Synopsis

Identifier: RM2008/00001/00 **Study Number:** B3I105940

Title:

A Randomized, Double-Blind, Placebo-Controlled, Crossover, Phase IIa Study to Evaluate Efficacy and Safety of the 3-Adrenergic Receptor Agonist Solabegron (GW427353) in Subjects with Irritable Bowel Syndrome

Investigators:

Investigator	Site Number	Hospital/ Institution and Address
Germany		
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
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[redacted]	[redacted]	[redacted] Germany
Australia		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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Study centers:

18 centers in 3 countries (7 centers in Germany, 6 centers in Australia, 5 centers in France)

Publications:

None at the time of this report

Study period:

Initiation Date: 21 AUG 2006

Completion Date: 14 JUN 2007

Phase of development: IIa

Primary Objective:

The primary objective was to determine whether solabegron provided adequate relief of IBS pain or discomfort compared to placebo.

Secondary Objectives are listed below:

1. Determine the safety and tolerability in IBS subjects.
2. Evaluate for positive treatment effects within bowel subgroups for secondary symptoms:
    - Urgency
    - Stool frequency
    - Stool consistency
    - Bloating (encompasses abdominal fullness or swelling)
    - A sensation of incomplete evacuation
    - Straining during a bowel movement.
3. Compare treatment groups for global improvement of IBS symptoms.
4. Compare treatment groups for global improvement of IBS pain or discomfort.
5. Compare treatment groups for changes in IBS-related quality of life.
6. Compare treatment groups for changes in bowel pattern.
7. To describe the exposure of both solabegron and its primary active metabolite (GW678953X) after 6 weeks of dosing in subjects with IBS.
8. To explore the relationship between exposure (AUC) of solabegron and its primary active metabolite (GW678953X) with clinical response/safety in subjects with IBS.

Methodology:

The study was a 26-week, multi-centre (Germany, France, Australia), randomized double-blind, placebo-controlled, two-period crossover study comparing oral placebo and solabegron (200 mg twice daily) for 6 weeks in IBS patients. A population of 102 adults with IBS participated in the study; males (29%) and females (71%). Patients and investigators were blinded to medication changes across treatment and washout periods. Subjects recorded weekly self-assessments of adequate relief of IBS pain and discomfort

(yes/no), daily self-assessments of IBS pain and discomfort (5-point verbal and 11-point numerical rating scales), lower GI symptoms; and a weekly global improvement scale (GIS) of symptoms via a dial-in interactive voice response system (IVRS). The safety and tolerability of solabegron compared to placebo was also assessed by adverse event reports, clinical laboratories, vital signs, and ECGs.

IBS symptoms were evaluated based on pain severity, percentage of pain-free days, bowel function symptoms, ratings on the Global Improvement Scale (GIS) and on the IBS Quality of Life (IBSQoL) questionnaire. Key results were reported by gender and age (<45, ≥45), IBS bowel habit subtype (frequency and stool consistency), and baseline pain parameters.

PK parameters for determination of GW427353 and active metabolite concentrations were assessed by blood samples taken at study visit Week 1 and 13.

Number of subjects:

A population of 102 adult males (29%) and females (71%) with IBS but otherwise healthy participated in the study. Subject disposition and demographics are provided in the following table.

Subject Disposition and Demographics:

Number of Subjects	
Subjects planned, N:	100
Subjects randomized, N:	102
Subjects included in safety population, n:	102
Subjects included in PK population, n:	98
Subjects included in ITT population	99
Subjects completed as planned, n (%):	69 (68)
Subjects withdrawn (any reason), n (%):	33 (32)
Subjects withdrawn for SAE, n (%):	0
Subjects withdrawn for AE, n (%):	9 (9)
Reasons for subject withdrawal, n (%)	
Lost to follow-up	3 (3)
Protocol violation	6 (6)
Subject decided to withdraw	12 (12)
Other	3 (3)
Demographics	
Age in Years, Mean (Range)	46.8 (23-65)
Sex, n (%)	
Female:	72 (71)
Male:	30 (29)
BMI, Mean (Range)	26.36 (17.29-47.88)

