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MONOGRAPH

ULIMORELIN

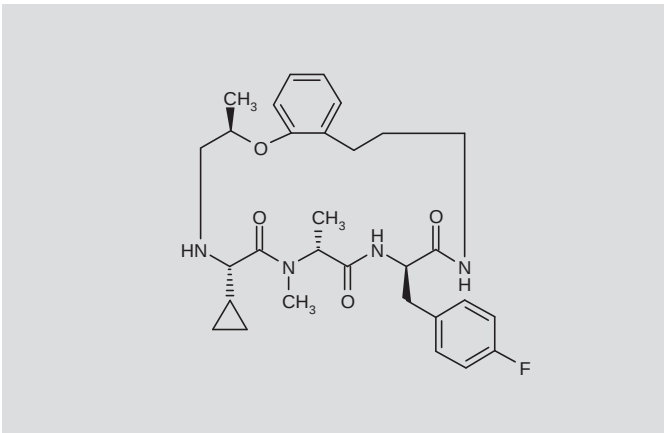
Prop INN; USAN

Ghrelin (GHS) Receptor Agonist
Treatment of Postoperative Ileus
Treatment of Gastroparesis

TZP-101

5(*S*)-Cyclopropyl-11(*R*)-(4-fluorobenzyl)-2(*R*),7,8(*R*)-trimethyl-2,3,4,5,6,7,8,9,10,11,13,14,15,16-tetradecahydro-1,4,7,10,13-benzoxatetraazacyclooctadecine-6,9,12-trione

InChI: 1S/C30H39FN4O4/c1-19-18-33-27(23-12-13-23)30(38)35(3)20(2)28(36)34-25(17-21-10-14-24(31)15-11-21)29(37)32-16-6-8-22-7-4-5-9-26(22)39-19/h4-5,7,9-11,14-15,19-20,23,25,27,33H,6,8,12-13,16-18H2,1-3H3,(H,32,37)(H,34,36)/t19-,20-,25-,27+/m1/s1



$C_{30}H_{39}FN_4O_4$
Mol wt: 538.6535
CAS: 842131-33-3
EN: 370875

SUMMARY

Hunger contractions consist of a series of strong contractions of the stomach that evolve to phase III of the migrating motor complex and move down the small intestine. Ghrelin is considered to be important for the initiation of hunger contractions and promotes gastric emptying. Other gastrointestinal endocrine and neuronal systems play powerful supplementary roles in the development of hunger. Macrocyclic template chemistry (MATCH™) has produced the macrocyclic peptidomimetic ulimorelin (TZP-101). By an action selectively directed to the ghrelin receptor, this peptide analogue has been shown to be able to stimulate gastric emptying in diabetic gastroparesis and relieve the associated symptom burden in gastroparesis, predominantly nausea and vomiting. Ulimorelin has also been shown to be effective in reducing postoperative ileus in colectomy. These effects are not associated with any serious adverse events. As ulimorelin opens up new indications for treatment, this will strengthen the possibility of relieving patients of symptoms related to stasis of contents in the upper gastrointestinal tract. Thus, ulimorelin is a promising pharmaceutical that should activate gastrointestinal regulatory systems in disorders associated with gastric hypomotility.

