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FULL-LENGTH ARTICLE

Mesenchymal Stromal Cell Therapy

Safety and efficacy of adipose-derived mesenchymal stem cell therapy in elderly Parkinson's disease patients: an intermediate-size expanded access program

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ABSTRACT

Objective: This intermediate-size expanded access program aimed to evaluate safety and clinical efficacy of multiple intravenous infusions of autologous, Hope Biosciences adipose-derived mesenchymal stem cell (HB-adMSC) therapy in elderly patients with Parkinson's disease (PD).

Methods: Ten eligible participants (aged 76–95 years) received six intravenous infusions each with 200MM autologous HB-adMSCs over 18 weeks, with the end of study (EOS) at week 26. Safety was assessed through adverse events (AEs) and serious adverse events (SAEs). Efficacy was measured through improvements in both motor and non-motor symptoms, utilizing scales including Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) parts I-IV, Parkinson's Disease Questionnaire-39 (PDQ-39), Parkinson's disease Fatigue Scale (PFS-16), Patient Health Questionnaire-9 (PHQ-9), and Visual Analog Scale (VAS). Analysis employed paired t-tests and Minimal Clinically Important Difference (MCID) thresholds for the patient-reported outcomes.

Results: Most AEs (37 out of 46) were mild in severity, with 5 SAEs reported, none attributed to the drug. No deaths occurred. Despite lack of statistical significance across the efficacy endpoints, modest yet clinically meaningful improvements with effect size > 0.3 were observed in several secondary efficacy endpoints (MDS-UPDRS part I & III, PDQ-39, and PHQ-9) at the EOS, nearing or surpassing the established MCID values.

Conclusions: The administration of autologous 200MM HB-adMSCs was found to be safe and well-tolerated in the elderly PD population. Although not achieving statistical significance, modest clinical improvements were noted across multiple secondary endpoints. These findings underscore the safety profile of the treatment in elderly patients and highlight the importance of evaluating clinical relevance alongside statistical measures for meaningful patient outcomes. Further investigation with a larger, randomized, placebo-controlled design is warranted to validate these observations.

Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder worldwide, following Alzheimer's disease. Characterized by symptoms such as tremor, rigidity, bradykinesia, and postural instability, PD results from the progressive loss of dopaminergic neurons in substantia nigra [1]. Current therapeutic approaches involving dopamine agonists, monoamine oxidase-B (MAO-B) inhibitors, and deep brain stimulation [2–4], primarily focus on symptom management but are incompetent to address the underlying neurodegenerative process.

In recent years, mesenchymal stem cell (MSC) therapy has emerged as a promising treatment approach for PD [5]. MSCs are known to exert potent paracrine effects by secreting trophic factors, cytokines, and extracellular vesicles, thereby significantly contributing to tissue repair, immune modulation, neuroprotection, and neuroregeneration [6,7]. Adipose-derived MSCs (adMSCs) offer advantages such as non-invasive isolation, low immunogenicity, and abundant supply, making them practical for clinical applications

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[8,9]. adMSCs also possess the ability to differentiate into various cell types, including neural progenitor cells, which may aid in neuronal regeneration [10]. Furthermore, adMSCs have demonstrated migratory capabilities, referred to as "homing," to neurodegenerative disease sites, enhancing their potential to contribute to neuroprotection and facilitate neuroregeneration [11–15].

In this study, we utilized multiple intravenous infusions of autologous HB-adMSCs to evaluate both safety and efficacy of the therapy in improving signs and symptoms of PD patients. Given the degenerative nature of the disease, it is challenging to demonstrate the effectiveness of a treatment along with functional improvements. Furthermore, it is important to note that the presence of statistical significance (or lack thereof), often determined by conventional statistical methodologies relying on p-value significance, may not consistently reflect the actual clinical changes in symptoms, when measured using patient-reported outcomes. This discrepancy becomes particularly pertinent in studies with limited sample sizes, where analyses may yield statistically non-significant findings, and consequently, the efficacy of a treatment may go undetected [16]. Since clinical significance does not invariably align with statistical significance [17], our approach incorporated a careful evaluation of treatment effects.

