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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: UK-390,957

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NCT NO.: 00219635

PROTOCOL NO.: A3871029

PROTOCOL TITLE: A Phase 2 multicentre, double-blind, placebo-controlled, flexible dose study to assess the efficacy and safety of oral UK-390,957 in men with premature ejaculation

Study Center(s): Twenty-two (22) centers in the United States (14), Canada (4), Australia (2) and the United Kingdom (2)

Study Initiation and Completion Dates: 20 January 2005 to 28 July 2005

Phase of Development: Phase 2

Study Objective(s):
Primary: To investigate the safety and efficacy of the UK-390,957 individual flexible dose group (doses of 2.5, 5 and 10 mg) compared with placebo

Secondary: The comparison of responder rates (based on a ≥ 2-fold increase in intravaginal ejaculatory latency time [IELT] from baseline) between the flexible dose arm and placebo at Week 8; modeling the individual dose response and assessment of patient reported outcomes

Additionally, a diagnostic tool that was under development for assessing premature ejaculation (PE) was completed at screening as part of the validation process.

METHODS

Study Design: This was a multicenter, double-blind, placebo-controlled, flexible dose study in men with PE. Subjects received either UK-390,957 or placebo. Subjects participated in 4 visits for efficacy and safety: screening, baseline (randomization) and 2 other visits that occurred after 4 and 8 weeks (end of treatment, EOT). The screening visit was followed by a 4-week washout period. Subjects also had a follow-up visit either in the clinic or by telephone contact 7 days after the end of the study to assess any adverse events (AEs) that occurred following drug discontinuation.

Number of Subjects (Planned and Analyzed):
Planned: 131 subjects (46 subjects in the placebo group and 92 subjects in the UK-390,957 flexible dose group)

Analyzed: 138 subjects (40 subjects in the placebo group and 91 subjects in the UK-390,957 flexible dose group)

Diagnosis and Main Criteria for Inclusion: Subjects were males, aged 18 years or older, who met the DSM-IV-TR™ criteria for PE and had been in a stable, monogamous, heterosexual relationship for at least 6 months. Subjects had to be willing to engage in at least 4 attempts of sexual intercourse between clinic visits and, during the 4-week run-in period, had at least 4 intravaginal penetrations of which at least 70% showed an IELT of ≤ 2 minutes.

Study Treatment: Subjects received either UK-390,957 in a flexible dose regimen (2.5 mg, 5 mg or 10 mg) or placebo. Initially, subjects randomized to study drug received 5 mg of UK-390,957. Study drug was taken orally 1 to 3 hours prior to sexual intercourse, not more than once daily for a period of 8 weeks. At Week 4, dose adjustment was allowed to optimize efficacy and minimize AEs.

Efficacy Evaluations: Intravaginal ejaculatory latency time (the time from the first point of entry of the penis into the vagina until the point of ejaculation) was measured for each intercourse attempt from screening until EOT using an embedded timer in the electronic diary along with responses to Diary Sexual Event Questions. The Index of Premature Ejaculation (IPE) was completed at all visits except at follow-up. The Sexual Quality of Life (SQoL) Questionnaire was completed at screening, baseline and at the EOT or early discontinuation visit. The Global Efficacy Questions (GEQs) were completed at the EOT or early discontinuation visit. From these sources the following endpoints were derived:

- *Primary*: IELT
- *Secondary*: IPE Satisfaction, Control and Distress domains, Diary Sexual Event Questions 1 and 2, GEQ Questions 1 and 2 and the SQoL, sexual confidence scale (SCS) and sexual relationship scale (SRS) general standardized total scores

Safety Evaluations: Safety evaluations (clinical monitoring, physical examinations, AEs and safety laboratory tests) were carried out at screening and at the EOT or early discontinuation visit and at the follow up visit if required. Blood pressure and pulse rate were determined at every visit. Electrocardiograms (ECGs) were recorded at screening only.

Statistical Methods: The intent-to-treat (ITT) population consisted of all randomized subjects. The Per Protocol (PP) population was a subset of the ITT population that excluded subjects with major violations of the inclusion/exclusion criteria, subjects who discontinued prematurely, poor compliers and those who took prohibited medication during the study. The Safety Analysis Set consisted of all subjects who had taken at least 1 dose of study medication.

