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Effects of TD-5108 on Gastrointestinal Transit and Bowel Function in Health and Pharmacokinetics in Health and Constipation

Mhd Louai Manini, M.D., Michael Camilleri, M.D., Michael Goldberg, M.D., Ph.D.[#], Seth Sweetser, M.D., Sanna McKinzie, M.S., Duane Burton, Shekman Wong, Ph.D.[#], Michael M. Kitt, M.D.[#], Yu-Ping Li, Ph.D.[#], and Alan R. Zinsmeister, Ph.D.^{*}

Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Mayo Clinic, Rochester, MN

^{*}Department of Health Sciences Research, Division of Biostatistics, Mayo Clinic, Rochester, MN

[#]Theravance, Inc., South San Francisco, CA

Abstract

Background—TD-5108 is a potent, selective high intrinsic activity serotonin 5-HT₄ receptor agonist.

Aim—To assess effects of TD-5108 on gastrointestinal transit and compare its pharmacokinetics (PK) in healthy volunteers (HV) and chronic constipation (CC) patients.

Methods—60 HV were randomly assigned, double-blind to placebo, 5, 15, 30 or 50 mg TD-5108 (single and 6-day dosing). Primary endpoints were colonic transit (geometric center at 24 hours, GC24) and ascending colon emptying (ACE) T_{1/2} after first dose. Secondary endpoints included gastric emptying (GE) T_{1/2} and colonic filling at 6 h (CF6).

Results—Single dose TD-5108 significantly accelerated GC24, ACE T_{1/2}, and CF6; 30 and 50° mg TD-5108 accelerated all 3 endpoints. With multiple doses, TD-5108 30 mg accelerated GC24, and overall accelerated GE T_{1/2} at 15–50 mg. PK studies showed dose proportionality in health, and no significant differences between health and chronic constipation with a 15 mg oral dose of TD-5108. Stimulation of bowel function after 15 mg TD-5108 were similar in CC and controls. There were no serious adverse events; notable adverse were the predictable GI effects such as diarrhea or altered bowel movements.

Conclusions—TD-5108 significantly accelerated intestinal and colonic transit after single dosing and accelerated gastric emptying after multiple dosing. Further studies of its potential as a gastrointestinal and colonic prokinetic are warranted.

Keywords

prokinetic; colon; motility; serotonergic; 5-HT₄

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Address for correspondence: Michael Camilleri, M.D., Mayo Clinic, Charlton 8-110, 200 First St. S.W., Rochester, MN 55905, Tele: 507-266-2305, camilleri.michael@mayo.edu.

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INTRODUCTION

Constipation affects 2 to 27% of the population in Western countries (1), and it negatively impacts quality of life and well being. Current treatment typically entails dietary fiber and osmotic laxatives as first line treatment, and stimulant laxatives (e.g., bisacodyl) or lubiprostone, a stimulator of chloride transport that increased stool volume (2) as second line approaches.

The rationale behind the use of serotonin type 4 (5-HT₄) receptor agonists in chronic constipation is based on activation of 5-HT₄ receptors on gastrointestinal motor neurons and interneurons, release of excitatory neurotransmitters such as acetylcholine and substance P and consequent propulsion of contents along the gastrointestinal (GI) tract. Tegaserod, a 5-HT₄ receptor agonist with modest clinical efficacy, was briefly available in the market for the treatment of chronic constipation (CC) and irritable bowel syndrome (3). This drug has now been withdrawn from the market because of increased risk of cardiovascular events possibly attributable to the drug (3). It has recently been shown that tegaserod interacts with multiple 5-HT receptors, including 5-HT_{2B} receptors, and this mixed pharmacology may have contributed to its limited clinical efficacy (4). Moreover, tegaserod has low oral bioavailability (10%), which may have contributed to limited efficacy (5,6).

