Protocol Registration Receipt
04/09/2009

Grantor: CDER IND/IDE Number: 48,487 Serial Number: 0332

Study to Assess the Effect Of Alosetron On Mucosal Blood Flow

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by:	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT00370032

Purpose

This study will look at colonic mucosal blood flow in subjects who have taken alosetron vs placebo and healthy volunteers vs diarrhea-predominant Irritable Bowel Syndrome (d-IBS) patients.

Condition	Intervention	Phase
Irritable Bowel Syndrome (IBS)	Drug: alosetron	Phase 4

Study Type: Interventional

Study Design: Treatment, Crossover Assignment, Double Blind, Randomized, Pharmacodynamics Study

Official Title: A Randomize, Placebo-controlled, Crossover Study to Measure the Effect of Alosetron on Mucosal Blood Flow in Female Healthy Volunteers and Diarrhea-predominant IBS Subjects

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Left Colon Mucosal Blood Flow (MBF) [Time Frame: Day 6 after each treatment period] [Designated as safety issue: Yes]

  On Day 6 of each treatment period; 1 hour after dosing, subjects underwent a flexible sigmoidoscopy with Laser Doppler Flowmetry (LDF) to measure Mucosal Blood Flow (MBF). There were no pre-treatment LDF procedure, MBF was compared between the Healthy volunteers and D-IBS cohorts using the flow rates from the placebo treatment period.

Secondary Outcome Measures:

- Rectal Mucosal Blood Flow (MBF) [Time Frame: Day 6 after each treatment period] [Designated as safety issue: Yes]

  On Day 6 of each treatment period approximately 1 hour after dosing, subjects underwent a flexible sigmoidoscopy with Laser Doppler Flowmetry (LDF) to measure Mucosal Blood Flow (MBF). There was no pre-treatment LDF procedure, MBF was compared between the Healthy and d-IBS cohorts using the flow rates from the placebo treatment period.
- Left Colon and Rectal Muscosal Blood Flow Cohort Comparisons [Time Frame: Day 6 after each treatment period] [Designated as safety issue: Yes]

  On Day 6 of each treatment period approximately 1 hour after dosing, subjects underwent a flexible sigmoidoscopy with Laser Doppler Flowmetry (LDF) to measure Mucosal Blood Flow (MBF). There was no pre-treatment LDF procedure, MBF was compared between the Healthy and d-IBS cohorts using the flow rates from the placebo treatment period.

Enrollment: 49

Study Start Date: December 2006

Study Completion Date: December 2007

Primary Completion Date: December 2007

Intervention Details:

Drug: alosetron

Other Names:

alosetron

Eligibility

Ages Eligible for Study: 18 Years to 49 Years

Genders Eligible for Study: Female

Accepts healthy volunteers.

Inclusion criteria:

- The subject signs and dates a written informed consent form prior to the initiation of any study-related activities.
- The subject is between 18 and 49 years of age at the time of the Screening Visit.
- The subject is female and either:
    - A healthy subject. Healthy subjects are defined as individuals who are free from clinically significant illness or disease as determined by their medical history (including family), physical examination, laboratory studies, and other tests.

OR

- A d-IBS patient per the Rome II criteria who has a normal result from a flexible sigmoidoscopy or colonoscopy, or flexible sigmoidoscopy plus barium enema, within 2 years of the Screening visit.
    - The subject demonstrates a negative urine pregnancy test result prior to investigational product administration and be either:
- Of non-childbearing potential (i.e., physiologically incapable of becoming pregnant)
- post-menopausal define as one year without menses in the absence of hormone replacement therapy.
- sterilization (via hysterectomy or bilateral tubal ligation)
- Of childbearing potential and agrees to one of the following acceptable non-hormonal contraceptive methods consistently and in accordance with both the product label and the instructions of a physician. Subjects will use effective contraceptive methods for at least one month prior to Screening and should continue to use the same contraceptive method throughout the study (Follow-up Visit).
- Complete abstinence from intercourse
- an intra-uterine device (IUD) inserted by a qualified physician, provided the IUD is not of the hormonal type and it has published data showing that the highest expected failure rate is less than 1% per year (not all IUDs meet this criterion)
- double barrier method if comprised of a spermicide with either a condom or diaphragm
- sterilization of partner The subject is ambulatory (defined as not depending exclusively on a wheelchair for mobility).

