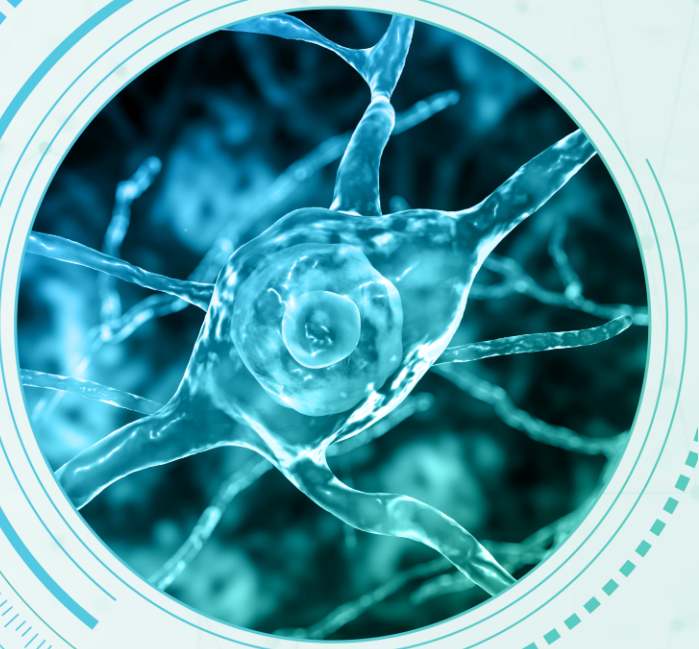
Safety, Tolerability, and Clinical Assessment of Bemdaneprocel for Parkinson's Disease: Results up to 18 Months From a Phase 1 Study



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Background and Objective

People with Parkinson's disease experience reduced health-related quality of life that persists despite standard treatment[1]

- Current standard treatments for Parkinson's disease motor symptoms do not address the loss of dopaminergic neurons[2]

Bemdaneprocel is an investigational therapy comprising dopaminergic neuronal progenitors derived from human embryonic stem cells[3,4]

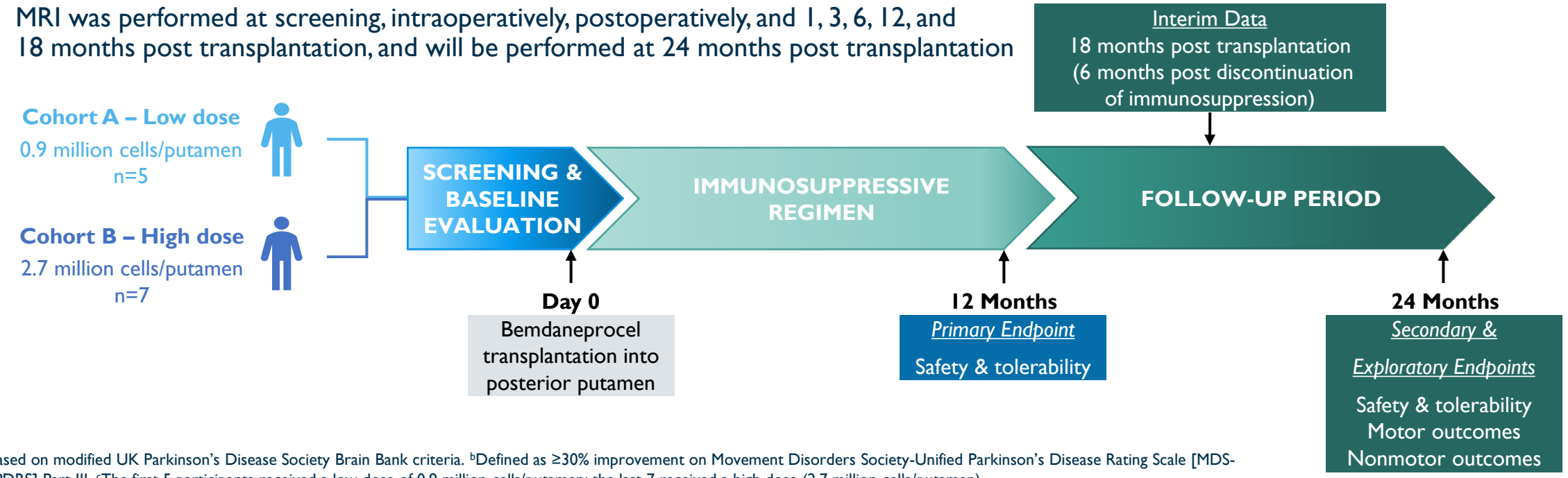
- Preclinical studies in rat and mouse models support safety and proof-of-concept[4,5]
- exPDite is a Phase 1 multicenter, multisite, open-label, nonrandomized study (NCT04802733)
- Primary results at 12 months post transplantation demonstrated that bemdaneprocel was generally safe and well tolerated; secondary and exploratory results supported the feasibility of stereotactic transplantation of bemdaneprocel, and suggested stability or improvement in motor outcomes[6]