For the primary analysis, log transformed Week 8 IELT values (mean of Weeks 5 to 8) were analyzed using analysis of covariance (ANCOVA) comparing UK-390,957 flexible dose with placebo and containing terms for log baseline IELT, center and treatment. The mean difference between the flexible dose group and placebo was calculated along with the 95% confidence interval (CI) for this difference. This difference and the confidence interval were back transformed (exponentiated) to give a ratio on the untransformed scale. This analysis was conducted using the ITT population and incorporated last observation carried forward (LOCF) for missing values. The analysis was also repeated for the PP population.

Secondary endpoints analyzed at Week 8 using ANCOVA were IPE, Diary Sexual Event Questions and SQoL assessments. These ANCOVA models included terms for baseline, center and treatment except for Diary Sexual Event Questions where the model included terms for center and treatment only. The GEQs were analyzed using logistic regression with model terms for center and treatment. All these secondary analyses were carried out using the ITT and PP population. Anchor based and distribution based methods were used to calculate the Minimally Important Difference (MID) for IELT and IPE (Satisfaction and Control domains) at Week 8.

RESULTS

Subject Disposition and Demography: A summary of subject disposition is presented in Table S1.

Table S1 Subject Disposition

Number of Subjects (%)	UK-390,957 Flexible Dose n (%)	Placebo n (%)
Treated	91	40
Completed	75 (82.4)	39 (97.5)
Discontinued	16 (17.6)	1 (2.5)
Adverse event	1 (1.1)	0
Subject defaulted[1]	12 (13.2)	1 (2.5)
Other	3 (3.3)	0
Analyzed for efficacy		
ITT	91 (100)	40 (100)
PP	66 (72.5)	35 (87.5)
Analyzed for safety		
Adverse events	91 (100)	40 (100)
Laboratory data	76 (83.5)	37 (92.5)

[1]Includes subjects lost to follow up and subjects no longer willing to continue in the study.

All subjects were males. Mean (SD) age was 42.1 (7.9) years, with a range of 27 to 62 years, in the UK-390,957 group and 42.9 (10.2) years, with a range of 19 to 66 years, in the placebo group. In both groups the majority of subjects (over 82%) were white. For both groups the mean duration of premature ejaculation was approximately 8.7 years with a range of 0 to approximately 45 years.

Efficacy Results:

Primary: The results for the primary efficacy endpoint, IELT, are presented in Table S2, below.

Table S2 Summary of IELT Data (Sec) (ITT Population)

Parameter	UK-390,957 Flexible Dose	Placebo
Baseline[1]	N = 90	N = 40
Mean (SD)	51.9 (30.7)	47.7 (28.0)
Geometric mean	41.3	40.7
Week 8	N = 81	N = 39
Mean (SD)	106 (115)	94.3 (145)
Geometric mean	64.9	56.2
Fold increase over baseline	1.6	1.4
Treatment difference[2] (95% CI)	0.16 (-0.20, 0.52)	
p-value	0.3900	
Fold increase over placebo[3] (95% CI)	1.17 (0.82, 1.68)	

[1]Baseline IELT is the average of the IELT values over the four-week run-in period.
[2]UK-390,957 minus placebo (N=80).
[3]UK-390,957 divided by placebo.

Secondary: The results of the secondary efficacy assessments are presented below. An assessment of the IELT data using the PP population is presented in Table S3.

Table S3 Summary of IELT Data (Sec) (PP Population)

Parameter	UK-390,957 Flexible Dose	Placebo
Baseline[1]	N = 66	N = 35
Mean (SD)	49.9 (29.6)	47.9 (29.3)
Geometric mean	38.9	40.3
Week 8	N = 65	N = 34
Mean (SD)	119 (124)	101 (155)
Geometric mean	76.0	58.0
Fold increase over baseline	1.9	1.4
Treatment difference[2] (95% CI)	0.36 (-0.03, 0.74)	
p-value	0.0697	
Fold increase over placebo[3] (95% CI)	1.43 (0.97, 2.11)	

[1]Baseline IELT is the average of the IELT values over the four-week run-in period.
[2]UK-390,957 minus placebo (N=64).
[3]UK-390,957 divided by placebo.