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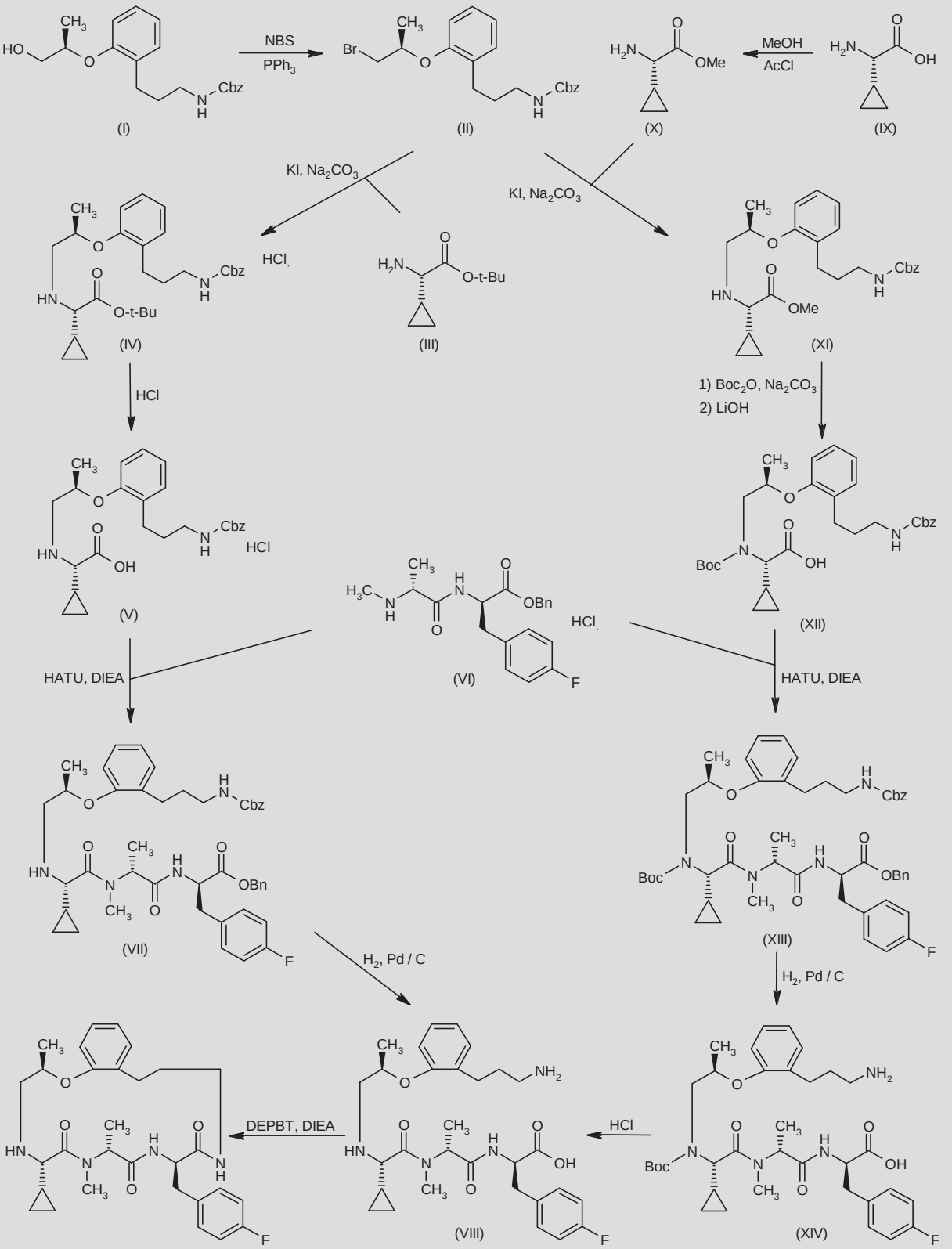
*Synthesis prepared by J. Bolòs, C. Estivill, R. Castañer. Thomson Reuters, Provença 398, 08025 Barcelona, Spain.

SYNTHESIS*

Ulimorelin can be prepared by bromination of *N*-(benzyloxycarbonyl)-2(*R*)-[2-(3-aminopropyl)phenoxy]propanol (I) with NBS and PPh_3 in CH_2Cl_2 giving the corresponding alkyl bromide (II), which is condensed with *tert*-butyl 2(*S*)-cyclopropylglycinate hydrochloride (III) in the presence of KI and Na_2CO_3 in DMF at 100 °C to yield the *N*-substituted amino ester (IV). Hydrolysis of ester (IV) by means of HCl affords the corresponding amino acid (V), which is coupled with benzyl *N*-methyl-D-alanyl-4-fluoro-D-phenylalaninate hydrochloride (VI) by means of HATU and DIEA in THF/CH_2Cl_2 to provide the protected tripeptide (VII). Simultaneous *N*- and *O*-deprotection of peptide (VII) by hydrogenolysis over Pd/C in EtOAc furnishes the deprotected linear tripeptide (VIII), which is finally submitted to intramolecular cyclization by means of DEPBT and DIEA in THF (1-4). Scheme 1.

Linear tripeptide (VIII) can alternatively be prepared by esterification of 2(*S*)-cyclopropylglycine (IX) using a solution of acetyl chloride in MeOH to produce the corresponding amino ester (X), which is then alkylated with the alkyl bromide (II) by means of Na_2CO_3 and KI in DMF at 100 °C to afford secondary amine (XI). Protection of amine (XI) by means of Boc_2O in the presence of Na_2CO_3 in THF/H_2O followed by saponification of the methyl ester group with LiOH·H_2O in THF/H_2O leads to the corresponding acid (XII), which is condensed with benzyl *N*-methyl-D-alanyl-4-fluoro-D-phenylalaninate hydrochloride (VI) by means of HATU and DIEA in THF/CH_2Cl_2 to generate the fully protected tripeptide (XIII). Partial deprotection of tripeptide (XIII) by hydrogenolysis over Pd/C in EtOAc produces peptide (XIV), which finally undergoes *N*-Boc group removal by means of HCl in dioxane/H_2O (1-4). Scheme 1.

Scheme 1. Synthesis of Ulimorelin



Intermediate (VI) can be prepared by esterification of 4-fluoro-D-phenylalanine (XV) with benzyl alcohol in the presence of *p*-TsOH in refluxing benzene, followed by neutralization of the resulting tosylate salt with Na_2CO_3 to provide benzyl 4-fluoro-D-phenylalaninate (XVI), which is coupled with *N*-(*tert*-butoxycarbonyl)-*N*-methyl-D-alanine (XVII) by means of EDC, 6-Cl-HOBt and DIEA in THF/CH_2Cl_2 to yield benzyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-D-alanyl-4-fluoro-D-phenylalaninate (XVIII). Finally, dipeptide (XVIII) is *N*-deprotected by means of HCl in dioxane (1-4). Scheme 2.

