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Dopaminergic neuronal cell therapy for Parkinson's disease: Results from a Phase 1 study of bemdaneprocel

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Introduction

Current treatments for Parkinson's disease (PD) do not address dopaminergic neuron loss, an underlying cause of disease. In addition, current treatments do not impact disease progression and lose effectiveness over time.[1,2]

Bemdaneprocel (BRT-DA01) is an investigational therapy comprised of dopaminergic neurons derived from pluripotent stem cells.[3] Studies in Parkinsonian mouse models showed no significant safety findings in biodistribution, toxicology or tumorigenicity studies. Preclinical efficacy was demonstrated in rats.[2]

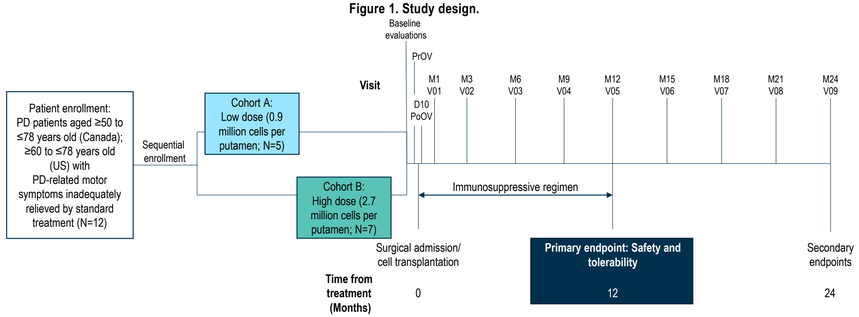
We report the Year 1 outcomes of a multi-center, multi-site, open-label, non-randomized, Phase 1 (NCT04802733) study to assess the safety and tolerability, as well as exploratory efficacy measures, of bemdaneprocel in participants with PD.

Participants, Methods & Analysis

Study population:

- Participants were sequentially recruited into this Phase 1 study. The first five participants were enrolled into the low-dose group (0.9 million cells per putamen) and subsequent participants were enrolled into the high-dose group (2.7 million cells per putamen) (**Figure 1**)
  - All participants were enrolled from 03 May 2021 through 30 March 2022

Figure 1. Study design.



D, Day; M, Month; PD, Parkinson's disease; PoOV, post-operative visit; PrOV, pre-operative visit; V, visit.

Methods:

- Cells were administered in a single session of stereotactically guided surgical injection into the posterior putamen bilaterally through a single burr hole on each side. Cells were delivered using three passes of the cannula on each side and 3 cell deposits per pass, for a total of 9 cell deposits per hemisphere (**Figure 2**)
- An immunosuppressive regimen was initiated intraoperatively and continued post-operatively for 1 year:
  - Participants were initiated on an immunosuppressive regimen of basiliximab 20 mg intravenously intraoperatively and post-operative on Day 4; methylprednisolone 500 mg intravenously prior to surgery, then tapered to oral prednisone and continued at 5 mg daily for 1 year; tacrolimus taken orally beginning on the day after surgery (Day 1) and then adjusted to a target trough blood level of 4–7 ng/mL for a period of 1 year

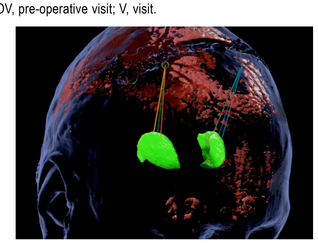


Figure 2. Surgical approach.
Depiction of the surgical tracks of administration.

Analysis:

- The primary objective of the study was to assess safety and tolerability, with a primary endpoint measuring the incidence of serious adverse events (SAEs) at 1-year post-transplant.
  - Safety was defined as 2 or fewer patients of Cohort A or Cohort B (a) developing 2 or more SAEs related to surgery, presence of transplanted cells or immunosuppression; (b) developing a tumor or abnormal tissue overgrowth related to presence of transplanted cells; (c) developing an intracerebral hemorrhage that is deemed to be life-threatening; (d) experiencing 1 or zero deaths
- In addition, the following secondary and exploratory endpoints were also assessed at Year 1
  - Changes from baseline in striatal fluorodopa (^{18}F-DOPA) uptake using positron emission tomography (PET)
  - Changes from baseline in the International Parkinson and Movement Disorder Society (MDS)-Unified Parkinson's Disease Rating Scale (UPDRS) motor sub-score in the OFF medication state
  - Changes from baseline in the number of hours in the ON state without troublesome dyskinesia, OFF state and ON state with troublesome dyskinesia
  - Feasibility, as defined by intra-operative delivery of at least 50% of the intended number of deposits per brain in >50% of subjects
  - Incidence and type of adverse events (AEs)

Results

Patient disposition

- Patient baseline characteristics were comparable across both cohorts (**Table 1**)
- All participants received their planned dosage
- All participants (N=12) were included in the safety and evaluable populations

Table 1. Baseline characteristics.