Exclusion criteria:

- The subject is taking oral contraceptive or other hormonal therapy.
- The subject has a concurrent illness or disability that may affect the interpretation of clinical data, or otherwise contraindicates participation in this clinical study (e.g., an unstable cardiovascular, autoimmune, renal, hepatic, pulmonary, endocrine, metabolic, gastrointestinal, hematologic, or neurological condition).
- The subject has constipation-predominant IBS (c-IBS) or alternating IBS per the ROME II criteria.
- The subject has current evidence of or history of chronic or severe constipation, or a history of sequelae from constipation.
- Evidence of a biochemical or structural abnormality of the digestive tract. These conditions include (but not limited to):
    - Current evidence, or history of (at any time in the past):

- GI/Bowel conditions:
- inflammatory bowel disease (Crohn's disease or ulcerative colitis)
- celiac disease
- laxative abuse (in the clinical judgement of the physician)
- gastrointestinal surgery (exceptions include ≥6 months post-surgery appendectomy, cholecystectomy, fundoplication without gas bloat, or hiatal hernia repair; ≥3 months post-surgery herniorrhaphy without bowel resection)
- gastroparesis
- GI malignancy
- carcinoid syndrome
- amyloidosis
- gastrointestinal adhesions
- ischemic colitis
- toxic megacolon
- impaired intestinal circulation
- gastrointestinal perforation
- gastrointestinal obstruction and/or stricture
- Ischemic cardiovascular conditions:
- coronary artery disease (CAD)
- significant atherosclerosis
- chronic pancreatitis
- diabetes
- thrombophlebitis or hypercoagulable state.
- Current evidence of (within the past 6 months):
- diverticulitis
- ileus
- symptomatic cholelithiasis
- proctitis.
- Current evidence of:
- Hemoccult (+) stool.

- The subject has a Body Mass Index (BMI) of ≥27.
- Mental impairment or inability or refusal to follow directions.
- The subject has current evidence of, or has been treated for a malignancy within the past five years (other than localized basal cell, squamous cell skin cancer or cancer in situ that has been resected).
- The subject exhibits evidence of hepatic dysfunction, viral hepatitis, or exhibits serum ALT (SGPT), AST (SGOT) values >2.5 times the upper limit of normal or alkaline phosphatase or bilirubin values >2.0 times the upper limit of normal.

- The subject displays renal impairment as evidenced by a serum creatinine value >2.0 mg/dl.
- The subject has used any medication within the seven days prior to dosing, unless approved by the investigator and GSK personnel. Section 9.1.
- The subject has used an investigational drug, or participated in an investigational study, within 30 days of the Screening Visit.
- The subject has a history of drug allergies (including but not limited to hypersensitivity responses to alosetron which, in the opinion of the investigator, contraindicates the subject's participation in this study.
- Subjects who have made a blood donation (>450mL) within 6 weeks prior to screening.
- The subject has a history of alcohol and/or substance abuse within the past two years.
- The subject is pregnant. The subject is breastfeeding.

Contacts and Locations

Locations

United Kingdom

GSK Investigational Site

London, United Kingdom, W1G 8HU

Investigators

Study Director:	GSK Clinical Trials, MD	GlaxoSmithKline

More Information

Responsible Party:	GSK (Study Director)
Study ID Numbers:	S3B40042
Health Authority:	United States: Food and Drug Administration

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Study Results

Participant Flow

Reporting Groups

	Description
d-IBS (Diarrhea Predominant - Irritable Bowel Syndrome)	Subjects with diarrhea-predominant irritable bowel syndrome. This group was randomize to EITHER 0.5 mg BID Alosetron or Placebo for 6 days followed by a flexible sigmoidoscopy; followed by a 7 day washout period; Then the subjects who were given study drug the first treatment period were given Placebo and vice versa for the next 6 days followed by a flexible sigmoidoscopy then had a 7 day follow up period.
Healthy Volunteers	Subjects with no clinical disease. This group was randomize to EITHER 0.5 mg BID Alosetron or Placebo for 6 days followed by flexible sigmoidoscopy then had a 7 day washout period; Then the subjects who were given study drug the first treatment period were given Placebo and vice versa for the next 6 days followed by another 7 day wash out period and a 7 day follow up period.

Treatment Period 1

	d-IBS (Diarrhea Predominant - Irritable Bowel Syndrome)	Healthy Volunteers
Started	24 [1]	25 [2]
Completed	24	24
Not Completed	0	1
Unable to perform sigmoidoscopy on Day 6	0	1

[1] Safety Population - all subjects who took at least one dose of study medication.

