectometry method. The mean t_{max} and terminal $t_{1/2}$ for velusetrag were 1.6-6 hours and 12-17.6 hours, respectively, for doses of 0.5-70 mg in the single-ascending-dose study. In the 14-day multiple-dose study in 48 healthy volunteers, the mean t_{max} and $t_{1/2}$ were 3 hours and 17 hours, respectively, suggesting that velusetrag is appropriate for once-daily dosing.

In a study of 60 healthy volunteers randomized to placebo or velusetrag 5, 15, 30 or 50 mg for 6 days, there was a dose-dependent increase in velusetrag and its active desmethyl metabolite, THRX-830449, which is a full agonist with comparable pharmacological properties to the parent drug (Fig. 1) (39, 47). Pharmacokinetic results showed accumulation at steady state proportional to the half-lives of the two compounds. Thus, after velusetrag is metabolized, THRX-830449 shows a similar concentration–time profile, full agonist biological activity and no toxic effects in laboratory tests or EKG parameters, such as corrected QT interval duration.

In vitro studies have shown that the pK_i and pEC_{50} values for THRX-830449 are 7.6 and 8.2, respectively, compared to 7.7 and 8.3, respectively, for velusetrag (Theravance data on file, cited in 39). On days 1 and 9, increases in C_{max} and AUC with dose were greater than proportional to the increase in dose in healthy volunteers. On day 9 of treatment, THRX-830449 showed greater than dose-proportional increases after exposure. The ratios of the active metabolite to the parent compound were about 0.3-0.4 for C_{max} and AUC on day 1 and 0.3-0.6 on day 9 of treatment. Terminal $t_{1/2}$ values for velusetrag and THRX-830449 were 10-13 hours and 17-30 hours, respectively (47).

After a single velusetrag dose of 15 mg in patients with chronic constipation and healthy controls, mean pharmacokinetic parameters, t_{max}, C_{max}, elimination $t_{1/2}$, $AUC_{0\text{-}24}$ and $AUC_{0\text{-}\infty}$, were not significantly different between groups (39, 47).

SAFETY

To date, 2 placebo-controlled trials in 60 healthy volunteers and 401 patients did not identify any cardiac rhythm abnormalities at doses that are also effective in the treatment of chronic constipation (39, 48). In the study in 60 healthy volunteers (mean age 35.0 ± 2.7 years, predominantly female and Caucasian), no serious adverse events were reported (39). Adverse events reported were either gastrointestinal-related, such as diarrhea in 50% and nausea in 33.3% of volunteers, or headache in 48%. These adverse events were typically dose-related. All the participants completed the treatment portion of the study. One of the 60 healthy volunteers developed asymptomatic junctional escape rhythm on electrocardiogram. There were no significant treatment effects of velusetrag on three baseline heart rate measurements. The study in 401 patients with chronic constipation by Rome III criteria (mean age 45.1 ± 10.5 years; 92% females and predominantly Caucasian) randomized to three doses of velusetrag (15, 30 or 50 mg) or placebo reported similar gastrointestinal adverse events (48). In the velusetrag-treated patients, overall, diarrhea was reported in 13% of patients and nausea in 8%. Headache was reported in 12.2% of patients in a dose-dependent manner. However, 6% (n = 18) of the velusetrag-treated patients discontinued the study due to adverse events during the treatment period. The most common reason for discontinuation was diarrhea (11 of 18), and to a lesser extent, nausea and headache.

CLINICAL STUDIES

The efficacy of velusetrag has been evaluated in phase II clinical trials. In a pharmacodynamic transit study, 60 healthy volunteers (mean age