<u>Objective:</u> To evaluate the safety of bemdaneprocel and its impact on motor outcomes up to 18 months post transplantation, 6 months post discontinuation of immunosuppression, in participants with Parkinson's disease

1. Lubomski M, et al. *J Mov Disord.* 2021;14(1):42-52. 2. Armstrong MJ, Okun MS. *JAMA.* 2020;323(6):548-560. 3. Kim TW, et al. *Cell Stem Cell.* 2021;28(2):343-355.e5. 4. Piao J, et al. *Cell Stem Cell.* 2021;28(2):217-229.e7. 5. Steinbeck, JA. *Nat Biotechnol.* 2015;33(2):204-209. 6. Henchcliffe C, et al. Presented at: International Congress of Parkinson's Disease and Movement Disorders; August 27–31, 2023; Copenhagen, Denmark.

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]
- ^{18}F-DOPA PET was performed at baseline, 12, 18 months post transplantation, and will be performed at 24 months post transplantation
- MRI was performed at screening, intraoperatively, postoperatively, and 1, 3, 6, 12, and 18 months post transplantation, and will be performed at 24 months post transplantation



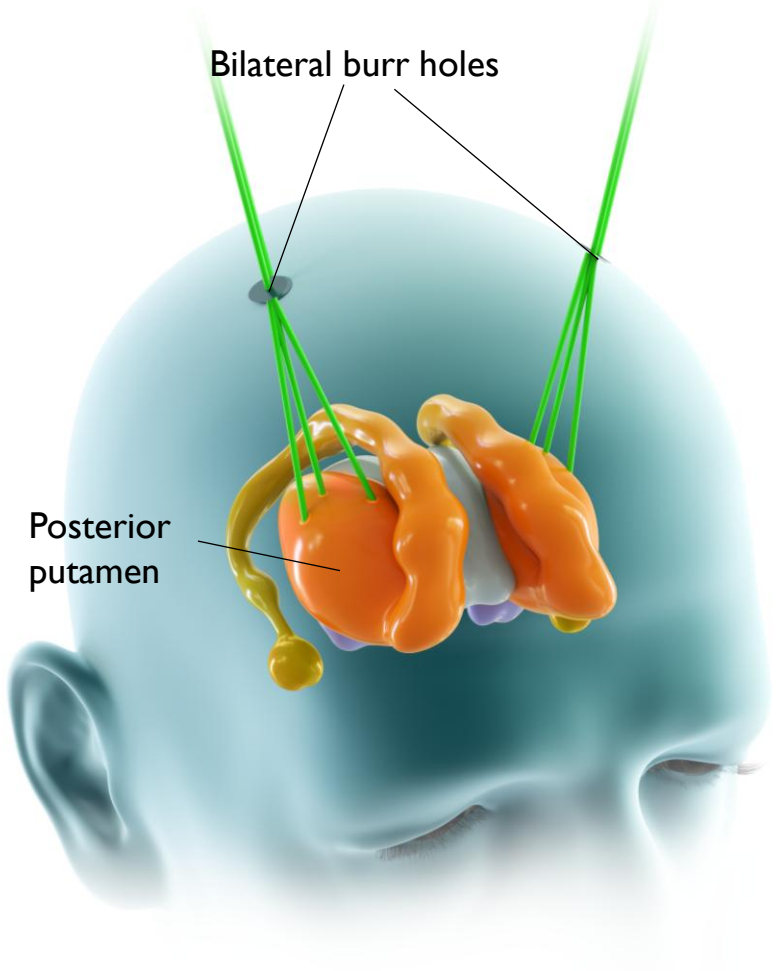
[a]Based on modified UK Parkinson's Disease Society Brain Bank criteria. [b]Defined as ≥30% improvement on Movement Disorders Society-Unified Parkinson's Disease Rating Scale [MDS-UPDRS] Part III. [c]The first 5 participants received a low dose of 0.9 million cells/putamen; the last 7 received a high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

Surgical Procedure

Immunosuppression was initiated during 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

- 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 putamen



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

Objectives and Endpoints

Objectives	Endpoints[a]
Primary	
Assess safety and tolerability of bemdaneprocel at 1 year post transplantation	Incidence of serious adverse events[b]
Secondary	
Assess evidence of survival of transplanted cells and motor effects at 1 and 2 years post transplantation	• Change from baseline in striatal ^{18}F-DOPA uptake using PET • **MDS-UPDRS (Part III OFF), good ON time**
Evaluate continued safety and tolerability at 1 and 2 years post transplantation	• **Incidence of serious adverse events** • **Incidence and type of adverse events**
Assess feasibility of transplantation	**Delivery of ≥50% of intended total number of deposits/brain in >50% of participants**
Exploratory	
Determine the effects of bemdaneprocel on motor and non-motor signs and symptoms of Parkinson's disease	Change from baseline • **MDS-UPDRS** (total, Parts I, **II**, and IV, and **Part III ON**) • Modified Schwab and England Activities of Daily Living • **Unified Dyskinesia Rating Scale** • **Hauser Diary** • MoCA • BAI-II • BDI-II • QUIP • NMSS • GCIS • LEDD • 10MWT
Assess the participant perception of quality of life	PDQ-39

