Prospective Study

Feasibility and Safety of Treatment of Painful Lumbar Degenerative Disc Disease with an Injectable Hydrogel Implant at One-year Follow-up

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Background: Degenerative disc disease (DDD) is the most common cause of chronic low back pain (CLBP). In DDD, proteoglycans within the nucleus pulposus break down and lose their ability to retain water, thereby reducing the volume of intervertebral discs and decreasing their weight-bearing capacity. Mechanical loading shifts to the annulus fibrosus, creating fissures and tears that leak crucial factors in the pain to cascade into the intradiscal space and trigger inflammation. When conventional treatments for CLBP fail, surgical options may be required. These surgeries carry risks and require months to heal. For intervertebral discs requiring augmentation, an implant in the form of an injectable, polymer-based hydrogel was developed for the percutaneous treatment of CLBP secondary to lumbar DDD. We hypothesize that the implant's hydrophilic properties will increase water retention and hydration, improve biomechanics, distribute axial loading more evenly across the annulus fibrosus, and reduce some mechanical sources of discogenic disc pain.

Objective: To evaluate the safety and efficacy of a novel, injectable hydrogel implant for the treatment of CLBP.

Study Design: Prospective, single-arm, multicenter feasibility and safety study.

Methods: Patients with CLBP lasting for longer than 6 months, DDD (modified Pfirrmann grades 4-8), competent outer annuli, numeric rating scale (NRS) scores ≥ 4, and Oswestry Disability Index (ODI) scores ≥ 30 were enrolled in 3 outpatient clinics in Canada and Colombia. The hydrogel implant, melted and equilibrated to 65°C, was injected intradiscally with a 17G needle under local anesthesia, using fluoroscopic guidance. The hydrogel cooled to approximately 42°C as it exited the needle directly into the nucleus. Patients were discharged that day. Clinical assessments included ODI and NRS (taken at one, 3, 6, and 12 months), radiographs, computed tomography, and magnetic resonance imaging (MRI) scans. The primary outcome was the successful insertion of the implant in a lumbar disc nucleus.

Results: Sixty patients (36 women, 24 men), 49.0 ± 9.3 years old, received 83 implants (one disc-level: n = 37; 2 disc-levels: n = 23). All patients were implanted successfully without complications during the procedure or at discharge. One patient died (for reasons unrelated to the device/procedure), and one patient was lost to follow-up, for n = 58 at the 12-month follow-up. Five patients (8.6%) experienced increased low back pain (LBP) or leg pain and/or leg paresthesia, due to what radiological procedures confirmed was partial implant migration. Migrated implant portions were removed endoscopically from those patients 2 weeks to 10 months after implantation, constituting a 6% (5/83) failure rate. Mean (standard error [SE]) ODI scores in the patients was 9.6 (1.7) at the final follow-up. In the full cohort, ODI scores improved from the baseline mean (SE) of 57.4 (1.5) to 12.7 (1.8) at one month and 11.2 (2.0) at 12 months ($P < 0.001$). NRS back pain scores improved from the baseline of 7.3 (0.2) to 2.2 (0.3) at one month and 2.1 (0.3) at 12 months ($P < 0.001$). NRS leg pain scores improved from the baseline of 5.5 (0.4) to 1.1 (0.2) at one month and 1.4 (0.3) at 12 months ($P < 0.001$). The number of disc levels treated was not correlated with outcomes.

Limitations: As was inherent to a feasibility and safety study, limitations included a relatively small patient cohort and lack of a control group.

Conclusion: A novel, injectable, polymer-based hydrogel implant was successfully inserted in 83 of the intervertebral discs of 60 patients for the effective treatment of CLBP secondary to DDD. Clinically significant improvements in function, LBP, and low leg pain were maintained through 12 months.

Key words: Chronic low back pain, degenerative disc disease, intervertebral disc, lumbar, lumbar disc level L1-S1, disc augmentation, hydrogel, implant, nucleus pulposus, annulus fibrosus, percutaneous treatment, minimally invasive procedure

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Low back pain (LBP) is the most common musculoskeletal problem worldwide, with 12% to 30% of adults experiencing this debilitating condition at any time (1). In the United States, the direct health care costs of LBP are estimated at $90 billion annually, with another $10 to $20 billion in lost wages and decreased productivity (2). LBP that persists for longer than 12 weeks after the treatment of the initial injury or underlying cause is considered chronic. Approximately 20% of people affected by acute LBP develop chronic LBP (CLBP) with persistent symptoms at one year; approximately 13% of the US adult population suffers from CLBP (3).

Degenerative disc disease (DDD) is the most common cause of CLBP, accounting for 17% to 43% of all cases (4-8). As the body ages, proteoglycans within the nucleus pulposus break down and lose their ability to retain water, thereby reducing the intervertebral disc volume and decreasing weight-bearing capacity (9). This change shifts the mechanical loading on the disc from the nucleus pulposus to the annulus fibrosus, which can create fissures and tears in the annulus (10,11) and thus predispose the body to extrusion of the nucleus pulposus and possible nerve compression, leading to pain (9). When proteoglycans break down, the annular fissures may leak proteases, cytokines, and neurogenic and angiogenic factors into the extra-discal space and trigger inflammatory mediators (e.g., IL-1β, IL-6, IL-8, and TNF-α) (12). These factors are crucial in the pain cascade and contribute to chemically induced, inflammatory, discogenic back pain (Fig. 1) (12). The degenerative changes to the disc can also impact the role cartilaginous endplates play in disc mechanics and the regulation and transportation of nutrients and metabolites.

