RESEARCH ARTICLE

Allogeneic Bone Marrow-Derived Mesenchymal Stem Cells for Parkinson's Disease: A Randomized Trial

Mya C. Schiess, MD,[1*] Jessika Suescun, MD,[1] Juan D. Martinez-Lemus, MD,[1] Charles Green, PhD,[2] Tia S. Thomas, BS,[3] Mohammad Shahnawaz, PhD,[4] Emily Tharp, MD,[1] Nikunj B. Satani, MBBS, MPH,[3] Jerome G. Saltarrelli, PhD,[5] Christopher Adams, MD,[6] Marie-Francoise Doursout, PhD,[7] Vanessa Thyne, MS,[1] Rula Abuamouneh, MS,[1] Elsa M. Rodarte, MD,[1] Sean I. Savitz, MD,[3] and Timothy M. Ellmore, PhD[8]

ABSTRACT: Background: Neuroinflammation contributes to Parkinson's disease (PD) progression and motor dysfunction. Allogeneic human mesenchymal stem cells (allo-hMSCs) may reduce neuroinflammation and improve motor symptoms.

Objectives: To evaluate the efficacy of repeated intravenous doses of 10×10^6/kg allo-hMSCs in improving motor symptoms in patients with PD (PwP).

Methods: In this phase 2, randomized, placebo-controlled trial (November 2020–July 2023), mild-to-moderate PwP received either three allo-hMSC infusions, one placebo followed by two allo-hMSC infusions, or three placebo infusions at 18-week intervals. Follow-up lasted 88 weeks. The primary outcome was a >70% posterior probability (PP) of a difference in the proportion of participants with ≥5-point improvement in OFF-medication Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale-Part III (MDS-UPDRS-III) at week 62. Bayesian analysis was conducted using R v4.2.0.

Results: Forty-five PwP were enrolled. A larger proportion of subjects achieved a ≥5-point improvement in MDS-UPDRS-III in the three-infusion arm compared with placebo at week 62 (mean difference [MD]: 5.0%, PP = 93.7%), translating to a 16.9-point improvement in MDS-UPDRS-III in the three-infusion arm compared with a 14.6-point improvement in the placebo arm. Conversely, fewer subjects in the two-infusion arm compared with placebo showed ≥5-point improvement at week 62 (MD: –62.4%, PP ≥ 99.9%), translating to only a 3.9-point improvement in MDS-UPDRS-III in the two-infusion arm. However, improvement in MDS-UPDRS-III was seen across all treatment arms. Adverse events were mild and transient.

Conclusions: Three infusions of 10×10^6 allo-hMSCs/kg improved motor function in mild-to-moderate PwP, while two infusions showed less improvement than placebo. To address this discrepancy, future studies should conduct functional potency assays to understand batch-to-batch variability affecting clinical efficacy.

[1]Movement Disorders Division, Department of Neurology, McGovern Medical School at UTHealth Houston, Houston, Texas, USA; [2]Center for Clinical Research & Evidence-Based Medicine, Department of Pediatrics, McGovern Medical School at UTHealth Houston, Houston, Texas, USA; [3]Institute for Stroke and Cerebrovascular Diseases, McGovern Medical School at UTHealth Houston, Houston, Texas, USA; [4]Mitchell Center for Alzheimer's Disease and Related Brain Disorders, Department of Neurology, McGovern Medical School at UTHealth Houston, Houston, Texas, USA; [5]Immunology & Organ Transplantation Division, Department of Surgery, McGovern Medical School at UTHealth Houston, Houston, Texas, USA; [6]Movement Disorders Division, Department of Neurology, University of Washington, Seattle, Washington, USA; [7]Department of Anesthesiology, McGovern Medical School at UTHealth Houston, Houston, Texas, USA; [8]Department of Psychology, The City College of the City University of New York, New York, New York, USA

*Correspondence to: Professor Mya C. Schiess, Adriana Blood Distinguished Chair in Neurology, Division Chief and Director of Movement Disorders & Neurodegenerative Diseases Program, University of Texas, McGovern Medical School at Houston, Houston, Texas, USA.

E-mail: mya.c.schiess@uth.tmc.edu

Relevant conflicts of interest/financial disclosures: M.C.S. received financial support from the 2019 Clinical Therapeutic Pipeline Program Award by The Michael J. Fox Foundation for Parkinson's Research (Grant IDs: MJFF-009634 and MJFF-023299). M.S. is an inventor of patent US10989718B2, filed by the University of Texas Health Science Center at Houston and Amprion, Inc. for the use of α-synuclein seed amplification assays (αSyn-SAA) utilizing the protein misfolding cyclic amplification (PMCA) technology for highly sensitive detection of αSyn aggregates in patients affected by synucleinopathies. All the other authors declare no competing interests.

Funding agencies: This work was supported by the 2019 Clinical Therapeutic Pipeline Program Award from The Michael J. Fox Foundation for Parkinson's Research (Grant IDs: MJFF-009634 and MJFF-023299), the Adriana Blood Distinguished Chair in Neurology Endowment, and philanthropic contributions from individuals and families affected by Parkinson's disease.

Received: 20 March 2025; **Revised:** 30 July 2025; **Accepted:** 11 August 2025

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.70028

Key Words: Parkinson's disease; mesenchymal stem cells; allogeneic stem cells; intravenous infusions; randomized controlled trial

Since the 1960s, when Carlsson, Hornykiewicz, Cotzias, and Yahr identified nigral dopamine deficits in Parkinson's disease (PD) and introduced dopamine replacement therapy, numerous pharmacological and neuromodulation treatments have effectively alleviated motor symptoms.[1] In regenerative medicine, PD has been a key target for cell-based therapies aimed at symptom improvement and disease modification, with various approaches explored clinically over the past decades.[2]

Stem cell therapy for PD has historically followed two approaches: cell transplantation and intravenous (IV) infusion.[2] Transplantation, the most studied method, involves the use of stem cells with a goal of differentiating these cells into dopaminergic neurons and restoring neurotransmission.[3] Ethical concerns regarding cell procurement, the invasive nature of implantation, tumorigenicity, immunogenicity, and complications such as treatment-resistant dyskinesias have limited their use, especially in mild-to-moderate PD. In contrast, IV infusions of mesenchymal stem cells (MSCs) have emerged as a promising and safe therapeutic option for PD. These multipotent cells have gained attention for their ability to modulate the peripheral immune system and, as a result, neuroinflammation, a key factor in PD pathophysiology.[4,5] MSCs offer several advantages, not just in terms of treatment delivery method, but they are also minimally immunogenic, have low tumorigenesis risk, are easy to procure and scale, and have few ethical concerns.[6]

In PD animal models, MSCs have been shown to reduce microglial activation and enhance dopamine neuron survival through a multitarget mechanism.[5] While some studies suggest MSCs may migrate to the substantia nigra and suppress microglial activation via direct interaction with dopaminergic cells,[7] 80%–90% become trapped in the lungs due to their size (15–30 μm) and the pulmonary vasculature's narrow capillaries, making direct engraftment rare and transient.[8,9] However, intravenously delivered MSCs or their derivatives (extracellular vesicles and exosomes) are believed to modulate neuroinflammation by releasing anti-inflammatory cytokines (eg, transforming growth factor-β [TGF-β], interleukin-10 [IL-10], prostaglandin E2 [PGE2]) that alter peripheral immune responses and reduce blood–brain barrier permeability.[6,7,10,11] They also produce neurotrophic factors (eg, brain-derived neurotrophic factor [BDNF], glial cell line-derived neurotrophic factor [GDNF], neurotrophin nerve growth factor [NGF]) that support neuronal survival and synaptic plasticity.[12] By targeting these mechanisms, MSC therapy may influence the underlying pathophysiology of PD.

