Imaging Outcomes of a Dopaminergic Neuronal Cell Therapy for Parkinson's Disease: 18-Month Results From a Phase 1 Study of Bemdaneprocel

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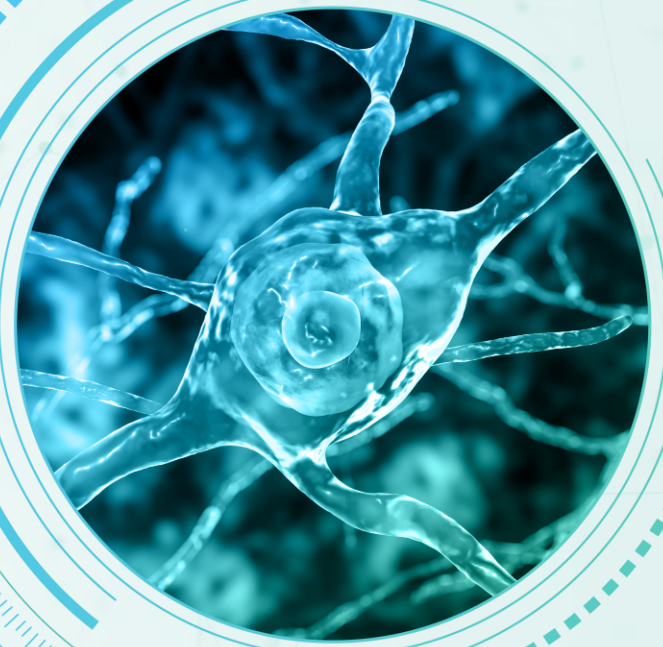


Background and Objective

Bemdaneprocel is an investigational therapy comprising dopaminergic neuronal progenitors derived from human embryonic stem cells[1,2]

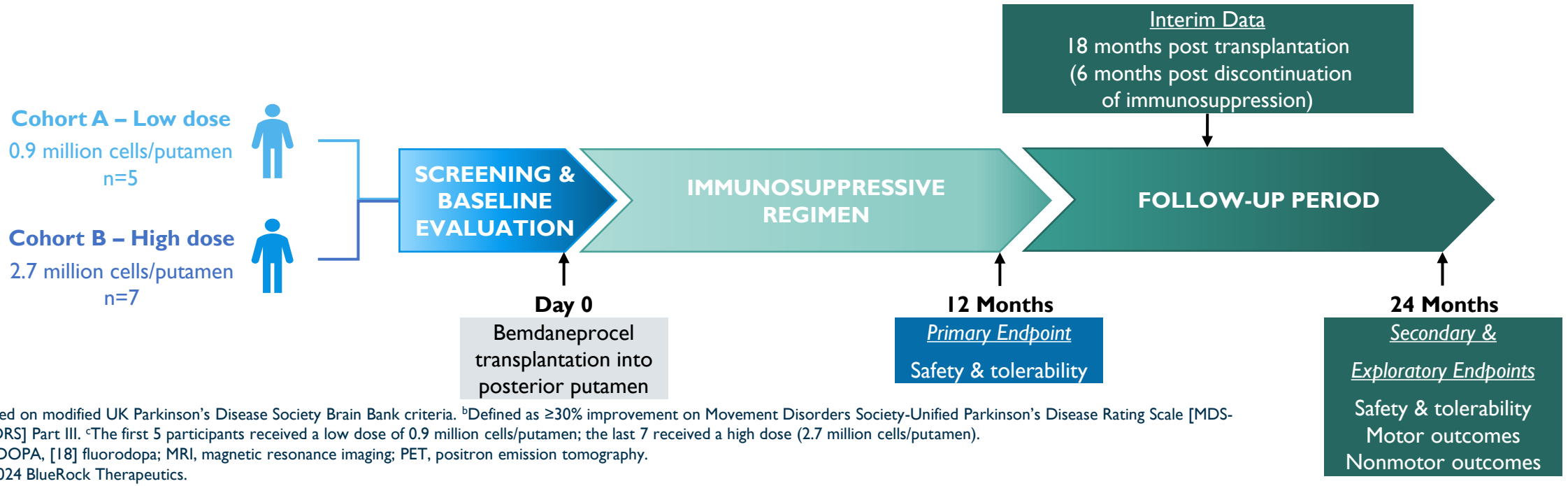
- Results from exPDite, a Phase 1 multicenter, multisite, open-label, nonrandomized study (NCT04802733), at 12 months post transplantation demonstrated bemdaneprocel was generally safe and well tolerated, supported the feasibility of stereotactic transplantation of bemdaneprocel, and suggested stability or improvement in motor outcomes[3]
  - A favorable safety profile, as well as stability or improvement in motor outcomes, were maintained at 18 months post transplantation
  - At 12 months post transplantation, ^{18}F-DOPA uptake was increased along the surgical track in the putamen, while signal declined in the caudate[3]