[a]Interim data cuts (18 months post transplantation) of endpoints reported here are indicated in bold; [b]Safety was defined as ≤2 participants in either cohort developing ≥2 SAEs related to surgery, presence of transplanted cells, or immunosuppression; or tumor or abnormal tissue overgrowth related to presence of transplanted cells; or intracerebral hemorrhage deemed life-threatening; and ≤1 death in either cohort.
10MWT, 10-meter walking test; ADL, activities of daily living; BAI-II, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory; GCIS, Global Clinical Impression Scale; LEDD, levodopa-equivalent daily dose; MDS-UPDRS, Movement Disorders Society-Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; NMSS, Parkinson's Disease Nonmotor Symptom Severity Scale; PDQ-39, Parkinson's Disease Questionnaire-39; PET, positron emission tomography; QUIP, Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease; SAE, serious adverse event.

Demographics

	Low Dose (n=5)	High Dose (n=7)	Total (N=12)
Age, years			
Mean (SD)	66.8 (6.8)	66.7 (4.8)	66.8 (5.4)
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 (%)			
Asian	0	1 (14.3)	1 (8.3)
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)

Q1, quartile 1; Q3, quartile 3; SD, standard deviation.

Baseline Characteristics

	Low Dose (n=5)	High Dose (n=7)	Total (N=12)
Time Since Parkinson's Disease Diagnosis, years			
Mean (SD)	11.0 (3.7)	7.8 (2.2)	9.1 (3.2)
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 (%)			
2	1 (20.0)	0	1 (8.3)
3	4 (80.0)	7 (100.0)	11 (91.7)
Hoehn and Yahr Stage (ON state), n (%)			
2	5 (100.0)	7 (100.0)	12 (100.0)

Q1, quartile 1; Q3, quartile 3; SD, standard deviation.

Safety and Tolerability:
18 Months Post Transplantation

	Low Dose (n=5)	High Dose (n=7)	Total (N=12)
Participants reporting, n (%) [number of events]			
TEAE	5 (100) [40]	7 (100) [38]	12 (100) [78]
Mild	1 (20) [29]	3 (43) [31]	4 (33) [60]
Moderate	3 (60) [10]	3 (43) [6]	6 (50) [16]
Severe	1 (20) [1]	1 (14) [1]	2 (17) [2]
Life-threatening, or death related to adverse event	0	0	0
TESAE	1 (20) [1][a]	2 (29) [2][b]	3 (25) [3]
Related to surgery	0	1 (14) [1]	1 (8) [1]
Related to transplanted cells	0	0	0
Related to immunosuppression	0	0	0
Deaths	0	0	0

No deaths, discontinuations, or graft-induced dyskinesias occurred

- All participants reported ≥1 TEAE, but most were mild or moderate in severity
- 3 TESAEs occurred; none were related to bemdaneprocel
- Feasibility of stereotactic administration was demonstrated: all participants received the intended number of cell deposits

[a] 1 incidence of brief hospitalization due to COVID.
[b] 1 incident of gastrointestinal hemorrhage, and 1 incidence of seizure. The TESAE of seizure lasted 10 minutes, was attributed to surgery, and resolved.
TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

TEAEs by System Organ Class:
18 Months Post Transplantation

	Total (N=12)		Total (N=12)
Participants reporting, n (%) [number of events]			
Nervous system disorders	8 (66.7) [11]	Renal and urinary disorders	2 (16.7) [2]
Infections and infestations	7 (58.3) [10]	Vascular disorders	2 (16.7) [3]
Musculoskeletal and connective tissue disorders	6 (50.0) [11]	Blood and lymphatic system disorders	1 (8.3%) [1]
Injury, poisoning, and procedural complications	5 (41.7) [7]	Ear and labyrinth disorders	1 (8.3%) [2]
Gastrointestinal disorders	4 (33.3) [10]	Endocrine disorders	1 (8.3%) [1]
General disorders and administration site conditions	4 (33.3) [6]	Eye disorders	1 (8.3%) [1]
Investigations	3 (25.0) [4]	Immune system disorders	1 (8.3%) [1]
Skin and subcutaneous tissue disorders	3 (25.0) [3]	Metabolism and nutrition disorders	1 (8.3%) [1]
Psychiatric disorders	2 (16.7) [2]	Respiratory, thoracic, and mediastinal disorders	1 (8.3%) [2]

