Title of Study

A Phase IIb, randomised, double-blind, placebo-controlled, parallel-group study investigating the efficacy and safety of apomorphine inhalation powder in subjects with "on-off" or "wearing off" effects associated with Parkinson's disease

Study Centre

This study was conducted at 16 centres in the United Kingdom, Germany, and Italy.

Study Period		**Phase of Development**
Date of first screening	12 January 2009	2b
Date of last completed	15 July 2010	

Objectives

- To identify optimal doses of apomorphine inhalation powder (VR040) for future evaluation in controlling the "on-off" and "wearing off" effects associated with fluctuating idiopathic Parkinson's disease (PD).

In-Clinic objectives:

- To determine the efficacy of VR040 in controlling the "on-off" and "wearing off" effects associated with fluctuating idiopathic PD as determined by Unified Parkinson's Disease Rating Scale - Part 3 (UPDRS III) assessments.
- To determine the safety/tolerability profile of VR040 as assessed by the incidence and severity of spontaneously reported adverse events (AEs), vital signs (with orthostatic challenge), electrocardiograms (ECGs), lung function tests, laboratory measurements, and physical examinations.

At-Home objectives:

- To determine the efficacy of VR040 in controlling the "on-off" and "wearing off" effects associated with fluctuating idiopathic PD as determined by subject Diary Card data.
- To determine the safety/tolerability profile of VR040 as assessed by the incidence and severity of spontaneously reported AEs.

Methodology

This was a clinic- and home-based, Phase 2b, randomised, double-blind, placebo-controlled, parallel-group, dose titration, multicentre study in subjects with fluctuating idiopathic PD.

Screening Period: During the Screening Period, subjects provided written informed consent, and they were assessed for eligibility including confirmation of dopaminergic responsiveness to standard prescribed levodopa (LD) treatment defined by ≥30% change (reduction) in UPDRS III score compared to the value pre-LD administration. With respect to this assessment, subjects were required to omit their standard prescribed anti-PD medication. Subjects were trained on using the Aspirair® inhaler and instructed to complete a Diary Card and to take domperidone (or an equivalent anti-emetic) for the 3 consecutive days prior to Visit 1.

In-Clinic Dosing Titration Period: Subjects were instructed to withhold doses of LD and dopaminergic treatment (and any other anti-PD medication) after midnight prior to Visit 1. At Visit 1, which occurred 3 to 14 days after screening, subjects were randomised to study treatment (VR040 or placebo). Before their first dose of study treatment, the subjects confirmed via the Disease State Assessment questionnaire that they were in an "off" state. The first dose of study treatment (1.5 mg fine particle dose [FPD] of VR040 or placebo) was then self-administered by subjects under medical supervision. Before and after the first dose of study drug, various study assessments to evaluate safety and efficacy were completed. The investigator compared the resultant data to pre-defined tolerability and efficacy criteria and decided if a second (same strength) study dose was to be administered. If the first dose was not tolerated, the subject was withdrawn from the study and was asked to return to the clinic in about 1 week for the Close-Out Visit. If the first dose was tolerated and efficacious, a second dose at the same strength was administered after a minimum dosing interval of 40 minutes. If this second dose was tolerated, the subject proceeded to the At-Home Dosing Period. If the first dose was tolerated but was not efficacious, the subject proceeded to Visit 2 for further dose titration. A subject continued to receive predefined escalated doses at Visits 2, 3, and 4 until an efficacious and tolerated dose was identified. Visits 2, 3, and 4 occurred after every 1 to 14 days. The same procedures were repeated for Visits 2, 3, and 4 with increasing doses of VR040 (2.5 mg FPD, 3.5 mg FPD, and 4.5 mg FPD, respectively) or placebo. However, at Visit 4, even if the first dose was not efficacious, if the first and second doses were tolerated, the subject proceeded to the At-Home Dosing Period on this tolerable dose.