Objective: To assess changes in ^{18}F-DOPA uptake and safety up to 18 months post transplantation, 6 months post discontinuation of immunosuppression, using PET and MRI

1. Kim TW, Piao J, Koo SY, et al. *Cell Stem Cell*. 2021;28(2):343-55.e5. 2. Piao J, Zabierowski S, Dubose BN, et al. *Cell Stem Cell*. 2021;28(2):217-29.e7. 3. Henchcliffe C, Sarva H, Lozano A, et al. Presented at: International Congress of Parkinson's Disease and Movement Disorders; August 27–31, 2023; Copenhagen, Denmark. ^{18}F-DOPA, [18] fluorodopa; MRI, magnetic resonance image; PET, positron emission tomography.

Trial Design

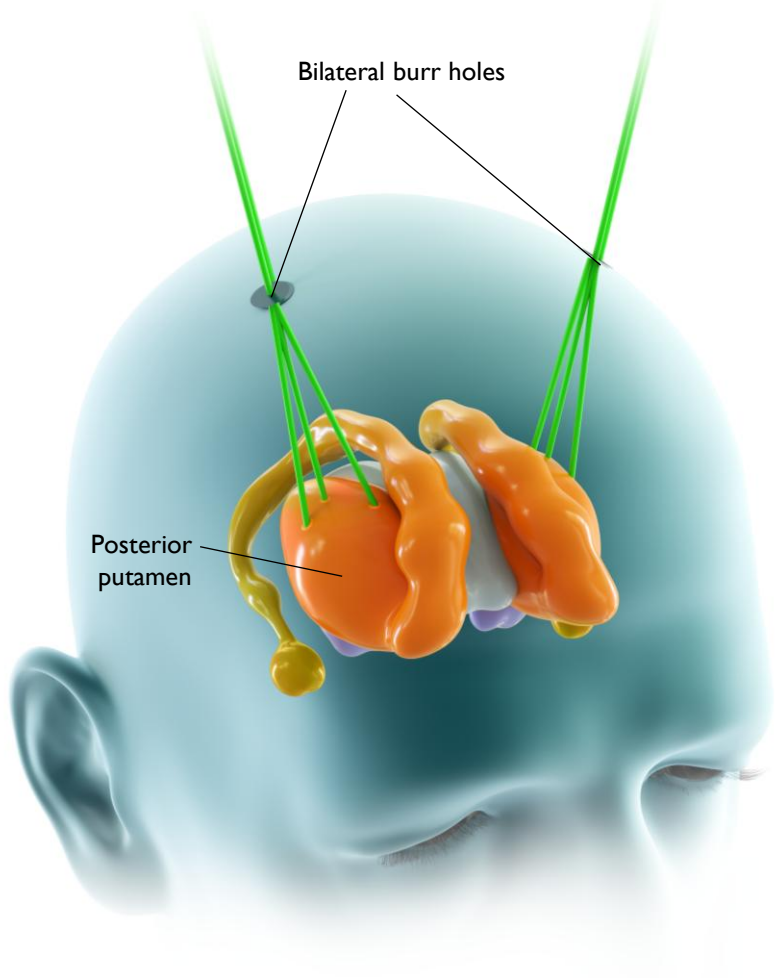
- Participants with Parkinson's disease with motor symptoms inadequately controlled by standard treatments were ≥50 to ≤78 years of age in Canada, or ≥60 to ≤78 in the US
  - Eligible participants had a diagnosis of idiopathic Parkinson's disease[a] for ≥3 to ≤20 years, levodopa response[b], and a Hoehn and Yahr score of 0–3 in ON state (Canada), or 0–2 in ON state and 3–4 in OFF state (US)
- A total of 12 participants enrolled sequentially[c]
- **Imaging assessments**
  - **^{18}F-DOPA PET:** at baseline, 12, 18, and 24 months post transplantation
  - **MRI:** at screening, intraoperatively, postoperatively, and 1, 3, 6, 12, 18, and 24 months post transplantation



[a]Based on modified UK Parkinson's Disease Society Brain Bank criteria. [b]Defined as ≥30% improvement on Movement Disorders Society-Unified Parkinson's Disease Rating Scale [MDS-UPDRS] Part III. [c]The first 5 participants received a low dose of 0.9 million cells/putamen; the last 7 received a high dose (2.7 million cells/putamen).
^{18}F-DOPA, [18] fluorodopa; MRI, magnetic resonance imaging; PET, positron emission tomography.