The main aim of this study was to assess safety and tolerability of administrating multiple intravenous infusions of adMSCs in elderly PD patients. The secondary objective was to evaluate the therapeutic efficacy by assessing changes in MDS-UPDRS scores and other patient-reported outcomes, examining improvements in both motor and non-motor symptoms of PD at the EOS. We used minimal clinically important difference (MCID) [18–21] to precisely evaluate treatment responsiveness, defined as the smallest change perceived as beneficial from the patient's or clinician's perspective [22].

Methods

Study design

This expanded access protocol was developed to test the safety and efficacy of autologous, HB-adMSC in improving signs and symptoms of patients with PD. The study included 10 subjects aged 76–95 years, diagnosed with Parkinson's disease. The total study duration was 26 weeks, during which the patients received six intravenous infusions of autologous HB-adMSCs over 18 weeks with a post-intervention follow-up at week 26. The study was approved by Western Institutional Review Board (IRB), in Olympia, Washington. All procedures were conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent for participation was provided by all subjects.

Patient eligibility

Inclusion criteria

(i) males and females aged 76–95 years; (ii) PD diagnosis for a minimum of six months, before treatment commencement; (iii) have banked their mesenchymal stem cells with Hope Biosciences; (iv) should be able to read, understand, and provide written consent; (v) able and willing to comply with the program requirements.

Exclusion criteria

(i) Patients with advanced PD, significant disability, wheelchair-bound/bedridden; (ii) any malignancy within five years before first infusion that may require surgery, chemotherapy, or radiation; (iii) uncontrolled high blood pressure > 140/90 mm/Hg; (iv) history of Heart Failure, Heart Attack (in the past 6 months before 1st infusion), Stroke (in the past 6 months), Hepatitis B/C, Human immunodeficiency virus (HIV) infection; (v) Hemoglobin (Hgb) <10 G/DL or >18 G/DL, Hematocrit (HCT) <30% or >54 %, Platelet count < 80 K/UL and or > 450 K/UL, White blood cell count WBC < 3.0 K/UL and > 12.0 K/UL, Alanine aminotransferase (ALT) of > 75 IU/L, Aspartate aminotransferase (AST) of > 75 IU/L, eGFR < 59 mL/min/1.73, Pre-prandial glucose > 130 MG/DL, Postprandial glucose > 200 MG/DL; (vi) patients who received any stem cell treatment in the past 6 months before 1st infusion; (vii) uncontrolled psychiatric disorder; (viii) history of addiction or dependency or current substance abusing or use; (ix) patients with kidney dialysis; (x) experimental drug received in the past 12 months before the first dose (except COVID-19 vaccinations); (xi) patients determined unsuitable for participation by the investigator for other reasons, such as, deep vein thrombosis (DVT), pulmonary embolus, cardiac arrhythmia, or those who have a prothrombotic condition, or who require persistent oxygen supplementation; (xii) patients who have recently undergone major surgery (in the past 6 months) including, heart surgeries, aortic aneurysm bypass, organ transplant, intracranial surgery, spinal laminectomy or fusion, amputation, resection of the lung, resection of esophagus, resection of a mediastinal mass, resection of bladder or prostate tumor and resection of kidney or ureter.

Isolation and administration of autologous HB-adMSCs

For HB-adMSCs isolation, emulsified fat from the subjects' abdomen was extracted via liposuction procedure performed by a licensed physician. 3–10.5 mL of adipose tissue (varied between subjects) was then treated with collagenase to separate stromal vascular fraction (SVF). The SVF was plated in Hope Biosciences' (HB)-103 medium and the resulting adherent cells were further expanded in HB-101 medium to establish a P0 culture. Cells were cryopreserved at passages 0, 1, and 2 to create a complete bank of each subject. For infusions, passage 2 cells were thawed and cultured to passage 4. 200MM HB-adMSCs were freshly harvested from passage 4 culture and packaged in 20 mL 0.9% sterile saline for each administration and administered within 96 hours of packaging. Product manufacturing was repeated for a total of six infusions per subject, with each infusion consisting of $2 \times 10^8 \pm$ 20% live, autologous HB-adMSCs administered over a treatment duration of 18 weeks. The infusions were scheduled as follows: Infusion 1 (week 0), Infusion 2 (week 2), Infusion 3 (week 6), Infusion 4 (week 10), Infusion 5 (week 14), and Infusion 6 (week 18).

