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Two years efficacy and safety outcomes of using allogeneic, pooled mesenchymal stromal cells for osteoarthritis of knee in a double-blind randomized placebo-controlled phase 3 study

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ABSTRACT

Objective: The aim of this study was to assess whether allogeneic cultured, pooled, bone marrow derived mesenchymal stromal cells (BMMSCs), has potential to impact progression of osteoarthritis (OA).
Method: Randomized, double blind, multicentric, placebo-controlled trial to assess efficacy and safety of BMMSCs in Grade 2 and 3 OA of knee. 146 patients were randomized, 73 patients each received either BMMSCs (25 million cells) or placebo followed by 20 mg HA. The primary end point was evaluation of WOMAC Composite Index and secondary end points were WOMAC sub-scores, VAS, magnetic resonance (MR) assessment (T2 mapping and cartilage volume).
Results: 58 patients from BMMSC arm and 60 patients from placebo arm completed 24 months follow-up. At 24 months follow up, WOMAC composite index and WOMAC sub scores showed significant improvements in cell arm as compared to placebo ($p < 0.0001$); T2 mapping showed there is no worsening of the cartilage in the medial femoral tibial compartment in BMMSC arm whereas placebo arm shows gradual worsening ($p < 0.0001$). Cartilage volume increased in BMMSC arm. At Day 90 & 730, Urinary C – terminal cross linked telopeptide of type II collagen significantly decreased in the cell arm and increased in the placebo arm (p-value<0.0001). 5 AEs

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were possibly related to the study drug and were local site administration effects. By 24 months follow-up, 4 patients in the placebo group underwent TKR versus 1 patient in the BMMSC arm.
Conclusions: This study demonstrates that BMMSC's is safe and effective for the treatment of grade 2 & 3 OA of knee.
Ctri registration: CTRI/2018/09/015785 [Registered on: September 20, 2018]

1. Introduction

Osteoarthritis is a chronic, progressive, degenerative condition with limited therapy options, and it imposes substantial economic burden on the individual and the health care systems. In India, prevalence of OA increased from 23.46 million in 1990 to 62.35 million in 2019 [1]. OA of the knee joints are 85 % of the cases [2].

In OA there is an imbalance in synthesis and release of various pro-inflammatory cytokines (IL-1α, IL-1β and tumor necrosis factor (TNF-α)) affecting cartilage metabolism and homeostasis leading to degradation of cartilage. Gradual increase in interferon γ in the joint worsens inflammation, leading to degradation of proteoglycans such as sulfated glycosaminoglycans [3,4].

Mild forms of OA are managed conservatively [5] and surgical intervention may be required in severe OA which includes total knee replacement (TKR) or corrective osteotomy. Lately, the field is shifting towards use of orthobiologics such as platelet rich plasma or cell therapy which offers pain relief ("symptom - modifying"), decreases cartilage degradation and possibly help in cartilage regeneration ("disease - modifying") [6].

Mesenchymal stromal cells (MSCs) due to their immunomodulatory and anti-inflammatory properties may be of value in OA joint regardless of its regenerative capacity [7]. MSCs injected locally in the OA microenvironment have the potential to stimulate resident chondroprogenitor cells and promote its differentiation to mature chondrocytes mediated by secretion of various factors (BMP and TGFβ1) [8].

In our previously published, one year follow up data of this phase 3, randomized, double blind, multicenter, placebo-controlled study we have shown that allogeneic, cultured and pooled bone marrow derived mesenchymal stromal cells (BMMSCs) provide short term clinical improvement in grade 2 and 3 knee OA. This intervention provided relief of pain and stiffness and improved physical function at 12 months follow up [9]. The purpose of this study is to report whether efficacy and safety continues at two years follow up, to highlight any difference in 12 and 24 months follow-up data on safety and efficacy parameters after a single intra-articular injection of BMMSCs and to evaluate whether MRI shows any evidence of chondro-protective or chondro-regenerative ability in mild to moderate OA.

2. Methods

2.1. Study design

This prospective phase 3 study was designed as a randomized, double blind, multi-centre, placebo – controlled study assessing the efficacy and safety of intra-articular injection of allograft BMMSCs in symptomatic grade 2 and 3 OA (based on the Kellgren and Lawrence radiographic criteria). The protocol was approved by the Indian FDA and institutional ethics committees of all 15 participating hospitals. The study was conducted as per the International Council for Harmonization Good Clinical Practice guidelines, principles of the Declaration of Helsinki, Schedule Y of the 1945 Drugs and Cosmetic Act, New Drugs and Clinical Trial Rules 2019 by Indian FDA and Ethical Guidelines for Biomedical Research on Human Participants, ICMR 2006. An independent data safety monitoring board was constituted comprising of drug safety physicians and expert in the therapeutic area to monitor the safety data during the study. The study was started on January 2019, and two years follow up of the patients were completed in July 2022.

A total of 146 patients were enrolled after informed consent. The CONSORT (Consolidated Standards of Reporting Trials) flowchart is given in Fig. 1. Seventy-three patients received 25 million BMMSC's in 2 ml suspension (1 ml each of CryoStor CS5 and PlasmaLyte-A) followed by 2 ml of mid – molecular hyaluronic acid (20 mg/2 ml). The placebo arm (n = 73) received 2 ml of placebo (CryoStor CS5 + PlasmaLyte-A) followed by hyaluronic acid. Injections were ultrasound-guided to confirm intra-articular placement and prepared in blinded syringes. Patients selected for participation were assigned randomly to 1:1 ratio of treatment/placebo arm and randomization was stratified by OA grade (Grade 2 and Grade 3) using block randomization (block size of 4), with codes generated using PROC PLAN in SAS (version 9.2 or later). The random allocation sequence was generated by unblinded, independent statistician of a CRO. In the study, participating patients, investigators, outcome assessors, data analysts and medical monitors were blinded after assignment to intervention. The detailed inclusion and exclusion criteria have been included in Table 1. During the study period the patients randomized were prohibited to use any other stem cell therapy, knee braces, intra-articular steroids, acupuncture therapy, opioids or pain patches, HA and platelet rich plasma. Patients were encouraged to do quadriceps strengthening exercises and to avoid squatting and sitting cross leg. Patients were followed up at 1 week, and 1, 3, 6, 12, 18 and 24 months after injection. The study was registered prospectively on the National Institutes of Health and Clinical Trials Registry-India Web site (CTRI/2018/09/015785).