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Subject Disposition and Demographics (Continued)

Height, Mean (Range)	167.8 (147-190)
Weight kg, Mean (Range)	74.61 (38.9-140.0)
Ethnicity, n (%)	
Hispanic or Latino:	0
Not Hispanic or Latino:	102 (100)
Race, n (%)	
Asian – Japanese/East Asian Heritage/South East Asian Heritage	1 (<1)
White	101 (>99)

Diagnosis and main criteria for inclusion:

Otherwise healthy ambulatory adult subjects (male or female) age >18 and < 65 years with a diagnoses of IBS consistent with the Rome II Criteria were eligible to participate. Written informed consent was obtained, and no other medical or protocol-specified disqualification noted.

Treatment administration:

All subjects were blinded to all switches in study medication throughout the study. Subjects were randomized to receive one of the 2 treatment sequences, in a 1:1 ratio.

AXBY: Solabegron (6 weeks), Placebo (6 weeks), Placebo (6 weeks), Placebo (6 weeks) or

BXAY: Placebo (6 weeks), Placebo (6 weeks), Solabegron (6 weeks), Placebo (6 weeks)

Criteria for evaluation:

Primary

Average adequate relief rate during the last 4 weeks of the treatment periods (Week 3 to 6 in Period 1 and Week 15-18 in Period 2)

Secondary

1. Adverse events grouped by body system.
2. Blood pressure, heart rate, and 12 – lead ECGs
3. Changes in laboratory values
4. Changes in weekly adequate relief rates during the treatment periods (Week 1 to 6. in Period 1 and Week 13-18 in Period 2).
5. The proportion of subjects with adequate relief of IBS pain and discomfort on all 4 of the last 4 weeks of the treatment phase treatment periods 1 and 2.
6. Ratings on the Global Improvement Scale (GIS).

7. Ratings on IBSQoL
8. Improvements in pain or discomfort and changes in pain severity scores and percentages of pain-free days.
9. Improvements in bowel function and changes in individual bowel symptoms.
    - Urgency
    - Stool frequency
    - Stool consistency
    - Bloating (encompasses abdominal fullness or swelling)
    - A sensation of incomplete evacuation
    - Straining during a bowel movement
10. Population PK parameters, such as oral clearance (CL) and oral volume of distribution (V) of solabegron and apparent CL and V of its primary active metabolite (GW678953X). Dependant upon the final compartmental model describing solabegron and the primary active metabolite (GW678953X) disposition, additional PK parameters may also be estimated.
11. Correlations between the PK of solabegron and its primary active metabolite (GW678953X) and relevant safety and efficacy endpoints.

Statistical methods:

This study was powered at 90% to detect a difference of 15% between solabegron 200mg and placebo, in the average rate of adequate relief of IBS pain or discomfort during the last 4 weeks of treatment (weeks 3-6 in period 1 and weeks 15-18 in period 2). A 40% response rate for placebo and a 55% response rate for GW427353 200 mg BID was assumed at the two-sided α=0.05 level, assuming a standard deviation of 36 as observed in a previous IBS study.

The primary efficacy endpoint, the average rate of adequate relief of IBS pain and discomfort over the last 4 weeks of treatment (Week 3-6 in Period 1 and Week 15-18 in Period 2) was compared between solabegron 200mg and placebo using analysis of variance (ANOVA). The model fitted sequence, period and regimen as fixed effects and subject within sequence as a random effect. The residual variance from the model was used to calculate 95% confidence intervals for the comparison between treatment groups.

In addition to the standard descriptive statistics (n, arithmetic mean, standard deviation, minimum, median and maximum) by regimen, the average rate of adequate relief of IBS pain and discomfort over the last 4 weeks of treatment (Week 3-6 in Period 1 and Week 15-18 in Period 2) was summarised by sequence and regimen to further investigate the crossover design utilised in this study.

