[1320]

Symptom/scale	Mean (SD) change from baseline at day 28		*P* value	Mean (SD) change from baseline average of D8, D15 & D28		*P* value
	20mg TZP-102 (*n*=21)	Placebo (*n*=23)		20mg TZP-102 (*n*=21)	Placebo (*n*=23)	
Total GCSI	−1.4 (1.07)	−0.7 (0.99)	0.029	−1.0 (0.86)	−0.5 (0.74)	0.029
Nausea	−1.5 (1.69)	−0.5 (1.44)	0.050	−1.3 (1.48)	−0.3 (1.21)	0.025
Stomach fullness	−1.6 (1.50)	−0.6 (1.31)	0.005	−1.1 (1.26)	−0.5 (1.19)	0.035
Early satiety	−1.4 (1.57)	−0.3 (1.19)	0.003	−1.0 (1.26)	−0.3 (0.85)	0.010
Postprandial fullness	−1.8 (1.37)	−0.9 (1.32)	0.033	− −1.3 (1.11)	−0.6 (1.08)	0.025
Stomach visibly large	−1.5 (1.47)	−0.7 (1.37)	0.040	−1.0 (1.06)	−0.6 (1.05)	0.159
Upper abdominal pain/Discomfort	−1.2 (1.23)	−0.5 (1.53)	0.046	−0.9 (0.97)	−0.4 (1.04)	0.058
Lower abdominal pain/discomfort	−1.0 (1.60)	−0.2 (1.20)	0.025	−0.9 (1.43)	−0.4 (0.91)	0.053

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Alosetron Treatment Led to Fewer Physician Contacts and Fewer Days of Lost Work Productivity Compared to Treatment with Traditional Therapy for Diarrhea-Predominant IBS (IBS-D)

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Purpose: To compare the impact of alosetron treatment with that of traditional therapy for IBS-D on healthcare resource use, productivity, and quality of life (QoL).
Methods: Female patients with IBS-D were enrolled in a randomized, open-label study to evaluate health care resource use, QoL, and productivity following treatment with alosetron (1 mg BID) versus traditional therapy for 24 weeks. Healthcare resource use was primarily measured as number of physician contacts and number of medications used during the treatment period. Improvement in IBS symptoms was assessed using the Global Improvement Scale (GIS) and QoL was assessed using the IBS-related QoL instrument. Total Lost Work Productivity was computed as: Days missed due to IBS + (Total days with IBS symptoms * (1 - % Effectiveness)).
Results: Of 2,456 patients enrolled, 2,256 were evaluable with a mean age of 48.8 yrs and mean duration of 12.2 yrs for IBS. Relative to traditional therapy, alosetron-treated patients reported significantly fewer physician contacts (P=0.032) for any health problem. Although the difference in total number of medications used during the treatment period was not statistically significant between groups, the alosetron group used fewer medications on average compared to the traditional therapy group (9.1 vs. 9.5). Compared to patients treated with traditional therapy, alosetron-treated patients reported significantly greater improvement in all 9 domains of the IBSQoL (P<0.001), and a significantly greater proportion of alosetron-treated patients were responders on the GIS (P<0.001). In both cases, benefit was evident at 4 weeks and sustained throughout the 6-month treatment period. The majority of patients (>70%) on traditional therapy were non-responders at the end of the study. Moreover, patients treated with traditional therapy missed more days from work (3.0 vs. 1.9 days; P<0.001) and lost more days of work productivity (5.0 vs. 3.2 days, P<0.001), compared to alosetron-treated patients. Alosetron-treated patients also reported significantly less restrictions on outdoor activities and attendance at social gatherings compared to patients on traditional therapy (P<0.001). With the exception of GI adverse events (AEs) of constipation and GI pain and discomfort, the incidence of other AEs was similar in both groups,
Conclusion: Alosetron therapy led to significantly greater improvements in IBS symptoms and QoL compared to traditional therapy. Subjects treated with traditional therapy used more healthcare resources in terms of physician time, missed more days of work, and reported significantly greater lost productivity time compared to alosetron-treated patients.
Disclosure: The manufacturer / provider for Alosetron is Prometheus Laboratories Inc. Dr Olden - Consultant and Speakers Bureau: Prometheus Laboratories Inc. Dr Shringarpure, Dr Nicandro and Dr Chuang - Employees and stockholders: Prometheus Laboratories Inc.

