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CLINICAL TRIAL REPORT

Early Clinical Results of Intervertebral Joint Stabilization by Injectable Load-Sharing Polymers

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Background: Genipin is a polymer-forming collagen bonding substance that can be dissolved in a buffered carrier and injected into disc annulus tissues. Therapeutic benefit is derived from the mechanical support provided by a large number of genipin polymers attached to collagen fibers in a degraded disc.

Study Design/Setting: IRB-approved prospective, multi-site, single-arm, 12-month feasibility studies were undertaken in two countries to evaluate the safety and efficacy of the genipin-based implant for treating discogenic chronic low back pain (CLBP).

Patient Sample: Twenty CLBP patients with symptomatic discs at one or two levels were enrolled in the study.

Outcome Measures: The primary safety endpoint was serious adverse events at 1 month, and the primary efficacy endpoint was reduction of pain and disability at 3 months. Secondary efficacy endpoints included reduction of pain and disability at 2 weeks, 1 month, 6 months, and 12 months; reduction of flexion–extension instability; increase in segmental lordosis and rotation; and patient satisfaction.

Methods: Fluoroscopic image-guidance was used to deliver two posterolateral injections of buffered genipin to each symptomatic disc. Flexion–extension radiographs were used to quantify joint kinematics at three time-points.

Results: Clinically meaningful improvements in pain and disability scores were reported in 80% or more of patients from 2 weeks to 1 year post-treatment. For the more severely unstable joints, treatment significantly reduced the instability score from a pre-treatment level of 2.4 standard deviations above the mean for an asymptomatic population to the asymptomatic mean at the 3-month follow-up.

Conclusion: These initial clinical data demonstrate the safety and efficacy of a genipin-based collagen tethering device capable of improving spinal joint stability while successfully addressing CLBP. This work merits additional randomized clinical studies.

Keywords: disc disease, lumbar spine, collagen, degenerative disc disease

Plain Language Summary

This clinical study provided initial evidence for the safety and effectiveness of a novel injectable treatment intended to address the core mechanical deficiencies contributing to the widespread problem of chronic low back pain. The injectable material is made up of a very large number of very small self-forming chains or tethers ("nano-tethers") that bond to the fibers of the degraded tissue matrix and constrain the movements of these fibers while carrying a portion of the normal applied loads. Preclinical experiments had shown the ability of the treatment to stabilize spinal joints and strengthen disc tissues, with repeated treatments effectively doubling the mechanical load support and joint constraint. Evaluations of treatment effectiveness included reductions of patient reported back pain and disability, and measures of joint instability and other motion characteristics from neutral standing and forward and backward bending X-rays. These initial study results demonstrated that the treatment was successful in providing stability to unstable spinal joints while also providing reductions in pain and disability comparable to common treatments for this disorder that either mask the pain or involve invasive surgery. The results also indicated that a single treatment may not be mechanically sufficient for patients with higher mechanical demand on their spines.

Introduction

Intervertebral disc degeneration (IDD) is a highly prevalent and progressive condition that involves early microstructural damage to the disc tissues leading to joint instability, loss of water-imbibing molecules, and increased solid phase load

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support in the annulus fibrosus.[1–3] Increased solid phase stresses combined with tissue degradation, along with a near absence of tissue repair, can result in the disc annulus being unable to withstand the stresses and strains of physiological loading, resulting in a degenerative cascade of further increases in tissue stresses and strains, additional tissue damage, and increased vulnerability to tissue overload.[4,5]

Disc degeneration in the lumbar spine is frequently the cause of chronic low back pain (CLBP). IDD-associated low back pain is the second most common pain condition, with reported point prevalence rates between 12% and 35%,[6] resulting in lost work time,[7,8] with 10–12% of the population disabled by CLBP.[2,9] Increasing mechanical insufficiency of degenerating discs can lead to overloading and degenerative changes in the adjacent joints and surrounding tissues.[10–12] At present, treatment options for this condition range from pain-masking strategies such as over-the-counter drugs, opioid and other non-opioid pain management, neuromodulation, nerve ablation, and steroid injections, to strategies that attempt to eliminate neural compression or improve load support in joint tissues, such as exercise, physical therapy, nucleus augmentation, stem cell treatments, discectomy, fusion, disc prostheses, and other surgical options.

The injectable, non-biologic, polymeric treatment strategy evaluated in this study relies on image-guided delivery of self-forming genipin polymers to the degraded annulus fibrosus. Genipin is a biocompatible, organic molecule that can bond at the terminal ends of the polymer to amines on proteins.[13–15] The therapeutic benefit of the device is derived from the inherent mechanical properties of a large number of genipin polymers that mechanically constrain the degraded disc fibrous collagen matrix, reducing aberrant deformations while carrying a portion of the disc loads, thereby mechanically stabilizing the intervertebral joint (Figure 1). The injectable genipin-based device will be referred to as IDSD (injectable disc stabilization device). Owing to the causal link between disc mechanical insufficiency, joint instability, and the generation of discogenic pain,[10,16] genipin polymers have demonstrated ability to reduce joint instability,[17–19] excessive disc bulge,[20] tissue overload,[21,22] and annular tearing,[23] suggesting that this novel treatment can address CLBP while also restoring joint stability and providing resistance to ongoing tissue degradation.

