Title of Study

A home based Phase IIb, multi-centre, randomised, double blind, placebo controlled, dose finding parallel group study to explore the optimal dose of inhaled VR004 in patients with erectile dysfunction (ED).

Study Centres

36 centres in the United Kingdom (UK)

Study Period		**Phase of Development**
Date of first enrollment	29 March 2005	2b
Date of last completed	03 May 2006	

Objectives

To explore, in patients of varied ED aetiology and severity, the efficacy of VR004 as measured by the primary and secondary efficacy questions.

To compare the efficacy of VR004 with that of placebo.

To examine the safety/tolerability profile of VR004, at all tested doses, as measured by the incidence and severity of spontaneously reported adverse events (AEs), changes in vital signs and lung function and the occurrence of abnormal laboratory test results.

Methodology

This was a randomised, double-blind, placebo controlled, single fixed dose as required, parallel group, multi-centre study in male patients with ED in a stable heterosexual relationship in the "at-home" environment.

Following Screening Visit 1 (Week -6, Visit 1), patients who were currently receiving any ED medication entered a two-week wash-out period, followed by a four-week no treatment run-in period. Patients who were not currently taking any ED medication at Screening Visit 1 (Week -6 Visit 1) entered the four-week, no treatment, run-in period immediately. Patients were then randomised and treated with the study drug for a maximum of 12 weeks. Patients attended the study site at Week -6 for consent, Week -4 to enter the no treatment run-in period, Week 0 for the Baseline Visit, Weeks 4 and 8 for assessment Visits 4 and 5, and Week 12 for the Final Visit (Visit 6).

The original scope of this study was to compare three doses (high, intermediate and low) against placebo. Six patients (5.5%), of the first 108 randomised (i.e. up to 07 Jun 2005), experienced hypotension during the orthostatic challenge. The unblinded data from these six patients were reviewed by an independent Safety Oversight Committee (SOC), which concluded that there was a concern with safety and the intermediate and high dose groups were terminated. For the second phase of the study, patients were only randomised to either the VR004 (low dose) or placebo group.

Number of Subjects (Planned and Analysed)

Planned: It was planned to recruit 500 consented patients into the no treatment run-in period. However following a safety review of the data after 108 patients had been randomised, further randomisation to the two higher dose levels was terminated. Those patients receiving either of these doses at home were allowed to continue without modification. The study randomisation continued with the placebo and VR004 (low dose) treatment groups only. Therefore, in addition to the 108 patients that were randomised during the first phase of the study, at least a further 104 patients were to be randomised to obtain at least a final total of 122 evaluable patients in the placebo and VR004 (low dose) treatment groups.

Analysed: A total of 503 patients gave consent and were screened and 211 patients were randomised (All Randomised population). A total of 180 patients were analysed in the Intent-to-Treat (ITT) population and 138 patients were analysed in the Per-Protocol (PP) population.

Diagnosis and Main Criteria for Inclusion

Males aged between 18 and 65 years (inclusive); in a stable heterosexual relationship, in which patient and partner were willing to attempt vaginal intercourse at least once per week during the trial; who had experienced ED for at least six months; who had experienced a spontaneous or treatment induction erection during the previous month; with no clinically significant blood test abnormalities; taking no prohibited medications and no previous medical history/ intercurrent illnesses, which could have compromised the safety of the patient in the study.

Test Product, Dose and Mode of Administration

Blisters, containing a dry powder formulation of apomorphine with a lactose carrier containing approximate nominal doses of 250, 430 or 520 µg. The Investigational product was administered using an Aspirair™ inhaler.

Note: The nominal doses specified in the protocol of approximately 250, 430 and 520 µg were subsequently confirmed as actual nominal doses of 310, 460 and 525 µg. Furthermore, the actual dose that reached the lungs (administered using an Aspirair inhaler) was confirmed as approximately 150, 250 and 300 µg.

Duration of Treatment

Patients could participate in the study for a maximum of 18 weeks. This included a two-week wash-out period (for patients who had existing ED medication), a four week no treatment run-in period and a 12-week Treatment Period.

Comparator Product, Dose and Mode of Administration

Placebo blisters, containing dry powder, identical in appearance to VR004. Placebo was administered using an Aspirair inhaler.

Criteria for Evaluation

The primary efficacy endpoints were the change in the proportion of "yes" answers to the Sexual Encounter Profile (SEP) question numbers 2 and 3 from Baseline (Week 0, Visit 3) to the last four weeks of study treatment.