When conservative treatments fail, patients often turn to epidural steroid injections (ESIs) and opioids to manage pain, regain function, and avoid surgery. The risks associated with opioids are well documented, and opioids are often ineffective in treating CLBP (13-15). ESIs reduce inflammation and relieve pain, but the effect is short-lived (lasting for months, not years). Managing pain in this way requires repeated injections, the effectiveness of which often decreases over time (16,17). When conservative care, ESIs, and opioids fail, patients must choose between continuing medical management or receiving surgery. Spinal fusion, in which the spinal disc between 2 or more vertebrae is removed and the adjacent vertebrae are fused by bone grafts and/or cage devices secured with screws, is a treatment option for advanced DDD with instability. However, the procedure is expensive and invasive, with potentially suboptimal outcomes for some patients whose CLBP is due to stable DDD (18,19). Total disc replacement is a motion-preserving surgical option designed to restore disc biomechanics and minimizes the stresses on adjacent discs that can result from fusion surgery, but this procedure is more commonly performed in the cervical spine (20,21). In the lumbar spine, complication rates following spinal fusion or total disc replacement range from 15% to 20%, and though the revision rate is typically between 3% and 10%, it has been reported to be as high as 39% (22).

A new, injectable, polymer-based hydrogel implant has been developed for the treatment of patients with DDD-caused CLBP whose outer annuli remain competent. We hypothesize that the implant's hydrophilic properties will increase water retention and hydration, improve biomechanics, distribute axial loading more evenly across the annulus fibrosus, and reduce the discogenic disc pain generated by some mechanical sources (23-26). To enable implant flowability, the hydrogel is heated to 65°C and injected percutaneously via a needle. The procedure is performed under local anesthesia at an outpatient surgery center. The hydrogel exits the needle directly into the nucleus and forms a contiguous solid implant to augment the native intervertebral disc when the substance cools to body temperature. The hydrogel biomaterial is a blend of polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP), with polyethylene glycol (PEG) as a viscosity excipient and barium sulfate (BaSO4) as a radio-opacifier. In addition to allowing for water absorption and flow, hydrogels facilitate nutrient transfer in a manner similar to the

natural nucleus pulposus, which consists of viscoelastic mucopolysaccharides composed of hydrophilic glycosaminoglycan side chains of proteoglycans (27). The hydrogel implant is stable to the osmotic disc environment (0.1-0.3 MPa). The fluid mechanical properties of the implant enable load distribution over the vertebral endplates and restore the natural biomechanics of the intervertebral disc (28-30). The viscoelastic implant is engineered to withstand the repetitive loading associated with the physiological conditions of the lumbar intervertebral disc.

The purpose of this prospective, single-arm, multicenter feasibility study was to evaluate the safety and efficacy of a novel hydrogel nucleus-augmentation injectable implant for the percutaneous treatment of CLBP secondary to DDD.

Methods

Patients

Sixty patients who were between 22 and 80 years of age and had had CLBP for at least 6 months were recruited at 3 clinical sites: one imaging and diagnostic outpatient clinic in a large urban center in Canada (n = 20) and 2 pain management clinics in 2 urban centers in Colombia (n = 40) (Fig. 2). Patients who showed clinical and imaging evidence of disc degeneration at one or 2 lumbar vertebral levels (L1 to S1) were included if their discogenic LBP had been unresponsive to conservative treatment for at least 6 months and if patients reported a numeric rating scale (NRS) score ≥ 4/10 and Oswestry Disability Index (ODI) score ≥ 30/100. The presence of DDD was confirmed with magnetic resonance imaging (MRI). Only patients with pain that originated from one or 2 degenerated discs of modified Pfirrmann grades (31) 4 to 8, a disc height of at least 5 mm, and a competent outer annulus capable of containing the implanted hydrogel, as confirmed by MRI and provocative and/or anesthetic discography, were included. Patients were excluded if they had received previous back surgery at the target level of the lumbar spine, a systemic or local infection or a history thereof, an annular tear or defect with free contrast extravasation into the epidural space during or after discography, sequestered or extruded disc herniation, neural compressive lesions, compressive myelopathy, Schmorl's nodes, neurogenic claudication caused by spinal stenosis, or severe osteoporosis. See Table 1 for complete inclusion and exclusion criteria. This study was approved by the Health Research Ethics Board of Alberta (HREBA.CTC-21-0076) and the Colombian National Food and Drug Surveillance Institute (clinical trial number 20181235766 y 20181237144 de 2018).

Implantation Procedure

Intradiscal implantation was completed with a 17G needle while patients were awake and under local anesthesia in an outpatient clinic. The injectable, polymer-based hydrogel implant (HYDRAFIL® System, ReGelTec,