Based on this rationale, we conducted a dose-finding, single-dose phase 1 trial using allogeneic bone marrow-derived MSCs (allo-hMSCs) from a healthy donor.[13] This approach leveraged the advantages of an allogeneic cell source, including large-scale production, no need for patient-specific harvesting, and the delivery of younger, more potent cells with reduced senescence.[14] The trial demonstrated that a single IV dose ranging from 1 to 10×10^6 allo-MSCs/kg was safe, well-tolerated, and non-immunogenic in patients with mild-to-moderate PD. Preliminary exploratory analyses indicated that those receiving the highest dose showed OFF-medication improvements on the Unified Parkinson's Disease Rating Scale (UPDRS) Motor subscale at 3, 12, 24, and 52 weeks post-infusion, with sustained symptomatic benefits over time.[13]

Building on these findings and recognizing the chronic, progressive nature of PD, we hypothesized that repeated doses of the highest safe allo-hMSC dose (10×10^6 MSCs/kg) could enhance and sustain its immunomodulatory effects, leading to clinical symptom improvement, as seen in other diseases.[15-18] To test this, we conducted a phase 2 double-blind, randomized, placebo-controlled trial to evaluate the efficacy of repeated allo-hMSC infusions in improving motor and non-motor symptoms in patients with PD (PwP).

Methods

Trial Design

This investigator-initiated, randomized, double-blind, placebo-controlled, phase 2 trial was conducted from November 2020 to July 2023 at a single center in Houston, Texas, USA. The study was approved by the Institutional Review Board (IRB) of The University of Texas Health Science Center at Houston and the Food and Drug Administration (FDA) under the Investigational New Drug: 16756. Written informed consent was obtained during the screening visit. An independent Data and Safety Monitoring Board oversaw the trial. The completed study is registered on ClinicalTrials.gov (NCT04506073). The full protocol is available in Supplement 1.

Participants

The trial enrolled men and women aged 50–79 years with a confirmed PD diagnosis based on the UK Brain Bank Criteria, verified by a movement disorders neurologist. Participants had to be on a stable medical regimen for at least 60 days before the first infusion. Key inclusion criteria included a modified Hoehn and Yahr (H&Y) stage ≤3 in the OFF-medication state, PD duration of 2–10 years, and a robust (>33%) response to dopaminergic therapy in the OFF-to-ON medication state. A full list of inclusion/exclusion criteria is available in Supplement 1.

MSCs Manufacturing and Expansion

Bone marrow was aspirated from a healthy donor under local anesthesia and screened for infectious diseases using FDA-approved kits at the Gulf Coast Regional Blood Center within 7 days of collection. Human leukocyte antigen (HLA) testing was also performed to later compare with donor-specific antibodies (DSA) in recipients. The marrow was transported to a cGMP facility at the Center for Cell and Gene Therapy (CAGT) at Baylor College of Medicine for FDA-compliant quality control, ensuring sterility, viability, and MSC identity according to International Society for Cell & Gene Therapy (ISCT) release criteria (CD90, CD73, CD105 positive; CD45, CD34, CD14, HLA-DR negative). MSC manufacturing began within 4 hr, with cells cultured in a Terumo Quantum Bioreactor.[19] Expansion used the fourth passage, with growth monitored through glucose and lactate levels. Once growth criteria were met, cells were harvested, suspended in Plasma Lyte A with 5% Flexbumin and 10% DMSO, aliquoted into treatment-ready doses, and cryopreserved using a controlled-rate freezer. The placebo, visually identical to the investigational product, contained only 5% buminate solution without allo-hMSCs. Infusion bags and IV lines were covered with an opaque cloth to maintain blinding.

Randomization

Eligible patients were randomized 1:1:1 using computer-generated stratified block randomization based on MDS-UPDRS-III scores (<30 = mild and 30 = moderate[20]) to one of three possible treatment groups: (1) three infusions of 10×10^6 allo-hMSCs/kg, (2) one placebo infusion followed by two 10×10^6 allo-hMSC infusions, or (3) three placebo infusions. Infusions were administered every 18 weeks over a total treatment period of 36 weeks. Details of the masking procedures can be found in the trial protocol in Supplement 1.

Clinical Assessments

At the baseline visit, participants underwent a comprehensive clinical evaluation, including MDS-UPDRS Parts I–IV in the OFF-medicine state, defined as no levodopa, monoamine oxidase inhibitors, catechol-o-methyltransferase inhibitors, or amantadine for at least 12 hr, and no dopamine agonists for at least 24 hr prior to evaluation. Lumbar puncture was performed, and cerebrospinal fluid was analyzed using α-synuclein seed amplification assays (αSyn-SAA) via the protein misfolding cyclic amplification (PMCA) method to verify an aggregation pattern consistent with PD.[21]

On infusion days (weeks 1, 18, and 36), allo-hMSCs or placebo were thawed following pre-infusion sterility confirmation. Cells were aliquoted into a 250 mL transfer pack containing 5% buminate at an infusion concentration of 1.5×10^7 cells/mL and transported in certified coolers (4°C–10°C) from the CAGT laboratory to the Texas Medical Center-Memorial Hermann Hospital Clinical Research Unit. The study drug was administered via antecubital vein access at 2 mL/min within 4 hr of thawing, followed by a 4-h monitoring period for adverse or hypersensitivity reactions.

Clinical efficacy and safety, including DSAs, were measured 9 weeks after each infusion and at weeks 62 and 88. If DSAs were detected between infusions, treatment was paused until antibody clearance was confirmed.

Outcomes

The primary outcome was a >70% probability of detecting a difference in the proportion of subjects with a ≥5-point improvement in MDS-UPDRS-III between any active treatment and placebo at 62 weeks (26 weeks after the last infusion). Complementary analyses applied a higher cut-off (≥11-point improvement in MDS-UPDRS-III) to assess a larger clinically important difference (CID) and extended follow-up to 88 weeks (52 weeks post-infusion) to evaluate the sustainability of effects. Both thresholds were based on the intermediate (5.2-point) and large (10.8-point) CID defined by Shulman et al.[22] Secondary exploratory outcomes included change from baseline to weeks 62 and 88 in MDS-UPDRS parts I–IV, Parkinson's Disease Questionnaire (PDQ)-39, and EuroQol 5-Dimension 5-Level (EQ-5D-5L). Additionally, the proportion of subjects achieving a ≥12-point improvement in the MDS-UPDRS Total score was assessed.

Statistical Analyses

Following our phase 1 trial demonstrating the safety of allo-hMSC therapy, we conducted a simulation to estimate the required sample size to detect an intermediate CID (5.2-point decrease from baseline[22]) after allo-hMSC treatment. Assuming 45 participants randomized

1:1:1 across three treatment groups and a medium effect size (~5.2-point difference in MDS-UPDRS-III), we performed 1000 Monte Carlo simulations using the normal approximation to the posterior distribution. The results indicated a 72% probability of detecting a treatment effect under the proposed study design.

Bayesian methods estimated the probability of the alternative hypothesis based on observed data, capturing the posterior distribution and assessing the posterior probability (PP) of the true parameter within a defined range. A PP of 50%–70% indicated weak certainty, 70%–90% moderate, 90%–95% strong, and >95% very strong certainty. Exploratory outcomes, including mean changes from baseline in MDS-UPDRS parts I–IV and total score, were analyzed using generalized linear modeling.

Priors for regression coefficients followed a $\sim$ Normal ($\mu = 0$, $\sigma^2 = 1 \times 10^4$) distribution, and level 1 error variances were $\sim$ Student-t-test ($\mu = 0$, df = 3, $\sigma^2 = 1 \times 10^2$). Level 2 variances followed Gelman's recommendations.[23] Priors for proportion comparisons were $\sim$ Beta ($\alpha = 1.0$, $\beta = 1.0$). Analyses applied intention-to-treat principles, addressing missingness through joint modeling of observed and missing data, a robust approach to ignorable missingness (missing completely at random [MCAR] and missing at random [MAR]).[24] Sensitivity analyses tested the robustness against missing data. Data were analyzed using R version 4.2.0. The full Statistical Analysis Plan is in Supplement 2.

Results

Trial Population

A total of 160 PwP were pre-screened, 49 underwent screening, and 45 were enrolled. Of these, 16 received three allo-hMSC infusions, 14 received one placebo infusion followed by two allo-hMSC infusions, and 15 received three placebo infusions. Baseline demographics and clinical characteristics are in Table 1. By week 62, 42 patients had completed all infusions and assessments; two withdrew, and one was excluded after a multiple system atrophy diagnosis (confirmed by αSyn-SAA, see Supplement 3).[25] Two additional patients discontinued due to unrelated health issues, leaving 40 patients who completed the 88-week follow-up (Fig. 1).