There is potential clinical utility for 5-HT₄ receptor agonists with greater selectivity for 5-HT₄ receptors, higher intrinsic activity, improved pharmacokinetics and improved efficacy relative to tegaserod. TD-5108 is a potent agonist at human 5-HT₄ receptors ($K_i = 20\text{nM}$, and $\text{EC}_{50} = 5\text{ nM}$ with respect to displacement of [³H]GR113808 binding and cyclic adenosine monophosphate accumulation, respectively, in HEK-293 cells expressing the 5-HT_{4(c)} receptor splice variant [7]) with high intrinsic activity, that displays preferential binding to the 5-HT₄ receptor compared with all other 5-HT receptor subtypes (selectivity of ≥ 500 -fold), and, at 3 μM , has no effect on human ether-à-go-go-related gene-encoded K⁺ channels (4,7). In the guinea pig colon longitudinal muscle myenteric plexus and rat esophagus tunica muscularis mucosa preparations, the intrinsic activities of TD-5108 are 95% and 100% of the 5-HT-induced maximum, respectively. In these tissues, the intrinsic activities of tegaserod are lower (65% and 80% of the 5-HT-induced maximum responses, respectively [7]). In vivo studies have shown that TD-5108 increases colonic transit in guinea pigs, relaxes the esophagus in rats, and increases contractility in multiple regions of the GI tract including the gastric antrum, duodenum, jejunum and proximal colon in conscious dogs with implanted strain gauges (8).

The aim of this study was to assess the effects of single and multiple administrations of 4 doses of TD-5108 (5, 15, 30, and 50 mg, the 3 higher doses evaluated in a concurrent Phase 2 clinical trial in patients with CC) on gastrointestinal transit times in healthy subjects, with emphasis on the whole colon and ascending colon (primary endpoints), as well as emptying of solids from stomach and small bowel. Effects on bowel function, pharmacokinetics of TD-5108, and tolerability were also assessed.

In a supplemental open study, pharmacokinetics and clinical effects of the 15 mg dose were assessed in CC and age matched healthy controls.

METHODS

Participants

Both studies were approved by the Mayo Clinic Institutional Review Board. All participants provided written informed consent. All were studied at the Clinical Research Unit at the Mayo Clinic.

Sixty healthy volunteers (ages for inclusion were 18 – 65 years) participated in the dose-response transit study. The main exclusion criteria were pregnancy, >3 positive responses (and none > mild severity) on an abridged Bowel Disease Questionnaire (9), history of dyspepsia, irritable bowel syndrome or significant gastrointestinal symptoms, acute illness, use of any medication that alters GI transit or any medication known to inhibit or induce CYP 3A4, and EKG QTc interval > 470 msec for women, >450 msec for men.

In the open-label, single-dose pharmacokinetic study, we assessed 11 CC patients and 11 healthy controls of similar age and gender. Inclusion and exclusion criteria were similar to above. There were no specific requirements regarding CC symptoms during the period leading up to the study.

Medication Metabolism, Pharmacokinetics and Safety in Phase IA studies

TD-5108 (5 to 70 mg) has been well tolerated in single and/or multiple dose studies in humans. Following single doses of 0.1 to 90 mg TD-5108, AUC and $C_{\max}$ increased in a dose proportional manner. Mean $T_{\max}$ ranged from 4 to 6 hours at doses up to 30mg. Elimination half-life ($t_{1/2}$) from plasma was ~ 13 hours (10).

The major metabolite (CYP3A4-mediated) detected in the plasma after oral TD 5108 is THRX 830449, which is a full agonist and approximately equipotent to TD 5108. Thus, pK_i and pEC_{50} values for THRX-830449 at the human recombinant 5-HT_{4(c)} receptor are 7.6 and 8.2, respectively compared to 7.7 and 8.3 for TD-5108, respectively. In healthy humans, at steady-state, the THRX-830449 to TD-5108 AUC ratio is ~ 0.5 following once daily dosing of TD-5108 (15 mg). The elimination $t_{1/2}$ of THRX-830449 after single and multiple dosing are 16 and 35 h respectively (Theravance data on file).