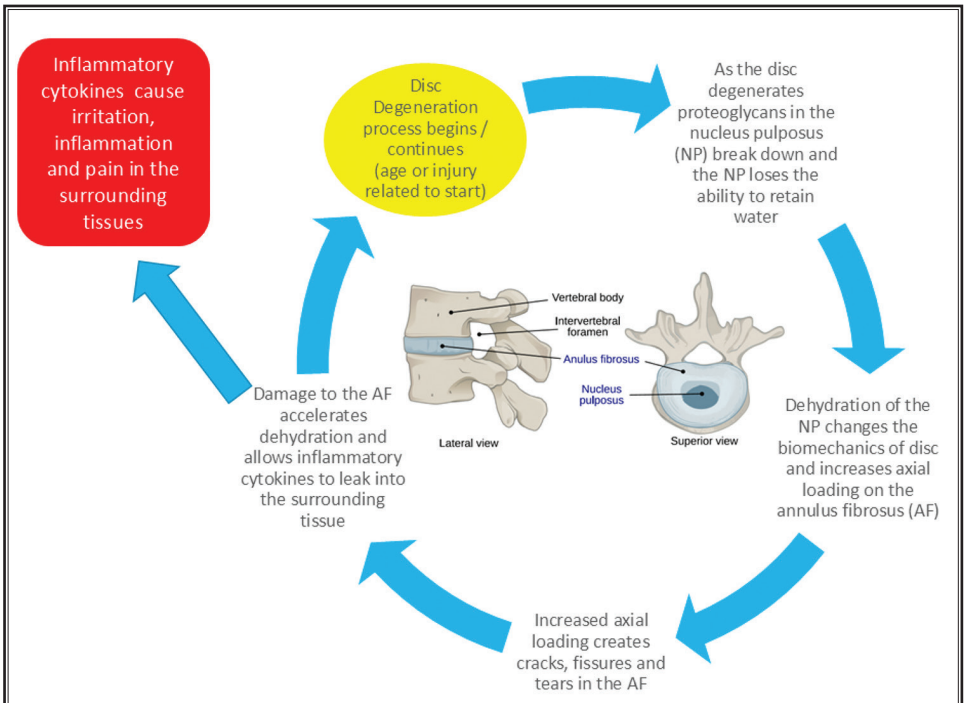

Fig. 1. *Cycle of degenerative disc disease.*

Inc.) was supplied as a single-use delivery system with a syringe prefilled with the implant device, a pressure gauge, and a commercially available 17G delivery needle. The implant was melted in an autoclave and equilibrated in a 65° C bath of sterile water prior to injection. With the patient in prone position, direct single-plane or biplanar fluoroscopic imaging was used to position the delivery needle in situ (Fig. 3). The identified lumbar disc was approached posterolaterally via Kambin's triangle in a conventional intradiscal approach (32,33). The delivery needle was inserted into the skin at the target access point for the affected nucleus pulposus. Then the delivery system was removed from the water bath and connected to the needle, and 1 mL to 3 mL of implant was injected while being monitored with real-time fluoroscopy. The hydrogel cooled as it flowed down the needle and exited directly into the nucleus at approximately 42°C. When the operator determined from patient anatomy and fluoroscopic imaging that the desired location was filled with sufficient hydrogel volume, the flow was stopped, and the delivery system was carefully removed. A stylet was inserted into the needle to displace the needle contents and left in place for 10 to 30 minutes to allow implant solidification and mitigate any risk of extravasation.

Patients were ambulatory within one to 2 hours after the injection. All patients were discharged on the day received their injections. Discharge instructions included limiting various movements and physical activity for the first 30 days following the procedure. Procedure-related pain resolved for most patients within 24 to 72 hours.

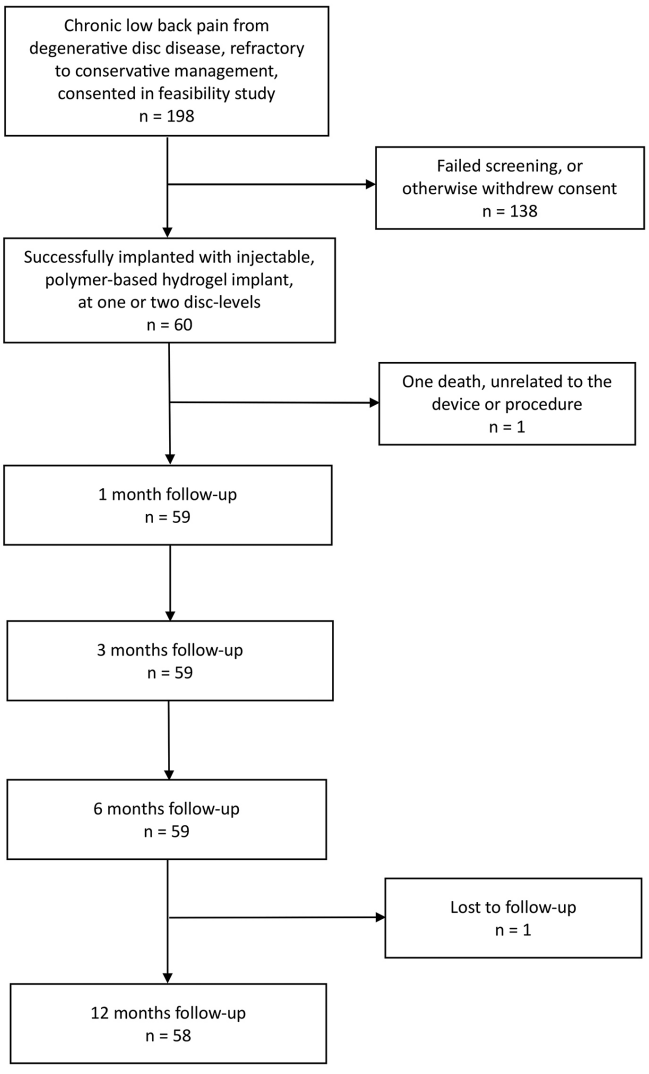

Fig. 2. *Patient flowchart.*

Clinical Assessment

Patients were assessed clinically with the ODI and the NRS for back pain and leg pain at the baseline and at one, 3, 6, and 12 months after the procedure. The ODI is a 10-item function scale with 6 choices for each item, is scored from 0% (no disability) to 100% (bedridden or maximal impairment) (34), and has a minimal clinically important difference (MCID) of 15% (35). The NRS is an ordinal pain scale scored from 0 (no pain) to 10 (extreme pain), with an MCID of 2.0 for patients with CLBP (35).

Radiographs (of standing lateral neutral position and of anteroposterior standing lateral position in flexion and extension), computed tomography (CT) scans, and MRI scans were collected at the baseline. Once all patients had received the injections, radiographs were collected at one, 6, and 12 months after the procedure, CT scans were collected at one and 6 months after the procedure, and MRI results were collected at 12 months after the procedure (Fig. 4).

