Title of Study

A Phase IIb, randomised, double-blind, placebo controlled, dose finding study assessing the haemodynamic safety and "at-home" efficacy of inhaled VR004 in patients with erectile dysfunction (ED)

Study Centre

This study was conducted at 40 study centres in the United Kingdom.

Study Period		**Phase of Development**
Date of first screening	09 Mar 2006	2b
Date of last completed	05 Mar 2007	

Objectives

- To explore, in patients with ED of varied aetiology and symptom severity, the maximum tolerated and minimally effective dose responses of VR004 by examining the efficacy and dose response at three different nominal doses (220 μg, 310 μg and 430 μg). Efficacy was measured by the co-primary and the secondary efficacy questions.
- To compare the efficacy of three doses of VR004 with that of placebo.
- To examine the haemodynamic safety and tolerability profile of VR004, at all tested doses, as measured by response to orthostatic challenge and the incidence and severity of spontaneously reported adverse events (AEs), vital signs, lung function and abnormal laboratory test results.

Methodology

This was a randomised, double-blind, placebo controlled, dose finding, multi-centre study in male patients with ED in a stable heterosexual relationship, evaluating haemodynamic safety in the clinical and at-home setting and efficacy in the "at home" environment. Patients who had experienced ED for at least 6 months were eligible to enrol in the study, subject to complying with inclusion and exclusion criteria.

Patients attended the study site at Week -6 (Screening Visit 1) for consent. Patients who were taking any previous ED medications attended the study site at Week -5 (Screening Visit 2) for a blood sample to be taken. This blood sample was taken at Screening Visit 1 for patients not receiving previous ED medication. In addition, patients attended the study site for the Orthostatic Challenge Visit at Week -4, and on passing the challenge, entered the 4-week no treatment run-in period. Patients then attended at Week 0 for the Baseline Visit, Weeks 4 and 8 for Clinical Visit 1 and Clinical Visit 2, and Week 12 for the Final Visit (Visit 7). Following randomisation at the Orthostatic Challenge Visit and after completing the 4-week no treatment run-in, patients used study treatment at home as required.

Number of Subjects (Planned and Analysed)

Planned: Up to a total of 800 patients were to give informed consent at Screening Visit 1, to attain 400 randomised patients at the Orthostatic Challenge Visit, to achieve 250 evaluable patients.

Analysed: 401 patients were randomised, with 389 patients included in the All Randomised (AR) population; 307 patients included in the Intent-to-Treat (ITT) population; and 241 patients included 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 study, who had experienced ED for at least 6 months, with no clinically significant blood test abnormalities, no known propensity to postural hypotension and no previous medical history/intercurrent illnesses, which may have compromised the safety of the patient in the study or the evaluation of the test drug.

Any patient who failed the orthostatic challenge at the Orthostatic Challenge Visit was not eligible to return to the site for the Baseline Visit.

Test Product, Dose and Mode of Administration

VR004 is a dry powder formulation of apomorphine with a mode of administration, lactose carrier.

VR004 was supplied in blisters containing nominal doses of 220 µg, 310 µg and 430 µg of apomorphine (or placebo). The dose that reached the lungs (administered using an Aspirair™ inhaler) was confirmed as approximately 100 µg, 150 µg and 200 µg.

One blister was used for each dose. Patients were requested to use study treatment at least once a week during the treatment period and could administer up to one blister in a single day.

Duration of Treatment

18 weeks maximum.

Patients who were receiving ED medication at Screening Visit 1 participated in this study for up to 18 weeks (2-week wash-out, 4-week no treatment run-in and up to 12-week treatment period).

Patients who were not taking ED medication at Screening Visit 1 participated in the study for up to 16 weeks (4 week no treatment run-in and up to 12-week treatment period).

Reference 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

Efficacy

The primary end-points of this study were the change in the proportion of "yes" answers from Baseline to the last 4 weeks of study treatment:

1. The Sexual Encounter Profile question number 2 (SEP2) measuring the ability to achieve vaginal penetration.
2. The Sexual Encounter Profile question number 3 (SEP3) measuring the ability to maintain an erection long enough for successful intercourse in patients with ED.

