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Phase II trial of intravenous human dental pulp stem cell therapy for Huntington's disease: a randomized, double-blind, placebo-controlled study

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Abstract

Background Huntington's disease (HD) is a rare, autosomal dominant neurodegenerative disorder caused by an expansion of cytosine-adenine-guanine (CAG) trinucleotide repeats in the huntingtin (HTT) gene. It manifests with motor, cognitive, and behavioural impairments, leading to progressive functional decline over approximately 20 years. Despite symptomatic treatments, no approved disease-modifying therapies are currently available, though experimental approaches are under investigation. Recent research has explored human dental pulp stem cells (hDPSCs) as a potential therapeutic approach due to their neurotrophic properties and ability to modulate neuroinflammation. This Phase II trial aimed to evaluate the safety and efficacy of NestaCell®, an allogeneic hDPSC-based therapy, in patients with HD.

Methods This randomised, double-blind, placebo-controlled trial included 35 patients assigned at a 2:2:1 ratio to receive hDPSCs at 1 million cells/kg, 2 million cells/kg, or placebo over nine intravenous infusions across 11 months. The primary endpoint was the Unified Huntington's Disease Rating Scale (UHDRS) Total Motor Score (TMS) change. Secondary outcomes included UHDRS Total Functional Capacity (TFC), Total Chorea Score (TCS), Functional Checklist (FC), and magnetic resonance imaging (MRI) based white matter quantification. Safety was assessed by monitoring treatment-emergent adverse events (TEAEs) and laboratory parameters.

Results Both doses demonstrated a favourable safety profile, with no increased incidence of adverse events compared to the placebo. No serious adverse event was deemed related to treatment. Both doses significantly improved UHDRS-TMS compared to placebo ($p=0.005$), while the 2 million cells/kg group showed significant benefits in UHDRS-TFC ($p=0.011$). Additional improvements were observed in the TCS and FC, suggesting a broader clinical impact. MRI analysis indicated a non-significant trend toward neuroprotection, with slower central nervous system (CNS) white and grey matter decline in treated patients.

Conclusions NestaCell® was well tolerated and showed statistically significant improvements in motor and functional outcomes in HD patients. While MRI trends suggest a potential neuroprotective effect, further investigation

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is warranted. These findings support the advancement to a Phase III trial to confirm efficacy and long-term safety in a larger cohort.

Trial registration: This study was registered on August 16, 2017, at ClinicalTrials.gov (identifier: NCT03252535; https://clinicaltrials.gov/search?cond=NCT03252535).

Keywords Huntington's disease, Stem cells, Unified Huntington's disease rating scale

Background

Huntington's disease (HD) is a rare, autosomal dominant neurodegenerative disorder caused by an expansion of cytosine-adenine-guanine (CAG) trinucleotide repeats in the huntingtin (HTT) gene on chromosome 4. Its global prevalence is estimated at 2.71 cases per 100,000 individuals [1], with 13,000 to 19,000 gene carriers in Brazil [2]. Signs typically manifest in the fourth decade of life, including motor, cognitive, and behavioural impairments, with chorea (involuntary movements) affecting approximately 90% of patients [3]. The disease follows a progressive course over an average of 20 years.

No disease-modifying therapies exist, although some treatments provide symptomatic relief [4]. Antipsychotic agents may alleviate chorea, hallucinations, delusions, and violent outbursts, albeit with a risk of exacerbating muscle rigidity. Antidepressants and anxiolytics are commonly used for psychiatric symptoms but may cause sedation, fatigue, or restlessness [5].

Tetrabenazine and valbenazine, both Vesicular Monoamine Transporter 2 (VMAT2) inhibitors, are approved for chorea management in HD. Their dopamine depletion mechanism is associated with depression, suicidality, sedation, and Parkinsonism-like symptoms. Valbenazine, with its longer half-life, offers improved tolerability but may prolong the QT interval. Both require careful monitoring, particularly in patients with psychiatric or cardiovascular risk factors [4, 6].

Among investigational therapies, tominersen [7, 8], an antisense oligonucleotide designed to reduce mutant huntingtin protein production, demonstrated dose-dependent reductions in cerebrospinal fluid mutant huntingtin levels with good tolerability, and a phase II study is currently underway. Pepinemab, a monoclonal antibody targeting semaphorin 4D to mitigate neuroinflammation, failed to show statistically significant improvements in the Unified Huntington's Disease Rating Scale (UHDRS) motor, functional or cognitive parameters [9]. Pridopidine, a Sigma-1 receptor agonist believed to enhance cellular protective pathways, has been evaluated in six clinical trials with conflicting findings—some studies reported clinical benefits in UHDRS measures such as Total Functional Capacity (TFC) and Total Motor Score (TMS), while others did not [10–14]. Laquinimod, an immunomodulatory agent with anti-inflammatory effects in the central nervous system, did not significantly impact UHDRS-TMS scores but appeared to slow caudate nucleus volume loss compared to placebo. However, significant cardiovascular concerns emerged in a multiple sclerosis study [15]. Bevantolol hydrochloride, a β1-adrenergic receptor antagonist with VMAT2 inhibitory properties, demonstrated a substantial reduction in chorea severity as measured by UHDRS Total Chorea Score (TCS). However, increased plasma prolactin levels were observed as a side effect [16]. Various vitamin and nutritional supplements, including cysteamine, creatine, eicosapentaenoic acid (EPA), and coenzyme Q10, have also been investigated for their potential benefits in HD, but results have been disappointing [17–20].

Recent research has explored human dental pulp stem cells (hDPSCs) as a potential treatment for neurodegenerative disorders, particularly HD. These cells originate from the neural crest during embryonic development and share several genetic markers with the central nervous system (CNS) [21–23]. The thawed hDPSCs express high levels of brain-derived neurotrophic factor (BDNF) and Nestin [23, 24]. Their low expression of MHC class II molecules enables administration without immunosuppression [25–27].

In a chemically induced rat model of HD, intravenous hDPSC administration increased the expression of DARPP-32 (dopamine- and cAMP-regulated neuronal phosphoprotein, a marker of medium spiny neurons), dopamine receptor type 2 (D2R), and BDNF compared to vehicle-treated controls [28]. Preclinical biodistribution studies in mice demonstrated that hDPSCs administered intravenously initially localize to the lungs before redistributing to multiple organs, including the CNS. Approximately 2% of administered cells were detected in the brain three days post-infusion, persisting for up to 30 days [29]. Toxicology assessments in C57BL/6 mice indicated good tolerability at doses up to 1 million cells per animal, proportionally 20 to 40 times higher than in this trial. While no direct toxicity was observed, cell aggregation posed a potential risk of thromboembolism. Studies in immunodeficient ("Nude") mice demonstrated no evidence of long-term engraftment, suggesting that the lack of engraftment is consistent with the absence of tumorigenic potential

[30]. A Phase I clinical trial evaluating NestaCell® in HD patients reported favourable tolerability and potential efficacy [31].