Summary statistics for the IPE Satisfaction, Control and Distress domains are summarized in Table S4, below.

Table S4 Subject IPE Standardized Domain Scores (ITT Population)

	UK-390,957 Flexible Dose	Placebo	Treatment Difference[1] Estimate (95% CI)		p-value
Satisfaction					
Baseline	N = 91	N = 40			
Mean (SD)	39.2 (24.7)	46.6 (24.0)			
Median	37.5	43.8			
Week 8	N = 83	N = 40			
Mean (SD)	53.2 (29.1)	50.2 (26.8)	8.47 (0.32, 16.6)[2]		0.0419
Median	62.5	56.3			
Control					
Baseline	N = 91	N = 40			
Mean (SD)	9.1 (12.9)	8.6 (12.9)			
Median	6.3	3.1			
Week 8	N = 83	N = 40			
Mean (SD)	29.7 (29.2)	14.8 (17.7)	14.5 (5.01, 24.0)[2]		0.0031
Median	18.8	6.3			
Distress					
Baseline	N = 91	N = 40			
Mean (SD)	28.0 (23.0)	36.6 (26.7)			
Median	25.0	37.5			
Week 8	N = 83	N = 40			
Mean (SD)	46.7 (28.4)	39.1 (28.1)	11.3 (1.33, 21.2)[2]		0.0266
Median	50.0	37.5			

[1]UK-390,957 minus placebo.
[2]Based on difference in adjusted means.

Summary statistics for the proportion of "satisfied" diary sexual events are summarized in Table S5.

Table S5 Proportion of "Satisfied" Events from Diary Sexual Event Questions (ITT Population)

	UK-390,957 Flexible Dose	Placebo	Treatment Difference[1] Estimate (95% CI)		p-value
Question 1[2]					
Week 8	N = 81	N = 39			
Mean (SD)	0.2 (0.32)	0.2 (0.26)	0.52 (0.01, 1.02)[3]		0.0437
Median	0.1	0.0			
Question 2[4]					
Week 8	N = 81	N = 39			
Mean (SD)	0.2 (0.32)	0.1 (0.25)	0.58 (0.07, 1.09)[2]		0.0263
Median	0.1	0.0			

[1]UK-390,957 minus placebo.
[2]Diary Question 1 was: "On this occasion, how satisfied were you with the effect of treatment on your sense of control over ejaculation?"
[3]Based on difference in adjusted means.
[4]Diary Question 2 was: "On this occasion, how satisfied were you with the effect of treatment on your time to ejaculation?"

Summaries of the statistical analysis at Week 8 for Global Efficacy Questions 1 and 2 are presented in S6.

Table S6 Statistical Analysis of GEQs Data (ITT Population)

Treatment	N	Positive response (%)	Treatment difference[1]	
			Odds ratio (95% CI)	p-value
Question [2]				
UK-390,957	47	48.9	2.28 (0.83, 6.22)	0.1086
Placebo	27	29.6		
Question 2[2]				
UK-390,957	47	78.7	1.56 (0.53, 4.60)	0.4219
Placebo	27	70.4		

[1]UK-390,957 minus placebo.
[2]These questions recorded the subject's overall perception of change in his ejaculatory function.

Results for SQoL-General, SCS and SRS standardized scores are presented in Table S7.

Table S7 SQoL-General, SCS and SRS Standardized Total Scores (ITT Population)

	UK-390,957 Flexible Dose	Placebo	Treatment Difference[1] Estimate (95% CI)		p-value
SQoL-General					
Baseline	N = 90	N = 39			
Mean (SD)	35.2 (23.6)	46.1 (24.7)			
Median	31.8	43.6			
Week 8	N = 35	N = 19			
Mean (SD)	51.2 (28.7)	64.2 (24.7)	-1.66 (-14.7, 11.4)[2]		0.7982
Median	54.5	65.5			
SCS					
Baseline	N = 90	N = 39			
Mean (SD)	40.4 (22.3)	48.3 (22.0)			
Median	40.0	50.0			
Week 8	N = 35	N = 19			
Mean (SD)	48.9 (25.8)	61.8 (18.1)	4.47 (-8.97, 17.9)[2]		0.5043
Median	43.3	63.3			
SRS					
Baseline	N = 90	N = 35			
Mean (SD)	61.8 (24.8)	71.6 (22.4)			
Median	64.0	72.0			
Week 8	N = 35	N = 19			
Mean (SD)	67.3 (25.5)	77.9 (23.7)	5.08 (-9.95, 20.1)[2]		0.4974
Median	64.0	84.0			

[1]UK-390,957 minus placebo.
[2]Based on difference in adjusted means.