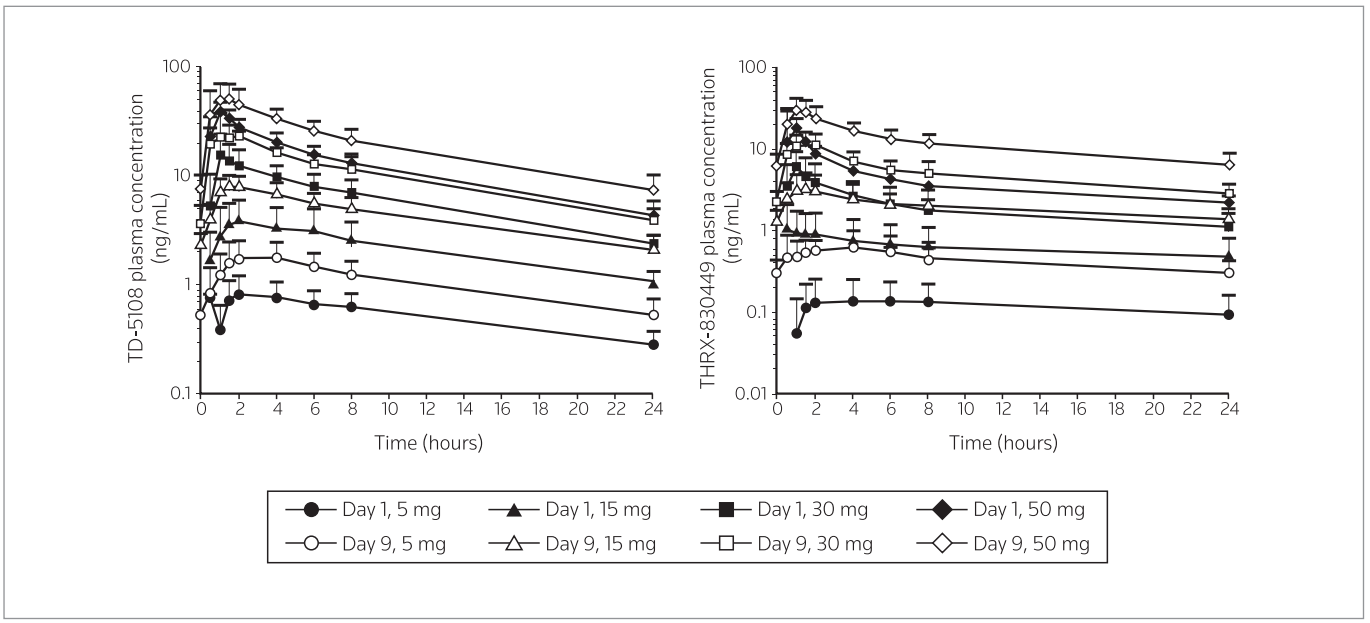


Figure 1. Plasma concentration–time curves on days 1 and 9 for TD-5108 (velusetrag) and THRX-830449. Plots show mean (+SD). Reproduced with permission by John Wiley and Sons from Manini, M.L., Camilleri, M., Goldberg, M., Sweetser, S., Mckinzie, S., Burton, D., Wong, S., Kitt, M.M., Li, Y.-P., Zinsmeister, A.R. *Effects of velusetrag (TD-5108) on gastrointestinal transit and bowel function in health and pharmacokinetics in health and constipation*. Neurogastroenterology & Motility 2010, *22*(1): 42-9, e7-8 (39).

35.0 ± 2.7 years, predominantly female and Caucasian) were randomly assigned in double-blind fashion to placebo, 5, 15, 30 or 50 mg velusetrag in a single-dose and multiple-dose design (39). A single dose of velusetrag significantly accelerated both overall colonic transit at 24 hours and ascending colon emptying $t_{1/2}$ (Fig. 2). During multiple dosing of velusetrag over 6 days, the 30-mg dose significantly accelerated overall gastric emptying $t_{1/2}$ (Fig. 2) and overall colonic transit (Fig. 3) with the doses of 15-50 mg. The dose-dependent stimulatory effect on gastric emptying suggests that this medication may be particularly useful for the increasingly recognized patients with dual delays in transit in the stomach and the colon.

In an open-label, single-dose pharmacokinetic study in patients with chronic constipation and matched healthy controls, 15 mg of velusetrag had similar effects on laxation and bowel function (39).

The ACCORD (a randomized, placebo-controlled, double-blind study of velusetrag for the treatment of chronic constipation) trial was a phase II study of velusetrag in 401 patients with chronic constipation (average age 45 years; average body mass index [BMI] 27.9 kg/m^2; 92% female; 69% white, 28% black, 2% Asian) (48). The primary efficacy endpoint was the change from baseline in the average number of SBMs per week averaged over the 4-week treatment period. Patients who received doses of 15, 30 and 50 mg achieved a statistically significant change in weekly SBM frequency relative to placebo. The bowel movement frequency was 3.6, 3.3 and 3.5 SBMs/week, respectively, for velusetrag 15, 30 and 50 mg compared to 1.4 SBMs/week for placebo ($P < 0.0001$) (Fig. 4). Figure 4 also shows that mean weekly SBM frequency dropped towards the rate observed in the placebo group during week 5, after treatment was discontinued. Efficacy appears to be highest during the first week of

