Study Title

A clinic-based, Phase 2a, randomised, double-blind, placebo-controlled, ascending-dose, single-centre study investigating the safety, tolerability, efficacy, and pharmacokinetics of VR040 in patients with established idiopathic Parkinson's Disease

Study Centre

Single centre in the UK

Study Period		**Phase of Development**
Date of first patient first visit	11 January 2006	2a
Date of last patient last visit	06 June 2006	

Objectives

- To explore the efficacy and dose response of VR040 in controlling "off" periods at 3 different doses, as measured by the primary and secondary efficacy criteria
- To compare the efficacy of 3 doses of VR040 with that of placebo
- To confirm the maximum tolerated dose (MTD) by examining the safety/tolerability profile and pharmacokinetics (PK) of VR040 as measured by the incidence and severity of spontaneously reported adverse events (AEs), vital signs, lung function, and abnormal laboratory test results
- To identify optimal doses for the next clinical study in patients

Methodology

A randomised, double-blind, placebo-controlled, ascending dose study of VR040 at nominal doses of 400 μg, 1000 μg, and 1600 μg (equivalent to fine particle doses of 200, 500, and 800 μg, respectively). Patients attended 3 or 4 visits, over a period of approximately 13 weeks. At Visit 1 patients were screened for eligibility. At Visit 2 (within 6 weeks following Visit 1) patients were randomised to receive either VR040 or placebo, such that 2 of the 8 patients in each dose cohort received placebo. Dose escalation to the next cohort was performed following blinded review of the data by the Investigator, Sponsor, and Independent Clinical Observer. Patients received 1 administration of study treatment via the Aspirair® inhaler, operated by the study nurse. Safety and efficacy assessments were performed immediately prior to dose administration and at pre-defined times post-administration. If no response to the treatment was observed after 10 minutes, as determined by self-assessment of disease state, patients were to be given a second administration at 12 minutes (at the same dose). The efficacy and safety assessments were again performed at pre-defined intervals. Visit 3, which occurred 4 to 10 days after Visit 2, consisted of safety assessments. Eight patients were invited to attend a fourth study visit (occurring 2 to 7 weeks after Visit 2), where inhaler ergonomic assessments were performed and inspiratory flow characteristics were determined.

Number of Subjects (Planned and Analysed)

Screened: 29 Intent-to-treat (ITT) population: 24
Randomised: 24 Per protocol (PP) population: 24

Main Criteria for Inclusion

- Patients with established idiopathic PD (via fulfilment of Steps 1 and 2 of the UK Brain Bank Criteria), of at least 3 years duration prior to study entry, who were on specific and optimised anti-Parkinson medication (levodopa and/or dopamine agonists), and with motor fluctuations.
- Patients with a modified Hoehn and Yahr disease severity scoring of between 2 and 4 in an "on" state.
- Men or women aged over 30 years.
- Patients who experienced motor fluctuations with recognisable "off" periods in control of motor symptoms, as assessed by the motor fluctuation questionnaire (patients were to have reported at least 1 "Yes" response to the questions in the motor fluctuation questionnaire).

Test Product, Dose and Mode of Administration

VR040 (containing apomorphine)

Mode of administration: Oral inhalation, via the Aspirair® inhaler (operated by a study nurse).

Duration of Treatment

Patients received a single administration of study treatment and a second administration if they did not respond to treatment within 10 minutes after receiving the first dose.

Comparator Product, Dose and Mode of Administration

Matching placebo

Mode of administration: Oral inhalation, via the Aspirair® inhaler (operated by a study nurse).

Criteria for Evaluation

Efficacy:

- Unified Parkinson's Disease Rating Scale Part III (UPDRS III): assessed prior to study drug administration and at 90 minutes post-administration.
- Disease state self-assessment: volunteered by patients when they felt that they had converted from an "off" to an "on" state, then performed every 10 minutes until patients confirmed that they had returned to an "off" state, or until 90 minutes post-dosing. If the patient required a second dose of study medication (to be given at 12 minutes post-administration of the first dose), the same process was followed. If the patient had still not responded 10 minutes after receiving the second dose, a disease state self-assessment was conducted at this time, with further assessments at 20, 35, and 50 minutes post-administration of the second dose.