Adverse experiences reported generally upon initiation of dosing with TD-5108, were mild in severity, consistent with prokinetic activity (e.g., diarrhea and nausea), and did not result in subject discontinuation (11).

Study Designs

The transit study in healthy subjects was a double-blind, placebo-controlled, parallel-group, randomized, trial evaluating effects of single and multiple doses of 5–50 mg TD-5108 on gastrointestinal and colonic transit and bowel function. Following a screening visit, subjects were randomized to one of four TD-5108 doses (5, 15, 30, and 50 mg) or placebo. The duration of double-blind treatment was for a total of 7 days, a single dose being given on Day 1, with drug-free observations on Days 2 and 3, multiple doses given on Days 4–9, and drug-free observations on Days 10 and 11. The 48 hour periods after the first and final doses of study drug were to complete the assessment of gastrointestinal transit of radioactive tracers using established methodology (12–16), and to obtain blood samples for pharmacokinetic studies on days 1 and 9 pre-dose and 30 minutes, 1.5, 2, 4, 6, 8 and 24 hours post-administration of study medication. We measured heart rate and blood pressure on each day participants attended the Clinical Research Unit for transit measurement (total 6 days) and EKG at entry and last day of pharmacodynamic study. Heart rate measurements (by clinical research unit nurses) were obtained three times prior to treatment (during two screen visits, and on the day of randomization prior to receiving the first dose of medication). A resting EKG was also obtained at the second screening visit (for safety bloods, urine and EKG). Heart rate was measured during the transit test, 4–6 days after initiation of study medication, and 24 hours after last dose of study medication. A second EKG was obtained 24 hours after the last medication dose.

The pharmacokinetic study in CC and age and gender matched controls was a parallel group evaluation of a single 15-mg dose of TD-5108, administered after an overnight fast, followed

by pharmacokinetic sampling for 48 hours (samples were collected at 1, 2, 4, 6, 8, 12, 18, 24, 36, and 48 hours). For safety, heart rate and blood pressure were monitored at times of blood draws during the pharmacokinetic study; clinical laboratory tests, and electrocardiograms were monitored before and after the pharmacokinetic sampling.

A bowel pattern diary was used to assess the time to first bowel movement after dosing, numbers of stools during the 48-hour post dose period, stool consistency (pictorial Bristol stool form score), and completeness of evacuation for an exploratory comparison of the clinical effects of TD-5108 in patients and controls.

Randomization, Dosing and Concealed Allocation

In the pharmacodynamic study, the first 8 subjects were equally randomized to receive one of three doses (15, 30, and 50 mg) of TD-5108 or placebo. Following a protocol amendment to incorporate the 5 mg dose into the study, the remaining 52 subjects were randomized to one of four doses (5, 15, 30, and 50 mg) of TD-5108 or placebo. For each daily dose, a total of 4 capsules were given, mixing capsule strengths of 0 (placebo) and 2.5, 10, and 15 mg in order to achieve the pre-specified dose. A separate allocation schedule was prepared for men and women to allow for stratification of 1 male to 2 females; this gender ratio was planned to reflect likely gender of the target population in the clinic. Only pharmacy personnel were allowed to see the randomization codes until the study data were locked; the code was then communicated to the study biostatistician (ARZ).

Measurement of Gastrointestinal and Colonic Transit

This was measured and analyzed as in multiple prior studies using validated scintigraphic assessments after a ^{99m}Tc -labeled meal (12–16). The methods are provided in detail in the Appendix which includes effect sizes demonstrable for primary responses (Appendix Table 2) for $n=12$ per group), and number of missing values in transit tests (Appendix Table 3).

Bowel Function Card

Stool frequency, stool form, ease of passage and completeness of evacuation (17–19) were recorded by the subjects using a bowel habit card for each bowel movement on study Days 1 through 11.

The stool diary data for each subject were summarized as mean frequency and time to first stool after dosing, stool consistency, ease of passage score, and proportion of complete evacuations following the first and last dose of study drug. In addition, these diary components were examined daily to assess the time course of drug effect and averaged over the total days of the treatment period for each subject. These per subject summary values were used in the analyses of treatment effects.