Outcome Measures

The primary outcome measure was the successful implantation of the injectable hydrogel implant into a lumbar intervertebral disc. As far as safety was concerned, a successful outcome was defined as freedom from serious device- or operation-related adverse events during the

procedure and at discharge. Serious adverse events assessed included nerve root injury or irritation, hematoma formation, allergic reaction, and an intradural or epidural injection.

Secondary outcome measures were: (a) improvement of ODI score; (b) decrease in NRS score; and (c) implant success or failure, all at 12 months after the procedure. Failure was defined as: deterioration in pain (NRS) or function (ODI) scores; implant removal or revision; or requirement for additional surgery, such as supplemental fixation.

Statistical Analysis

Data were summarized using descriptive statistics. Continuous demographic variables are reported as means and SDs. Continuous functional and pain variables are reported as means and standard errors (SEs). Categorical variables are reported as counts and percentages. Data are reported for the full cohort ("All 60") and for the subset of patients 21-60 ("Last 40"). Comparisons between baseline and follow-up scores for the full cohort and for the Last 40 subset were performed using Wilcoxon rank-sum tests. Spearman

Table 1: *Patient inclusion and exclusion criteria*

Inclusion Criteria	Exclusion Criteria
Predominant low back pain and symptoms of DDD of the lumbar region of ≥ 6 months duration.	Presence of disc herniation that accounts for the majority of the patient's symptoms.
Symptoms are not resolved or reduced following 6 months of conservative treatment, i.e., pain medication and/or physical therapy.	Evidence of Modic type 3 changes, trans-endplate disc herniations, or Schmorl's nodes.
Male or female patients, aged 22 to 80 years, inclusive.	Previous back surgery at the target level of the lumbar spine.
Presence of DDD (36) on MRI with global disc degeneration. Modified Pfirrmann grades (31) 4 to 8 as characterized by MRI.	Neurogenic claudication due to spinal stenosis.
Presence of one or two symptomatic discs exhibiting degeneration contained within a competent outer annulus, according to MRI, provocative discography, and/or anesthetic discography at L1-S1.	Symptomatic disc with a height of less than 5 mm at the target level or compressive myelopathy.
Present with NRS Back pain level ≥ 4 out of 10 and ODI score ≥ 30 out of 100.	Annular tear or defect that shows free contrast extravasation into the epidural space during or after discography
Legally competent and able to understand the nature, scope and aim of the clinical investigation; signed informed consent form in a language in which they are fluent.	Failure to understand informed consent, or participation in any other clinical study.
	Evidence of severe compression of cauda equina.
	History of or current systemic or local infection
	Spinal segmental instability (spondylolysis or spondylolisthesis: Grade >1), spinal canal stenosis, isthmus pathology, scoliosis (Cobb angle >20 at the incident level), or other deformity conditions that may compromise the study.
	Patients with arachnoiditis or active tumors in the spinal region.
	Patients with low back pain of non-spinal or unknown etiology.
	Patients with severe osteoporosis or metabolic bone disease.
	Morbidly obese patients, i.e., BMI >35.
	Diagnosis of diabetes mellitus.
	Sensitivity or allergy to the implant materials.
	Patients who are pregnant or are trying to become pregnant during the course of the trial (due to risks of additional radiation exposure).
	History of or current abuser of alcohol or drugs as per DSM-V.
	Prisoners or wards of the courts.
	Patients involved in active litigation including worker's compensation cases.

DDD = degenerative disc disease; MRI = magnetic resonance imaging; L1 = lumbar vertebral body 1; S1 = sacral vertebral body 1; NRS = numeric rating scale; ODI = Oswestry Disability Index; BMI = body mass index; DSM-V = Diagnostic and Statistical Manual of Mental Disorders.

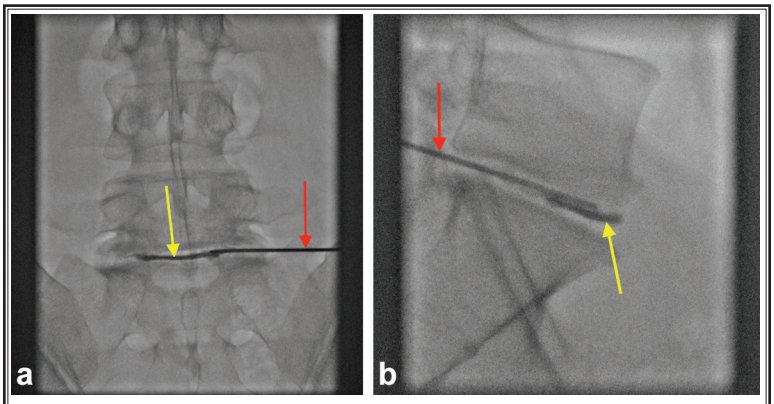

Fig. 3. *Intraoperative direct fluoroscopy images taken upon completion of needle insertion (red arrow) and injection of 1.5 mL hydrogel implant (yellow arrow) into the lumbar disc nucleus between L5 and S1 vertebrae in a 38-year-old male patient: a) anteroposterior view; b) lateral view.*