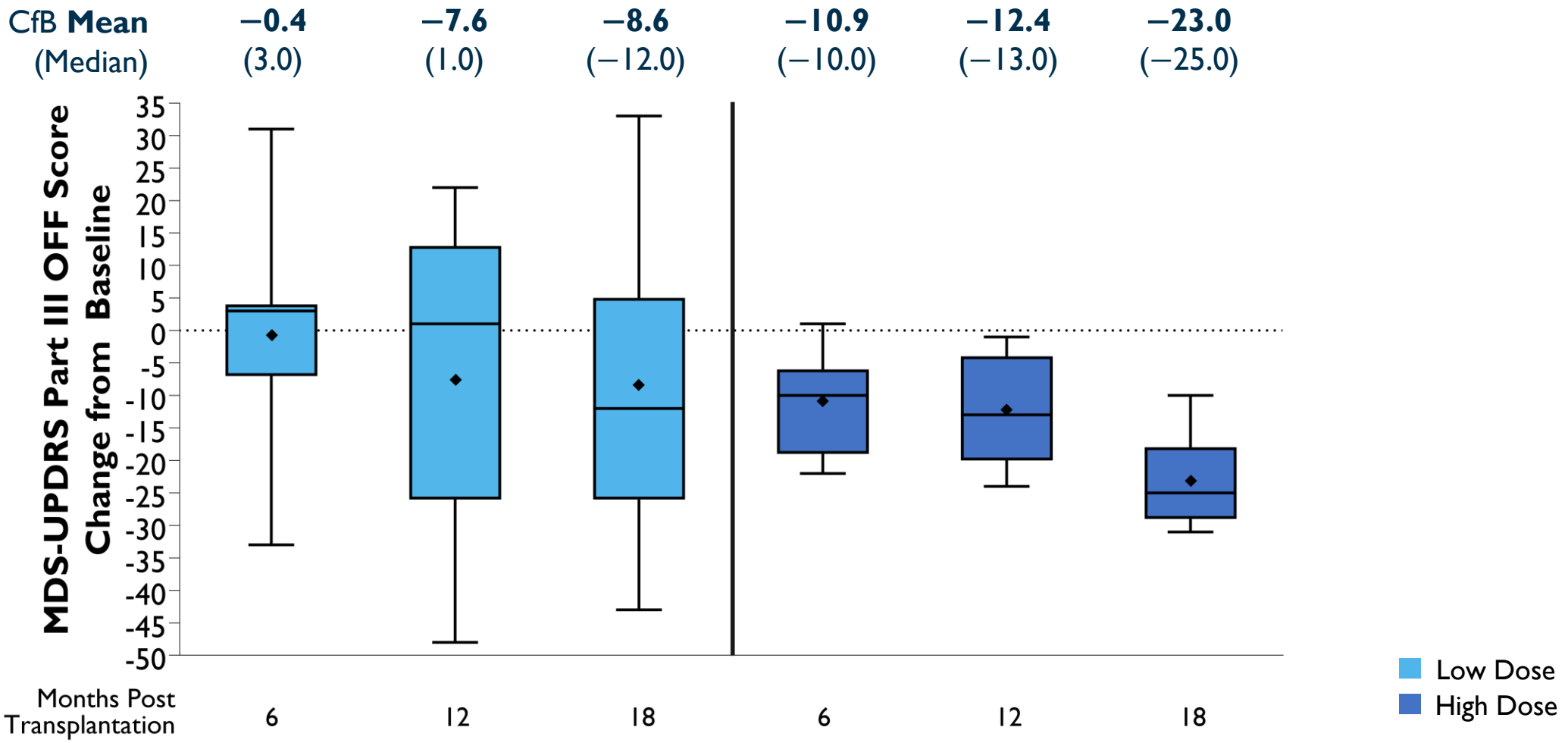
TEAE, treatment-emergent adverse event.

Nervous System Disorder and Infection and Infestation TEAEs: 18 Months Post Transplantation

	Total (N=12)		Total (N=12)
Participants reporting, n (%) [number of events]			
Nervous system disorders	**8 (66.7) [11]**	**Infections and infestations**	**7 (58.3) [10]**
Dyskinesia	2 (16.7%) [2]	COVID-19	4 (33.3%) [4]
Tremor	2 (16.7%) [2]	Cellulitis	1 (8.3%) [1]
Cubital tunnel syndrome	1 (8.3%) [1]	Fungal skin infection	1 (8.3%) [1]
Headache	1 (8.3%) [1]	Oral herpes	1 (8.3%) [1]
Lethargy	1 (8.3%) [1]	Pneumonia	1 (8.3%) [1]
On and off phenomenon	1 (8.3%) [1]	Post viral fatigue syndrome	1 (8.3%) [1]
Paraesthesia	1 (8.3%) [1]	Urinary tract infection	1 (8.3%) [1]
Poor quality sleep	1 (8.3%) [1]		
Seizure	1 (8.3%) [1]		

TEAE, treatment-emergent adverse event.