The secondary end-points of this study were changes in:

1. International Index of Erectile Function (IIEF) overall score.
2. IIEF erectile function (EF) domain (questions 1-5 and 15) score.
3. All other IIEF functional domain scores.
4. The change in the proportion of "yes" answers from Baseline to that seen over the study treatment period for SEP2 and SEP3.

Safety

1. Change in vital signs following orthostatic challenge.
2. Adverse events (AEs) - the number of AEs, the proportion of patients having at least one AE, and AEs by coded terms were presented.
3. Clinical laboratory evaluations - including mean change from baseline and incidence of clinically abnormal results.
4. Vital signs - including mean change from baseline.
5. FEV_1 - including mean change from the pre-dose FEV_1 at the Orthostatic Challenge Visit to Clinical Visit 1, Clinical Visit 2 and the Final Visit.

Statistical Methods

Demographic and efficacy analyses were carried out using the Per Protocol (PP) and Intent to Treat (ITT) populations. The safety analysis was carried out on the All Randomised (AR) population.

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

Summary statistics were presented for continuous variables, by way of number of patients (n), mean, standard deviation (SD), median, minimum and maximum and by way of group frequencies and percentages for categories of categorical variables. For all efficacy parameters, comparison of treatment groups (i.e. active doses vs. placebo) was performed using Generalised Linear Models or Cochran-Mantel-Haenszel (CMH) test unless otherwise stated.

Safety data were summarised for all patients in the AR population. Summary tables were presented for the following safety endpoints: vital signs following orthostatic challenge, (treatment-emergent) AEs, clinical laboratory evaluations, vital signs and lung function tests.

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). A summary of the primary efficacy results for the PP population is shown below. The ITT population results were generally similar to the PP population results.

Summary of Primary Efficacy Endpoints (PP Population)

	220 µg VR004 N = 54	**310 µg VR004** N = 64	**430 µg VR004** N = 64	**Placebo** N = 59
Sexual Encounter Profile Q2				
Proportion of Positive Responses:				
Baseline	58.0%	61.2%	70.1%	61.7%
Last 4 weeks	71.4%	66.0%	82.6%	60.9%
Change from Baseline	+13.4%	+6.4%	+13.9%	-1.1%
P-value	<0.001	<0.001	<0.001	
Sexual Encounter Profile Q3				
Proportion of Positive Responses:				
Baseline	26.6%	28.9%	33.8%	30.9%
Last 4 weeks	49.1%	44.7%	61.9%	32.4%
Change from Baseline	+22.5%	+17.1%	+29.1%	+1.2%
P-value	<0.001	<0.001	<0.001	

Analysis results using generalized linear modelling: Proportion of responses in last 4 weeks = treatment group + baseline proportion of responses.

The secondary efficacy variables included the IIEF scores and SEP2 and SEP3 (over the entire study treatment period). The statistical comparisons for the secondary endpoints were not powered to show significance.

For the PP population at Final Visit (Week 12/Early Discontinuation), the change in overall IIEF score from Baseline (Week 0) was +5.3 (220 μg VR004), +7.3 (310 μg VR004), +9.3 (430 μg VR004) and +1.9 (placebo). Statistical analysis showed a significantly greater overall IIEF score in the 310 μg (p=0.049) and 430 μg (p=0.002) VR004 dose groups in comparison to placebo. Significant differences were also shown between each VR004 dose group and placebo at Visit 5 (Week 4), and between the 310 μg (p=0.040) and placebo groups at Visit 6 (Week 8).

The change in IIEF EF domain score from Baseline (Week 0) to Final Visit (Week 12/Early Discontinuation) showed a dose-related response (+2.7 [220 μg VR004], +3.8 [310 μg VR004], +4.6 [430 μg VR004], +1.6 [placebo]). Similar results were shown for the ITT population. Statistical analysis showed a significantly greater overall IIEF score in the 430 μg (p=0.005) VR004 dose group only in comparison to placebo. Significant differences were also shown between each VR004 dose group and placebo at Visit 5 (Week 4), and between the 310 μg (p=0.020) and 430 μg (p=0.032) VR004 dose groups and placebo at Visit 6 (Week 8).