- UPDRS upper limb component: the first UPDRS upper limb assessment was conducted as soon as patients confirmed (via disease state self-assessment) that they had converted from an "off" to an "on" state, then conducted every 10 minutes, until patients confirmed that they had returned to an "off" state, or until 90 minutes post-dosing. If the patient had not responded to the first dose of study medication by 10 minutes post-dose, an UPDRS upper limb assessment was performed at this time (10 minutes). The second dose was given at 12 minutes, and the next UPDRS upper limb assessment was then performed when patients confirmed they had converted to an "on" state, with further assessments made every 10 minutes until patients confirmed that they had returned to an "off" state, or until 90 minutes post-dosing (whichever occurred sooner). If the patient had still not responded 10 minutes after receiving the second dose, a UPDRS upper limb assessment was conducted at this time, with further assessments at 20, 35, and 50 minutes post-administration of the second dose.

Safety:

- Vital signs (including pulse rate and blood pressure [BP]) were recorded at Visits 1 and 2. At Visit 2, vital signs were recorded prior to dosing and at pre-defined time points post-dose.
- A 12-lead electrocardiogram (ECG) was performed at Visits 1 and 2. At Visit 2, an ECG was performed prior to dosing and at 90 minutes post-dose.
- A lung function test (forced expiratory volume in 1 second [FEV1]) was performed at Visits 1 and 2. At Visit 2, FEV1 was performed prior to dosing and at 90 minutes post-dose.
- Blood samples were taken for routine laboratory tests (haematology and biochemistry) at Visits 1 and 3.
- Adverse events were recorded at Visits 2 and 3.
- Concomitant medications were recorded at Visits 1, 2, and 3.
- A pregnancy test was performed (for females of child-bearing potential) at Visit 2.

Pharmacokinetics:

Blood samples for PK analysis were taken at Visit 2, prior to dosing and at pre-defined time points post-administration. The following variables were calculated: area under the concentration-time curve between 0 and 90 minutes (AUC_{0-90}), area under the concentration-time curve between 0 minutes and infinity (AUC_{0-inf}), time to maximum concentration (t_{max}), maximum concentration (C_{max}), half life ($t_{1/2}$), and terminal rate constant (k).

Statistical Methods

There were 3 patient populations defined for the study analyses:

- The all available patient population included all patients who consented to be in the study, including screening failures and patients who were randomised but did not receive a dose of study medication.
- The ITT population included all patients who were randomised and received at least 1 dose of study treatment.
- The PP population included all patients in the ITT population who completed the study without major violation of the protocol.

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

For all categorical efficacy variables, comparison of treatment groups was performed using Generalised Linear Models (SAS®: PROC GENMOD) or Cochran-Mantel-Hänszel test unless otherwise stated. Other efficacy variables were analysed using appropriate statistical methods such as analysis of variance techniques (continuous data) and survival techniques (time-to-event data).

Data from the patients randomised to placebo in each of the 3 cohorts were pooled.

Primary Efficacy Endpoints

- The proportion of patients “on” at any time post-dosing.
- Time to improvement from “off” to “on” disease state.

Secondary Efficacy Endpoint

- Duration that patients remain in an “on” state.

Efficacy Results

This proof of concept study employed a fixed-dose design. Consequently, patients were not titrated to an individual optimal dose level. For example, a patient randomised to the intermediate (1000 µg) group and who did not convert from "off" to "on" state did not receive treatment at the higher dose level. Furthermore, the study was not powered for meaningful statistical comparisons.

VR040 induced conversion from an "off" to an "on" state in 5 out of 18 patients (27.8%), compared to 1 out of 6 (16.7%) patient in the placebo group. The median onset of therapeutic effect in VR040 responders was 10 minutes, and the onset was as rapid as 4 minutes after inhalation of VR040. The median duration of effect in VR040 responders was 10 minutes, and duration was up to 40 minutes in some patients. In an exploratory analysis of patients converting to an "on" state or a "partial on" state, 10/18 patients (55.6%) treated with VR040 responded, compared to 4/6 patients (66.7%) treated with placebo. The median onset of converting to an "on" state or a "partial on" state was 10 minutes after inhalation of VR040, and the median duration of effect was 25 minutes (duration was up to 62 minutes in some patients).

In addition, VR040 at the highest dose (1600 µg) had a positive impact, as indicated by the UPDRS upper limb assessment, on idiopathic PD features during this study.

Pharmacokinetic Results

VR040 was rapidly absorbed with peak apomorphine plasma concentration observed 1-3 minutes post-inhalation. Dose proportionality was observed for $AUC_{(0-t)}$, $AUC_{(0-inf)}$, and C_{max} (see table below).