Surgical Procedure

- Bemdaneprocel was administered stereotactically into the posterior putamen bilaterally through a single burr hole on each side in a single session
  - A total of 9 cell deposits were made along 3 tracks in each hemisphere



Immunosuppression was initiated prior to transplantation and continued for 1 year post transplantation

- **Basiliximab** (20 mg, IV): intraoperatively and on postoperative day 4
- **Methylprednisolone** (500 mg, IV): initiated on day 0, tapered to **prednisone** (5 mg, PO) and continued for 1 year
- **Tacrolimus** (PO, BID): initiated on postoperative day 1 and adjusted to a target trough blood level of 4–7 ng/mL for 1 year

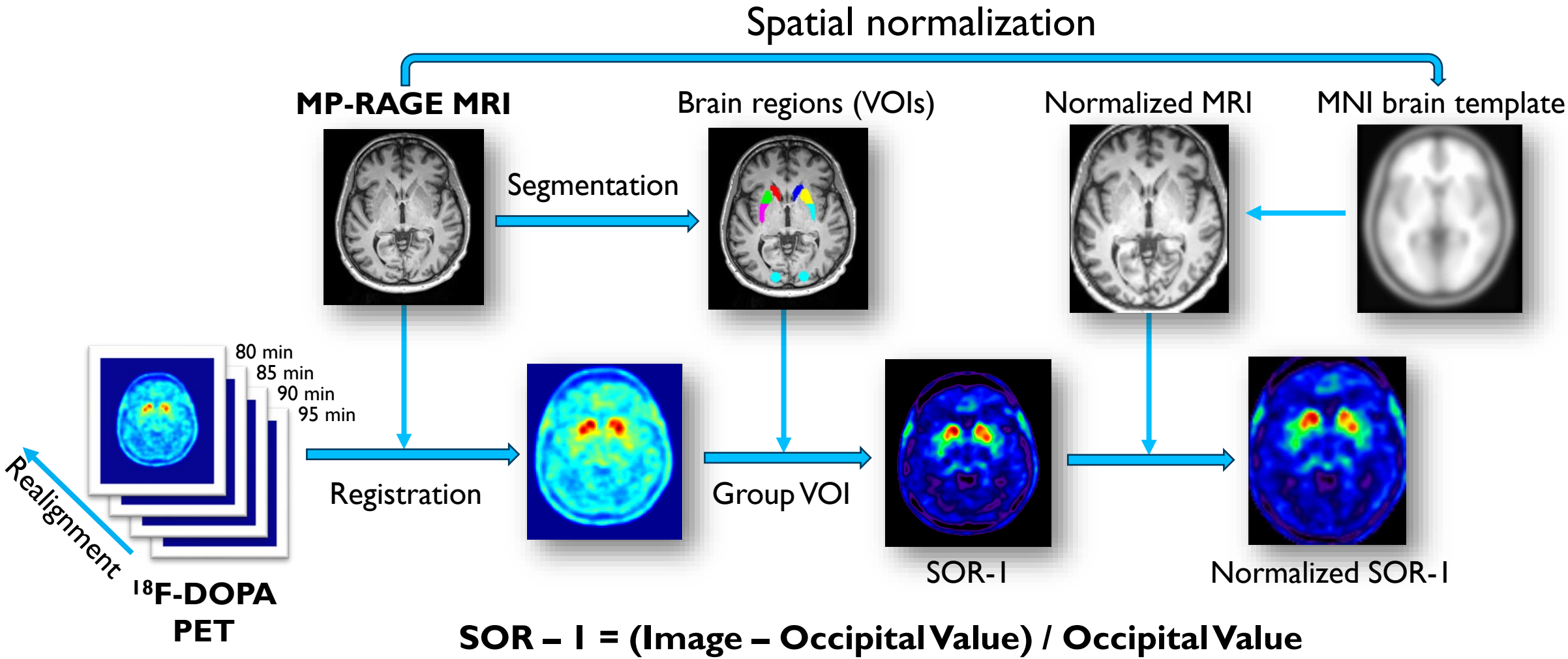
BID, twice daily; IV, intravenous; PO, oral.

Demographics and Baseline Characteristics

	All (N=12)
Age, years	
Mean (SD)	66.8 (5.4)
Median (Q1, Q3)	67.0 (64.5, 70.0)
Sex, n (%)	
Male	9 (75.0)
Female	3 (25.0)
Race	
Asian	1 (8.3)
White	8 (66.7)
Other	2 (16.7)
Multiple	1 (8.3)
Time since PD diagnosis, years	
Mean (SD)	9.1 (3.2)
Median (Q1, Q3)	9.0 (5.9, 11.5)
Hoehn and Yahr stage (OFF state), n (%)	
2	1 (8.3)
3	11 (91.7)
Hoehn and Yahr stage (ON state), n (%)	
2	12 (100.0)

PD, Parkinson's disease; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.