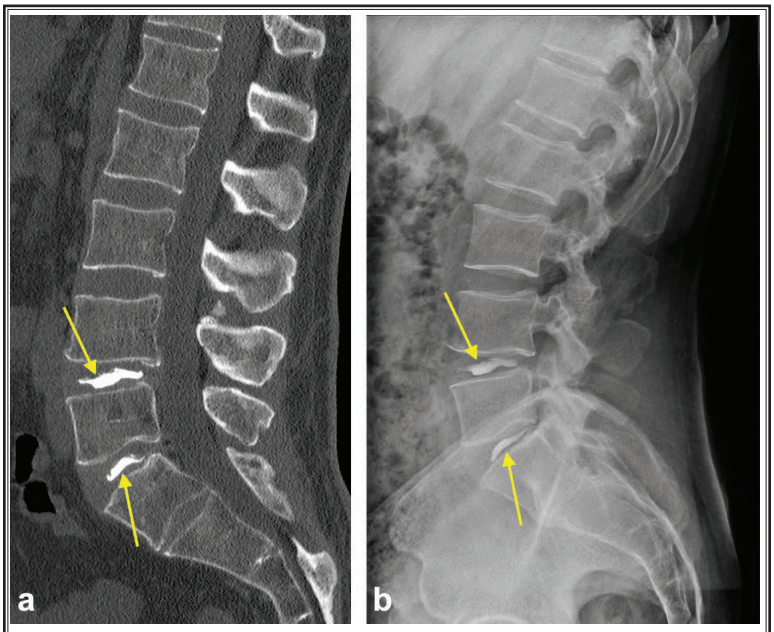

Fig. 4. *Lumbar spine of male patient, age 44 years at time of implantation, with injectable hydrogel (yellow arrow) implanted in the lumbar disc nucleus between L4 and L5 and between L5 and S1 vertebrae, with 1.0 mL injected per level: a) sagittal view CT image at one month after implantation; b) sagittal view radiograph at 6 months after implantation.*

correlation tests evaluated correlation effects between implant volume and Pfirrmann grade as well as between number of levels treated and functional and pain values. A *P*-value < 0.05 was considered significant.

Results

Sixty patients (24 men and 36 women) were enrolled and treated between August 5, 2020, and March 23, 2022. The mean (± SD) age of the cohort was 49.0 ± 9.3 (range: 22.1 to 69.6) years, with a mean (± SD) body mass index (BMI) of 27.7 ± 3.8 (Table 2). Most patients were of either Mestizo (57%) or Caucasian heritage (30%) (Table 2). The mean time between discography and implantation was 25.0 ± 24.4 (median 21, minimum 2, maximum 163) days for 56 patients when the discography procedure date was recorded. Patients were implanted at one disc-level (n = 37) or 2 disc-levels (n = 23), adding up to 83 treated discs. Thirty-eight (45.8%) treated discs were Pfirrmann grade 4 or 5, and 39 (47.0%) treated discs were Pfirrmann grade 6, 7, or 8 (Table 3). All patients were followed for at least 12 months.

All the patients were implanted successfully and experienced no serious adverse events during the procedure or at discharge. Fifty-eight of 60 (97%) patients completed the 12-month follow-up visit. One patient was lost to follow-up. One patient died from causes unrelated to the device or the procedure.

Two patients reported extended procedure-related LBP (at one day and 7 days after the procedure) and were prescribed additional analgesics. In both cases, their pain scores and ODI scores had improved from the baseline at the one-month follow-up.

During the 12 months following the procedure, 5 of 58 patients (8.6%) experienced 5 device-related complications that required implant removal, for a 6% failure rate based on 83 implanted devices. Those patients reported increased LBP or lower limb pain and/or lower limb paresthesia or numbness. In each case, radiographs and CT showed partial implant migration out of the disc annulus. The migrated portions of the implants were removed by a neurosurgeon using an endoscopic approach at 2 weeks, one month, 6 months, 9 months, and 10 months after the implant procedure, while the remaining portion of the implant within the nucleus was left in place. No patient required supplemental fixation. At 12 months follow-up, the mean ODI

Table 2. *Patient demographics at baseline.*

Demographic	All (n = 60)		Women (n = 36)		Men (n = 24)	
	Mean ± SD	Median (Min, Max)	Mean ± SD	Median (Min, Max)	Mean ± SD	Median (Min, Max)
Age (years)	49.0 ± 9.3	49.0 (22.1, 69.6)	50.0 ± 9.6	51.2 (22.1, 67.8)	47.6 ± 8.9	48.9 (30.7, 69.6)
BMI (kg/m^2)	27.7 ± 3.8	27.5 (18.7, 37.8)	27.1 ± 3.8	27.3 (18.7, 33.6)	28.6 ± 3.7	27.7 (22.3, 37.8)
Height (m)	1.68 ± 0.09	1.69 (1.51, 1.90)	1.65 ± 0.08	1.62 (1.51, 1.85)	1.74 ± 0.07	1.74 (1.60, 1.90)
Weight (kg)	78.8 ± 13.5	78.3 (54.0, 122.5)	73.2 ± 10.2	74.4 (54.0, 90.7)	87.1 ± 13.6	84.0 (61.4, 122.5)
Pfirrmann Grade*	5.5 ± 1.5	5 (2, 8)	5.6 ± 1.7	5 (2, 8)	5.4 ± 1.9	5 (2, 8)
Ethnicity^	N (%)		N (%)		N (%)	
Hispanic or Latino	6 (10%)		4 (7%)		2 (3%)	
Mestizo	34 (57%)		21 (35%)		13 (22%)	
Caucasian	18 (30%)		11 (18%)		7 (12%)	
Nigerian	1 (2%)		0 (0%)		1 (2%)	
Mediterranean	1 (2%)		0 (0%)		1 (2%)	

*All discs, total n = 83.
^Categorical variable, reported as n and percentage in brackets

score of the 5 patients who underwent revision was 9.6 ± 1.7. All 5 revision procedures were performed on the first 20 patients treated, prior to a change in the screening procedure to evaluate the competency of the annulus. None of the last 40 patients treated required a revision procedure through the 12 months of follow-up.