At-Home Dosing Period: During the At-Home Dosing Period (up to 32 days in duration), subjects took their study medication for the treatment of sudden "on-off" or "wearing off" episodes up to 5 times per day. Subjects recorded required diary card data. Halfway through the At-Home Dosing Period (i.e., 14 ± 2 days after the optimal dosing visit), subjects returned to the clinic for Visit 5. If adequate efficacy (based on the diary data) and tolerability (based on the reported AEs) of the At-Home dose of study medication was confirmed, the subjects continued with the applicable Visit 5 safety assessments and resumed the At-Home Dosing Period at their current dose level. If the At-Home dosing regimen was found inadequate, there was the option to increase the dose of study medication by up to 2 dose levels at this visit (depending on the tolerability and efficacy of the increased doses). If the subject was already at the highest dose level, the subject was withdrawn and returned for the Close-Out Visit. If the current At-Home dose had not been tolerated, the dose of study medication was reduced to the next lower dose, and the subject continued with the applicable Visit 5 safety procedures and assessments. If the lower dose was not tolerated and/or efficacious, the subject was withdrawn and returned for the Close-Out Visit. If the subject was already at the lowest dose and did not tolerate it, the subject was withdrawn and returned for the Close-Out Visit. The subject continued with the applicable Visit 5 safety and efficacy procedures and assessments.
Visit 6 (End-of-Treatment Visit) occurred 14 ± 2 days after Visit 5.
Visit 7, the Close-Out Visit, occurred up to 7 days after Visit 6 or when a subject discontinued early from the study.

Number of Subjects (Planned and Analysed)
A total of 66 subjects were planned to be randomised in a 2:1 ratio to VR040 or placebo to provide 63 evaluable subjects (42 in the active treatment group and 21 in the placebo group) for the In-Clinic Dosing Titration Period and 57 evaluable subjects (38 in the active treatment group and 19 in the placebo group) for the At-Home Dosing Period. A total of 73 subjects were screened. Of these, 57 subjects were randomised: 41 subjects were randomised to ascending doses of VR040, and 16 subjects were randomised to placebo. Subjects were randomised centrally in blocks of 3, and the slight imbalance between the treatment groups is due to the number of sites requiring assignment of incomplete blocks. Data were collected for screen failures but only recorded in the database if they experienced an AE during the Screening Period. There were 16 screen failures but 1 subject (Subject 106-003) experienced an AE of respiratory tract infection and was included in the All Available Subject (AAP) population. The AAP population consisted of 58 subjects: 1 screen failure experiencing an AE and 57 randomised subjects. Two subjects (Subject 305-004 in the VR040 group and Subject 304-012 in the placebo group) were randomised but did not receive any dose. The ITT population consisted of 55 treated subjects: 40 subjects receiving VR040 and 15 subjects in the placebo group. Of these, 42 subjects (29 VR040 and 13 placebo) were included in the Per-Protocol (PP) population for the In-Clinic Dosing Titration Period. A total of 39 subjects completed the In-Clinic Dosing Titration Period: 29/40 subjects in the VR040 group and 10/15 subjects in the placebo group. However, one subject (Subject 102-001) who entered the At-Home Dosing Period did not receive any dose during that period and was not included in the mITT population. Of the 38 subjects who entered the At-Home Dosing Period, received a dose, and had diary data (the mITT population), 21 subjects completed both parts of the At-Home Dosing Period: 19/28 subjects in the VR040 group and 2/10 subjects in the placebo group. The PP population for the At-Home Dosing Period included 29 subjects (20 VR040 and 9 placebo).

Diagnosis and Main Criteria for Inclusion

Male and female subject between the ages of 30 and 90 years with a clinical diagnosis of PD of at least 5 years duration; who fulfilled Steps 1 and 2 of the United Kingdom (UK) Brain Bank Criteria, classified as Hoehn and Yahr Stage II-IV in an "on" state; had suffered from motor fluctuations associated with fluctuating idiopathic PD and a minimum of a 2-hour average daily "off" time; and showed dopaminergic responsiveness at Screening to standard prescribed anti-PD treatment (defined by ≥30% change [reduction] in UPDRS III score compared to the pre-LD-dose value) were included in the study.

Subjects had to be optimised on oral therapy, including LD, not greater than 1500 mg/day (in combination with decarboxylase inhibitors) at least 30 days before Screening; also, subjects had to be receiving (for at least 30 days), or had received in the past, but discontinued due to AEs, at least 1 of the following types of medications: dopamine agonist (DA), catechol-O-methyltransferase inhibitor (COMT), or monoamine oxidase B inhibitor (MAOB). Subjects had to understand (with carer assistance) their daily PD medications.

Test Product, Dose and Mode of Administration

Test product: VR040 (apomorphine inhalation powder)

Dose: Delivered doses of 1.8, 2.8, 4.0 and 5.8 mg apomorphine hydrochloride, equivalent to fine particle doses (FPDs) of 1.5, 2.5, 3.5, and 4.5 mg and nominal doses of 2.3, 3.5, 5.0, and 7.3 mg (see the following table).