The analyses indicated that the crossover design utilized in this study was not valid. One assumption of this design is that the investigated disease is stable over the study period, and hence will have similar baseline characteristics for each period. This key assumption was not validated in this study. The average pain severity based on the 5-point pain scale, notably decreased between baseline and the end of the first placebo washout (mean of weeks 9-12). Nearly half (48%) of the subjects would not have qualified for inclusion into the study based on their pain scores after the first placebo washout. Therefore as the key crossover design assumption was violated, the Period 1 only analyses provided the primary inference in this study as pre-specified in the analysis plan. A similar ANOVA model to that outlined above was therefore used for the period 1 only analysis.

Summary:

Safety:

Common Adverse Events

An overall summary of the most common adverse events occurring in ≥3 or more subjects in any treatment group starting on-treatment is provided in the table below. A larger number of subjects receiving solabegron (51%) than placebo (41%) reported AEs. The most frequently reported AEs were nasopharyngitis, headache, nausea, and gastroenteritis reported by 11%, 9%, 6% and 6% of the subjects receiving solabegron and 4%, 3%, 2%, and 1% of the subjects receiving placebo, respectively.

Overall Summary of the Most Common Adverse Events Occurring in ≥ 3 Subjects in any Treatment Group Starting On-Treatment

Event	Solabegron 200mg N=87	PBO bd N=93	PBO bd - X Washout 1 N=80	PBO bd - Y Washout 2 N=72
	n (%)	n (%)	n (%)	n (%)
Any event	44 (51)	38 (41)	16 (20)	17 (24)
Nasopharyngitis	10 (11)	4 (4)	1 (1)	2 (3)
Headache	8 (9)	3 (3)	2 (3)	3 (4)
Nausea	5 (6)	2 (2)	0	1 (1)
Gastroenteritis	5 (6)	1(1)	0	1 (1)
IBS	4 (5)	1 (1)	1 (1)	2 (3)
Abdominal pain	1 (1)	4 (4)	0	0
Abdominal pain upper	1 (1)	2 (2)	0	1 (1)
Abdominal distension	0	1 (1)	2 (3)	0
Contusion	3 (3)	0	1 (1)	0
Cough	4 (5)	0	0	0
Diarrhoea	3 (3)	1 (1)	0	0

Common Adverse Events by Age

Adverse events were evaluated by 2 age categories (<45 age group and ≥ 45 age group). In general, the frequency and nature of AEs between the 2 age groups while receiving solabegron was similar. However, headache was reported more frequently in the ≥ 45 age than the <45 age group (12% vs. 6%). A summary of the overall frequency of AEs by age group is provided below.

Age Group	Solabegron N=87 n/N (%)	PBO bd N=93 n/N (%)	PBO – X Washout 1 N=80 n/N (%)	PBO - Y Washout 2 N=72 n/N (%)
<45	19/35 (54)	15/41 (37)	6/33 (18)	6/29 (21)
≥45	25/52 (48)	23/52 (44)	10/47 (21)	11/43 (26)

Common Adverse Events by Gender

Adverse events were evaluated by gender. Overall females (56%) receiving solabegron reported more AEs than males (38%). In particular, there were more reports of nasopharyngitis (14% vs. 4%) and headache (11% vs. 4%) in females than males. A summary of the overall frequency of AEs by gender is provided below.

Gender	Solabegron 200mg N=87	PBO bd N=93	PBO - X Washout 1 N=80	PBO - Y Washout 2 N=72
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
F	35/63 (56)	27/67 (40)	10/60 (17)	15/57 (26)
M	9/24 (38)	11/26 (42)	6/20 (30)	2/15 (13)

Drug-Related Adverse Events

An overall summary of all drug-related AEs reported by ≥2 or more subjects in any treatment group on treatment is provided in the table below. Approximately 39% (45/115) of the reported AEs were considered drug-related. The number of drug-related AEs events was similar between the solabegron and placebo treatment periods. Of note was the higher number of headaches (5%) reported during solabegron administration than placebo (0%) and the lack of any reports of dizziness or fatigue during solabegron administration compared to 2% each during the placebo treatment period.

