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PROPRIETARY DRUG NAME/INN: UK-390,957

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

NCT #: 00219609

PROTOCOL NO.: A3871028

PROTOCOL TITLE: A Phase 2 Multi-Center, Open Label, Long-Term Extension Trial to Assess the Safety of Oral UK-390,957 Administered as Required in Adult Men With Premature Ejaculation

Study Centers: Subjects were randomized in 81 centers across 14 countries: 43 in United States; 6 each in Australia and Canada; 4 in Israel; 3 each in Czech Republic, Germany and Turkey; 2 each in Austria, Italy, Norway, Poland, Sweden and United Kingdom; and 1 in France.

Study Initiation and Completion Dates: 23 January 2005 to 08 March 2006. The study was terminated prematurely.

Phase of Development: Phase 2.

Study Objective: To evaluate the long-term safety and tolerability of oral UK-390,957 administered to adult men with premature ejaculation who had successfully completed 1 of the Pfizer trials A3871022, A3871027 or A3871029.

METHODS

Study Design: This was a global, multi-center, open label, long-term extension study. Subjects, who had completed 1 of the studies A3871022, A3871027 or A3871029 without any treatment-related serious adverse events (SAEs) or protocol violations, were offered enrolment into this study. Subjects received UK-390,957 orally prn 1 to 3 hours prior to sexual intercourse not more than once daily for a period of 52 weeks. During the first 8 weeks, 2 dose adjustments could occur to minimize adverse events (AEs) and optimize efficacy as measured by subject report and physician judgment. After 8 weeks, the subjects remained on a stable dose.

The study consisted of 7 visits (screening visit followed by visits at Weeks 4, 8, 12, 24, 36 and 52). Subjects had a follow up either in the office or by telephone contact 14 days after the end of the study to assess for any AEs following drug discontinuation.

Number of Subjects (planned and analyzed): In total, up to 1058 subjects who completed 1 of the studies A3871022 (n = 460), A3871027 (n = 460) or A3871029 (n = 138) could qualify to enter this global extension study. A total of 651 subjects were assigned to study treatment.

Diagnosis and Main Criteria for Inclusion: Male subjects ≥18 years of age, who had successfully completed a previous Phase 2 study and who continued to have a monogamous stable heterosexual relationship were included in the study.

Study Treatment: UK-390,957 (2.5 to 10 mg) was administered orally with a glass of water in the form of round film-coated white tablet. Subjects took the tablets prn between 1 and 3 hours prior to anticipated sexual intercourse not more than once daily for a period of 52 weeks. All subjects started with the 5 mg dose once daily prn. At Week 4, the dosage could be increased to 10 mg to optimise efficacy or decreased to 2.5 mg to minimize AEs. At Week 8 further dose adjustment could occur. Subjects on 10 mg of UK-390,957 could decrease to 5 mg, while those on 2.5 mg could increase to 5 mg if efficacy was insufficient. The final titration was at Week 8.

Efficacy Evaluations: No efficacy evaluations were done in this study.

Safety Evaluations: At screening, safety test results obtained at the end of study visit from the parent studies were used as the baseline laboratory tests. Subjects rolling over within 30 days of the follow-up visit had the tests repeated only if a clinically significant change occurred since the follow-up visit. Subjects rolling over between 31 to 60 days of the follow-up visit had their laboratory tests repeated. Monitoring of AEs was done throughout the study and any ongoing AEs from prior studies were documented. Laboratory tests (hematology and blood chemistry) were performed and vital signs (sitting blood pressure and pulse rate) were recorded at all visits. Physical examinations and electrocardiograms (ECGs) were done at Week 52 and follow-up if clinical symptoms suggested a problem.

Statistical Methods: Not applicable as this was a safety study. Safety data for the whole duration of the study (up to 52 weeks) was subject to clinical review and was summarized using standard algorithms and study report table formats.

RESULTS

Subject Disposition and Demography: A total of 651 subjects were assigned to study treatment and 640 discontinued. The majority of the discontinuations were due to the early termination of the study by the sponsor. Subject evaluation groups are summarized in Table S1.

Table S1. Subject Evaluation Groups

Number of subjects (%)	UK-390,957 (2.5 to 10 mg)
Treated	651
Completed	11 (1.7)
Discontinued	640 (98.3)
Related to study drug:	28 (4.3)
Adverse event	28 (4.3)
Not related to study drug:	612 (94.0)
Adverse event	8 (1.2)
Other	500 (76.8)
Subject defaulted	104 (16.0)
Analysed for safety:	
Adverse events	651 (100.0)
Laboratory data	623 (95.7)

All the subjects in the study were males. The mean age of the subjects was 42.3 years (range 19 to 73 years).

Efficacy Results: Not Applicable.

Safety Results: The incidence of treatment-emergent AEs (all causalities and treatment related) is summarized in Table S2.