Tolerability Evaluations

In both studies, adverse events reported by subjects were recorded on the case report form and characterized in terms of severity, duration, and action (if any) taken with respect to administration of study drug. Adverse events were mapped to preferred terms in MedDRA (Medical Dictionary for Regulatory Affairs). When healthy subjects received study treatment and did not attend the Clinical Research unit (Days 4–7), they were contacted by telephone to assess any adverse events that were documented and recorded. Clinical laboratory evaluations and serum and urine for detection of pregnancy were analyzed at the Mayo Clinic laboratory at screening and at specified other times.

Pharmacokinetics

The pharmacokinetic analysis was similar for the two studies (for details see appendix). Blood samples (anticoagulated with potassium EDTA) were stored on ice and then centrifuged (3000 rpm for 10 min, 2–8°C) to obtain plasma. Plasma samples were frozen at –60 to –80°C until assayed. Pharmacokinetic samples were analyzed at CEDRA Corp (Austin, Texas). All plasma samples were analysed using a validated liquid chromatography-tandem mass spectrometry method for TD-5108 and its metabolite THRX-830449. The assay was validated for a range of 0.100 to 100 ng/mL based on the analysis of 0.200 mL of human plasma.

Statistical Analysis

Details of the statistical analysis and power are provided in the Appendix. In summary, the effects of treatment on primary and secondary response measures were assessed using analysis of covariance (ANCOVA) models including all subjects randomized for each comparison based on the intent-to-treat (ITT) paradigm. ANCOVA (adjusting for gender and BMI) was used to estimate effects of treatment on change in heart rate between baseline and during treatment for 4–6 days as well as 24 hours after the last dose of medication.

Effects on bowel function and other clinical observations in the pharmacokinetic study with 15 mg dose in chronic constipation and controls in CC are reported descriptively.

RESULTS

Participants, Study Conduct and Completion

Demographic data for the 60 healthy subjects in the transit study are shown in Appendix Table 1A. Baseline characteristics across the groups were similar. Appendix Figure 1 shows the participant flow chart. Sixty randomized participants completed their courses of study medication, and 56 completed all of the multiple image measurements of transit and diaries; 3 completed 0–8 hour imaging studies and all diaries, and 1 developed an adverse event (at 30 mg for nausea and vomiting) and was unable to provide imaging or diary data. One subject receiving the 50 mg dose developed a junctional escape rhythm on electrocardiogram, but was asymptomatic and still completed 0–8 hour transit data.

Appendix table IB shows the demographics of healthy and constipated participants in the pharmacokinetic study; all individuals in this study completed all study procedures.

Pharmacokinetics in health and patients with constipation

These are described in the appendix; in general they showed dose proportionality in health, and no significant differences between health and chronic constipation with a 15 mg oral dose of TD-5108.

Effect of TD-5108 on Gastrointestinal and Colonic Transit

Overall, single dose TD-5108 was associated with dose-related acceleration of small bowel and colonic transit; with multiple dosing, there was a significant overall effect on gastric emptying and effect of 30 mg TD-5108 on colonic transit.

Gastric and small bowel transit—Gastric emptying $T_{1/2}$ (Figure 1) was not significantly accelerated after the single dose on day 1; on Day 9, after 6 consecutive days of TD-5108 treatment ($p=0.002$ overall) there was statistically significant acceleration of gastric emptying $t_{1/2}$ ($p=0.002$ overall) with 15, 30 and 50 mg doses of TD-5108 all significant vs. placebo.

Colonic filling at 6 hours (Figure 2) was significantly accelerated on Day 1 ($p=0.038$ overall), with acceleration noted with individual doses of 30 and 50 mg doses vs. placebo. With multiple dosing (data not shown), the effect of TD-5108 on colonic filling was not statistically significant ($p=0.197$).