2.2. Preparation and release criteria for BMMSCs

The methodology of isolating bone marrow, preparation of a master cells bank, working cell bank (WCB), and preparation of BMMCSs and its release criteria has been published previously [9–13]. Briefly, 60 ml of bone marrow aspirate was diluted (1:1) with knockout DMEM (Thermo Fisher Scientific Life Sciences, Waltham, MA, http://www.thermofisher.com), and was centrifuged at 1,800g for 10 min to remove the anticoagulant. Bone marrow mononuclear cells were isolated by the density gradient centrifugation (1.077 g/ml) method. BMMSCs were isolated by plastic adherence from the donor's Bone marrow mononuclear cells and cultured until passage 1. A donor master cell bank constituted from MSCs from an individual BM sample was created and maintained under cryopreserved conditions. Subsequently, a WCB was prepared by combining MSCs from three donors and cryopreserved for manufacturing BMMSCs and further expanding the pooled WCB for additional passages for manufacturing BMMSCs (U.S. patent number 8956862, dated February 17, 2015). For the work described in this article, pooled BMMSCs from three different individual donors were cultured, harvested, and characterized at passage 5 and cryopreserved in liquid nitrogen as the final product [14]. BMMCSs was assessed for identity, purity, impurity, potency, sterility, and genetic stability using prior described methods to meet manufacturer specification before releasing for the study [9]. The process flowchart of release criteria of BMMSC and its production and are given in Supplementary Table 1 and Fig. 1. The long-term stability of product (25 million cells/vial) was assessed over 36 months following ICH guidelines. Stability was monitored by evaluating viable cell count, viability, purity, and TSP-2 secretion (potency marker). Cell count and viability were measured using the Vi-Cell XR Analyzer (Beckman Coulter), while immunophenotyping for positive (CD105, CD73, CD90) and negative markers (CD34, CD45) was performed via flow cytometry. TSP-2 levels were quantified using the Quantikine ELISA kit. Impurities such as residual BSA and trypsin were analyzed using ELISA.

A short-term hold time study was conducted by thawing three vials, reconstituting with CryoStor® CS5, and storing at room temperature for

up to 120 min. Cell count and viability were assessed at 0, 15, 30, 60, 90, and 120 min.

2.3. Study end points

The primary endpoint was the change in the total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score at 12 months (measured using visual analogue scale (VAS) of 0–100 mm). Secondary endpoints included changes in WOMAC sub-scores (pain, stiffness, physical function) at 24 months, patient-reported pain using the VAS, magnetic resonance (MR) assessment (T2 mapping and cartilage volume), and biomarker levels of urinary C – terminal cross linked telopeptide of type II collagen (CTX-II) and serum IL-10. Safety was evaluated based on adverse events (AEs), treatment-emergent AEs (TEAEs), and clinical laboratory results.

2.4. MRI acquisition and analysis

MRI of the knee was performed in all patients at baseline, 6 month, 12 months and 24 months follow up post-injection. Patients were scanned in the feet first supine position on a 3.0-T system with a dedicated knee coil to optimize signal reception. Magnetic resonance (MR) sequences were as follows: proton density (PD) – FS Axial (FOV 120 × 120 mm; TR 4530 ms; TE 22 ms; slice thickness 3 mm; flip angle: 90°); PD – FS Sagittal & PD-FS Coronal (FOV 120 × 120 mm; TR 4707 ms; TE 22 ms; slice thickness 3 mm; flip angle: 90°); T2 weighted sagittal (FOV 120 × 120 mm; TR 3000 ms; TE 80 ms; slice thickness 3.0 mm; flip angle: 90°) and 3D Fast Field Echo sagittal (FOV 160 × 170 mm; TR 23 ms; TE 12 ms; slice thickness 1.0 mm). Regions of interest for cartilage T2 mapping was performed on serial sagittal images (24 slices) on a standard MR workstation (Philips Intellispace, Best, Netherlands) using a standard MR cartilage assessment tool available on this workstation. T2 mapping calculated the T2 relaxation times of the articular cartilage in 6 predefined sub-compartments which were further subdivided into 3 layers (superficial, deep and intermediate) and the relaxation time was calculated in each subdivision. The results summated, and an average value for T2 mapping in millisecond (ms) calculated. Lower T2 values signifies healthier articular cartilage. Cartilage volume was calculated manually using two separate 5 mm 3 – dimensional sagittal images in maximum intensity projection, one at the level of the midportion of the medial and another at the level of the midportion of the lateral femoro-tibial compartments and reported as mm^3. MRI assessments were performed by a single radiologist blinded to all the parameters at all time-points.

2.5. Biomarkers

Biomarkers of interest were measured using ELISAs, as per manufacturer's recommendations, in (a) urine CTX-II; Immunodiagnostic Systems Holdings PLC; (b) serum IL-10; ELK Biotechnology CO Ltd.

