PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.
For publications based on this study, see associated bibliography.

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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

NCT NO.: 00219583

PROTOCOL NO.: A3871027

PROTOCOL TITLE: A Phase 2b, Multi-Centre, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Assess the Efficacy and Safety of Oral UK-390,957 in Men With Premature Ejaculation.

Study Centers: There were 50 study centers in 14 countries.

Study Initiation and Completion Dates: 18 August 2004 to 03 June 2005

Phase of Development: Phase 2b

Study Objectives:

To define the dose response (including the least effective dose) and to evaluate the efficacy, safety and tolerability of four dosages of UK-390,957 versus placebo, when taken *prn* (as needed), no more frequently than once daily, 1 to 3 hours prior to sexual intercourse over a 12-week period, in adult men with premature ejaculation.

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled, dose-response study with a parallel group design. The study consisted of a 4-week run-in period, a 12-week treatment period, and a follow-up telephone contact at least 14 days after the end of treatment. For subjects with ongoing treatment-related adverse events at the end of treatment or with early discontinuation, a follow up visit was required 14 days later. Following the 4-week run-in period, subjects were stratified into one of two groups: those with an intravaginal ejaculatory latency time (IELT) ≤1 minute and those with an IELT >1 minute but ≤2 minutes, both on at least 70% of occasions. At the Baseline Visit (Visit 2), subjects who met the study entry criteria were randomized within the strata to receive placebo or UK-390,957 (1mg, 2.5mg, 5mg, or 10mg). Treatment Visits (Visit 3 and Visit 4) and an End of Treatment Visit (Visit 5) occurred 4, 8, and 12 weeks, respectively, after randomization.

Number of Subjects (Planned and Analyzed): In order to maintain a 1:1 ratio of the ≤1 minute and the >1 to ≤2 minutes IELT populations, a combined sample size of 64 subjects per treatment group was planned. Simulations were carried out to support the sample size determination, and as a result, it was decided to randomize 92 subjects per treatment group, and to aim for at least 64 completers per treatment group (ie, a total of 460 randomized subjects). In total, 476 subjects were randomized to study treatment.

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

Study Treatment: Study drug was presented as tablets of 1mg (size 8 mm), 2.5mg (6 mm), 5mg (8 mm) and 10mg (10 mm) UK-390,957. Matching placebo tablets of corresponding size were provided. Each dose was comprised of three tablets, to maintain the blind, as follows:

UK-390,957 1mg:	One UK-390,957 1mg tablet, one 6mm placebo tablet and one 10mm placebo tablet
UK-390,957 2.5mg:	One UK-390,957 2.5mg tablet, one 8mm placebo tablet, and one 10mm placebo tablet
UK-390,957 5mg:	One UK-390,957 5mg tablet, one 6mm placebo tablet, and one 10mm placebo tablet
UK-390,957 10mg:	One UK-390,957 10mg tablet, one 6mm placebo tablet, and one 8mm placebo tablet
Placebo:	One 6mm placebo tablet, one 8mm placebo tablet, and one 10mm placebo tablet

Study drug was taken orally with a glass of water between 1 and 3 hours prior to anticipated sexual intercourse. Study drug was taken as required (*prn*) but not more than once daily for a period of 12 weeks. A maximum number of 84 doses were taken.

Efficacy Evaluations: IELT was measured by an embedded timer in the Electronic Diary from screening to the end of treatment along with responses to Diary Sexual Event Questions. In the final 4 weeks of treatment, IELT was measured only in the ≤1 minute stratum. Index of Premature Ejaculation (IPE) was completed at all visits except at follow up. Sexual Quality of Life (SQoL) questionnaire was completed at the Screening Visit, Baseline Visit, Visit 4 and End of Treatment or Early Discontinuation Visit. The Global Efficacy Questions (GEQs) were completed at Visit 4 and End of Treatment or Early Discontinuation Visit.

Pharmacokinetic Evaluations: Four pharmacokinetic blood samples were collected (two samples post dose at Visits 3 and 4) for a population pharmacokinetic analysis.

Safety Evaluations: Physical examinations, sitting vital signs, supine ECGs and clinical laboratory tests were performed at screening and at various intervals throughout the study. Adverse events (AEs) were recorded at all visits from the Baseline Visit (Visit 2). A non-anonymized genotyping blood sample was collected at screening.