Colonic transit—The pre-specified primary pharmacodynamic endpoints were ascending colon (AC) emptying $t_{1/2}$ and colonic geometric center at 24 h after single administration of TD-5108.

AC emptying $t_{1/2}$ —There was a significant overall treatment effect of TD-5108 on AC emptying $t_{1/2}$ on Day 1 ($p<0.001$, Figure 2), with linear dose response. Pairwise comparisons revealed a significant acceleration compared to placebo by TD-5108, at 30 and 50 mg doses ($p<0.001$, Figure 2). Although not significant, the average AC $t_{1/2}$ with 15 mg TD-5108 dose was ~7 hours faster than with placebo.

After multiple dosing, there was no overall significant effect of TD-5108 on AC $t_{1/2}$ compared to placebo (data not shown). However, the average AC $t_{1/2}$ values with 15 and 30 mg doses were similar after single and multiple dosing (10 and 9.5 hours for 15 mg and 5.5 and 7.5 hours for 30 mg); the effect of 50mg TD-5108 on AC $t_{1/2}$ with multiple dosing was not consistent relative to single dose (mean 11 [multiple dosing] vs 3.9 [single dosing] hours).

Overall colonic transit time assessed by geometric center—After single dosing, treatment effects on overall colonic transit were significant for GC at 24 and 48 hours ($p<0.001$ and $p=0.001$ respectively, Figure 2), with significant individual dose effects for 30 and 50 mg vs. placebo at 24 hours. With multiple dosing, the overall effect of TD-5108 on colonic transit was not significant, though the dose of 30 mg was significant vs. placebo (Dunnett's test with correction $p<0.05$). Although not statistically significant, the GC at 24h with the 15 mg dose was ~1 unit greater than that of placebo after both single and multiple doses and similar to the effect of the 30 mg dose with multiple dosing. Increases in colonic GC at 4 and 8 hours after single doses of TD-5108 were also significant (data not shown).

Effects of TD-5108 on Bowel Function in Healthy Controls

Using the "mean " (per subject) diary data for Days 1 and Days 4 through 9, considered as the "treatment period", there were overall treatment effects ($p<0.001$) with increased stool frequency for 30 and 50 mg doses relative to placebo ($p<0.05$, Figure 3), on average ~2.5 more bowel movements on Day 1 and ~1 more bowel movement/day on Day 9.

There were also overall treatment effects of an increase in Bristol stool form score (overall $p=0.012$, Figure 3), with significant effects with 15, 30, and 50 mg. This effect was more apparent on Day 1 than later. As would be expected in healthy subjects, there were no significant overall treatment effects for ease of stool passage and completeness of evacuation (data not shown).

Correlation between Bowel Transit and Bowel Function on Day 1

Appendix Table 6 summarizes the correlation matrix between transit parameters and bowel function on Day 1, after a single administration of TD-5108. Overall colonic transit at 4 to 48 hours and ascending colon emptying were significantly correlated with number of stools, stool consistency and ease of passage.

Tolerability in the Transit Study

There were no serious adverse events; 4 subjects discontinued due to an adverse event. Notable adverse events (mostly predictable GI effects such as diarrhea/altered bowel movements or

borborygmi) are shown in Table 1. The incidence of nausea and headache tended to be dose related. The incidence of nausea, occasionally with vomiting, was less than that of diarrhea.

Clinical laboratory test results, vital sign measurements prior to dosing, and periodic electrocardiograms did not indicate any clinically significant changes. One patient (on 30 mg dose) experienced palpitations and one (on 50 mg dose) developed asymptomatic junctional escape rhythm on electrocardiogram.

The effects of TD-5108 on changes in heart rate relative to the average of three baseline measurements of heart rate (obtained during screening and prior to treatment initiation) are shown in figure 4. The data plotted show the change in heart rate while on medication for the prior 5–6 days, the change from baseline to 24 hours after last dose of study medication, and the change in heart rate recorded by electrocardiogram between baseline and on treatment for the prior 5–6 days. The ANCOVA models (adjusting for gender and BMI) for all the changes in heart rate did not detect significant treatment effects ($p=0.096$, $p=0.92$, $p=0.48$, respectively).