To ensure safety and efficacy of the investigational drug, final product release criteria were set as follows: Viability (≥ 70%), Appearance (opaque white to faint yellow with no settlement), USP71 sterility (no organism seen), Mycoplasma (negative), Endotoxin (≤ 10 EU/mL), Gram stain (no organism seen) and Identity/purity by MSC-defining surface markers CD73 & CD29 (> 75%) and CD31 & CD45 (< 5%). All products successfully met the cGMP compliant quality control standards (Supplementary Table S1).

Primary and secondary endpoints

Primary safety assessments included incidence of adverse events (AEs) and serious adverse events (SAEs). Safety was also assessed through changes in laboratory parameters (biochemistry, hematology, and coagulation panel), vital signs, and physical examination from baseline to week 26.

Secondary endpoints involved evaluating changes in motor and nonmotor symptoms of PD. These changes were assessed using MDS-UPDRS (parts I-IV) and Visual Analog Scale (VAS). Quality-of-life assessments included, Parkinson's disease Questionnaire Summary Index (PDQ-39 SI), Parkinson's disease Fatigue Scale (PFS-16), and Patient Health Questionnaire-9 (PHQ-9). These outcomes were measured at baseline and at weeks 2, 6, 10, 14, 18, and 26, with efficacy quantified as change from baseline at the EOS (week 26).

Movement disorder society unified Parkinson's disease rating scale (MDS-UPDRS)

MDS-UPDRS is a standard rating tool used to gauge PD progression across four parts: part I: Non-motor Experiences of Daily Living;

part II: Motor Experiences of Daily Living; part III: Motor Examination; part IV: Motor Complications. Each parkinsonian symptom is assessed using a five-point Likert-type scale (0–4), where higher scores indicate more severe impairment [23]. The minimum changes needed to arbitrate clinical significance have been established as an improvement of −2.64 points for part I, −3.05 for part II [24], −3.25 [25] for part III, and −0.9 for part IV [26].

Parkinson's disease questionnaire-39 (PDQ-39)

The PDQ-39 evaluates health-related quality of life in PD patients. It has 39 self-reported items across eight domains: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. The PDQ-39 Summary Index (SI) is calculated by summing scores from each domain and dividing by 8 (sum of dimension scores/8). Higher scores indicate greater impairment. The MCID threshold for PDQ-39 SI improvement had been established as −4.72 points [20].

Patient health questionnaire (PHQ-9)

The PHQ-9 is a self-administered nine-item diagnostic instrument utilized for evaluating the severity of depression, and it has been extensively employed as a screening tool in PD patients. Each question is rated on a scale from 0 (not at all) to 3, (nearly every day), with an overall score ranging from 0 to 27. Higher scores indicate greater severity of depressive symptoms. MCID threshold for improvement on PHQ-9 scale has been previously estimated as −1.7 [27].

Parkinson's fatigue scale (PFS-16)

PFS-16 is another validated instrument used to assess the influence of fatigue on daily activities in the patients with PD [28]. It is a Likert-based scoring scale that consists of 16 self-reported questions, divided into two subscales: one focused on the physical manifestations of fatigue encompassing seven questions, and the other focusing on the impact of fatigue on daily functioning, consisting of 9 questions. The participants rate the responses on a scale ranging from 1 (strongly disagree) to 5 (strongly agree) [29]. While psychometric evaluations of the PFS-16 scale provided consistent and reliable results, estimates of the MCID for this scale have not yet been established [30].

Visual analog scale (VAS)

We utilized VAS, a validated tool for assessing both motor and non-motor symptoms associated with PD [31,32]. With VAS, our objective was to quantify PD motor symptoms such as muscle cramps and tremors, as well as to evaluate non-motor symptoms including anxiety, sense of smell, pain, and others. This scale ranged from zero to ten centimeters, with zero indicating no symptoms and ten representing the worst symptoms possible. Clinical changes in the VAS scores were assessed using estimated MCID of −1.9 [33].