Statistical Methods: The primary efficacy analysis was to calculate the Lowest Effective Dose (LED). The isotonic regression mean estimates were calculated from the raw treatment means for the log-transformed Week 8 change from baseline IELT values using the Min-Max algorithm. A linear response between the mean estimates of the adjacent doses was assumed to produce the estimated dose response curve. The LED was calculated as the UK-390,957 dose that gave a 1.5 fold improvement over placebo (equivalent to a 0.405 difference between UK-390,957 and placebo on the log scale). Log-transformed Week 8 IELT values were analysed using analysis of covariance (ANCOVA) to compare UK-390,957 doses with placebo. Four sensitivity analyses, to explore the impact of electronic diary date and time errors on the intent-to-treat (ITT) analysis, were also conducted.

Other secondary analyses using ANCOVA were Diary Sexual Event Questions, IPE and SQoL assessments, all at Weeks 8 and 12.

Adverse event, laboratory and other safety data were clinically reviewed, listed and summarized.

RESULTS

Subject Disposition and Demography: Subject disposition for the 2 strata are summarized in Table S1 and Table S2.

Table S1. Subject Disposition for the ≤2 minute stratum

	UK-390,957				Placebo
Number (%) of Subjects:	**1mg**	**2.5mg**	**5mg**	**10mg**	
Treated	96	96	94	96	94
Completed	77 (80.2)	75 (78.1)	70 (74.5)	77 (80.2)	73 (77.7)
Discontinued	19 (19.8)	21 (21.9)	24 (25.5)	19 (19.8)	21 (22.3)
Analysed for Efficacy					
Intent-to-treat	96 (100)	96 (100)	94 (100)	96 (100)	94 (100)
Per Protocol	59 (61.5)	61 (63.5)	60 (63.8)	68 (70.8)	58 (61.7)
Analysed for Safety					
Adverse Events	96 (100)	96 (100)	94 (100)	96 (100)	94 (100)
Laboratory Data	82 (85.4)	80 (83.3)	82 (87.2)	80 (83.3)	80 (85.1)
Vital signs	91 (94.8)	86 (89.6)	89 (94.7)	93 (96.9)	87 (92.6)
ECG	91 (94.8)	84 (87.5)	86 (91.5)	90 (93.8)	86 (91.5)

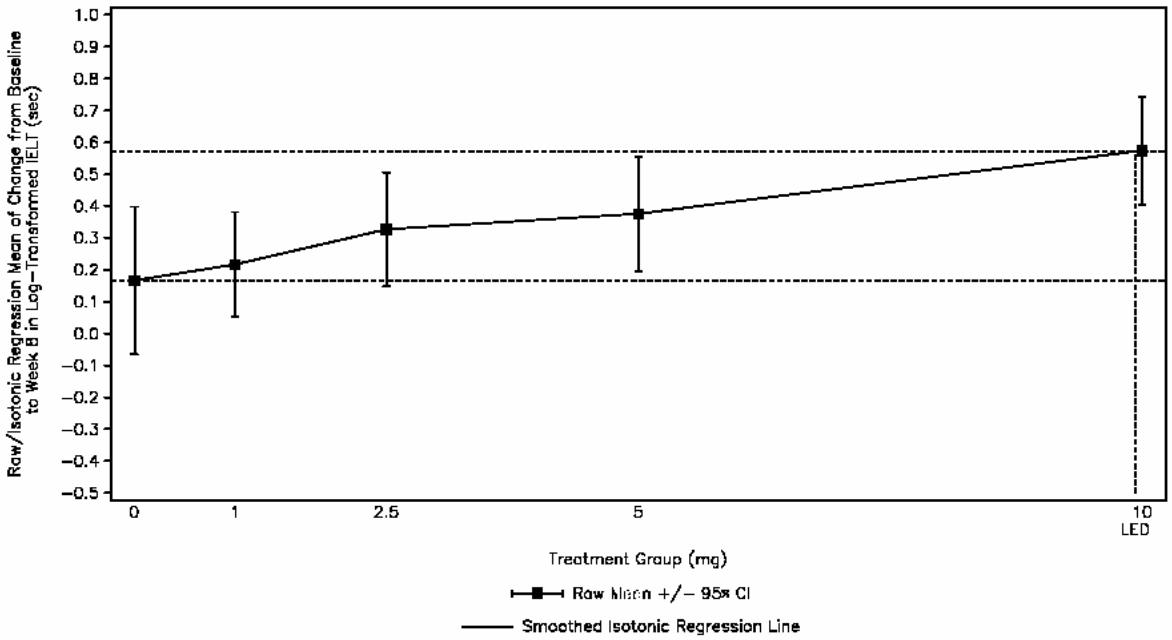
Table S2. Subject disposition for the ≤1 minute stratum