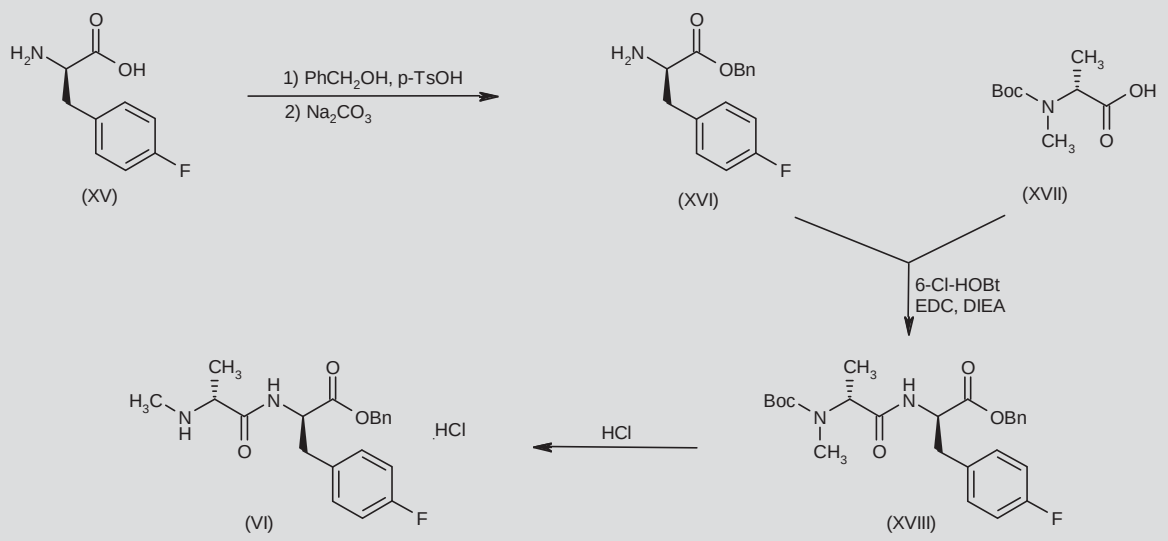
BACKGROUND

During fasting between meals, gastric contractions (hunger pangs) occur to signal emptiness of the upper gut and the need for meal ingestion in order to keep up with metabolic needs. More precisely, these contractions consist of a cycle of quiescence and contractions known as the migrating motor complex (MMC). Different phases of the MMC in the upper gastrointestinal (GI) tract have been associated with the action of different GI hormones. Figure 1 shows the strong contractions that occur predominantly in the antrum, are propagated in aboral direction and are temporally related to hunger sensation and appetite.

The stomach and small intestine display a cyclic motility pattern referred to as the MMC and characterized by a long period of quiescence or very low motor activity (phase I), followed by periods of short nonpropulsive erratic contractions (phase II), to finally be replaced by high-amplitude propulsive contractions (phase III) (5, 6), after which this cyclic motility starts over again. Figure 1 shows a tracing of phase III of MMC taken from a multi-channel antro–duodeno–jejunal motility recording of a test subject during a hunger pang. In man, the complete MMC recycles with irregular intervals of about 100-180 minutes, where phase III occupies about 5-7 minutes. Of all MMCs that occur, about 60% of phase III's begin in the antrum, whereas the rest begin in the duodenum or jejunum (7). The MMCs move down the small intestine to terminate at different points in the distal small intestine. The MMCs are also accompanied by a parallel increase in intestinal blood flow, gallbladder emptying, gastric and pancreatic secretions (6). Upon food ingestion, MMC activity is abruptly replaced by a less well characterized fed motility pattern throughout the stomach and small intestine (5).

It is a common belief that phase III of the MMC should push the upper GI tract clear from undigested foodstuff that is not removed during gastric and intestinal fed motility, and prevent bacterial overgrowth of the small intestine and (6, 8). The occurrence of MMCs in the antrum is also believed to be a physiological biomarker of hunger sensations, as Itoh described phase III contractions as "hunger contractions" (9). Later, phase III contractions of MMCs, which spontaneously originate in the stomach, were shown to correlate with hunger sensation, whereas a similar correlation was not observed for MMCs originating in the small intestine (10, 11), which is why hunger sensations appear to arise primarily from the stomach. In terms of endocrine regulation, observations suggest a role for motilin being released in relation to phase III of the gastric MMC to promote hunger contractions, or by ghrelin acting in a similar manner (12). In basic physiological studies, we have found ghrelin to stimulate gastric emptying and hunger sensations (13) by mechanisms involving antral contractile motility (14). This effect appears to be brought about by vagal nerve activation (15-17), and to a lesser extent, via receptors within the enteric nervous system (18, 19).

