Study Title

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

Study Centre

11 centres (9 centres in the United Kingdom and 2 centres in Serbia) screened patients, and 9 of these centres randomised patients.

Study Period		**Phase of Development**
Date of first patient first visit	26 March 2007	2a
Date of last patient last visit	29 August 2007	

Objectives

- To explore the efficacy of VR040 in controlling "off" periods as measured by the primary and secondary efficacy criteria in patients with idiopathic Parkinson's disease (PD) who have motor fluctuations with recognisable motor "off" periods.
- To compare the efficacy of VR040 with that of placebo.
- To explore the safety/tolerability profile of VR040 as measured by the incidence and severity of spontaneously reported adverse events (AEs), vital signs, electrocardiograms (ECGs), lung function and laboratory test results.
- To explore the pharmacokinetic (PK) profile of VR040.

Methodology

This was a clinic-based, Phase 2a, randomised, double-blind, placebo-controlled, ascending-dose, multicentre study of VR040 in patients with established idiopathic PD at approximate nominal doses of 3200 µg, 4800 µg, 6400 µg and 9000 µg equating to approximate fine particle doses of 1500 µg, 2300 µg, 3000 µg and 4000 µg, respectively.

Study participation included a Screening Visit, dose escalation at 1 or 2 Treatment Visits and an End-of- Study Visit. Dopaminergic challenge was performed at Screening to assess dopaminergic responsiveness of the patients. Patients were randomised to study treatment (VR040 or placebo) in the ratio of 2:1 (active:placebo). During Visit 1, the first dose of study treatment (3200 µg nominal dose of VR040 or placebo) was administered to patients via the Aspirair® inhaler; all administrations of study drug were performed by the study staff. Pre and post each administration of study drug, various study assessments including safety measures were completed. Once the patient had returned to an "off" state, a possible second dose of study treatment (4800 µg nominal dose of VR040 or placebo) was administered. If appropriate, a similar sequence of events occurred at Treatment Visit 2, with active drug doses of 6400 µg or placebo and then 9000 µg or placebo administered. At any time during the treatment period, if a patient did not tolerate treatment and/or optimal efficacy to the treatment was achieved, the patient discontinued dose escalation and proceeded to the End-of-Study Visit.

A subset of patients provided blood samples for PK analysis at 1 treatment administration at 1 dosing visit (Visit 1 or Visit 2).
Number of Subjects (Planned and Analysed) Planned: 48; Randomised: 47 (Intent-to-treat [ITT] Population: 47 [32 active, 15 placebo]; Per-protocol [PP] Population: 46 [31 active, 15 placebo]; PK Population: 10)
Main Criteria for Inclusion • Male and female patients aged between 30 and 90 years. • Patients who were diagnosed with advancing idiopathic PD of at least 5 years duration and classified as Hoehn & Yahr stage II-IV in "on" state. • Patients who experienced motor fluctuations associated with advancing PD and receiving optimised oral therapy, including levodopa (LD) 300 to 1500 mg/day (in combination with decarboxylase inhibitors), for at least 30 days before Screening.
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 Each patient was to participate in this study for up to a maximum of about 30 weeks.
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:** • The Unified Parkinson's Disease Rating Scale III (UPDRS III): assessed at Screening and at each time-point at Visits 1 and 2 post-dose • Disease state self-assessment: volunteered by patients when they felt that they had converted from an "off" to an "on" state. • The time to improvement from "off" to "on" disease state and the duration of therapeutic effect.

Safety:

The safety variables assessed during this study were as follows:

1. Incidence of treatment-emergent adverse events (TEAEs) during the treatment period
2. Changes in laboratory tests from Screening to End-of-Study Visit; incidence of clinically abnormal results. Concomitant medications were recorded at Visits 1, 2, and 3.
3. Changes in lung function test (forced expiratory volume in 1 second [FEV1]) and vital signs (comparisons of pre- and post-dosing for each treatment administration and from Screening to End-of- Study Visit), 12-lead traditional ECG recordings (measured at Screening, at pre-dose Visits 1 and 2 and at End-of-Study Visit) and 12-lead continuous Holter ECG recordings (commenced pre-dose at Visits 1 and 2 through about 90 minutes post-dose).

Pharmacokinetics

For a subset of patients, a blood sample for the PK analysis was taken at pre-dose and at 1, 4, 7, 20, 30, 50, 70 and 90 minutes post-dose at 1 of their treatment administrations at 1 of their dosing visits (Visit 1 or Visit 2). 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 plasma concentration (t_{max}), maximum drug concentration in plasma (C_{max}), terminal half- life ($t_{1/2}$) and terminal rate constant (λz).