PET and MRI Analyses



SOR – 1 = (Image – Occipital Value) / Occipital Value

^{18}F-DOPA, [18] fluorodopa; MNI, Montreal Neurological Institute; MP-RAGE, magnetization-prepared 180 degrees radio-frequency pulses and rapid gradient-echo; MRI, magnetic resonance imaging; PET, positron emission tomography; SOR, striatal-to-occipital ratio; VOI, voxel-of-interest.

Voxel-Based Group Analysis[1-3]

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^{18}F-DOPA uptake at baseline, 12 months, and 18 months was measured by SOR for each participant within regions of interest defined by voxel-based brain mapping analysis at a group level

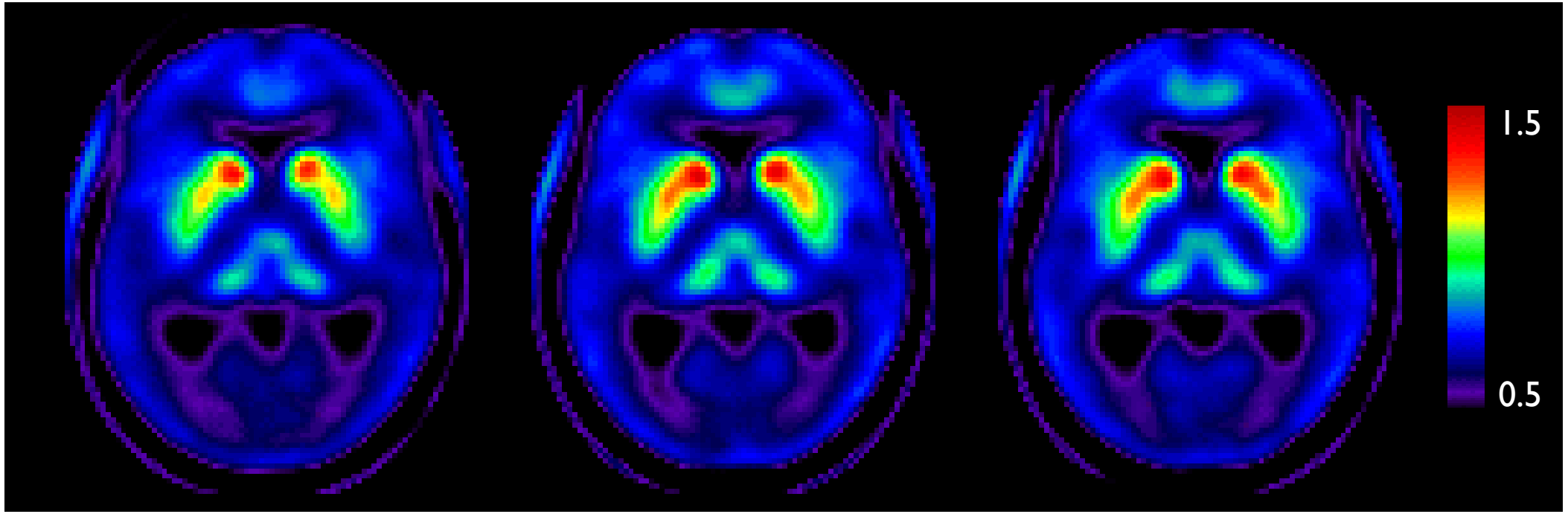
Maps of ^{18}F-DOPA uptake were created from images of SOR–1 and spatially transformed into the standard brain space (MNI) via individual MRI

Changes from baseline were assessed using Student's paired *t*-test in SPM12 for each voxel (baseline vs 12 months and baseline vs 18 months)

t-Maps of significant changes in ^{18}F-DOPA uptake were overlaid on a standard MRI brain template to determine the anatomical locations of significant clusters

1. Ma Y, Tang C, Chaly T et al. *J Nucl Med*. 2010;51(1):7-15. 2. Nakamura T, Dhawan V, Chaly T, et al. *Ann Neurol*. 2001;50:181–187. 3. Ma Y, Feigin A, Dhawan V, et al. *Ann Neurol*. 2002;52:628–634.
^{18}F-DOPA, [18] fluorodopa; MNI, Montreal Neurological Institute; MRI, magnetic resonance image; SOR, striatal-to-occipital ratio; SPM, Statistical Parametric Mapping.