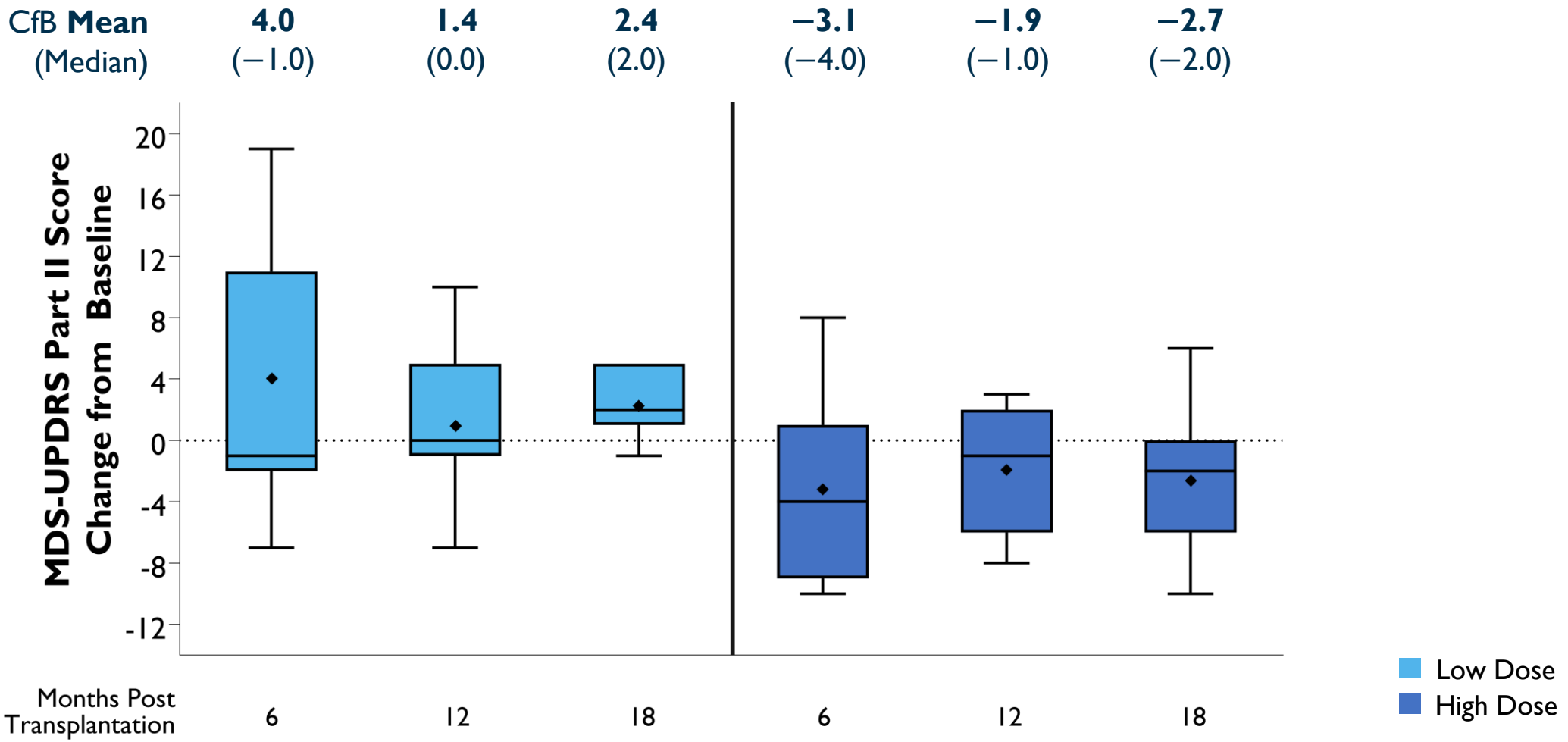
MDS-UPDRS Part III OFF Scores:
Change From Baseline at 18 Months Post Transplantation



- Baseline MDS-UPDRS Part III OFF scores were (mean [median]) 43.2 (44.0) in the low-dose cohort and 49.0 (51.0) in the high-dose cohort

MDS-UPDRS Part III contains 18 items with a subscore range of 0 to 132 points; higher scores indicate more severe motor symptoms. Horizontal lines represent median; diamonds represent mean; boxes represent Q1 and Q3; whiskers represent extreme values. CfB, change from baseline; MDS-UPDRS, Movement Disorders Society-Unified Parkinson's Disease Rating Scale; Q1, quartile 1; Q3, quartile 3.

