Synopsis

Identifier: ZM2006/00205/00 **Study Number:** B3P104833

Title: An Eight-Week Randomized, Double-Blind, Placebo-Controlled, Parallel Group Proof of Concept Study to Assess the Efficacy, Safety and Tolerability as well as the Pharmacokinetic Profile of oral Solabegron (GW427353) 125 mg and 50 mg Administered Twice Daily vs. Placebo in Women with Overactive Bladder

Investigator(s): Multicenter study

Study center(s): 54 centers in 14 countries randomized subjects for this study.

Publication(s): There were no publications at the time of this report

Study Period: 18May2006 to 15Feb2007 **Phase of Development:** IIA

Objectives:

Primary:. To compare the efficacy of solabegron 125 mg and 50 mg, administered twice daily, to that of placebo in female subjects with OAB including symptoms of urgency with urge incontinence and frequency which may be associated with nocturia, but without bladder related pain.

Secondary: To evaluate the safety and tolerability of solabegron 125 mg and 50 mg administered twice daily, compared with that of placebo in female subjects with OAB including symptoms of urgency with urge incontinence and frequency which may be associated with nocturia, but without bladder-related pain.

To characterize the pharmacokinetic relationship of solabegron and its primary metabolite (GW678953X) in female subjects with OAB including symptoms of urgency with urge incontinence and frequency which may be associated with nocturia, but without bladder-related pain.

Methodology: This was a double-blind, randomized, placebo-controlled, parallel group, multicenter study. Subjects entered a one or two week treatment free run-in period depending on OAB medication status. Eligible subjects were randomized and treated for a period of 8 weeks during which they received solabegron 125 mg or 50 mg twice daily or matching placebo. Subjects returned for a follow-up assessment one week after completing treatment; therefore, total time in the study was approximately 11 weeks.

Number of subjects:

Number of Subjects Planned, N=240	Placebo	Solabegron 50mg	Solabegron 125mg
Randomised, N	85	88	85
Completed, n (%)	79 (93%)	72 (82%)	72 (85%)
Total number subjects withdrawn, n (%)	6 (7%)	16 (18%)	13 (15%)
Withdrawn due to adverse events n (%)	1 (1%)	10 (11%)	5 (6%)
Withdrawn due to lack of efficacy n (%)	0	0	0
Withdrawn for other reasons n (%)	5 (6%)	6 (6%)	8 (9%)

Diagnosis and main criteria for inclusion: Female subjects (≥18 and ≤80 years of age) with OAB symptoms as recorded during the three days prior to randomization including: mean of ≥8 micturitions/24 h; mean of ≥1 incontinence episode/24 h; mean of ≥1 urgency episode/24 h; mean volume voided of ≤250 mL/micturition and mean total urine volume of ≤3000 mL/24 h were eligible for the study.

Treatment administration: Study treatment was supplied as solabegron 25 mg and 100 mg white tablets with matching placebo. Batch numbers were: 051113074 (placebo), 061114642, 061114646 (solabegron 25 mg), and 061114640 (solabegron 100 mg).

Criteria for evaluation: An electronic diary was used to record OAB symptoms over a three day period prior to the Day 0, Week 4 and Week 8 visits. The primary efficacy measure was percentage change from Baseline to Week 8 in the number of incontinence episodes over 24 h. Other efficacy measures included the percent change from Baseline to Week 4 in the number of incontinence episodes over 24 h as well as the percent change and actual change from Baseline to Week 4 and Week 8 in the following: number of incontinence episodes, urge incontinence episodes, micturitions, urgency episodes, nocturia episodes, nocturnal voids, volume of urine voided per micturition, and the maximum volume voided per micturition. Changes from Baseline to Week 4 and Week 8 in the severity of urgency episodes, improvement in OAB symptoms and subject's responses to the Overactive Bladder Questionnaire (OABq) and Patient's Perception of Bladder Condition (PPBC) were also assessed. Safety evaluations included adverse events (AEs), hematology, clinical chemistry, urinalysis, electrocardiograms (ECGs), cuff blood pressure (BP) measurements and ambulatory BP monitoring (ABPM), as well as measurements of post-void residual urinary volume (PVR).