Statistical Methods

There were 4 patient populations defined for the study analyses:

- All Available Patient Population: All patients who consented for the study were used for patient accountability and listings.
- ITT Population: All patients who were randomised, received a dose of study treatment in the clinic and had at least one available post-dose efficacy measurement.
- PP Population: All patients in the ITT Population who participated in the study without major protocol deviation.
- PK Population: A subset of patients underwent blood sampling for PK analysis at each dose, with no individual patient being selected on more than 1 occasion. The dose at which a patient was to undergo blood sampling for PK analyses was determined in a random manner. A list that assigned patients to the dose for PK sampling was generated electronically, specifying the kit number and the selected dose level (1-4). The PK sampling was weighted so that more patients were assigned to the 2 higher doses in anticipation that patients may be withdrawn prior to reaching the fourth dose.

Demographic and efficacy analyses were carried out using the PP and ITT Populations. The safety analysis was carried out on the ITT Population. Summary statistics were presented for continuous variables, by way of number of patients, geometric mean, coefficient of variation (% CV), standard deviation (SD), median, minimum and maximum and by way of group frequencies and percentages for categories of categorical variables. For all categorical efficacy parameters, comparison of treatment groups was performed using Generalised Linear Models or Cochran-Mantel-Hänszel test unless otherwise stated. Other efficacy parameters were analysed using appropriate statistical methods such as analysis of variance techniques (continuous data) and survival techniques (time to event data). The data included in the primary and secondary efficacy analyses were restricted to the information collected while the patient was receiving his or her maximum dose. Information was pooled over doses within treatment group, so that tables and figures included only the overall summaries of response to VR040 and placebo.

Efficacy Analysis

Primary Efficacy Endpoint

Maximum change in the UPDRS III score from pre-dose to post-dose, which relates to the highest dose of the active drug received by an individual patient versus placebo.

Secondary Efficacy Endpoints

- Time to improvement from "off" to "on" state after treatment administration.
- Proportion of patients converting from "off" to "on" state anytime after treatment administration.
- Duration for which patients remain in an "on" state after treatment administration.

Primary and secondary efficacy parameters were summarised by dose.

Safety Analyses

Safety data were summarised and presented in tables for all patients (ITT Population): AEs, clinical laboratory evaluations, vital signs, FEV_1, and 12-lead ECG recordings.

Pharmacokinetic Analysis

- C_{max} – Maximum Plasma Concentration
- t_{max} – Time to Maximum Plasma Concentration
- λz – Terminal Rate Constant
- $t_{1/2}$ – Terminal Half-life
- $AUC_{0\text{-}90}$ – Area Under the Plasma Concentration Time Curve
- $AUC_{0\text{-}inf}$ – Area Under the Plasma Concentration Time Curve to Infinity

Results

Treatment with VR040 had an appreciable impact on motor features of PD during this study as the active treatment group demonstrated the following compared with the placebo group:

- Statistically significant improvements in the active group compared with the placebo group, at the highest dose received, in the mean maximum change in the total UPDRS III score (P = 0.016).
- A higher number of patients (20, 62.5%) converted to an "on" state at any time post-dosing in the active treatment group compared with the placebo group (5, 33.3%).
- A statistically significant more rapid time to improvement from an "off" to an "on" disease state for the active group compared to placebo (P = 0.048).
- The median duration for which the active treatment group remained in an "on" state was 72 minutes (and duration was up to 169 minutes in some patients) compared with 65 minutes for the placebo group.

Pharmacokinetic Results

VR040 was rapidly absorbed with peak plasma concentration observed at 1 to 20 minutes post-inhalation. A very rapid attainment of mean t_{max} of 2 to7 minutes after dose administration was noted. There was no apparent dose-response relationship between the mean values for $AUC_{0-9)}$, $AUC_{0-in)}$ and C_{max} and the dose of VR040 administered.

		Treatment Group – VR040			
		3200 µg	**4800 µg**	**6400 µg**	**9000 µg**
		(1500 µg)	**(2300 µg)**	**(3000 µg)**	**(4000 µg)**
Parameter	**Statistic**	**(N=5)**	**(N=1)**	**(N=3)**	**(N=1)**
AUC_{0-90} (ng.min/mL)	Mean (SD)	103.89 (71.58)	642.35	385.62 (190.10)	645.52
AUC_{0-inf} (ng.min/mL)	Mean (SD)	171.58 (145.87)	675.77	458.17 (15.47)	817.17
C_{max} (ng/mL)	Mean (SD)	3.68 (2.55)	26.60	16.00 (15.47)	21.80
λz (l/min)	Mean (SD)	0.018 (0.008)	0.03	0.02 (0.00)	0.02
t_{max} (min)	Mean (SD)	2.2 (1.6)	7.0	7.3 (11)	4.0
$t_{1/2}$ (min)	Mean (SD)	58.73 (31.53)	20.32	32.44 (3.51)	31.23

Safety Results:

Overall, VR040, at doses of 3200 μg, 4800 μg, 6400 μg and 9000 μg, was well tolerated. There were no clinically significant differences observed between active treatment groups (including all dose levels) and the placebo group for any safety variable. Few patients experienced TEAEs, and there were no notable differences in types or frequencies of TEAEs between treatment groups. Nervous system disorders were reported by all patients on the day of dosing. In the VR040 3200 μg dose group the following TEAEs were reported by 1 patient each: dizziness, dysgeusia, somnolence and orthostatic hypotension. In the VR040 6400 μg dose group the following TEAEs were reported by 1 patient each: somnolence, yawning and flushing. In the placebo group the following TEAEs were reported by 1 patient each: "on" and "off" phenomenon, somnolence and hypertensive crisis.

All of the TEAEs reported on the day of dosing in the active treatment groups were considered related to study drug, whereas none of the TEAEs on the day of dosing in the placebo groups were considered related to study drug.

In the VR040 group the following TEAEs were reported between study visits by 1 patient each: constipation, dyspepsia, peripheral oedema, contusion, "on" and "off" phenomenon, Parkinsonism and abnormal dreams. In the placebo group the following TEAEs were reported by 1 patient each: head injury and abnormal dreams.

None of the TEAEs reported by the active treatment group between study visits was considered related to study treatment compared with 1 of 2 TEAEs reported between study visits by patients in the placebo group. All TEAEs were rated as mild or moderate in severity. One serious adverse event (SAE) was reported; this SAE of digestive system disorder (constipation) was reported by 1 patient in the active treatment group and occurred between study visits. This SAE was not considered related to study drug. There were no withdrawals due to AEs, and no deaths were reported during the study.

There was no evidence of an effect of VR040 on changes in clinical laboratory parameters. There was no dose- or treatment-related pattern of changes in vital signs. For most ECG variables, changes over time as measured by 12-lead continuous Holter ECG were comparable across treatment groups. The absence of significant QT-interval prolongation suggests that this formulation of apomorphine, in the doses studied, has no important pro- arrhythmic manifestations.

Pre- and post-dose heart rate and PR interval values were similar among groups including the placebo group. The mean and median heart rates in the post-dose populations were slightly higher than those in the pre-dose groups; this change, however, was clinically insignificant. The mean changes in PR interval were not clinically meaningful. The QRS intervals were normal in all patients prior to dosing, and no clinically relevant changes were recorded after dosing. Uncorrected QT intervals decreased slightly post dose in 3 of the 4 VR040 groups and in the placebo group compared to the values recorded prior to dosing, with a minimal

prolongation reported in the VR040 6400 µg dose group; these changes were not clinically significant. None of the individual 90-minute post-dose ECG values was considered to show clinically significant changes or abnormalities.
Mean changes in FEV_1 and % FEV_1 from pre-dose to 90-minutes post-dose varied among treatment groups. No evidence of dose-related changes was observed in lung function.

Conclusions

Treatment with VR040 had an impact on idiopathic PD motor features as compared with placebo. VR040 demonstrated a statistically significant improvement in the mean change in the total UPDRS III score at the highest dose received; demonstrated a statistically significantly shorter time to improvement from an "off" to an "on" disease state. In addition, administration of VR040 was successful in aborting "off" periods and debilitating periods of complete or partial immobility with the therapeutic effect typically lasting for ~70 minutes post-dose administration.
Overall, VR040, at doses of 3200 µg, 4800 µg, 6400 µg and 9000 µg, was well tolerated. There were no important differences observed between active treatment groups and the placebo group for any safety variable. Few patients experienced TEAEs, and there were no notable differences in types or frequencies of TEAEs between treatment groups. All TEAEs were rated as mild or moderate in severity. One SAE was reported; this SAE of digestive system disorder (constipation) was reported by a patient in the active treatment group and occurred between study visits. This SAE was not considered related to study drug. There were no withdrawals due to AEs, and no deaths were reported during the study.
There was no evidence of an effect of VR040 on changes in clinical laboratory parameters, vital signs, ECG (Holter and traditional ECG) parameters and lung function. None of the individual post-dose ECG values were considered to show clinically significant changes or abnormalities. There was no significant QT- interval prolongation, which suggests that this formulation of apomorphine, in the doses studied, has no important pro-arrhythmic manifestations.
Pharmacokinetic analysis confirmed that VR040 was absorbed with peak plasma concentration observed at 1 to 20 minutes post-inhalation. A very rapid attainment of mean tmax of 2 to 7 minutes after dose administration was noted. There was no apparent dose-response relationship between the mean values for $AUC_{0\text{-}90}$, $AUC_{0\text{-}inf}$ and C_{max} and the dose of VR040 administered. However, the C_{max} data suggest an increase in delivery efficiency at VR040 6400 µg compared with VR040 3200 µg.