Secondary efficacy endpoints included the overall International Index of Erectile Function (IIEF) score, the IIEF Erectile Function Domain score (questions 1 5 and 15), other IIEF Functional Domain scores, the Global Assessment Questions, the onset and duration of action questions and the change in the proportion of "yes" answers from Baseline to that seen over the study treatment period for SEP2 and SEP3.

Safety

The primary safety parameter was the assessment of pulse and blood pressure during orthostatic challenge testing following the first dose in the clinic at Baseline (Week 0, Visit 3).

Secondary safety parameters included the incidence of treatment emergent AEs during the Treatment Period, changes in laboratory tests from Baseline (Week 0, Visit 3) to the end of the study, changes in vital signs from Screening to Final Visit, and changes in lung function (i.e. forced expiratory volume in one second [FEV_1]) from Baseline (Visit 3) to Visits 4, 5 and Final Visit (Visit 6).

Statistical Methods

All patients who had been randomised and received at least one at-home dose of study treatment were included in the ITT population. All patients who had been randomised, had received at least six at-home doses of study treatment, and who avoided a pre defined list of violation criteria, were included in the PP population.

Summary statistics were presented for continuous variables, by way of n, mean, standard deviation (SD), median, minimum and maximum and by way of group frequencies and percentages for categories of categorical variables. Percentages were to be calculated using the total patients per treatment group.

For all efficacy parameters, comparison of treatment groups was to be performed using Generalised Linear Models or Fisher's Exact test unless otherwise stated.

The safety data were to be summarised for all patients in the ITT population. Summary tables were presented for the following safety endpoints: AEs, clinical laboratory evaluations, vital signs and lung function tests. Patient acceptability of the Aspirair TM inhaler was to be assessed by a questionnaire at the Final Visit.

Summary - Conclusions

Efficacy Results

The primary efficacy endpoints included the change in the proportion of positive responses for SEP2 and SEP3 from Baseline to the last 4 weeks (on-dose sexual attempts only).

The primary efficacy results for the PP population are summarised below. Results were similar for the ITT population.

	250 µg VR004 N = 63	430 µg VR004 N = 12	520 µg VR004 N = 14	Placebo N = 49
SEP2				
Proportion of Positive Responses:				
Baseline	60.2%	58.3%	54.1%	65.1%
Last 4 weeks	69.1%	89.1%	79.2%	59.1%
Change from Baseline	+8.9%	+30.8%	+25.1%	-6.0%
P-value	0.001*	<0.001*	<0.001*	
SEP3				
Proportion of Positive Responses:				
Baseline	31.7%	36.4%	34.2%	32.7%
Last 4 weeks	47.4%	59.9%	62.4%	37.0%
Change from Baseline	+15.7%	+23.5%	+28.1%	+4.3%
P-value	0.054	0.002*	0.002*	

P-value is comparison to placebo using generalised linear modelling.

The secondary efficacy variables included the IIEF scores, Global Assessment Questions, onset and duration of action questions, and SEP2 and SEP3 (over the entire study treatment period).

For the PP population, at Final Visit (Week 12/Early Discontinuation), the change in overall IIEF score from Baseline (Week 0) was +4.4 (250 µg VR004), +15.5 (430 µg VR004), +13.5 (520 µg VR004) and –1.6 (placebo). Statistical analysis results showed significant differences at each visit between the intermediate and high VR004 dose groups in comparison to placebo. For the ITT population at Final Visit (Week 12/Early Discontinuation), only the 520 µg VR004 groups showed a significantly greater overall IIEF score in comparison to placebo (p=0.005).

The percentages of patients with a normal IIEF score (i.e. $\geq$26) at Final Visit (Week 12/Early Discontinuation) were 27.0% (250 µg), 41.7% (430 µg), 50.0% (520 µg) and 10.2% (placebo) for the PP population. Similar results occurred for the ITT population.

For the PP population, when asked "Has the treatment you have been taking over the past 4 weeks improved your erections?" the highest percentage of 'yes' responses occurred in the 430 μg VR004 group (8/12 patients [66.7%]). In comparison to placebo, statistical significance was shown in each VR004 treatment group (p=0.031 [250 μg VR004]; p<0.001 [430 μg VR004]; p<0.001 [520 μg VR004]).

