2 STUDY SYNOPSIS

Name of Sponsor/Company: Oxford BioMedica (UK) Ltd	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*For National Authority Use Only*
Name of Finished Product: ProSavin®		
Name of Active Ingredient: Lentiviral vector		

TITLE OF STUDY:
A Phase I/II Study of the Safety, Efficacy and Dose Evaluation of ProSavin®, Administered using Stereotactic Injection to the Striatum of Patients with Bilateral, Idiopathic Parkinson's Disease.

INVESTIGATORS:
This study was conducted by 6 investigators: Professor S Palfi (Principal Investigator, France); Professor P Remy; Dr B Jarraya; Professor R Barker (Principal Investigator, United Kingdom [UK]); Dr C Watts; Dr P Buttery.

STUDY CENTRES:
This study was conducted at 2 sites in 2 countries: Neurosurgery Department, Henri Mondor Hospital, France and The University of Cambridge Centre for Brain Repair, Cambridge, UK.

PUBLICATIONS:
Palfi S, Gurruchaga JM, Ralph GS *et al*. Long-term safety and tolerability of ProSavin, a lentiviral vector-based gene therapy for Parkinson's disease: a dose escalation, open-label, phase 1/2 trial. Lancet 2014; 383 (9923): 1138-46 (published online 10 Jan 2014)

STUDY PERIOD:	**DEVELOPMENT PHASE:**
First patient recruited: 14 January 2008 Last patient completed: 06 August 2012	I/II

OBJECTIVES:

Primary:

- To assess the safety of ProSavin®, injected bilaterally directly into the post-commissural putamen of patients with bilateral idiopathic Parkinson's disease (PD). Up to 3 dose levels (total vector load of 2 x 10^7 transducing units [TU], 4 x 10^7 TU or 10 x 10^7 TU) were assessed.
- To assess the patients for clinical efficacy following ProSavin administration.

Secondary:

- To assess the extent of L-dihidroxyphenylalanine (L-DOPA) therapy reduction following administration of ProSavin.

METHODS:
This was a Phase I/II dose determination study conducted in two parts to assess whether ProSavin was safe and efficacious. The first part was an open-label dose-escalation design. Three dose levels (2 x 10^7, 4 x 10^7 or 10 x 10^7 TU) were assessed in the first open-label phase of the study, in 4 cohorts. If satisfactory efficacy, as recommended by the Data Monitoring Committee (DMC), was observed at a particular dose level by 3 months after the last patient had been administered ProSavin, then 12 patients were to be enrolled in the second phase of the study, in a double-blind (patient and assessor) randomised manner to confirm the robustness of this observation. It was planned that 8 patients were to receive the selected dose of ProSavin and 4 patients were initially to receive sham surgery (without bone and dural penetration). Patients undergoing sham surgery in this part of the study were to have the option of active treatment with the selected dose of ProSavin 6 to 12 months after the study had been completed. However, following DMC review, it was decided not to proceed with the double-blind phase of the study.

After screening procedures confirmed eligibility, patients were hospitalised and ProSavin was injected bilaterally on 1 occasion into the post-commissural putamen nucleus via stereotactic injection. For patients in Cohorts 1 and 2a, ProSavin was administered to each of 4 and 5 separate tracts, respectively. However, for patients in Cohorts 2b and 3, ProSavin was administered to each of three separate tracts in order to avoid increasing surgical time. A minimum observation period of 28 days occurred between dosing the patients in Cohorts 1, 2a, and 2b and the first patient in Cohort 3. The remaining patients in Cohort 3 could be dosed in

parallel. At least 90 days elapsed between dosing patients from different cohorts. Following ProSavin administration, patients were assessed weekly for the first month post ProSavin administration. Assessment then took place monthly for the next 2 months (Months 2 and 3), then quarterly from 6 months until 12 months post ProSavin administration. All patients enrolled in France underwent positron emission tomography (PET) scans using ^{18}F-DOPA and ^{11}C-Raclopride at screening and 6 months following ProSavin administration. Following completion of the 12-month time point, patients were asked to consent to a separate open-label safety follow-up study (PS1-001-09), the results of which will be reported separately. Patients entered under Version 4.0 of the protocol were assessed quarterly from 6 months post ProSavin administration for 3 years (36 months) before consenting to Study PS1-001-09. In this study, long term annual monitoring continued alongside the standard of care therapy for life. If ProSavin demonstrated no clinical efficacy in any of the patients after 1 year following administration, then the patient could be offered alternative therapies such as deep brain stimulation of the subthalamic nucleus.

NUMBER OF PATIENTS:
Planned: Up to 27
Screened: 17
Randomised: 15
Completed: 15

INDICATION AND MAIN CRITERIA FOR INCLUSION:
Consenting male or female patients aged between 48 and 65 years with bilateral idiopathic PD diagnosed >5 years ago. Patients must have been Hoehn and Yahr Stage 3 and 4, and had a Unified Parkinson's Disease Rating Scale (UPDRS) (Part III) score of between 20 and 60 in the "OFF" state. Patients must have been responsive to dopaminergic therapy (50% improvement in UPDRS [Part III] between the "OFF" and "ON" states) and have motor fluctuations. Patients must have been willing to have their current treatment withdrawn for up to 24 hours prior to surgery and, therefore, been in an "OFF" state for surgery. Patients must also have been willing to have their L-DOPA dosage reduced/withdrawn at regular intervals following surgery to allow for the assessment of ProSavin in the absence of concomitant anti-parkinsonian medication.

TEST PRODUCT:
ProSavin was supplied in a Tris-hydrochloride/sodium chloride buffer formulated with sucrose and mannitol as cryo-protectants. The final formulation buffer was prepared in HyQ "Water for Injection" quality water, and the pH adjusted to 7.3 with sterile national formulary grade hydrochloric acid, followed by 0.2-µm sterile filtration. ProSavin was administered intrastriatally under general anaesthesia.

COMPARATOR PRODUCT:
Not applicable.

DURATION/FOLLOW-UP:
Each patient's participation started with a screening visit and ended at Month 12 (or Month 36 for patients entered under Version 4.0 of the protocol).

CRITERIA FOR EVALUATION:
Safety: Safety was assessed by evaluation of adverse events (AEs), humoral antibody response, safety laboratory tests, psychological tests, neuropsychological tests, polysomnography, ProSavin distribution, vital signs, physical examinations, hallucinations, electrocardiogram (ECG), and magnetic resonance imaging (MRI).
Efficacy: The primary efficacy endpoint was the total score and its percentage change from Screening in the patients' UPDRS Part III.
The secondary efficacy endpoints were: the number of patients who responded (ie, had a 50% reduction in total score for UPDRS Part III); UPDRS Part I, II and IV scores; the percentage change in the percentage of time during the waking day that the patient was in the "OFF" state as assessed by patient diaries from screening; the percentage change from screening in the patients' total score on activity of daily living using the Parkinson's Disease Questionnaire (PDQ-39); the percentage change from screening in the L-DOPA daily dose; the percentage change in dyskinesia rating scale from screening; the patients' response to ProSavin administration by assessment using the UPDRS Part III, 12 months following surgery; the percentage change from screening in motor cortical activity with the use of transcranial magnetic stimulation (TMS) (for patients enrolled in France only); the percentage change from screening in the nigrostriatal dopamine levels with the use of PET scans using ^{18}F-DOPA and ^{11}C-Raclopride (for patients enrolled in France only).

STATISTICAL METHODS:
Patients in Cohorts 1 and 2a were followed up until Month 36 in this study, whereas patients in Cohorts 2b and 3 were followed up until Month 12 within this study and subsequently entered the long-term follow-up study PSI-001-09. Data were, therefore, presented for all available visits in the outputs. Generally, efficacy endpoints were summarised using patient profile plots, mean plots, listings and summary tables. Safety endpoints were summarised using listings, with some AE summary tables. No formal statistical analyses were performed as Phase I of the study was not a randomised controlled study. For continuous variables, summary statistics including number of patients, mean, minimum and maximum were presented. For categorical variables, per category, the absolute counts (n) and percentages (%) of patients with data were presented. The efficacy endpoints were assessed at Month 6 unless otherwise stated.

RESULTS:
Demography: In total, 15 patients were enrolled in the study across 4 cohorts: 3 patients in each of Cohorts 1, 2a and 2b, and 6 patients in Cohort 3. All patients completed the study and continued into the follow-up study. Most patients in the study were Caucasian and two-thirds of patients were male. Mean time since PD diagnosis was 13.9 years.
Safety: Overall, 251 AEs were reported during the study; 15 of those being reported pre-surgery in 7 patients and 236 being reported post-surgery in 15 patients. Of all AEs, 222 were mild in intensity, 28 were moderate in intensity and 1 was of unknown intensity. There were no severe AEs. All patients experienced at least 1 AE during the study. In total 14/15 patients (93%) experienced at least 1 treatment-related AE. The most common treatment-related AEs were "ON" and "OFF" phenomenon and dyskinesia. One patient in Cohort 1 experienced a mild serious adverse event (SAE) of hernia pain that was not considered to be related to study drug. There were no deaths, other significant AEs or AEs leading to withdrawal.
Two patients experienced clinically significant evaluations in laboratory parameters during the study. One patient in Cohort 1 had clinically significant evaluations for biochemistry and specific proteins at Month 6, and 1 patient in Cohort 2a had clinically significant evaluations for biochemistry and lipids at Month 3, and for lipids at Month 12. Four patients experienced clinically significant MRI results at Day 7: 1 patient in Cohort 2b, and 3 patients in Cohort 3. No patient experienced a clinically significant ECG or chest X-ray result during the study.
Antibody responses were not detected against any ProSavin component in patients in Cohorts 1, 2a or 2b up to 24 months (Cohort 1 only) and 12 months following ProSavin administration. However, ProSavin-associated antibodies were detected in a least one post-treatment serum sample from 4 of 6 patients in Cohort 3. ProSavin deoxyribonucleic acid and ribonucleic acid sequences were not detected in the majority of blood and urine samples. Where sequences were detected, they were present at a level that was below the lower limit of quantification with the exception of white buffy coat samples for 4 patients (1 patient in Cohort 2a and 3 patients in Cohort 3) and for one plasma sample for 1 patient in Cohort 3. In all cases, the sequences disappeared spontaneously and appeared to be of no clinical significance. There were no other notable results for any of the other safety parameters.
Efficacy: The primary efficacy endpoint was the total score and its percentage change from Screening in the patients' UPDRS Part III. The mean percentage change from baseline in UPDRS Part III was comparable across the cohorts. There was a decrease in the mean UPDRS Part III score in the "OFF" state at each post-baseline time point, although the mean percentage decrease and the maximum percentage decrease was greatest for both the "ON" and "OFF" states for patients in Cohort 2b at Month 6. Overall, there were 4 responders (defined as a reduction from Screening of 50% or more for the UPDRS Part III total score): 1 patient in each of Cohorts 1, 2a, 2b and 3.
Results for the secondary efficacy endpoints are summarised below:
<u>UPDRS Part I, II, IV scores:</u> for each part of the UPDRS and the UPDRS total score, the mean score over time was comparable across the cohorts.
<u>Patient diary:</u> the mean percentage of the total day that patients were asleep in the "ON" state and "OFF" states was comparable across the cohorts.
<u>PDQ-39 single index score:</u> there was a mean percentage decrease in the PDQ-39 single index total score in all applicable cohorts at Month 6, with the largest mean decrease observed in Cohort 1.
<u>L-DOPA equivalent dose:</u> mean percentage change in L-DOPA equivalent dose over time was comparable across the cohorts. Each post baseline mean L-DOPA equivalent dose showed a percentage change decrease. In total, 11 out of 15 patients at Months 6 and 12 required a reduction in L-DOPA equivalent dose compared to baseline. Of the 4 patients at Month 12 that did not require a decrease in L-DOPA equivalent dose, 3 patients showed no change and 1 patients had a small increase in L-DOPA equivalent dose

compared to baseline.
Dyskinesia rating scale: at Month 6, for the "ON" state, a mean percentage decrease (representing a desirable response) was seen in cohort 2a only, with no change in cohort 1 and an increase in dyskinesia in cohorts 2b and 3. The largest mean percentage increase (representing an undesirable response) was observed in Cohort 2b. The largest mean percentage decrease was observed in Cohort 1 at Month 3. For the "OFF" state, there were insufficient data to analyse mainly due to the rating scale prior to cohort 2b only being assessed in the "ON" state.
Positron emission tomography (PET) scan: There was no significant overall difference in ^{18}F-L-DOPA Ki values between baseline and Month 6. A significant dose effect (p=0.02; Kruskal Wallis test) of putaminal binding potentials change between baseline and Month 6 was observed in the low (Cohort 1), mid (Cohorts 2a and 2b) and high (Cohort 3) dose groups, respectively. In the total population, the change in binding potentials at Month 6 relative to baseline was significantly higher in the target putamen region compared to the control uninjected caudate nucleus region (p=0.03; Friedman analysis of variance). Patients receiving the highest ProSavin dose (Cohort 3) exhibited a significant change in binding potentials relative to baseline in the putaminal subregions (anterior putamen; p=0.046 and posterior putamen; p=0.027; Wilcoxon test).
TMS: due to low patient numbers, no conclusions can be drawn for TMS.
Results for the other efficacy endpoints are summarised below:
Hoehn and Yahr stage: at Month 6, just over half of all patients (53%) were at Stage 2 in the "ON" state compared to 27% at Screening. No patient was at Stage 5 at any time point during the study.
Clinical Global Impression (CGI): overall, most patients were considered to be minimally improved at Days 7 or 28.
Upper limb videoscopy: due to low patient numbers, no conclusions can be drawn for this endpoint.

CONCLUSIONS:

- The study demonstrated that ProSavin administered at doses of 2 x 10^7, 4 x 10^7 and 10 x 10^7 TU was safe and well tolerated.
- There was a mean percentage decrease in the UPDRS Part III in both the "ON" and "OFF" states. Responders (defined as a reduction from Screening of 50% or more for the UPDRS Part III total score) were observed in each of the 4 cohorts (1 patient in each cohort). This was consistent with the expected placebo response rate and did not support a dose response.
- In all cohorts, there was a mean percentage decrease in L-DOPA equivalent dose at each post baseline time point; however, a consistent dose-response was not observed.
- Based on these results, it was concluded that the double-blind section of the study should not be conducted due to inadequate efficacy responses observed during the open-label upward titration.

DATE OF FINAL REPORT: 23 August 2013

DATE OF FINAL REPORT AMENDMENT 1: 22 May 2015

RATIONALE FOR FINAL REPORT AMENDMENT 1:

Subsequent to finalisation of the original Clinical Study Report, further new or amended data were identified following additional monitoring that had not been included in the original report. This included new medical history and adverse event entries, as well as additional concomitant and anti-parkinsonian medications, plus the associated updated standardised data coding. As a result of this, the following updates have been made to the original report and associated documents and included in this amendment:

- Tables 14.2.5, 14.3.1.1.1, 14.3.1.1.3, and 14.3.1.2 have been updated
- Listings 16.2.4.4, 16.2.4.8.1, 16.2.4.8.3, 16.2.6.5.1, 16.2.6.5.2 and 16.2.7 have been updated
- In-text Tables 11, 12 and 16, and associated descriptive texts have been updated
- Explanatory footnotes and clarifications have been added to Table 14.2.2 and Listings 16.2.2.1.1, 16.2.6.6, 16.2.6.9.1 and 16.2.6.9.2.
- Appendix 16.1.10 has been updated.

During the update of the Clinical Study Report the text relating to the adverse events and dyskinesia assessments were also corrected to accurately reflect the data; additionally some typographical corrections were made.
These additional data and corrections do not impact the overall results and conclusions for the study, or the GCP compliance statement on the front page of the report.