Clinical Observations after Single 15 mg Dosing in Chronic Constipation and Healthy Controls

There were no serious adverse events, and no subjects discontinued due to an adverse event. Table 2 summarizes the clinical results in patients and controls which were quite similar for time to first bowel movement, number of bowel movements in the first 24 hours after dosing, and average stool consistency. Patients reported fewer bowel movements resulting in a sensation of complete evacuation. Notable adverse events (diarrhea, borborygmi, nausea, and headache) were reported with generally similar frequency by patients and subjects.

Clinical laboratory test results, blood pressure measurements, and electrocardiograms did not indicate any clinically significant changes. Vital sign changes from pre-dose suggested an approximate 10 bpm increase in heart rate following administration of 15 mg TD-5108 (table 3).

DISCUSSION

We have reported two clinical evaluations of TD-5108, a highly selective 5-HT₄ receptor agonist with high intrinsic activity. The dose-response transit study showed that TD-5108 administration is associated with acceleration of colonic and orocecal transit after single dose administration to healthy subjects (the primary study endpoint) with substantive and significant effects on gastric and colonic transit also observed with multiple dosing. In an evaluation of patients with chronic constipation and matched healthy control subjects, TD-5108 pharmacokinetics and effects on laxation and bowel function were similar in chronic constipation and health.

It is notable that, with single and multiple dosing, there are dose-related effects of TD-5108 on ascending colon emptying. The ascending colon is known for its high capacity for fluid reabsorption (20,21). Given the decrease in stool consistency observed with TD-5108 on single dosing, it would be reasonable to hypothesize that prokinetic effects on small intestinal (as measured by colonic filling at 6 hours) as well as enhanced colonic transit contribute to accelerated emptying of the ascending colon. The enhanced transit would be expected to allow the stool to more rapidly pass sites which reabsorb this fluid, resulting in looser stool consistency and concomitant increases in stool frequency.

Effects of multiple dosing with TD-5108 on colonic transit were similar in magnitude to single-dose results at most doses, except for the 50 mg dose, suggesting that some degree of tolerance had developed, particularly at this dose (see Figure 2). Despite the lack of overall statistical

significance on small bowel and colonic transit with multiple dosing, the 30 mg TD-5108 dose accelerated colonic transit. Note that both colonic filling and colonic transit measurements were significantly greater or faster with placebo after multiple dosing, contributing to the absence of overall significance with these endpoints after multiple dosing. Given the fact that the metabolite THRX-830449 is also a potent 5-HT₄ receptor agonist with a relatively long $t_{1/2}$, we considered the possibility that the metabolite remaining from the single dose on day 1 may have influenced observations after multiple dosing. We perceive this as unlikely given the multiple dosing occurred from days 4–9, and transit was measured days 9–11. Based on its pharmacology and pharmacokinetics, THRX-830449 may well contribute to the increases in gastrointestinal transit noted with TD-5108 treatment in this study.

Substantial numerical differences in colonic transit (e.g., average difference over placebo of 1 geometric center unit at 24 hours, which is clinically detectable as a change in stool consistency) were observed after multiple dosing. The study was not powered to identify the effect of multiple dosing of TD-5108 because of the unknown degree of tachyphylaxis in the response to a high intrinsic activity agonist such as TD-5108.

Single doses of TD-5108 were not associated with an effect on gastric emptying and this contrasts with the demonstrated effects of the single dose of TD-5108 on colonic transit. However, with multiple dosing, there was evidence of accelerated gastric emptying. This effect was statistically significant and the average reduction in $t_{1/2}$ of 25 minutes would be clinically relevant. Significant acceleration of gastric emptying with multiple dosing in healthy participants is notable, since acceleration of gastric emptying has not always been observed with this class of agents in healthy subjects. In this respect, effects of TD-5108 are consistent with the effects observed in healthy subjects with ATI-7505 (17) and tegaserod (22,23), but not with prucalopride (24). An effect on gastric emptying supports the investigation of TD-5108 in disorders of the upper gastrointestinal tract such as gastroparesis.