The primary objective of this study was to determine the optimal dose of hDPSC based on the TMS of the UHDRS. Secondary objectives included evaluation of the effects of hDPSC on other UHDRS domains, including the Cognitive Assessments (CA), Behavioural Assessment (BA), Functional Assessment (FA), Independence Scale (IS), and TFC. Additional secondary endpoints assessed: the Hamilton Depression Rating Scale (HAM-D), overall disease severity using the Clinical Impression of the Severity Index (CIBIS), body mass index (BMI), and MRI imaging-based disease progression. The safety objective compared the incidence, classification, and severity of adverse events (AEs) across treatment groups.

Methods

Study design

This was a prospective, randomized, double-blind, placebo-controlled trial. The study included a three-month screening and baseline stabilization period (V-3 to V-1), after which participants were randomized at V0 in a 2:2:1 ratio to receive either hDPSC 1 million cells/kg (lower dose, n = 14), hDPSC 2 million cells/kg (higher dose, n = 14), or placebo (n = 7).

Treatment was administered in three cycles, each consisting of three-monthly intravenous infusions: Cycle 1 at V0, V1, and V2; Cycle 2 at V4, V5, and V6; and Cycle 3 at V8, V9, and V10. Each cycle was separated by a 60-day interval, leading to nine intravenous administrations over 10 months (Fig. 1).

Outcome measures were assessed at baseline (V0) and the end of each treatment cycle (at V3, V7, and V11). Brain MRI scans were obtained at V-3 (97 days before V0) and V11 (330 days after V0).

Study population

All participants provided signed informed consent and met the inclusion criteria: age between 21 and 65 years, CAG repeat expansion of 40 to 49, a UHDRS-TMS of at least 5, and a UHDRS-TFC between 8 and 11. Exclusion criteria were participation in another clinical trial within the past 12 months, juvenile-onset HD, epilepsy, major neurocognitive disorder, or decompensated psychiatric illness, history of cancer, history of allergy to bovine-derived products, any decompensated illness except HD, active infection, contraindications to MRI (e.g., pacemakers or surgical clips), alcohol or drug abuse (per DSM-V criteria), or positive serology for HIV-1/2, HTLV-I/II, HBV (HBsAg, Anti-HBc), HCV (anti-HCV-Ab), or syphilis (FTA-ABS). Patients requiring immunosuppressants or with any condition deemed to increase study risk as determined by the investigator were also excluded. To support participant retention and ensure adherence to scheduled visits, the sponsor provided logistical assistance as needed, including air travel and hotel accommodations.

Intervention

The hDPSCs used in this study were developed through a collaboration between Instituto Butantan, a leading Brazilian research institute, and Cellavita, a Brazilian biotechnology company specialising in regenerative medicine. The investigational product, NestaCell®, consists

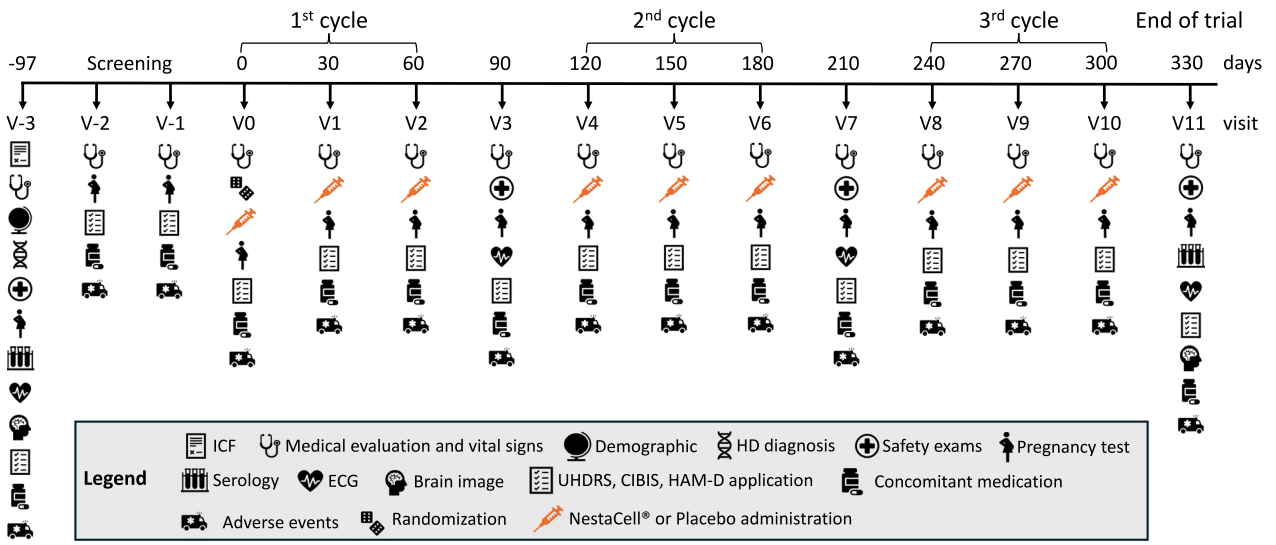

Fig. 1 Sequence and duration of study periods

of stem cells derived from the pulp of deciduous teeth donated by healthy individuals aged 5 to 12 years. The procedure was approved by an ethics committee (approval number 52375916.1.0000.5412), and written informed consent was obtained from both donors and their legal guardians for the use of their teeth in clinical research.

We selected hDPSCs from paediatric donors due to the ease and minimal invasiveness of collecting exfoliated deciduous teeth, which poses a negligible donor burden. Although SHED (Stem Cells from Human Exfoliated Deciduous Teeth) and hDPSCs may share a source, the cells used in this study differ in isolation methods, expansion protocols, and functional properties [23, 32, 33]. Thus, they are not equivalent in terms of regulatory classification or biological behaviour. Compared to adult-derived hDPSCs, those from younger donors demonstrate greater proliferative capacity, reduced immunogenicity, and enhanced differentiation potential—characteristics that support the consistency and potency of our final cell therapy product.

Donor eligibility criteria included full immunisation, no history of blood transfusions, and no high-risk exposure to communicable diseases. Blood samples were collected and tested for transmissible infectious agents, including HCV, HBV, HIV-1/2, HTLV-I/II, Chagas disease, syphilis, CMV, Parvovirus B19, EBV.