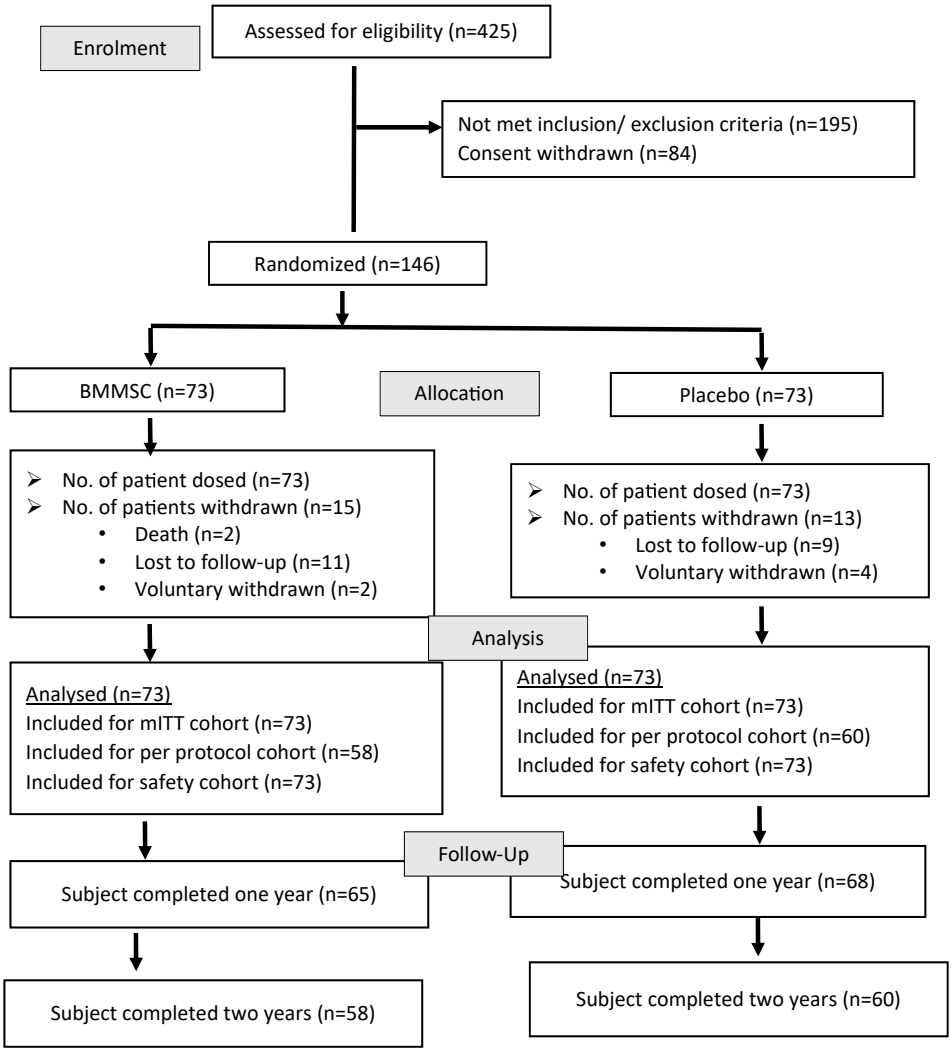


Fig. 1. CONSORT flow chart showing the number of patients screened, randomized, followed up and analyzed.

Table 1
Subject eligibility criteria.

Inclusion criteria:

1. Males and females in the age range of 40–65 years (both inclusive)
2. BMI <30 kg/m2
3. History of primary osteoarthritis of the knee characterized by pain which requires analgesic intake
4. Radiological criteria: X-ray knee joint showing radiographic evidence of grade 2 to 3 osteoarthritis based on the Kellgren and Lawrence radiographic criteria
5. Self-reported difficulty in at least one of the following activities attributed to knee pain: lifting and carrying groceries, walking 400 m, getting in and out of a chair, getting up from squatting or cross leg position or going up and down stairs
6. Patient on analgesic medication for OA for 6 weeks based on Investigator feedback
7. Willing to refrain from any other stem cell treatment for 2 years during the study.
8. Female patients of childbearing age who were willing to use accepted methods of contraception during the study
9. Patients who were willing to provide written informed consent including audio-video consent

Exclusion criteria:

1. X-ray (evaluated by central radiologist) showing any of the following: a) Grade 0, 1 and 4 osteoarthritis based on the Kellgren and Lawrence radiographic criteria
   b) Subchondral sclerosis (involving both medial and lateral femorotibial compartments of knee joints)
2. MRI knee showing any of the following: a) ACL/PCL tears (complete tears will be excluded)
   b) Meniscal tears: Grade 3 tears - defined as increased signal intensity on PD sequences extending up to either articular surface. It also includes root tear but excludes RAMP tear. Grade 3 complete root tears will only be excluded.
   c) Patients with exclusive patello-femoral arthritis
   d) Grade 0, 1 and 4 arthritis as per the proposed grading on MRI
3. Prior or ongoing medical conditions (e.g., concomitant illness, psychiatric condition), alcoholism, smoking, tobacco chewing or drug abuse, medical history, physical findings, ECG findings or laboratory abnormality that in the investigator's opinion could adversely affect the safety of the subject, makes it unlikely that the course of treatment or follow-up would be completed, or could impair the assessment of study results.
4. History of surgery or major trauma to the study joint
5. Arthroscopy on the study joint in the previous 12 months
6. Signs of active study joint inflammation including redness, warmth, and/or, if qualifying with osteoarthritis of the knee, a large, bulging effusion of the study knee joint with the loss of normal contour of the joint at the screening visit or at the baseline examination
7. Acute exacerbations of the study joint in the past 6 weeks
8. Patients who had received intra-articular steroids or hyaluronan within the last 3 months
9. Patients who had taken any stem cell treatment in the past by any route of administration
10. Infections in or around the study knee
11. Patients awaiting a replacement of knee or hip joint
12. Patients with other conditions that cause pain in the knee joint
13. Patients with gross deformity (varus by x-ray of the knee or flexion deformity >10° by gonometer) of the knee joint based on PI judgment
14. Significantly incapacitated or disabled and would be categorized as ACR Functional Class IV (largely or wholly incapacitated), or unable to walk without assistive devices.
15. Patients with any secondary causes of arthritis e.g., rheumatoid arthritis, systemic lupus erythematous, ulcerative colitis, psoriasis, rheumatic or inflammatory disease
16. Patients with BMI ≥30 kg/m2
17. Positive hepatitis B surface antigen, hepatitis C antibody test, Anti human immunodeficiency virus – I & II (HIV – I & II) antibody test, TPHA or CMV (IgM)
18. History of Bleeding disorders
19. Known hypersensitivity to hyaluronan products or animal sera or constituents of IMP
20. Pregnant, breast-feeding, planned pregnancy during the study, or women of childbearing potential not using adequate contraception

Samples were collected at baseline and at 7, 30, 90, 180, 365, 540 and 730 days after injection.

2.6. Statistical analysis

The detailed statistical analysis plan using SAS package (version 9.4) and sample size calculation was published earlier [9]. Three cohorts were considered for the analysis: The modified intention-to-treat (mITT), per protocol and safety cohort. Analysis for primary efficacy endpoints using the mITT cohort was the primary approach for analysis. The secondary efficacy analysis was performed using the mITT cohort. Sample size calculation input was taken based on the change of WOMAC composite index score from baseline to 6 months for cell and placebo arm from the completed phase 2 study [12]. To establish superiority of 25 million dose of stempeucel® when compared with placebo with 90 % power, alpha of 0.05, two-sided test was applied, and the study required 51 evaluable patients per group. To account for drop-out rate of 30 %, the study required 73 evaluable patients per group with a total of 146 patients in the study. The efficacy analyses were conducted using the mITT cohort, and the safety evaluations using the safety cohort (all patients randomized and received the study drug). Data were assessed for normality (Shapiro-Wilk test), followed by t-tests or non-parametric Mann Whitney test/Signed Ranked tests as appropriate. AEs and TEAEs were summarized by frequency, severity, and causality as per MedDRA Primary System Organ Class and Preferred Terms. All AEs were summarized in terms of severity (mild, moderate, severe), action taken, relatedness, expectedness and outcome. Certain secondary efficacy endpoints and biomarkers were analyzed using a generalized estimating equation (GEE) model with longitudinal analysis [15,16]. The Last Observation Carried Forward method was not used to handle missing data in the analysis of efficacy parameters.