Mean ^{18}F-DOPA Uptake



Baseline

12 Months Post Transplantation

18 Months Post Transplantation
(6 months post discontinuation of immunosuppression)

Mean image = Sum (all SOR-1 images at each visit) / sample size

^{18}F-DOPA, [18] fluorodopa; SOR, striatal-to-occipital ratio.

^{18}F-DOPA Uptake

12 and 18 Months Post Transplantation

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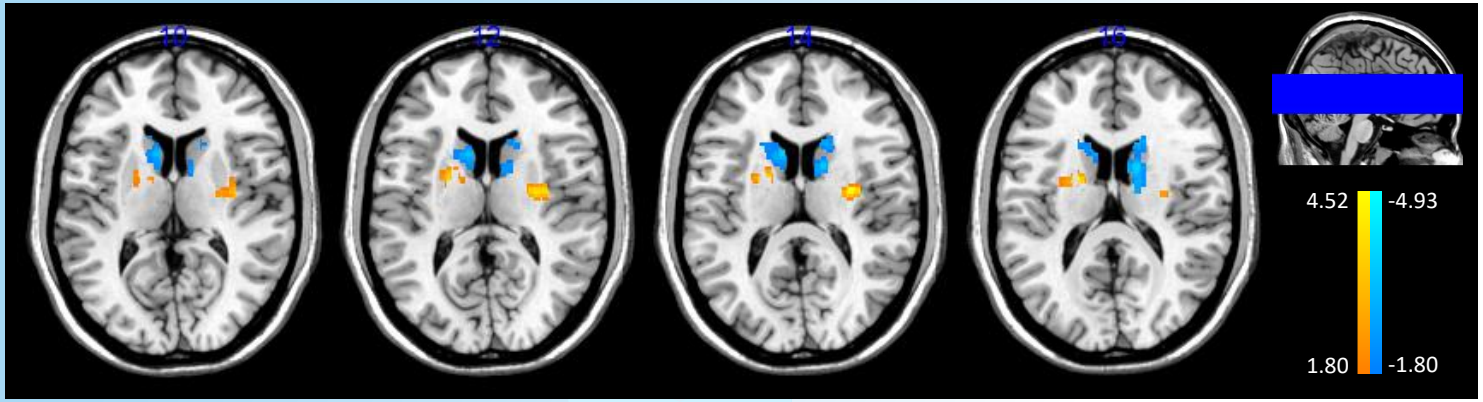
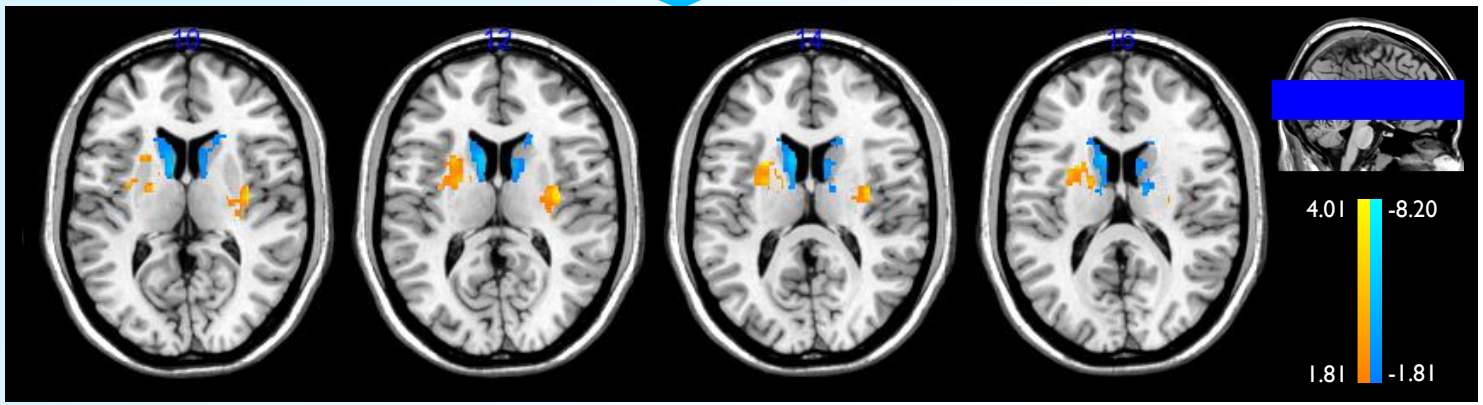
12 months



