Sponsor
Novartis

Generic Drug Name
SMS995 / Octreotide acetate

Trial Indication(s)
Investigational

Protocol Number
CSMS995A2101

Protocol Title
A multi-center, randomized, double-blind, placebo-controlled, crossover study in women with irritable bowel syndrome to evaluate feasibility and reproducibility of barostat assessments of colorectal sensation during colorectal distention and its pharmacological modulation using octreotide

Clinical Trial Phase
Phase I

Study Start/End Dates
25 Feb 2008 to 28 Feb 2009

Reason for Termination
Not applicable

Study Design/Methodology
This study employed a multi-center, randomized, double-blind, placebo-controlled, crossover design in female patients with irritable bowel syndrome (IBS)). Each patient participated in screening period and a total of 7 visits including an end of study evaluation 1 to 4 days after the last barostat procedure or at early termination. The study was completed as planned.

Centers
7 centers in 4 countries: Canada (1), Sweden (1), United Kingdom (3), and United States (2)

Objectives:

Primary objective(s)

- To assess intra-patient reproducibility of barostat assessments of colorectal sensory functions and compliance in irritable bowel syndrome (IBS) patients using repeated baseline barostat measurements
- To assess which was the most robust colorectal sensory parameter to detect a treatment-related difference in colorectal perception using the ascending method of limits (AML) and random phasic distension (RPD) protocols

Secondary objective(s)

- To evaluate whether a treatment-related difference in colorectal pressure thresholds for first sensation, first desire to defecate, urgency, discomfort and pain perception can be detected using the AML barostat protocol
- To evaluate whether a treatment-related difference in sensory intensity ratings for gas, urgency, discomfort and pain can be detected using the RPD barostat protocol
- To assess inter-site differences in the pressure thresholds for first sensation, first desire to defecate, urgency, discomfort and pain perception in the AML and in the sensory intensity ratings for gas, urgency, discomfort and pain in the RPD barostat protocol

Test Product (s), Dose(s), and Mode(s) of Administration

Octreotide acetate, 1.25µg/kg, subcutaneous administration

Statistical Methods

- Variation of the different endpoints without treatment
  - Separately for each endpoint:
  - ANOVA on data from barostat assessments 1, 2 and 4 (baseline, treatment-free), including a random subject effect
  - Estimation of the intraindividual standard deviation, with 95% CI
- Susceptibility of the different endpoints to a drug effect
  - Separately for each endpoint:
  - ANCOVA on data from barostat assessments 3 and 5 (crossover), including a random subject effect and baseline covariates (barostat assessments 2 and 4)
  - Estimation of the treatment effect, octreotide vs. placebo, with 95% CI and (two-sided) p-value
- No adjustment for multiplicity

Colorectal (more precisely rectal) compliance was assessed using a nonlinear mixed effects emax model for modeling the relationship of applied pressure to resulting barostat volume.

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Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Females aged 18-65 years
- A positive diagnosis of IBS
- Subjects must either have been surgically sterilized, hysterectomized at least 6 months prior to screening, be postmenopausal or be using a double-barrier local contraception.
- Able to communicate well with the investigator, to understand and comply with the requirements of the study. Understand and sign the written informed consent.

Exclusion criteria

- History of or evidence for structural diseases/conditions that affect the gastrointestinal system
- Other diseases or conditions that in the opinion of the Investigator significantly affect colorectal sensitivity
- Evidence of occult blood at stool analysis, or history of rectal bleeding
- Using or planning to use drugs or agents during the study period that alter GI physiology and visceral perception

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Participant Flow Table

Patient disposition (All subjects)

Disposition Reason	Octreotide /Placebo N=26	Placebo/ Octreotide N=26	None N=4	Total N=56
Completed	23 (88.5%)	26 (100%)	0	49 (87.5%)
Discontinued	3 (11.5%)	0	4 (100%)	7 (12.5%)
Adverse Event(s)	2 (7.7%)		2 (50.0%)	4 (7.1%)
Subject withdrew consent			2 (50.0%)	2 (3.6%)
Administrative problems	1 (3.8%)			1 (1.8%)