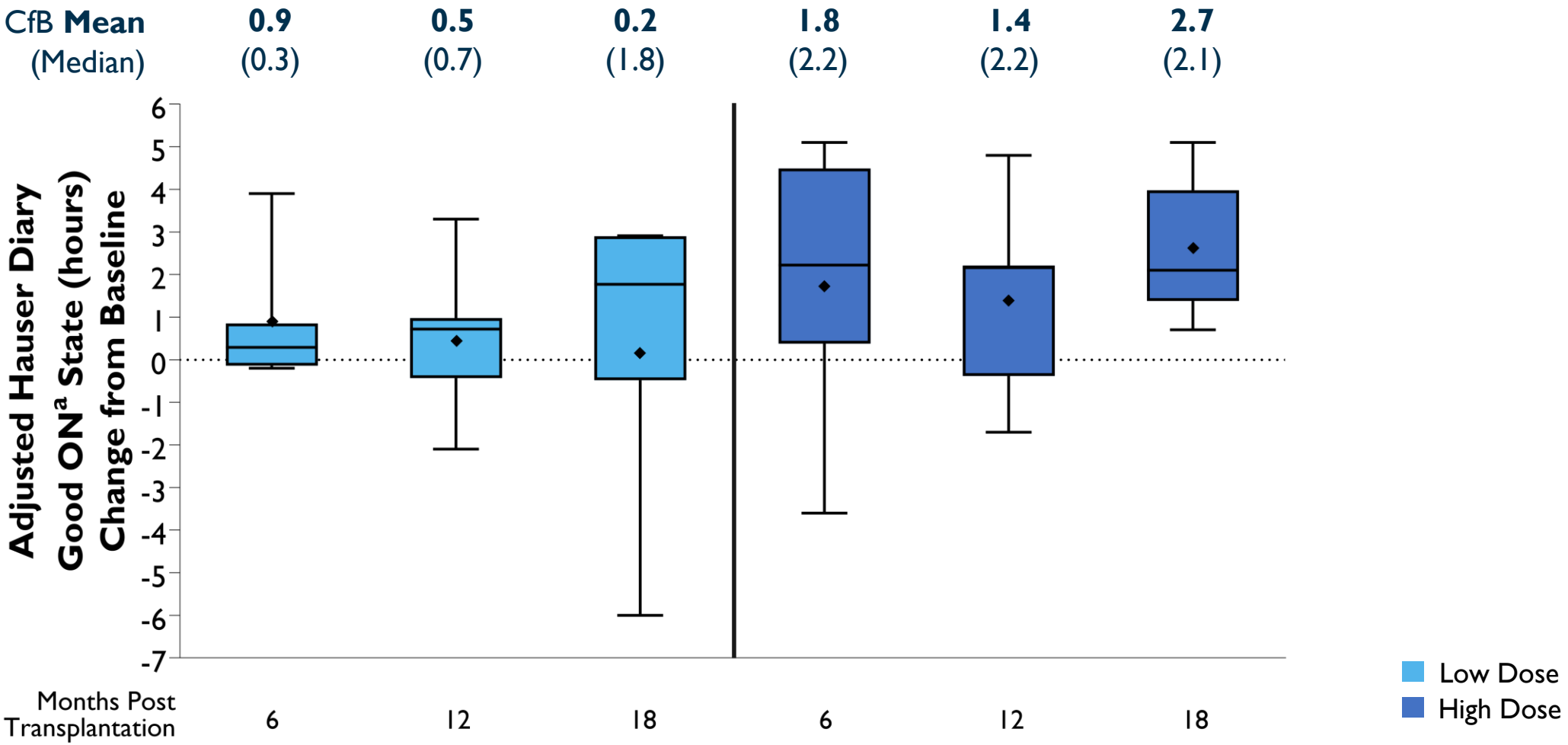
MDS-UPDRS Part II:
Change From Baseline at 18 Months Post Transplantation



- Baseline MDS-UPDRS Part II scores were (mean [median]) 10.8 (10.0) in the low-dose cohort and 12.7 (11.0) in the high-dose cohort

MDS-UPDRS Part II contains 18 items with a subscore range of 0 to 52 points; higher scores indicate more severe motor symptoms. Horizontal lines represent median; diamonds represent mean; boxes represent Q1 and Q3; whiskers represent extreme values. CfB, change from baseline; MDS-UPDRS, Movement Disorders Society-Unified Parkinson's Disease Rating Scale; Q1, quartile 1; Q3, quartile 3.

