Drugs of the Future 1999, 24(1): 38-44

CCC: 0377-8282/99

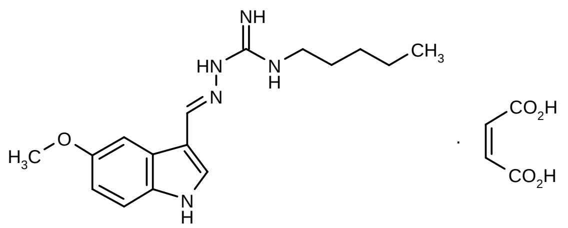
Tegaserod Maleate

Prop INNM

5-HT_4 Agonist
Prokinetic
Treatment of Irritable Bowel Syndrome

HTF-919
SDZ-HTF-919
Zelmac™

2-[(5-Methoxy-1*H*-indol-3-yl)methylene]-*N*-pentylhydrazinecarboximidamide monomaleate
1-(5-Methoxy-1*H*-indol-3-ylmethyleneamino)-3-pentylguanidine monomaleate



$C_{16}H_{23}N_5O.C_4H_4O_4$ Mol wt: 417.4633

CAS: 189188-57-6
CAS: 145158-71-0 (as free base)

EN: 251605

Synthesis

The alkylation of thiosemicarbazide (I) with methyl iodide in hot ethanol gives the corresponding *S*-methyl derivative (II), which is treated with pentylamine (III) in refluxing methanol to yield N^1-amino-N^3-pentylguanidine hydroiodide (IV). Finally, this compound is condensed with 5-methoxy-1*H*-indole-3-carbaldehyde (V) by means of HCl in methanol (1, 2). Scheme 1.

Introduction

Irritable bowel syndrome (IBS) is a commonly observed disorder that is characterized by symptoms of abdominal pain associated with diarrhea and/or constipation. It is frequently associated with psychological disorders including anxiety, stress and depression, and recent studies indicate that central nervous system modulation and autonomic activity may contribute to chronic gastrointestinal symptoms. Over the last decade, epidemiological, physiological and psychosocial data have contributed to an improved understanding and treatment of IBS (3), as can be seen by the existing treatment strategies outlined in Table I. Nevertheless, current therapy for specific symptoms of IBS is not satisfactory. Therefore, several new strategies aimed at correcting putative dysfunction of IBS are being investigated, as shown in Tables II and III.

Table I: Therapy for specific symptoms of IBS (from Prous Science Ensemble database).

ABDOMINAL PAIN
Antispasmodics
Anticholinergics
Dicyclomine HCl
Hyoscine butylbromide
Direct acting smooth muscle relaxants
Alverine citrate
Mebeverine HCl
Peppermint oil
CONSTIPATION
Bulking agents
Dietary fiber
Sterculia
DIARRHEA
Loperamide
Dietary fiber
PSYCHOLOGICAL DISORDERS
Antidepressants
5-HT reuptake inhibitors (may also exert analgesic activity)
Fluoxetine
Sertraline
Anxiolytics
Benzodiazepines

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Scheme 1: Synthesis of Tegaserod Maleate