18 months

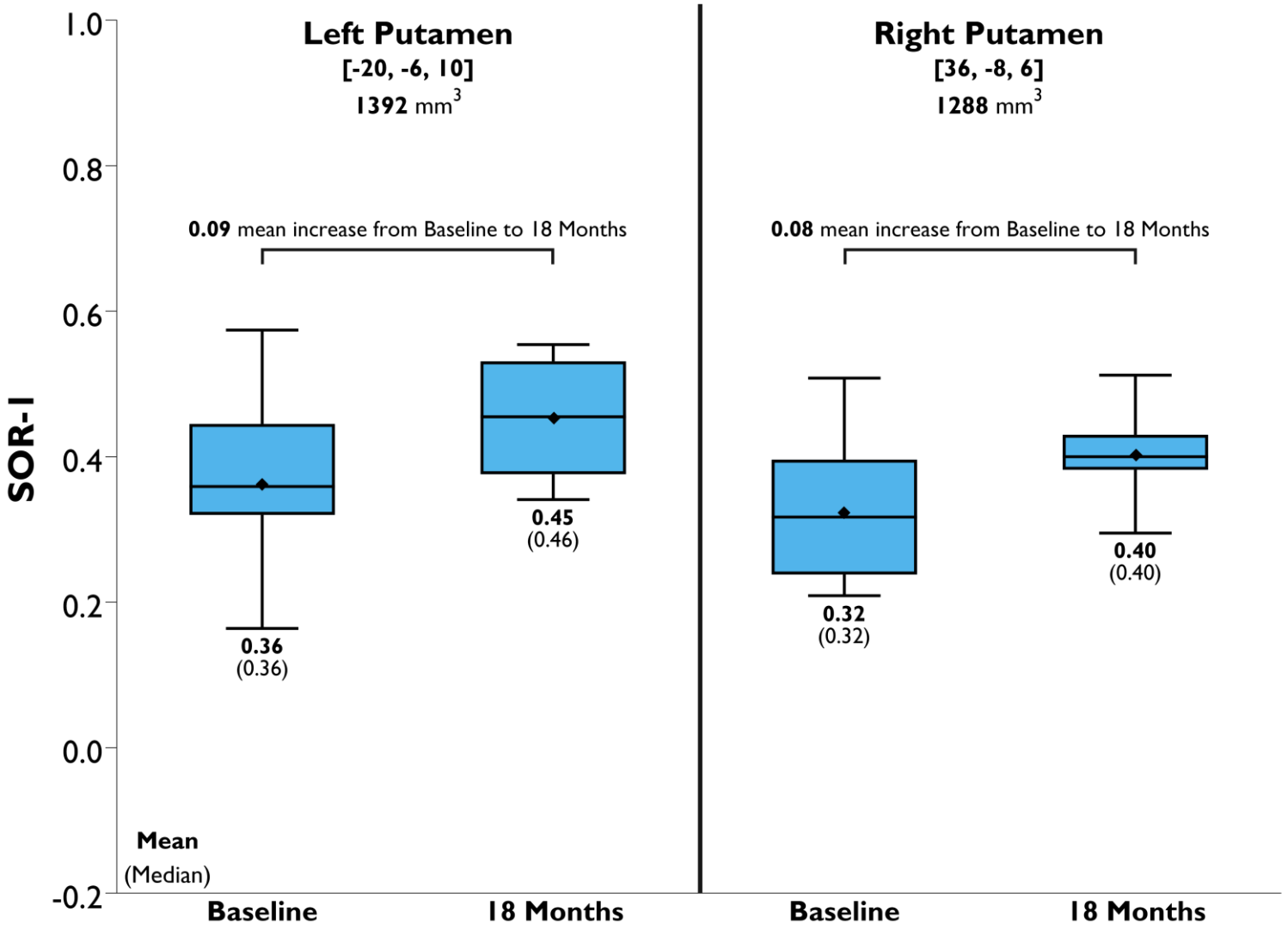


- Compared with baseline, group-level analysis of ^{18}F-DOPA uptake at 12 and 18 months post transplantation revealed clusters of increased ^{18}F-DOPA PET signal within the striatal hypothesis testing space
- ^{18}F-DOPA uptake was stable or increased in the putamen at 18 months post transplantation (6 months post discontinuation of immunosuppression)

Voxels with increase: orange; voxels with decrease: blue. ^{18}F-DOPA, [18] fluorodopa; PET, positron emission tomography.