Teeth were processed within 48 h of collection. The cells were isolated from dental pulp and expanded as described elsewhere [32, 33]. At Cellavita, the dental pulp was isolated and transferred to a 12.5 cm^2 flask (Corning®) for cell culture. The cells were cultivated in DMEM-F12 supplemented with 200 mM L-glutamine (Dulbecco's Modified Eagle's Medium, Gibco/Life Technologies), 10–15% fetal bovine serum (FBS, HyClone), and 100X MEM NEAA (Gibco/Life Technologies Brasil). In passage zero (0), 50 mg/mL of gentamicin (Sigma Aldrich®) was used. For passages 1 to 5, cultures were maintained with 10,000 U to 10 mg/mL of penicillin/streptomycin (Sigma Aldrich®). The pulp and hDPSCs were incubated at 37 °C in a humidified incubator with 5% CO_2 and 95% air.

Cells were expanded until passage 2, followed by cryopreservation, in a medium composed of 20% FSB, DMEM-F12 and 10% dimetilsulfóxido (DMSO), to establish a master cell bank (MCB) at − 150 °C. After thawing, cells were expanded until passage 5, then cryopreserved in liquid nitrogen at − 150 °C to form the active component (AC). The procedure is described in more detail elsewhere [32, 33].

On the day of administration, the AC was thawed, washed, and resuspended in 0.9% saline. The final product was filled in 10- or 20-mL syringes at a concentration of 2 million cells/mL. Each participant received 3 to 8 syringes depending on body weight and randomisation group. Each syringe was administered slowly, followed by a 10 mL saline flush to ensure complete cell delivery.

Cells from the MCB, the AC, and the final product underwent comprehensive quality control prior to clinical use. Testing of MCB and AC included cell viability, immunophenotyping, quantification of BDNF secretion, in vitro differentiation potential, screening for human viral genes, karyotyping, and testing for sterility, endotoxins, and mycoplasma.

For the final product, due to the limited post-thaw stability of 4 h, quality control included sterility testing, endotoxin and mycoplasma assessment, and visual inspection for cell clumping. Further details on each analysis performed are provided in Table 1.

Phenotypic characterisation confirms the expression of CD105, CD90, and CD73 (≥ 90%) and Nestin (≥ 70%), while lacking expression of CD34, CD45, CD11b, and CD19 (≤ 2%), consistent with the profile of mesenchymal stem cells [34]. Low expression of HLA-DR (≤ 2%) minimises the risk of immunogenicity (Fig. 2). These cells exhibit a fibroblast-like morphology in vitro (Fig. 3), with a viability rate of 70% or higher [35]. The hDPSCs demonstrate in vitro potential for chondrogenic and osteogenic differentiation and secrete BDNF at concentrations ≥ 1 ng/mL. The demonstration of chondrogenic and osteogenic potential serves as a standard quality control measure for confirming the cells stemness [34].

The NestaCell® manufacturing process complies with Good Manufacturing Practices (GMP) as required by the Brazilian Regulatory Authority and is protected by a US patent, US 20160184366 A. Genetic stability is confirmed throughout production via karyotyping using comparative genomic hybridization (CGH). The cells are sterile, with no detectable bacteria, fungi, or mycoplasma, and exhibit endotoxin levels below 5 EU/kg.

Rationale for dose selection

The doses used in this study (1 and 2 million cells/kg) were the same as those in the Phase I SAVE-DH trial with NestaCell®. These were selected based on a review of published stem cell trials, where doses typically ranged from 0.3 to 10 million cells/kg [36–42], or fixed doses from 20 to 300 million cells. Most studies used 1 million cells/kg per administration [43–48], with variable schedules. In these trials, adverse events were rare and mostly mild, such as infusion-related reactions, headache, or fatigue.

Outcomes

Motor, functional, behavioural, and verbal fluency assessments of the cognitive domain of the UHDRS were

Table 1 The release analyses conducted on master cell banking (MCB), the active component (AC), and NestaCell® product

Production step	Analysis batch release	Analysis details
MCB AC NestaCell®	Viability and cell count	Method: Trypan blue 0.4% exclusion Equipment: TC20™ Automated Cell Counter
MCB AC	Immunophenotyping	Method: Flow cytometry using monoclonal antibodies against CD105, CD90, CD73, CD34, CD45, CD11b, CD19 (BD Biosciences), as well as HLA-DR and Nestin Equipment: FACSCalibur (BD Biosciences)
MCB AC	BDNF secretion quantification	Method: ELISA using the Human BDNF ELISA Kit (Invitrogen) Equipment: SpectroStarNANO (BMG LABTECH)
MCB AC	In vitro differentiation into mesodermal lineages	Method: Culture in tissue-culture vessels with lineage-specific differentiation media Osteogenic Medium: StemPro® Osteocyte/Differentiation Basal Medium + Osteogenesis Supplement (Gibco) Chondrogenic Medium: StemPro® Chondrocyte Differentiation Basal Medium + Chondrogenesis Supplement (Gibco)
MCB AC NestaCell®	Sterility TESTING	Method: Direct inoculation using Fluid Thioglycollate Medium (THIO) and Casein Soy Broth (TSB), both from Merck
MCB AC NestaCell®	Mycoplasma detection	Method: Bioluminescence assay using the MycoAlert™ PLUS Kit (Lonza) Equipment: GloMax®-Multi Jr Luminometer
MCB AC NestaCell®	Endotoxin testing	Method: Limulus Amebocyte Lysate (LAL) assay using Endosafe® nexgen-PTS™ cartridges Equipment: Endosafe® nexgen-PTS™
MCB AC	Karyotype analysis	Method: Array-CGH using the KaryoNIM® STEM CELLS platform to detect genomic instability
NestaCell®	Cell clumping assessment	Method: Visual inspection of the final product