1322

Phase II Clinical Evaluation of SP-304, a Guanylate Cyclase-C Agonist, for Treatment of Chronic Constipation

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Purpose: Uroguanylin (UG) and guanylin (GN) are physiological agonists of guanylate cyclase-C (GC-C) receptors. Activation of GC-C receptor promotes intracellular synthesis of cGMP and subsequent activation of the cystic fibrosis transmembrane conductance regulator (CFTR), resulting in fluid and bicarbonate secretion into the intestinal lumen. Optimum volume of fluid secretion in the proximal intestine is critical for normal bowel movement and for complete defecation. Thus, oral treatment with a GC-C agonist is expected to promote spontaneous bowel movement (SBM) and to reduce abdominal pain and bloating. SP-304 is a superior analog of UG that appears to mimic physiological functions of UG in the GI tract. In T84 cell assays, SP-304 exhibits an 8-fold higher binding affinity to GC-C receptors than UG. The present trial is designed to evaluate efficacy and safety in chronic constipation (CC) patients.
Methods: This phase II clinical study (double-blind, placebo-controlled, randomized with cohorts of 0.3, 1, 3 and 9 mg repeated daily dose for 14-days) in CC patients has completed enrollment and dosing of the first 2 of 4 cohorts. CC patients are being evaluated primarily for safety and efficacy of SP-304. Bowel habits (stool frequency, consistency, straining, time to first BM and completeness of evacuation) and degree of abdominal discomfort were monitored daily using patient diary. Patient reported outcomes of severity of constipation and overall relief were evaluated weekly.
Results: A total of 14 sites open in the U.S. are presently evaluating SP-304 in CC patients. Total enrollment for the study is 80 patients. At present, 40 patients have been dosed, and the 1.0 mg and 3.0 mg dosage arms have been completed. Patients are currently being dosed at 9 mg. We recently added a fourth dosage arm of 0.3 mg to the study. To date, no unexpected safety issues have been reported and based on the blinded review some patients in each cohort are experiencing improvements in bowel function. Phase II clinical data will be discussed to highlight pharmacodynamic and safety profile of SP-304 in CC patients.
Conclusion: GC-C agonists are rapidly emerging as a new class of drug can-

bind to a common GC-C receptor to stimulate fluid secretion in the gut. The present study demonstrates that SP-304 possesses a similar clinical profile as other GC-C agonists, based on the early clinical observations. Complete phase II clinical data on safety & efficacy in CC patients will be discussed.
Disclosure: Dr Shailubhai-Employee Dr Talluto-Employee Dr Steve Comiskey-Employee Dr John Foss-Employee Dr Alan Joslyn-consultant Dr Gary Jacob-Employee.

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High Resolution Anorectal Manometry in Healthy Egyptian Population: Age, Gender, and Parity Influence