3. Results

3.1. Long term stability and hold - time study

Allogeneic BMSCs cryopreserved in 1 mL of CryoStor® CS5, maintained stability under cryogenic storage (−185 °C to −196 °C) over 36 months. All batches consistently met the specification of ≥20 million viable cells per vial, with viability >80 % (Fig. 2: A, B). Surface marker expression remained within acceptance criteria: CD 105, CD 90 and CD 73 ≥ 90 %, CD45 and CD34 ≤ 10 %, confirming phenotypic stability. TSP-2 levels were ≥10 ng/million cells at all time points till 36 months, demonstrating preserved potency (Fig. 2C). Residual BSA and trypsin levels was below 50 ng/mL and 30 ng/mL, respectively and were within the established release limits (Fig. 2 D, E).

A hold time study was also conducted to evaluate product stability after thawing and reconstitution. Results demonstrated stable viability, and cell counts across all time points (Fig. 2 F, G), confirming that CS5 effectively preserves cell viability for up to 120 min during post-thaw handling.

3.2. Clinical outcomes

Baseline characteristics were balanced between arms, and baseline WOMAC and VAS scores demonstrated moderate to severe pain

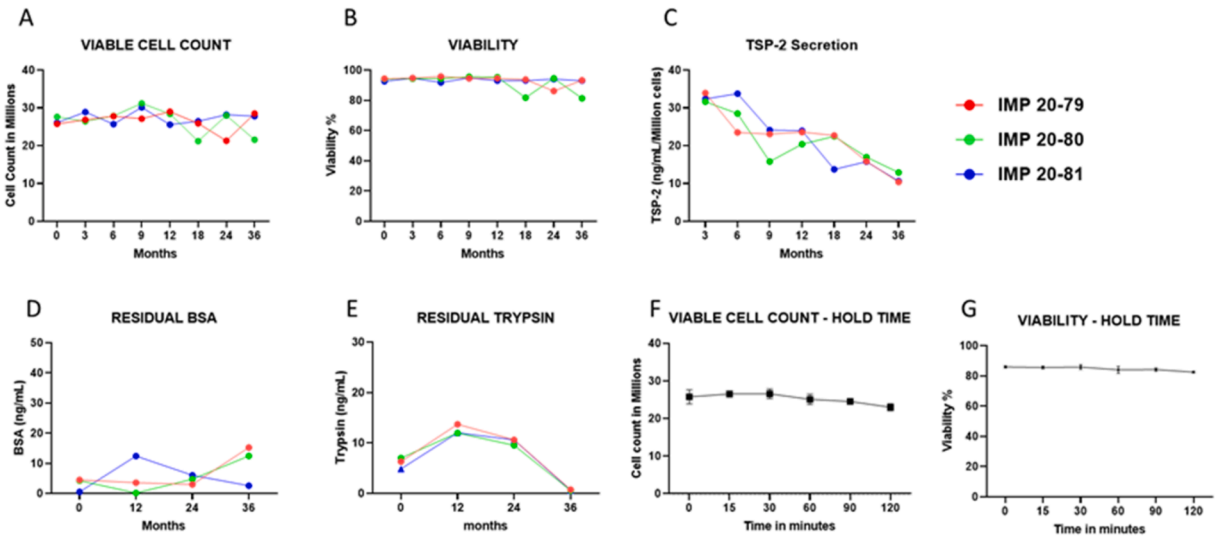


Fig. 2. Long term stability and hold time study of BMMSC. Fig A to C: Viable cell count, cell viability, and TSP2 secretion levels for three batches of BMMSC assessed up to the 36-month time point. Fig D to E: Impurity analysis showing residual BSA and trypsin levels remained below the specified release criteria. Fig F to G: Hold-time study demonstrating a viable cell count of ≥20 million and cell viability >80 %.

symptoms [9]. The summary of patient demographics and disposition at baseline is given in Table 2. At 24 months, 58 patients in the BMMSC arm and 60 in the placebo arm completed follow-up.

WOMAC total score (mm), showed significant improvements in BMMSC as compared to placebo arm at month 12 (mean difference: −632.74; 95 % CI [−791.57 to −473.91], P < 0.0001; percentage difference: −45.44 %; 95 % CI [−55.88 to −34.99]), and at month 24 follow-up (mean difference: −952.43; 95 % CI (−1132.82 to −772.04)), P < 0.0001; percentage difference: −71.43 %; 95 % CI [−84.41 to −58.44]) (Fig. 3 (A, B), Supplementary Table 2). A similar trend was seen in all WOMAC sub scores (WOMAC pain decreased by −73.12 %; (p < 0.0001), 95 % CI (−86.56 to −59.68) WOMAC stiffness decreased by −77.25 % (p < 0.0001), 95 % CI (−96.54 to −57.95) and WOMCA physical function decreased by −71.46 % (p < 0.0001), 95 % CI (−84.81 to −58.10) compared to placebo arm at 2 years follow up (Fig. 3 (C, D, E). Fig. 3 (F) presents the heatmap for WOMAC total score at two years follow up showing higher frequency of patients in cell arm having a reduction in WOMAC total score as compared to the placebo. Overall, 74.0 % patients in cell arm and 17.8 % patients in placebo showed 20 %–100 % improvement in WOMAC total score (Fig. 3 (G)). VAS score (mm), showed significant improvements in cell arm as compared to placebo at month 12 (mean difference: −41.33; 95 % CI [−51.69 to −30.98], P < 0.0001; percentage difference: −41.33 %; 95 % CI [−51.69 to −30.98]), and at 24 months follow up (mean difference: −64.04; 95 % CI [−75.99 to −52.09], P < 0.0001; percentage difference: −64.04 %; 95 % CI [−75.99 to −52.09]) (Fig. 3 (H)). Compared to 12 months at 24 months follow up both the WOMAC total score, sub scores and VAS showed consistent improvement (WOMAC total score improved from −45.44 % to −71.43 %; VAS improved from −41.33 % to −64.04 %).