Overall Summary of Drug-Related Adverse Events in ≥3 Subjects in any Treatment Group Starting On-Treatment

Event	Solabgron 200mg N=87	PBO bd N=93	PBO - X Washout 1 N=80	PBO - Y Washout 2 N=72
	n (%)	n (%)	n (%)	n (%)
Any event	12 (14)	16 (17)	7 (9)	3 (4)
Irritable bowel syndrome	3 (3)	1 (1)	1 (1)	2 (3)
Nausea	3 (3)	1 (1)	0	1 (1)
Headache	4 (5)	0	0	0
Abdominal distension	0	1 (1)	2 (3)	0

Fatal Events

No subjects died during the conduct of this study.

Non-Fatal Serious Adverse Events

There were 5 non-fatal SAEs (ankle fracture, incisional hernia, infective gastroenteritis, severe endosalpingiosis, and cholecystitis) reported during the conduct of the study and four were reported on solabegron. None of the SAEs were considered drug-related. There was one pregnancy on-study, with normal delivery noted at follow-up.

Efficacy:

Protocol Specified Primary Objective

The primary objective of this study was to determine whether solabegron provided adequate relief of IBS pain or discomfort compared to placebo. The primary efficacy endpoint was calculated by determining the average adequate relief rate of IBS pain and discomfort during Week 3-6 (Period 1) and Week 15-18 (Period 2) of treatment using the last observation carried forward (LOCF) approach for missing data.

The point estimate provides the best estimate of the true difference between regimens and the 95% confidence interval provides a credible range in which the true difference is likely to be contained. The analysis was based on the ITT population (N=99).

As noted in the table below for the primary comparison there was a difference of 3% between solabegron and placebo in the average adequate relief rate during the last 4 weeks of the treatment periods. This difference was not statistically significant. It had been anticipated that at least a 15% difference would be observed.

Point Estimates (95% CI's) for the Average Adequate Relief Rate during the Last 4 Weeks of the Treatment Periods Week 3-6 (Period 1), Week 15-18 (Period 2) (LOCF) (ITT Population)

ITT Population	GW427353 Mean	Placebo Mean	Difference (95% CI)
Primary comparison (LOCF): Solabegron 200mg - Placebo	0.43	0.40	0.03 (-0.07, 0.12)

Failure of key assumptions of the crossover design

One of the key assumptions of a crossover design is for the investigated disease to be stable in nature, and hence have similar baseline characteristics for each period. As outlined in the table below, the average baseline pain severity based on the 5-point pain scale, decreased between baseline and the end of the first placebo washout, violating this assumption.

Mean of the 5-Point Pain Scale at Baseline and at the End of the First Placebo Washout Period (ITT Population)

Sequence	AXBY	BXAY
Baseline (Mean: 2 weeks screening)	2.26	2.33
Placebo washout (Mean: weeks 9-12)	1.45	1.46

Furthermore, one of the inclusion criteria for the study was that 'during the two-week screening phase, the subject must have reported an average IBS pain or discomfort score ≥ 1.5 (on a 5-point pain scale)'. As outlined in the table below, 48% of the patients at the end of the first placebo washout phase would not have qualified for inclusion into the study based on this pain criterion. The percentage of subjects with an average pain score <1.5 at the end of the first placebo washout was 61% and 35% for those who had received solabegron and placebo in period 1, respectively.

Percentages of Subjects Above and Below the 5-Point Pain Scale Inclusion Criteria at the End of the First Placebo Washout Phase (ITT Population)

Pain score	Total	AXBY	BXAY
<1.5	48%	61%	35%
≥ 1.5	52%	39%	65%

Due to a statistically significant by-treatment crossover period effect, additional pre-specified analyses were performed on the initial treatment period, comprising a randomized double-blind parallel comparison between solabegron (200 mg twice daily) (n=47) and placebo (n=52).