	UK-390,957				Placebo
Number (%) of Subjects:	**1mg**	**2.5mg**	**5mg**	**10mg**	
Treated	53	50	46	54	49
Completed	42 (79.2)	37 (74.0)	36 (78.3)	46 (85.2)	36 (73.5)
Discontinued	11 (20.8)	13 (26.0)	10 (21.7)	8 (14.8)	13 (26.5)
Analysed for Efficacy					
Intent-to-treat	53 (100)	50 (100)	46 (100)	54 (100)	49 (100)
Per Protocol	35 (66.0)	33 (66.0)	35 (76.1)	44 (81.5)	32 (65.3)
Analysed for Safety					
Adverse Events	53 (100)	50 (100)	46 (100)	54 (100)	49 (100)
Laboratory Data	44 (83.0)	42 (84.0)	42 (91.3)	47 (87.0)	39 (79.6)
Vital signs	50 (94.3)	44 (88.0)	43 (93.5)	52 (96.3)	44 (89.8)
ECG	50 (94.3)	44 (88.0)	42 (91.3)	50 (92.6)	44 (89.8)

Demographics and baseline characteristics were similar for all treatment groups. All subjects were male, the majority were caucasian (94%), and at entry ranged in age from 19 to 73 years. All subjects had a primary diagnosis of premature ejaculation, with the mean duration since first diagnosis ranging from approximately 6 to 8 years.

Efficacy Results: Primary efficacy endpoint IELT at Week 8 in the ITT population. For the ≤2 minute stratum, all treatment groups showed a prolongation of mean IELT at Week 8 from baseline. The dose-response curve is shown in Figure S1. The LED was estimated at 9.93mg. No LED was found in the PP population. LEDs, as determined by the four sensitivity analyses, ranged from 7.8mg to 6.0mg.

Figure S1 Dose Response Curve of IELT at Week 8 – ITT



No confidence interval was calculable as the LED for at least one jackknife sample was not found.
The LED for IELT was defined as the dose that produced a 1.5 fold increase over double-blind placebo; this is equivalent to an increase over double-blind placebo of 0.405 on the log scale. The dashed horizontal lines indicate the placebo response and the increase over placebo.

Mean IELT in the UK-390,957 10mg group was statistically significantly longer at Week 8 compared with placebo (Table S3). In the PP population, the longest mean IELT also occurred in the UK-390,957 10mg group; however, the difference was not statistically significant compared with placebo.

Table S3. Statistical analysis of log-transformed IELT (sec) at Week 8 – ITT

Treatment	n	Treatment difference** (95% CI)	p-value	Fold increase over Placebo (95% CI)
UK-390,957 1mg	87	0.05 (-0.21, 0.31)	0.6998	1.05 (0.81, 1.37)
UK-390,957 2.5mg	85	0.12 (-0.14, 0.39)	0.3591	1.13 (0.87, 1.48)
UK-390,957 5mg	85	0.18 (-0.09, 0.44)	0.1871	1.19 (0.92, 1.56)
UK-390,957 10mg	87	0.36 (0.10, 0.62)	0.0072*	1.44 (1.10, 1.87)

*Statistically significant at 5% level
**UK-390,957 minus Placebo (n=82)

For the ≤1 minute stratum, results for IELT at Week 8 were similar to that for the ≤2 minute stratum. LEDs in the ITT population at Week 8 and Week 12 were 8.25mg and 2.45mg, respectively.

Secondary efficacy endpoints For IPE, subjects in the UK-390,957 10mg group scored statistically significantly higher on the Satisfaction, Control and Distress domains at Weeks 8

and 12 than those in the placebo group (Table S4). Subjects in the UK-390,957 5mg group also scored statistically significantly higher on the Control domain at Week 12 compared with placebo. Similar results were produced by the four sensitivity analyses.