Primary Outcome

Clinically Important Difference in MDS-UPDRS-III at Week 62

A greater proportion of subjects in the three-infusion group achieved a ≥5-point improvement in MDS-UPDRS-III compared with placebo at week 62 (mean difference [MD]: 5.0%, 95% credible Bayesian interval [95% CrI]: −2.3% to 24.8%, PP = 93.7%; Figure 2A). Using a more stringent threshold (≥11 points), more subjects in the three-infusion group improved compared with placebo (MD: 13.3%, 95% CrI: −6.1% to 37.8%, PP = 91.5%; Fig. 2B). Conversely, fewer subjects in the two-infusion group met the ≥5-point (MD: −62.4%, 95% CrI: −85.5% to −32.1%, PP ≥99.9%; Fig. 2A) and ≥11-point (MD: −63.8%, 95% CrI: −86.0% to −32.5%, PP ≥99.9%; Fig. 2B) thresholds compared with placebo. Sensitivity analyses are detailed in Supplement 4.

Secondary Outcomes

Results for other secondary clinical outcomes, including changes from baseline in MDS-UPDRS Parts I, II, III, IV, Total, PDQ-39, and EQ-5D-5L index scores, are summarized in Table 2.

Change from Baseline in MDS-UPDRS-III

At week 62, the OFF-medication MDS-UPDRS-III score in the three-infusion group improved by −16.9 points (95% CrI: −19.5% to −14.2%), the two-infusion group by −3.9 points (95% CrI: −6.9% to −1.1%), and the placebo group by −14.6 points (95% CrI: −17.5% to −11.6%) from baseline (Table 2). Change in mean MDS-UPDRS-III scores per visit are summarized in Figure 3. The difference between the three-infusion and placebo groups at week 62 was −2.3 points (95% CrI: −6.1% to 1.6%, PP = 87.8%; Table 2), while the difference between the two-infusion and placebo groups was +20.6 points (95% CrI: −37.6% to 24.5%, PP ≥99.9%; Table 2).

By week 88, the difference between the three-infusion and placebo groups had widened to −3.3 points (95% CrI: −7.3% to 0.7%, PP = 94.7%), and the two-infusion group remained worse than placebo by +9.0 points (95% CrI: 4.8% to 13.0%, PP ≥99.9%; Table 2).

Clinically Important Difference in MDS-UPDRS-III at Week 88

A higher percentage of subjects in the three-infusion group achieved at least a 5-point improvement (MD: 11.5%, 95% CrI: 0.8% to 34.5%, PP = 98.4%; Fig. 2A) and an 11-point improvement (MD: 42.4%, 95% CrI: 15.6% to 69.1%, PP ≥99.9%; Fig. 2B) in MDS-UPDRS-III at week 88 compared with placebo. Conversely, fewer subjects in the two-infusion group showed a 5-point improvement (MD: −54.6%, 95% CrI: −80.5% to −23.1%, PP ≥99.9%; Fig. 2A) or an 11-point improvement (MD: -43.1%, 95% CrI: −69.8% to −13.6%, PP = 99.7%; Fig. 2B) compared with placebo.

TABLE 1 *Baseline characteristics of the study participants*

Characteristic	Three allo-hMSC (N = 16)	One placebo followed by two allo-hMSC (N = 14)	Three placebo (N = 15)	*P*-value
Age (years)	64.3 ± 8.6	66.9 ± 6.4	68.6 ± 6.2	0.38
Female, n (%)	12 (75.0)	11 (78.6)	12 (80.0)	0.94
Hispanic, n (%)	6 (37.5)	2 (14.3)	2 (13.3)	0.26
Race, n (%)				0.64
Asian	0 (0.0)	0 (0.0)	1 (6.7)	
White	16 (100.0)	14 (100.0)	14 (93.3)	
Clinical subtype, n (%)				0.51
Tremor dominant	8 (50.0)	8 (57.1)	5 (33.3)	
Akinetic-rigid	8 (50.0)	5 (35.7)	9 (60.0)	
Mixed	0 (0.0)	1 (7.1)	1 (6.7)	
Disease duration, years	3.1 ± 1.9	2.5 ± 2.1	3.5 ± 2.0	0.26
LEDD (mg)	711.0 ± 338.7	603.4 ± 241.5	847.6 ± 407.5	0.26
H&Y score[a]				0.42
1.5	1 (6.3)	3 (21.4)	3 (20.0)	
2	9 (56.3)	7 (50.0)	4 (26.7)	
2.5	6 (37.5)	4 (28.6)	7 (46.7)	
3	0 (0.0)	0 (0.0)	1 (6.7)	
MDS-UPDRS[b]	66.1 ± 13.3	62.9 ± 22.1	65.9 ± 23.2	0.79
Part 1	11.7 ± 4.4	8.9 ± 6.1	12.2 ± 5.9	0.32
Part 2	11.3 ± 5.5	11.6 ± 7.3	13.4 ± 7.9	0.76
Part 3	37.1 ± 9.9	36.6 ± 9.0	35.3 ± 11.1	0.56
Part 4	6.0 ± 3.0	5.9 ± 3.4	5.0 ± 4.4	0.51
MoCA[c]	28.1 ± 1.2	27.5 ± 1.3	27.3 ± 1.7	0.38
PDQ-39[d]	24.8 ± 13.5	14.1 ± 8.8	19.4 ± 14.7	0.08
EQ-5D-5L[e]	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.79

Note: Plus-minus values are means ± standard deviation (SD). All scores and rating scales, except for the MoCA, were administered in the OFF-medication state.
[a]H&Y scores range from 0 to 5, with higher scores indicating more disability.
[b]Total scores on the MDS-UPDRS Parts I–IV range from 0 to 260, with higher scores indicating more severe impairment.
[c]MoCA scores range from 3 to 30, with higher scores indicating better cognition.
[d]PDQ-39 scores range from 0 to 100, with higher scores indicating worse health status.
[e]EQ-5D-5L index scores range from 0 to 1, with higher scores indicating full health.
Abbreviations: allo-hMSCs, human allogeneic bone marrow-derived mesenchymal stem cells; LEDD, levodopa equivalent daily dose; H&Y, Hoehn & Yahr; MDS-UPDRS, Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; PDQ-39, Parkinson's Disease Questionnaire; EQ-5D-5L, EuroQol 5-Dimension 5-Level index score.

Clinically Important Difference in MDS-UPDRS Total

More participants in the three-infusion group achieved at least a 12-point improvement at week 62 (MD: 22.0%, 95% CrI: −21.0% to 49.4%, PP = 96.3%) and week 88 (MD: 48.4, 95% CrI: 23.9% to 74.0%, PP ≥99.9%). Fewer participants in the two-infusion group showed improvement relative to placebo at week 62 (MD: −43.0, 95% CrI: −71.2% to −8.3%, PP = 99.1%) and at week 88 (MD: −20.8, 95% CrI: −53. 1% to 14.1%, PP = 87.8%; Supplement 5).

Safety

A total of 10 mild and transient treatment-emergent adverse events were reported, with no severe events (Supplement 6). In the three-infusion arm, one patient experienced general malaise, another had transient