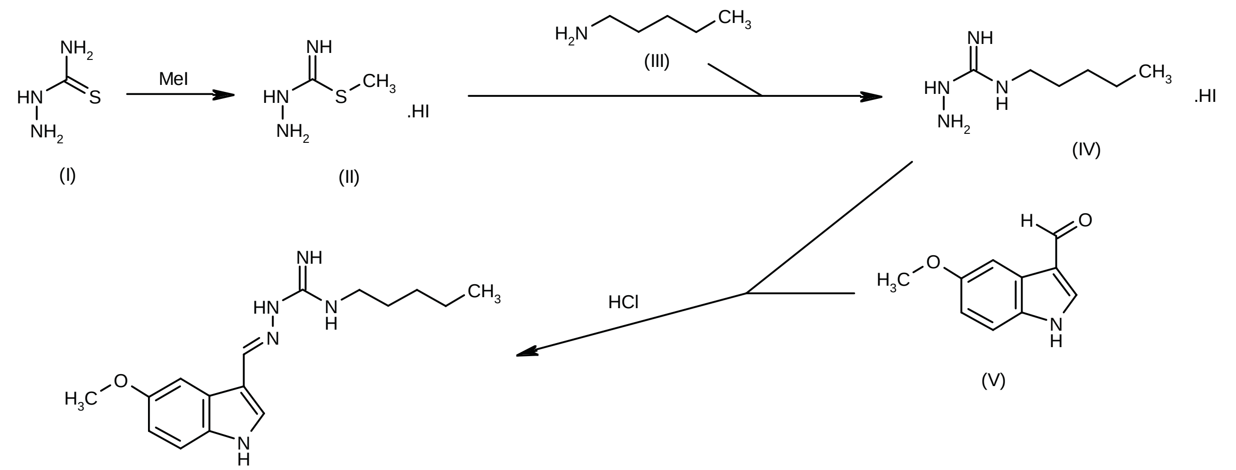


Table II: Drugs under development for the treatment of IBS (from Prous Science Ensemble database).

Drug Targets	Status	Manufacturer
Opioid receptors		
μ-Receptor antagonists		
LY-246736 (ADL-8-2698)	Phase I	Adolor; Roberts (acquired from Lilly)
κ-Receptor agonists		
Fedotozine tartrate	NDA filed	Jouveinal; Glaxo Wellcome; Warner Lambert
Muscarinic receptors		
Muscarinic antagonists		
LY-315535	Phase I	Roberts (acquired from Lilly)
LY-316108 (NNC-11-2192)	Preclinical	Lilly; Novo Nordisk
Muscarinic M_3 antagonists		
Darifenacin	Phase III	Pfizer
J-104129	Preclinical	Banyu
J-106366	Preclinical	Banyu
YM-905	Preclinical	Yamanouchi
Adrenoceptors		
α_2-Adrenoceptor antagonist		
YNS-15P	Preclinical	Nippon Shinyaku
β_3-Adrenoceptor agonist		
GS-332	Preclinical	Tokyo Tanabe
Serotonin receptors		
5-HT_3 antagonists		
Alosetron HCl	Phase II	Glaxo Wellcome
Cilansetron	Phase II	Solvay
YM-114	Phase II	Yamanouchi
5-HT_4 antagonists		
SB-207266	Phase II	SmithKline Beecham
LY-353433	Preclinical	Roberts (acquired from Lilly)
5-HT_4 partial agonists		
SDZ-HTF-919	Phase II	Novartis
5-HT_3 antagonists/5-HT_4 agonists		
Renzapride*	Research	Alizyme
5-HT_3/5-HT_4 antagonists		
FK-1052	Phase II	Fujisawa
CCK receptors		
CCK_A antagonists		
Loxiglumide	Clinical	Rotta, Kaken, Tokyo Tanabe
Dexloxiglumide	Phase III	Rotta
Nonabsorbed, high-molecular weight polymer		
Calcium polycarbophil		
Colonel	NDA filed	Fujisawa; Hokuriku Seiyaku

*Using colon-specific drug delivery technology licensed from BTG.

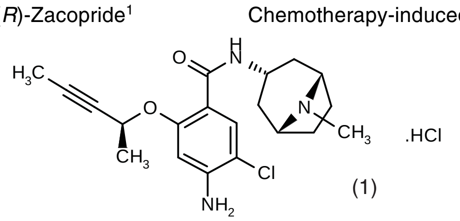
Table III: New therapeutic targets described in recent patent literature as potential approaches for the treatment of IBS (from Prous Science Ensemble database).

Drug Targets	Patent Number	Manufacturer
Somatostatin sst_2 agonists	WO 9844921; WO 9844922; WO 9744037; WO 9744339; WO 9744041; WO 9744321;	Merck & Co.
	WO 9701579	Novartis
CRF[1] antagonists	EP 812831; WO 9808846	Pfizer
	WO 9639400	Neurocrine Biosciences
	WO 9847874; WO 9847903	Neurocrine Biosciences/Janssen
	WO 9729110; WO 9729109; WO 9714684	
	WO 9744038	DuPont Merck
	WO 9808821	Agouron
β_3-Adrenoceptor agonists	JP 98152488; WO 9715549	Tokyo Tanabe
	WO 9746556	Merck & Co.
	JP 96157470; JP 96165276; WO 9616038	Dainippon
Histamine H_3 antagonists	WO 9729092	James Black Foundation
	WO 9847898[2]	Synthélabo
5-HT_7 antagonists	EP 738513	Lilly
cGMP-PDE[3] inhibitors	WO 9743287	ICOS
	WO 9703985	Glaxo Wellcome
Potassium channel activators (smooth muscle relaxants)	WO 9802413; WO 9748682	American Home Products
NK_1 and NK_2 antagonists	WO 9725322; EP 791592; WO 9807722	Pfizer
	US 5712397	Boehringer Ingelheim

[1]Corticotropin-releasing factor, whose hypersecretion may play an important role in diseases such as anxiety, depression and inflammatory disorders. [2]Also 5-HT_4 antagonist. [3]cGMP-specific phosphodiesterase.