	Cohort A (N=5)	Cohort B (N=7)	Total (N=12)
Age, years			
Mean (SD)	66.8 (6.80)	66.7 (4.79)	66.8 (5.41)
Median (Q1, Q3)	67.0 (65.0, 67.0)	68.0 (64.0, 70.0)	67.0 (64.5, 70.0)
Sex, n (%)			
Male	4 (80.0)	5 (71.4)	9 (75.0)
Female*	1 (20.0)	2 (28.6)	3 (25.0)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	0	1 (14.3)	1 (8.3)
Black or African American	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White†	3 (60.0)	5 (71.4)	8 (66.7)
Other	1 (20.0)	1 (14.3)	2 (16.7)
Multiple	1 (20.0)	0	1 (8.3)
Time since PD diagnosis, years			
Mean (SD)	11.0 (3.68)	7.8 (2.19)	9.1 (3.21)
Median (Q1, Q3)	12.7 (8.9, 13.7)	8.2 (5.3, 10.2)	9.0 (5.9, 11.5)
Hoehn and Yahr Stage (OFF state), n (%)			
0 & 1	0	0	0
2	1 (20.0)	0	1 (8.3)
3	4 (80.0)	7 (100)	11 (91.7)
4 & 5	0	0	0
Hoehn and Yahr Stage (ON state), n (%)			
0 & 1	0	0	0
2	5 (100)	7 (100)	12 (100)
3, 4 & 5	0	0	0

*No female patients were of childbearing potential. †No patients were of Hispanic or Latino ethnicity. Q, quartile; SD, standard deviation.

Safety

- There were no reports of an AE or SAE related to bemdaneprocel (**Table 2**)
- There was 1 SAE of seizure that was transient attributed to the surgical procedure reported in Cohort B

Table 2. Summary of treatment-emergent serious adverse events (TESAEs) at Year 1.

	Cohort A (N=5)			Cohort B (N=7)		
Subjects reporting, n (%) [Total number of events]	0 events	1 event	≥2 events	0 events	1 event	≥2 events
TESAE	4 (80.0)	1 (20.0) [1]*	0	6 (85.7)	1 (14.3) [1]	0
Related to surgery	5 (100)	0	0	6 (85.7)	1 (14.3) [1]	0
Related to cell product	5 (100)	0	0	7 (100)	0	0
Related to immunosuppressive drugs	5 (100)	0	0	7 (100)	0	0
Tumor or abnormal tissue overgrowth related to presence of transplanted cells	5 (100)	0	0	7 (100)	0	0
Intracerebral hemorrhage that is deemed to be life-threatening	5 (100)	0	0	7 (100)	0	0
Deaths		0			0	

*1 incidence of brief hospitalization due to COVID.

- 11/12 participants reported TEAEs (66 events in total; **Table 3**)
- Most TEAEs were mild or moderate in severity
  - One severe TEAE was reported
- There were no discontinuations or deaths in the study
- There were no graft-induced dyskinesias seen in either cohort

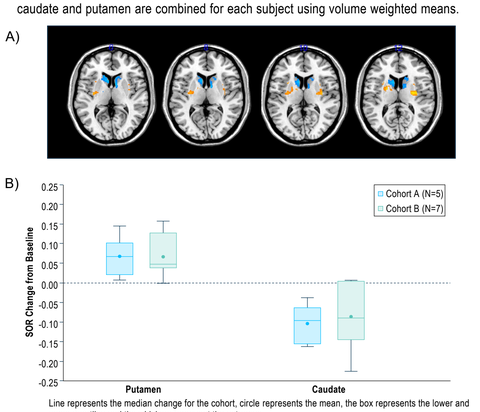
Table 3. Summary of treatment-emergent adverse events (TEAEs).

	Cohort A (N=5)	Cohort B (N=7)	Total (N=12)
Subjects reporting, n (%) [Total number of events]			
TEAE	5 (100) [39]	6 (85.7) [27]	11 (91.7) [66]
TEAE by maximum Common Terminology Criteria for Adverse Events (CTCAE) Grade, n (%) [Total number of events]			
Grade 1: Mild	1 (20.0) [28]	3 (42.9) [24]	4 (33.3) [52]
Grade 2: Moderate	3 (60.0) [10]	3 (42.9) [3]	6 (50.0) [13]
Grade 3: Severe	1 (20.0) [1]	0	1 (8.3) [1]
Grade 4: Life-threatening	0	0	0
Grade 5: Death related to AE	0	0	0