Statistical methods: Two hundred fifty-eight subjects were randomized to yield the estimated 192 evaluable subjects (64 per treatment arm) needed for 80% power assuming a treatment difference of 27% between solabegron and placebo and a standard deviation of 54% for the primary endpoint. The Intent-to-Treat (ITT) population (all subjects randomized to study treatment) was the primary population for all analyses. Due to ≥20% of the ITT population having major protocol violations, selected analyses were performed using the Per Protocol (PP) population (subjects in the ITT population without major protocol violations). The primary endpoint of this study was the percentage change from Baseline to Week 8 in the number of incontinence episodes per 24 h. Subjects who got worse by more than 100% were censored at 100% worsening. The last

available post-Baseline assessment on, or before Week 8 was used in the calculation. Treatment groups were compared in terms of the censored data of percentage change from Baseline to Week 8 in the number of incontinence episodes per 24 h using an Unpaired Student's t-test from a general linear model with effects for treatment group, number of incontinence episodes per 24 h at Baseline, and pooled center. For the primary endpoint, results for the solabegron 125 mg treatment group were compared with those for the placebo treatment group at the two-sided 5% level. If the p-value was not significant at the 5% level, rigorous testing would have stopped. Since the p-value was significant at the 5% level, results for the solabegron 50 mg treatment group were compared with placebo at the two-sided 5% level. This sequential testing procedure preserved the family-wise error rate at 5% by conforming to the principles of closed testing procedures.

Summary:

Efficacy: There was a statistically significant difference in percent change from Baseline to Week 8 (and Week 4) in incontinence episodes over 24 h for the solabegron 125 mg treatment group compared with the placebo treatment group.

Percent Change from Baseline in Incontinence Episodes per 24 h (LOCF, ITT Population)

	Placebo	Solabegron	
LOCF, Censored Data	N=85	50mg N=88	125mg N=85
Week 8 (Primary Endpoint)			
n	81	75	75
Baseline mean	4.4	5.1	4.6
Week 8 mean % change (SD)	-52.9 (49.02)	-54.7 (41.11)	-65.5 (34.21)
Week 8 adjusted mean % change (SE)	-51.8 (4.59)	-54.7 (4.80)	-64.9 (4.79)
Adjusted mean difference (%) from Placebo	--	-2.9	-13.1
95% CI	--	[-15.9, 10.1]	[-26.1, -0.1]
p-value	--	0.66	0.048
Week 4 (Secondary Endpoint)			
n	81	75	74
Baseline mean	4.4	5.1	4.5
Mean % change (SD)	-41.2 (50.81)	-53.4 (39.79)	-61.4 (30.42)
Adjusted mean % change (SE)	-39.8 (4.60)	-53.7 (4.81)	-60.4 (4.84)
Adjusted mean difference (%) from Placebo	--	-13.9	-20.6
95% CI	--	[-26.9, -0.8]	[-33.7, -7.5]
p-value	--	0.037	0.002

Statistically significant reductions from Baseline to Weeks 4 and 8 in the number of micturitions over 24 h were also observed for the solabegron 125 mg treatment group compared with the placebo treatment group. There was also a statistically significant increase from Baseline to Week 8 in volume voided for the solabegron 125 mg treatment group compared with the placebo treatment group. No statistically significant differences in the number of urgency episodes, nocturia episodes, or noturnal voids were demonstrated.

Pharmacogenetics: There was some evidence that subjects with the Trp64Arg polymorphism in the β_3 adrenergic receptor had an increase in response to solabegron as measured by incontinence and micturition; however, the small number of subjects and departure from the expected dose response pattern (effect was greatest in the 50 mg solabegron treatment group) limits further conclusions.

Safety: In general, the number of subjects experiencing at least one AE was comparable across the treatment groups. The most frequently reported AEs were headache and nasopharyngitis.

Common Post-Randomization Adverse Events (>=2% Incidence in Any Treatment Group) (ITT Population)