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Baseline Characteristics

Summary of Demographics, Safety analysis set

		Octreotide /Placebo N=26	Placebo/ Octreotide N=26	None N=2	Total N=54
Age (years)	Mean (SD)	41.3 (12.70)	30.1 (10.25)	46.0 (14.14)	36.1 (12.82)
	Median	42.0	25.0	46.0	34.5
	Range	20 - 63	20 - 58	36 - 56	20 - 63
Predominant race - n(%)	Caucasian	23 (88.5 %)	25 (96.2 %)	2 (100 %)	50 (92.6 %)
	Asian	2 (7.7 %)	1 (3.8 %)	0	3 (5.6 %)
	Other	1 (3.8 %)	0	0	1 (1.9 %)
Ethnicity - n(%)	Chinese	1 (3.8 %)	0	0	1 (1.9 %)
	Indian (India subc)	1 (3.8 %)	1 (3.8 %)	0	2 (3.7 %)
	Mixed ethnicity	1 (3.8 %)	0	0	1 (1.9 %)
	Other	23 (88.5 %)	25 (96.2 %)	2 (100 %)	50 (92.6 %)
Body Mass Index (kg/m^2)	Mean (SD)	26.73 (4.642)	23.26 (4.126)	33.26 (0.106)	25.30 (4.862)
	Median	27.35	22.95	33.26	24.77
	Range	19.4 - 35.0	17.1 - 33.5	33.2 - 33.3	17.1 - 35.0
Weight (kg)	Mean (SD)	72.28 (14.509)	64.15 (10.489)	85.65 (0.495)	68.86 (13.358)
	Median	67.25	64.15	85.65	66.85
	Range	50.4 - 102.1	47.6 - 88.0	85.3 - 86.0	47.6 - 102.1
Height (cm)	Mean (SD)	164.2 (7.00)	166.4 (6.41)	160.5 (0.71)	165.1 (6.67)
	Median	161.5	165.5	160.5	163.5
	Range	154 - 180	151 - 180	160 - 161	151 - 180

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Summary of Efficacy

Primary Outcome Result(s)

Intra-Patient Variability (SD) and Treatment Effects (TE) (Pharmacodynamic analysis set)

Attributes	EPs	Intra-patient SD estimate	(95% CI)*	n[a]	TE Estimate** (O-P)	95% CI	n[b]	p-value
AML (mm Hg)	First sensation	4.8	(4.2, 5.6)	53	0.9	(-1.8, 3.6)	50	0.505
	First desire to defecate	3.6	(3.2, 4.2)	53	0.4	(-2.2, 3.0)	50	0.766
	Urgency	4.7	(4.1, 5.5)	53	-0.2	(-2.7, 2.3)	50	0.881
	Discomfort	4.6	(4.1, 5.4)	53	-0.5	(-3.1, 2.0)	50	0.671
	Pain	4.6	(4.1, 5.4)	53	1.0	(-1.3, 3.3)	49	0.398

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Intra-Patient Variability (SD) and Treatment Effects (TE) (Pharmacodynamic analysis set)

Attributes	EPs	Intra-patient SD estimate	(95% CI)*	n[a]	TE Estimate** (O-P)	95% CI	n[b]	p-value
RPD 12 mm Hg on VAS	Gas	17.5	(15.4, 20.4)	54	-0.6	(-7.6, 6.5)	47	0.873
	Urgency	17.6	(15.5, 20.5)	54	7.1	(-0.1, 14.3)	48	0.053
	Discomfort	17.4	(15.3, 20.3)	54	4.3	(-1.9, 10.6)	48	0.170
	Pain	14.5	(12.7, 16.9)	54	2.1	(-0.8, 5.0)	48	0.158
RPD 24 mm Hg on VAS	Gas	19.9	(17.4, 23.1)	54	-6.4	(-13.8, 0.9)	47	0.083
	Urgency	15.8	(13.9, 18.4)	54	1.0	(-7.0, 8.9)	47	0.811
	Discomfort	16.6	(14.5, 19.3)	54	1.2	(-6.6, 9.0)	47	0.764
	Pain	19.2	(16.8, 22.3)	54	2.6	(-5.5, 10.7)	47	0.517
RPD 36 mm Hg on VAS	Gas	16.6	(14.2, 20.0)	48	0.4	(-10.3, 11.1)	34	0.935
	Urgency	14.4	(12.4, 17.2)	48	-4.0	(-13.5, 5.5)	34	0.396
	Discomfort	15.9	(13.7, 19.0)	48	-1.7	(-12.6, 9.2)	34	0.749
	Pain	18.3	(15.7, 21.9)	48	1.7	(-10.6, 14.0)	34	0.778