Table S4. Statistical Analysis of IPE Standardized Domain Scores– ITT

	Week	Treatment	n	Adjusted mean (SE)	Treatment difference**	
					Estimate (95% CI)	p-value
Satisfaction	8	UK-390,957 1mg	88	50.12 (2.82)	4.13 (-2.97, 11.23)	0.2534
		UK-390,957 2.5mg	87	49.86 (2.80)	3.87 (-3.32, 11.06)	0.2908
		UK-390,957 5mg	87	48.94 (2.84)	2.95 (-4.19, 10.09)	0.4172
		UK-390,957 10mg	88	59.78 (2.68)	13.79 (6.67, 20.90)*	0.0002
		Placebo	82	45.99 (2.88)		
	12	UK-390,957 1mg	88	51.62 (2.79)	3.54 (-3.47, 10.55)	0.3209
		UK-390,957 2.5mg	87	50.73 (2.77)	2.66 (-4.44, 9.75)	0.4623
		UK-390,957 5mg	87	51.79 (2.81)	3.72 (-3.33, 10.76)	0.3003
		UK-390,957 10mg	88	63.55 (2.65)	15.47 (8.45, 22.50)*	<0.0001
		Placebo	83	48.07 (2.84)		
Control	8	UK-390,957 1mg	88	26.83 (3.06)	5.50 (-2.20, 13.21)	0.1611
		UK-390,957 2.5mg	87	27.63 (3.03)	6.31 (-1.48, 14.09)	0.1119
		UK-390,957 5mg	87	28.97 (3.10)	7.65 (-0.13, 15.43)	0.0538
		UK-390,957 10mg	87	40.91 (2.94)	19.59 (11.78, 27.39)*	<0.0001
		Placebo	82	21.32 (3.14)		
	12	UK-390,957 1mg	88	27.11 (3.10)	4.48 (-3.29, 12.25)	0.2578
		UK-390,957 2.5mg	87	27.73 (3.06)	5.10 (-2.75, 12.94)	0.2022
		UK-390,957 5mg	87	32.19 (3.13)	9.56 (1.72, 17.40)*	0.0170
		UK-390,957 10mg	87	45.48 (2.97)	22.85 (14.98, 30.72)*	<0.0001
		Placebo	83	22.63 (3.17)		
Distress	8	UK-390,957 1mg	88	42.23 (3.00)	4.27 (-3.27, 11.80)	0.2667
		UK-390,957 2.5mg	87	43.23 (2.96)	5.26 (-2.35, 12.88)	0.1750
		UK-390,957 5mg	87	43.85 (3.03)	5.89 (-1.72, 13.49)	0.1287
		UK-390,957 10mg	87	51.57 (2.87)	13.60 (5.98, 21.22)*	0.0005
		Placebo	82	37.96 (3.07)		
	12	UK-390,957 1mg	88	43.68 (3.00)	2.59 (-4.94, 10.12)	0.4993
		UK-390,957 2.5mg	87	44.68 (2.97)	3.59 (-4.01, 11.20)	0.3535
		UK-390,957 5mg	87	44.50 (3.03)	3.41 (-4.18, 11.01)	0.3775
		UK-390,957 10mg	87	54.43 (2.88)	13.34 (5.73, 20.95)*	0.0006
		Placebo	83	41.09 (3.06)		

*Statistically significant at 5% level
**UK-390,957 minus Placebo

For the Diary Sexual Event Questions, statistically significantly more 'satisfied' events in response to both questions were reported by subjects in the UK-390,957 10mg group at Weeks 8 and 12 than those in the placebo group. Similar results were reported by subjects in the UK-390,957 2.5mg group, with the exception of Question 1 at Week 12.

For SQoL-General, subjects in the UK-390,957 5mg and 10mg groups had statistically significantly higher scores at Week 12 than those in the placebo group. For Sexual

Confidence Scale (SCS), subjects in the UK-390,957 2.5mg, 5mg and 10mg groups had statistically significantly higher scores at Week 12 than those in the placebo group. For Sexual Relationship Scale (SRS), all treatment groups had higher mean scores at Weeks 8 and 12 from baseline but none were statistically significantly different from placebo.