Statistical methods

GraphPad PRISM version 9.2.0 (San Diego, CA, USA) was used to analyze the data. Data for all the secondary outcome measures were checked for normality using Shapiro-Wilk W test, that indicated normal distribution. Since, the data passed normality, paired t-tests were conducted for all the variables to determine statistical significance before and after the treatment (set at $p < 0.05$, two-tailed). Descriptive statistics were calculated for each of the outcome measures at baseline (pre-treatment) and at the EOS (week 26) timepoints and were described with mean ± SD. Calculation of the changes in the outcome measures associated with HB-adMSC therapy, from baseline to EOS (week 26), were represented as Δ = week 0 − week 26 for PDQ-39 SI, PFS-16, PHQ-9, VAS, and for MDS-UPDRS parts I-IV. Clinical relevance of these changes was determined using the available established minimal clinically important difference (MCID) values to evaluate the treatment effect for the patient reported measures. Furthermore, to allow for a proper interpretation of a clinically significant change, effect size (ES) statistic for all efficacy measures was also calculated using Cohen's d and interpreted as small (≥ 0.2), medium (≥ 0.5) and large (≥ 0.8) [34]. For most applications, MCID value for a given instrument ranged between small (0.2) and medium (0.5) ES.

Results

Study subjects

For this intermediate size expanded access program, N = 10 subjects with the ages between 76 and 95 years were screened and enrolled into the study without any screen fails. The selection of participants for this program adhered to inclusion and exclusion criteria, and only individuals who met all the specified inclusion criteria and did not meet any of the exclusion criteria were deemed eligible to participate. All 10 subjects received the treatment drug (autologous 200MM HB-adMSCs) and completed all study procedures to the EOS

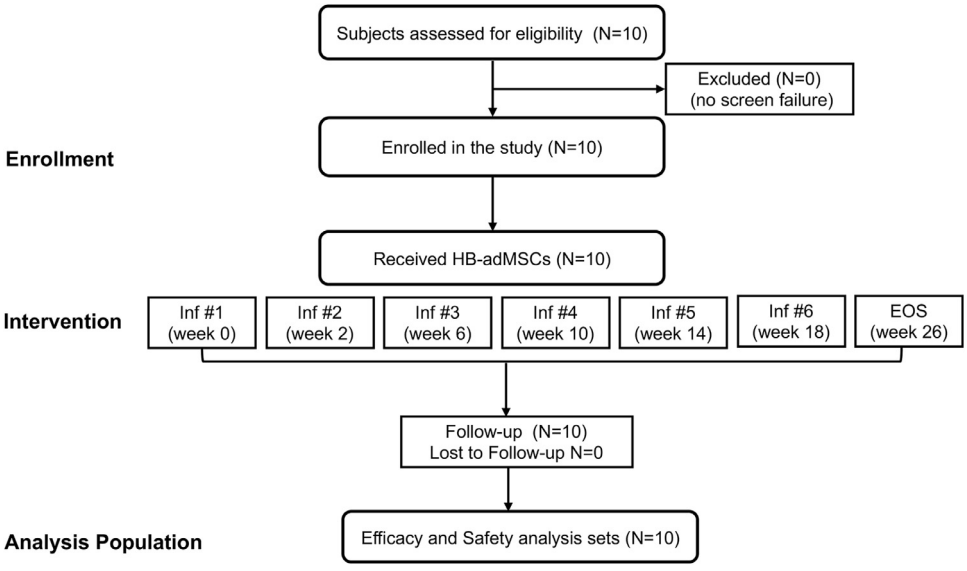

Fig. 1. Schematic CONSORT flow diagram for the intermediate-size expanded access program. A total of 10 subjects with Parkinson's disease were screened and enrolled into the study to receive the treatment (6 infusions of HB-adMSCs). EOS, end of study; Inf, infusion.

Table 1
Baseline characteristics and demographics (N = 10 subjects).

Age (years)		79.4 (3.95)
Sex	Male	7 (70.0)
	Female	3 (30.0)
Ethnicity	Hispanic or Latino	1 (10.0)
	Not Hispanic or Latino	9 (90.0)
Race	Asian	2 (20.0)
	White	8 (80.0)
Height (cm)	175.51 (11.69)	
Baseline Weight (kg)	79.38 (18.68)	
Baseline BMI (kg/m^2)	25.74 (5.46)	

BMI, body mass index; statistics represented: Mean (SD); N (%).