Materials and Methods

Trial Design

A single-arm, multi-site medical device early-phase clinical study with 12-month follow-up was conducted sequentially in two countries to evaluate the safety of IDSD and to obtain preliminary efficacy data. Prior to study commencement, national and regional ethics committee approval was obtained from the Medical Device Authority, Ministry of Health Malaysia (www.nmrr.gov.my; registration ID: NMRR-16-699-30700; institute/sponsor: LMH Biotech; PI: Harwant Singh; year NMRR accepted: 2016; online registry search URL: https://v1nmrr.nih.gov.my/fwbPage.jsp?fwbPageId=PublicDirectoryOfResearchList&fwbAction=List) and Bellberry Regional Ethics Committee of Australia (ANZCTR registration number: ACTRN12619000307101). The enrollment period in the Malaysian arm of the study was from June to October 2016, with all treatments and data collection conducted at the Pantai Medical Centre in Kuala Lumpur, Malaysia. Enrollment in the 50-participant Australian arm began in March 2019 and has not been terminated to date. Four separate institutions/sites have been utilized: Hurstville Private Hospital, Genesis Research Services, PainMedSA, and Sydney Spine and Pain. This clinical investigation was conducted in compliance with the principles that have their

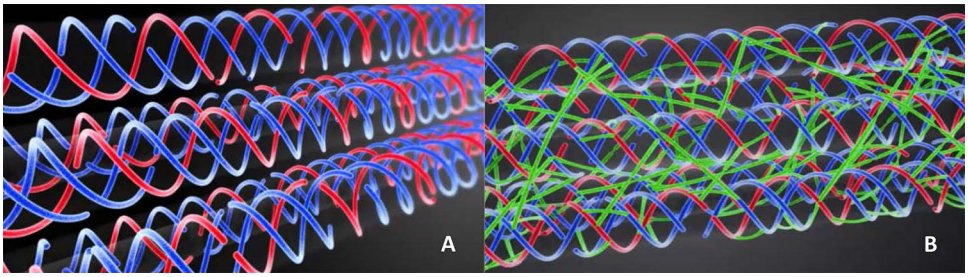

Figure 1 (**A**) Schematic of tropocollagen molecules (the basic structural unit of collagen, represented as two blue helices and one red helix) in a subfibril of the annulus fibrosus matrix; (**B**) a similar schematic after the addition of genipin oligomer "tethers" (green bands) attached to the subfibril, creating a reinforced construct that is more robust than the native (degraded) subfibril.

origin in the latest version of the Declaration of Helsinki, the clinical investigation plan, requirements of the approving ethics committee and local regulatory authorities, ICH GCP and ISO 14155. Written informed consent was obtained from all study participants prior to enrollment in the study. De-identified individual participant data that support the findings of this study are available from the corresponding author upon reasonable request within 3 years of publication of this article. Available data include participant-related outcome measures and kinematic data as processed by Medical Metrics. Other study documents, including the study protocol and investigator brochure, are available upon reasonable request.

One intention of this preliminary study was to provide data to determine whether there is a need for a second injection of genipin polymers to effectively double the number of load-supporting genipin polymers for patients having higher mechanical loading on their discs, based on patient demographics. It has previously been demonstrated[24] that there are sufficient collagen bonding sites in the annulus to effectively double the number of load-supporting genipin polymers, proportionally increasing the joint stabilization effects.[19] The current study has not authorized a second set of injections, but patient demographic data (primarily patient weight and body mass index [BMI]) were obtained in part to correlate with patient-reported outcomes and inform future clinical study designs.

Patient Selection

Patient eligibility criteria included adults 18–60 years old; symptomatic IDD at one or two levels (visual analog scale [VAS] ≥40 mm or numeric rating scale [NRS] ≥4, Oswestry Disability Index [ODI] ≥30%, ≥3 months of pain); greater amount of back pain compared to radiating pain, confirmed by physical examination, magnetic resonance imaging (MRI) or discography with concordant pain; and failed non-operative treatment. Exclusion criteria were greater than mild facet arthrosis; other causes of back pain; previous index level surgery or recent (<3 months) interventions; or spondylolisthesis or stenosis or infection or tumor or scoliosis >15 degrees. MRI scans were taken to assist with assessing the symptomatic level(s) and for planning injection volumes on target discs. If a penetrating annular fissure was suspected by previously diagnosed sciatica, or posterolateral high-intensity zone or a focal disc protrusion on MRI, discography was performed to detect the presence of a penetrating tear. Participants underwent the injection procedure within 30 days of baseline assessments.