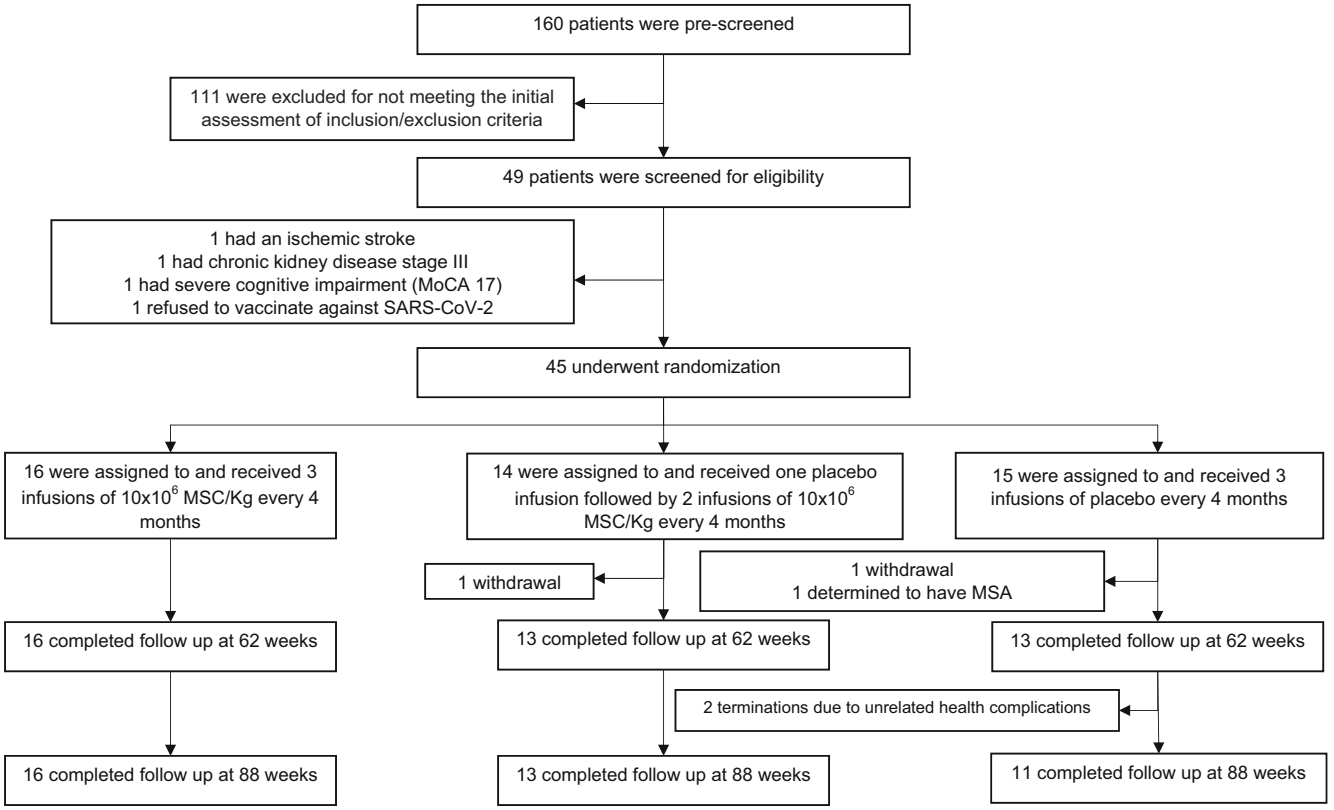


FIG. 1. Screening, Randomization, and Follow-Up. MoCA: Montreal Cognitive Assessment. SARS-CoV-2: Severe Acute Respiratory Syndrome-Coronavirus 2. allo-hMSC: Human Allogeneic Bone Marrow-Derived Mesenchymal Stem Cells. MSA: Multiple System Atrophy.

hypertension not requiring medication, and one reported vomiting. The two-infusion arm reported only constitutional symptoms (fatigue, flu-like symptoms, and headache) that resolved. Initially, three patients exhibited a panel reactive antibody response, which was presumed to be DSA. However, HLA typing confirmed that two of these cases were unrelated to the donor. The remaining case with matching HLA typing belonged to a patient in the placebo arm and was deemed unrelated after unblinding.

Discussion

In this phase 2 randomized trial involving mild-to-moderate PwP, subjects received three infusions, administered every 18 weeks of either (1) 10×10^6 allo-hMSCs/kg in all three infusions, (2) one placebo infusion followed by two infusions of 10×10^6 allo-hMSCs/kg, or (3) three placebo infusions. The treatment period lasted 36 weeks, followed by assessments at week 62 (26 weeks after the last dose) and week 88 (52 weeks after the last dose).

Current FDA guidelines recommend that when using patient-reported outcomes, a prespecified endpoint be defined to support the use of a drug for a given disease.[26] They have also emphasized the importance of innovative clinical trial design and specifically cite Bayesian statistical approaches as a way to analyze small sample sizes more efficiently. To align with these recommendations, clinical efficacy was assessed using the concept of CID. The predefined threshold for relevance was a 5-point improvement in MDS-UPDRS-III in the OFF-medication state, corresponding to an intermediate CID.[22]

The primary outcome was met, with 5% more patients in the three-infusion group achieving a ≥5-point improvement in OFF-medication MDS-UPDRS-III at week 62 compared with placebo (PP = 93.7%). By week 88, this difference increased to 11.5% (PP = 98.4%). Using a more stringent threshold of ≥11-point improvement, the three-infusion group outperformed placebo by 13.3% at week 62 (PP = 91.5%) and by 42.4% at week 88 (PP ≥99.9%).

Further evaluation of the MDS-UPDRS-III data showed that these group-level differences translated into a 16.9-point improvement in the OFF-medication MDS-UPDRS-III in the three-infusion group and a 14.6-point improvement in the placebo group from baseline to week 62, resulting in a 2.3-point difference (95% CrI: −6.1% to 1.6%), with an 87.8% posterior probability that a true difference exists between these two arms under the Bayesian perspective, as

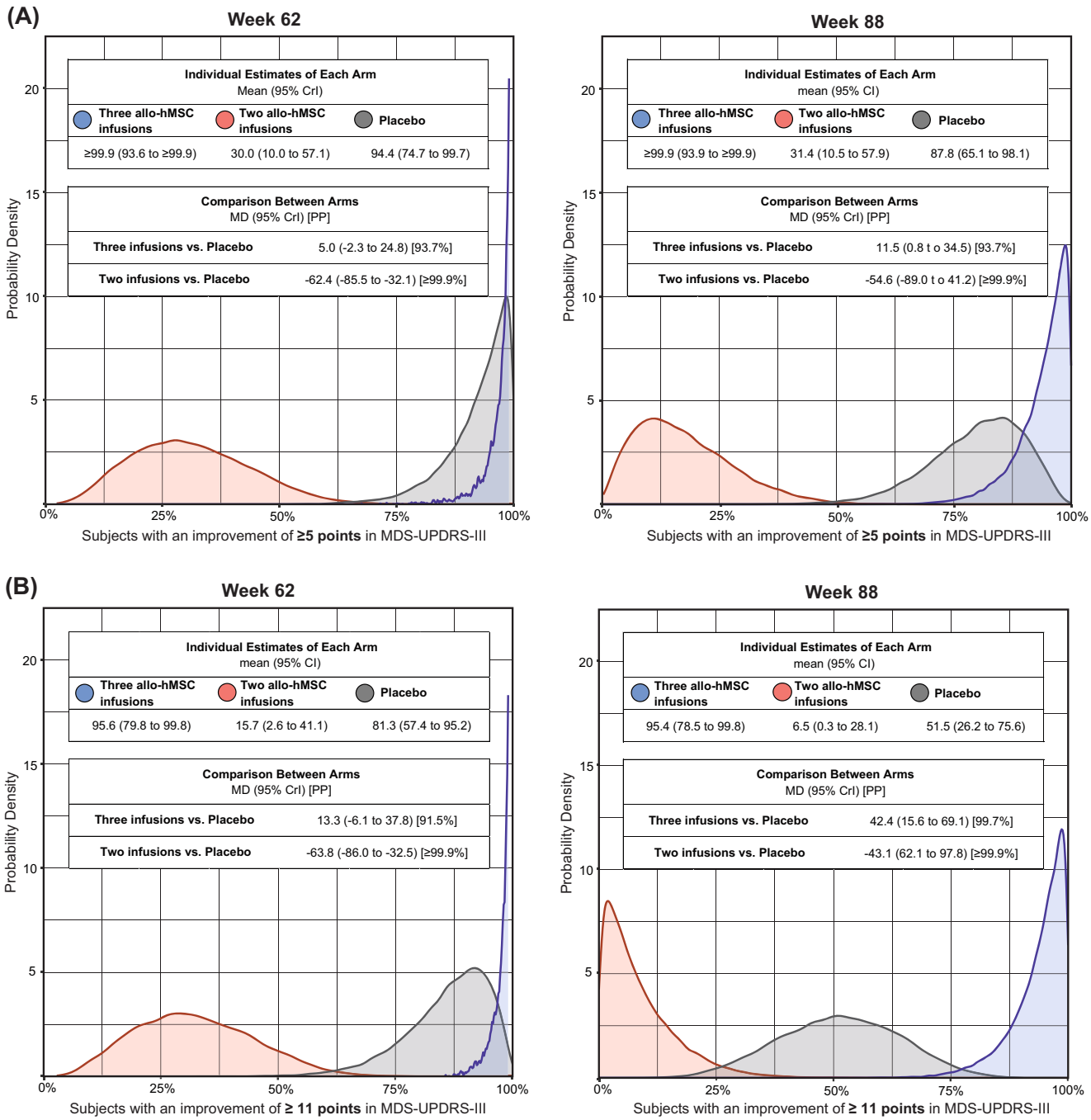


FIG. 2. Proportion of patients with Parkinson's disease achieving moderate and large clinically important improvement in Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale-Part III (MDS-UPDRS-III) scores after treatment with human allogeneic bone marrow–derived mesenchymal stem cells (allo-hMSCs). (A) Percentage achieving moderate clinically important difference (CID) (≥5-point decrease from baseline to week 62). (B) Percentage achieving large CID (≥11-point decrease from baseline to week 88). Posterior probability (PP) thresholds: 50%–70% = weak certainty, 70%–90% = moderate certainty, 90%–95% = strong certainty, >95% = very strong certainty. Density plots illustrate estimate precision (narrow base = higher precision; wide base = greater uncertainty). CrI, credible interval; MD, mean difference.

