Autologous Stem Cell Therapy for Chronic Lumbar Disc Disease; Initial Phase 2 Clinical Safety and Feasibility Data of Intradiscal Injections of Hypoxic Cultured Mesenchymal Stem Cells

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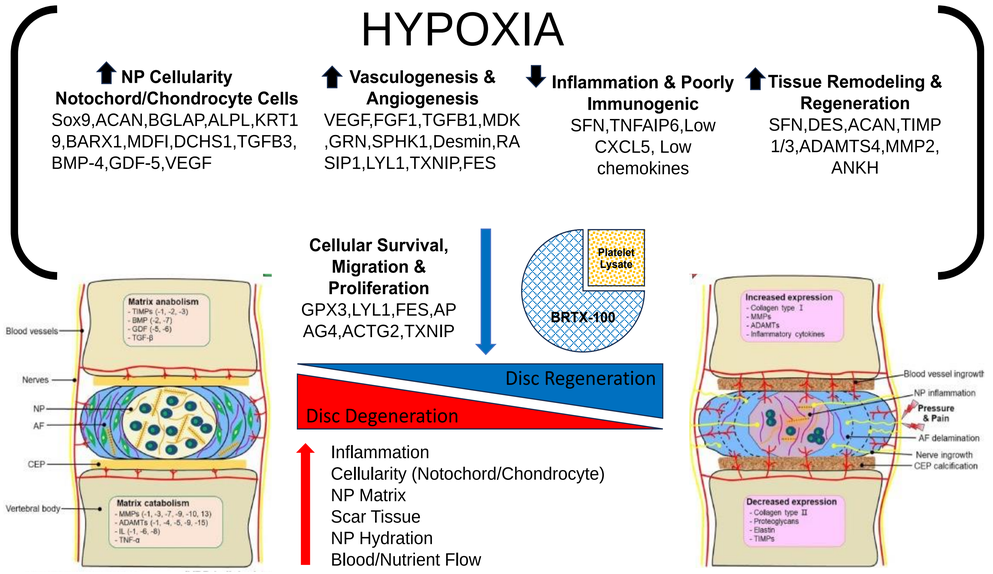
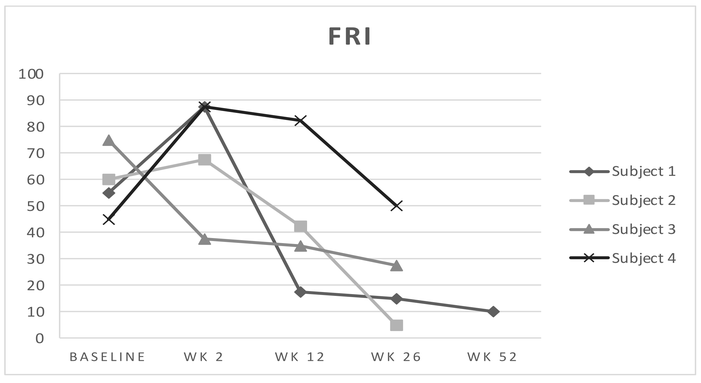
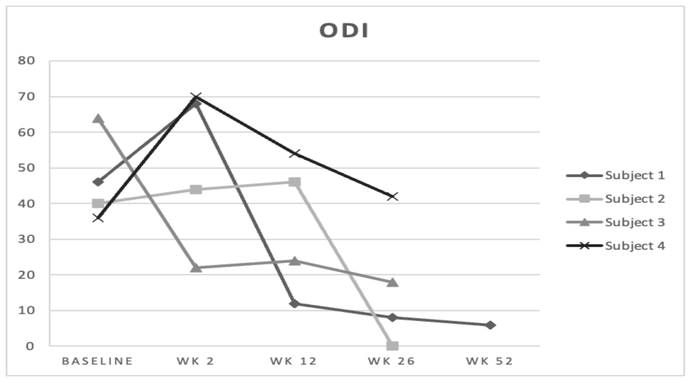
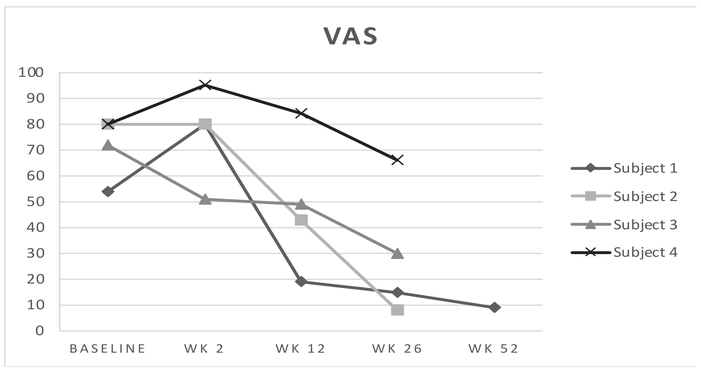
INTRODUCTION: Chronic lumbar disc disease (cLDD) is a common, often confounding problem for patients and physicians. In the United States (U.S.), at least 80% of adults experience at least one episode of lower back pain during their lifetime. Low back pain is the most common cause of disability among Americans between 45 and 65 years of age and imposes the highest economic burden on the U.S. healthcare system. The standard of care for treating cLDD involves conservative non-surgical approaches or surgical interventions that target symptomatic relief and musculoskeletal stabilization. Currently, there is no clinical therapy targeting the reversal of disc degeneration or that addresses intervertebral disc cell homeostasis. Hypoxic culturing of mesenchymal stem cells (MSCs) produces many desirable biological effects that may impact the therapeutic activity of the MSCs post-transplant into the limited nutrient, low oxygen tension microenvironment of the degenerative disc. The use of this cell-based biologic for treating cLDD is a promising therapeutic strategy, due to their *ex vivo* hypoxic engineering and known orthobiologic, immuno-modulatory and anti-inflammatory properties. Here we report early blinded clinical safety and feasibility data in subjects (n=4) treated as part of the safety run-in cohort in a Phase 2 trial to targeting cLDD (NCT04042844).