Pre-Defined Adequate Relief Rate Analyses During Treatment Period 1

As noted in the table below, there was a borderline statistically significant difference of 15% (last observation carried forward); and statistically significant differences between solabegron and placebo of 22% (observed cases) and 18% (missing=non responder) in the average adequate relief rate during the last 4 weeks of Period 1. These differences were considered clinically meaningful as a difference of at least a 15% had been anticipated.

Point Estimates and 95% CI's for the Average Adequate Relief Rate during the Last 4 Weeks of Treatment Period 1 (ITT Population)

Comparison	Analysis	GW427353 Mean	Placebo Mean	Difference (95% CI)
Solabegron 200mg – Placebo	LOCF	0.48	0.33	0.15 (-0.01, 0.31)
Solabegron 200mg – Placebo	Observed cases	0.50	0.28	0.22 (0.06, 0.39)
Solabegron 200mg - Placebo	M-NR	0.47	0.29	0.18 (0.03, 0.32)

Adequate Relief Rate during Treatment Period 1 by IBS-subtype

The adequate relief rate during Period 1, average over Weeks 3-6, for solabegron was compared to placebo for the total population by IBS Sub-type, based on stool frequency and stool consistency assessed during screening. For IBS Sub-type by Stool Frequency Constipation was defined as < 3 stools/week, Other-IBS as ≤ 3 stools/day - ≥ 3 stools/week, and Diarrhoea as > 3 stools/day. For IBS Sub-type by Stool Consistency was defined as average Bristol Stool Form Scale score during screening; ≤ 2 for Constipation, 2 - < 4 for Other-IBS, and ≥ 4 for Diarrhoea. For the Constipation-IBS subtype a higher rate of adequate relief was achieved in both the Stool Frequency analysis population (23%) and the Stool Consistency analysis population (22%), however given the small number of subjects (n=3) with the Constipation subtype no meaningful conclusions can be drawn. The Other-IBS subtype reported a higher rate of adequate relief in both the Stool Frequency (25%) and Stool Consistency population (17%). There was no difference between solabegron treatment and placebo for the IBS subtype of Diarrhoea.

Adequate Relief Rate during Treatment Period 1 by Gender

The table below summarizes the average adequate relief rate for treatment period 1 by gender. The analysis by gender showed a clinical benefit of solabegron only in female patients, with a difference from placebo in adequate relief rate of 23% (54% for solabegron vs. 31% for placebo, p=0.019). With only 30 male patients enrolled (29%) definitive conclusions on gender specificity of clinical benefit may be premature.

Point Estimates (95% CIs) for Average Adequate Relief Rate During Last Four Weeks of Treatment Period 1 for Total Population and by Gender (LOCF) (ITT Population)

ITT Population	GW427353 Mean	Placebo Mean	Difference (95% CI)
Total Solabegron 200mg - Placebo	0.48	0.33	0.15 (-0.01, 0.31)
Females Solabegron 200mg - Placebo	0.54	0.31	0.23 (0.04, 0.42)
Males Solabegron 200mg - Placebo	0.34	0.37	-0.02 (-0.32, 0.27)

Secondary Objectives

Adequate Relief of Pain and discomfort on all 4 of the last 4 weeks of Period 1

The proportion of subjects with adequate relief of IBS pain and discomfort on all 4 of the last 4 weeks during the treatment phase Period 1, average over Weeks 3-6, was compared between solabegron 200mg and placebo using logistic regression. The odds ratio of having adequate relief on IBS pain and discomfort on all 4 of the last 4 weeks was 2.24 for subjects receiving solabegron compared to subjects receiving placebo, this was not statistically significant.

Pain-free Days

The mean change from baseline in the percentage of pain and discomfort-free days for the total population in Period 1, average over Weeks 3-6 for subjects receiving solabegron was 21.9% compared to 12.9% for subjects receiving placebo. Similarly, for females the mean change from baseline for solabegron was 27.3% compared to 13.8% for placebo, whereas for males the mean changes from baseline were 10.6% and 10.7%, respectively. With only 30 male patients enrolled (29%) definitive conclusions on gender specificity of clinical benefit may be premature.