summarized in Figure 3. Unlike frequentist confidence intervals, which do not provide any information regarding the relative probability that various values in the interval are more or less likely, Bayesian credible intervals do provide this information. Thus, despite the "overlapping" credible intervals, the analysis supports an 87.8% probability that the three-infusion and placebo arms differ by 2.3 points.

Additionally, the timing of motor improvement in the three-infusion group was noteworthy: a 12.9-point reduction in MDS-UPDRS-III was observed by week 9, just 9 weeks after the first infusion. In contrast, the

TABLE 2 *Change from baseline in motor and non-motor symptoms, and quality of life assessments in patients with Parkinson's disease after treatment with allogeneic bone marrow-derived mesenchymal stem cells*

	Change from baseline by arm						Difference in change from baseline across arms					
	Three allo-hMSCs		One placebo followed by two allo-hMSCs		Three placebos		Three allo-hMSCs vs. placebo			Two allo-hMSCs vs. placebo		
Characteristic	Mean (95% CrI)		Mean (95% CrI)		Mean (95% CrI)		MD (95% CrI) [PP]			MD (95% CrI) [PP]		
MDS-UPDRS-I												
Week 62	−3.7	(−5.4 to −2.0)	−0.1	(−2.1 to 1.9)	−2.2	(−4.1 to −0.4)	−1.47	(−4.0 to 1.0)	[88.1%]	2.2	(−0.5 to 4.8)	[94.6%]
Week 88	−2.9	(−4.8 to −1.0)	−0.1	(−2.3 to 2.0)	−2.5	(−4.7 to −0.3)	−0.4	(−3.2 to 2.5)	[60.5%]	2.4	(−0.6 to 5.4)	[94.3%]
MDS-UPDRS-II												
Week 62	−4.6	(−6.3 to −2.8)	−3.4	(−5.3 to −1.4)	−5.6	(−7.5 to −3.7)	1	(−1.6 to 3.6)	[78.6%]	2.2	(−0.5 to 4.9)	[94.8%]
Week 88	−4.9	(−6.6 to −3.2)	−3.9	(−5.8 to −2.1)	−3.6	(−5.4 to −1.7)	−1.3	(−3.9 to 1.2)	[85.6%]	−0.4	(−3.0 to 2.2)	[61.7%]
MDS-UPDRS-III												
Week 62	−16.9	(−19.5 to 14.2)	−3.9	(−6.9 to −1.1)	−14.6	(−17.5 to −11.6)	−2.3	(−6.1 to 1.6)	[87.8%]	10.6	(6.5 to 14.6)	[>99.9%]
Week 88	−15.9	(−18.6 to −13.2)	−3.6	(−6.6 to −0.7)	−12.6	(−15.7 to −9.5)	−3.3	(−7.3 to 0.7)	[94.7%]	9	(4.8 to 13.0)	[>99.9%]
MDS-UPDRS-IV												
Week 62	−1.42	(−2.9 to −0.0)	−0.8	(−2.4 to 0.8)	−1.5	(−3.1 to 0.04)	0.12	(−2.0 to 2.3)	[54.4%]	0.8	(−1.5 to 3.0)	[75.7%]
Week 88	−2	(−3.3 to −0.8)	−0.6	(−2.0 to 0.8)	−1.3	(−2.8 to 0.2)	−0.7	(−2.7 to 1.3)	[76.7%]	0.7	(−1.4 to 2.7)	[75.0%]
MDS-UPDRS Total[a]												
Week 62	−26.7	(−31.4 to −21.8)	−7.4	(−12.8 to −2.1)	−24.5	(−29.8 to −19.2)	−2.15	(−9.1 to 4.8)	[73%]	17.1	(9.7 to 24.2)	[≥99.9%]
Week 88	−26.1	(−30.5 to −21.6)	−7.9	(−12.9 to −2.9)	−20.1	(−25.2 to −14.9)	−5.9	(−12.7 to 0.8)	[95.8%]	12.2	(5.2 to 19.1)	[99.9%]
PDQ-39[b]												
Week 62	−3.1	(−7.9 to 1.6)	−1	(−6.2 to 4.1)	−0.06	(−5.2 to 4.9)	−3.1	(−9.9 to 3.8)	[81.5%]	−0.97	(−7.7 to 5.9)	[61%]
Week 88	−0.51	(−7.8 to 6.8)	1.9	(−5.2 to 9.1)	8.5	(0.8 to 16.0)	−8.9	(−19.3 to 1.6)	[95.5%]	−6.6	(−16.1 to 3.0)	[90.9%]
EQ-5D-5L[c]												
Week 62	0.02	(−0.02 to 0.07)	0.07	(0.02 to 0.12)	0	(−0.05 to 0.05)	0.02	(−0.05 to 0.09)	[71.5%]	0.06	(−0.008 to 0.13)	[96%]
Week 88	0.03	(−0.03 to 0.10)	0.03	(−0.04 to 0.09)	−0.04	(−0.11 to 0.03)	0.07	(−0.02 to 0.17)	[94.4%]	0.07	(−0.03 to 0.16)	[92.6%]

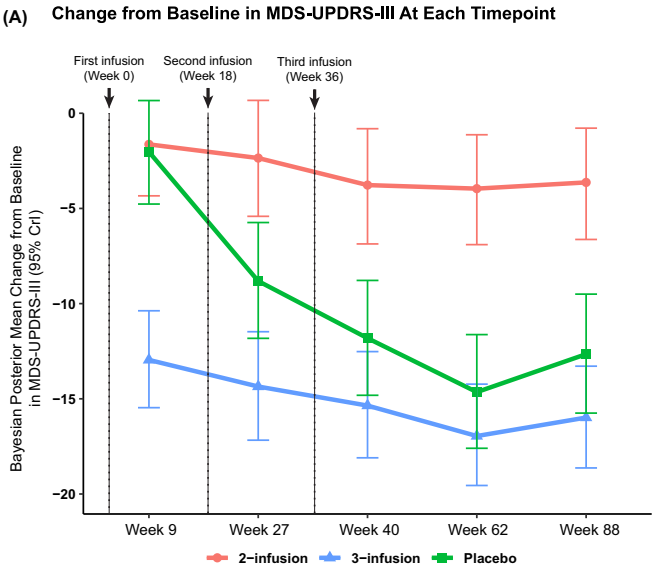
PP thresholds are as follows: 50%–70% indicates weak certainty, 70%–90% moderate certainty, 90%–95% strong certainty, and >95% very strong certainty.

[a]Total scores on the MDS-UPDRS Parts I–IV range from 0 to 260, with higher scores indicating more severe impairment.

[b]PDQ-39 scores range from 0 to 100, with higher scores indicating worse health status.

[c]EQ-5D-5L index scores range from 0 to 1, with higher scores indicating full health.

Abbreviations: allo-hMSCs, human allogeneic bone marrow-derived mesenchymal stem cells; 95% CrI, 95% credible Bayesian interval; MD, mean difference; PP, posterior probability; MDS-UPDRS, Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale; PDQ-39, Parkinson's Disease Questionnaire; EQ-5D-5L, EuroQol 5-Dimension 5-Level index score.



