Study Title

Phase II, double-blind, intermittent dose, placebo controlled, randomised, two-period crossover study to investigate the effect of inhaled doses of VR776 administered via Aspirair® inhaler on intravaginal ejaculatory latency time (IVELT) measured by stopwatch in male patients with premature ejaculation

Study Centre

One centre in the UK

Study Period	**Phase of Development**
14th July 2006 to 15th March 2007	2

Objectives

Primary:

- To measure the effectiveness, compared with placebo, of 1 mg and 2 mg doses of VR776 administered via the Aspirair® inhaler on intravaginal ejaculatory latency time (IVELT) measured by stopwatch and recorded by the partner during sexual intercourse.

Secondary:

- To assess the safety and tolerability of intermittent, single and as required use of repeat inhaled doses of VR776 in healthy male patients with premature ejaculation.
- To assess the patients' satisfaction and control of ejaculation during treatment with 1 mg and 2 mg doses of VR776 administered via the Aspirair® inhaler compared with placebo.

Methodology

This was a double-blind, placebo controlled, intermittent dose study with two independent, 2-period, 2-treatment crossovers in patients with premature ejaculation. Patients were treated with either 1 mg or 2 mg VR776 and placebo.

There were four study treatment sequences with patients receiving:

- 1 mg VR776 per dose in period 1 and placebo in period 2.
- Placebo in period 1 and 1 mg VR776 per dose in period 2.
- 2 mg VR776 per dose in period 1 and placebo in period 2.
- Placebo in period 1 and 2 mg VR776 per dose in period 2.

Suitable patients were screened and entered the run-in period, during which they were asked to complete a diary recording IVELT each time they attempted intercourse. Patients with a confirmed mean IVELT of ≤ 2 minutes during the run-in period entered the dosing phase of the study. Patients attended the study centre for two clinic dosing days at the beginning of treatment periods 1 and 2, when pharmacokinetic and certain safety parameters were assessed. Patients were discharged for 17 days with instructions to administer VR776 using the Aspirair® inhaler before intercourse on between 3 and 5 occasions.

A diary card was to be completed for attempted intercourse following the administration of study treatment. Patients were not to use the inhaler in the 48 hours preceding the visit at the start of treatment period 2 to ensure washout of the study medication.

Number of Subjects (Planned and Analysed)

Planned: It was planned to enrol a total of 40 patients, to achieve 20 patients receiving 1 mg VR776/placebo and 20 patients receiving 2 mg VR776/placebo.

Analysed: 72 patients were screened and 40 patients were enrolled and completed the study, with 20 patients randomised to receive 1 mg VR776/placebo and 20 patients randomised to receive 2 mg VR776/placebo.

Main Criteria for Inclusion

Healthy males between 18 and 65 years of age (inclusive) with a documented medical history of premature ejaculation and a mean IVELT of ≤ 2 minutes during the study run-in period.

Test Product, Dose and Mode of Administration

VR776 is a dry powder formulation containing clomipramine and magnesium stearate (excipient). Treatment consisted of 1 mg and 2 mg VR776 in a sealed foil blister for use in the Aspirair® inhaler. Doses used were 1 mg and 2 mg per administration.

Duration of Treatment

Each subject participated in the study for approximately 8 weeks.

Reference Therapy, Dose and Mode of Administration

Placebo consisted of lactose as the carrier plus magnesium stearate excipient in a sealed foil blister for use in the Aspirair® inhaler.

Criteria for Evaluation

Efficacy

IVELT as recorded by stopwatch by the patient's partner, patient sexual satisfaction, global assessment including ejaculatory control, and acceptability of the Aspirair® inhaler were evaluated.

Pharmacokinetics

Plasma samples were collected to enable qualitative assay of plasma clomipramine levels.

Safety

Adverse events (AEs), physical examination, vital signs with orthostatic challenge, haematology, clinical chemistry, 12-lead ECG, continuous cardiac monitoring (pre-dose to 1 hour post-dose), lung function, cough and neurological changes were evaluated.