Twenty CLBP patients (10 female, 10 male, aged 24–55 years, four racial groups) were enrolled in the studies. Two enrolled participants did not meet study inclusion–exclusion criteria, and one was not fully treated owing to imaging equipment failure during the injection procedure, leaving 17 fully treated participants meeting the inclusion–exclusion criteria (Table 1). Both of the patients who did not meet the criteria in the study had clinical and imaging evidence suggesting

Table 1 Patient Data

Participant ID	Treatment Date	Weight (kg)	Gender	BMI (kg/m^2)	Age (Years)	Level(s) Treated
PMC-001	6/22/2016	65.2	F	24.8	32	L4–L5
						L5–S1
PMC-004	6/22/2016	NA	M	NA	43	L4–L5
						L5–S1
PMC-003	6/22/2016	65	F	27.3	24	L4–L5
PMC-002	6/22/2016	63	F	25.6	30	L5–S1
PMC-005	10/31/2016	NA	F	NA	33	L5–S1
02-002	3/21/2019	112	M	34.19	55	L4–L5
						L5–S1

(*Continued*)

Table 1 (Continued).

Participant ID	Treatment Date	Weight (kg)	Gender	BMI (kg/m^2)	Age (Years)	Level(s) Treated
01-001	7/2/2019	74	M	25.31	46	L4–L5
05-001	6/24/2020	54.5	F	21.83	40	L5–S1
05-008	8/26/2020	113	F	39.56	36	L4–L5
05-009	8/12/2020	102.9	M	31.94	43	L3–L4
						L5–S1
04-006	10/13/2020	90.5	M	29.55	37	L4–L5
						L5–S1
05-016	10/21/2020	73.8	F	28.65	41	L5–S1
04-009	10/27/2020	110	M	33.95	39	L4–L5
						L5–S1
04-015	12/8/2020	86.9	M	24.85	25	L4–L5
						L5–S1
04-014	2/9/2021	102	M	29.48	44	L4–L5
						L5–S1
04-016	6/22/2021	144	F	48.67	41	L5–S1
05-024	5/5/2021	64.4	M	21.39	44	L4–L5

insufficient peripheral disc integrity to prevent immediate loss of the injectable device from the disc, in addition to other excluding factors such as more than two spinal levels affected, severe facet arthrosis, and known psychological comorbidities. One participant was lost to follow-up prior to the 6-month assessment. The 17 treated participants had an average pre-treatment VAS pain score of 58.6 (range 22–85) and average ODI of 46.2% (range 34–66%). A total of 25 lumbar discs were treated, with eight of the 17 treated participants meeting the inclusion–exclusion criteria receiving IDSD injections at two levels. Five participants had a BMI greater than 30 kg/m^2 and eight weighed more than 85 kg.

Procedure

Fluoroscopic image-guidance was used to deliver two posterolateral injections of IDSD to the mid-coronal plane of each hemi-annulus (left and right) of each symptomatic disc using a 21 Ga Chiba needle. An 18 Ga "introducer" needle is first inserted along the 30-degree ipsilateral oblique on the mid-axial plane of the target disc, contacting but not penetrating into the annulus. The 21 Ga needle is inserted via the introducer and advanced gradually to the mid-coronal plane in either the right or left lateral annulus, 5–10 mm from lateral, anterior, and posterior borders of the annulus. This positioning will ensure that the injection is made into the hemi-annulus (right or left) and not into the nucleus pulposus of the disc (Figure 2). The injectate contained 50% contrast agent plus 48 mM genipin and a 50 mM EPPS–phosphate buffer solution. The volume of IDSD injected per side (0.5–1.0 mL) was determined based on the disc's axial plane width and depth (anterior–posterior) dimensions from the screening MRI. The procedure may be repeated for a second affected spinal level. Within 1 hour following the procedure, the participant was positioned in a vertical posture: sitting, standing, or walking. This posture facilitates axial compression of the disc to expel excess fluid from the disc. The participant was instructed to not perform deep bends or severe twists within 4 hours after the procedure.