Mode of administration: VR040 was administered using the Aspirair® inhaler.

Duration of Treatment

Each subject was to participate in this study for up to a maximum of about 17 weeks through Visit 7 (the Close-Out Visit).

Reference Product, Dose and Mode of Administration

Reference therapy: Matching placebo inhalation powder (identical in appearance to VR040).

Mode of administration: The placebo inhalation powder was administered using the Aspirair® inhaler.

Criteria for Evaluation

Efficacy:

The efficacy parameters included the UPDRS III assessments, Disease State Assessment questionnaire results, and Diary Card information.

Safety:

The safety parameters included the incidence of treatment-emergent AEs (TEAEs) during the treatment period; changes in laboratory tests from Screening to the End-of-Treatment Visit (or Close-Out Visit, if applicable); changes in physical examination from Screening to the Close-Out Visit; and changes in vital signs, ECG recordings, forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV_1) from pre-dose to post-dose for each treatment administration at drug assessment visits and from Screening to the End-of- Treatment or Close-Out Visit.

Statistical Methods

All statistical methods were based on the International Conference on Harmonisation (ICH)-E9 Guidance for Industry "Statistical Principles for Clinical Trials". All statistical programming and analyses were performed using SAS®, Version 9.2. All planned analyses presented are from the final Statistical Analysis Plan (SAP) dated 08 June 2010.

There were 4 subject populations defined for study analyses:

- All Available Subject (AAP) population: All subjects who had consented for the study. This population included all screening failures with AEs and all randomised subjects (whether or not receiving treatment).
- Intent-to-Treat (ITT) population: All subjects who had been randomised and received at least 1 dose of study treatment in the clinic.
- Modified ITT (mITT) population: All subjects in the ITT population who had entered the At-Home Dosing Period and had Diary Card data available.
- Per-Protocol (PP) population: All subjects in the ITT population who participated in the study without a major protocol deviation. The PP population was defined at 2 time points: In-Clinic Dosing Titration Period (PP population—In-Clinic) and At-Home Dosing Period (PP population—At-Home).

The AAP population was used for subject accountability and listings. Demographic and efficacy analyses were carried out using the PP (In-Clinic and At-Home), ITT (In-Clinic), and mITT (At-Home) populations. The safety analyses were carried out on the ITT population.

Continuous variables were summarised by the number of subjects evaluated (N), minimum, maximum, mean, least squares mean (LS mean), 95% confidence interval (CI), median, standard deviation (SD), and standard error (SE).

Categorical variables were presented as the number of non-missing observations and percentages. The denominator for each percentage was the number of subjects within the population treatment arm as appropriate (unless otherwise specified).

No adjustment for multiplicity was required as both co-primary endpoints needed to be significant.

All hypotheses were tested at the 5% (2-sided) significance level unless stated otherwise. The co-primary efficacy endpoints were powered at 80% to detect a change in "off" time per day of 2 hours (SD: 2.5), and a difference of 12 (SD: 16) in the maximum change in UPDRS III between the treatment groups. The study was not powered for secondary endpoints.

- For all categorical efficacy parameters, comparison of treatment groups was performed using generalised linear models or the 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 in the clinic included the information collected while the subject received the optimal dose level (last efficacious dose received), or the last dose received (for subjects who did not reach an optimal dose level).
- The data included in the primary and secondary efficacy analyses for the overall At-Home Dosing Period included all acceptable diary information ("acceptable" defined as having no more than 6 lines [30- minute periods] with no response or >1 response) from both parts of the period for subjects who completed the study without dose adjustment; or the diary information corresponding to the first part of the At-Home Dosing Period for subjects who did not continue after Visit 5; or the diary information corresponding to the second part of the At-Home Dosing Period for subjects who completed the study with adose adjustment at Visit 5/5b. For analyses of each part of the At-Home Dosing Period, data included diary information from all days of the part being used in the analysis.
- Information was sometimes pooled over doses within treatment group, so that tables and figures included only the overall summaries of response to VR040 and placebo.

Co-Primary Efficacy Endpoints

One of the co-primary efficacy endpoints, the change from baseline in "off" time per day, was derived from the 3-consecutive-day subject diary information completed prior to Visit 1 and prior to Visits 5 and 6 during the At- Home Dosing Period. The other co-primary efficacy endpoint, the maximum change in total UPDRS III score from pre-dose to post-dose, was determined from In-Clinic measurements.

Secondary Efficacy Endpoints

The key secondary endpoints were as follows:

- Proportion of "off" events per day aborted by study treatment
- Interval between dose administration and onset of "on" state*
- Period from onset of "on" state to return to an "off" state**
- Mean daily duration of "on" without dyskinesias
- Mean daily duration of "on" with non-troublesome dyskinesias
- Mean daily duration of "on" with troublesome dyskinesias

*Derived from the Diary Card: the onset of action of study medication.

**Derived from the Diary Card: the duration of action of study medication.

Primary Safety Endpoints

- AEs – the number of AEs, the proportion of subjects having at least 1 AE, and AEs by coded terms were presented.
- Clinical laboratory evaluations – including mean change from Screening to the last value (recorded at the End-of-Treatment Visit or the Close-Out Visit) and incidence of clinically abnormal results.
- Vital signs – comparison of pre- and post-dosing results at each treatment administration and from Screening to the Close-Out Visit. This information was presented for each dose level of VR040 and for the last dose received of placebo.
- FVC and FEV_1 – comparison of pre- and post-dosing results at each treatment administration and from Screening to the Close-Out Visit. This information was presented for each dose level of VR040 and for the last dose received of placebo.
- ECGs – comparison of pre- and post-dosing results at each In-Clinic treatment administration and from Screening to the Close-Out Visit. This information was presented for each dose level of VR040 and for the last dose received of placebo.
- Physical examination – comparison of results from Screening to the Close-Out Visit.

Summary Results

Efficacy Results:

The study was powered to conduct statistical comparisons for the co-primary endpoints only.

In-Clinic Dosing Titration Period, Co-Primary Efficacy Endpoint

- A statistically significant and clinically relevant reduction from baseline in the mean best (lowest) post-dose total UPDRS III score was observed in the VR040 group (LS mean [SE]: -18.7 [2.2]) compared with the placebo group (LS mean [SE]: -10.3 [3.2]) during the In-Clinic Dosing Titration Period (LS mean difference: -8.4; 95% CI: -15.5, -1.2; p = 0.023).

In the VR040 group, 24/40 (60%) subjects achieved Optimal Efficacy compared to 5/15 (33.3%) subjects in the placebo group (p = 0.144).

- Of the 24 responders in the VR040 group, Optimal Efficacy was achieved by 8 (33.3%) subjects on 1.5 mg, 9 (37.5%) subjects on 2.5 mg, 5 (20.8%) subjects on 3.5 mg, and 2 (8.3%) subjects on 4.5 mg FPD.

At-Home Dosing Period

Co-Primary Efficacy Endpoint

- A greater reduction from baseline in the mean "off" time per day was observed in the VR040 group (LS mean [SE]: -148.4 [32.0] minutes) compared with the placebo group (LS mean [SE]: -47.9 [49.7] minutes) during the last 3 days of the At-Home Dosing Period; the difference between groups (LS mean difference: -100.5; 95% CI: -212.9, 12.0) was meaningful, but not statistically significant at the 5% level (p = 0.078).

Key Secondary Efficacy Endpoints

- Diary card data collected during the entire At-Home Dosing Period demonstrated that VR040 aborted 85.0% of 1071 treated "off" episodes compared to placebo, which aborted 13.0% of 262 treated "off" episodes.
- The median proportion of treated "off" episodes aborted daily by VR040 treatment (75.84%) was greater compared with the median proportion of treated "off" episodes aborted daily by placebo (4.35%) during the entire At-Home Dosing Period. The median difference between the groups was statistically significant (p <0.001). The median proportions of treated "wearing off" and treated "sudden off" episodes aborted daily by VR040 treatment (64.29% and 33.31%, respectively) were also significantly greater compared with the proportions of episodes aborted by placebo (0% and 3.85%, respectively); p < 0.001 and p = 0.026, respectively.
- The onset of action (interval between dose administration and onset of "on" state) was more rapid in the VR040 group (median time: 5.5 minutes) compared with the placebo group (median time: 15.0 minutes) during the entire At-Home Dosing Period; the difference between groups was statistically significant (p<0.001). Some (9/26) subjects converted to the "on" state as early as within the first 2 minutes post dosing. The onset of action following "wearing off" and "sudden off" episodes was more rapid in the VR040 group (median time: 5 minutes and 7 minutes, respectively) compared with the placebo group (median time: 10 minutes and 15 minutes, respectively); the difference between groups was significant for "sudden off" episodes (p < 0.001).

- The median duration from the onset of an "on" state to the return to an "off" state was 56 minutes for the 85.0% of aborted "off" episodes for the VR040 group compared with 68 minutes for the 13.0% of aborted "off" episodes for the placebo group during the entire At-Home Dosing Period. The median duration from the onset of an "on" state to the return to an "off" state following "wearing off" episodes was shorter for the VR040 group (49 minutes) compared with the placebo group (80 minutes), and the median duration from the onset of an "on" state to the return to an "off" state following "sudden off" episodes was similar in the VR040 group (60 minutes) and the placebo group (57 minutes). Differences between groups were not statistically significant.
- At Screening, most daily "on" time, for all subjects, was without dyskinesia or with non-troublesome dyskinesia. Subjects in the VR040 group experienced an increase in mean daily "on" time with no dyskinesia or with non-troublesome dyskinesia compared with the placebo group during the last 3 days of the At-Home Dosing Period, but the difference between groups was not statistically significant. The median of the mean daily duration of "on" state with troublesome dyskinesia did not change from Screening in either group.

Safety Results

Despite the use of an orthostatic challenge, successive doses being administered over a short period, and some subjects choosing not to administer a concomitant anti-emetic, no safety concerns, beyond expected dopaminergic effects, were identified post VR040 exposure in-clinic and at-home. Although slightly more than in the placebo group, relatively few VR040 subjects reported treatment-related AEs with these being mild or moderate in severity. There was a low incidence of typical dopaminergic stimulation effects such as nausea, hypotension, and somnolence. Furthermore, there was no indication of local tolerability issues post treatment administration. No clinically relevant changes in lung function were observed. Monitoring of 12-lead ECGs did not identify any QTcB absolute values or changes from pre-dose to post-dose beyond regulatory criteria indicative of potential safety concerns.

Adverse Events During In-Clinic Dosing Titration Period

Overall, 12 (30.0%) subjects experienced 30 TEAEs in the VR040 group and 3 (20.0%) subjects experienced 3 TEAEs in the placebo group. On the day of study drug dosing, 11 (27.5%) subjects in the VR040 group and none in the placebo group reported TEAEs. Most of the TEAEs in the VR040 group were reported following the administration of the VR040 1.5 mg and 2.5 mg doses, which were the doses most administered. The most commonly affected System Organ Classes (SOCs) in the VR040 group were nervous system disorders and vascular disorders (17.5% of subjects each), followed by general disorders and administration site conditions (5.0%). The most frequently reported TEAEs in the VR040 group were dizziness and hypertension reported by 4 (10.0%) subjects each.

Overall, 10 (25.0%) subjects in the VR040 group and no subject in the placebo group had treatment-related TEAEs. Most of the treatment-related TEAEs in the VR040 group were reported following administration of VR040 1.5 mg and 2.5 mg doses. The most frequently reported treatment-related TEAE was dizziness reported by 4 (10.0%) subjects.

Adverse Events During At-Home Dosing Period

Overall, 10 (35.7%) subjects experienced 23 TEAEs in the VR040 group and 2 (20.0%) subjects experienced 2 TEAEs in the placebo group. About 25% of subjects reported TEAEs after the administration of VR040 1.5, 2.5, and 3.5 mg, and about 50% of subjects after the administration of VR040 4.5 mg.

In the VR040 group, the most commonly affected SOCs were gastrointestinal disorders (14.3% of subjects), respiratory, thoracic and mediastinal disorders (14.3%), and nervous system disorders (10.7%). The most frequently reported TEAE in the VR040 group was nausea reported by 3 (10.7%) subjects, followed by palpitations, cough, and yawning (reported by 2 [7.1%] subjects each). In the placebo group, 1 subject reported nausea, and 1 subject reported epistaxis.

Overall, 6 (21.4%) subjects in the VR040 group and 2 (20.0%) subjects in the placebo group had treatment- related TEAEs. Most treatment-related TEAEs were reported following administration of VR040 1.5 mg and 2.5 mg doses. The most frequently reported treatment-related TEAEs in the VR040 group were palpitations, nausea, and yawning, reported by 2 (7.1%) subjects each. The treatment-related TEAEs reported in the placebo group were nausea and epistaxis, reported by 1 (10.0%) subject each.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths or severe TEAEs were reported. There were 2 subjects who experienced SAEs during the study; 1 subject in the placebo group who had a serious SAE of periarthritis (frozen shoulder) prior to receiving study drug, and 1 subject in the VR040 group who had a serious TEAE of hypertensive crisis following administration of the first dose of study drug. The SAE of hypertensive crisis was of moderate intensity and was considered by the investigator as possibly related to study drug although the medical monitor considered it more likely related to venlafaxin, a concomitant medication the subject was taking for depression. The event resolved without sequelae on the same day, and the study drug was discontinued due to this event. There were no SAEs reported during the At-Home Dosing Period.

A total of 4 subjects in the VR040 group and none in the placebo group discontinued the study with AEs reported as the primary reason for withdrawal. One subject withdrew during the In-Clinic Dosing Titration Period due to the SAE of hypertensive crisis described above. One subject experienced orthostatic hypotension and dizziness leading to discontinuation during the In-Clinic Dosing Titration Period. A further subject experienced an AE of mild dizziness leading to discontinuation which started during the In-Clinic Dosing Titration Period, but withdrew during the At-Home Dosing Period. During the At-Home Dosing Period, one subject experienced palpitations, muscle spasms, and freezing phenomenon, which led to study discontinuation.

A further subject experienced AEs of vertigo (2 episodes), and palpitations (2 episodes) which led to study discontinuation, although these AEs were not the primary reason for withdrawal. All of these events were considered to be treatment-related.

Other Safety Parameters: Screening/Baseline to Visit 7 (close-out)

The changes from baseline in the mean values of haematology and biochemistry parameters at Visits 2 through 7 were generally small. Mean values at baseline and at Visit 7 (close-out) were consistently within normal limits for both groups. The values of a few haematology and biochemistry parameters were below or above normal limits at Screening, but did not change or worsen at Visit 7 (close-out). Although there were isolated changes in the values of haematology and biochemistry parameters at Visit 7 (close-out), no trend toward increasingly abnormal results over time was noted. There was no evidence of a clinically significant effect of VR040 on laboratory parameters.

The mean changes in vital signs (pulse, systolic BP, and diastolic BP) measured from baseline to close-out evaluations were minor and did not differ appreciably between the VR040 group and the placebo group. The mean changes in vital signs measured from pre-dose to 32 minutes post dose were minimal and did not differ appreciably between dose groups. The frequency of changes did not differ appreciably between groups and no trend towards dose-relationship was observed.

The mean changes in lung function (FVC [L], FEV_1 [L], FEV_1 [percent predicted]) measured from Screening to Visit 7 were minor and did not differ appreciably between the VR040 group and the placebo group.

The mean changes from baseline to Visit 7 in PR intervals, QRS intervals, QT intervals, QTcB intervals, and heart rates were minor and not clinically relevant. The results of ECG showed no signal of any effect on heart rate and PR and QRS interval durations. None of the changes were clinically relevant.

Most of the physical examination results were normal at Screening and remained normal throughout the study for both treatment groups. Few results were clinically significant at Screening and remained significant at Visit 7. Although there were isolated changes in the physical examination results at Visit 7 (close-out), no trend toward increasingly abnormal results over time was noted.

Summary - Conclusions

This study demonstrated that VR040 treatment resulted in:

- Clinically relevant and statistically significant "in-clinic" UPDRS III reductions compared to placebo subjects.
- More effective control, compared to placebo, of "on-off" and "wearing off" episodes in subjects with fluctuating idiopathic PD of Hoehn and Yahr staging II-IV.
- Reproducible and clinically relevant reductions in mean daily "off" time as assessed by subject diaries during a 4-week At-Home Dosing Period.
- Rapid and durable therapeutic benefit.
- The majority (over 90%) of the increased "on" time not being associated with troublesome dyskinesia.
- A positive safety profile post administration of multiple daily doses, sometimes over relatively short intervals, in a population comprising primarily apomorphine-naïve PD subjects.
- Reported adverse events generally consistent with dopaminergic stimulation.

The described outcomes are consistent with those previously reported from clinical study VR040/2/003, particularly with respect to UPDRS III improvements, rapidity and durability of therapeutic benefit, and safety/tolerability considerations.

It is concluded that VR040 dose exploration clinical studies have demonstrated that the majority of subjects are successfully treated with FPDs between 1.5 and 3.5 mg. Little additional therapeutic benefit is derived from exposure to the highest study FPD of 4.5 mg.