Partial migration of the hydrogel implant was noted in 3 additional patients at the one-month follow-up. These patients reported significant improvements in ODI and NRS back pain scores (< 50%) through the 12 months of follow-up, so no intervention was undertaken.

The full cohort of patients reported improvements in ODI and NRS scores at the one-month follow-up, and those improvements were maintained through 12 months. The ODI score improved significantly, from mean 57.4 ± 1.5 at the baseline to 12.7 ± 1.8 at one month ($P < 0.001$) and 11.2 ± 2.0 at 12 months ($P < 0.001$) after the procedure (Fig. 5, Appendix). The NRS back pain score also showed significant improvement, from mean 7.3 ± 0.2 at the baseline to 2.2 ± 0.3 at one month ($P < 0.001$) and 2.2 ± 0.3 at 12 months ($P < 0.001$) after the procedure (Fig. 6, Appendix). Similarly, the NRS leg pain score improved significantly, from mean 5.3 ± 0.4 at the baseline to 1.1 ± 0.2 at one month ($P < 0.001$) and 1.4 ± 0.3 at 12 months ($P < 0.001$) following the procedure (Fig. 7, Appendix). At 12 months, 54 of 58 (93.1%) patients who completed the follow-up visit met the MCID for ODI and NRS back pain scores. A

Table 3. *Pfirrmann grades of treated discs (n = 83) at baseline.*

Pfirrmann Grade	n	%
Grade 2	3	3.6%
Grade 3	3	3.6%
Grade 4	14	16.9%
Grade 5	24	28.9%
Grade 6	17	20.5%
Grade 7	10	12.0%
Grade 8	12	14.5%

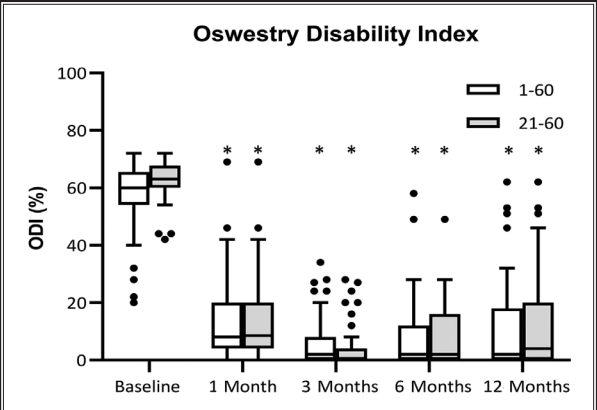

Fig. 5. *Box plot of Oswestry Disability Index score at baseline and following injectable hydrogel implantation, for all patients (1-60) and for the last 40 patients (21-60). The line represents the median; box limits represent upper and lower quartiles; Tukey error bars represent 1.5x interquartile range; and outliers are shown as individual dots. Asterisks indicate significant difference from baseline (P <. 001).*

sub-analysis of only the last 40 patients demonstrated similar results with slightly smaller ranges (Figs. 5, 6, and 7 and Appendix).

The number of disc levels treated was not correlated with the outcomes: patients who had one disc-level treated had statistically similar NRS back pain and ODI outcomes to patients with 2 disc-levels treated, at all time points (lowest $P = 0.3383$ at 3 months for back pain as measured on the NRS).

The volume of implant material injected ranged from 1 mL to 3 mL, with the last 15 patients in the study receiving less injectable material, between one and 1.5 mL. Discs with more advanced nucleus pulposus degeneration were predisposed to hold more gel than were less degenerated discs. The volume of implant material injected was not correlated with Pfirrmann grade (R = -0.1175; $P = 0.2902$). Implant volume was not correlated with NRS back pain or ODI scores at the baseline or at any time point following injection in the 38 patients who underwent single-level treatment and were evaluated for that parameter (lowest $P = 0.0653$ at one month for ODI).

At the 12-month follow-up, 96.4% of patients were very satisfied (39/56; 69.6%) or satisfied (15/56; 26.8%) with the treatment. When asked if they would recommend the procedure, 51 of 56 (91%) patients said yes, 4 of 56 (7%) patients said yes with reservations, and one (2%) patient said no.

Discussion

A novel injectable, polymer-based hydrogel augmentation implant for the percutaneous treatment of CLBP secondary to DDD was injected successfully in all (100%) targeted intervertebral discs (n = 83) in 60 patients across 3 clinical sites in 2 countries. In the 12 months following the implantation, 5 device-related complications (6%) required endoscopic, partial implant removal. Clinically significant improvements in function, LBP, and leg pain were observed within one month after the procedure and were maintained at the 12-month follow-up.

Five revision procedures were performed on 5 patients across the 83 disc-levels treated. All revision procedures occurred in the first cohort of patients treated (n = 20), and the patients' symptoms of pain or paresthesia were resolved by the removal of the migrated portion of the implant. No revision procedures were required in the next 40 patients treated with revised screening procedures that included re-evaluation of the annulus via discography, suggesting that the proposed hydrogel therapy could be performed with an acceptable safety profile. Moreover, a migrated hydrogel implant can be removed via an endoscopic procedure and does not limit future surgical options.