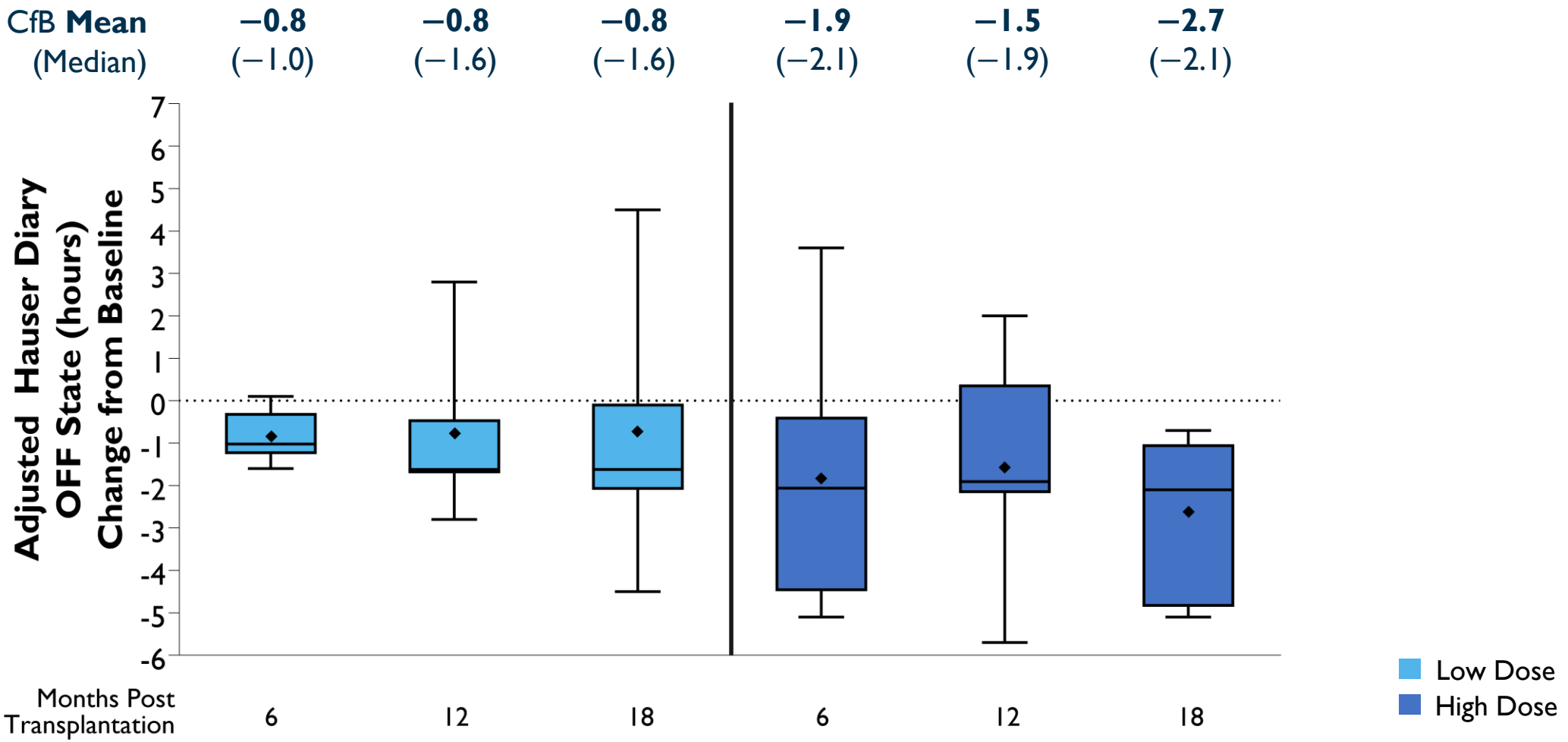
Adjusted Hauser Diary Good ON Times:
Change From Baseline at 18 Months Post Transplantation



- Baseline adjusted Hauser diary Good ON times were (mean [median]) 12.0 hours (13.2) in the low-dose cohort and 10.9 hours (10.4) in the high-dose cohort

[a]Good ON state is the sum of ON state without dyskinesia and ON state with non-troublesome dyskinesia. Hauser Diary time is adjusted for 16-hour waking days. Horizontal lines represent median; diamonds represent mean; boxes represent Q1 and Q3; whiskers represent extreme values. CfB, change from baseline; Q1, quartile 1; Q3, quartile 3