Scheme 2. Synthesis of Intermediate (VI)



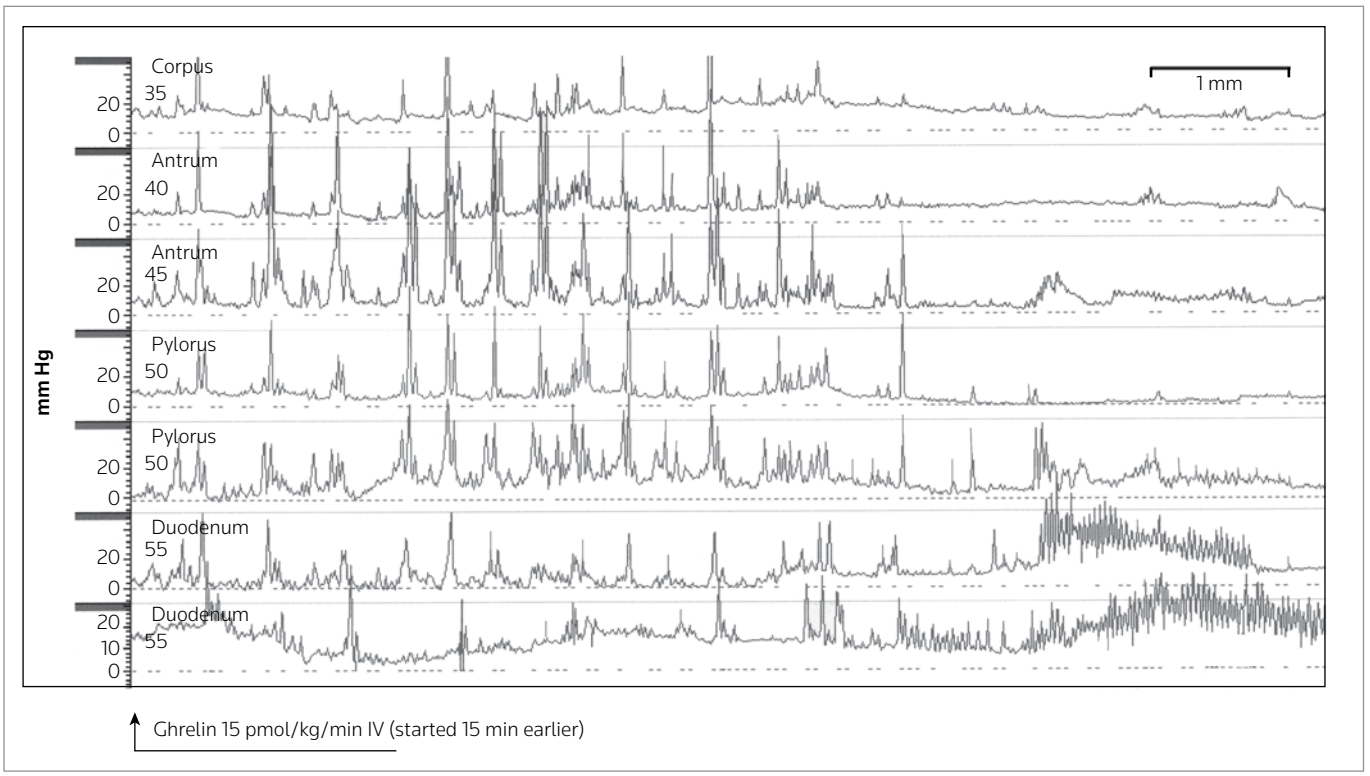


Figure 1. Phase III of the migrating motility complex (MMC) as initiated by ghrelin. High-amplitude pressure waves are seen propagating from the gastric antrum aborally into the duodenum and jejunum. Phase III usually coincides with hunger sensations, referred to as hunger pangs.

Ghrelin is a 28-amino-acid peptide and is derived from the rat stomach. The peptide is a natural ligand for the growth hormone secretagogue receptor type 1 (20), now referred to as the ghrelin receptor (21). Ghrelin in its active form is elaborated from the non-acylated peptide (des-acyl-ghrelin), by a unique post-translational acylation process of the third serine residue. This modification is mediated by the ghrelin *O*-acyl transferase (*GOAT*) enzyme in the gut (22). Ghrelin has the ability to release growth hormone (GH), stimulate appetite and modulate fat utilization (23-25). The prokinetic effect of ghrelin is usually apparent with high blood concentrations of ghrelin, as achieved after exogenous administration of ghrelin or ghrelin receptor agonists (26). The release of this hormone from endocrine cells within the stomach (where the largest amounts are found) increases plasma ghrelin concentrations in humans during fasting. Plasma concentrations of ghrelin increase before mealtimes and drop directly after food intake, which is why a role for ghrelin in meal initiation has been suggested (27). Being a naturally occurring stimulator of gastric motility, ghrelin receptor agonists have been forwarded as attractive in the search for new pharmacological principles for a gastric prokinetic.

Gastroparesis is a disorder of gastric contractility and emptying. Prevailing symptoms are characterized by nausea, early satiety, postprandial excessive fullness, bloating and abdominal pain (28). Gastroparesis occurs most commonly in association with diabetes and hyperglycemia, but also after abdominal surgery and gastric infections, as well as idiopathically. Currently, the only prokinetic option in gastroparesis is metoclopramide, often with inadequate therapeutic response due to adverse central nervous system (CNS) effects. Therefore, there is an unmet need for treatment options for this disorder.