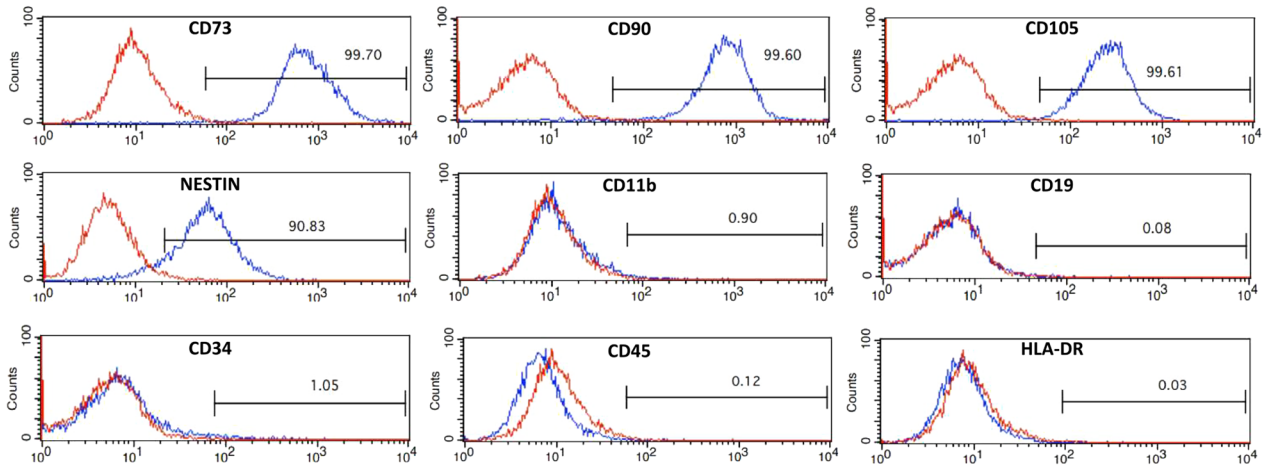

Fig. 2 The flow cytometry analysis of hDPSCs is in passage 5. The figure shows that the hDPSCs were negative for CD11b, CD19, CD34, CD45, and HLA-DR and were positive for CD73, CD90, CD105 in Accordance International Society for Cellular Therapy and nestin

conducted as described [49]. The primary (and most secondary) outcomes were selected following key publications in HD, most of which utilise the UHDRS as their principal endpoint [4, 9, 11, 12, 14–18, 50, 51]. The Wechsler Digit Span Test replaced the UHDRS Symbol-Digit Modalities Test [52], and a modified Stroop test (Victoria version) was used [53]. Higher TMS and BA scores indicate poorer motor and behaviour performance, respectively. Higher TFC scores correspond to better functional capacity. Higher Digit Span and verbal fluency scores, as well as lower Stroop scores, indicate better cognitive performance. A change of approximately 3 points per year on the UHDRS-TMS is generally considered representative of the natural disease progression and may be interpreted as a clinically meaningful decline [54]. The CIBIS incorporated evaluations from the investigator,

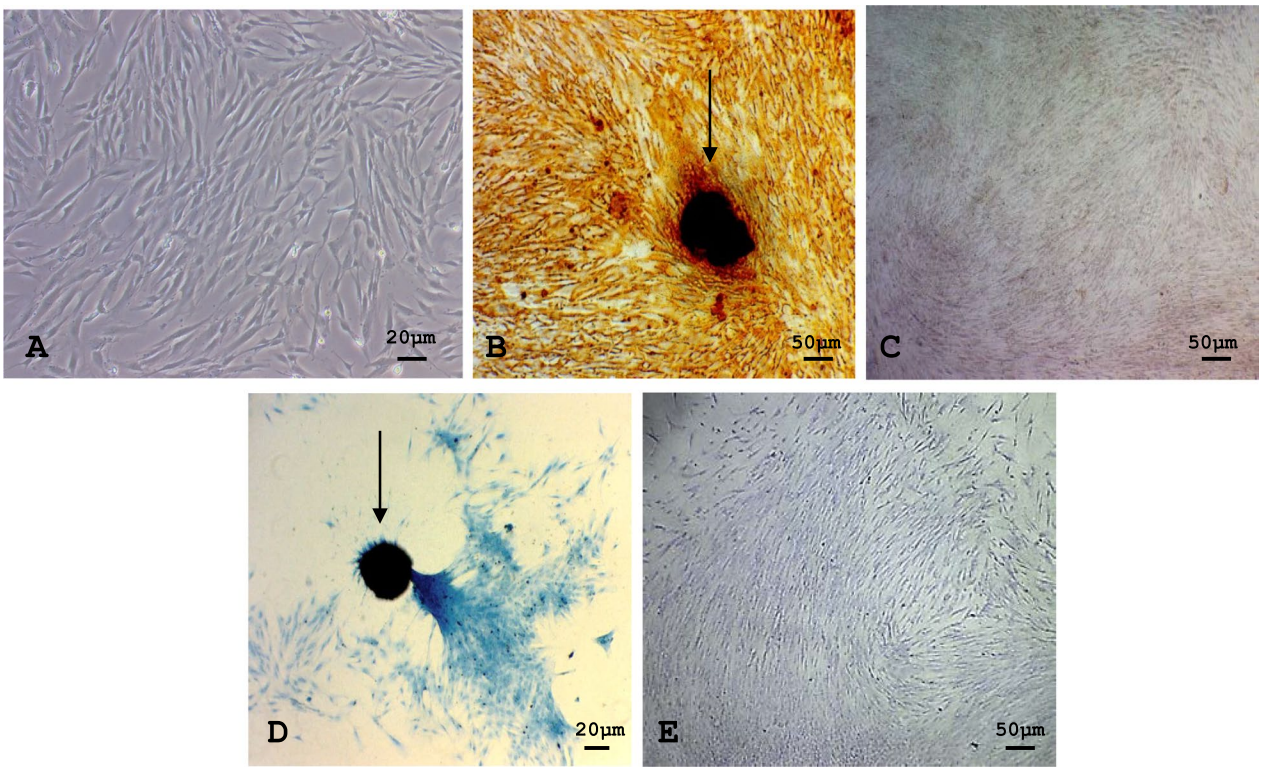

Fig. 3 Photomicrograph of human dental pulp stem cells (hDPSCs) at passage 5 **A**. The osteogenic differentiation of hDPSCs at passage 5 is demonstrated through the application of Alizarin Red staining, conducted after induction with Osteocyte/Differentiation Basal Medium StemPro® (Gibco) supplemented with Osteogenesis Supplement (Gibco) **B**, accompanied by a negative control **C**. Chondrogenic differentiation of hDPSCs at passage 5 is illustrated through the formation of a micromass subsequent to induction with Chondrocyte Differentiation Basal Medium StemPro® (Gibco) paired with Chondrogenesis Supplement (Gibco) **D**, along with a negative control **E**. The magnification used for these observations is 40×for panels **A** and **B**, and 10×for panels **C**, **D**, and **E**

the patient, and the caregiver [55]. Depressive symptoms were assessed using the HAM-D [56, 57]. BMI was calculated as usual [58, 59]. Structural and diffusion-weighted MRI scans were acquired using 1.5 Tesla (T) T1-weighted devices and processed with Diffusion Tensor Imaging—Fractional Anisotropy (DTI-FA) [60]. When necessary, scans were obtained under consented sedation to mitigate chorea movement artifacts**.**

Randomization and blinding

Randomization was performed using a pre-generated list of continuous numbers, arranged in eight blocks of five patients each, using SAS® version 9.4. Eligible patients were assigned sequential numbers based on the order of eligibility confirmation.

Blinding was ensured by separating responsibilities between a blinded and a non-blinded team. The investigator and all outcome assessors remained blinded throughout the study. A non-blinded pharmacist prepared the investigational product, while a non-blinded nurse administered the infusion intravenously, ensuring that syringes remained concealed from the patient's view.