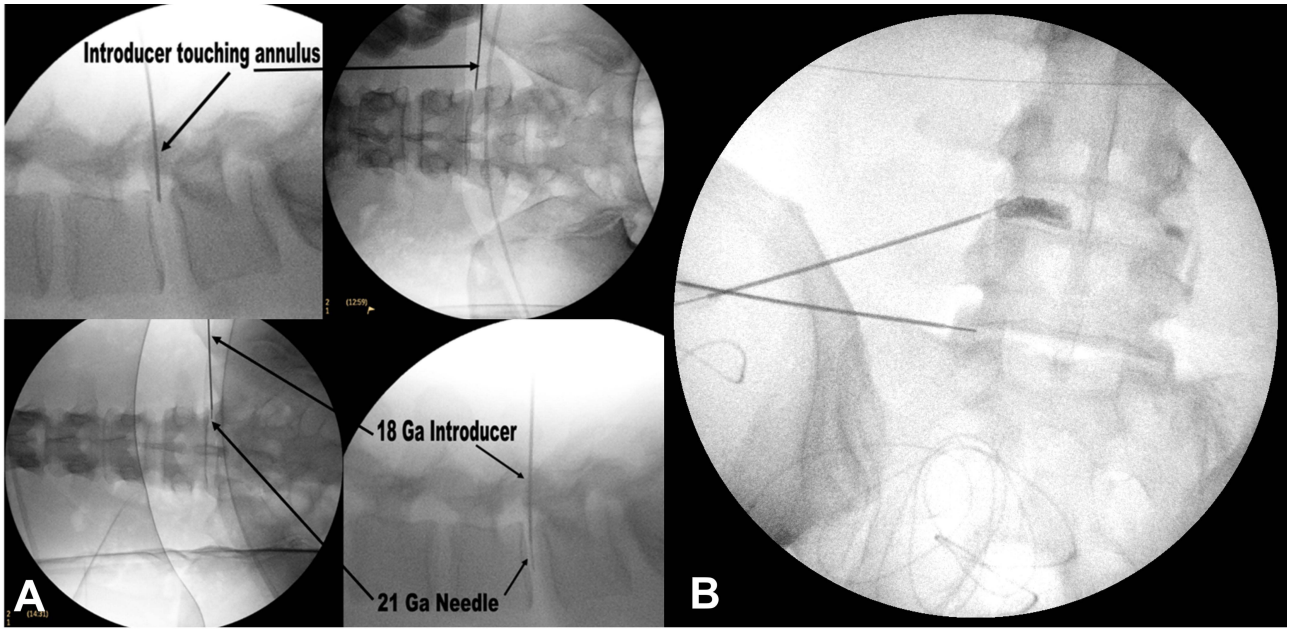

Figure 2 Injectable disc stabilization device (IDSD) delivery: fluoroscopic images. (**A**) Lateral and anterior–posterior images showing an 18 Ga introducer needle contacting the outer posterolateral annulus and a 21 Ga needle placed in the mid-lateral annulus; (**B**) contrast agent shows the device placement in the hemi-annulus following a posterolateral injection.

Outcome Measures

The primary endpoints in this study were the occurrence of serious adverse events (SAEs) by 30 days post-procedure and the reduction of patient-reported VAS pain and ODI disability at 3 months. The VAS is a subjective pain rating scale for acute and chronic pain that has been in use since the 1920s. The ODI (Oswestry Low Back Pain Disability Questionnaire) has been in use since 1980 and is considered the "gold standard" of low back pain functional outcome tools. Safety and efficacy endpoints were also assessed at 1–2 week follow-up, 1 month (efficacy), 3 months (safety), and at 6- and 12-month follow-ups.

Secondary efficacy endpoints included the reduction of segmental flexion–extension instability and the increase in segmental and global lumbar range of motion (ROM) and segmental standing lordosis compared to baseline, device- or procedure-related adverse events, change in disc height of treated levels, reduction of pain medications compared to baseline, and participant satisfaction. Participant satisfaction was assessed at the 3, 6, and 12-month follow-ups on a −2 to +2 Likert scale.

Kinematic metrics were assessed from neutral standing and flexion–extension bending radiographs of the L1–S1 spine taken at baseline and at 1 and 3 months post-procedure using the Medical Metrics Inc. (MMI) calibration marker and protocol. Although a somewhat nebulous concept, lumbar spinal joint instability has commonly been considered to involve an excessive amount of anterior–posterior translation associated with flexion–extension rotation. An objective quantitative metric for lumbar segmental instability based on the ratio of intervertebral translation to intervertebral rotation measured from flexion–extension radiographs was suggested by Weiler et al in 1990.[25] Later studies demonstrated that an amount of segmental translation per degree of rotation (TPDR) that is above the amount seen in an asymptomatic, radiologically normal population can be a useful indicator of sagittal plane lumbar joint instability.[26,27] These studies suggested that a comparison of measured TPDR, for instance, from a symptomatic joint, with the asymptomatic baselines can provide an objective measure of joint instability. Because there are different means and distributions of TPDR for each spinal level in a normal, asymptomatic population, the discrepancy between a measured TPDR and the asymptomatic mean for that level is best assessed by quantifying the difference in terms of standard deviations from the asymptomatic mean. In other words, a lumbar joint with a measured TPDR that is 2 standard deviations greater than the mean of the asymptomatic population at that level would be quantifiably and reasonably more unstable than a joint with a TPDR that is 0.5 standard deviations from the asymptomatic mean. The Quantitative Stability Index (QSI) used in this study is a metric that indicates the number of standard deviations difference between a measured

TPDR and the mean value of an asymptomatic, radiographically normal population at that level.[26] QSI calculations are less reliable and therefore not calculated by MMI when the segmental rotation is less than 3 degrees.

The clinical protocol required pre- and post-procedure reporting of opioid and non-opioid analgesic use by the site investigators at all regular follow-ups and unscheduled visits. The protocol discouraged the use of post-treatment opioid use outside the peri-procedure time period, but left this decision to the discretion of the clinician investigators, primarily because of the early-stage nature of the investigation with no prior clinical evidence regarding pain relief by a strictly mechanically functioning medical device. Owing to inconsistencies in the frequency of analgesic use reported at different clinical sites, and questions of accuracy regarding claimed medication use, only a general qualitative assessment of the effect of treatment on pain medication use could be made in this initial study.