Postoperative ileus (POI) refers to a paucity of GI motility after surgery before normal bowel function resumes, and affects primarily the stomach and colon, and to a lesser extent the small intestine. POI is an inevitable response to major abdominal surgery and is associated most commonly with bowel resections, but it is also recognized after urological and gynecological surgeries, and may occur with non-GI-related procedures such as extraperitoneal surgery, joint replacement and cardiovascular surgery. Delayed gastric emptying and disrupted intestinal motility are the main factors behind POI. As patients with POI often endure symptoms of nausea and vomiting, abdominal pain and cramping, bloating, abdominal distension and the inability to pass stools, this was considered another likely indication for ulimorelin.

PRECLINICAL PHARMACOLOGY

Ulimorelin is a selective, small-molecule ghrelin receptor agonist with potent binding affinity (K_i = 16 nM) and full agonist activity (EC_{50} = 29 nM; E_{max} = 111%) for the cloned human recombinant ghrelin receptor (29). The compound is considered to have a superior profile to previous ghrelin receptor agonists based on its comparatively low propensity to cause receptor desensitization (30).

A stimulatory effect for ulimorelin (0.03-3.0 mg/kg i.v.) has been demonstrated in animal models of gastric emptying in naive rats and in models of delayed GI transit caused by high caloric intake (creating a state of gastroparesis), abdominal surgery and pharmacological interventions (31, 32). As ghrelin exerts a wide spectrum of activities, including stimulation of GH release, feeding and GI motility, attempts have been made to separate these effects pharmacologically by administering the drug intracerebroventricularly (i.c.v.) or peripherally (i.v.). Ulimorelin administered i.v. was found to accelerate gastric emptying of a liquid meal (2% methylcellulose) in a similar manner to ghrelin administered i.v. Ulimorelin administered i.c.v. also stimulated cumulative food intake in a manner similar to ghrelin given i.c.v. However, ulimorelin was found not to elicit significant GH release upon either central or peripheral administration. Neither did ulimorelin alter ghrelin-induced GH release. Thus, data in rats indicate that the GH response to ghrelin is distinct from the GI and appetite-stimulating responses. These observations made clear that the centrally mediated responses and peripherally mediated motility effects of the stomach are pharmacologically associated, consistent with the concept of ghrelin as a brain–gut peptide, while the additional ghrelin action on GH secretion should be considered a supplementary mechanism.

In animal experiments, ulimorelin has been studied in a model of human POI, where rats were subjected to "running of the bowel" surgery to induce ileus. The small intestine and cecum were then exteriorized for inspection during 5 minutes and covered with saline-soaked gauze for a total of 10 minutes until abdominal incision was closed with sutures. Ulimorelin (0.03-1.0 mg/kg i.v.) was found to improve GI transit in this animal model. Since determining factors for the development of POI are surgical manipulation and GI effects of opioid receptor agonists for the management of pain, the effect of ulimorelin was investigated in rats subjected to surgery, morphine treatment, or both. Results showed that ulimorelin was equally effective against delayed GI transit induced by surgery, morphine or the combination of these interventions. The prokinetic effect of ulimorelin was also more marked in the stomach than in the small intestine (31). Furthermore, ulimorelin stimulated gastric emptying in naive rats with 100-fold greater potency than metoclopramide (33).

Ulimorelin has also been studied on colonic transit and food intake in rats using the same POI model (32). In these experiments, the effects of ulimorelin on the postsurgical colonic transit time, fecal pellet output and food intake were evaluated. Ulimorelin or vehicle was administered at 15 minutes, 2 hours and 4 hours post-surgery, with increasing bolus infusions of ulimorelin (0.03-1.0 mg/kg i.v.). Under anesthesia, fasted rats were treated with morphine and subjected to laparotomy. Following surgery, the animals were placed in clean home cages and fecal pellet output and food intake were monitored for 48 hours. Ulimorelin dose-dependently decreased time to first bowel movement and increased fecal output at 12 and 24 hours post-surgery compared to vehicle. The data confirm that ulimorelin can improve colonic function in postoperative ileus, suggesting that the agent may be useful for shortening and optimizing hospitalization periods in the clinical setting to accelerate GI transit and shorten the time to the first bowel movement following surgery.

PHARMACOKINETICS AND METABOLISM

Healthy subjects were investigated in a single-dose study of ulimorelin with doses escalated from 20 to 600 μg/kg by 30-minute i.v. infusion (34). Blood and urine samples were collected for 24 hours for pharmacokinetic analyses. Pharmacokinetics revealed less than dose-proportional kinetics for ulimorelin, with maximal plasma levels increasing with dose from 497 to 8070 ng/mL over the studied dose range. The average area under the curve $(AUC)_{0-\infty}$ increased from 4710 to 72,200 h.ng/mL over that same dose range. Both C_{max} and $AUC_{0-\infty}$ displayed a linear increase from 20 to 80 μg/kg, but then leveled off between 160 and 600 μg/kg. The mean $t_{1/2}$ was estimated to be 13 hours, independent of dose. The systemic clearance was low, with average values extending from 5.1 to 10.6 mL/h/kg over the whole dose range. The volume of distribution of ulimorelin was small, ranging from 0.084 to 0.160 L/kg over the dose range studied. Pharmacodynamic evaluation has shown that a single 30-minute i.v. infusion of ulimorelin does not affect plasma levels of insulin-like growth factor I (IGF-I), ghrelin, glucose, or noradrenaline up to 4 hours after onset of infusion. However, a 24-hour evaluation of IGF-I after ulimorelin 320 and 600 μg/kg showed increased IGF-I plasma levels. During a period up to 4 hours from the start of infusion, a significant, dose-dependent and temporary increase in plasma GH levels was observed, concomitant with a dose-dependent decrease in insulin and increase in adrenaline. Further pharmacodynamic analyses suggested that ulimorelin at doses as low as 40 μg/kg expresses activity at the ghrelin receptor.