Similarly, the significant effects on orocecal transit with the initial dose of TD-5108 suggest that this 5-HT₄ receptor agonist accelerates small intestinal transit in addition to gastric emptying and colonic transit.

Some degree of receptor desensitization to TD-5108 might be expected for an agonist with high intrinsic efficacy. However, it is not clear that desensitization would take place in patients with chronic constipation. For example, prucalopride, another 5-HT₄ receptor agonist with high intrinsic activity which was efficacious in accelerating transit after 7 days' treatment (25), shows sustained clinical efficacy in patients with chronic constipation (26) and in the 4-week Phase 2 study of TD-5108, statistically and clinically significant activity was apparent at the end of the study (27).

Effects of TD-5108 on colonic transit were positively correlated with bowel function on Day 1 (increased frequency with 30 and 50 mg, and reduced stool consistency with 15, 30, and 50 mg). These effects are similar to those reported in healthy subjects (11), consistent with an elimination half-life consistent with once daily administration (10,11), and clinical efficacy demonstrated in a 401 patient, placebo-controlled 4-week, parallel group, Phase 2 dose-ranging (15, 30, 50 mg) trial in adults with chronic constipation (27). In the current study, effects on bowel function were quite similar in patients with chronic constipation and controls following a single 15 mg dose. Thus, pharmacodynamic observations with TD-5108 in healthy subjects are consistent with the drug's potential in the phase 2 study of 401 patients (27).

Pharmacokinetic results showed dose-dependent increases in concentrations of both TD-5108 and its active metabolite, THRX-830449, with accumulation at steady-state proportional to the half-lives of the compounds. Concentrations of the metabolite were ~30% of those of TD-5108. Since the metabolite is approximately equipotent at, and similarly selective for, the 5-HT₄

receptor (Theravance, data on file), both the metabolite and parent drug could contribute to the activity of TD-5108.

In the present studies, TD-5108 appears to be well tolerated up to the highest dose tested. Adverse effects of diarrhea, borborygmi, nausea, and headache were expected for a 5-HT₄ receptor agonist. Dizziness (i.e., lightheadedness) reported by several subjects in the transit study was not reported at 50 mg. Four subjects discontinued the transit study for an adverse experience, including headache and insomnia, nausea and vomiting, palpitations, and junctional escape rhythm, the latter observed in a healthy participant with sinus bradycardia at screening. In the placebo controlled trial in healthy volunteers, there was no significant treatment effect on heart rate during or 24 hours after the last dose of medication. While there was a ~ 10 bpm increase in heart rate following administration of 15 mg TD-5108, in the absence of a placebo control group, this observation is difficult to interpret. The significance of the single observations of palpitations (noted with TD-5108 at 30 mg) and asymptomatic junctional escape rhythm (with 50 mg dose) is uncertain, considering the limited number of subjects in this study. In ~540 healthy subjects or patients with chronic constipation treated with TD-5108 for up to 28 days, one patient with constipation experienced palpitations placebo group and one healthy volunteer had junctional escape rhythm following TD-5108 at 70 mg (Theravance, data on file).

It appears that the newer generation of 5-HT₄ receptor agonists may be less prone to induce tachycardia with repeated administration; thus, DeMaeyer et al (28) compared porcine cardiac and stomach 5-HT₄ receptor pharmacology in response to prucalopride, and demonstrated desensitization only in the former. This suggests that any potential arrhythmogenic effects will be reduced over time. Similar studies have not been conducted with TD-5108, and ultimately careful clinical studies of safety will be essential.

In summary, results of this study support further development of TD-5108 for the treatment of disorders associated with impaired gastrointestinal motility including chronic constipation, C-IBS, gastroparesis and postprandial distress (dyspepsia) syndrome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Dose-related effect of TD-5108 on gastric emptying after Day 1 and Days 4–9 of treatment. Note there is a significant effect after multiple doses of treatment, but not at Day 1.