Statistical Methods

All patient-reported outcomes and kinematic metrics were reported using descriptive statistics. Since there were some missed follow-ups in the patient-reported outcomes, mixed models for repeated measures (MMRM) analyses were used to evaluate VAS and ODI changes over time, with and without stratification by weight category. Changes in kinematic metrics were evaluated using paired two-tailed *t*-tests, with $p<0.05$ considered statistically significant.

Results

After each investigator's first patient, the procedures were complete within 20 minutes, including two-level procedures. Seventeen patients with CLBP completed at least 3-month post-procedure assessments, 16 completed 12-month assessments, and the first five completed 24-month assessments.

Safety Outcomes

The safety of the injectable polymeric device was assessed in all 20 enrolled participants, including the two participants who did not satisfy the inclusion–exclusion criteria and the participant who was not fully treated owing to imaging system failure. There were no incidents of intra-operative SAEs. A total of one SAE was reported for a patient not satisfying inclusion–exclusion criteria. The participant had a previously diagnosed anxiety disorder, and the event involved a "severe anxiety disorder" related to a pain flare resulting in an immediate hospital admission, thus triggering the SAE report. The pain flare was quickly resolved with an epidural steroid injection (ESI).

In total, 24 adverse events (AEs) were reported. AEs included unrelated events such as motor vehicle accidents, COVID-19 infection, pregnancy, and pre-admission fever. Six AEs were related to the procedure, three were related to the device, and three were related to both the procedure and the device. AEs potentially related to the device included radiating pain to the leg, diminishing over time and completely resolved by 9 weeks (the patient declined an earlier ESI) (1); temporary (less than 1 week) radiating mild pain to the hips, legs, or buttocks (2); mild reaggravation of leg pain experienced after discography (1); temporary, mild dysesthesia to the dorsum of the foot (1); and 1 day of mild fever (1). AEs related to the procedure included intense bilateral somatic referred pain following discharge (nerve irritation by the injection needle), resolved within 48 hours (1); tingling on the right middle toe (1); radiating pain to the leg from reagent extravasation (physician error), diminishing over time, treated with an ESI injection, and completely resolved by the 9-week point (1); mild to moderate radiating pain, resolved in less than 1 week (2); observation of a partial leak during the final injection prompting the use of pregabalin (Lyrica), with no morbidity reported (1); 1 day of mild fever (1); mild low back pain, resolved before the 2-week visit (1); and mild reaggravation of leg pain experienced after discography (1).

Needle penetration, removal, and reinsertion on the left side of the disc in the first patient led to extravasation of a portion of the injectate outside the disc in the region of the left side nerve roots. In another injection procedure, there was a noticeable rise in injection pressure at the approximately 0.5 mL injection point associated with extravasation of injectate from the L5/S1 disc. This injection pressure-related extravasation has not been reported in other cases or seen with ex vivo cadaveric disc injections. On the contralateral side injection, there was evidence of extravasation some time after the injection, related to removal of the needle. An extension tube was used in this injection, and the extension tube was not disconnected from the needle prior to removal of the needle. It was concluded that the injection pressure issue and the leakage during needle removal on the contralateral side were due to the use of extension tubing. One procedure

involved a small amount of subcutaneous leakage of reagent with the withdrawal of an exceptionally long (25 cm) needle post-injection. This patient was morbidly obese (BMI=48.7 kg/m^2), necessitating the long injection needle. No morbidity was associated with this subcutaneous leakage.

Patient-Reported Outcomes

Clinically meaningful improvements in pain and disability scores occurred in 94% of patients at the 3-month time-point, with a mean reduction in VAS of 49.8% (58.6 to 21.4) and a mean percentage reduction in ODI of 59.7% (46.2% to 18.6%). Table 2 shows the VAS pain and ODI disability summary statistics for each study time-point. The percentage of patients with excellent results (both VAS and ODI reduced by 50% or more from baseline values) or good results (VAS decreased by 20 mm or more and/or ODI decreased by 20% or more) was 80% or more from 2 weeks post-treatment to 2 years (only five patients were assessed at 24 months). Figure 3 shows baseline and follow-up VAS mean pain scores by weight category. Figure 4 shows baseline and follow-up ODI mean disability percentages by weight category.

Table 3 summarizes reductions in VAS pain scores from baseline over time by weight category. The mean improvement at 12 months was more than twice as large for those ≤85 kg in weight compared to those >85 kg (−45.6 vs −18.4) and the median was almost five times larger (−50 vs −11). MMRM analysis determined that all mean improvements in VAS were larger than zero at all time-points for both weight strata, with probability values from 0.0232 to >0.0001. The residuals plot was approximately normal, with no large outliers. This gives confidence that inferences from this model are valid.

Table 4 summarizes reductions in ODI disability percentages from baseline over time by weight category. Similarly to VAS, ODI improvements at each time-point for both weight strata were robust despite the small sample size. MMRM analysis determined that all mean improvements in ODI were larger than zero at all time-points for both weight strata, with probability values from 0.0372 to >0.0001. The residuals plot was not as symmetric as for VAS, but was sufficient to permit parametric analyses.