Subsequent studies have shown that the pharmacokinetics in healthy volunteers and gastroparesis patients are similar. There is an increased drug clearance at high plasma concentrations, resulting in a lower tendency for drug accumulation after multiple dosing. Significant protein binding of ulimorelin, primarily to α_1-acid glycoprotein, of more than 99% indicates that the fraction of free drug rather than the total plasma concentration should be taken into account for risk assessments in humans based on animal safety data (35).

SAFETY

When tested for safety in a number of single- and multiple-dose toxicity studies, ulimorelin has not demonstrated any specific target organ toxicity. The human safety aspects were studied in a dose-escalating study in subjects who underwent continuous cardiac monitoring, 12-lead electrocardiograms, and assessment for orthostatic hypotension, injection-site tolerability, vital signs and adverse events during the 24-hour post-dose period (34). For the initial dose of 20 μg/kg, a safety factor of approximately 80 was applied to the human equivalent dose, that dose level being derived from the no observed adverse effect level (NOAEL) of 3 mg/kg in the 14-day dog toxicity study (on the mg/kg basis corrected for body surface area). Ulimorelin was well tolerated, with a few episodes of headache, lower abdominal pain, diarrhea and dizziness. At the highest dose of 600 μg/kg, two subjects experienced short-lasting bradycardia. All adverse events were self-limited. Mean arterial blood pressure and heart rate decreased from baseline approximately 45-60 minutes after the start of infusion at higher doses. No other significant changes were observed. In the initial phase I safety study ulimorelin displayed a promising safety profile for upcoming prolonged use. In later phase II studies, vomiting and temporary

bradycardia occurred at high doses of 320 and 600 μg/kg (36). Also, a slight elevation of blood sugar seems to occur (37). In another study, hyperglycemia (11%), nausea (7%) and diarrhea (5%) were seen with ulimorelin, and abdominal pain, urinary tract infection, nasopharyngitis, back pain and headache occasionally occurred (38). Specifically in patients with severe symptoms of gastroparesis such as nausea and vomiting, headache and nausea were noted as common side effects (39).

CLINICAL STUDIES

Following the conclusion of the first preclinical animal study which showed that ulimorelin was effective against slow GI transit caused by surgery or opioid intervention alone and in parallel, a step was taken to test the drug for the first time in man, primarily to evaluate safety aspects. Escalating doses of ulimorelin of 20-600 μg/kg were administered as a 30-minute i.v. infusion (34). The escalation steps for each successive dose cohort depended on the safety results observed in the preceding dose cohort. Of the 48 volunteers enrolled in the study, 9 experienced some type of adverse event, none serious, and none discontinued the study. In the electrocardiogram analysis, a dose-dependent decrease in heart rate was seen at 30 through 90 minutes after the start of the infusion. This was most notable at the two highest doses of 320 and 600 μg/kg. Commensurate with this, two subjects in the 600 μg/kg dose group experienced bradycardia, compared with no subjects in any other dose group; one patient also experienced dizziness.

Subsequently, a phase II study was carried out as a proof-of concept study with the aim of assessing the safety and efficacy of ulimorelin in diabetic patients with symptomatic gastroparesis (36). In an in-house study in adults with type 1 or type 2 diabetes, ulimorelin (80, 160, 320 or 600 μg/kg i.v.) was compared to placebo in a crossover manner following a test meal. In order to secure gastric emptying, blood glucose levels were stabilized using a hyperinsulinemic–euglycemic clamp. The primary endpoints were gastric half-emptying time and latency, while secondary endpoints included gastroparesis symptoms and endocrine responses. Results showed that ulimorelin significantly reduced solid meal half-emptying time by 20% and latency time by 34% versus placebo. There were also reductions in overall postprandial symptom intensity of 24% and postprandial fullness of 37% following ulimorelin administration. Adverse events were mild and self-limiting and there were no identifiable differences in the numbers or types of adverse events between ulimorelin and placebo. The study concluded that ulimorelin is well tolerated in diabetic patients with moderate to severe chronic gastroparesis, with significant improvements in gastric emptying.