For the GEQs, the percentage of positive responses to both questions was statistically significantly higher at Week 8 in the UK-390,957 2.5mg, 5mg and 10 mg groups and at Week 12 in the UK-390,957 5mg and 10 mg groups compared with the placebo group.

Pharmacokinetic Results: The population pharmacokinetics of UK-390,957 are presented in a separate report.

Safety Results: An overall summary of adverse events is presented in Table S5.

Table S5. Overall Summary of AEs

	UK-390,957				Placebo
	1mg (n=96)	2.5mg (n=96)	5mg (n=94)	10mg (n=96)	(n=94)
All causality					
No. of adverse events:	60	60	70	117	42
No. (%) of subjects with:					
Adverse events	39 (40.6)	33 (34.3)	38 (40.4)	53 (55.2)	28 (29.8)
Serious adverse events	4 (4.2)	2 (2.1)	1 (1.1)	0	1 (1.1)
Severe adverse events	3 (3.1)	2 (2.1)	4 (4.3)	0	2 (2.1)
Discontinuation due to AEs	3 (3.1)	2 (2.1)	5 (5.3)	4 (4.2)	2 (2.1)
Dose reduction/temporary discontinuation due to AEs	1 (1.0)	0	0	0	0

The most frequently reported AEs are summarized in Table S6.

Table S6. Incidence of AEs by frequency (≥5 subjects)

All causality (treatment related)	UK-390,957 1mg (n=96)	UK-390,957 2.5mg (n=96)	UK-390,957 5mg (n=94)	UK-390,957 10mg (n=96)	Placebo (n=94)
Nausea	4 (4)	4 (4)	12 (12)	25 (25)	2 (1)
Headache	5 (2)	3 (2)	4 (3)	11 (9)	3 (2)
Influenza	4	3	1	6	1
Dizziness	1 (1)	0	6 (6)	6 (6)	0
Diarrhoea	2 (2)	1 (1)	2 (1)	5 (4)	3 (1)
Nasopharyngitis	2	1	2	3	1
Flatulence	1	1 (1)	3 (3)	3 (3)	0
Vertigo	0	2 (2)	1 (1)	4 (4)	0
Dry mouth	0	3 (3)	0	2 (2)	2 (2)
Back pain	4	2 (1)	0	1	0
Erectile dysfunction	0	2 (2)	1 (1)	2 (2)	2 (1)
Upper respiratory tract infection	4	1	0	0	1
Insomnia	2 (1)	0	0	4 (4)	0
Flushing	0	0	2 (2)	3 (3)	0
Palpitations	1 (1)	1 (1)	2 (1)	1 (1)	0

The majority of AEs (95%) were mild or moderate in severity. The number of discontinuations was low. The most common AEs leading to discontinuation were nausea (7 reports) and dizziness (4 reports). There was one death during the study. This was a 47 year old white male who died from a cerebral hemorrhage after 28 days of receiving UK-390,957 2.5mg. The cause of his death was not considered treatment related by the investigator. A further 7 subjects reported 8 serious adverse events. All were considered unrelated to treatment by the investigator. There was no evidence of a clinically meaningful effect of UK-390,957 on vital signs, ECGs or laboratory test parameters.

CONCLUSIONS:

- UK-390,957 produced a dose-related prolongation of IELT at Week 8, with the lowest effective dose of UK-390,957 estimated at approximately 10mg. Mean IELT was statistically significantly longer after treatment with UK-390,957 10mg compared with placebo.

- UK-390,957 10mg was statistically significantly superior to placebo at improving: the Satisfaction, Control and Distress Domain scores of the IPE at Weeks 8 and 12; the number of 'satisfied' events from the Diary Sexual Event Questions at Weeks 8 and 12; SQoL-General and SCS scores at Week 12; and the percentage of positive responses to the GEQs at Weeks 8 and 12.

- UK-390,957 5mg was statistically significantly superior to placebo at improving: the Control Domain score of the IPE at Week 12; SQoL-General and SCS scores at Week 12; and the percentage of positive responses to the GEQs at Weeks 8 and 12.

- UK-390,857 2.5mg was statistically significantly superior to placebo at improving: SCS scores at Week 12 and the percentage of positive responses to the GEQ s at Week 8.

- UK-390,957 was well tolerated. The discontinuation rate due to treatment-related AEs was low and no treatment-related serious adverse events were reported.