	Number (%) of Subjects		
Preferred Term	Placebo N=85	Solabegron 50mg N=88	Solabegron 125mg N=85
Subjects with an AE	35 (41%)	34 (39%)	32 (38%)
Headache	7 (8%)	7 (8%)	7 (8%)
Nasopharyngitis	9 (11%)	7 (8%)	5 (6%)
Dry mouth	3 (4%)	5 (6%)	1 (1%)
Constipation	4 (5%)	3 (3%)	1 (1%)
Diarrhoea	2 (2%)	2 (2%)	3 (4%)
Nausea	3 (4%)	1 (1%)	3 (4%)
Urinary tract infection	1 (1%)	4 (5%)	2 (2%)
Abdominal pain	2 (2%)	1 (1%)	2 (2%)
Fatigue	2 (2%)	3 (3%)	0
Hypertension	0	2 (2%)	3 (4%)
Somnolence	0	4 (5%)	1 (1%)
Abdominal pain upper	4 (5%)	0	0
Cystitis	1 (1%)	1 (1%)	2 (2%)
Dizziness	0	3 (3%)	1 (1%)
Pain in extremity	2 (2%)	1 (1%)	1 (1%)
Pharyngolaryngeal pain	1 (1%)	2 (2%)	1 (1%)
BP increased	1 (1%)	0	2 (2%)
Haematuria	3 (4%)	0	0
Insomnia	0	2 (2%)	1 (1%)
Hot flush	0	2 (2%)	1 (1%)
Abdominal distension	0	2 (2%)	0
Cough	0	2 (2%)	0
Flatulence	2 (2%)	0	0
Gastrointestinal pain	0	2 (2%)	0
Influenza	0	0	2 (2%)
Pyrexia	0	2 (2%)	0
Weight increased	0	2 (2%)	0
Musculoskeletal chest pain	0	0	2 (2%)

AEs leading to withdrawal were reported for 1 (1%), 10 (11%) and 5 (6%) subject(s) in the placebo, solabegron 50 mg and solabegron 125 mg groups, respectively. Two subjects in each solabegron treatment group withdrew as a result of hypertension-related AEs: 2 subjects in the solabegron 50 mg group (2 AEs of hypertension) and 2 in the solabegron 125 mg treatment group (1 AE of hypertension and 1 AE of increase in BP). Other AEs leading to withdrawal were each reported by only one subject each in the study.

Two SAEs were reported during the study (urosepsis and depression) both by subjects in the solabegron 50 mg treatment group. Neither SAE was considered related to study medication. One additional SAE of bladder cancer was reported after completion of the study for a subject in the placebo treatment group. No deaths were reported.

There were no changes of note in clinical chemistry or hematology values over time. There were no changes from Baseline in HbA1c. There were no noteworthy changes in ECG parameters or morphology. No subjects had PVR >250mL at any time during the study. Twenty percent of subjects in the solabegron 125 mg treatment group showed a ≥20 mmHg change from Baseline in cuff systolic BP, compared with 9% and 11% in the 50 mg and placebo treatment groups, respectively. Eleven percent and 15% of subjects showed a ≥15 mmHg change from Baseline in cuff diastolic BP in the solabegron 125 mg and 50 mg treatment groups, respectively, compared with 5% in the placebo treatment group. No changes in heart rate were noted between the placebo treatment group and the solabegron treatment groups. There were no significant treatment differences for mean changes from Baseline to Week 8 in ambulatory systolic BP, diastolic BP, mean arterial pressure and heart rate during the 24 h of measurement. However, more subjects in the 125 mg treatment group (24%) showed a mean increase of ≥6 mmHg change from Baseline to Week 8 in 24 h ambulatory systolic BP compared with subjects in the 50 mg (11%) and placebo (10%) treatment groups.

Conclusions:

- Over the eight-week treatment period, statistically significant improvements were seen for the solabegron 125 mg treatment group compared to the placebo treatment group in the percent change in incontinence episodes, change in micturitions and change in volume voided per micturition. There were no statistically significant differences between the solabegron treatment groups and the placebo group in the reduction of urgency episodes. However, slight numerical decreases from placebo were observed.
- Although a treatment difference from placebo of 27% in the primary endpoint was expected, a 13.1% difference was observed (p=0.048).
- Solabegron was well tolerated. Overall, AEs did not differ between the placebo and active treatment groups. However, more subjects in the solabegron treatment groups withdrew from the study due to an AE compared to the placebo treatment group. There were no changes of note in clinical chemistry, hematology or ECG parameters. Urinary retention was not observed.

- There were no significant treatment differences for mean changes from Baseline to Week 8 in ambulatory systolic BP, diastolic BP, mean arterial pressure or heart rate during the 24 h of measurement. However, more subjects in the 125 mg treatment group showed a mean increase of ≥6 mmHg from Baseline in 24 h ambulatory systolic BP compared to subjects in the placebo and 50 mg treatment groups.
- Subjects in the PGx population with the Trp64Arg polymorphism did not show a decrease in response to solabegron.

Date of Report: 20 Aug 2007