Statistical Methods

Mean IVELT during sexual intercourse were assessed by pairwise comparison of active treatment versus placebo using a non-parametric Wilcoxon Signed Rank Test. Mean levels of satisfaction at each attempted intercourse were assessed by pairwise comparison of active treatment versus placebo using an analysis of variance (ANOVA). Control over ejaculation was compared by McNemar's chi-squared test.

The maximum plasma concentration and time to maximum concentration were obtained directly from the plasma concentration-time data for clomipramine. The area under the plasma concentration versus time curve to the last data point was calculated using the linear trapezoidal method. AE frequencies were summarised by treatment, according to system

organ class and preferred term, severity grade and relationship to treatment. The incidence of AEs indicative of cough was also considered separately.

Changes in laboratory findings from baseline were summarised over the course of the study and presented as shift tables of patients experiencing parameters outside the normal range. Neurological assessments were summarised according to the number of abnormal findings.

Efficacy Results

A total of 39 patients was included in the ITT population, comprising 20 patients in the 1 mg VR776/placebo dose group and 19 patients in the 2 mg VR776/placebo dose group. Thirty-six patients were included in the PP population, comprising 20 patients in the 1 mg VR776 dose group and 16 patients in the 2 mg VR776 dose group.

The change in IVELT time between run-in and the active and placebo treatment periods is shown in the table below.

Mean ± SD	**IVELT Time (minutes)**	
	1 mg VR776 Group (N = 20)	**2 mg VR776 Group (N = 19)**
Run-In Period	1.16 ± 0.602	0.988 ± 0.510
Placebo Treatment Period	1.799 ± 0.521	1.525 ± 0.753
Difference between Run-In Period	0.637 ± 1.125	0.536 ± 0.617
VR776 Treatment Period	1.858 ± 1.025	2.203 ± 1.471
Difference between Run-In and VR766	0.696 ± 0.705	1.214 ± 1.280
Difference between VR776 and Placebo	0.059 ± 1.025	0.678 ± 1.201

No significant difference was seen between IVELT when comparing 1 mg VR776 and placebo dosing. However, there was a significant difference between IVELT when comparing 2 mg VR776 and placebo dosing (p=0.0108). These differences are most apparent when the cumulative percentage increase in IVELT is calculated for the two dose groups (see table below).

Percentage increase in IVELT	**>25% n (%)**	**>50% n (%)**	**>100% n (%)**	**>200% n (%)**
1 mg dose group, N = 20	5 (25)	5 (25)	2 (10)	0
2 mg dose group, N = 19	10 (53)	6 (32)	3 (16)	1 (5)

The change in sexual satisfaction score comparing run-in, active treatment and placebo did not show a significant difference when comparing 1 mg or 2 mg VR776 with placebo. The responses for control over ejaculation for the run-in, active treatment and placebo treatments are presented in the table below.

	Very Good n (%)	**Good** n (%)	**Fair** n (%)	**Poor** n (%)	**Very Poor** n (%)
Run-In	0	0	4 (20.0)	8 (40.0)	8 (40.0)
Placebo	0	2 (10.0)	8 (40.0)	7 (35.0)	3 (15.0)
1 mg VR776	0	0	11 (55.0)	7 (35.0)	2 (10.0)
Run-In	0	0	5 (26.3)	8 (42.1)	6 (31.6)
Placebo	0	3 (15.8)	4 (21.1)	12 (63.2)	0
2 mg VR776	1 (5.3)	6 (31.6)	7 (36.8)	3 (15.8)	2 (10.5)

No significant difference was seen in control over ejaculation when comparing the 1 mg VR776 treatment group with placebo. However, 7 patients who reported poor/very poor control over ejaculation when receiving placebo treatment reported very good/good/fair control when treated with 2 mg VR776. This resulted in a significant difference in control over ejaculation when comparing 2 mg VR776 treatment with placebo (p=0.0082). There were no notable differences in the overall effect of the study medication, satisfaction with sexual intercourse, distress caused by premature ejaculation or relationship difficulties caused by premature ejaculation when comparing 1 mg VR776 treatment with placebo. However, more patients in the 2 mg VR776 treatment group reported a very good/good effect of study medication compared with placebo (42% versus 21%) and a very good/good satisfaction with sexual intercourse compared with placebo (47% versus 32%).