Sample size and statistical analysis

The sample size was based on clinical and regulatory considerations rather than formal statistical calculations. According to the FDA guidance "Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products" [61], smaller sample sizes may be appropriate for life-threatening conditions where potential benefits could justify higher uncertainty. Given the rarity of Huntington's disease, the limited manufacturing capacity of the investigational product, and the early-phase nature of the trial, a total of 35 participants was considered both feasible and adequate to meet the study objectives.

The Intention-to-Treat (ITT) population comprised all 35 patients who signed the informed consent form (ICF) and underwent randomization. The Per Protocol (PP) population included 32 patients who completed all nine doses of the investigational product (13 in the lower-dose group, 12 in the higher-dose group, and 7 in the placebo group).

All analyses in this report were conducted on the ITT population, except for MRI assessments, which were

performed on a subset of the PP population (20 treated and four placebo), excluding scans deemed unreliable due to chorea movements.

Efficacy was assessed using the Mixed Model for Repeated Measures (MMRM), estimating longitudinal changes normalized to one year. The analysis compared: (1) pooled NestaCell® doses versus placebo; (2) individual NestaCell® dose levels versus placebo, and (3) inter-dose differences within the NestaCell® treatment groups. A two-tailed significance level of 5% was applied for group comparisons. UHDRS domains, CIBIS, and HAM-D scores were analysed at baseline, weeks 3, 7, and 11. MRI data on whole-brain white matter changes, assessed by diffusion tensor imaging (DTI) between V-3 and V11 (about 407 days apart) were summarized descriptively without hypothesis testing.

Safety assessments

Safety analyses focused on treatment-emergent adverse events (TEAEs), coded by the Medical Dictionary for Regulatory Activities (MedDRA, Version 24.1, September 2021). Additional safety assessments included hematologic and biochemical parameters, urine analyses, electrocardiograms (ECGs), and vital signs, recorded before, during, and after treatment. Comparative tables of TEAEs and safety parameter changes provided a structured evaluation of safety outcomes.

Results

Participant flow

The trial screened 49 patients for eligibility and randomized 35. Fourteen participants failed screening: seven did not meet the minimum motor or functional UHDRS criteria, three tested positives on serological screening, two withdrew consent, one had fewer than 40 CAG repeats, and one was excluded at the investigator's discretion. Participants were assigned to receive NestaCell® 1 million cells/kg (n = 14), NestaCell® 2 million/kg (n = 14), or placebo (n = 7). A total of 32 patients (91.4%) completed the study, including 13 (92.9%) in the 1 million/kg group, 12 (85.7%) in the 2 million/kg group, and all 7 (100%) in the placebo group. One patient in the 1 million/kg group withdrew informed consent. Two patients in the 2 million/kg group were discontinued due to decompensated active psychiatric illness (Fig. 4).

Baseline data

Table 2 summarizes baseline demographic characteristics and UHDRS domain values.

Outcomes

The primary endpoint was assessed by the change in the total motor score of the UHDRS-TMS from V0 to V11, normalized to one year (Table 3 and Fig. 5A). A significant difference was observed between the pooled treatment groups and the placebo group (p = 0.005), as well as between the 1 million/kg group and placebo ($p = 0.009$) and the 2 million/kg group and placebo ($p = 0.017$). No statistically significant difference was found between the two active treatment groups ($p = 0.898$). Both doses of NestaCell® were associated with clinical improvement, whereas the placebo group exhibited disease progression, supporting the therapeutic benefit of NestaCell® for the primary outcome.

As secondary outcomes, the trial evaluated changes in all UHDRS domains, CIBIS, HAM-D, and BMI (Table 3)

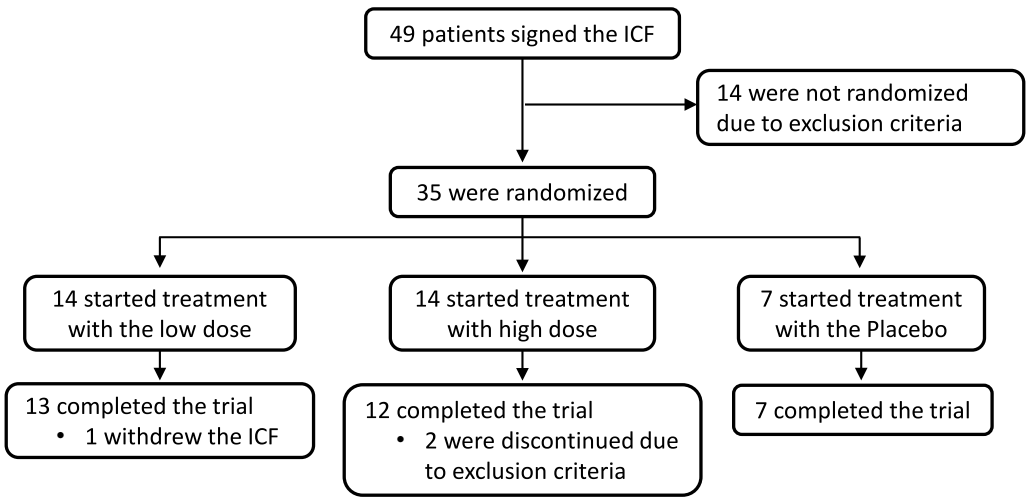

Fig. 4 Study flowchart. ICF, Informed Consent Form; ITT, Intent-to-treat statistical analysis population; PP, Statistical analysis population per protocol. *Last visit performed. Low dose, 1×10^6 million cells/kg; High dose, 2×10^6 million cells/kg

Table 2 Demographic and UHDRS domains at the baseline (V0)

Characteristics	1 million/kg (N = 14)	2 million/kg (N = 14)	Treated (N = 28)	Placebo (N = 7)
Age (years)	51.6 (9.4)	43.7 (8.5)	47.7 (9.7)	50.9 (12.0)
Height (m)	1.63 (0.08)	1.61 (0.10)	1.62 (0.09)	1.66 (0.06)
Weight (kg)	65.5 (14.0)	68.7 (14.5)	67.1 (14.1)	69.3 (14.0)
CAP Scale	106.7 (18.6)	97.5 (11.5)	102.1 (15.9)	110.7 (12.0)
Years with symptoms	10.1 (3.6)	7.4 (2.1)	8.7 (3.2)	10.1 (3.3)
UHDRS-TMS	43.6 (23.8)	20.7 (11.8)	32.2 (21.8)	38.0 (7.5)
UHDRS-CA				
Verbal Fluency Test	12.4 (6.1)	18.6 (9.2)	15.5 (8.3)	10.6 (5.5)
Digit Span	7.8 (2.7)	10.4 (3.5)	9.1 (3.4)	8.4 (2.1)
Stroop P1	49.1 (31.1)	30.1 (12.5)	39.6 (25.2)	36.3 (11.1)
Stroop P2	46.3 (32.6)	36.5 (26.6)	41.4 (29.6)	44.9 (17.5)
Stroop P3	64.1 (49.8)	64.4 (74.2)	64.3 (62.0)	81.1 (44.9)
UHDRS-BA	3.0 (4.4)	9.6 (10.0)	6.3 (8.3)	7.6 (6.4)
UHDRS-FA				
UHDRS-FC	17.6 (4.9)	18.9 (3.7)	18.2 (4.3)	15.0 (1.6)
UHDRS-IS	76.4 (10.1)	81.4 (9.5)	78.9 (9.9)	70.0 (8.2)
UHDRS-TFC	8.1 (2.1)	8.4 (2.6)	8.3 (2.3)	6.7 (1.4)