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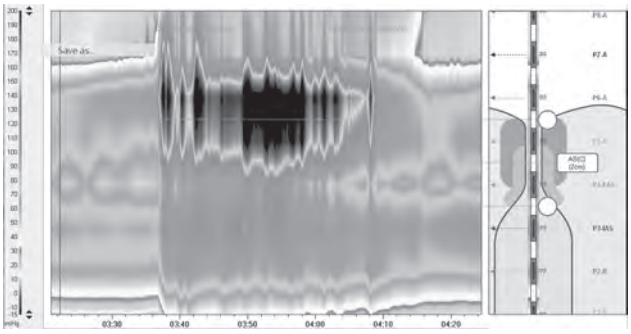
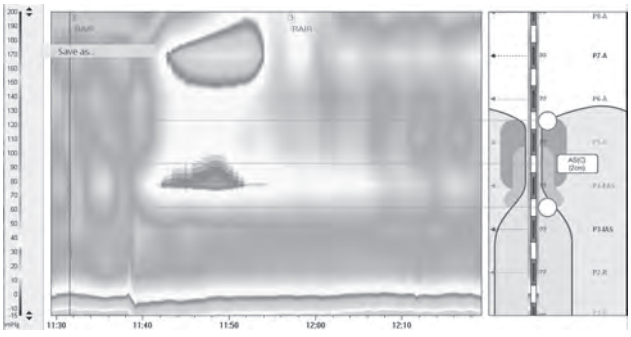
Purpose: The aim was to study High Resolution Anorectal Manometry (HRAM) in Egyptian population and the influence of age, gender and parity on manometric parameters.
Methods: We studied 22 healthy volunteers 10 males and 12 females with median age 42 y (range: 18-61 y) by using solid state probe with 8 transducers 1 cm spaced with a rectal balloon mounted at the tip. The system is plotting graphs with high resolution topography and conventional pressure waves tracing as well (Solar GI MMS). Probe was introduced through the anal verge so the balloon is located at the rectum and the sensors at the rectum and anal canal. External EMG electrodes were applied on either sides of anus. Subjects were asked to relax, squeeze the anal sphincter, bear down, and cough to measure anal pressures at these situations. Rectal sensation and recto-anal inhibitory reflex (RAIR) were evaluated by stepwise intermittent (10 ml) balloon distention. Finally balloon expulsion test was done.
Results: Anal resting and maximum squeeze pressure were significantly higher in males than females (median; range: 61; 45-71 and 140.0; 67-224 vs. 42; 32-67 and 117; 58-220 respectively, P<0.05), while squeeze time, pressure increase to cough, push relaxation, RAIR, rectal sensation, and EMG were comparable in males and females. Age negatively correlated with some anorectal parameters (table 1), similarly parity negatively correlated with anal resting (r=-0.52, p <0.05) and squeeze pressure (r=-0.56, p<0.05). All subjects were able to expel the balloon.
Conclusion: HRAM helps understanding anorectal physiology. It is influenced by age, gender, and parity. This study can aid in diagnosis anorectal dysfunction in Egyptian population.



[1323] High resolution topography of maximum anal squeeze.



[1323] High resolution topography of RAIR.

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Is There a Unifying Pathophysiology of Medically Unexplained Symptoms in GW Veterans?

2010 Presidential Poster

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Purpose: The prevalence of irritable bowel syndrome (IBS), dyspepsia, chronic fatigue syndrome (CFS) and other medically unexplained symptoms (MUS) in Gulf War (GW) veterans is high. It has been suggested that these problems are different manifestations of a common disorder. The aim of this study was to determine whether these independent symptoms based subgroups exist in GW veterans.
Methods: GW veterans (1990-1991) registered in two registries at two major Medical Centers were mailed the validated Bowel Disease Questionnaire inquiring about their bowel habits and somatic symptoms specifically inquiring about symptoms of CFS (fatigue, joint pain, general stiffness, headache, insomnia) and MUS (including backache, shortness of breath, palpitation, eye pain, dizziness, hot and cold spells, anxiety, and nervousness). Definition of IBS and dyspepsia were based on Rome III criteria. Data was analyzed using Hierarchical cluster analysis with average linkage using symptoms of IBS, dyspepsia, CFS, and other MUS.
Results: Data from 433 GW veterans registered at the two VA Medical Centers were analyzed. This population consisted of predominantly men (86%) with a median age 48 years (range 34-76). The prevalence of IBS, dyspepsia, and symptom components of CFS, and MUS is described in Table 1. There was significant overlap among all three disorders. Almost half (49.1%) of GW veterans with dyspepsia had IBS and 74% with IBS had dyspepsia. Forty-eight percent of GW veterans with IBS and 39% with dyspepsia also reported symptoms of CFS. The simultaneous presence of IBS, dyspepsia and CFS were reported by 12% of GW veterans. Cluster analysis suggests the presence of four clusters. IBS and dyspepsia form two separate clusters, third consists of CFS, and the fourth consists of other MUS (Figure).
Conclusion: MUS is common in GW veterans. Although IBS, dyspepsia, CFS, and MUS commonly co-exist, they form separate clusters. This would suggest that the pathophysiology of MUS in GW veterans cannot be explained by one unifying hypothesis and a single treatment is unlikely to be helpful.

[1323] Table 1. Correlation between age and manometry

	Anal pressure			Rectal sensation			
	Resting	Max squeeze	Cough increase	1st sensation	1st urge	Intense urge	Max tolerable
r	−0.44	−0.49	−0.371	−0.553	−0.420	−0.508	−0.380
P value	.039	.027	.051	.008	.05	.016	0.061