Table S2. Incidence of Treatment-Emergent Adverse Events (All Causalities and Treatment Related)

Number of subjects (%)		UK-390,957 (2.5 to 10 mg) All Causalities	UK-390,957 (2.5 to 10 mg) Treatment Related
Subjects evaluable for AEs:	651		
Number of AEs		756	417
Subjects with AEs		351 (53.9)	243 (37.3)
Subjects with SAEs		12 (1.8)	1 (0.2)
Subjects with severe AEs		21 (3.2)	5 (0.8)
Subjects discontinued due to AEs		37 (5.7)	28 (4.3)
Dose reduced or temporary discontinuation due to AEs		56 (8.6)	50 (7.7)

One subject experienced an AE and was prescribed a prohibited medication by the general practitioner. This constituted a protocol violation and the subject was discontinued. However, the AE action was recorded as permanently discontinued.

There were no deaths reported in the study. A total of 13 subjects experienced 18 non-fatal SAEs during the study (Table S3). SAEs resulting in study discontinuation included 1 subject with atherosclerosis and angina, 1 subject with suicide attempt, 1 subject with anterior ischemic optic neuropathy and 1 subject with torn Achilles tendon and pulmonary embolus. One SAE (anterior ischemic optic neuropathy) was assessed as possibly related to study drug by the investigator. In this case, the investigator considered that the most likely cause of the event was diabetes mellitus and hypoglycemia, but that a contribution of study drug could not be excluded. In the sponsor's opinion, the subject's history of hypertension and diabetes mellitus, along with the long-term use of treatment with insulin provided the

most feasible explanation for the event, and that there was no plausible mechanism for linking the event to study drug.

As previously described, the majority of subject discontinuations were due to early study termination by the sponsor.

Table S3. Serious Adverse Events

Age (yrs)	Event term	Onset day*	Action taken	Outcome	Causality**
33	Multiple fractures Car accident Splenic hemorrhage	96	Post therapy: drug previously discontinued	Recovering	Not related
57	Left cerebral infarction	29	No action taken	Recovered	Not related
51	Gallbladder colic	211	No action taken	Recovered	Not related
39	Malignant tumor on base of tongue	47	Multiple challenge / rechallenge / interrupt	Recovered	Not related
58	Angina Atherosclerosis	39	Permanently discontinued	Recovered	Not related
33	Right third finger soft tissue abscess secondary to spider bite	246	No action taken	Recovered	Not related
47	Exacerbation of GERD Vasovagal syncope	64 67	No action taken No action taken	Recovered Recovered	Not related Not related
42	Suicide attempt	174	Permanently discontinued	Recovered	Not related
47	Anterior ischemic optic neuropathy	19	Permanently discontinued	Not Recovered	Related
30	Exacerbation diverticulitis	163	No action taken	Recovered	Not related
35	Torn Achilles tendon right leg Pulmonary embolus	127	Permanently discontinued	Recovered	Not related
65	Malignant melanoma	228	Post therapy: treatment period completed	Unknown	Not related
46	Chronic diverticulitis	40	Post therapy: drug previously discontinued	Recovered	Not related

GERD = Gastroesophageal reflux disease. *Days relative to the day of starting active therapy (Day 1). **In relationship to the study drug.

The most common all causalities AE leading to discontinuation was nausea (n=10), followed by diarrhea (n=6) and anxiety (n=4). Except for 2 AEs of anxiety, the most common AEs leading to discontinuations were considered treatment related. In addition, 4 subjects discontinued due to treatment related laboratory abnormalities of increased bilirubin (n=2), increased transaminases (n=1), and abnormal liver function test (n=1).

The most frequently reported (occurring in more than 10 subjects) treatment-emergent AEs (all causalities and treatment related) are summarized in Table S4.

Table S4. Incidence of Treatment-Emergent Adverse Events (Occurring in More Than 10 Subjects)

	UK-390,957 (2.5 to 10 mg)	
Number of Subjects (%)	**All Causalities**	**Treatment Related**
Nausea	117 (18.0)	115 (17.7)
Headache	51 (7.8)	41 (6.3)
Dizziness	40 (6.1)	37 (5.7)
Insomnia	28 (4.3)	24 (3.7)
Upper respiratory tract infection	27 (4.1)	0 (0)
Diarrhea	23 (3.5)	18 (2.8)
Influenza	22 (3.4)	0 (0)
Nasopharyngitis	19 (2.9)	1 (0.2)
Hypertension	15 (2.3)	6 (0.9)
Flatulence	13 (2.0)	11 (1.7)
Sinusitis	12 (1.8)	0 (0)

Nausea was the most frequently reported treatment-emergent AE followed by headache, dizziness and insomnia. The majority of these commonly reported AEs were considered to be treatment related and most of the AEs were mild or moderate in severity.

CONCLUSIONS: UK-390,957 was well tolerated in this study population. There were no deaths reported during the study. One treatment related (anterior ischemic optic neuropathy) and 17 non treatment related SAEs were reported. Nausea was the most commonly reported treatment related AE, followed by headache, dizziness and insomnia.