The ODI scores improved significantly from the baseline, by 78.4% at one month after the procedure and by 89.3%, 86.4%, and 80.9% at 3, 6, and 12 months

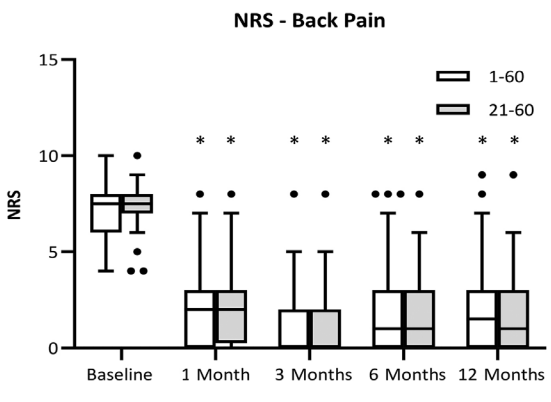

Fig. 6. *Box plot of numeric rating scale for back pain score at baseline and following injectable hydrogel implantation, for all patients (1-60) and for the last 40 patients (21-60). The line represents the median; box limits represent upper and lower quartiles; Tukey error bars represent 1.5x interquartile range; and outliers are shown as individual dots. Asterisks indicate significant difference from baseline ($P < 0.001$).*

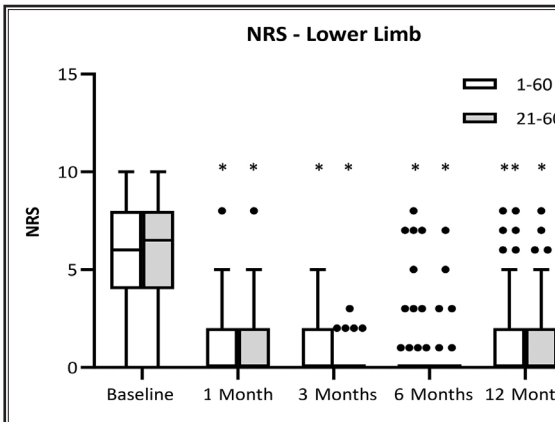

Fig. 7. *Box plot of numeric rating scale for leg pain score at baseline and following injectable hydrogel implantation, for all patients (1-60) and for the last 40 patients (21-60). The line represents the median; box limits represent upper and lower quartiles; Tukey error bars represent 1.5x interquartile range; and outliers are shown as individual dots. Asterisks indicate significant difference from baseline (*$P < 0.001$; **$0.001 < P < 0.01$).*

after the procedure, respectively. Based on a MCID of 15 points of improvement in ODI scores (35), 94.8% of patients experienced a clinically meaningful improvement in function. Patients demonstrated similar statistically significant improvements in NRS back pain scores (70.5, 78.9, 76.8, and 70.9 points at one, 3, 6, and 12 months follow-up, respectively) compared to the baseline, with 96.6% of patients experiencing a clinically meaningful reduction in NRS back pain scores (≥ 2 points) (35). Since screening procedures were revised somewhat after the first 20 patients, we conducted a sub-analysis of patient-reported outcome measures of the final 40 patients only. Unsurprisingly, this group demonstrated similar results to the full cohort, since the protocol changes were made to address safety concerns rather than severity of symptoms.

In cases of DDD, when proteoglycans in the nucleus pulposus degrade, they lose their ability to retain water, changing the biomechanical forces acting on the disc and potentially causing biomechanically induced pain (9). We hypothesized that the implant's hydrophilic properties would increase water retention and hydration and that the injectable hydrogel implant would augment the degenerated intervertebral disc to distribute axial loading more evenly across the disc and reduce the mechanical sources of discogenic disc pain (23-26). Disc degeneration also shifts loading on the intervertebral disc from the nucleus pulposus to the annulus fibrosus, creating annular fissures and tears (10,11), which can lead to the release of proteoglycan degradation products such as proteases, cytokines, and inflammatory mediators (e.g., IL-1β, IL-6, IL-8, and TNF-α) into the extra-discal space and produce chemically induced, inflammatory, discogenic back pain (12). Considering the large reductions in pain and disability reported by the patients in our study, particularly the improvements in leg pain, we are exploring the possibility that the injectable hydrogel may also fill in annular fissures and thereby reduce or prevent leakage of inflammatory mediators into the extra-discal space (Fig. 8). In vitro and in vivo studies are underway to explore this concept and help elucidate the complex relationships among the generators of pain in DDD.

We aimed to identify and include patients with only, or primarily, discogenic leg pain. However, we did not necessarily exclude patients who had some leg pain, and a large improvement in leg pain was observed. Perhaps improving spine biomechanics and preventing leakage of inflammatory cytokines from the disc by filling annular fissures helped resolve leg pain as well.

Patients with disc degeneration of Pfirrmann grades 5 to 8 were included, representing a wide range of disc degeneration. The primary concern for this study was the presence of a competent annulus, such that the injectable hydrogel could be held in place. The extent of disc degeneration was a lesser concern, provided there was sufficient space (i.e., disc degeneration) to support the hydrogel. Six discs with Pfirrmann grades 2 or 3 were included, since patient inclusion was at the discretion of the individual doctors, and imaging was not evaluated at a central core facility. This issue has been corrected for the randomized clinical trial, which has a screening committee in place to review all potentially eligible patients.

Limitation

This project has limitations inherent to a feasibility and safety study, including the relatively small patient cohort and the lack of a control group. However, a