When asked "Would you continue to take the treatment you have been taking over the last 4 weeks if it were freely available?" the highest percentage of 'yes' responses occurred in the 520 μg VR004 group (8/14 patients [57.1%]). In comparison to placebo, statistical significance was shown in the 430 μg VR004 (p=0.011) and the 520 μg VR004 (p<0.001) groups, but not the 250 μg VR004 group (p=0.403).

In the PP population, when asked, "On average, over the past 4 weeks, how long after you took the drug did you first notice its effect", for the patients who responded to VR004 treatment (particularly the 430 μg and 520 μg groups), most patients reported onset of erection within 5 minutes of dosing, and over 80% of patients responded within 10 minutes. Some patients responded within 1 minute of dosing.

When asked "On average, over the past 4 weeks, for how long did you maintain your erection?", most patients in each treatment group answered between '2-10 minutes' at each visit. No patients in the 430 μg and 520 μg VR004 group answered 'not at all'. It was also observed that the duration of action was sufficient to permit the successful completion of sexual intercourse for 47%, 60% and 62% of on-drug attempts for patients (PP population) randomised to the low, intermediate and high dose groups, respectively. This was in comparison to 37% in the placebo group.

In the PP population, for the SEP2 and SEP3 (over the entire study period), statistical analysis showed significant improvements between each VR004 treatment group and placebo (p<0.001 for each comparison).

In the PP population, for the SEP2 and SEP3 (all sexual attempts with or without study treatment), statistical analysis showed significant improvements between each VR004 treatment group and placebo (p<0.05 for each comparison).

Safety Results

Overall, there were 167 AEs in 83/211 patients (39.3%). This included 57 AEs in 31/86 patients (36.0%) in the 250 μg VR004 group, 6 AEs in 6/23 patients (26.1%) in the 430 μg VR004 group, 45 AEs in 14/26 patients (53.8%) in the 520 μg VR004 group, and 59 AEs in 32/76 patients (42.1%) in the placebo group.

Overall, the most frequent AEs by preferred term were headache (18/167 AEs [10.8%]), nasopharyngitis (17/167 AEs [10.2%]) and cough (12/167 AEs [7.2%]).

There were 57 related AEs in 26/211 patients (12.3%) and the majority of AEs were mild (84/167) or moderate (73/167), with a small number of severe AEs (10/167). Four patients (1.9%) had a severe, related AE (orthostatic hypotension [3], and migraine).

There were no deaths or SAEs during the study and there were 16 treatment-emergent AEs in 11/211 patients (5.2%) that lead to the withdrawal of the patient.

Overall, 10/211 patients (4.7%) had an AE on the day of the orthostatic challenge and nine of these patients were withdrawn due to the AE. This included six patients who had orthostatic hypotension (250 µg [2], 430 µg [1], 520 µg [3]) that lead to withdrawal following an independent SOC review. The mean time to onset for the AEs of orthostatic hypotension was 0.09 hours (approximately 5.4 minutes), mean duration was 0.77 hours (approximately 46.2 minutes), and they all resolved without sequelae.

During the orthostatic challenge, 8/211 patients (3.8%) had an absolute systolic blood pressure $\leq$ 85 mmHg and/or diastolic blood pressure $\leq$ 45 mmHg, and 37/211 patients (17.5%) had a fall in blood pressure of $\geq$ 30 mmHg systolic and/or $\geq$ 20 mmHg diastolic.

For haematology and biochemistry laboratory parameters, there were no clinically significant changes between Screening and Final Visit for each treatment group.

Two patients each had an abnormal laboratory result that was recorded as an AE (i.e. increased blood glucose and abnormal liver function test). The Investigator considered both AEs to be unlikely to be related to the study medication.

Mean FEV_1 values were similar between treatment groups at each visit. There was no clinically significant change from Baseline (Week 0) to Visit 4 (Week 4), Visit 5 (Week 8) or Final Visit (Week 12/Early Discontinuation).

Vital signs (systolic, diastolic blood pressure and pulse rate) were similar between treatment groups at each visit, and there were no clinically significant changes between Screening and Final Visit (Week 12/Early Discontinuation).

Conclusions:

Although the intermediate (430 µg) and high (520 µg) VR004 dose groups were terminated following recommendations by the SOC, the overall safety and tolerability profile of VR004 was generally comparable to placebo with the exception of orthostatic symptoms. The number of patients recording a blood pressure below the protocol threshold values was similar per group.