No patients in the 2 mg VR776 treatment group reported extreme distress due to premature ejaculation (compared with 11% following placebo). There were no notable differences in the relationship difficulties caused by premature ejaculation when comparing 2 mg VR776 treatment with placebo.

Pharmacokinetic Results

All patients given an active dose of VR776 showed plasma exposure to clomipramine. The clomipramine C_{max} occurred between 1 and 10 minutes postdose and median C_{max} values were 7.91 ng/mL following 1 mg VR776 and 12.4 ng/mL following 2 mg VR776. Median AUC_{0-30} values increased with increasing dose, doubling the dose from 1 mg to 2 mg resulted in a 1.8-fold increase in AUC_{0-30}, which was approximately proportional. Median T_{max} value was 1 minute following the 1 mg VR776 dose and 2 minutes following the 2 mg dose. No metabolism to N-dMCMI was observed within the 4-hour study assessment period.

Safety Results

The overall incidence of AEs was higher following VR776 treatment, occurring in 70% of patients receiving 1 mg VR776 (compared with 35% for placebo) and in 85% of patients receiving 2 mg VR776 (compared with 20% for placebo). The most common AEs associated with active treatment were cough (55% of patients in the 1 mg VR776 group; 70% of patients in the 2 mg VR776 group), throat irritation (50% of patients in the 1 mg VR776 group; 70% of patients in the 2 mg VR776 group) and respiratory tract irritation (5% of patients in the 1 mg VR776 group; 35% of patients in the 2 mg VR776 group). These AEs occurred repeatedly during the study, usually in association with VR776 dosing. All events were considered possibly or probably related to the study medication. Most AEs were mild or moderate in severity, with 1 patient in the 1 mg VR776 group experiencing an episode of severe throat irritation following active treatment which lasted 2 minutes. Detailed analysis showed that no patients had abnormal coughing recorded prior to or following placebo dosing or prior to active treatment.

Following administration of 1 mg VR776, 45% of patients had abnormal coughing recorded 10 minutes postdose and 20% had abnormal coughing recorded 1 hour postdose. Following administration of 2 mg VR776, 65% of patients had abnormal coughing recorded 10 minutes postdose and 30% had abnormal coughing recorded 1 hour postdose.

No deaths, serious adverse events or AEs leading to study discontinuation were observed during the study. No clinically significant neurological findings were reported during the study. Clinical laboratory values that fell outside the normal reference range were seen in a number of patients, however, none were deemed clinically significant.

Minor changes in vital signs were noted when treatment with VR776 was compared with placebo dosing, but none of the changes were considered clinically relevant. No notable changes in lung function parameters were seen during the study. No significant ECG changes were reported during the study and there were no clinically significant changes in QTc interval. No relevant changes were seen in continuous cardiac monitoring.

Conclusions

- This study showed that 2 mg VR776 administered by inhalation has clinical efficacy in patients with premature ejaculation, showing a statistically significant increase in intravaginal ejaculatory latency time and improved control over ejaculation.
- Plasma levels of VR776 following inhalation administration were variable between patients but overall, AUC increased proportionally between doses. The median T_{max} for inhaled VR776 was 1- 2 minutes, consistent with rapid onset of clinical efficacy for this formulation.
- Inhaled VR776 was safe and reasonably well tolerated at doses of 1 mg and 2 mg, with the most common side effects comprising cough, throat irritation and respiratory tract irritation.
- There were no clinically significant cardiovascular changes and no clinically significant changes in ECG or QTc intervals.
- There were no clinically significant neurological findings.
- There were no clinically significant changes in lung function.