Parameter		Treatment Group		
		VR040 400 µg (N = 6)	**VR040 1000 µg (N = 6)**	**VR040 1600 µg (N = 6)**
$AUC_{(0-t)}$ (ng•min/mL)	Mean (SD)	47.50 (10.04)	168.81 (90.20)	270.75 (37.97)
$AUC_{(0-inf)}$ (ng•min/mL)	Mean (SD)	56.70 (12.94)	216.93 (99.30)	301.57 (36.64)
C_{max} (ng/mL)	Mean (SD)	3.03 (0.71)	10.0 (8.39)	11.92 (1.17)
k	Mean (SD)	0.01 (0.00)	0.01 (0.00)	0.02 (0.00)
$t_{1/2}$ (min)	Mean (SD)	37.27 (8.90)	37.10 (5.54)	25.70 (2.47)
t_{max} (min)	mean (SD)	1.0 (0.0)	2.6 (2.6)	2.2 (1.1)

Safety Results

Overall, 5 (20.8%) patients were reported as experiencing at least 1 treatment-emergent adverse event (TEAE) less than 24 hours post-dose (1 patient in the VR040 400 µg group and 2 patients each in the VR040 1600 µg and placebo groups). None were considered related to study medication except for paraesthesia in the VR040 400 µg group, headache in the VR040 1600 µg group and hypoaesthesia, headache, and ocular hyperaemia in the placebo group which were considered to be possibly related to treatment. All events were mild or moderate in severity.

One (4.2%) patient reported peripheral oedema and severe arthralgia ≥ 24 hours post-dose; neither was considered related to study drug. No patient in the VR040 1000 µg group, VR040 1600 µg group, and the placebo group experienced any TEAE ≥ 24 hours post-dose.

Because of the relatively small number of patients and small number of reported AEs, it is not possible to establish any clear pattern of relationship between dose, occurrence, and frequency of AE.

No serious or severe related AEs were reported. There were no withdrawals due to AEs.

Laboratory and vital signs parameters were similar between the treatment groups and gave no reasons of any concerns.

No patient had clinically significant out-of-range laboratory values.

Although a number of changes in the values of vital signs were observed at the second dose of VR040 or placebo, these were not associated with any symptomatic events. There were some non-clinically significant changes in the ECG measurements at post-dose Visit 2 compared with ECG measurements at pre-dose Visit 2, but changes across the treatment groups were comparable. From the QTc data, one patient (Patient 28) in the VR040 1600 µg group had a > 30 msec increase in the QTc interval post dose. However, none of the QTc measurements showed any abnormal changes between pre- and post-dose, and none of the QTc measurements exceeded 500 msec.

In the placebo group and in each of the VR040 dosing groups, a small decline in FEV_1 was observed between pre- and post-dosing. There was no evidence of a dose related effect on FEV_1 results, with the greatest decrease from pre-dose values occurring in the VR040 400 µg group.

None of the changes that occurred from pre- to post-dose in FEV_1 values were of clinical significance. No patient withdrew from the study due to AEs. There was no dose-related pattern of AEs, and there were no clinically significant changes in laboratory or vital sign parameters.

Conclusions

VR040 was well tolerated, and no serious adverse events (SAEs) were reported at any dose during the study. Most TEAEs were considered mild to moderate. No consistent dose-related pattern was evident in the occurrence of AEs and treatment-related AEs, laboratory results, ECG values, lung function, or vital sign measures. No patient experienced an SAE or discontinued from the study due to an AE. Based on the safety analysis, the MTD of VR040 was not determined from the dose range studied.

PK analysis confirmed that maximum apomorphine plasma concentrations were measured 1-3 minutes after dosing. Furthermore, dose proportionality was demonstrated for $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, and C_{max}.

Whilst the study was not powered for meaningful statistical comparisons, VR040-induced conversion to an "on" state from an "off" state was observed in 5 out of 18 patients. The median onset of therapeutic effect in responders was 10 minutes (and the onset was as rapid as 4 minutes) after inhalation of VR040. The median duration of effect in VR040 responders was 10 minutes (duration was up to 40 minutes in some patients).

In an exploratory analysis of patients converting to an "on" state or a "partial on" state, 10/18 patients (55.6%) treated with VR040 responded, compared to 4/6 patients (66.7%) treated with placebo. The median onset of converting to an "on" state or a "partial on" state was 10 minutes after inhalation of VR040, and the median duration of effect was 25 minutes (duration was up to 62 minutes in some patients). No patient was fully converted to an "on" state in the low dose (VR040 400 µg) group, suggestive of a no-effect level.