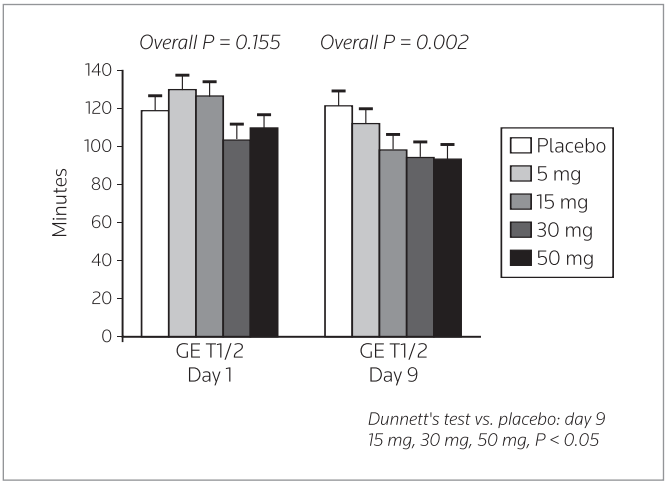
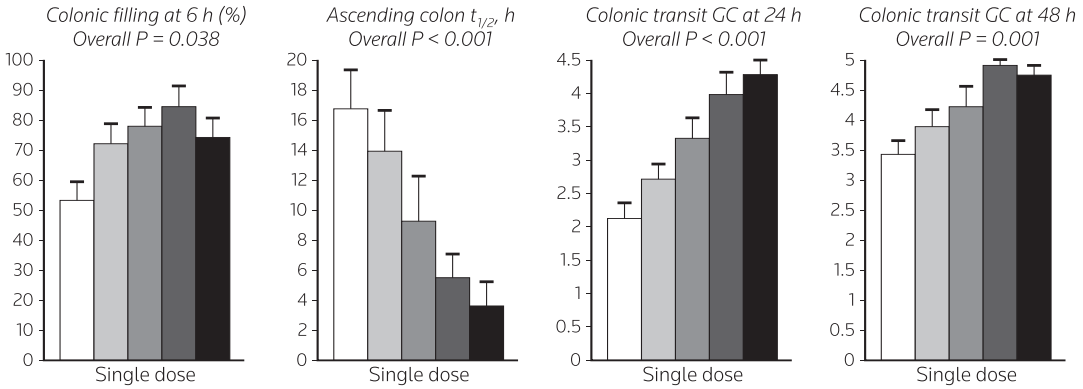
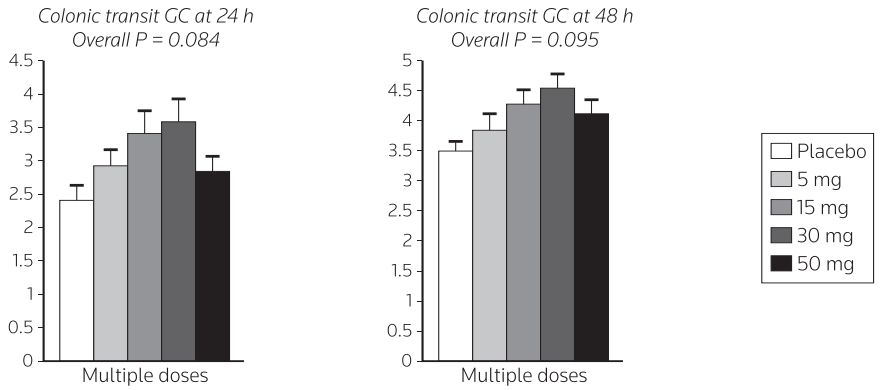


Figure 2. Dose-related effect of velusetrag on gastric emptying (GE) of solids after day 1 and days 4-9 of treatment. Reproduced with permission by John Wiley and Sons from Manini, M.L., Camilleri, M., Goldberg, M., Sweetser, S., Mckinzie, S., Burton, D., Wong, S., Kitt, M.M., Li, Y.-P., Zinsmeister, A.R. *Effects of velusetrag (TD-5108) on gastrointestinal transit and bowel function in health and pharmacokinetics in health and constipation*. Neurogastroenterology & Motility 2010, 22(1): 42-9, e7-8 (39).

treatment, a phenomenon that was also observed in trials with other colonic prokinetics and secretagogues. This is commonly thought to reflect a "washout effect", when an effective medication is used in patients with chronic constipation. Therefore, there does not appear



Dunnett's test: Single dose data for CF6, AC $t_{1/2}$ and GC 24 and 48 hours with 30 mg, 50 mg TD-5108 vs. placebo: $P < 0.05$



Dunnett's test: Multiple dose data
30 mg TD-5108 vs. placebo: $P < 0.05$

Dunnett's test: Multiple dose data
15 mg TD-5108 vs. placebo: $P < 0.088$
30 mg TD-5108 vs. placebo: $P < 0.055$

Figure 3. Dose-related effects of TD-5108 (velusetrag) on small bowel transit and overall colonic transit geometric center (GC), which is the weighted average of count proportions in different colonic regions and stool (where 1 = ascending colon and 5 = stool) at 24 and 48 hours after day 1 (single dosing) or days 4-9 (multiple dosing) of treatment. Reproduced with permission by John Wiley and Sons from Manini, M.L., Camilleri, M., Goldberg, M., Sweetser, S., Mckinzie, S., Burton, D., Wong, S., Kitt, M.M., Li, Y.-P., Zinsmeister, A.R. *Effects of velusetrag (TD-5108) on gastrointestinal transit and bowel function in health and pharmacokinetics in health and constipation*. Neurogastroenterology & Motility 2010, *22*(1): 42-9, e7-8 (39).