A summary of the MID estimates is presented in Table S8, below.

Table S8 Summary of MID Estimates for Log Transformed ILET and the IPE Satisfaction and Control Domains (ITT Population)

Parameter	Anchor-based Approach	Distribution-based Approach	
	MID	Small Effect MID	Moderate Effect MID
ILET (log-transformed)	1.73 (95% CI: 1.31, 2.28)	1.15 to 1.24	1.42 to 1.70
IPE Satisfaction Domain	14.2 (95% CI: 7.1, 21.3)	3.33 to 4.91	8.33 to 12.3
IPE Control Domain	30.2 (95% CI: 23.0, 37.4)	2.54 to 4.81	6.35 to 12.0

Safety Results: An overall summary of AEs is presented in Table S9.

Table S9 Overall Summary of All Causality Adverse Events

Number of Subjects (%)	UK-390,957 Flexible Dose N = 91 n (%)	Placebo N = 40 n (%)
Number of Adverse Events	79	20
Subjects with:		
Adverse events	44 (48.4)	17 (42.5)
Serious adverse events	1 (1.1)	0
Discontinuations due to adverse events	1 (1.1)	0

A summary of all AEs reported by more than 2 subjects in any treatment group is presented in Table S10.

Table S10 Incidence of Adverse Events by Frequency (≥ 2 Subjects)

All Causality	UK-390,957 Flexible Dose N = 91 n (%)	Placebo N = 40 n (%)
Upper abdominal pain	2 (2.2)	1 (2.5)
Nausea	13 (14.3)	1 (2.5)
Upper respiratory tract infection	3 (3.3)	2 (5.0)
Pain in jaw	2 (2.2)	0
Dizziness	6 (6.6)	0
Headache	7 (7.7)	2 (5.0)
Somnolence	4 (4.4)	0
Sleep disorder	2 (2.2)	0
Ejaculation failure	2 (2.2)	0
Sinus congestion	2 (2.2)	1 (2.5)

There were no deaths during the study.

One subject in the UK-390,597 group reported 2 serious AEs (SAEs) during the study. This subject was hospitalized with a fractured right hallux and muscular strain of his lower back after an accidental fall. At the time of the event the subject was receiving study treatment at the 5 mg level.

One subject in the UK-390,597 group permanently discontinued treatment due to an emergent AE. This subject had a severe anxiety attack, which was not considered to be treatment-related. At the time of the event, the subject was receiving study treatment at the 5 mg level.

The median changes from baseline to last observation in any of the laboratory test parameters did not vary significantly among the treatment groups. There was no evidence of a relationship between study treatment and laboratory test parameters. The median changes from baseline to last observation for sitting systolic blood pressure were small. The median changes from baseline to last observation for sitting diastolic blood pressure were 0.00 for both treatment groups.

CONCLUSION(S):

The fold increase in log-transformed IELT for the UK-390,957 flexible dose group over placebo was 1.17 for the ITT population. Analysis of the Week 8 IELT values for the ITT population showed no statistically significant increases over placebo for the UK-390,957 group at the 5% level. For the PP population the estimate of the fold increase over placebo was greater (1.43) but not statistically significant at the 5% level.

For the following secondary endpoints the comparisons of UK-390,957 with placebo were statistically significant at the 5% level: the Satisfaction, Control and Distress domains of the IPE and the mean numbers of satisfied events from the Diary Sexual Event Questions 1 and 2.

UK-390,957 was well tolerated by subjects with premature ejaculation. One subject discontinued from the study due to a non-treatment-related AE. The most common all causality and treatment-related AEs after UK-390,957 were nausea, headache and dizziness. All treatment-related AEs were mild or moderate. Serious adverse events were reported by 1 subject during active treatment although they were not related to treatment. There were no relevant laboratory abnormalities.