(week 26), without any withdrawals (Figure 1). The majority of the study participants were male, comprising 70% of the population, with a mean (SD) age of 79.4 (3.95) years. The racial composition identified 80% of subjects as white, with 90% reported non-Hispanic or Latino ethnicity (Table 1**)**. A summary of medical history of study subjects is provided in Supplementary File: Table S2.

Safety

Adverse events

A total of 46 adverse events (AEs) were recorded during the entire duration of the study for N = 9 subjects, out of which 37 were mild, 6 were moderate and three were severe. The majority of the AEs (41 out of 46) were considered unrelated to the treatment drug; 5 AEs (all mild) were considered "definitely" or "probably" related to the study drug, that included incidences of influenza-like symptoms and fatigue. A total of five serious AEs (SAEs) were reported during the study period that were all unrelated to the investigational product. All six infusions were well tolerated by the study subjects. No Deaths were reported during the entire duration of the treatment. Most frequently reported AEs were influenza, fatigue, headaches, dizziness, constipation, pneumonia, dysuria, dyspnea, cardiac failure, arthralgia, freezing phenomenon and gait disturbance **(S**upplementary File: Table S3).

Safety laboratory tests

Standard laboratory tests (hematologic, biochemistry, and coagulation panel) were performed at baseline and at EOS. Evaluation of these laboratory measures at EOS showed no significant differences compared to baseline. Additionally, assessments of vital signs, weight, and physical examination indicated no clinically significant changes. Detailed descriptive statistics for all safety-related laboratory results are provided in Supplementary File: Table S4.

Efficacy

To evaluate the efficacy of HB-adMSC therapy for changes in motor symptoms from baseline to EOS, assessments included MDS-UPDRS part II, III and IV along with VAS of motor symptoms (such as muscle spasms). For the evaluation of non-motor symptoms, assessments comprised MDS-UPDRS part I, PDQ-39 Summary Index, PHQ-9, PFS-16, and VAS measurements of non-motor symptoms (such as pain). Overall, the HB-adMSC therapy demonstrated clinical efficacy with small to near-medium effect sizes in multiple efficacy outcome measures **(**Figure 2**)**.

MDS-UPDRS I-IV

MDS-UPDRS part II did not exhibit any statistically significant or clinically relevant changes at the EOS, compared to baseline ($p > 0.05$; ES = 0.08). Similarly, MDS-UPDRS IV scores showed no improvement; instead, a slight worsening was observed at EOS, although it did not meet the established MCID of +0.8 points for worsening [26] (Figure 2; Table 2).

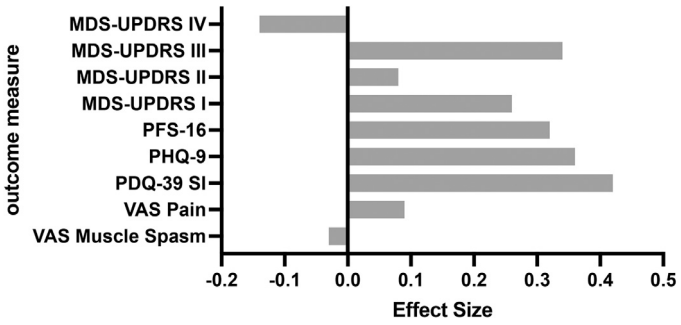

Fig. 2. Cohen's d effect sizes for the efficacy outcome measures at EOS (week 26). EOS: end of study; MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PHQ-9: Patient Health Questionnaire-9; PDQ-39 SI: Parkinson's Disease Questionnaire-39 Summary Index; PFS-16: Parkinson's Fatigue Scale-16; VAS: Visual Analog Scale; Cohen's d effect size: 0.2 = small; 0.5 = medium, and 0.8 = large.

For MDS-UPRS part III, while statistical significance was not detected, clinically significant improvements were noted at EOS with a small ES of 0.34. These improvements attained clinical significance, with the MCID surpassing the established threshold of −3.25 points [25] (Table 2). Specifically, a notable MCID of −5.4 points was observed at EOS (week 26), with 70% of the subjects achieving improvement (reduction) in MDS-UPDRS III scores exceeding the established MCID, indicating clinical significance. Also, to assess non-motor symptoms of PD, MDS-UPDRS part I scores were evaluated. Slight improvements (Cohen's d = 0.26) were observed in MDS-UPDRS part I scores at EOS, however, these improvements did not reach the established MCID (Table 2).