[2] Safety Population - all subjects who took at least one dose of study medication.

Washout Period

	d-IBS (Diarrhea Predominant - Irritable Bowel Syndrome)	Healthy Volunteers
Started	24	24
Completed	23	22
Not Completed	1	2
Withdrawal by Subject	0	1
Lost to Follow-up	0	1
Adverse Event	1	0

Treatment Period 2

	d-IBS (Diarrhea Predominant - Irritable Bowel Syndrome)	Healthy Volunteers
Started	23	22
Completed	23	22
Not Completed	0	0

Follow-up Period

	d-IBS (Diarrhea Predominant - Irritable Bowel Syndrome)	Healthy Volunteers
Started	23	22
Completed	22	22
Not Completed	1	0
Withdrawal by Subject	1	0

Baseline Characteristics

Reporting Groups

	Description
d-IBS	Diarrhea-predominant irritable bowel syndrome. This group was randomize to EITHER 0.5 mb BID Alosetron or Placebo for 6 days followed by a flexible sigmoidoscopy; followed by a 7 day washout period; Then the subjects who were given study drug the first treatment period were given Placebo and vice versa for the next 6 days followed by another wash out period and a 7 day follow up period.
Healthy Volunteers	Volunteers without clinical disease. This group was randomize to EITHER 0.5 mb BID Alosetron or Placebo for 6 days followed by a flexible sigmoidoscopy; followed by a 7 day washout period; Then the subjects who were given study drug the first treatment period were given Placebo and vice versa for the next 6 days followed by another wash out period and a 7 day follow up period.

Baseline Measures

	d-IBS	Healthy Volunteers	Total
Number of Participants	22	22	44
Age, Continuous [units: years] Mean (Standard Deviation)	33.2 (8.8)	26.9 (5.8)	29.99 (7.42)
Gender, Male/Female [units: participants]			
Female	22	22	44
Male	0	0	0
Race/Ethnicity, Customized [units: participants]			
White/Caucasian/European	17	16	33
African American	3	2	5
Central/South Asian	1	1	2
East Asian	1	0	1
South East Asian	0	2	2
Mixed Race	0	1	1

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Left Colon Mucosal Blood Flow (MBF)
Measure Description	On Day 6 of each treatment period; 1 hour after dosing, subjects underwent a flexible sigmoidoscopy with Laser Doppler Flowmetry (LDF) to measure Mucosal Blood Flow (MBF). There were no

	pre-treatment LDF procedure, MBF was compared between the Healthy volunteers and D-IBS cohorts using the flow rates from the placebo treatment period.
Time Frame	Day 6 after each treatment period
Safety Issue?	Yes

Analysis Population Description

Per Protocol Population - the population used for the primary and secondary outcome analyses. The population consisted of all randomized subjects who completed the study with MBF measurements for both treatment periods.

Reporting Groups

	Description
d-IBS Placebo	Subjects with diarrhea-predominant irritable bowel syndrome. In Treatment Period 1 this group was first randomized to Placebo for 6 days followed by a flexible sigmoidoscopy; followed by a 7 day washout period; Then, in Treatment Period 2 the subjects were given Alosetron 0.5 mg (BID)for 5 days and on the 6th day one dose and a flexible sigmoidoscopy; followed by another wash out period of 7 days and a 7 day follow up period.
d-IBS Alosetron	Subjects with diarrhea-predominant irritable bowel syndrome. In Treatment Period 1, this group was randomized to 0.5 mb BID Alosetron for 5days and 1 dose on the 6th day followed by a flexible sigmoidoscopy; followed by a 7 day washout period; Then, in Treatment Period 2 the subjects were given Placebo for the next 6 days followed by another 7 day wash out period and a 7 day follow up period.
Healthy Volunteers Placebo	Subjects without Clinical disease. In Treatment Period 1 this group was first randomized to Placebo for 6 days followed by a flexible sigmoidoscopy; followed by a 7 day washout period; Then, in Treatment Period 2 the subjects were given Alosetron 0.5 mg (BID)for

	Description
	5 days and on the 6th day one dose and a flexible sigmoidoscopy; followed by another wash out period of 7 days and a 7 day follow up period.
Healthy Volunteers Alosetron	Subjects without clinical disease. In Treatment Period 1 this group was randomized to 0.5 mb BID Alosetron for 5days and 1 dose on the 6th day followed by a flexible sigmoidoscopy; followed by a 7 day washout period; Then,in Treatment Period 2 the subjects were given Placebo for the next 6 days followed by another 7 day wash out period and a 7 day follow up period.