(B) Individual Estimates per Arm:

Week	Three allo-hMSC	One placebo followed by two allo-hMSC	Placebo
Week 9	-12.957 (-15.465 to -10.375)	-1.634 (-4.338 to 1.073)	-2.030 (-4.769 to 0.667)
Week 27	-14.355 (-17.173 to -11.476)	-2.354 (-5.414 to 0.675)	-8.816 (-11.823 to -5.740)
Week 40	-15.356 (-18.099 to -12.520)	-3.773 (-6.864 to -0.812)	-11.815 (-14.814 to -8.781)
Week 62	-16.955 (-19.552 to -14.229)	-3.960 (-6.901 to -1.129)	-14.647 (-17.598 to -11.627)
Week 88	-15.985 (-18.631 to -13.285)	-3.633 (-6.629 to -0.783)	-12.654 (-15.750 to -9.501)

Estimates are presented as mean differences (95% Bayesian credible intervals)

(C) Pairwise Comparison of Treatment Arms:

Week	Three allo-hMSC vs. Placebo	Two allo-hMSC vs. Placebo
Week 9	-10.92 (-14.491 to -7.321) [100%]	0.40 (-3.268 to 4.09) [58.6%]
Week 27	-5.53 (-9.553 to -1.458) [99.6%]	6.46 (2.276 to 10.529) [99.8%]
Week 40	-3.55 (-7.439 to 0.394) [96.2%]	8.01 (3.835 to 12.112) [100%]
Week 62	-2.31 (-6.178 to 1.617) [87.8%]	10.65 (6.564 to 14.643) [100%]
Week 88	-3.33 (-7.377 to 0.788) [94.7%]	9.01 (4.807 to 13.032) [100%]

Estimates are presented as mean differences (95% Bayesian credible intervals) [posterior probability]

FIG. 3. Trajectories of Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale-Part III (MDS-UPDRS-III) improvement by treatment group. (A) Posterior mean trajectories with 95% credible intervals (CrI) for the two-infusion, three-infusion, and placebo groups. (B) Estimates are presented as mean differences (95% Bayesian credible intervals). (C) Pairwise comparisons at each time point, presented as mean differences (MD), 95% CrI, and posterior probabilities (PP) of a true difference between groups. PP thresholds: 50%–70% = weak certainty, 70%–90% = moderate certainty, 90%–95% = strong certainty, >95% = very strong certainty.

two-infusion group showed only a modest 3.7-point reduction at week 40, 4 weeks after their second infusion, which was less improvement than that observed in the placebo group during the same period (Fig. 3). These findings support the idea that allo-hMSCs might exert their therapeutic effects relatively soon after administration, likely due to enhanced activation in a more reactive immune microenvironment. Earlier delivery may therefore trigger stronger MSC-mediated modulation and clinical benefit, while later infusions, which may occur in a less inflamed or more altered immune state, may lead to reduced efficacy. This timing is consistent with prior cell therapy studies that have reported clinical improvements within weeks of administration.[12,27,28] Further research is needed to clarify how systemic inflammatory markers evolve over time after allo-hMSC infusions and whether the therapeutic response varies depending on the number of doses administered.

Conversely, and unexpectedly, the group receiving a placebo followed by two allo-hMSC infusions showed less improvement than the group that received placebo throughout the study. The two-infusion arm showed only a 3.9-point improvement in MDS-UPDRS-III over 62 weeks, compared with the 14.6-point improvement in the placebo arm, translating to 64.4% fewer patients reaching the 5-point improvement threshold (30.0% vs. 94.4%). Although this finding may seem counterintuitive, it is important to note that studies on PD progression suggest an average annual motor decline (increase) of approximately 2.4 points in MDS-UPDRS-III scores.[29] Yet in this trial, all treatment groups showed improvement in their motor scores over the 88 weeks of participation; an outcome that may, in part, reflect a placebo effect.

In PD trials, the placebo effect is well-documented and linked to expectation-induced dopamine release in the striatum, accounting for up to 55% of clinical responses.[30] In fact, an analysis of 17 PD interventional studies showed that placebo responses can persist for up to a year.[31] This residual placebo effect may have influenced the results since our primary outcome was assessed at week 62, which was 26 weeks or approximately 6 months after the last infusion. By week 88, and with a more stringent threshold (≥11-point improvement in OFF-medication MDS-UPDRS-III), the differences between the three-infusion and placebo groups widened, supportive of a waning placebo response.

We recognize, however, that one would expect a placebo effect to be similar across arms, which was not the case in this study. The placebo arm had a robust improvement, while the two-infusion arm had relatively modest improvement, suggesting that the placebo effect does not fully explain why the placebo arm did relatively better than the two-infusion arm.

Another possible explanation for the difference in the magnitude of improvement between treatment arms is that despite no statistically significant differences between groups (Table 1), there exists some unmeasured difference between participants in each arm. Even with rigorous randomization and standardized procedures, clinical trials cannot possibly measure every variable that is important to the disease process, especially in a phenotypically heterogenous disease like PD. While our measurements try to capture the most important

variables, there are many lifestyle factors, like diet, physical activity, and frequency of bowel movements, that were not fully captured in this study. These factors are known to have a role in both reducing systemic inflammation and in PD progression.[32] We can, perhaps, see this potential difference reflected in the trend towards slightly higher (worse) PDQ-39 scores in the three-infusion group compared with the two-infusion group. This finding could suggest that participants in the three-infusion group were "worse" in some unmeasured way, with more potential to benefit from MSC therapy.

A third possibility for the difference in magnitude of improvement is variability in the functional potency of each batch of MSCs, leading to differences in the cell bags administered to patients. Although using a single donor reduces variability, batch-to-batch differences may still occur due to expansion conditions, passage number, and cryopreservation during manufacturing.[33,34] These variations can affect the therapeutic function of MSCs and, theoretically, their clinical effects. Current quality control standards require MSC batches to meet minimal characterization criteria, including surface marker profiling (eg, CD73, CD90, CD105) to confirm identity.[35] However, these tests do not necessarily correlate with functional potency or the ability of MSCs to induce meaningful biological effects.[34] As a result, some batches may contain a higher proportion of immunomodulatory and neuroprotective subpopulations, while others may have less effective cell subtypes,[36] potentially contributing to the heterogeneous clinical outcomes observed. Further studies on functional potency assays are needed to better characterize and assess the biological activity of MSCs in PwP, ensuring product consistency and effectiveness. Integrating these potency assessments with clinical endpoint data from this trial will offer valuable insights for optimizing MSC therapy in future studies.

Beyond motor scores, quality-of-life outcomes offer additional insight into the overall therapeutic impact of the intervention. In this trial, both PDQ-39 and EQ-5D-5L index scores favored the allo-hMSC treatment groups over placebo. This suggests that patients experienced meaningful improvements in daily functioning and well-being, even in the absence of substantial motor gains, as seen in the two-infusion groups. Notably, these improvements were sustained through week 88 in both active arms, with the gap between treatment and placebo widening over time. This discrepancy between the quality-of-life measures and motor outcomes highlights the importance of incorporating multidimensional endpoints into PD trials, as subjective improvements may not always align with clinician-rated motor outcomes.[37] Moreover, while MDS-UPDRS-III is considered an objective assessment, it has known limitations. Motor performance can fluctuate due to fatigue, comorbidities, or day-to-day variability,[38] and may not fully reflect overall function. These limitations highlight the importance of complementing motor scales with patient-reported outcomes and biomarker-based measures.

Although we did not include biomarker assessments in this report, future trials should incorporate objective measures to better characterize biological responses and interpret between-group differences. Fluid biomarkers of inflammation (eg, interleukin [IL]-6, tumor necrosis factor-α, IL-10) can reflect the immunomodulatory effects of MSC therapy, which are believed to contribute to its clinical benefits.[6] Markers of neurodegeneration, such as serum neurofilament light chain (NfL), offer insight into the rate of neuronal injury and may help track disease stabilization.[39] Biomarkers of αSyn aggregation, including oligomeric or phosphorylated αSyn in cerebrospinal fluid (CSF) or plasma[40] and αSyn-SAA in CSF,[41] may reflect changes in pathogenic species or the seeding activity of misfolded αSyn, providing a potential readout of disease-specific biology in response to treatment. Imaging biomarkers such as [^{18}F]-dihydroxyphenylalanine positron emission tomography to assess dopaminergic function, neuromelanin-sensitive magnetic resonance imaging (MRI) to evaluate nigral neuron integrity, and free-water diffusion MRI as a proxy for microglial activation could further help distinguish true treatment effects from placebo responses or baseline variability.[42] Although no single biomarker reliably correlates with motor outcomes in PD,[43] their inclusion remains important for capturing treatment-related biological activity. The unexpected underperformance of the two-infusion group, despite receiving active therapy, underscores the potential value of these measures in clarifying treatment variability. Incorporating some of these selective biomarkers into future studies will be essential for interpreting clinical outcomes, guiding dosing strategies, and refining patient selection.