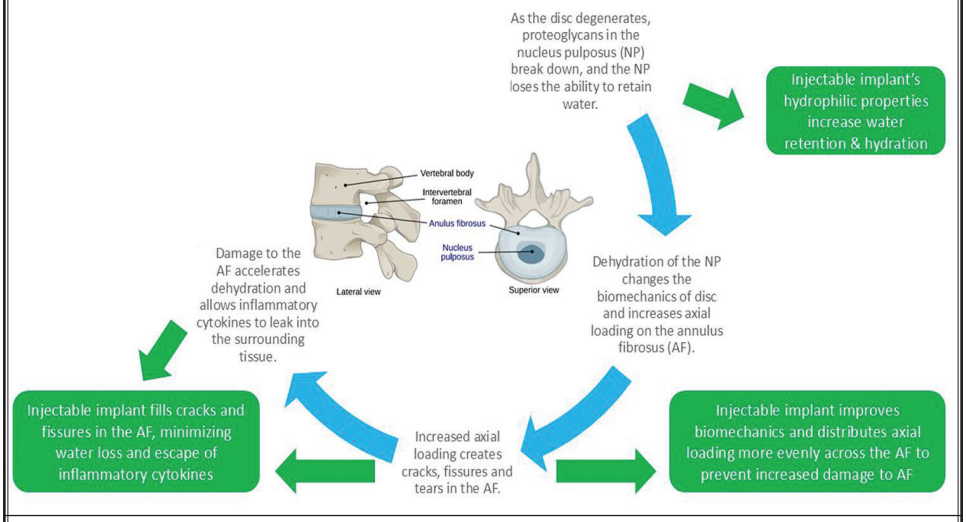

Fig. 8. *Proposed mechanism of action of the injectable hydrogel implant.*

strength of this study is that it has been conducted at 3 different sites in 2 countries, which improves the generalizability of the results. The NRS and ODI scores, although validated, are limited to a generalization of CLBP and cannot distinguish the potential effects or improvements in discogenic-specific pain or the effects of new pain resulting from different pain generators.

Conclusion

In conclusion, this early feasibility study indicates that the injectable hydrogel implant may be used safely to effectively treat CLBP caused by mid- to late-stage lumbar DDD. The hydrogel implant does this by functionally augmenting the intervertebral disc to provide biomechanical support and fill cracks and fissures in the annulus. A larger, randomized, controlled clinical trial was approved by the Food and Drug Administration and began patient recruitment in 2024.

Author Contributions

OCL: Conception and design of the work; acquisition, analysis, or interpretation of the data; drafting and critical review of the manuscript; final approval of the manuscript.

AS: Acquisition, analysis, or interpretation of the data; critical review of the manuscript; final approval of the manuscript.

KC: Acquisition, analysis, or interpretation of the data; critical review of the manuscript; final approval of the manuscript.

KA: Acquisition, analysis, or interpretation of the data; critical review of the manuscript; final approval of the manuscript.

PDN: Conception and design of the work; acquisition, analysis, or interpretation of the data; critical review of the manuscript; final approval of the manuscript.

DPB: Conception and design of the work; acquisition, analysis, or interpretation of the data; critical review of the manuscript; final approval of the manuscript.

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Appendix. *ODI, NRS Back Pain, and NRS Lower Limb Pain for the full patient cohort (All 60) and the Last 40 patients, from baseline to 1 year follow-up*

	Oswestry Disability Index (ODI)		NRS Back Pain		NRS Lower Limb Pain	
Patient Cohort	**All 60**	**Last 40**	**All 60**	**Last 40**	**All 60**	**Last 40**
Baseline - N	60	40	60	40	60	40
Mean (SE)	57.5 (1.5)	63.0 (1.1)	7.3 (0.2)	7.4 (0.2)	5.5 (0.4)	5.6 (0.3)
Median (IQR)	60.0 (54.0-65.5)	63.0 (60.0-67.8)	7.5 (6.0-8.0)	7.5 (7.0-8.0)	6.0 (4.0-8.0)	6.5 (4.0-8.0)
Range	20.0, 72.0	42.0, 72.0	4.0, 10.0	4.0, 10.0	0.0, 10.0	0.0, 10.0
1 Month - N	59	40	59	40	59	40
Mean (SE)	12.6 (1.8)	14.0 (2.4)	2.2 (0.3)	2.2 (0.3)	1.1 (0.2)	1.0 (0.3)
Median (IQR)	8.0 (4.0-20.0)	8.5 (4.0-20.0)	2.0 (0.0-3.0)	2.0 (0.3-3.0)	0.0 (0.0-2.0)	0.0 (0.0-2.0)
Range	0.0, 69.0	0.0, 69.0	0.0, 8.0	0.0, 8.0	0.0, 8.0	0.0, 8.0
3 Months - N	59	40	59	40	59	40
Mean (SE)	5.8 (1.2)	4.7 (1.3)	1.1 (0.2)	1.0 (0.3)	0.7 (0.2)	0.3 (0.1)
Median (IQR)	2.0 (0.0-8.0)	0.0 (0.0-4.0)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.0 (0.0-0.0)
Range	0.0, 34.0	0.0, 28.0	0.0, 8.0	0.0, 8.0	0.0, 5.0	0.0, 3.0
6 Months - N	59	40	59	40	59	40
Mean (SE)	7.8 (1.5)	8.0 (1.7)	1.7 (0.3)	1.6 (0.3)	0.8 (0.3)	0.5 (0.2)
Median (IQR)	2.0 (0.0-58.0)	2.0 (0.0-49.0)	1.5 (0.0-3.0)	1.0 (0.0-3.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Range	0.0, 58.0	0.0, 28.0	0.0, 8.0	0.0, 8.0	0.0, 8.0	0.0, 7.0
12 Months - N	58	39	58	39	58	39
Mean (SE)	11.1 (2.0)	12.9 (2.7)	2.1 (0.3)	2.0 (0.3)	1.4 (0.3)	1.2 (0.4)
Median (IQR)	2.0 (0.0-62.0)	4.0 (0.0-20.0)	1.5 (0.0-3.0)	1.0 (0.0-3.0)	0.0 (0.0-2.0)	0.0 (0.0-2.0)
Range	0.0, 62.0	0.0, 62.0	0.0, 9.0	0.0, 9.0	0.0, 8.0	0.0, 8.0

NRS = numeric rating scale; SE = standard error of the mean; IQR – interquartile range