There was no trend towards increasing or decreasing use of pain medications by study participants over the course of the study. There was no reported use of pre- or post-treatment analgesics in nine of the 17 participants, with two participants reporting a decrease in analgesic use compared to pre-treatment, three reporting increased use of analgesics post-treatment, and three reporting no change from pre-treatment. With no apparent trends in increased or decreased analgesic use post-treatment, these results suggest that the use of analgesics did not bias the other study data.

Patient satisfaction data were generally favorable. On average, participants (satisfaction data were not acquired from the first five participants) indicated that they were satisfied with the results of their procedure at the 3-month follow-up (+0.9) and 6-month follow-up (+0.8). Average satisfaction with their results was still positive but dropped to +0.4 at 12 months. Participants generally agreed or strongly agreed that they would have this treatment again when questioned at 3 months (+1.5), 6 months (+1.3), and 12 months (+0.9) post-procedure. Likewise, participants generally agreed or strongly agreed that they would recommend this treatment to family or friends when questioned at 3 months (+1.5), 6 months (+1.5), and 12 months (+1.0) post-procedure.

Table 2 Summary Statistics for VAS Pain and ODI Disability Scores and Percentage Reductions at All Study Time-Points

Visit	N	Mean VAS Pain	Std. Dev.	Reduction from Baseline	Mean ODI Disability (%)	Std Dev (%)	Reduction from Baseline
Baseline	17	58.6	14.5	–	46.2	9.5	–
1–2 wk	17	25.6	19.2	56.3%	26.2	16.5	43.3%
1 mo	17	19.4	14.6	67.0%	19.6	13.0	57.5%
3 mo	16	21.4	22.1	63.4%	18.6	16.1	59.7%
6 mo	16	29.9	20.2	48.9%	20.8	14.0	55.1%
12 mo	15	24.9	21.8	57.4%	22.5	19.1	51.3%

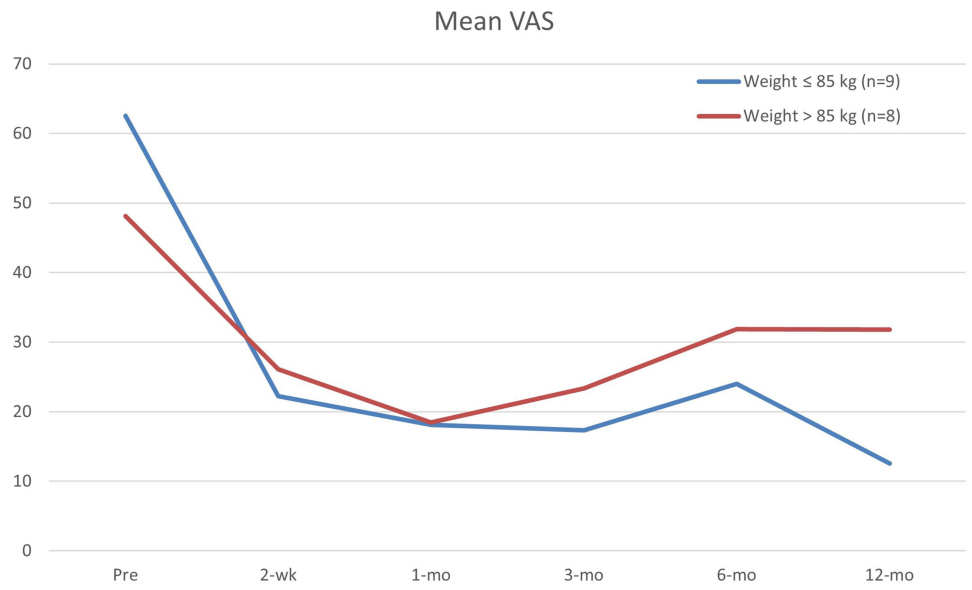

Figure 3 Visual analog scale (VAS) pain scores over time by weight category.

Figure 4 Oswestry Disability Index (ODI) disability percentages over time by weight category.

Kinematic Results

Pre- and post-procedure neutral standing and flexion–extension kinematic data were collected for 24 treated discs from 16 of the 17 participants. Fifteen segmental instability (QSI) data points from treated discs were not calculated owing to the segment having less than 3 degrees of flexion–extension segmental rotation. From the remaining data points, QSI of treated discs was reduced by 0.2 and 0.6 standard deviations at the 1-month and 3-month follow-ups, respectively. These reductions were not statistically significant. However, four of the treated discs were clinically unstable pre-treatment (QSI >1.5, meaning that the instability, as quantified by TPDR, was more than 1.5 standard deviations above the mean for an asymptomatic, radiographically normal population). Following treatment, each of these unstable segments had

Table 3 Summary Statistics for Reduction of VAS Pain from Baseline by Weight Category and Visit

Weight Category	Visit	N	Mean	95% Confidence Interval	Probability
>85 kg	1–2 wk	8	−24.75	[−17.18,−32.32]	**0.0015**
	1 mo	8	−33.38	[−25.40,−41.35]	**<0.0001**
	3 mo	8	−27.00	[−1.53,−52.47]	**0.0102**
	6 mo	8	−18.25	[−1.98,−34.52]	**0.0232**
	12 mo	8	−18.38	[−3.55,−33.20]	**0.0121**
≤85 kg	1–2 wk	9	−40.33	[−24.91,−55.75]	**<0.0001**
	1 mo	9	−44.44	[−33.43,−55.45]	**<0.0001**
	3 mo	9	−45.22	[−30.78,−59.66]	**0.0003**
	6 mo	9	−37.50	[−22.98,−52.02]	**0.0005**
	12 mo	9	−45.57	[−34.03,−57.11]	**<0.0001**

Note: Bold probability values indicate that the difference from baseline values was statistically significant.

