

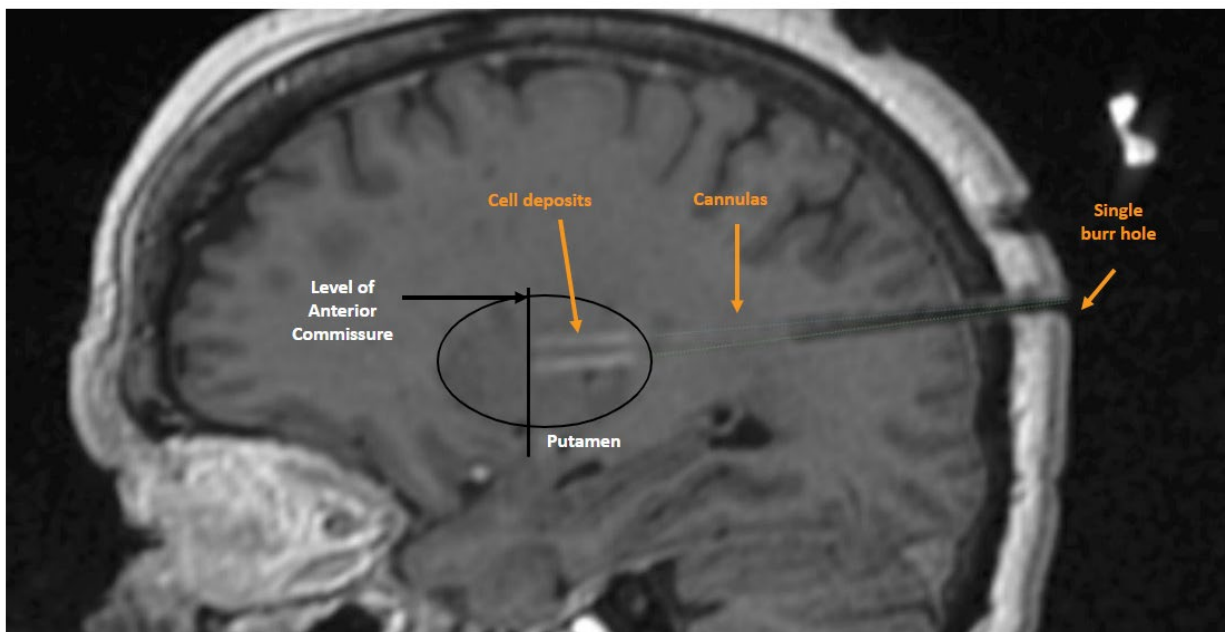
TITLE: Safety, tolerability, and efficacy of intracranial delivery of autologous iPSC-derived dopaminergic precursors in moderate to advanced Parkinson's Disease

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BACKGROUND: About one million Americans are living with Parkinson's Disease (PD), and about 60,000 are newly diagnosed annually. Current therapies address symptoms of PD, but do not address loss of dopaminergic neurons.

METHODS: A first-in-human, open-label, phase 1/2a trial evaluating safety, tolerability, and efficacy of intracranial implantation of two escalating doses of autologous induced pluripotent stem cell (iPSC)-derived dopaminergic neuronal precursor cells (DANPCs) in subjects with moderate to advanced PD. The primary study objective is to assess the safety and tolerability of bilateral administration of autologous DANPCs into the posterior putamen. A secondary objective is to evaluate the clinical efficacy of DANPC administration, as measured by changes from baseline in multiple patient- and clinician-reported PD-specific outcome measures.



Sagittal MRI View showing trajectories for cell placement

RESULTS: All three subjects in this first cohort received five million DANPCs per putamen and have completed six months of follow-up. No hemorrhages nor serious intra- or post-operative complications have been observed. No severe graft-induced dyskinesia have

been observed. The most common adverse event was tongue swelling. All results to date indicate that a dose of five million DANPCs can be safely delivered into the post-commissural putamen using intraoperative MRI guidance. Real time MRI confirmed precision implantation of DANPCs into the intended target.

At six months there was an average improvement of 45% (range 33-55%) in the part III MDS-UPDRS “off” score compared to baseline as well as an average improvement of 71% (range 41-93%) in the MDS-UPDRS Part II score. There was an average reduction of two hours in adjusted “off time” and a 1.5-hour average increase in adjusted “good on” time.

	Mild	Moderate	Severe	Relatedness to product/procedure
Swollen tongue		2		Procedure
Back pain	1			Procedure
Hypoesthesia	1			Procedure
Incision site pain	1			Procedure
Musculoskeletal stiffness	1			Procedure
Tongue injury	1			Procedure
Urinary retention		1		Procedure
Post-LP Headache		1		Not related

(Baseline → 6mo)	Patient 1	Patient 2	Patient 3	Average
MDS-UPDRS III OFF score	49 → 33 (33% improvement)	42 → 19 (55% improvement)	42 → 22 (48% improvement)	45.3 % improvement
MDS-UPDRS II	15 → 1 (93% improvement)	17 → 10 (41% improvement)	15 → 2 (80% improvement)	71.3 % improvement
Adjusted change in OFF Time	4.1→1.8 hrs (2.3 hr improvement)	2.3 → 2.5	6.7 → 2.7 (4 hr improvement)	2 hr off time reduction
Adjusted change in "good" ON Time	11.9 → 14.2 (2.3 hr improvement)	13.4 → 12.9	8.4 → 11.1 (2.7 hr improvement)	1.5 hr increase in good on time

CONCLUSIONS: Early data from three patients show that precision intracranial delivery of DANPCs was safe and well-tolerated. Both patient reported and clinician reported outcomes show early signs of efficacy, and continued follow up and evaluation of a higher-dose cohort is ongoing.