The grade wise change in WOMAC total score was also evaluated and the change from baseline for KL grade II at month 6 (mean difference −484.4; percentage change −35.1 %), month 12 (mean difference −651.2; percentage change −47.7), month 24 (mean difference – 858.4; percentage change −64.4) as compared to KL grade III at month 6 (mean difference −557.0; percentage change −34.8 %), month 12 (mean difference −628.9; percentage change −40.3), month 24 (mean difference – 858.4; percentage change −56.8). As both the mean and percentage changes are comparable at each visit, hence it is concluded that BMMSCs are equally effective in both KL grades, and no relationship effect is observed with respect to grade of OA.

3.3. MRI outcomes: T2 mapping and cartilage volume

The average cartilage scores/T2 mapping scores in medial femorotibial compartment (femoral condyle) in the cell arm were maintained within normal range (≤39 ms), baseline (38.1 ± 6.57), month 12 (38.8 ± 6.93) and month 24 (36.3 ± 5.16). In the placebo arm the T2 relaxation time values were above normal range, baseline (41 ± 6.42), month 12 (42 ± 27.44), and month 24 (40 ± 4.37) and the change from baseline was significant (p < 0.0001) at month 12 and month 24 follow up (Fig. 4). At day 365, the change from baseline average cartilage score increased by 0.2 ± 5.46 ms and 2.2 ± 28.89 ms in BMMSC and placebo arm, respectively and at day 730, the change from baseline the score decreased by −1.1 ± 6.13 ms and increased by 1.0 ± 4.42 ms in BMMSC and placebo arm respectively. However, the difference between the arms was not significant at any time point. The lateral femorotibial compartment did not show any differences in either of the arms. At 24 months follow up it was seen that T2 relaxation time was similar as at 12 months follow up (within normal range) showing evidence of chondroprotection as compared to placebo arm which had persistent abnormal values at both timepoints.

Cartilage volume was evaluated by the GEE method and showed that the cell arm had an increase in an average volume of 34.07 mm^3 on month 12 and 49.81 mm^3 at month 24 in the femoro-tibial compartment as compared to placebo arm irrespective of time, which wasstatistically not significant.

3.4. Biomarkers: CTX – II and IL-10

The mean change in CTX – II (urine) estimation and IL-10 from baseline to month 24 follow up is shown in Table 3. The difference between the two groups was not significant. Additional analysis for CTX – II using GEE method in the cell arm showed a decrease in values (month 12 (−7.79 ng/mmol); month 24 (−0.04 ng/mol) as compared to placebo arm irrespective of time which was not significant.

3.5. Safety profile

A total of 135 treatment-emergent adverse events (TEAEs) were reported in 59 patients—64 TEAEs in 26 patients (BMMSC arm) and 71 TEAEs in 33 patients (placebo) (Table 4). Five AEs in four patients (three

Table 2
Summary of Patient disposition & demographic characteristics (safety cohort).

Variable	Statistics	BMMSC N = 73 n(%)	Placebo N = 73 n(%)	Total N = 146 n(%)	p-value
Number of patients enrolled		73 (100)	73 (100)	146 (100)	NA
Number of patients dosed		73 (100)	73 (100)	146 (100)	NA
Number of patients completed one year duration of study		65 (89.0)	68 (93.2)	133 (91.1)	NA
Number of patients completed two-year duration of study		58 (79.5)	60 (82.2)	118 (80.8)	NA
Age (years)	n	73	73	146	0.074[a]
	Mean	51.6	53.6	52.6	
	SD	6.77	6.78	6.82	
	Min	40.0	40.0	40.0	
	Median	51.0	53.0	52.0	
	Max	64.0	65.0	65.0	
Height (cm)	n	73	73	146	0.336[a]
	Mean	159.0	157.8	158.4	
	SD	6.89	7.74	7.33	
	Min	144.0	140.0	140.0	
	Median	158.0	158.0	158.0	
	Max	174.0	174.0	174.0	
Weight (kg)	n	73	73	146	0.227[a]
	Mean	67.1	65.4	66.2	
	SD	8.41	9.05	8.75	
	Min	48.7	43.1	43.1	
	Median	68.0	66.0	66.5	
	Max	89.0	85.0	89.0	
BMI (kg/m^2)	n	73	73	146	0.514[a]
	Mean	26.5	26.2	26.4	
	SD	2.58	2.99	2.79	
	Min	20.8	18.9	18.9	
	Median	26.5	26.6	26.6	
	Max	29.8	30.0	30.0	
Sex	Female	47 (64.4)	51 (69.9)	98 (67.1)	0.481[b]
	Male	26 (35.6)	22 (30.1)	48 (32.9)	
Race	Asian	73 (100.0)	73 (100.0)	146 (100.0)	NA
	Caucasian	0	0	0	
	African	0	0	0	
	Others	0	0	0	
Grade wise patients	Grade II	36	38	74	0.7406
	Grade III	37	35	72	

N = Total number of patients in the specified treatment group, n = Total number of patients in a given category.
[a] p-value calculated using T-test.
[b] p-value calculated using Chi-square test.

in cell arm, one in placebo) were considered possibly/probably related to the study drug and were injection site swelling and pain which resolved with symptomatic treatment. The most common TEAEs in the cell arm included arthralgia and pyrexia. In the placebo arm, the most common were pyrexia, dyslipidemia, and hyponatremia. Eleven serious adverse events (SAEs) occurred in nine patients—seven in cell arm, four in placebo—but were unrelated to the study drug. The SAEs recorded in the BMMSC arm were – intestinal obstruction (2 events), corona virus infection (3 events), gastroenteritis, fever with thrombocytopenia. The SAEs recorded in placebo arm were – corona virus infection (2 events), transient ischemic attack and hypertension. Two COVID-19-related deaths occurred in the cell arm as study was conducted during the COVID pandemic. During the two-year follow-up, five patients had TKR—four in the placebo arm and one in the BMMSC arm.

4. Discussion

The main findings in this 2-year follow up study are that allogeneic bone marrow derived, pooled MSCs are safe and provide sustained improvement in pain, stiffness and physical function of the knee in symptomatic mid-grade OA. Further using analytical tools including MR of the knee joint (T2 mapping and cartilage volume) and biomarkers (CTX – II and IL-10) there was evidence of maintained cartilage collagen content, hydration and evidence of chondro-preservation and/or chondro-protection. These findings along with reduced biomarkers of chondral degeneration are consistent with the observed sustained benefit in clinical outcome measures.