Figure 2.

Dose-related effects of TD-5108 on colonic filling at 6 hours, ascending colon emptying $t_{1/2}$ and overall colonic transit at 24 and 48 hours after Day 1 or Days 4–9 of treatment. Note there are significant effects on colonic filling, ascending colon and overall colonic transit demonstrable at Day 1 and a clear linear dose response. After multiple doses of treatment, there is still an effect of medication on transit parameters, though the effect of the highest dose (50 mg) appears to be lower with multiple dosing at 24 and 48 hours.

Figure 3.

Comparison of mean number of stools per day (panel above) and mean stool consistency each day (panel below) over the 9 day period of the study. Note the significant effect at Day 1, with some loss of efficacy over time. Overall, there is a significant effect of TD-5108 over placebo ($p < 0.05$); a sub-analysis of Day 1 data showed significant increase in stool frequency and consistency with 5, 15, 30 and 50 mg doses.

Figure 4.

Dose-related effects of TD-5108 on change in heart rate relative to average of three baseline measurements of heart rate obtained during screening and prior to treatment initiation. The data show the change in heart rate while on medication for the prior 5–6 days (depending on the date of scheduled transit measurement), as well as the change from baseline to 24 hours after last dose of study medication. The changes in heart rate recorded by electrocardiogram between baseline and on treatment for the prior 5–6 days are also plotted. P values from the ANCOVA are shown.

Table 1

Notable Adverse Events by Treatment Group in Gastrointestinal Transit Study; Number (%) of Subjects^a

	TD-5108 Dose (n=)				
System Organ Class / Preferred Term	Placebo (12)	5 mg (13)	15 mg (11)	30 mg (13)	50 mg (11)
Gastrointestinal Disorders	5 (42%)	7 (54%)	9 (82%)	10 (77%)	7 (64%)
Diarrhea	0 (0%)	4 (31%)	7 (64%)	9 (69%)	4 (36%)
Nausea	1 (8%)	1 (8%)	4 (36%)	7 (54%)	4 (36%)
Bowel sounds abnormal	0 (0%)	1 (8%)	1 (9%)	1 (8%)	2 (18%)
Stomach discomfort	1 (8%)	1 (8%)	0 (0%)	1 (8%)	2 (18%)
Vomiting	1 (8%)	1 (8%)	0 (0%)	2 (15%)	1 (9%)
Nervous System Disorders	4 (33%)	6 (46%)	7 (64%)	9 (69%)	7 (64%)
Headache	4 (33%)	5 (38%)	3 (27%)	8 (62%)	7 (64%)
Dizziness	0 (0%)	4 (31%)	5 (45%)	4 (31%)	0 (0%)

^aReported by more than one subject or in more than 2 dose groups.

Table 2

Effects of a Single 15-mg Dose of TD-5108 in Patients with Chronic Constipation and Healthy Control Subjects.

	Chronic constipation	Healthy Controls
N	11	11
Time to first BM after dosing (hours after dosing)	1.57 (0.9, 2.6)	2.83 (1.4, 4.5)
Numbers of BMs in the first 24 hours	4.4 ± 2.11	2.8 ± 1.47
Number (%) of complete spontaneous bowel movements	16/48 (33%)	22/31 (71%)
Average stool consistency (Bristol scale)	5.3 ± 1.21	5.5 ± 1.34
Notable Adverse Event reports (number (%))		
Diarrhea	10/11 (91%)	8/11 (82%)
Abnormal bowel sounds (borborygmi)	6/11 (55%)	6/11 (55%)
Nausea	1/11 (9%)	1/11 (9%)
Headache	10/11 (91%)	7/11 (64%)
Heart rate increase 4 hours after dosing (bpm)	9.4 ± 8.24	10.2 ± 9.55

Note the effects on bowel function and proportions with events suggest stimulation of bowel function or laxation was similar in the two groups. Data show number, %, mean ± SD or median (95%CI)