Values are presented as means and (standard deviations). CAP: CAG- Age Product. Unified Huntington Disease Rating Scale (UHDRS); Total Motor Score (TMS); Cognitive Assessment (CA); Stroop: P1 (Poster 1), P2 (Poster 2), P3 (Poster 3); Behavioural Assessment (BA); Functional Assessment (FA); Functional Checklist (FC); Independence scale (IS); Total Functional Capacity (TFC)

Table 3 Consolidated efficacy results

	1 million/kg n = 14	2 million/kg n = 14	Treated N = 28	Placebo n = 7
UHDRS-TMS	−4.23** (2.70)	−3.70* (2.90)	−4.06** (1.87)	7.79 (3.64)
UHDRS-CA				
Verbal Fluency Test	−1.41 (1.23)	2.41 (1.35)	0.92 (1.72)	0.92 (1.72)
Digit Span	0.01 (0.56)	0.32 (0.59)	0.15 (0.39)	0.08 (0.77)
Stroop P1	27.23 (9.23)	15.41 (9.72)	21.91 (6.67)	12.48 (12.58)
Stroop P2	35.56 (15.45)	−1.04 (16.33)	18.17 (11.38)	26.08 (21.58)
Stroop P3	28.53 (12.79)	−19.85 (13.54)	5.45 (9.87)	23.51 (17.86)
UHDRS-BA	−2.06 (1.64)	−2.68 (1.71)	−2.32 (1.17)	1.35 (2.23)
UHDRS-FA				
UHDRS-FC	−0.94 (0.86)	1.11* (0.91)	0.02 (0.64)	−2.93 (1.25)
UHDRS-IS	−0.74 (2.16)	2.65 (2.29)	0.85 (1.57)	−3.40 (3.14)
UHDRS-TFC	0.15 (0.51)	1.53* (0.54)	0.81 (0.38)	−0.87 (0.73)
CIBIS	−0.09 (0.12)	−0.11 (0.13)	−0.10 (0.08)	0.13 (0.17)
HAM-D	−0.56 (0.82)	−0.92 (0.84)	−0.73 (0.58)	−0.52 (1.13)
BMI	0.19 (0.50)	−0.38 (0.52)	−0.09 (0.36)	−0.37 (0.71)

Values are presented as means (standard error) of the individual differences between V0 to V11. Unified Huntington Disease Rating Scale (UHDRS); Total Motor Score (TMS); Cognitive Assessment (CA); Stroop: P1 (Poster 1), P2 (Poster 2), P3 (Poster 3); Behavioural Assessment (BA); Functional Assessment (FA); Functional Checklist (FC); Independence scale (IS); Total Functional Capacity (TFC); Clinical Impression of the Severity Index (CIBIS); Hamilton depression rating scale (HAM-D). Lower scores on the TMS, Stroop, (BA), CIBIS, and HAM-D indicate better outcomes, while higher scores on the Verbal Fluency Test, Digit Span, and FA reflect improvement

The p-value was obtained using the mixed model for repeated measures (MMRM). * $P < 0.05$; ** $P < 0.01$

and brain imaging assessments using MRI (Fig. 6) from V0 to V11. For UHDRS-TFC (Table 3 and Fig. 5B), MMRM analysis identified a significant difference between the placebo and 2 million/kg groups ($p = 0.011$), with a trend towards benefit for the lower dose compared to placebo ($p = 0.068$). The UHDRS-FC also showed a significant improvement in the 2 million/kg group compared to placebo. These findings suggest that NestaCell® may mitigate the functional decline characteristic of Huntington's disease. The other UHDRS domains and

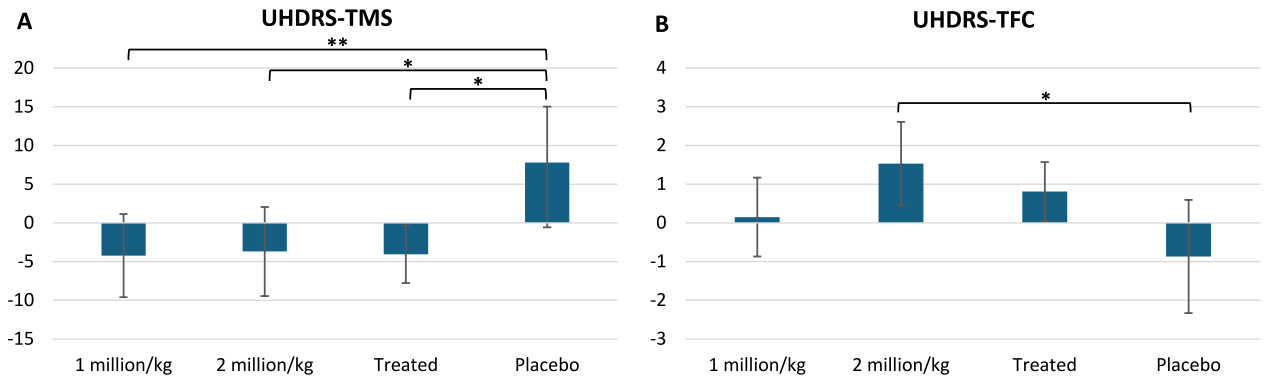

Fig. 5 Changes in UHDRS-TMS and UHDRS-TFC between visits V0 and V11. **A** UHDRS-TMS – lower scores indicate improvement in motor function. **B** UHDRS-TFC—higher scores indicate improvement in functional capacity. Values represent means with 95% confidence intervals. *$P < 0.05$; **$P < 0.01$

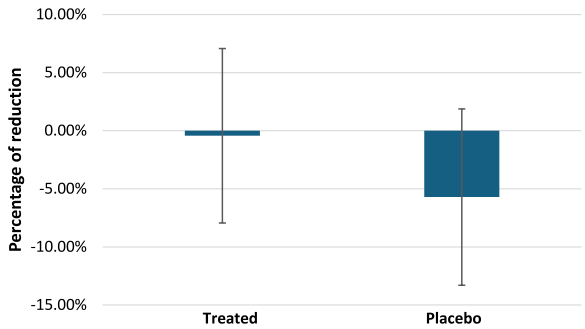

Fig. 6 Whole encephalic white matter by DTI. Means and 95% Confidence Interval

CIBIS, HAM-D, suicide domain of the HAM-D, and BMI showed no significant differences between the treated and placebo groups.