Table 4 Summary Statistics for Reduction of ODI Disability Percentages from Baseline by Weight Category and Visit

Weight Category	Visit	N	Mean (%)	95% Confidence Interval (%)	Probability
>85 kg	1–2 wk	8	−13.25	[−8.26,−18.24]	**0.0153**
	1 mo	8	−21.50	[−16.61,−26.39]	**0.0002**
	3 mo	8	−22.00	[−11.19,−32.81]	**0.0008**
	6 mo	8	−19.25	[−9.21,−29.29]	**0.0006**
	12 mo	8	−11.50	[−2.18,−20.82]	**0.0372**
≤85 kg	1–2 wk	9	−26.00	[−12.17,−39.83]	**0.0022**
	1 mo	9	−31.11	[−18.93,−43.29]	**<0.0001**
	3 mo	9	−33.33	[−21.94,−44.72]	**0.0001**
	6 mo	9	−29.25	[−17.80,−40.70]	**0.0002**
	12 mo	9	−33.59	[−23.74,−48.26]	**0.0005**

Note: Bold probability values indicate that the difference from baseline values was statistically significant.

reductions in QSI at the 1-month follow-up (range 0.4–2.8) and at the 3-month follow-up (range 1.5–3.1). The mean reductions in QSI at 1 month (2.0) and 3 months (2.4) were statistically significant (p=0.034, p=0.037) despite the small number of data points in this subset. The corresponding 1-month and 3-month VAS scores for these four patients were reduced by an average of 75% and 77%, respectively. Similarly, the corresponding 1-month and 3-month ODI percentages dropped by an average of 58% and 75%, respectively.

There was a statistically significant 1.7-degree (30%) mean increase in segmental rotation for treated discs (p=0.018) at the 3-month follow-up. Likewise, there was a significant 1.1-degree (8%) increase in segmental standing lordosis in treated discs (p=0.012). There was no consistent change in disc height following treatment. The increase in mean global

(L1–S1) range of motion at 3 months was 2.3 degrees (not statistically significant). After removing two outliers (obese patients experiencing a fall-off in initial treatment effects), there was a statistically significant (p=0.016) 5.2-degree average increase in global lumbar ROM at the 3-month time-point.

Fall-Off in Improvement for Participants with High Mechanical Demand

Sufficient data were collected to indicate a load-support threshold corresponding to participant weight. Figures 3 and 4 and Tables 3 and 4 indicate a fall-off in initial improvements after the 1-month follow-up exclusively occurring among participants exceeding 85 kg. Seventy-five percent (six of eight) of the "high-demand" (weight >85 kg) participants experienced a pain flare (large temporary increase in pain) or a loss of treatment effect (reduction of pain and disability from baseline levels) at a follow-up between 3 months and 12 months post-procedure. Conversely, participants weighing 85 kg or less did not experience a similar consistent drop-off in clinical benefit (none of nine participants). This difference in apparent duration of treatment effect was readily observable in the data. The difference in mean improvement in VAS scores between weight classes was statistically significant by the 12-month time-point (F=5.27, p=0.0376). The same trend was observed with the ODI disability data; however, the difference between the high-demand and normal-demand cohorts did not reach statistical significance (F=2.20, p=0.1604).

Discussion

For well over a century, the primary intention of most non-palliative treatments for progressive disc degeneration and the associated chronic pain has been to address the mechanical deficiencies of degraded lumbar intervertebral joints – from joint immobilization for fusions, to more recently developed motion-constraining devices, including the advent of disc regenerative technologies. Several factors have limited the success of these mechanical restorative strategies, including morbidity from surgical invasiveness, an inability to restore or replicate the complex spinal joint architecture and mechanics, the harsh biological environment of degenerative discs, and healthcare cost considerations. The need for an immediately effective, long-lasting, micro-invasive means for stabilizing spinal joints and mechanically supporting degraded disc tissues, not dependent on disc biology, is well supported and currently unmet.

The one-year results of this prospective multi-site single-arm study have demonstrated procedure and device safety, as well as clinically relevant positive patient-reported outcomes in over 80% of patients from 1–2 weeks' follow-up through to 12 months. The absence of SAEs and serious complications is what would be expected for a micro-invasive injectable treatment. Beyond favorable reductions in pain and disability, the IDSD treatment provides added load support[20–23] to degraded disc tissues and increases spinal joint stability,[17–19] as confirmed in a limited capacity by the kinematic data acquired in this study. It is reasonable to assume that these restorative mechanical effects of the genipin load-sharing nano-tethers produced the favorable patient-reported outcomes in this study. These results support the use of a treatment strategy to address the core mechanical deficiencies of the spinal disc that contribute to discogenic pain, rather than merely masking the pain, especially in patients with early to mid-stage IDD.