The percentages of patients with a normal IIEF score (i.e. ≥26) at Final Visit (Week 12/Early Discontinuation) showed a dose-related increase (18.5% [220 μg], 21.9% [310 μg], 32.8% [430 μg] and 15.3% [placebo]) for the PP population. Similar results occurred for the ITT population.

In the PP and ITT populations, 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 and ITT populations, 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 543 AEs in 217/389 patients (55.8%). This included 90 AEs in 50/97 patients (51.5%) in the 220 μg VR004 group, 168 AEs in 63/105 patients (60.0%) in the 310 μg VR004 group, 185 AEs in 57/98 patients (58.2%) in the 430 μg VR004 group, and 100 AEs in 47/89 patients (52.8%) in the placebo group.

Overall, the most frequent AEs by preferred term were headache (69/543 AEs [12.7%]), upper respiratory tract infection (30/543 AEs [5.5%]) and nasopharyngitis (24/543 AEs [4.4%]). However, headache occurred less frequently in the placebo group in comparison to the VR004 dose groups.

There were 151 related AEs in 49/389 patients (12.6%), with slightly more related AEs occurring in the VR004 dose groups than placebo (i.e. 19 AEs in 9/97 patients [220 μg VR004], 37 AEs in 15/105 patients [310 μg VR004], 77 AEs in 18/98 patients [430 μg VR004], 18 AEs in 7/89 patients [placebo]).

The majority of AEs were mild (376/543 AEs [69.2%]) or moderate (148/543 AEs [27.3%]), with a small number of severe AEs (19/543 AEs [3.5%]). There were 3/389 patients (0.8%) with a severe, related AE. Events included orthostatic hypotension (220 μg VR004) and hypotension (220 μg VR004) on the occasion of the orthostatic challenge, and nausea (310 μg VR004) and dyspnoea (310 μg VR004) which did not occur of the day of the orthostatic challenge. There were no severe, related AEs in the 430 μg VR004 or placebo groups.

There were no deaths and none of the 3 SAEs during the study (skin cancer, pulmonary embolism, and prostate cancer) were related to the study medication.

Overall, 22/389 patients (5.7%) had study medication stopped due to an AE and 20/389 patients (5.1%) were withdrawn from the study due to an AE. There were 13/389 patients (3.3%) who had a treatment-related AE which led to withdrawal, with 8/389 patients (2.1%) recording the AE on the day of the orthostatic challenge.

Dizziness (3.9% of patients), orthostatic hypotension (1.0% of patients), hypotension (0.8% of patients), nausea (2.1% of patients), and vomiting (0.8% of patients) generally occurred shortly after dosing and resolved without sequelae. Events of this nature that did not occur within 3 hours of dosing were considered unrelated to the study drug.

During the orthostatic challenge, 4/389 patients (1.0%) had absolute blood pressure ≤85 mmHg systolic and/or ≤ 45 mmHg diastolic (i.e. 3.1% patients [220 μg VR004] and 1.0% patients [310 μg VR004]). There were 51/389 patients (13.1%) who had a fall in blood pressure of ≥ 30 mmHg systolic and/or ≥ 20 mmHg diastolic (i.e. 15.5% patients [220 μg VR004], 11.4% patients [310 μg VR004], 15.3% patients [430 μg VR004], 10.1% patients [placebo]).

For haematology and biochemistry laboratory parameters, there were no clinically significant changes between Screening and Final Visit for each treatment group, except for those considered to be AEs.

Mean FEV_1 values were similar between treatment groups at each visit. There was no clinically significant change from baseline (Week -4) to Visit 5 (Week 4), Visit 6 (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), except for those considered to be AEs.

Conclusions

- In comparison to placebo, all doses of VR004 investigated (i.e. 220 μg, 310 μg, and 430 μg) were efficacious in terms of the key primary endpoints in patients with ED of varied aetiology and severity.
- The overall haemodynamic safety and tolerability profile of VR004 was generally comparable to placebo. Although the number of related AEs was dose-dependent, there were no safety concerns in patients treated with VR004 in the at-home environment.