Table IV: 5-HT_4 receptor agonists/partial agonists under development (from Prous Science Ensemble database).

Compound	Indication	Status	Manufacturer
1. E-3620[1]	IBS; chemotherapy-induced emesis	Phase II	Eisai
2. Itasetron[1]	Anxiety; chemotherapy-induced emesis	Phase III	Boehringer Ingelheim
3. Mosapride citrate	Gastroesophageal reflux	Launched-98[2]	Dainippon; Astra
4. Prucalopride	IBS	Phase III	Janssen
5. Renzapride HCl[1]	IBS	Phase II	Alizyme
6. SDZ-HTF-919	IBS	Phase III	Novartis
7. (*R*)-Zacopride[1]	Chemotherapy-induced emesis	Phase II	Synthélabo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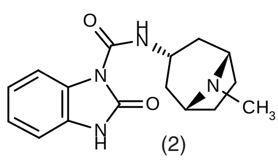
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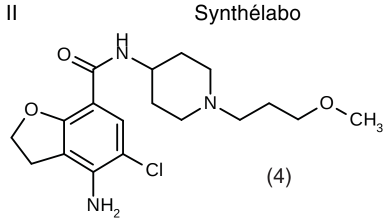
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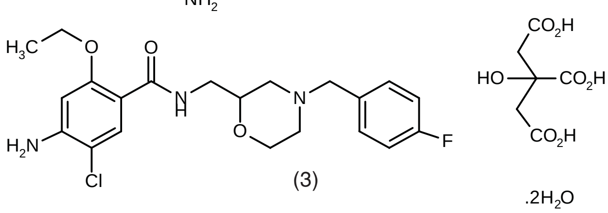
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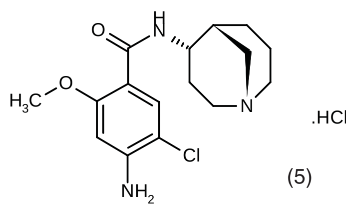
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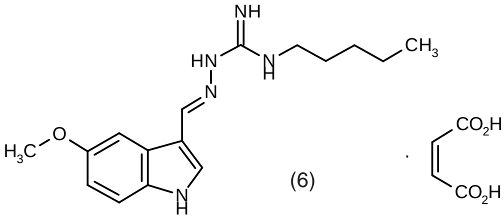
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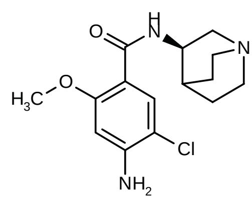
(7)

[1]Also 5-HT_3 antagonist. [2]Launched in Japan and phase II in Europe.

The serotonin 5-HT$_4$ receptor has been found to play a key role in visceral sensitivity and gastrointestinal motility. Modulation of 5-HT$_4$ receptors may, therefore, normalize gut function in patients with IBS. 5-HT$_4$ antagonists reduce the hyperreactivity component of IBS (4) and remarkable progress has been made in the development of this class of compounds. Only a few innovative developments have emerged during recent years in the area of 5-HT$_4$ receptor agonists (5).

Activation of 5-HT$_4$ receptors results in enhanced esophageal clearance and gastric emptying, hastening intestinal and colonic transit. Three classes of nonselective 5-HT$_4$ receptor agonists have been described to date: indolalkylamines (*e.g.*, serotonin), benzamides (*e.g.*, cisapride and metoclopramide) and benzimidazolones (*e.g.*, BIMU-8), and are being studied for a range of potential indications. Table IV lists 5-HT$_4$ receptor agonists in clinical development and the indications for which they are being studied. In the search for new agents to treat IBS, scientists at Novartis designed and synthesized a series of indole carbazimidamides, which were evaluated as 5-HT$_4$ receptor agonists. From this series, SDZ-HTF-919 (tegaserod maleate) was shown to be a partial 5-HT$_4$ agonist and was selected for further evaluation (1) (Table V).