to be induction of tachyphylaxis over the 4-week trial. In addition, the efficacy of velusetrag doses of 15, 30 and 50 mg in the clinical trial appears to parallel the results in the pharmacodynamic study (39), and the 50-mg dose does not appear to be more effective than the two lower doses of 15 and 30 mg. Patients receiving velusetrag also had a faster time to their first bowel movement following the initial dose of the medication compared to placebo. Velusetrag was well tolerated and the most common adverse events were gastrointestinal-related effects (diarrhea 13% and nausea 12.2%) and headache (12.2%), but these were mild to moderate in severity (48, 49). Diarrhea and headache were typically observed on the first 2 days of dosing and lasted no longer than 7 days. These events did not result in significant subject discontinuation (48). Only 6% (n = 18) of the velusetrag-treated patients discontinued the study; the most common reason was diarrhea (11 of 18).

DRUG INTERACTIONS

Studies evaluating the drug interactions of velusetrag are limited. In vivo studies of velusetrag showed that it did not significantly inhibit P-glycoprotein (Pgp)-mediated efflux transport in Caco-2 cells at the concentration of 100 μM. Thus, the interaction of velusetrag with other Pgp substrates is low. Studies in human liver microsomes showed no significant inhibitory effect of 10 μM velusetrag on CYP3A4, but moderate inhibition of up to 57% was observed on the

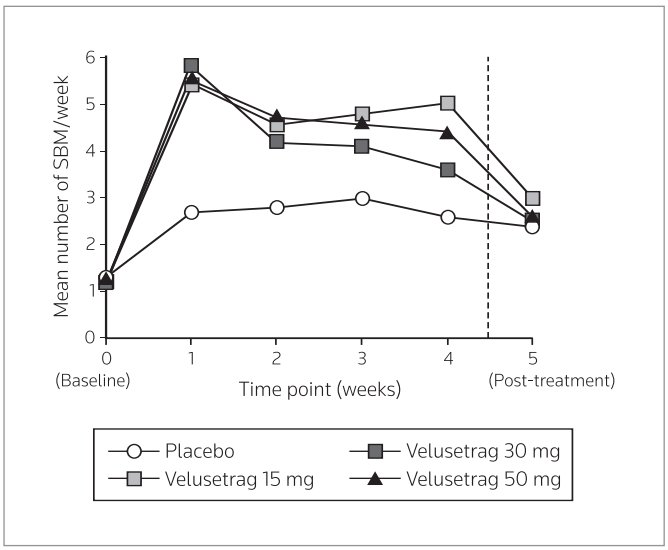


Figure 4. The effects of velusetrag and placebo on mean weekly spontaneous bowel movement (SBM) frequency during each week of treatment and during week 5 after treatment was discontinued. Reproduced with permission by John Wiley and Sons from Goldberg, M., Li, Y.P., Johanson, L.F., Mangel, A.W., Kitt, M., Beattie, D.T., Kersey, K., Daniels, O. Clinical trial: *The efficacy and tolerability of velusetrag, a selective 5-HT4 agonist with high intrinsic activity, in chronic idiopathic constipation – A 4-week, randomized, double-blind, placebo-controlled, dose-response study*. Alimentary Pharmacology & Therapeutics 2010, 32(9): 1102-12 (48).

metabolic activity of CYP1A2, 2C9, 2C19 and 2D6. Additional studies evaluating the major metabolite THRX-830449 (10 μM) showed no inhibition of the metabolic activity of CYP 3A4, 1A2, 2C9, 2C19 and 2D6. These data suggest a low risk of inhibition of the major drug-metabolizing enzymes and of drug interactions for velusetrag and its major metabolite (Theravance data on file). Commonly used drugs that are metabolized by these enzymes (50) and for which there should not be drug–drug interactions with velusetrag are: erythromycin (CYP3A4), levofloxacin (1A2), warfarin (2C9), proton pump inhibitors, clopidogrel (2C19), antidepressants (tricyclic, selective serotonin and serotonin/norepinephrine reuptake inhibitors) and codeine (2D6).

SOURCE

Theravance, Inc. (US).

ACKNOWLEDGMENTS/DISCLOSURES

The authors gratefully acknowledge David Beattie, PhD, for providing access to pharmacokinetic information that is on file at Theravance. Dr. Camilleri received a research grant from Theravance to study the pharmacodynamics and pharmacokinetics of velusetrag. These data appear in reference 39. After completion of all research studies and publication, Dr. Camilleri served as a consultant to Theravance. Dr. Vazquez-Roque states no conflicts of interest.

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