Pain is a key symptom of OA and a primary reason patients seek treatment. It is typically measured using patient-reported outcome measures such as WOMAC Pain and VAS scales. PROM selection depends on factors such as ease of use, cost, and assay sensitivity, which is the ability to distinguish between effective and placebo treatments [17]. In a meta-analysis of 135 trials, VAS showed the highest sensitivity, outperforming multi-item tools like WOMAC. VAS, a single-question PROM, had a 42 % higher effect size than WOMAC Pain [18]. In this study, WOMAC Pain decreased by 73 % and VAS by 64 % over two years versus placebo. VAS measures average 24-h pain, while WOMAC evaluates both weight-bearing and non-weight-bearing pain, hence co-relation of the two may not be possible. A 1-point change in VAS correlated with a 0.57-point change in WOMAC pain, particularly reflecting weight-bearing pain [19].

TKR is often the last resort for OA patients unresponsive to conservative treatment. However, return to work (RTW) post-TKR can be limited, especially in physically demanding jobs [20–22]. Patients with higher physical demanding jobs have been reported with poor RTW outcomes with an odds ratio of 3.3 [23,24] versus patients in nonmanual work have an observed 1.5 to 2.6 increased probability of successful RTW following TKR [25]. Hence the ability to delay or avoid TKA is advantageous in patients with mid stage disease. In this study, all 5 patients who underwent TKR were in Grade 3 KL radiographic criteria. Of these, 4 patients were in the placebo arm and 1 in the BMSSC arm, suggesting MSC therapy may delay or prevent TKR, lowering both direct and indirect healthcare costs [26].

T2 mapping is a non-invasive imaging technique used to assess cartilage degeneration in OA and monitor regeneration after stem cell

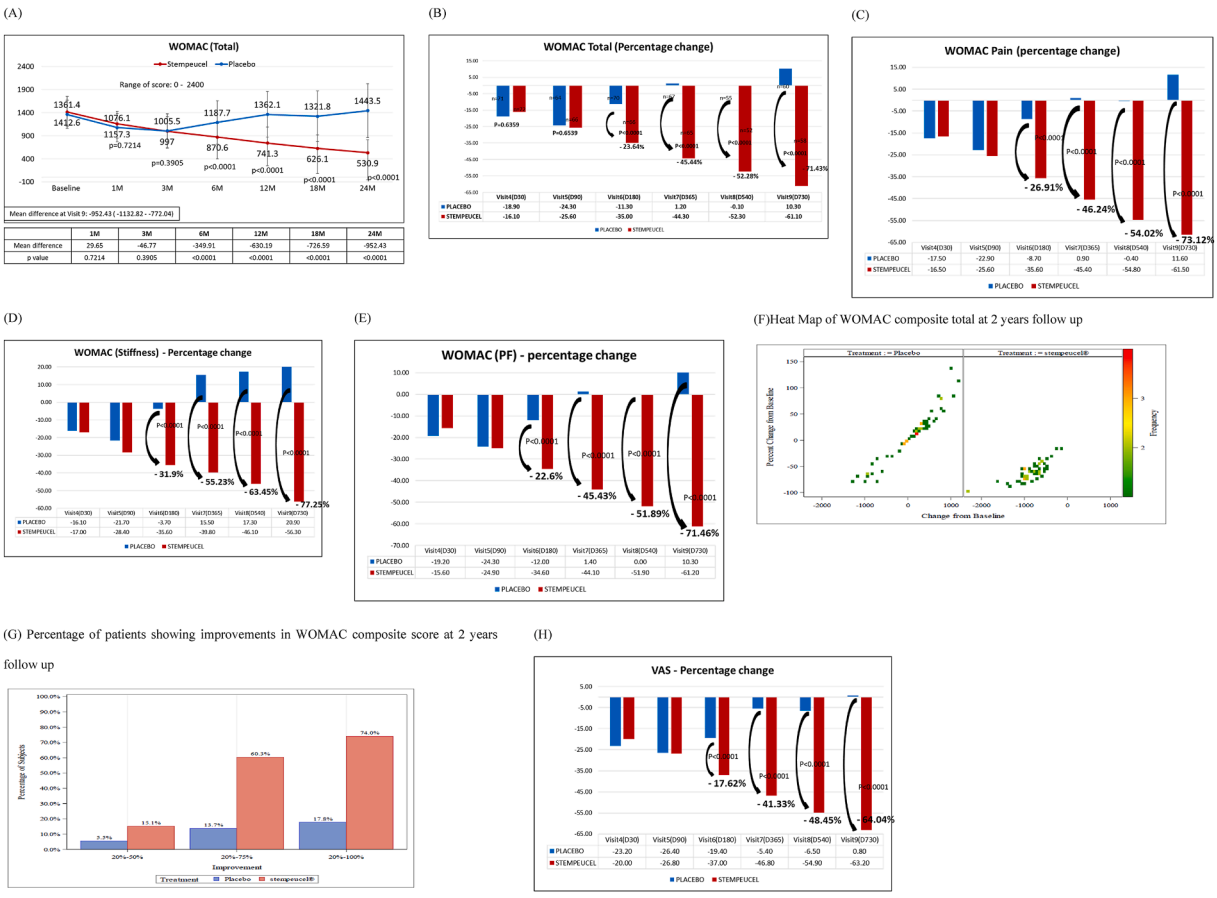


Fig. 3. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total scores and subscore & T2 mapping relaxation time score. (A) Mean values of the WOMAC score over time (B) Percentage change in the WOMAC total score over time (C) Percentage change of WOMAC pain score over time (D) Percentage change of WOMAC stiffness score over time (E) Percentage change of WOMAC physical function score over time (F) Heat Map of WOMAC total score at 2 years follow up (G) Percentage of patients showing improvements in WOMAC composite score at 2 years follow up (H) Percentage change of VAS score over time.