Pain Severity Scores

The mean 5-point pain severity score at baseline and change from baseline for Period 1, averaged over Weeks 3-6 for the total population and by gender indicated no difference in subgroups at baseline and no difference in change from baseline between subjects treated with solabegron vs. placebo. The percentage of subjects receiving solabegron at the end of the first placebo washout phase with an average 5-point pain score <1.5 was 61%, compared to 35% of the patients receiving placebo.

There was a significant decrease in the 11-Point pain scale in an exploratory analysis of female subjects during Period 1 ($p< 0.05$); with no significant changes in other sub-group analyses.

Individual Bowel Symptoms

No benefit was demonstrated with solabegron compared to placebo in change from baseline in Period 1 for the bowel symptoms of urgency, frequency, consistency, bloating, incomplete evacuation, and straining.

Global Improvement Scale of IBS Symptoms

There were no significant differences between solabegron and placebo during Period 1 in the proportion of subjects reporting global improvement in any individual symptom of IBS or in global improvement of overall IBS symptoms.

Normalization of Bowel Patterns

The change from baseline in the mean percentage of days for a normal bowel pattern during Period 1 was 24.2% for subjects treated with solabegron compared to 12.1% for placebo. Similarly, the mean percentage of days change in baseline for a normal bowel pattern was 20.5% and 26.0% for males and females, respectively, treated with solabegron compared to 11.1% and 12.6% for males and females, respectively, on placebo.

Health Outcomes Results from the IBS QoL Questionnaire

Results of the IBS 30 item quality of life patient self report questionnaire indicated that subjects receiving solabegron had greater improvements in quality of life (i.e., higher scores) than placebo in 7 out of the 9 domains. These seven domains consisted of emotional health, mental health, sleep, energy, food/diet, social, and role-physical. The sexual relations domain appeared to be equivalent between the two treatment groups and subjects receiving placebo had higher scores in the physical functioning domain compared to solabegron.

Conclusions:

- One of the key assumptions of a crossover design is for the investigated disease to be stable in nature, and hence have similar baseline characteristics for each period. The average baseline pain severity based on the 5-point pain scale, decreased between baseline and the end of the first placebo washout, violating this assumption and study conclusions are based on Period 1 only.
- For the primary objective of the study, adequate relief of IBS pain or discomfort compared to placebo, there was a borderline statistically significant difference of 15% (last observation carried forward); and statistically significant differences of 22% (observed cases) and 18% (missing=non responder) in the average adequate relief rate during the last 4 weeks of the treatment period.

- During the first six week treatment period (Period 1), a separation was evident between solabegron and placebo for the proportion of subjects with adequate relief at each week. The solabegron response decreases upon blinded switch to placebo at week 7; which was then maintained throughout the placebo washout phase, indicative of an active solabegron response during weeks 1-6.
- Analysis of gender showed a clinical benefit of solabegron only in female patients, with a difference from placebo in adequate relief rate of 23% (54% for solabegron vs 31% for placebo, p=0.019). Significantly more female patients on solabegron compared with those on placebo reported a >50% decrease on an 11-point pain score and an increase in % pain-free-days per week. With only 30 male patients enrolled (29%) definitive conclusions on gender specificity of clinical benefit may be premature.
- Solabegron effect on average adequate relief rate was confined to the 68 patients with alternating bowel symptoms (Other-IBS), avg. adequate relief rate of 60% for solabegron vs 35% for placebo (p=0.013).
- Solabegron was well-tolerated. The nature and frequency of AEs, drug-related AEs, and the maximum intensity levels of AEs, in the solabegron treatment group were marginally higher but similar to that seen in the placebo group. There were 4 non-fatal SAEs in the solabegron treatment group and 1 on placebo treatment; however, none were considered related to study drug. There were no deaths in the study.
- There were no overall clinically significant laboratory or vital signs findings (clinical laboratories, cuff blood pressure, or ECGs).

Date of Report:

July 2008