PDQ-39 SI

Compared to the baseline, mean (SD) PDQ-39 SI score improved from 23.79 (12.45) to 18.35 (13.33) at EOS (week 26), demonstrating clinically significant improvements with a near-medium ES = 0.42 (Table 2; Figure 2). Moreover, the improvements in PDQ-39 SI score at week 26 surpassed the established MCID of −4.72 points [20] , reaching −5.45, indicating clinically relevant enhancements, with 50% of patients achieving improvements ≥ MCID at EOS.

PHQ-9

Noticeable improvements were observed in the PHQ-9 scores with the mean (SD) values declining from 6.3 (5.12) at the baseline to 4.6 (4.35) at the EOS (week 26). Although these reductions did not demonstrate statistical improvement, but they were associated with a near-medium effect size (ES=0.36; Figure 2), implicating clinical significance. Also, the MCID of −1.7 points (Table 2) was observed which is comparable to the referenced MCID [27], representing ~27% reduction in the severity of symptoms, with 40% of subjects achieving improvements, compared to the baseline.

PFS-16

At the end of the study, no statistically significant difference was observed in the PFS-16 score ($p>0.05$). However, indications of clinical improvements were evident, associated with a small effect size (Cohen's d=0.32; Figure 2). Post-therapy, the mean (SD) PFS-16 score decreased from 47.80 (14.96) at baseline to 42.50 (18.03) at the EOS, demonstrating a reduction in fatigue from baseline by −5.3 points (Table 2). Additionally, 70% of the patient population showed improvements in PFS-16 scores at EOS compared to baseline. Nonetheless, the MCID threshold for PFS-16 has not been established for patients with PD, thus the extent of improvement remains uncertain.

VAS

To assess motor and non-motor symptoms respectively, VAS for muscle spasm and pain were evaluated and those did not show any

Table 2
Change from baseline to end of study (week 26) in efficacy endpoints for N = 10 subjects.

Outcome measure	Baseline		Week 26 (EOS)		*p*-value	ES[d]	MCID	MCID[Ref]
	mean ± SD	95% CI	mean ± SD	95% CI				
PDQ-39 SI	23.79 ±12.45	14.89-32.70	18.35 ±13.33	8.81-27.89	0.1094	0.42	−5.44	−4.72
PHQ-9	6.3 ± 5.12	2.64-9.96	4.6 ± 4.35	1.49-7.71	0.2552	0.36	−1.7	−1.7
PFS-16	47.8 ±14.96	37.10-58.50	42.5 ±18.03	29.60-55.40	0.1973	0.32	−5.3	N.E.
MDS-UPDRS I	10.5± 4.48	7.29-13.70	9.3 ± 4.88	5.81-12.79	0.5203	0.26	−1.2	−2.64
MDS-UPDRS II	12.5 ± 7.39	7.21-17.79	11.9 ± 8.49	5.83-17.97	0.7753	0.08	−0.6	−3.05
MDS-UPDRS III	27.7 ± 16.07	16.20-39.20	22.3 ± 15.75	11.03-33.57	0.2511	0.34	−5.4	−3.25
MDS-UPDRS IV	1.9 ± 4.01	−0.97-4.77	2.4 ± 3.13	0.16-4.64	0.6707	−0.14	+0.5	−0.9
VAS Muscle Spasm	0.94 ± 1.44	−0.08-1.97	0.98 ± 1.71	−0.23-2.21	0.9425	−0.03	+0.04	−1.9
VAS Pain	1.98 ± 2.10	0.47-3.47	1.79 ± 1.97	0.38-3.19	0.6585	0.09	−0.19	−1.9

MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale
PHQ-9: Patient Health Questionaaire-9
PDQ-39 SI: Parkinson's Disease Questionnaire-39 Summary Index
PFS-16: Parkinson's Fatigue Scale-16
MCID[Ref]: Reference Minimal Clinically Important Difference, calculated as Δ = week 0 − week 26 (negative MCID indicates improvement)
ES[d] (Cohen's d effect size): 0.2=small; 0.5=medium, and 0.8=large.
N.E.: not established.

statistically or clinically relevant changes at EOS, compared to baseline (Figure 2). Also, the total VAS scores for pain and muscle spasm remained far below the established MCID of −1.9 points (Table 2).