This study was followed by a double-blind, randomized, placebo-controlled trial to evaluate the safety and efficacy of ulimorelin as multiple doses in patients with moderate to severe diabetic gastroparesis with obvious symptoms (34). Patients with diabetes were adaptively randomized to receive a single 30-minute i.v. infusion of 20, 40, 80, 160, 320 or 600 μg/kg ulimorelin or placebo for 4 days in a row. Symptoms were evaluated daily by the patients using the Gastroparesis Cardinal Symptom Index (GCSI) and the Gastroparesis Symptom Assessment (GSA), as well as by clinicians who rated gastroparesis symptoms on day 4 during treatment. The outcome of the study showed 80 μg/kg to be the most effective dose. On the last treatment day, there was a significant improvement on ulimorelin compared with placebo in the severity of loss of appetite, as well as vomiting scores, for that dose group. Also at 80 μg/kg, the proportion of patients with > 50% improvement in vomiting score was significantly higher than with placebo (Fig. 2). Compared with placebo, GSA scores for postprandial fullness significantly improved with ulimorelin at 80 μg/kg. Finally, clinicians rated the 80 μg/kg group better than placebo for reduction of overall symptom scores. Taken together, ulimorelin was found to be safe, well tolerated and effective at acutely addressing symptoms of gastroparesis.

In a randomized subset data study of patients with severe diabetic gastroparesis, drug efficacy was assessed by symptom improvement employing the GCSI nausea/vomiting subscale (39). From a mean severity score for GCSI nausea/vomiting of 4.45 ± 0.44, significant improvements over placebo were found in the ulimorelin 80 μg/kg group for end-of-treatment changes, with a reduction in nausea/vomiting score of –3.82 ± 0.76 and in GCSI total score of –3.14 ± 0.78. Significant effects were maintained at the 30-day follow-up assessment, with a long-term reduction of –2.02 ± 1.63 and –1.99 ± 1.33. The proportion of days with vomiting was significantly reduced in the 80 μg/kg group (on average 1.2 days vomiting for 4 treatment days) compared with placebo (on average 3.2 days vomiting for 4 treatment days). The results were interpreted as a stimulatory motility effect for ulimorelin on the stomach, even in severe gastroparesis. Since ulimorelin is similar to ghrelin in its biological actions, it is logical to draw conclusions from the endogenous peptide to the pharmaceutical. In this context, it is of interest that ghrelin can inhibit emesis (40), which would speak in the direction of appetite and nausea as opposites of the same spectrum, i.e., ghrelin, which increases appetite, would also decrease nausea (41). Such a role for ghrelin may be involved in the reduction of nausea/vomiting scoring observed in patients with diabetic gastroparesis after i.v. administration of ulimorelin (39).

In parallel to this, previous studies on POI in rats were extended to involve humans. A phase IIb study in postoperative ileus after partial colectomy was conducted (37). Adults undergoing open partial colectomy were adaptively randomized to receive various doses of ulimorelin (20-600 μg/kg) or placebo by 30-minute i.v. infusion within an hour of surgical closure and then daily for up to 7 days. The primary efficacy endpoint was time to first bowel movement; secondary endpoints were the return of GI function within 72 hours and time to readiness for discharge. In this setting with open abdominal surgery, ulimorelin was found to shorten the time to first bowel movement at doses of 80-480 μg/kg. The median time to first bowel movement was reduced by 10-22 hours compared to placebo. A significant number of patients treated with ulimorelin achieved recovery by 72 hours post-surgery compared with placebo. Compared with placebo, the median time to readiness for hospital discharge was significantly shortened by 20.4 hours at the 480 μg/kg ulimorelin dose (hazard ratio [HR]: 1.69) (Fig. 3). The most common adverse events were nausea and vomiting, which were less pronounced in the ulimorelin group compared with the placebo group. To summarize, after abdominal surgery, ulimorelin can accelerate GI recovery following partial bowel resection surgery by approximately 24 hours compared to placebo.