MRI analyses were affected by chorea-related motion artifacts, leading to the exclusion of unreliable DTI-FA scans from either V-3 or V11. The final dataset comprised 11 patients in the 1 million/kg group, 9 in the 2 million/kg group (total of 20 in pooled treatment groups), and 4 in the placebo group. Figure 6 illustrates the percentage change in total white matter volume (DTI-FA) between V-3 and V11, indicating a trend toward higher white matter loss in placebo-treated patients than those receiving NestaCell®.

Safety

A total of 121 treatment-emergent adverse events (TEAEs) were reported, with 92 occurring in treated patients (1 million/kg: 43; 2 million/kg: 49) and 29 in the placebo group. TEAEs were observed in 88.6% of participants, including 85.7% of treated patients (both dose groups) and 100% of placebo recipients (Table 4).

One serious adverse event (SAE) occurred in the 1 million cells/kg group: a participant was hospitalised for sinusitis. The event was mild and deemed unrelated to the investigational product. Hospitalisation was primarily due to the participant's underlying clinical condition related to Huntington's disease.

Six treatment-related adverse events (classified as possible, likely/probable, or certain) were reported. Four cases involved hair alterations, including increased hair growth or reversion of grey hair to dark. Additionally, one patient in the placebo group experienced moderate dyspnoea (classified as possibly related), and one patient in the 1 million/kg group developed phlebitis at the injection site.

TEAEs classified by organ systems were evenly distributed across groups (Table 5). The most frequently reported events were psychiatric disorders. These occurred in 8 treated patients (28.6%) and four placebo patients (57.1%), including depression (14.3% in treated patients, 0% in placebo) and depressive mood (10.7% in treated patients, 14.3% in placebo). Gastrointestinal disorders were the second most common, affecting six treated patients (21.4%) and five placebo patients (71.4%), with diarrhoea (7.1% in treated patients, 28.6% in placebo), nausea (7.1% in treated patients, 0% in placebo), and vomiting (0% in treated patients, 28.6% in placebo). The third most frequent TEAEs were injuries, intoxications, and procedural complications, reported in 8 treated patients (28.6%) and one placebo patient (14.3%), primarily involving falls (17.9% in treated patients, 14.3% in placebo).

Vital signs, including heart rate, arterial blood pressure, respiratory rate, and body temperature, were monitored before, during, and after administration of the investigational product. No clinically significant changes were observed.

Table 4 Treatment-emergent adverse events (TEAEs) by causality, intensity, and severity

	1 million/kg n = 14		2 million/kg n = 14		Treated n = 28		Placebo n = 7	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Total TEAEs	43	12 (85.7)	49	12 (85.7)	92	24 (85.7)	29	7 (100)
Serious TEAEs	1	1 (7.1)	0	0	1	1 (3.6)	0	0
Related Serious TEAEs	0	0	0	0	0	0	0	0
TEAEs intensity	43	12 (85.7)	49	12 (85.7)	92	24 (85.7)	29	7 (100)
Mild	20	2 (14.3)	26	2 (14.3)	46	4 (14.3)	21	3 (42.9)
Moderate	23	10 (71.4)	22	9 (64.3)	45	19 (67.9)	8	4 (57.1)
Severe	0	0	1	1 (7.1)	1	1 (3.6)	0	0
Related severe TEAEs	0	0	0	0	0	0	0	0
Treatment-related TEAEs	3	3 (21.4)	2	2 (14.3)	5	5 (17.9)	1	1 (14.3)
TEAEs that resulted in treatment withdrawal	0	0	0	0	0	0	0	0
TEAEs that resulted in death	0	0	0	0	0	0	0	0
Unexpected TEAEs	1	1 (7.1)	0	0	1	1 (3.6)	0	0

TEAEs—Treatment-emergent adverse events. N = number of TEAEs. n = number of patients. () = percentage of patients within the group

Table 5 Treatment-emergent adverse events (TEAEs) by organ-affected class as defined by MedDRA Version 24.1 Sep/2021

TEAEs by organ class	1 million/kg n = 14		2 million/kg n = 14		Treated n = 28		Placebo n = 7	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Number of TEAEs	43	12 (85,7)	49	12 (85,7)	92	24 (85,7)	29	7 (100)
Skin and subcutaneous tissue	7	5 (35.7)	3	2 (14.3)	10	7 (25.0)	0	0
Immune system	0	0	0	0	0	0	2	1 (14.3)
Metabolism and nutrition	4	4 (28.6)	4	3 (21.4)	8	7 (25.0)	1	1 (14.3)
Nervous system	5	2 (14.3)	6	4 (28.6)	11	6 (21.4)	0	0
Blood and lymphatic system	0	0	2	2 (14.3)	2	2 (7.1)	0	0
Connective and musculoskeletal tissue	4	4 (28.6)	2	2 (14.3)	6	6 (21.4)	1	1 (14.3)
Gastrointestinal	2	2 (14.3)	6	4 (28.6)	8	6 (21.4)	8	5 (71.4)
General and administration site conditions	1	1 (7.1)	2	2 (14.3)	3	3 (10.7)	0	0
Psychiatric	2	2 (14.3)	13	6 (42.9)	15	8 (28.6)	5	4 (57.1)
Kidney and urinary	1	1 (7.1)	2	2 (14.3)	3	3 (10.7)	0	0
Respiratory, thoracic, and mediastinal	1	1 (7.1)	4	4 (28.6)	5	5 (17.9)	1	1 (14.3)
Vascular	0	0	0	0	0	0	1	1 (14.3)
Infections	5	4 (28.6)	3	3 (21.4)	8	7 (25.0)	1	1 (14.3)
Investigations	0	0	0	0	0	0	4	2 (28.6)
Injuries	10	6 (42.6)	2	2 (14.3)	12	8 (28.6)	2	1 (14.3)
Medical and surgical procedures	1	1 (7.1)	0	0	1	1 (3.6)	3	2 (28.6)

TEAEs—Treatment-emergent adverse events. N = number of TEAEs. n = number of patients. () = percentage of patients within the group

Discussion

This Phase II trial of NestaCell®, a novel allogeneic hDPSC therapy, demonstrated good tolerability and potential clinical benefit in patients with Huntington's Disease. No serious treatment-related adverse events were observed, and the therapy was generally well tolerated. Mild phlebitis and reversible hair changes were the only treatment-associated adverse events, supporting a favourable safety profile.