Overall, despite lack of statistical significance, several secondary efficacy outcomes (MDS-UPDRS III, PDQ-39 SI, and PHQ-9) demonstrated clinically significant efficacy at EOS (week 26) compared to baseline, with the MCIDs surpassing the established thresholds (Figure 3).

Discussion

Despite lacking a definitive reparative treatment for PD, existing pharmacological therapies are associated with controversial side effects, underscoring the need for alternative strategies. Recently, MSC therapy has gained considerable attention for its potential regenerative approach in PD. Pre-clinical studies show MSCs can promote neuronal survival, modulate neuroinflammation, and stimulate endogenous neurogenesis in PD models [35–37]. Moreover, efficacy of MSCs has also been indicated in multiple clinical studies utilizing

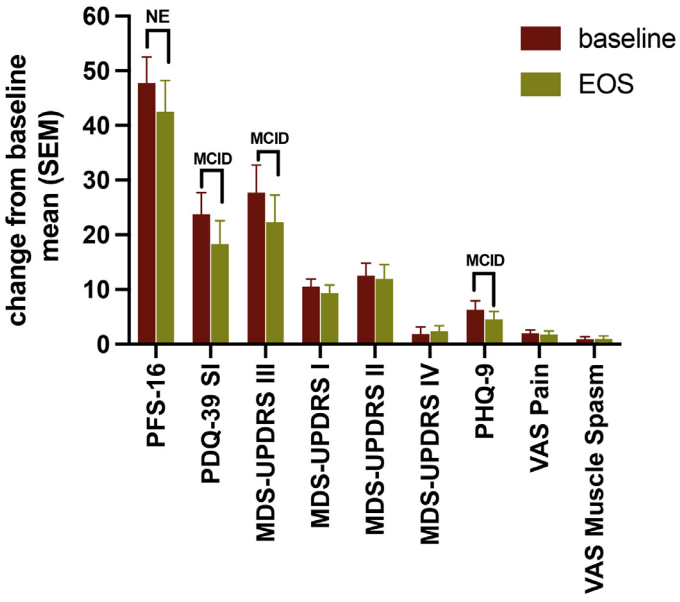

Fig. 3. Changes from baseline at EOS (week 26) in efficacy outcome measures. PDQ-39 SI, MDS-UPDRS III and PHQ-9 scores showed improvements in scores compared to baseline, surpassing the established MCID (minimum clinically important difference) thresholds. NE: not established.

MSCs from various sources [38,39]. This study is among the few that utilized multiple infusions of adipose-derived MSC therapy for elderly patients with PD. The results of this study demonstrated clinical efficacy in multiple outcome measures with a small to near-medium effect size. Another study by Shigematsu et al. [14], also utilizing repeated adMSC infusions demonstrated improvement trends in MDS-UPDRS scores across all three enrolled subjects, however, the study lacked additional clinical assessments to corroborate the results.

In this study, we employed various outcome measures to assess the efficacy of multiple infusions of HB-adMSCs in improving motor and non-motor symptoms in elderly PD patients. The results of several efficacy assessments (MDS-UPDRS III, PDQ-39 SI, PHQ-9, and PFS-16) implicated clinical significance with small to near-medium effect sizes at EOS compared to baseline. The treatment with HB-adMSC was well-tolerated by the elderly PD patients, highlighting its safety profile. Although statistical significance was not achieved for any of the efficacy endpoints, minimal clinical benefit was observed in some of the secondary efficacy endpoints (Cohen's d > 0.3 for PDQ-39, PHQ-9, PFS-16, and MDS-UPDRS part III). Compared to baseline, clinically significant improvements were seen at the EOS visit at 26 weeks as implicated by PDQ-39 SI, PHQ-9, PFS-16, as well as changes in MDS-UPDRS part III. MCID values for each of these measures reached beyond the reference MCID and were associated with clinically relevant effect sizes. Although MDS-UPDRS part I also revealed improvements with a small effect size, the improvement did not reach the reference MCID threshold. MDS-UPDRS II score changes showed limited treatment benefit (MCID was far below the reference MCID of −3.05) and was associated with a trivial ES. This could be attributed to the fact that MDS-UPDRS II assessment possesses inherent psychometric limitations [40], potentially obscuring clinically meaningful benefits. MDS-UPDRS part IV score showed mild worsening (MCID of +0.5), however, this worsening was not clinically relevant; reference MCID threshold for MDS-UPDRS IV for worsening is +0.8 [26].