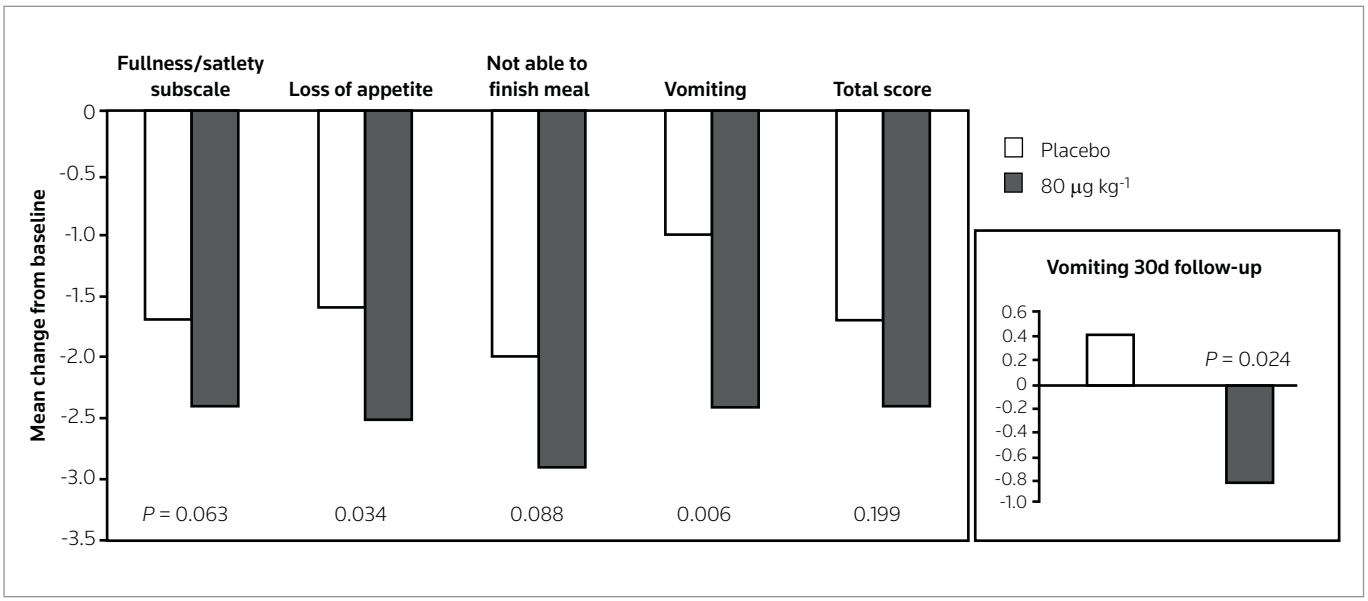


Figure 2. Day 4 Gastroparesis Cardinal Symptom Index (GCSI) mean change from baseline in scores for the fullness/satiety subscale, individual symptoms of loss of appetite, inability to finish a meal, vomiting and the total score. Numbers that are more negative indicate greater improvement in symptoms. The graph to the right shows the mean change from baseline in the scores for vomiting at the 30-day follow-up assessment. *P* values are shown comparing ulimorelin to placebo. Reproduced with permission from Ejskjaer, N., Dimcevski, G., Wo, J., Hellström, P.M., Gormsen, L.C., Sarosiek, I., Søfteland, E., Nowak, T., Pezzullo, J.C., Shaughnessy, L., Kosutic, G., Mccallum, R. *Safety and efficacy of ghrelin agonist TZP-101 in relieving symptoms in patients with diabetic gastroparesis: A randomized, placebo-controlled study*, Neurogastroenterol Motil 2010, *22*(10): 1069-e281.

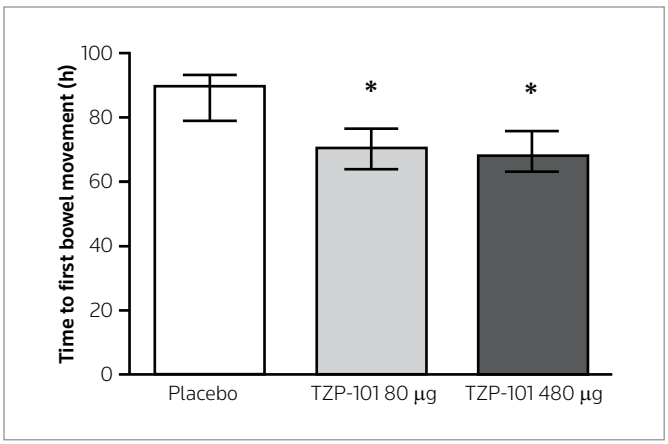


Figure 3. Acceleration in time to primary and secondary gastrointestinal (GI) events relative to placebo for the 80 and 480 ìg/kg ulimorelin dose groups. $P < 0.05$. Reproduced with permission from Popescu, I., Fleshner, P., Pezzullo, J., Charlton, P., Kosutic, G., Senagore, A. *The ghrelin agonist TZP-101 for management of postoperative ileus after partial colectomy: A randomized, dose-ranging, placebo-controlled clinical trial*, Dis Colon Rectum 2010, 53(2): 126-34.

Taken together, 6 clinical trials of ulimorelin have been carried out involving 577 subjects, 365 of whom received ulimorelin. These trials have shown ulimorelin to be a safe and effective treatment for improving various symptoms associated with GI motility disorders. Two multinational phase III trials for the management of POI have been initiated. Each trial will enroll 300 patients at approximately 50 sites in North America and Europe.

As a further development of ulimorelin, the orally administered drug TZP-102 has been shown to improve symptoms within 1 week of treatment initiation, significantly reducing symptoms of nausea, early satiety, postprandial excessive fullness and the total GCSI. In addition, improvement of abdominal pain and discomfort has been noted (42; presented by John Wo at the American College of Gastroenterology Annual Scientific Meeting, October 20, 2010).

Ulimorelin is now in phase III clinical development for the management of POI. In addition, ulimorelin is undergoing development as a treatment for patients suffering from other GI motility disorders, such as gastric stasis and functional dyspepsia. In these conditions gastrokinetics appear to be logical and are considered therapeutically relevant, although a true symptomatic benefit of drug treatment has been difficult to prove.

SOURCES

Originated by Tranzyme Pharma, Inc. (US) and developed in collaboration with Norgine BV (NL).

DISCLOSURES

Per Hellström has carried out clinical trials with ulimorelin for Tranzyme Pharma.

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