There were some baseline imbalances in outcomes used to assess efficacy, such as milder disease in the 2 million cells/kg group. However, both hDPSC doses met the primary efficacy endpoint by significantly improving the UHDRS-TMS. The consistency across both treated groups reinforces the reliability of the findings. Improvements were also observed in UHDRS-TFC, a key secondary endpoint, with a significant effect noted in the higher-dose group compared to the placebo group. A

trend toward white matter preservation on MRI supports possible neuroprotective effects, although these findings need confirmation.

In the context of other investigational therapies for HD, NestaCell® offers a differentiated profile. The GENERATION HD1 trial of tominersen, an antisense oligonucleotide targeting mutant huntingtin mRNA, was terminated early due to lack of efficacy and safety concerns, particularly with more frequent dosing [8]. Other HTT-lowering approaches have been limited by challenges in achieving target engagement without off-target effects or excessive suppression of wild-type HTT, which is essential for normal neuronal function [7, 62]. In contrast, NestaCell® is assumed to exert its effects through paracrine mechanisms, without altering endogenous gene expression.

Other pharmacological strategies have also produced modest or inconsistent results. Pridopidine failed to meet primary endpoints in the PRIDE-HD trial, with only exploratory signals in early-stage patients [14]. Laquinimod and PBT2 demonstrated some imaging or cognitive benefits, respectively, but no clear impact on motor or functional outcomes [15]. Pepinemab, a monoclonal antibody targeting semaphorin 4D to reduce glial activation and neuroinflammation, did not yield significant improvements in UHDRS motor, functional, or cognitive scores despite promising preclinical rationale [9]. This highlights the challenge of translating anti-inflammatory strategies into clinically meaningful benefits in HD.

Bevantolol, a β1-adrenergic antagonist with VMAT2 inhibitory properties, showed a reduction in chorea severity in a small clinical study, as measured by the UHDRS-TCS. However, its use was associated with increased plasma prolactin levels, and its repurposing as a cardiovascular agent may pose safety concerns in patients with autonomic dysfunction or psychiatric comorbidities, which are common in HD. In contrast, NestaCell® showed improvements in both motor and functional domains, suggesting broader clinical efficacy and fewer systemic risks [16].

Cell-based therapies have shown neuroprotective and tissue-repair potential in preclinical models of HD [63]. However, only one prior clinical trial in HD has evaluated cell therapy: a Phase II study using fetal ganglionic eminence cells via intracerebral grafting. The trial found no clinical benefit and reported issues, including unchanged motor decline, graft rejection, and a high rate of procedural adverse events [50]. In contrast, NestaCell®, derived from hDPSCs, offered superior outcomes and several advantages, including non-invasive cell collection, standardised manufacturing processes, and the convenience of intravenous administration.

Although the study was conducted at a single site with a limited number of participants, these features are common in early-phase trials for rare diseases. In addition to the small sample size and baseline imbalances, other limitations should be acknowledged. Suboptimal MRI quality prevented meaningful volumetric analyses in many cases, and neurofilament light chain (NfL) data, an emerging biomarker for neurodegeneration, were not collected. Furthermore, the COVID-19 pandemic disrupted recruitment and follow-up schedules, potentially introducing additional variability.

Despite these constraints, NestaCell® demonstrated statistically significant improvements in core clinical measures, including UHDRS-TMS and TFC. Given the progressive nature of HD, where patients typically decline by ~ 3 points per year on the UHDRS-TMS [54], even disease stabilisation may be considered clinically meaningful. The current findings justify further investigation in a larger, multicentre Phase III trial to validate efficacy, monitor long-term safety, and explore biomarker correlations.

Conclusions

In summary, this study demonstrated that NestaCell® has the potential to offer a meaningful therapeutic benefit for patients with HD. Given its good safety profile, promising efficacy data, and potential disease-modifying effects, NestaCell® may represent a novel approach to treating a disease that remains challenging to manage. Future studies with a larger cohort are warranted to confirm these findings.

Abbreviations

BA	Behavioural assessment
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
CA	Cognitive assessment
CAG	Cytosine-adenine-guanine
CIBIS	Clinician interview-based impression of severity
CNS	Central nervous system
D2R	Dopamine receptor type 2
DARPP-32	Dopamine- and cAMP-regulated neuronal phosphoprotein
DTI	Diffusion tensor imaging
ECG	Electrocardiogram
EPA	Eicosapentaenoic acid
FA	Functional assessment
FS	FreeSurfer
HAM-D	Hamilton depression rating scale
HD	Huntington disease
HTT	Huntingtin gene
hDPSCs	Human dental pulp stem cells
ICF	Informed consent form
ITT	Intention-to treat
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
PCR	Polymerase chain reaction
SAE	Serious adverse event
TEAE	Treatment-emergent adverse events
TFC	Total functional capacity
TMS	Total motor score
UHDRS	Unified Huntington's disease rating scale

Supplementary Information

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Additional file 1

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Author contributions
JMSF, LF, IK conceived and designed research; JMSF & LF collected data and conducted research; EP, LHY & IK analysed and interpreted data; EP & LHY wrote the initial paper; JMSF, CVW, LF & IK revised the paper; JMSF, EP, CVW, LHY, LF & IK had primary responsibility for final content. All authors have read and approved the manuscript. Authors' relationships and activities: All authors declare that no relationships or activities might bias their work or be perceived as biased.

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Data availability
The datasets generated and analysed during the present study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol "*Avaliação da Dose-Resposta do Produto Investigacional Cellavita HD após Aplicação Intravenosa em Participantes com Doença de Huntington*" was first approved by the ethical committee of *Faculdade de Medicina de Jundiai* (Approval number: 52375916.1.0000.5412) on 4, February 2016, conformed to the ICH-E6 guidelines. The last amendment was approved on December 26, 2019. All participants provided written informed consent before recruitment. This study was registered on clinicaltrials.gov (Identifier: NCT03252535). The investigational product evaluated in this study was originally developed under the name Cellavita HD. In March 2020, it was registered under the trademark NestaCell®. Both names refer to the same cell-based product. In this manuscript, the current designation NestaCell® is used consistently; however, the original name Cellavita HD is retained when citing regulatory documents—such as the ethics committee approval—where that designation was originally employed.

Consent for publication
Written informed consent was obtained from all patients, all authors, and the Sponsor for the publication of this report.

Competing interests
EP & CVW are employees of the study sponsor. IK & CVW are listed as inventors on the NestaCell® patent and hold associated commercial rights. JMSF, LF & LHY declare no competing interests.

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