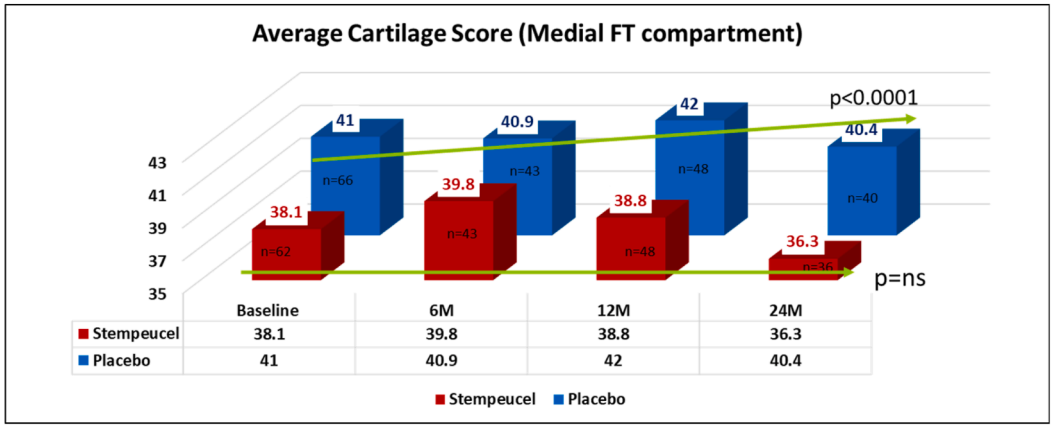


Fig. 4. T2 mapping showing average cartilage score of Medial Femorotibial compartment (femoral condlyle) in cell and placebo arms.

therapy. It measures T2 relaxation times, which increase with cartilage damage due to loss of proteoglycans and collagen disorganization [27,28]. It has been used in previous published studies to comment on the structural outcome of cartilage regeneration techniques [29,30]. In a pilot study comparing autologous BM-MSCs (60 million) to HA (6 ml) in knee OA patients, the BM-MSC arm showed a greater T2-relaxation time reduction (38 % vs. 12 %) at 12 months, indicating chondro-regeneration [31]. Another study in Grade IV OA patients treated with arthroscopic abrasion and ADMSCs (50 million at baseline and 6 months) showed favourable T2 mapping results at 12 and 36 months, with progressive cartilage maturation reflected in improved T2 values (41.7 ms–40.0 ms) [32]. These findings are like our study which showed T2 relaxation times within normal range in the cell arm at all time points, indicating chondro-preservation or chondro-protection (30). Additionally, cartilage volume increased by 34.07 and 49.81 mm^3 at 12 and 24 months, respectively, in the BMMSC arm, supporting chondro-protection as a key mechanism of action as published earlier [33].

Table 3
Analysis of assessment of biomarkers: (IL-10[serum] & CTX-II [urine]).

Parameter	Visit	Statistics	BMMSC (N = 73)		Placebo (N = 73)		Mean difference (95 % CI)	p-value
			Actual Value	Change from baseline	Actual Value	Change from baseline		
IL-10 (serum) (pg/ml)	Baseline	n	73	–	73	–	–	–
		Mean	0.083		0.558			
		SD	0.4469		4.6058			
	Visit 3 (day 7)	n	72	72	72	72	0.09 (−1.16 - 1.34)	0.2405[b]
		Mean	0.185	0.101	0.578	0.012		
		SD	0.9122	1.0326	2.3241	5.2495		
		p-value	0.1250[a]		0.0078[a]			
	Visit 4 (day 30)	n	70	70	71	71	0.11 (−1.59 - 1.81)	0.9858[b]
		Mean	0.462	0.376	0.830	0.264		
		SD	2.0011	2.0721	4.9809	6.8977		
		p-value	0.0313[a]		0.0625[a]			
	Visit 5 (day 90)	n	66	66	63	63	0.66 (−0.45 - 1.78)	0.6137[b]
		Mean	0.415	0.323	0.305	−0.342		
		SD	1.5968	1.6238	1.1859	4.2610		
		p-value	0.0625[a]		0.0625[a]			
	Visit 6 (day 180)	n	56	56	59	59	0.48 (−0.91 - 1.87)	0.4519[b]
		Mean	0.029	−0.079	0.114	−0.562		
		SD	0.2205	0.5601	0.8749	5.2131		
		p-value	>0.9999[a]		>0.9999[a]			
	Visit 7 (day 365)	n	52	52	50	50	0.27 (−1.46 - 2.01)	0.4657[b]
		Mean	0.143	0.051	0.574	−0.223		
		SD	0.4861	0.7182	2.7152	6.2677		
		p-value	0.0625[a]		0.0156[a]			
	Visit 8 (day 540)	n	37	37	30	30	1.47 (−1.02 - 3.96)	0.1823[b]
		Mean	0.632	0.516	0.371	−0.957		
		SD	1.5881	1.7379	1.1867	7.3512		
		p-value	0.0010[a]		0.1250[a]			
	Visit 9 (day 730)	n	39	39	44	44	1.35 (−0.76 - 3.46)	1.0000[b]
		Mean	0.875	0.751	0.305	−0.601		
		SD	2.8427	2.9324	0.6604	6.0167		
		p-value	0.0005[a]		0.0002[a]			
CTX-II (urine) (ng/mmol)	Baseline	n	73	–	73	–	–	–
		Mean	462.104		417.845			
		SD	372.5276		235.2729			
	Visit 3 (day 7)	n	72	72	72	72	0.28 (−168.33–168.89)	0.7725[b]
		Mean	576.840	113.873	526.956	113.592		
		SD	597.8259	524.0595	539.3486	499.1582		
		p-value	<0.0001[a]		<0.0001[a]			
	Visit 4 (day 30)	n	70	70	71	71	−15.92 (−143.76–111.93)	0.6762[b]
		Mean	480.365	9.834	446.742	25.752		
		SD	430.4995	467.3798	301.6967	278.0614		
		p-value	<0.0001[a]		<0.0001[a]			
	Visit 5 (day 90)	n	66	66	63	63	−128.40 (−275.53–18.74)	0.1384[b]
		Mean	433.682	−44.784	510.056	83.612		
		SD	351.8456	400.9378	488.9263	443.2939		
		p-value	<0.0001[a]		<0.0001[a]			
	Visit 6 (day 180)	n	56	56	59	59	57.20 (−180.59–294.98)	0.7952[b]
		Mean	529.805	62.448	426.187	5.252		
		SD	802.5774	774.3038	517.4391	487.6463		
		p-value	<0.0001[a]		<0.0001[a]			
	Visit 7 (day 365)	n	52	52	49	49	−17.25 (−184.90–150.40)	0.9271[b]
		Mean	508.643	32.568	449.360	49.815		
		SD	371.9569	428.2594	406.3407	420.2063		
		p-value	<0.0001[a]		<0.0001[a]			
	Visit 8 (day 540)	n	37	37	30	30	−6.98 (−198.53–184.56)	0.7968[b]
		Mean	485.983	−4.413	369.438	2.572		
		SD	439.2138	486.0393	261.1506	219.8225		
		p-value	<0.0001[a]		<0.0001[a]			
	Visit 9 (day 730)	n	39	39	44	44	−52.40 (−241.99–137.19)	0.4062[b]
		Mean	480.385	−12.498	442.896	39.903		
		SD	592.4402	552.9093	266.8516	288.8805		
		p-value	<0.0001[a]		<0.0001[a]			

N = Total number of patient's in the specified treatment group.
n = Total number of patient's in a given category and treatment group.
[a] p-value calculated using Signed Rank test.
[b] p-value calculated using Mann Whitney test.