Pharmacological Actions

SDZ-HTF-919 is an aminoguanidine indole compound and partial serotonin agonist with high specificity and potency at the 5-HT$_4$ receptor subtype. In the field-stimulated guinea pig ileum model SDZ-HTF-919 displayed partial agonist activity (pEC$_{50}$ = 8.3) demonstrated by an intrinsic activity of 0.2 relative to serotonin. The affinity of this compound for 5-HT$_3$ receptors, on the other hand, was low (pK$_D$ < 6) (1, 6, 7). Due to its 5-HT$_4$ receptor agonist activity, it exerts potent prokinetic activity *in vitro* in the guinea pig ileum peristaltic model, with an EC$_{50}$ of 20 nmol/l (6) (Table VI).

The peristaltic reflex induced by mucosal stimuli is known to be mediated by intrinsic sensory calcitonin gene-related peptide (CGRP) neurons activated by 5-HT released from enterochromaffin cells. Using SDZ-HTF-915 as a selective 5-HT$_4$ agonist, the role of 5-HT$_4$ receptors in initiating the peristaltic reflex was studied in human small intestine and in rat and guinea pig colon. In all three species, the compound caused a concentration-dependent release of CGRP at the site of stimulation, as well as the release of vasoactive intestinal peptide (VIP) and substance P (SP) at the site of stimulation. Circular muscle

Table V: Affinities of selected serotonin 5-HT$_4$ receptor agonists/partial agonists in [^{3}H]-GR-13808 binding studies (from Prous Science MFLine database).

Compound	Parameter	Value	Material	Refs.
BIMU-8	K_i	12.6-25.1	Guinea pig striatum	17, 18
	K_i	257.0	Rat striatum	19
	K_i	33.9	Guinea pig ileum	18
	K_d[1]	25.1	Mouse colliculi	20
	IC_{50}	12.6	Guinea pig brain	21
Cisapride	Ki	14.3	Guinea pig striatum	18
	K_i	29.0	Guinea pig ileum	18
	K_i	30.2	Rat striatum	22
	K_d[1]	51.3	Mouse colliculi	20
	IC_{50}	23.0	Guinea pig brain	21
E-3620	K_i	2.0	Rat striatum	22
Metoclopramide	K_i	546	Guinea pig striatum	18
	K_i	1080	Guinea pig ileum	18
	K_i	398	Rat striatum	22
	K_d[1]	3981	Mouse colliculi	20
	IC_{50}[2]	1412	Guinea pig striatum	23
	IC_{50}	883	Guinea pig brain	24
Mosapride	K_i	69.9	Guinea pig striatum	18
	K_i	84.2	Guinea pig ileum	18
	IC_{50}	113.0	Guinea pig brain	21
Renzapride	K_i	40.4-100.0	Guinea pig striatum	17, 18
	K_i	125.0	Guinea pig ileum	18
	K_d[a]	97.7	Mouse colliculi	20
SDZ-HTF-919	K_d[3]	14.4	Calf caudate	25
	K_d[3]	18.2	Human caudate	25
SKK-47029	IC_{50}	0.4	Rat brain	26
SL-65.0102	K_i	6.6	Not reported	27
(*R*)-Zacopride	K_d[1]	1071	Mouse colliculi	20

[1]Calculated from pK$_d$ values obtained in [^{3}H]-GR-13808 binding studies. [2]Calculated from pIC$_{50}$ values. [3]Calculated from pK$_d$ values in [^{125}I]-SB-207710 binding studies.

Table VI: Pharmacological profile of 5-HT$_4$ receptor agonists/partial agonists (from Prous Science MFLine database).