^{18}F-DOPA uptake

- At a group level there was an increase in ^{18}F-DOPA uptake in the posterior putamen (transplant site), which did not associate with the degree of baseline ^{18}F-DOPA uptake (**Figure 3**)
  - A decrease in ^{18}F-DOPA was observed in the caudate nucleus (distant from the site of transplantation)

Figure 3. Group level analysis of ^{18}F-DOPA PET uptake in the striatum.
A) Voxel based analysis of the ^{18}F-DOPA PET data was conducted. Voxel clusters with low p-value (P<0.05) group level changes between baseline and 1 year SOR signal within the caudate and putamen are displayed (voxels with increase in orange, voxels with decrease in blue). B) Change in striatal-to-occipital ratio (SOR) from baseline limited to voxel clusters with low p-values (P<0.05). Changes within these clusters for the caudate and putamen are combined for each subject using volume weighted means.

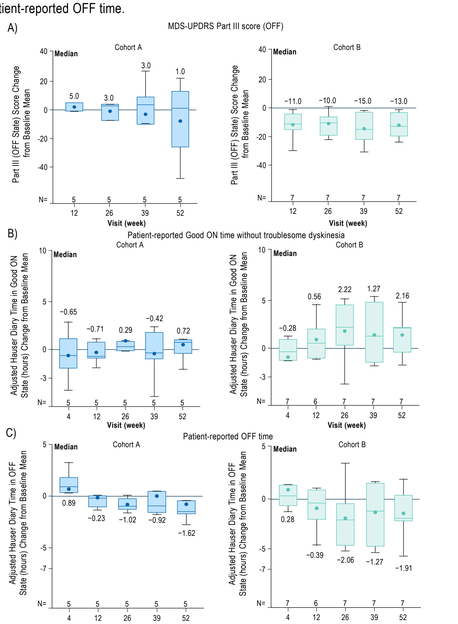


Line represents the median change for the cohort, circle represents the mean, the box represents the lower and upper quartiles and the whiskers represent the extremes.

Clinical outcomes

- An improvement in MDS-UPDRS Part III OFF time and patient-reported ON and OFF time was seen (**Figure 4; Table 4**)
  - Improvements in median clinical scores were greater in Cohort B compared with Cohort A

Figure 4. Change from baseline in Cohort A (Blue) and Cohort B (Teal) in A) MDS-UPDRS Part III score (OFF); B) Patient-reported Good ON time without troublesome dyskinesia; C) Patient-reported OFF time.



Line represents the median change for the cohort, circle represents the mean, the box represents the lower and upper quartiles and the whiskers represent the extremes. Patient-reported ON time with troublesome dyskinesia demonstrated no clinically meaningful change through Week 52 (**Table 4**).

Table 4. Change in clinical outcomes at Year 1 from baseline.

	Cohort A (N=5)	Cohort B (N=7)
Change in MDS UPDRS Part III Score at Year 1 from baseline, median (Q1, Q3)		
OFF state	1.0 (−26.0, 13.0)	−13.0 (−20.0, −4.0)
Patient-reported change in clinical scores at Year 1 from baseline, median (Q1, Q3)*		
Good ON time without troublesome dyskinesia	0.72 (−0.4, 1.0)	2.16 (−0.4, 2.2)
OFF time	−1.62 (−1.7, −0.4)	−1.91 (−2.2, 0.4)
ON time with troublesome dyskinesia	0.72 (−0.7, 2.0)	0.0 (−0.3, 0.0)

*Reported via Hauser Diary

Conclusions

- Bemdaneprocel was generally safe and well tolerated in these 12 participants at 1-year post-transplantation
- The stereotactic surgical delivery and therapeutic regimen was feasible, with all participants receiving the planned dose of bemdaneprocel and tolerating the 1-year immunosuppression regimen
- Evidence of bemdaneprocel survival and engraftment was demonstrated in the posterior putamen by ^{18}F-DOPA PET imaging
- Analysis of clinical scores may suggest improvement in MDS-UPDRS Part III (OFF state), a decrease in OFF time, and an increase in Good ON time without troublesome dyskinesia
  - No graft-induced dyskinesias occurred through 1 year
  - Although efficacy trends were present across both cohorts, Cohort B showed a greater magnitude of changes. However, it is important to note that these efficacy analyses are limited by the small sample size and the uncontrolled trial design, and interpretation must therefore be cautious

1. Armstrong MJ and Okun MS. *JAMA*. 2020;323:548–560. 2. Piao J, et al. *Cell Stem Cell*. 2021;28:217–229. 3. Kim TW, et al. *Cell Stem Cell*. 2021;28:343–355.

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