Measurements of biomarkers for cartilage degradation in urine and anti-inflammatory marker in serum can also provide useful insights into this potential mechanism of action of MSCs in effecting cartilage regeneration and repair in knee OA. Urinary CTX-II is a better-known OA biochemical marker that has achieved a superior predictive profile [34], is found to be associated with radiographic severity [35] and pain in patients with early OA [36]. Chahal et al. has shown that urinary CTX-II decreased at 12 months' time at highest dose (50 million) of

Table 4
Summary of treatment emergent adverse events.

System Organ Class (commonest Preferred Term)	BMMSC (n = 73)	Placebo (n = 73)
	Number of Events (number of patients)	Number of Events (number of patients)
Number of patients with at least one AE	64 (26)	71 (33)
Blood and Lymphatic system disorders (Anaemia)	1 (1)	3 (2)
Ear and Labyrinth Disorders (Vertigo positional)	1 (1)	0
Gastrointestinal Disorders (intestinal obstruction)	3 (2)	4 (3)
General Disorders and administration site conditions (injection site joint pain/swelling)	10 (7)	6 (5)
Infections and Infestations (Corona virus infection)	10 (7)	6 (5)
Injury, Poisoning and Procedural complications (Ligament sprain/injury)	3 (3)	1 (1)
Investigations	6 (6)	8 (5)
Metabolism and Nutrition Disorders (Dyslipidaemia, Hypercholesterolaemia)	6 (6)	9 (8)
Musculoskeletal and Connective Tissue Disorders (arthralgia, join swelling)	15 (9)	31 (17)
Neoplasms Benign, Malignant & Unspecified (including cysts and polyps) (Lipoma)	1(1)	0
Nervous system Disorders (Headache)	0	3 (3)
Respiratory, Thoracic and Mediastinal Disorder (Cough)	3 (3)	0
Skin and Subcutaneous Tissue Disorders (Lichenoid Keratosis)	2 (2)	1 (1)
Vascular Disorders (hypertension)	2 (2)	1 (1)

Data are shown as number of events (number of patients), Some patients had more than on adverse event.

BM-MSCs and using the mid dose (10 million) the levels decreased at all time points till 12 months [37]. Interestingly, in this study, the catabolic biomarker significantly decreased at month 3, 18 and 24 in the cell arm as compared to the placebo arm at these time points suggestive of a chondroprotective effect as previously reported [38] although diurnal variations in these biomarker readings preclude definitive conclusions. IL-10 is an anti-inflammatory cytokine that plays a role in the inflammatory process of OA. BMMSCs can modulate the level of this cytokine, potentially playing a therapeutic benefit by reducing inflammation and pain [39]. This study has shown significant increase from the baseline in serum IL-10 values in the cell arm at month 3, 18 and 24 as compared to the significant decrease values at the same time points in the placebo arm, thereby reducing inflammation and pain in these patients.

A prior systematic review [40] analyzed data from 1924 patients undergoing intra-articular stem cell-based injections and found a 12.3 % rate of transient AEs—mainly short-term swelling and pain at the injection site—typically resolving within a week, with no serious complications reported. Similarly, in this study, 4.1 % of patients in the cell arm experienced mild, self-limiting injection site reactions. No serious adverse events (joint infection, sepsis, neoplasm, embolism or death) were related to the study drug, supporting the safety of BM-MSC therapy.

This study had a few limitations. First, follow-up was limited to two years; longer-term data would help assess sustained benefits and safety. Second, histological analysis was not performed due to its invasive nature, despite MRI and clinical improvements. Third, MRI was assessed by a single blinded radiologist as per the accepted norms of the Indian regulators; ideally, evaluations should involve two independent blinded radiologists with third radiologist as an adjudicator. Fourth, synovial fluid cytokine analysis was not done due to ethical concerns. Finally, in future studies it would be interesting to look at the efficacy of use of newer techniques like MSC derived exosomes as it has few ethical issues, no risk of tumour formation and low immunogenicity.

5. Conclusion

Allogeneic, cultured and pooled BMMSCs are safe and effective in the treatment of grade 2 and 3 knee osteoarthritis. The intervention is simple, does not require surgery, easy to administer, provides sustained relief of pain, stiffness, improves physical function, and prevents worsening of cartilage quality and improved cartilage volume for at least 24 months follow-up.

Authors contribution

Pawan Kumar Gupta: responsible for concept and design of the work, analysis and interpretation of the data, collection and assembly of data, drafting the article, final approval of the version to be published and agreement to be accountable for all aspects of the work including taking responsibility for the integrity of the work as a whole, from inception to finished article.

Sunil Maheshwari, Joe Joseph Cherian, Vijay Goni, Arun Kumar Sharma, Sujit Kumar Tripathy, Keerthi Talari, Vivek Pandey, Parag Kantilal Sancheti, Saurabh Singh, Syamasis Bandyopadhyay, Naresh Shetty, Surendra Umesh Kamath, Purohit Sharad- Prahaldbhai and Jijy Abraham - responsible for acquisition, analysis and interpretation of the data, collection and assembly of data, reviewing the work for important intellectual content, final approval of the version to be published and agreement to be accountable for all aspects of the work.

Suresh Kannan, Nikhil N. Verma and Uday Kumar - responsible for interpretation of data, critical revision of the article for important intellectual content, final approval of the version to be published and agreement to be accountable for all aspects of the work.

Declaration of Generative AI in scientific writing

No support from AI was taken for scientific writing.

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Conflict of interest

Pawan Kumar Gupta, Jijy Abraham, Suresh Kannan and Uday Kumar are employees of Stempeutics Research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2025.100723.

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