Compound	Parameter	nM	5-HT4 agonist activity	Material	Refs.
BIMU-8	EC_{50}^{1}	70.8	↑ cAMP production	Mouse colliculi neurons	20
	EC_{50}	31.5	↓ Carbachol-ind. contractions	Rat esophagus muscle	21
	EC_{50}	66.3	↑ Electrically ind. contractions	Guinea pig ileum	21
	EC_{50}	43.0	↑ Electrically ind. contractions	Guinea pig ileum	20
Cisapride	EC_{50}^{1}	70.1	↑ cAMP production	Mouse colliculi neurons	20
	EC_{50}	420	↓ Carbachol-ind. contractions	Rat esophagus muscle	28
	EC_{50}	39.1	↓ Carbachol-ind. contractions	Rat esophagus muscle	21
	EC_{50}^{2}	1000	↑ Electrically ind. contractions	Guinea pig ileum	29
	EC_{50}	47.6	↑ Electrically ind. contractions	Guinea pig ileum	21
E-3620	EC_{50}	150	↓ Carbachol-ind. contractions	Rat esophagus muscle	30
Metoclopramide	EC_{50}^{1}	4467	↑ cAMP production	Mouse colliculi neurons	20
	EC_{50}^{2}	2512	↑ Electrically ind. contractions	Guinea pig ileum	29
	EC_{50}	5.7	↑ Electrically ind. contractions	Guinea pig ileum	19
Mosapride	EC_{50}	2300	↓ Carbachol-ind. contractions	Rat esophagus muscle	28
	EC_{50}	208.4	↓ Carbachol-ind. contractions	Rat esophagus muscle	21
	EC_{50}	73.2	↑ Electrically ind. contractions	Guinea pig ileum	21
Renzapride	EC_{50}^{1}	114.8	↑ cAMP production	Mouse colliculi neurons	20
SDZ-HTF-919	EC_{50}^{2}	126.0	↑ Electrically ind. contractions	Guinea pig ileum	1
	EC_{50}^{1}	5.0	↑ Electrically ind. contractions	Guinea pig ileum	7
SK-951	EC_{50}	14.0	↓ Carbachol-ind. contractions	Rat esophagus muscle	31
SKK-47029	EC_{50}	30.0	↓ Carbachol-ind. contractions	Rat esophagus muscle	28
	EC_{50}	38.0	↓ Contractions	Rat esophagus muscle	26
(*R*)-Zacopride	EC_{50}^{1}	3162	↑ cAMP production	Mouse colliculi neurons	20

[1]Calculated from pEC_{50} values. [2]Calculated from pD_2 values.

relaxation and contraction accompanied release of VIP and SP, respectively. From this study it was concluded that a low concentration of title compound applied directly to the intestinal mucosa can trigger a physiological reflex that enhances colonic propulsive activity, with a decreased likelihood of side effects due to the need for distribution in the body (8).

In vivo in female dogs, colonic transit was stimulated in the first hour after administration of SDZ-HTF-919 (0.03, 0.1 and 0.3 mg/kg); the first dose was given by i.v. bolus, with subsequent doses by s.c. injection at 8 and 16 h. Colonic transit was measured by radioscintigraphy and colonic motility by pneumohydraulic perfusion manometry. Significant increase in colonic transit was detected in the first hour after administration of SDZ-HTF-919, even at the lowest dose, as compared to controls. No effect was seen on stomach or small bowel transit, or on quantitative pressure indices in the small bowel or colon. This animal study supports the potential utility of SDZ-HTF-919 as a stimulant of colonic transit and motility in mammals, as well as confirming the role of 5-HT$_4$ receptors in the control of colonic motor function (9).

In another study in dogs, the gastrointestinal motility-stimulating activity of SDZ-HTF-919 was found to be similar in both the fasted and fed states. Four adult dogs were equipped with implanted strain gauges at various points in the gastrointestinal tract. Animals in the fasted or fed state were intravenously administered the title compound, its main metabolite or vehicle, with two doses of the compound (0.1 and 0.3 mg/kg) given to each animal in random order. Phase 2-like motility was stimulated significantly in the antrum, duodenum and jejunum at both dose levels, with respective increases of 236, 166 and 240% at the higher dose in the fasted state; colonic motility was not stimulated significantly. Studied in the fed state, motility indices in the antrum, duodenum, jejunum and colon increased by 169, 92, 99 and 80%, respectively, at the higher dose of SDZ-HTF-919. Administration of the main metabolite (1 or 3 mg/kg i.v.) in the fasted state did not affect motility at any point in the gastrointestinal tract, and therefore was not studied further. The title compound did not affect the rate of emptying of liquids, but significantly accelerated solid-phase emptying at the higher dose level. Impaired gastric emptying induced by acoustic stress returned to normal following administration of 0.1 or 0.3 mg/kg i.v. SDZ-HTF-919, indicating that the compound is able to neutralize hormonal factors and neural activities that contribute to impaired gastric emptying (10).