Measured Values

	d-IBS Placebo	d-IBS Alosetron	Healthy Volunteers Placebo	Healthy Volunteers Alosetron
Number of Participants Analyzed	22	22	19	19
Left Colon Mucosal Blood Flow (MBF) [units: ml per minute per 100 grams of tissue] Mean (Standard Deviation)	125.6 (38.6)	117.5 (37.71)	130.7 (40.12)	121.6 (51.26)

Statistical Analysis 1 for Left Colon Mucosal Blood Flow (MBF)

Groups	d-IBS Placebo, d-IBS Alosetron
Method	Other [paired t-test Hommel-Simes]
P-Value	0.131
Mean Difference (Final Values)	-8.1
95% Confidence Interval	-18.4 to 2.157

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

Statistical Analysis 2 for Left Colon Mucosal Blood Flow (MBF)

Groups	Healthy Volunteers Placebo, Healthy Volunteers Alosetron
Method	Other [paired t-test Hommel-Simes]
P-Value	0.131
Mean Difference (Final Values)	-9.11
95% Confidence Interval	-21.2 to 2.997

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

2. Secondary Outcome Measure:

Measure Title	Rectal Mucosal Blood Flow (MBF)
Measure Description	On Day 6 of each treatment period approximately 1 hour after dosing, subjects underwent a flexible sigmoidoscopy with Laser Doppler Flowmetry (LDF) to measure Mucosal Blood Flow (MBF). There was no pre-treatment LDF procedure, MBF was compared between the Healthy and d-IBS cohorts using the flow rates from the placebo

	treatment period.
Time Frame	Day 6 after each treatment period
Safety Issue?	Yes

Analysis Population Description

Reporting Groups

	Description
d-IBS Placebo	Subjects with diarrhea-predominant irritable bowel syndrome. In Treatment Period 1 this group was first randomized to Placebo for 6 days followed by a flexible sigmoidoscopy; followed by a 7 day washout period; Then, in Treatment Period 2 the subjects were given Alosetron 0.5 mg (BID)for 5 days and on the 6th day one dose and a flexible sigmoidoscopy; followed by another wash out period of 7 days and a 7 day follow up period.
d-IBS Alosetron	Subjects with diarrhea-predominant irritable bowel syndrome. In Treatment Period 1 this group was randomized to 0.5 mb BID Alosetron for 5days and 1 dose on the 6th day followed by a flexible sigmoidoscopy; followed by a 7 day washout period; Then, in Treatment Period 2 the subjects were given Placebo for the next 6 days followed by another 7 day wash out period and a 7 day follow up period.
Healthy Volunteers Placebo	Subjects without Clinical disease. In Treatment Period 1 this group was first randomized to Placebo for 6 days followed by a flexible sigmoidoscopy; followed by a 7 day washout period; Then, in Treatment Period 2 the subjects were given Alosetron 0.5 mg (BID)for 5 days and on the 6th day one dose and a flexible sigmoidoscopy; followed by another wash out period of 7 days and a 7 day follow up period.
Healthy Volunteers Alosetron	Subjects without clinical disease. In Treatment Period 1 this group was

	Description
	randomized to 0.5 mb BID Alosetron for 5days and 1 dose on the 6th day followed by a flexible sigmoidoscopy; followed by a 7 day washout period; Then,in Treatment Period 2 the subjects were given Placebo for the next 6 days followed by another 7 day wash out period and a 7 day follow up period.

Measured Values

	d-IBS Placebo	d-IBS Alosetron	Healthy Volunteers Placebo	Healthy Volunteers Alosetron
Number of Participants Analyzed	22	22	22	22
Rectal Mucosal Blood Flow (MBF) [units: ml per minute per 100 grams of tissue] Mean (Standard Deviation)	173 (45.52)	159.1 (51.73)	149.1 (39.82)	140.3 (56)

3. Secondary Outcome Measure:

Measure Title	Left Colon and Rectal Muscosal Blood Flow Cohort Comparisons
Measure Description	On Day 6 of each treatment period approximately 1 hour after dosing, subjects underwent a flexible sigmoidoscopy with Laser Doppler Flowmetry (LDF) to measure Mucosal Blood Flow (MBF). There was no pre-treatment LDF procedure, MBF was compared between the Healthy and d-IBS cohorts using the flow rates from the placebo treatment period.
Time Frame	Day 6 after each treatment period
Safety Issue?	Yes

Analysis Population Description

Population: modified per protocol to include placebo information only.