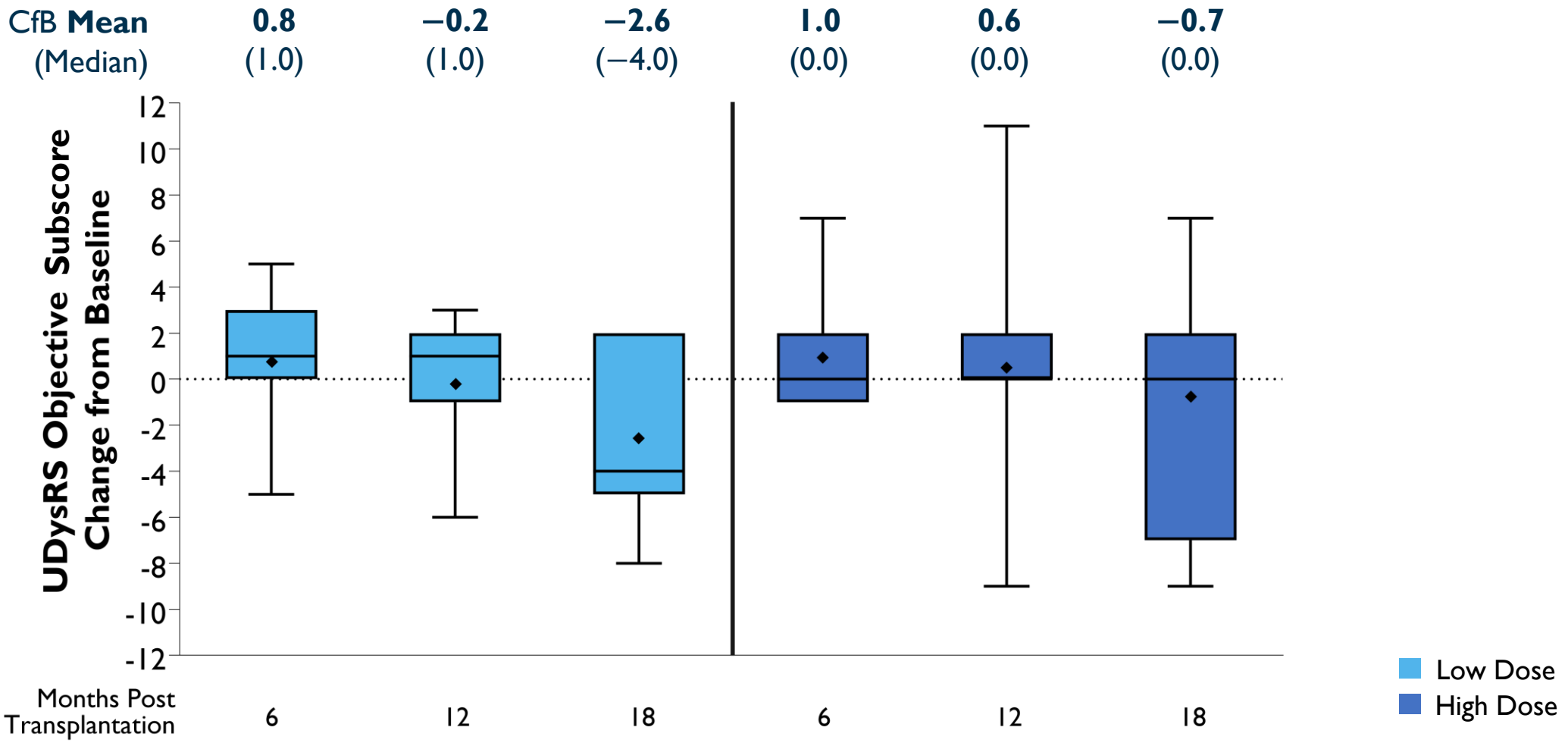
Adjusted Hauser Diary OFF Times:
Change From Baseline at 18 Months Post Transplantation



- Baseline adjusted Hauser diary OFF times were (mean [median]) 3.2 hours (2.6) in the low-dose cohort and 5.0 hours (5.6) in the high-dose cohort

Hauser Diary time is adjusted for 16-hour waking days. Horizontal lines represent median; diamonds represent mean; boxes represent Q1 and Q3; whiskers represent extreme values.
CfB, change from baseline; Q1, quartile 1; Q3, quartile 3.

UDysRS Objective Subscores:
Change From Baseline at 18 Months Post Transplantation



- Baseline UDysRS objective subscores were (mean (median]) 10.6 (14.0) in the low-dose cohort and 2.3 (0.0) in the high-dose cohort

The UDysRS Objective Subscore is made up of Part 3 (Impairment) and Part 4 (Disability). The objective subscale consists of 11 items on a scale of 0 (normal) to 4 (severe), with a total possible score of 44; higher scores represent more severe symptoms. Horizontal lines represent median; diamonds represent mean; boxes represent Q1 and Q3; whiskers represent extreme values.
CfB, change from baseline; Q1, quartile 1; Q3, quartile 3; UDysRS, Unified Dyskinesia Rating Scale.

Conclusions

Bemdaneprocel was well tolerated, with no major safety issues in all 12 participants through 18 months

- No serious adverse events were attributed to the transplanted cells or immunosuppression
- No graft-induced dyskinesias were reported throughout the 18 months
- All participants will be asked to enroll in a long-term extension study for continued evaluation of safety and efficacy

Exploratory outcomes were stable or improved through 18 months, 6 months post discontinuation of immunosuppression

- Participants in the high-dose cohort trended more strongly toward improvement compared with participants in the low-dose cohort
- These findings should be interpreted carefully given the small, open-label nature of this study

These findings support the continued development of bemdaneprocel for the treatment of people with Parkinson's disease