This trial has several limitations. First, sample and effect size estimations were calculated based on UPDRS rather than MDS-UPDRS. This decision was based on our phase 1 study, which demonstrated allo-hMSC safety using UPDRS,[13] because UPDRS was the prevalent scale at the time, leading us to use this measure for our estimates. By the onset of the current phase 2 trial, along with the broader PD research community, we transitioned to utilizing MDS-UPDRS. Second, the small sample size limited statistical power; however, Bayesian analysis provides posterior probability insights, enabling more informed decision-making.[44] Regulatory agencies, including the FDA, endorse Bayesian methods in early trials for their flexibility and stronger inference in small samples.[45] Third, generalizability is impacted in two ways: (1) the dropout rate, although low (3/45 patients, 5%), could affect the external

validity of the findings, despite using sensitivity analyses to address this; and (2) as a single-site trial with only one MDS-UPDRS rater, generalizability could be further limited. Although MDS-UPDRS is reliable, its low within-subject consistency can affect longitudinal assessments.[46] Future trials should incorporate multiple sites and raters to improve generalizability. Lastly, the lack of a validated potency assay for this allo-hMSC product limits the correlation between clinical outcomes and cell characteristics. As part of the standard stem cell manufacturing and regulatory process, we will evaluate potency in available batches to define a functional profile, ensuring consistent and effective cell production for future larger trials.

Conclusions

To our knowledge, this is the first randomized, placebo-controlled trial using three repeated intravenous doses of 10×10^6 allo-hMSCs/kg. The study met its primary endpoint of efficacy: there is a >70% chance that treatment with three doses of 10×10^6 allo-hMSCs/kg improved motor scores in mild-to-moderate PD compared with placebo. There was a profound improvement in the placebo group and a less robust improvement in the two-infusion group, which warrants further investigation and clinical trials. The treatment was well-tolerated, with all reported adverse events being mild and transient. There were no severe treatment-related adverse events or reports of immunogenicity or tumorigenicity. These findings support the safety and potential for efficacy of a non-invasive, scalable, and ethically favorable stem cell therapy for PD. Additional functional potency assays are required to ensure consistency and reliability of allo-hMSC batches. Further large-scale, multicenter studies are needed to demonstrate the full therapeutic potential of allo-hMSCs for reducing motor and non-motor symptoms in PD.

Author Roles: (1) Research Project: A. Conceptualization, B. Visualization, C. Investigation, D. Data Curation, E. Methodology; (2) Statistical Analysis: A. Formal Analysis; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Editing; (4) Other: A. Resources, B. Project Administration, C. Supervision, D. Funding Acquisition.
M.C.S.: 1A, 1B, 1C, 1E, 3A, 3B, 4B, 4C, 4D.
J.S.: 1A, 1D, 1E, 3A, 3B, 4B, 4D.
J.D.M.-L.: 1B, 1D, 3A, 3B, 4B.
C.G.: 1A, 1E, 2A, 3B, 4A.
T.S.T.: 1B, 2A, 3B.
M.S.: 3B, 4A, 4D.
E.T.: 1B, 3A, 3B.
N.B.S.: 3B, 4A, 4D.
J.G.S.: 3B, 4A, 4D.
C.A.: 1C, 3B, 4C.
M.-F.D.: 1A, 3B, 4A.
V.T.: 1D, 3B, 4B.
R.A.: 1D, 3B, 4B.
E.M.R.: 3B, 4A, 4C.
S.I.S.: 1A, 3B, 4A.
T.M.E.: 1A, 1C, 1D, 1E, 3A, 3B.

Acknowledgments: We extend our heartfelt gratitude to the patients and their families for participating in the trial. We further thank the Clinical Research Unit at Memorial Hermann Hospital for their excellent nursing staff and facilities, Drs. Mei Zhuyong and Adrian Gee from the Center for Cell and Gene Therapy at Baylor College of Medicine for manufacturing the cells in their cGMP facility, and the Mitchell Center for Alzheimer's Disease at UTHealth Houston for conducting the baseline αSyn-SAA/PMCA assays.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Lees AJ, Tolosa E, Olanow CW. Four pioneers of L-dopa treatment: Arvid Carlsson, Oleh Hornykiewicz, George Cotzias, and Melvin Yahr. Mov Disord 2015;30(1):19–36. https://doi.org/10.1002/mds.26120
2. Wang F, Sun Z, Peng D, et al. Cell-therapy for Parkinson's disease: a systematic review and meta-analysis. J Transl Med 2023;21(1):601. https://doi.org/10.1186/s12967-023-04484-x
3. Wu Y, Meng X, Cheng WY, et al. Can pluripotent/multipotent stem cells reverse Parkinson's disease progression? Front Neurosci 2024;18:1210447. https://doi.org/10.3389/fnins.2024.1210447
4. Vij R, Prossin A, Tripathy M, et al. Long-term, repeated doses of intravenous autologous mesenchymal stem cells for a patient with Parkinson's disease: a case report. Front Neurol 2023;14:1257080. https://doi.org/10.3389/fneur.2023.1257080
5. Unnisa A, Dua K, Kamal MA. Mechanism of mesenchymal stem cells as a multitarget disease-modifying therapy for Parkinson's disease. Curr Neuropharmacol 2023;21(4):988–1000. https://doi.org/10.2174/1570159X20666220327212414
6. Heris RM, Shirvaliloo M, Abbaspour-Aghdam S, et al. The potential use of mesenchymal stem cells and their exosomes in Parkinson's disease treatment. Stem Cell Res Ther 2022;13(1):371. https://doi.org/10.1186/s13287-022-03050-4
7. Chao YX, He BP, Tay SS. Mesenchymal stem cell transplantation attenuates blood brain barrier damage and neuroinflammation and protects dopaminergic neurons against MPTP toxicity in the substantia nigra in a model of Parkinson's disease. J Neuroimmunol 2009;216(1–2):39–50. https://doi.org/10.1016/j.jneuroim.2009.09.003
8. Fischer UM, Harting MT, Jimenez F, et al. Pulmonary passage is a major obstacle for intravenous stem cell delivery: the pulmonary first-pass effect. Stem Cells Dev 2009;18(5):683–692. https://doi.org/10.1089/scd.2008.0253
9. Eggenhofer E, Benseler V, Kroemer A, et al. Mesenchymal stem cells are short-lived and do not migrate beyond the lungs after intravenous infusion. Front Immunol 2012;3:297. https://doi.org/10.3389/fimmu.2012.00297
10. Kim YJ, Park HJ, Lee G, et al. Neuroprotective effects of human mesenchymal stem cells on dopaminergic neurons through anti-inflammatory action. Glia 2009;57(1):13–23. https://doi.org/10.1002/glia.20731
11. Gordon J, Lockard G, Monsour M, Alayli A, Choudhary H, Borlongan CV. Sequestration of inflammation in Parkinson's disease via stem cell therapy. Int J Mol Sci 2022;23(17):10138. https://doi.org/10.3390/ijms231710138
12. Ekrani ST, Mahmoudi M, Haghmorad D, Kheder RK, Hatami A, Esmaeili SA. Manipulated mesenchymal stem cell therapy in the treatment of Parkinson's disease. Stem Cell Res Ther 2024;15(1):476. https://doi.org/10.1186/s13287-024-04073-9
13. Schiess M, Suescun J, Doursout MF, et al. Allogeneic bone marrow-derived mesenchymal stem cell safety in idiopathic Parkinson's disease. Mov Disord 2021;36(8):1825–1834. https://doi.org/10.1002/mds.28582