Reporting Groups

	Description
d-IBS Placebo - Left Colon	Subjects with diarrhea-predominant irritable bowel syndrome . Modified per protocol. Subjects Left Colon Mucosal blow flow under placebo.
d-IBS Placebo - Rectal	Subjects with diarrhea-predominant irritable bowel syndrome. Modified per protocol. Subjects Rectal Mucosal blow flow under placebo.
Healthy Volunteers Placebo - Left Colon	Subjects without Clinical disease. Modified per protocol. Subjects Left Colon Mucosal blow flow under placebo.
Healthy Volunteers Placebo - Rectal	Subjects without clinical disease. Modified per protocol. Subjects Rectal Mucosal blow flow under placebo.

Measured Values

	d-IBS Placebo - Left Colon	d-IBS Placebo - Rectal	Healthy Volunteers Placebo - Left Colon	Healthy Volunteers Placebo - Rectal
Number of Participants Analyzed	22	22	19	22
Left Colon and Rectal Muscosal Blood Flow Cohort Comparisons [units: ml per minute per 100 grams of tissue] Mean (Standard Deviation)	135.1 (38.6)	178.9 (45.52)	149.9 (40.12)	166.6 (39.82)

Reported Adverse Events

Reporting Groups

	Description
d-IBS Placebo	diarrhea-predominant irritable bowel syndrome
d-IBS Alosetron	
Healthy Volunteers Placebo	
Healthy Volunteers Alosetron	

Serious Adverse Events

	d-IBS Placebo	d-IBS Alosetron	Healthy Volunteers Placebo	Healthy Volunteers Alosetron
Total # participants affected/at risk	0/	0/	0/	0/

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	d-IBS Placebo	d-IBS Alosetron	Healthy Volunteers Placebo	Healthy Volunteers Alosetron
Total # participants affected/at risk	12/	10/	11/	11/
Gastrointestinal disorders				
Abdominal Distention †				
# participants affected/at risk	1/24 (4.17%)	0/23 (0%)	1/24 (4.17%)	3/23 (13.04%)
# events				
Abdominal Pain Upper †				

	d-IBS Placebo	d-IBS Alosetron	Healthy Volunteers Placebo	Healthy Volunteers Alosetron
# participants affected/at risk	1/24 (4.17%)	1/23 (4.35%)	1/24 (4.17%)	2/23 (8.7%)
# events				
Constipation †				
# participants affected/at risk	0/24 (0%)	4/23 (17.39%)	0/24 (0%)	1/23 (4.35%)
# events				
Diarrhoea †				
# participants affected/at risk	2/24 (8.33%)	0/23 (0%)	1/24 (4.17%)	0/23 (0%)
# events				
Nausea †				
# participants affected/at risk	0/24 (0%)	2/23 (8.7%)	0/24 (0%)	0/23 (0%)
# events				
Infections and infestations				
Dizziness †				
# participants affected/at risk	2/24 (8.33%)	1/23 (4.35%)	0/24 (0%)	0/23 (0%)
# events				
Rhinitis †				

	d-IBS Placebo	d-IBS Alosetron	Healthy Volunteers Placebo	Healthy Volunteers Alosetron
# participants affected/at risk	2/24 (8.33%)	3/23 (13.04%)	3/24 (12.5%)	2/23 (8.7%)
# events				
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain †				
# participants affected/at risk	0/24 (0%)	0/23 (0%)	2/24 (8.33%)	1/23 (4.35%)
# events				
Nervous system disorders				
Headache †				
# participants affected/at risk	2/24 (8.33%)	0/23 (0%)	3/24 (12.5%)	3/23 (13.04%)
# events				
Skin and subcutaneous tissue disorders				
Pruritus †				
# participants affected/at risk	2/24 (8.33%)	0/23 (0%)	0/24 (0%)	0/23 (0%)
# events				

† Indicates events were collected by systematic assessment.

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

GSK agreements may vary with individual investigators, but will not prohibit any investigator from publishing. GSK supports the publication of results from all centers of a multi-center trial but requests that reports based on single-site data not precede the primary publication of the entire clinical trial.

Limitations and Caveats:

Results Point of Contact:

Name/Official Title: GSK Response center
Organization: GlaxoSmithKline
Phone: 866-435-7343
Email: