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A phase IIb, randomised, double-blind, placebo-controlled, dose-ranging investigation of the safety and efficacy of NTCELL® [immunoprotected (alginate-encapsulated) porcine choroid plexus cells for xenotransplantation] in patients with Parkinson's disease

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ABSTRACT

Introduction: Regenerative therapies in Parkinson's disease aim to slow neurodegeneration and re-establish damaged neuronal circuitry. Neurotrophins are potent endogenous regulators of neuronal survival, development and regeneration. They represent an attractive regenerative treatment option in Parkinson's disease. Porcine choroid plexus produces a number of neurotrophins, and can be safely delivered to the striatum in an encapsulated formulation (termed NTCELL®) to protect them from immune attack. NTCELL® has shown regenerative potential in animal models of stroke, Huntington's disease and Parkinson's disease. Following promising results from an initial open label safety study of intra-striatal delivery of NTCELL® in human subjects, we sought to specifically investigate the safety and efficacy of NTCELL® for the treatment of Parkinson's disease.

Methods: 18 patients aged 56–65 years with idiopathic Parkinson's disease of at least 5 years duration were randomised to receive either sham surgery (general anaesthesia and partial thickness burr holes) or intra-striatal delivery of NTCELL® (the 3 groups in the treatment arm receiving incremental NTCELL® doses).

Results: At 26 weeks, we found no significant difference in total UPDRS scores ('on' and 'off'), UPDRS motor scores ('on' and 'off'), PDQ-39, UDysRS, timed walk or modified Hoehn and Yahr stage between patients implanted with NTCELL® and patients undergoing sham procedure. There were no serious adverse events or xenogeneic viral transmission during the study.

Conclusion: The study did not meet its primary efficacy end-point of a change in UPDRS at 26 weeks post-intervention compared with baseline. Stereotactic NTCELL® implantation was safe and well tolerated.

Regenerative therapies in Parkinson's disease (PD) aim to slow neurodegeneration and promote new neuronal connections within the diseased brain. Two main neuro-regenerative strategies have been trialled in humans to-date. The first aspires to replace defunct dopaminergic neurons with other cells capable of dopaminergic transmission. The majority of this work has been carried out using fetal mesencephalic tissue. Open-label trials using this strategy suggested a 30–40% improvement in overall symptomatic status, but the treatment failed to show benefit in the controlled trial setting [1]. Interpreting and explaining such disparate findings has been difficult, but in part

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may relate to significant heterogeneity in the grafted tissue used, as well as differences in immunosuppression and follow-up [1]. However, recent reports of cell survival and long-term symptomatic benefit in some patients offers hope that true neuro-regeneration can be achieved [2,3].

Neurotrophic factors are potent regulators of neuronal survival, development and regeneration and represent another attractive regenerative treatment option for PD. They are the basis of the second neuro-regenerative strategy, which aims not to replace lost neurons, but rather to use neurotrophins to promote the health and survival of viable neurons and encourage the sprouting of new connections in order to re-establish damaged neuronal networks. Glial cell-line derived neurotrophic factor (GDNF), one such neurotrophin, and its analogue neurturin have been delivered to the human striatum via implanted pump devices and viral vectors respectively [4,5]. Despite early optimism from both animal and open-label human studies, GDNF and neurturin failed to show clear clinical benefit in the randomised trial setting [4,5]. The approach to GDNF therapy was problematic, not only due to the requirement for direct infusion into brain tissue (neurotrophins are blood-brain barrier impermeable) and technical issues with the infusion system, but also because only one neurotrophic factor was delivered, which does not mimic the true in-vivo state, where many neurotrophins act together to promote growth and differentiation of neural tissues. Porcine choroid plexus transplantation potentially solves a number of these issues.

Porcine choroid plexus cells secrete large volumes of cerebrospinal fluid containing multiple neurotrophins, anti-oxidants and molecular chaperones (Supplementary Table 1) [6] which in-vivo, maintain and regenerate neural tissues and potentially re-establish damaged neuronal circuitry.

Xenotransplantation of porcine choroid plexus cells has shown promise in animal models of neurological diseases. This has been exploited in the form of an encapsulated preparation of such cells called NTCELL®. In a rodent model of stroke, NTCELL® administration significantly reduced the extent of cerebral infarction and associated behavioral deficits [7]. Similarly, in rodent quinolinic acid models of Huntington's disease, NTCELL® reduced striatal lesion volume, weight loss and motor impairments [8]. In a Parkinson's model using MPTP-lesioned Rhesus monkeys, NTCELL® improved neurological scores, possibly by promoting tyrosine hydroxylase (TH) positive fibre growth in the grafted striatum [9].

Xenografting carries a risk of immune rejection. To overcome this, choroid plexus cells can be encapsulated-in NTCELL® this is done using alginate–poly-L-ornithine–alginate microcapsules which permit the inward passage of nutrients and the outward passage of compounds secreted by choroid plexus cells, while protecting the cells from immune recognition and allowing implantation without immunosuppression. At post-mortem in non-human primate studies, NTCELL® did not induce a host inflammatory reaction beyond that expected from the surgical intervention [9]. Furthermore, the implanted NTCELLs® remained viable at 6 months post grafting in a rodent model [6]. In contrast to stem cell therapies, NTCELL® does not appear to have neoplastic potential [10].

A second concern, particular to xenografting, is the development of zoonoses. Porcine endogenous retroviruses (PERVs) are gamma retroviruses released from normal pig cells which are potentially infectious to human tissue. In this study, porcine choroid plexus cells were isolated from a closed herd of Auckland Island pigs, which are non-transmitters of PERVs [11]. The Auckland Islands are a remote, sub-Antarctic Island group south of New Zealand. Feral pigs from these islands have had essentially no contact with other pigs or humans for about 150 years. Such quarantine makes them unique due to their freedom from pathogenic micro-organisms and parasites relevant to xenotransplantation.

An important problem in studies of regenerative therapy in PD is the lack of a high-fidelity animal model. This means that animal models can only be broadly indicative of possible benefit in the human disease, and that human studies are necessary to determine efficacy. The animal studies described above led us to investigate the feasibility and tolerability of NTCELL® administration to humans with idiopathic PD. We have previously performed an open-label study whereby 4 patients with idiopathic PD (who were at a stage when they would normally be eligible for deep brain stimulation(DBS)) underwent an un-blinded administration of NTCELL® via unilateral implantation into the putamen. The results of this study have been reported elsewhere [12] and indicated that xenotransplantation of NTCELL® was feasible and well tolerated, with a suggestive signal of efficacy.

This data from the Phase I human trial, along with indications of neuroregeneration in animal models led to the current Phase IIb study. We sought to determine the safety and efficacy of NTCELL® for PD by investigating increasing doses of bilateral putaminal NTCELL® administration in three groups. The stepped dosing with nested placebo and review after each cohort allowed: control over safety; placebo control; and investigation of a dose effect.

1. Methods

1.1. Encapsulated choroid plexus preparation

Neonatal Auckland Island Pigs were bred and the tissues harvested by trained staff at Living Cell Technologies (LCT) Inc. (Auckland, NZ) using protocols approved by the LCT Animal Ethics Committee under the Guidelines of the National Animal Ethics Advisory Council of New Zealand. Neonatal porcine choroid plexus cells were harvested aseptically from newborn (6–15 days old) piglets. Choroid plexus clusters were prepared and maintained in culture for seven days after which they were encapsulated within alginate-polyornithine capsules (600–660 μm in diameter) as described previously [6]. The bioactivity of NTCELL® was confirmed by measuring their VEGF secretion using respective ELISA kits according to the suppliers instructions (R&D Systems, Inc, MN USA) as described previously [6].

1.2. Patient selection

Patients aged 56–65 years with idiopathic PD (diagnosed using the Queen Square Brain Bank criteria) of at least 5 years duration who were expected to meet the criteria for deep brain stimulation in the future were eligible for the study. Individuals with possible secondary or atypical Parkinson's as well as those with a history of central nervous system infection or focal neurological deficits were excluded (see Supplementary Table 2 for a full list of inclusion and exclusion criteria). Subjects were recruited from a pool of patients attending neurology outpatient clinics for Parkinson's disease in the upper North Island of New Zealand. Medication for Parkinson's disease and other coexisting disease conditions were permitted. Immunosuppressive medications for other disease conditions were not permitted at any time during the study.

1.3. Patient consent and ethical approval

Informed consent was obtained according to the principles of the declaration of Helsinki and conformed to the US Department of Health & Human Services guidance for industry on source animal, product, preclinical and clinical issues concerning the use of xenotransplantation products in humans (2003); and the New Zealand Ethics Committee recommendations. Similarly, spouses/close contacts of patients were required to provide their informed consent for blood samples to be taken for ongoing monitoring. The clinical trial was approval by Medsafe and by the Northern A Regional Ethics Committee branch of the New Zealand Health and Disability ethics committee. The clinical trial is registered with Clinicaltrials.gov: NCT02683629.

1.4. Study design

This was a phase IIb, randomised, double-blind, placebo-controlled, stepped dose investigation of the safety and efficacy of NTCELL® in patients with PD. Participants were divided into three groups of six patients. Within each group, 4 patients were dosed with NTCELL® and 2 were randomly assigned to placebo (sham surgery). Dosed patients in group 1 received 40 NTCELL® microcapsules (± 5%) bilaterally (total of 80 microcapsules, approximately 24 μL), those in group 2 received 80 NTCELL® microcapsules (± 5%) bilaterally (total of 160 microcapsules, approximately 48 μL) and those in group 3 a total of 120 NTCELL® microcapsules (± 5%) bilaterally (total of 240 microcapsules, approximately 72 μL). The sample size was based on the results of the Phase I study and recognition that a substantial improvement would be necessary to justify invasive treatment.

1.5. Implantation procedure

The implant and sham surgery were performed under general anaesthesia. For the implant, NTCELL® microcapsules were introduced bilaterally into 2 sites in each infero-medial putamen, 3 mm apart, each along a 1 cm tract, using a catheter system inserted via a burr hole in the cranium. CT/MRI fusion targeting and surgical planning was performed using the Medtronic Stealth Stereotactic Planning Software. For the sham surgery, patients received bilateral scalp incisions and partial thickness burr holes without penetration of the dura. Randomisation was performed after surgical planning was completed. The surgical staff, the reporting neuro-radiologist and the LCT Qualified Technician preparing the NTCELL® microcapsules for surgery were the only persons unblinded to the patient's allocation. The operative site after wound closure appeared identical in both implant and placebo groups. The patients, the investigator and the assessors remained blinded to the patients' allocation for the duration of the study.

1.6. Follow-up assessments

During the pre-intervention period, the assessments detailed below were performed twice, at least 3 days apart. The last baseline assessment was performed no longer than 2 weeks prior to the intervention. At weeks 1, 4, 12, 20 and 26 post-intervention, all patients underwent a full physical examination, electrocardiography, xenogeneic viral analyses, laboratory blood testing (blood count, electrolytes, renal and liver function) and a standardised assessment battery including the Unified Parkinson's disease rating scale (UPDRS), Modified Hoehn and Yahr Staging, Unified Dyskinesia Rating Scale (UDysRS), walking time and Parkinson's Disease Questionnaire (PDQ-39). At weeks 8 and 26, patients had an MRI brain. Contacts with whom grafted recipients may exchange bodily fluids also provided blood samples at the time of the transplantation and at 1 year for PERV DNA and RNA testing.

1.7. Outcomes

The pre-specified primary outcomes were:

- Change in Unified Parkinson's Disease Rating Scale (UPDRS Part III in the ‘off’ state) over 26 weeks post-intervention compared with baseline
- The occurrence of adverse events (AEs) and serious adverse events (SAEs)
- Clinical and laboratory evidence of xenogeneic infection in transplant recipients
- Clinical and laboratory evidence of xenogeneic infection in spouses

Secondary outcome measures included change at 26 weeks in the UPDRS Part III in the ‘on’ state, total UPDRS ‘off’ and ‘on’, Quality of life as assessed by PDQ-39, L-dopa dosage, dyskinesia (assessed by the UDysRS), Modified Hoehn and Yahr stage and changes in walking time.

Table 1
Baseline demographic and clinical features summarised by dose groups, including the combined sham procedure group using means and standard deviations.

	Placebo	Group 1 NTCELL®	Group 2 NTCELL®	Group 3 NTCELL®
	(n = 6)	(n = 4)	(n = 4)	(n = 4)
Age (years)	59.5 ± 2.0	60.7 ± 2.2	59.9 ± 2.2	61.8 ± 3.0
BMI (Kg/m2)	26.4 ± 5.2	26.4 ± 1.8	26.9 ± 2.4	28.8 ± 4.6
M:F	3:3	2:2	2:2	3:1
UPDRS Total 'OFF′	55.5 ± 15.8	61.5 ± 10.6	59.5 ± 15.8	57.8 ± 6.7
UPDRS Total 'ON′	31.2 ± 12.9	25.8 ± 5.4	34.3 ± 8.5	27.0 ± 5.9
UPDRS Motor 'OFF′	32.7 ± 7.5	36.5 ± 8.9	35.3 ± 7.8	37.3 ± 7.0
UPDRS Motor 'ON′	19.0 ± 7.2	13.0 ± 3.6	19.3 ± 5.3	17.5 ± 5.7

M = male; F = female; BMI = body mass index; UPDRS= Unified Parkinson's disease rating scale.

1.8. Statistical analysis

The change in outcome measures from baseline to week 26 in each dose group and in the sham procedure group were calculated using pairwise comparisons generated from a 1-way ANOVA which compared the four groups. A two-tailed p-value < 0.05 without correction for multiple comparison was used to indicate statistical significance.

2. Results

2.1. Patients

Between April 2016 and April 2017, 18 patients (10 men, 8 women) were recruited. Baseline demographic and clinical features are summarised by dose groups, including the combined sham procedure group using means and standard deviations (Table 1). There were no clinically relevant differences in age, gender or baseline PD severity between the treatment and control groups (Table 1). The total dose of anti-Parkinsonian medication was calculated as levodopa equivalents. There were no differences in anti-Parkinsonian medication doses at 26 weeks compared with baseline.

2.2. Efficacy

At 26 weeks, we found no significant difference in total UPDRS scores (‘on’ and ‘off’), UPDRS motor scores (‘on’ and ‘off’), PDQ-39, UDysRS, timed walk or modified Hoehn and Yahr stage between patients implanted with NTCELL® and patients undergoing sham procedure (Table 2, Supplementary Material Fig. 1).

When looking at the 3 differently dosed groups, we found that patients in Group 2 improved on both total UPDRS ‘on’(decrease of 12.0 ± 11.2, p = 0.01) and motor UPDRS ‘on’ scores (decrease of 6.5 ± 2.7, p = 0.02) compared to placebo(Table 2, Supplementary Material Fig. 2).

2.3. Safety

There were no SAEs attributable to the intervention. There were 118 AEs in 17 of the 18 participants; nearly all AEs were mild or moderate in intensity (see Table 3). Two of the 3 severe AEs were reported by sham surgery patients (arthritis and intervertebral disc protrusion); the third (self-resolving nausea) was in a Group 3 participant.

Patients in group 3 were found to have larger areas of haemosiderin staining in the implanted putamen on postoperative susceptibility-

Table 2
Summary of changes from baseline (positive indicates decline) at week 26 in measured variables, summarised by dose groups, including the combined sham procedure group using means and standard deviations.

		Placebo	Group 1 NTCELL®	Group 2 NTCELL®	Group 3 NTCELL®	p-value
		(n = 6)	(n = 4)	(n = 4)	(n = 4)	
Change from baseline at week 26	UPDRS total ON	4.67 (6.15)	−8.50(9.61)	12.00(11.20)	−2.50(1.29)	0.01
	UPDRS total OFF	10.17(15.42)	6.75(10.34)	13.75(11.87)	0.25(9.74)	0.49
	UPDRS motor ON	1.50(5.39)	−8.50(9.33)	6.50(2.65)	−1.00(5.48)	0.02
	UPDRS motor OFF	4.67(12.21)	3.50(8.89)	7.25(2.99)	3.00(7.35)	0.91
	PDQ-39	2.38(9.86)	0.35(4.20)	9.61(6.71)	4.62(7.30)	0.38
	UDysRS total ON	0.33(8.55)	−1.00(5.94)	11.25(11.79)	−4.00(6.16)	0.1
	UDysRS total OFF	0.17(1.33)	0.50(1.73)	−2.25(4.57)	−3.25(5.91)	0.38
	Timed walk ON	−0.33(2.50)	0.00 (1.16)	0.25(0.96)	−0.25(1.71)	0.96
	Timed walk OFF	−1.83 (3.60)	−1.00(2.45)	−0.75 (1.71)	−0.75(3.10)	0.92

UPDRS = Unified Parkinson's disease rating scale; UDysRS = Unified dyskinesia rating scale; PDQ-39 = 39-item Parkinson's Disease Questionnaire. p-value is generated from the 1-way ANOVA comparing the changes amongst the four groups.

weighted MRI scanning [median 122.5 mm^2 (interquartile range 85–161 mm^2)] compared with patients in groups 1 and 2 [median 59 mm^2 (interquartile range 53–70 mm^2)] suggesting that this volume of microcapsules likely exceeds the maximum tolerated dose (see Fig. 1).

All PERV DNA and RNA samples from patients and close contacts were negative. PERV screening will continue on an annual basis to 2 years post implantation and every 10 years after that.

3. Discussion

This is the first study to examine the efficacy and safety of encapsulated porcine choroid plexus (NTCELL®) in a population of patients with PD. The study failed to meet its primary efficacy end-point of a change in UPDRS at 26 weeks post-intervention compared with baseline. It is however interesting to observe the significant improvement in both total and motor UPDRS 'on' scores in transplanted patients in Group 2 compared to placebo. Though speculative, it is conceivable that this finding may represent a dose-dependent treatment effect not seen in Group 1 due to under-dosing of NTCELL, and not evident in group 3 due to the putaminal microlesions produced by high-volume NTCELL implants. In animals, targeted putaminal lesions have been shown to produce deficits in motoric and executive function [13,14]. Putaminal lesions in man can produce a variety of movement disorders, ranging from hyperkinetic disorders such as dystonia and chorea through to Parkinsonism [15,16]. Isolated bilateral putaminal lesions are rare, being generally seen in cases of poisoning with methanol or cyanide, haemorrhage or ischemia. Such bilateral putaminal lesions have however been associated with Parkinsonism [17,18]. Most of our Group 3 patients had large areas of putaminal haemosiderin deposition

Table 3
Summary of adverse events broken down by clinical severity, potential relationship to implant procedure and by individual organ system affected.

	Intensity				
	Placebo	NTCELL 40	NTCELL 80	NTCELL 120	Total
Mid	14	28	4	23	69
Mode rate	15	11	11	9	46
Severe	2			1	3
Total	31	39	15	33	118
Relationship					
Unrelated	24	26	12	27	89
Possibly Related to implant procedure itself	6	11	1	6	24
Possibly Related to NTCELL Implanted	1	2	2		5
Total	31	39	15	33	118
System Organ class SOC	Placebo	NTCELL 40	NTCELL 80	NTCELL 120	Total
Ear and labyrinth disorders	1				1
Eye disorders		1	1	4	6
Gastrointestinal disorders	5	2	2	5	14
Ganeral disorders and administration site conditions		2		1	3
Infections and infestations	3	3	3	2	11
Injure, poisoning and procedural complications	5	3	4	3	15
Investigations	2	2		1	5
Musculoskeletal and connective tissue disorders	5	7	3	5	20
Neoplasms benign and unspecified (incl cysts and polyps)		1			1
Nervous system disorders	10	13	2	3	28
Psychiatric disorders		1		5	6
Renal and urinary disorders		1			1
Respiratory, thoracic and mediastinal disorders		1		3	4
Vascular disorders		2		1	3
Total	31	39	15	33	118

SOC = system organ class.

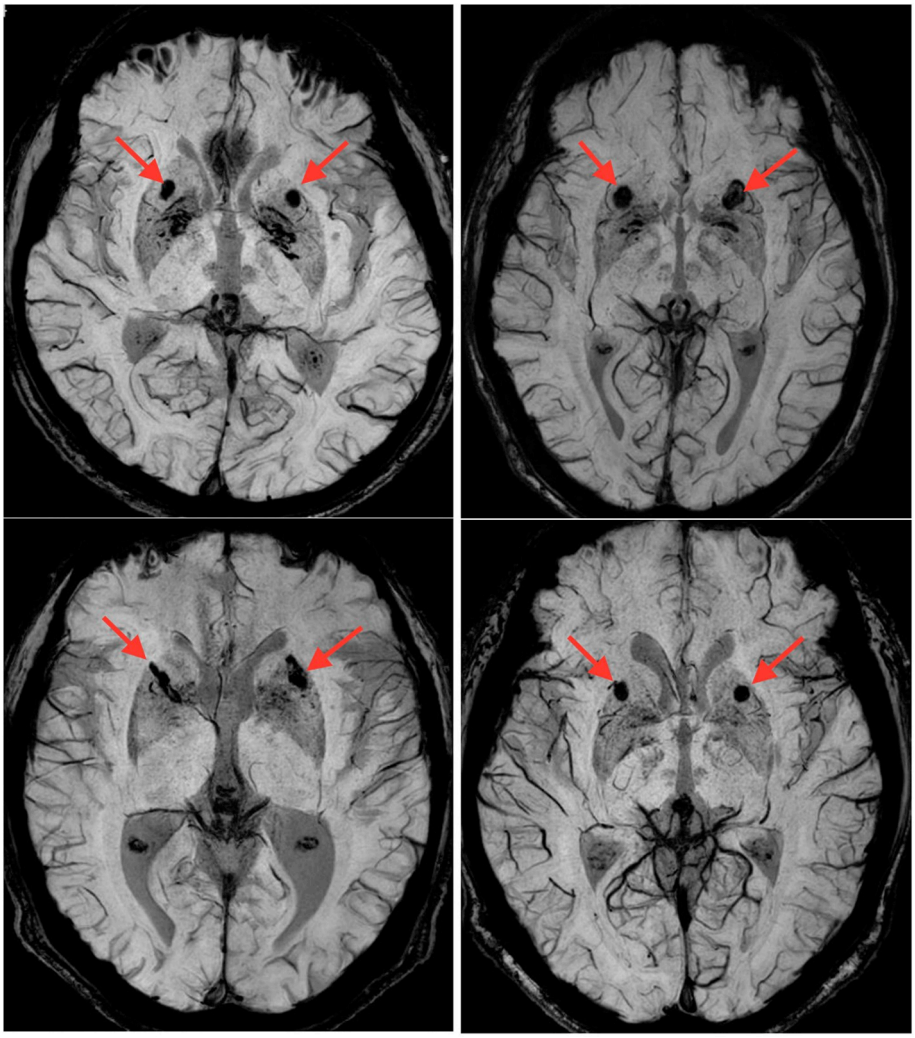

Fig. 1. Axial minimum intensity projection (mIP) susceptibility weighted imaging (SWI) MRI sequences from all 4 implanted patients in group 3 demonstrating significant bilateral putaminal haemosiderin staining (red arrows) which reflects procedure-related microhaemorrhage. Supplementary Material Table 1: Gene expressions for neurotrophins and growth factors, antioxidant systems, and plaque protein chaperones (updated from Skinner et al., 2009). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

on post-procedure susceptibility-weighted MRI sequences (Fig. 1), implying iatrogenic putaminal lesioning from high volume NTCELL® delivery. Any resulting Parkinsonism may have masked the improvements provided by the NTCELL® derived neurotrophins. It is unclear whether significant recovery from these bilateral putaminal lesions is likely to occur [14].

Other potential explanations for the overall lack of improvement include:

1. Short follow-up duration: Open-label trials using putaminal GDNF infusion showed continued improvement up to 12 months [19], and the one double-blind GDNF study ended after 6 months, without showing clinical improvement, but with increased (18)F-dopa uptake on PET imaging [20]. In addition, a recent (albeit negative) trial of gene delivery of the trophic factor neurturin, a GDNF structural and functional analogue, via an adeno-associated type-2 vector (AAV2) suggested that one may need to wait at least 12 months to see a treatment effect [5]. It may be that the clinical effects of NTCELL® neurotrophin delivery will be seen in a delayed fashion. We will follow-up our cohort of patients for 2 years to investigate this possibility.
2. Stage of disease: Re-establishment of striatal neural networks requires a significant surviving population of nigral dopaminergic neurons with their striatal projections so that the neurotrophins can promote the development of new connections [9]. Our patients were at a relatively advanced stage of PD, and thus will have had a limited supply of 'healthy' dopaminergic neurons available to sprout new fibres [21].
3. The normal signaling pathways for neurotrophins may be disrupted in the presence of alpha-synuclein pathology, rendering these less effective [22].

Despite failing to meet its primary end-point, our study had some interesting findings. We confirmed our initial safety study [12] findings that stereotactic NTCELL® implantation is safe and well tolerated. We established that the dose limit for alginate microcapsule implantation into a single putamen is in the region of 120 microcapsules as indicated by hemosiderin staining on MRI. The lack of PERV transmission in our cohort again underpins the suitability of Auckland Island pigs as a source of xenogeneic material for use in human studies.

The main limitations of this study were the short duration of follow-up and the small sample size, both factors which may have impacted our ability to show clear benefit from our intervention. We plan to continue to follow all patients for 2 years and the results of this longer follow-up will be reported in due course.

Declarations of interest

None.

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CRediT authorship contribution statement

Barry Snow: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Writing - original draft.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.11.015.

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