14. Li C, Zhao H, Cheng L, Wang B. Allogeneic vs. autologous mesenchymal stem/stromal cells in their medication practice. Cell Biosci 2021;11(1):187. https://doi.org/10.1186/s13578-021-00698-y
15. Shigematsu K, Ishii K, Tahara K, Komori N, Yamagishi H. Repeated intravenous infusion of autologous adipose-derived stem cells improves cognitive function. Alzheimers Dement 2021;17-(Suppl. 9):e049907. https://doi.org/10.1002/alz.049907
16. Shigematsu K, Ideno M, Komori N, Yamagishi H. Repeated intravenous infusion of adipose tissue-derived stem cells as a promising treatment for amyotrophic lateral sclerosis. Med Hypotheses 2023; 181:111205. https://doi.org/10.1016/j.mehy.2023.111205
17. Sun SJ, Li F, Dong M, et al. Repeated intravenous administration of hiPSC-MSCs enhance the efficacy of cell-based therapy in tissue regeneration. Commun Biol 2022;5(1):867. https://doi.org/10.1038/s42003-022-03833-8
18. Kim N, Min GJ, Im KI, et al. Repeated infusions of bone-marrow-derived mesenchymal stem cells over 8 weeks for steroid-refractory chronic graft-versus-host disease: a prospective, phase I/II clinical study. Int J Mol Sci 2024;25(12):6731. https://doi.org/10.3390/ijms25126731
19. Hanley PJ, Mei Z, Durett AG, et al. Efficient manufacturing of therapeutic mesenchymal stromal cells with the use of the Quantum Cell Expansion System. Cytotherapy 2014;16(8):1048–1058. https://doi.org/10.1016/j.jcyt.2014.01.417
20. Skorvanek M, Martinez-Martin P, Kovacs N, et al. Differences in MDS-UPDRS scores based on Hoehn and Yahr stage and disease duration. Mov Disord Clin Pract 2017;4(4):536–544. https://doi.org/10.1002/mdc3.12476
21. Shahnawaz M, Tokuda T, Waragai M, et al. Development of a biochemical diagnosis of Parkinson disease by detection of alpha-synuclein misfolded aggregates in cerebrospinal fluid. JAMA Neurol 2017;74(2):163–172. https://doi.org/10.1001/jamaneurol.2016.4547
22. Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ. The clinically important difference on the Unified Parkinson's Disease Rating Scale. Arch Neurol 2010;67(1): 64–70. https://doi.org/10.1001/archneurol.2009.295
23. Gelman A. Prior distributions for variance parameters in hierarchical models (comment on article by Browne and Draper). Bayesian Anal 2006;1(3):515–534.
24. Dey DK, Ghosh SK, Mallick BK. Generalized Linear Models: A Bayesian Perspective. Boca Raton, FL: CRC Press; 2000.
25. Tharp E, Martinez-Lemus JD, Schiess MC, Ellmore TM, Suescun J, Shahnawaz M. Role of alpha-synuclein seed amplification assay in Parkinson's disease clinical trials: a case of misdiagnosis. Clin Park Relat Disord 2024;11:1–3. https://doi.org/10.1016/j.prdoa.2024.100274
26. U.S. Food and Drug Administration. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Silver Spring, MD: U.S. Food and Drug Administration; 2025 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims.
27. Venkataramana NK, Kumar SK, Balaraju S, et al. Open-labeled study of unilateral autologous bone-marrow-derived mesenchymal stem cell transplantation in Parkinson's disease. Transl Res 2010; 155(2):62–70. https://doi.org/10.1016/j.trsl.2009.07.006
28. Boika A, Aleinikava N, Chyzhyk V, Zafranskaya M, Nizheharodava D, Ponomarev V. Mesenchymal stem cells in Parkinson's disease: motor and nonmotor symptoms in the early posttransplant period. Surg Neurol Int 2020;11:380. https://doi.org/10.25259/SNI_233_2020
29. Holden SK, Finseth T, Sillau SH, Berman BD. Progression of MDS-UPDRS scores over five years in de novo Parkinson disease from the Parkinson's Progression Markers Initiative cohort. Mov Disord Clin Pract 2018;5(1):47–53. https://doi.org/10.1002/mdc3.12553
30. Goetz CG, Wuu J, McDermott MP, et al. Placebo response in Parkinson's disease: comparisons among 11 trials covering medical and surgical interventions. Mov Disord 2008;23(5):690–699. https://doi.org/10.1002/mds.21894
31. Arshad U, Rahman F, Hanan N, Chen C. Longitudinal meta-analysis of historical Parkinson's disease trials to inform future trial design. Mov Disord 2023;38(9):1716–1727. https://doi.org/10.1002/mds.29514
32. Chtioui N, Duval C, St-Pierre DH. The impact of an active lifestyle on markers of intestinal inflammation in Parkinson's disease: preliminary findings. Clin Park Relat Disord 2025;12:100301. https://doi.org/10.1016/j.prdoa.2025.100301
33. Capelli C, Cuofano C, Pavoni C, et al. Potency assays and biomarkers for cell-based advanced therapy medicinal products. Front Immunol 2023;14:1–18. https://doi.org/10.3389/fimmu.2023.1186224
34. Fernandez-Santos ME, Garcia-Arranz M, Andreu EJ, et al. Optimization of mesenchymal stromal cell (MSC) manufacturing processes for a better therapeutic outcome. Front Immunol 2022;13:1–19. https://doi.org/10.3389/fimmu.2022.918565
35. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006;8(4): 315–317. https://doi.org/10.1080/14653240600855905
36. Khan RS, Newsome PN. A comparison of phenotypic and functional properties of mesenchymal stromal cells and multipotent adult progenitor cells. Front Immunol 2019;10:1–16. https://doi.org/10.3389/fimmu.2019.01952
37. Mischley LK, Lau RC, Weiss NS. Use of a self-rating scale of the nature and severity of symptoms in Parkinson's disease (PRO-PD): correlation with quality of life and existing scales of disease severity. NPJ Parkinsons Dis 2017;3:20. https://doi.org/10.1038/s41531-017-0021-5
38. Janssen Daalen J, van der Heiden M, Meinders M, Post B. Motor symptom variability in Parkinson's disease: implications for personalized trial outcomes? Mov Disord 2025;40(5):975–979. https://doi.org/10.1002/mds.30133
39. Backstrom D, Linder J, Jakobson Mo S, et al. NfL as a biomarker for neurodegeneration and survival in Parkinson disease. Neurology 2020;95(7):e827–e838. https://doi.org/10.1212/WNL.0000000000010084
40. Majbour NK, Vaikath NN, van Dijk KD, et al. Oligomeric and phosphorylated alpha-synuclein as potential CSF biomarkers for Parkinson's disease. Mol Neurodegener 2016;11:7. https://doi.org/10.1186/s13024-016-0072-9
41. Coughlin DG, Shifflett B, Farris CM, et al. Alpha-synuclein seed amplification assay amplification parameters and the risk of progression in prodromal Parkinson disease. Neurology 2025;104(5): e210279. https://doi.org/10.1212/WNL.0000000000210279
42. Depierreux F, Parmentier E, Mackels L, et al. Parkinson's disease multimodal imaging: F-DOPA PET, neuromelanin-sensitive and quantitative iron-sensitive MRI. NPJ Parkinsons Dis 2021;7(1):57. https://doi.org/10.1038/s41531-021-00199-2
43. Vijiaratnam N, Foltynie T. How should we be using biomarkers in trials of disease modification in Parkinson's disease? Brain 2023; 146(12):4845–4869. https://doi.org/10.1093/brain/awad265
44. Sondhi A, Segal B, Snider J, Humblet O, McCusker M. Bayesian additional evidence for decision making under small sample uncertainty. BMC Med Res Methodol 2021;21(1):1–8. https://doi.org/10.1186/s12874-021-01432-5
45. Ionan AC, Clark J, Travis J, et al. Bayesian methods in human drug and biological products development in CDER and CBER. Ther Innov Regul Sci 2023;57(3):436–444. https://doi.org/10.1007/s43441-022-00483-0
46. Evers LJW, Krijthe JH, Meinders MJ, Bloem BR, Heskes TM. Measuring Parkinson's disease over time: the real-world within-subject reliability of the MDS-UPDRS. Mov Disord 2019;34(10):1480–1487. https://doi.org/10.1002/mds.27790

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.