Intra-Patient Variability (SD) and Treatment Effects (TE) (Pharmacodynamic analysis set)

Attributes	EPs	Intra-patient SD estimate	(95% CI)*	n[a]	TE Estimate** (O-P)	95% CI	n[b]	p-value
RPD 48 mm Hg on VAS	Gas	16.8	(13.5, 22.3)	28	-1.6	(-14.8, 11.5)	15	0.781
	Urgency	7.5	(6.0, 9.9)	28	-4.6	(-15.7, 6.5)	15	0.368
	Discomfort	15.1	(12.2, 19.9)	28	-8.9	(-20.3, 2.5)	15	0.110
	Pain	14.3	(11.5, 19.0)	28	-8.0	(-17.6, 1.7)	15	0.093

* Confidence Interval

** Treatment Effect estimate (Octreotide – Placebo)

[a] # of subjects for variability estimation

[b] # of subjects for treatment effect estimation

Secondary Outcome Result(s)

Refer to Primary Outcome section for secondary outcome results.

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Summary of Safety

Safety Results

Adverse events overall and specific events (Safety analysis set)

	Run-in N=54		Octreotide N=49		Placebo N=48	
	n	(%)	n	(%)	n	(%)
Patients with AE(s)	10	(18.5)	11	(22.4)	7	(14.6)
Preferred term						
Abdominal distension			1	(2.0)		
Abdominal pain			1	(2.0)		
Abdominal pain upper			2	(4.1)	1	(2.1)
Abdominal tenderness			1	(2.0)		
Accident	1	(1.9)				
Arthropod bite	1	(1.9)				
Back pain	1	(1.9)			1	(2.1)
Blood glucose increased	1	(1.9)				
Diarrhoea			2	(4.1)		
Ear canal injury	1	(1.9)				
Fatigue			1	(2.0)		
Flatulence			1	(2.0)		
Flushing			1	(2.0)	1	(2.1)
Headache	2	(3.7)	4	(8.2)	1	(2.1)
Hot flush			1	(2.0)		
Injection site pain			1	(2.0)		

Adverse events overall and specific events (Safety analysis set)

	Run-in N=54		Octreotide N=49		Placebo N=48	
	n	(%)	n	(%)	n	(%)
Irritable bowel syndrome	1	(1.9)				
Nausea			2	(4.1)	2	(4.2)
Non-cardiac chest pain			1	(2.0)		
Occult blood positive	1	(1.9)				
Presyncope			1	(2.0)		
Rectal haemorrhage	2	(3.7)			1	(2.1)
Red blood cells urine	1	(1.9)				
Thyroid neoplasm	1	(1.9)				
Urinary tract infection					2	(4.2)
Vomiting			1	(2.0)	1	(2.1)

Serious Adverse Events and Deaths

There were no deaths reported in the study and 3 patients experienced SAEs during the study.

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Subjects with Serious Adverse Events by body system and preferred term (Safety analysis set)

Body system	Adverse event (preferred term)	Run-in N=54 n (%)	Octreotide N=49 n (%)	Placebo N=48 n (%)	Total N=54 n (%)
- any body system			1 (2.0)	2 (4.2)	3 (5.6)
Gastrointestinal disorders	- Total			2 (4.2)	2 (3.7)
	Abdominal pain upper			1 (2.1)	1 (1.9)
	Rectal haemorrhage			1 (2.1)	1 (1.9)
Nervous system disorders	- Total		1 (2.0)		1 (1.9)
	Presyncope		1 (2.0)		1 (1.9)

Date of Clinical Trial Report

18 Nov 2010