Due to the known existence of ventricular arrhythmia and sudden death in some patients treated with the gastrointestinal prokinetic agent cisapride, the potential cardiac toxicity of SDZ-HTF-919 and its major metabolite was tested in the isolated rabbit heart. Unlike cisapride, neither the title compound nor its glucuronide metabolite had any effect on the QT interval over the dose range of 0.1-10 μM. Thus, the compound was found to be devoid of cardiotoxic potential over a concentration range consistent with therapeutic clinical dosages (11).

Pharmacokinetics and Pharmacodynamics

In the first instance of clinical testing of SDZ-HTF-919, the compound was administered to three cohorts each of 12 healthy male volunteers in a double-blind, placebo-controlled, randomized, parallel-group, ascending-dose trial. The study drug was administered orally as single and multiple (b.i.d. x 14 days) doses of 25, 50 and 100 mg. Systemic exposure (dose-normalized to 25 mg) was 25 ± 12, 19 ± 11 and 26 ± 10 h.ng/ml for the three respective dose levels in the single-dose study; respective values in the multiple-dose study were 26 ± 12, 23 ± 12 and 33 ± 12 h.ng/ml. Steady-state drug concentrations were reached after 8 days of daily dosing, with moderate drug accumulation observed. Pharmacokinetic analysis of single- and multiple-dose studies indicated dose proportionality of C_{max} and AUC. Loose stool was reported 2-4 h postdosing and lasted for about 10 h. Total colonic transit time decreased by an average of 4.8 h with the active drug compared to 1.8 h with placebo. SDZ-HTF-919 was generally well tolerated, although reports of headache were more frequent at the highest dose. No severe adverse events were reported, indicating that the maximum tolerated dose was not reached in this study (12).

Clinical Studies

The pharmacodynamic profile of SDZ-HTF-919 was further elucidated in a human model of slow colonic transit in 60 healthy volunteers. Colonic transit was prolonged via dietary means, following which volunteers were administered active drug (1, 5, 25 or 100 mg b.i.d.) or placebo according to a randomized, double-blind, parallel-group design; 12 volunteers were included in each dose group. During three study periods, subjects consumed either a self-selected diet, a liquid formula diet with soluble fiber supplement, or a fiber-supplemented diet in combination with either the 5-HT_4 agonist or placebo. SDZ-HTF-919 was well tolerated at all dose levels, although loose stools and headache were more frequent at higher doses. Stool frequency decreased following intake of a fiber-supplemented diet, and increased in subjects administered twice-daily SDZ-HTF-919 at doses of 25 and 100 mg. Stools were softer with all but the lowest dose of the active drug. Fiber supplementation prolonged colonic transit time by an average of 45 h; addition of SDZ-HTF-919 significantly shortened this parameter at the lowest dose only. The lack of effect of the 5-HT_4 agonist at both the lowest and highest doses may indicate a biphasic dose-response relationship for total colonic transit time, but further study is required to clarify this issue (13).

In another study in volunteers, a barostat-manometry apparatus was implanted in the descending colon in 24 subjects, and colonic tone and phasic motility were determined in the fasted and fed states and following administration of the study drug or placebo. Fasting motility index increased following administration of SDZ-HTF-919 but not placebo; colonic tone was not affected in either group. Overall, colonic tone and motility index increased in both groups following ingestion of a 1000-kcal liquid meal; the early (0-30 min) postprandial increase in tone was diminished and the late (90-150 min) increase was prolonged in subjects administered SDZ-HTF-919 as compared to those on placebo (14).

In a double-blind, placebo-controlled, parallel-group phase II trial in 547 patients with constipation-predominant IBS (C-IBS), treatment with SDZ-HTF-919 resulted in improvements in symptoms of abdominal discomfort, pain, bloating and constipation. Subjects in the study were randomized to 12 weeks of treatment with SDZ-HTF-919 (0.5, 2, 6 or 12 mg b.i.d.) or placebo. Patients in the 2-mg group showed significant improvements over placebo based on the Subject's Global Assessment (SGA) of overall gastrointestinal symptoms, abdominal discomfort and constipation. The drug's efficacy was maintained over the 12-week treatment period, and it was well tolerated. Transient diarrhea and flatulence were more frequent with the study drug than with placebo. The 2-mg dose, and possibly the 12-mg dose, was considered useful in improving overall symptoms of C-IBS (15).

SDZ-HTF-919 (Zelmac®) is currently in phase III clinical trials (16).

Manufacturer

Novartis AG (CH).

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