MCID remains to be determined for PFS-16. However, estimates exist for several other fatigue scales frequently used in PD, such as Fatigue Severity Scale (FSS), Multidimensional Fatigue Inventory (MFI), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), [30]. Cross-sectional studies in Systemic Lupus Erythematosus, Rheumatoid Arthritis, and Multiple Sclerosis have reported MCID estimates for FSS ranging from 0.08 to 0.4 for clinically significant improvements [41], with a 10-15% change suggested as clinically significant [42]. Similarly, MCIDs for MFI total scale ranged from 6.8 to 9.6 for improvement [41,42] and for FACIT-F scale ranged from 2.2

to 5.5 [43]. Although MCID responsiveness for these scales is not determined in PD, the PFS-16 MCID in our study aligned well with MCIDs for several fatigue scales in other diagnostic areas.

HB-adMSC therapy demonstrated a strong safety profile with no treatment-related adverse or serious adverse events. Additionally, the observed effect sizes indicated modest clinical benefit of HB-adMSC therapy, as evidenced by improvements in PDQ-39 SI, PFS-16, PHQ-9, MDS-UPDRS III scores, with the changes exceeding respective MCID estimates. These findings suggest that HB-adMSC therapy holds promise as a potential treatment option for patients with Parkinson's disease, offering both safety and potential efficacy benefits.

The current study has several limitations. Firstly, our efficacy assessments indicated wide confidence intervals stemming from the small sample size of 10 subjects, limiting precision and introducing uncertainty in estimating mean differences. Despite potential clinical significance, this constraint may impact the reliability and interpretation of results. Moreover, the small sample size restricted the ability to achieve statistical significance, thus limiting the applicability of conventional statistical methods. Secondly, the study was unblinded with no placebo comparator, potentially introducing bias. Thirdly, the utilization of generalized MCID thresholds to assess clinical efficacy may have influenced the results. Given that the current study population consisted of individuals with mild to moderate disease severity, caution is advised when generalizing the findings in the patients with more advanced disease stages. Lastly, this was a short-term 26-week study. Future studies with longer follow-up are needed to ensure long-term safety and treatment benefits of HB-adMSC therapy for PD patients.

Conclusions

Administration of multiple infusions of HB-adMSCs was safe and well-tolerated by the elderly patient population over a 26-week period, with mostly mild AEs. Few SAEs reported during the study duration were unrelated to the investigational drug. Despite the absence of statistical significance, treatment of elderly patients with PD using multiple infusions of autologous, HB-adMSCs implicated potential clinical efficacy. Nevertheless, the observed safety profile and clinical efficacy across several secondary outcome measures with HB-adMSC therapy warrant further investigation. These findings provide rationale for conducting larger, long-term, placebo-controlled studies to comprehensively evaluate the safety and efficacy of HB-adMSC therapy in PD patients.

Declaration of competing interest

Donna Chang, Hosu Kim, and Hyeonggeun Park are shareholders of Hope Biosciences LLC. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

CRediT authorship contribution statement

Ridhima Vij: Formal analysis, Writing – original draft, Writing – review & editing. **Hosu Kim:** Resources, Investigation, Writing – review & editing. **Hyeonggeun Park:** Resources, Investigation. **Thanh Cheng:** Investigation, Supervision. **Djamchid Lotfi:** Investigation, Supervision. **Donna Chang:** Conceptualization, Project administration, Writing – review & editing.

Consent for publication

A written consent form for publication of the clinical details was obtained from all subjects.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcyt.2024.09.004.

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