^{18}F-DOPA Uptake: Putamen

Baseline to 18 Months Post Transplantation

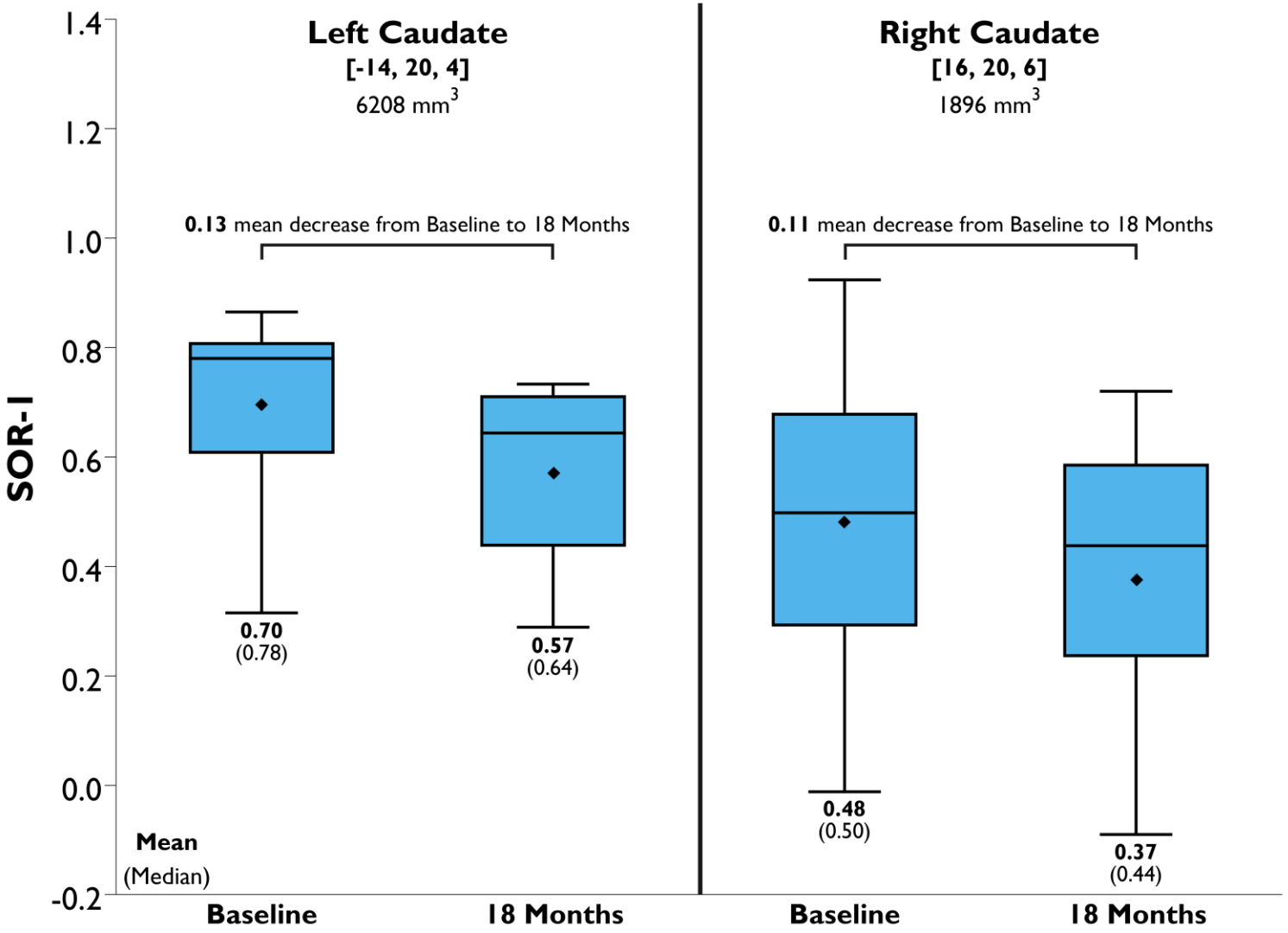


- Increases in mean SOR-I were observed in the largest clusters identified within the left and right putamen at 18 months post transplantation (n=11)
- These clusters are interpreted to be associated with bemdaneprocel
- At 18 months post transplantation, participants were off immunosuppression for 6 months

^{18}F-DOPA, [18] fluorodopa; SOR, striatal-to-occipital ratio.