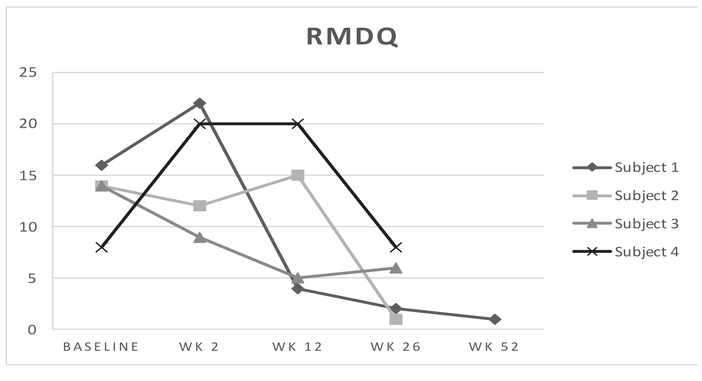
METHODS: An ongoing Phase 2, double-blind randomized, saline-controlled, multicenter study designed to evaluate the safety and efficacy of a single intradiscal injection of autologous hypoxic cultured mesenchymal stem cells (hMSCs) combined with autologous platelet lysate in subjects with single disc chronic lumbar disc disease (cLDD) with 12-month safety and efficacy and 24-month long-term safety endpoints. Approximately 99 subjects will be randomized 2:1 to the treatment or control arm. Because this is a first-in-man study a safety run-in component with a 3+3 design for the initial subjects dosed with 40×10^6 cells was performed. To accomplish this, the randomization scheme was shifted to a 3:1 allotment of intradiscal hMSCs or saline. A 14-day safety follow-up period elapsed between dosing of each of the first four (4) subjects. Dosing of each subject in the safety run-in component was reviewed by an independent medical monitor which included physical examinations, laboratory values and reported AEs/SAEs, pain and function scales used; Visual Analog Scale (VAS), Oswestry Disability Index (ODI), Short Form Survey (SF-12), Roland Morris Disability Questionnaire (RMDQ), and Functional Rating Index (FRI). At the end of dosing of all four subjects an independent medical monitor and the Data and Safety Monitoring Board (DSMB) reviewed the data in order to determine whether any AEs/SAEs were associated to dose limiting toxicities (DLTs). This study is sponsored and funded by BioRestorative Therapies and conducted under an FDA Investigational New Drug application and IRB approved.











RESULTS: All four subjects underwent successful dosing of either a 40×10^6 cell dose of hMSCs or saline at a 3:1 randomization ratio. Two subjects experienced a moderate (Grade 2) adverse event, one possibly related to the investigational product and one not related to the investigational product, and one of two subjects that experienced an AE also experienced a severe (Grade 3) adverse event not related to the investigational product and one event definitely related to the study therapy. All AEs were non-serious and related to expected increased post-procedural back pain. The two remaining subjects of the safety run-in cohort did not experience any AEs/SAEs during and post dosing of either a 40×10^6 cell dose of hMSCs or saline. DSMB review of the clinical data of the safety run-in component of this trial demonstrated that there were no AEs/SAEs that were related to dose limiting toxicities, and that the Phase 2 trial using a 40×10^6 cell dose of hMSCs could continue without any protocol changes and enter into open enrollment across all 16 sites in the U.S. Patient reported outcomes VAS, ODI, SF-12, RMDQ, and FRI used to measure pain and function were also collected during the safety run-in period.

DISCUSSION: This safety run-in component of our ongoing Phase 2 clinical trial using autologous hypoxic cultured MSCs formulated with autologous platelet lysate demonstrated for the first time that a cell dose of 40×10^6 did not result in AEs/SAEs that were related to dose limiting toxicity. Previous clinical studies have demonstrated that the harsh microenvironment of the disc could impact high cell dose viability and result in a non-efficacious or the worsening of clinical outcomes. Although this is blinded and early clinical data it is important to note that the VAS, ODI, SF-12, RMDQ, and FRI collected during the safety run-in period at week 26 and 52 post injection demonstrated a positive trend and did not show significant worsening of pain and function.