^{18}F-DOPA Uptake: Caudate

Baseline to 18 Months Post Transplantation

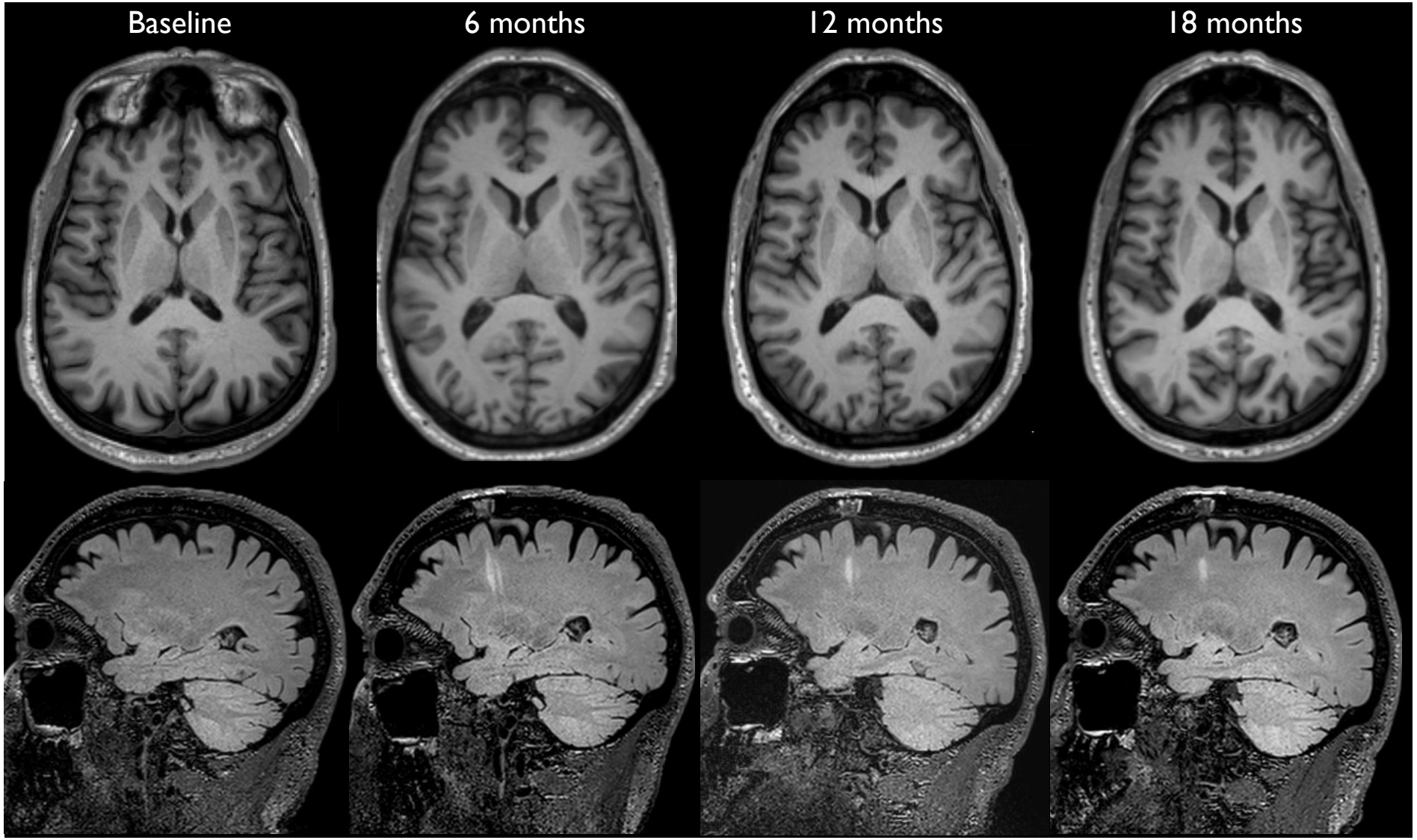


- Decreases in mean SOR-I were observed in the largest clusters identified within the left and right caudate at 18 months post transplantation (n=11)
- Decreased ^{18}F-DOPA uptake in the caudate is interpreted to indicate continued neurodegeneration associated with Parkinson's disease pathology

^{18}F-DOPA, [18] fluorodopa; SOR, striatal-to-occipital ratio.

Progression of MRI

Through 18 Months Post Transplantation



- No evidence of intracerebral hemorrhage, mass lesion, and/or cellular overgrowth
- Transplanted cells indiscernible on MRI
- Expected finding of bilateral tracks accompanied by surrounding gliosis

MRI, magnetic resonance image.

Conclusions

Increased ^{18}F-DOPA PET signal in the posterior putamen is consistent with survival of bemdaneprocel at 12 and 18 months post transplantation

- Bemdaneprocel survival continued after cessation of immunosuppression at 12 months post transplantation
- Decreased ^{18}F-DOPA PET signal in the caudate is indicative of continuing progression of Parkinson's disease
- These findings comport with findings from an independent analysis

MRI assessments of target volume did not reveal evidence of cell overgrowth, tumor formation, or other safety concerns up to 18 months post transplantation

These analyses demonstrate bemdaneprocel survival for 6 months post discontinuation of immunosuppression, or 18 months post transplantation, and continued dopaminergic signaling in the putamen

^{18}F-DOPA, [18] fluorodopa; MRI, magnetic resonance image; PET, positron emission tomography.

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^{18}F-DOPA, [18] fluorodopa; CT, computed tomography; PET, positron emission tomography.