IDSD treatment was found to be fast acting, with treatment effects seen in all but one of the participants at 1–2 weeks post-procedure. This rapid response is in sharp contrast to surgical approaches, which typically require a significant period of post-surgical recovery and rehabilitation, and to biological therapies, such as protein-rich plasma or stem cells, which typically require 6 or more weeks to achieve a desirable effect. In addition, treatment effects appear to be long lasting, with continued or improved clinical results at 12 months in 80% of patients treated in this study. In contrast, ESIs rarely have a treatment effect longer than 3 months.

Comparisons of ODI disability reduction with alternative treatments for CLBP demonstrate similar or superior results for IDSD. A randomized controlled trial (RCT)[28] evaluating outcomes for axial CLBP from four or more ESIs per year demonstrated reductions in ODI from baseline of 50.8%, 50.2%, and 49.8% at 3, 6, and 12 months, respectively. These reductions are slightly less than the 59.7%, 55.1%, and 51.3% reductions in the present study. An RCT evaluating the effectiveness of intraosseous basivertebral nerve ablation (a treatment intended to treat vertebrogenic pain)[29] reported 47.9%, 46.7%, and 46.7% reductions in ODI from baseline, and a prospective study evaluating a total lumbar disc replacement (ProDisc II)[30] reported 53.0%, 56.0%, and 48.6% reductions in ODI at the same follow-up time-points. Of these three existing approaches, only the total disc replacement provides mechanical load support to a degraded disc,

albeit with considerably greater invasiveness, complication rates and severity, and requiring greater post-procedure rehabilitation.

These early clinical data contain the temporary pain flares and fall-off of treatment effects experienced exclusively by higher-demand participants (weighing >85 kg). The need for a second treatment for high-demand patients was not unexpected, as the product was designed to provide an effective but not maximal level of mechanical stabilization, leaving amplification of the treatment effect to the discretion of the treating physician. Prior to these clinical data, the sufficiency of added mechanical load support from a single IDSD treatment corresponding to a simple indicator of patient mechanical demand – patient weight – could not be established from animal, laboratory, or analytical models. Therefore, these results suggest that the next clinical study protocol should authorize a second IDSD treatment for participants weighing more than 85 kg by the 1-month follow-up. This is a significant finding of the present study.

Mean segmental instability, as determined by QSI, was reduced across all treated levels at the 3-month follow-up; however, this reduction was not statistically significant. Regarding the subset of treated discs that were found to be clinically unstable pre-treatment (where instability was more than 1.5 standard deviations above the asymptomatic mean), there were statistically significant mean reductions in QSI at the 1-month and 3-month follow-ups, with the 3-month QSI restored to the asymptomatic mean, and the corresponding VAS and ODI scores reduced by 77% and 75%, respectively. This result affirms one of the mechanisms for pain relief associated with this treatment approach – stabilizing painful, unstable joints. The ability of IDSD to stabilize spinal joints was first demonstrated in ex vivo studies.[17–19]

The statistically significant increases observed in ROM and degrees of standing lordosis are objective metrics known to correspond to a reduction of pain and pain avoidance.[31,32] It is important to note that increased stability of treated lumbar motion segments did not reduce segmental ROM, but was instead accompanied by an increase in segmental ROM. This result agrees with earlier ex vivo study results,[17] which demonstrated that a genipin treatment reduced laxity in the minimally constrained region (neutral zone) of the flexion–extension motion curve without making the joint excessively stiff and over-constrained at the limits of flexion–extension. This is arguably a preferred form of joint stabilization – potentially eliminating aberrant motions and stresses at adjacent joints, while also reducing elevated strains and demand on adjacent musculoligamentous structures.

The absence of significant change in treated-level disc height in this study signaled that the treatment was well tolerated by the discs and surrounding tissues and that there were no changes in disc hydration. While discs were stabilized, the disc levels and segmental geometries were not different or abnormal, as would be the case with a disc replacement, nucleus augmentation, or fusion.

A temporary and fully treatable inflammatory response beginning 2–3 days after leakage of IDSD outside the disc is the primary source of adverse events associated with this treatment. Consequently, the device is indicated for patients with degraded symptomatic discs that are capable of retaining the injectable device (ie, collapsed discs or discs having fissures that penetrate the periphery of the disc should not be treated with this device). Pre-treatment discography may be necessary for patients with suspected penetrating disc fissures, although the treatment path when a penetrating fissure is confirmed has not yet been determined. Additional criteria will be determined as additional prospective data are produced. While this non-biologic nano-tethering approach can effectively reinforce spinal discs and stabilize joints at any stage of disc degeneration, IDSD may be best suited to meet the currently unmet need in early to mid-stage CLBP patients of reducing mechanical degradation that can progress to decades of back pain and disability. By providing additional mechanical support, IDSD may counteract the mechanically induced aspects of the degenerative process that lead to a cascade of detrimental changes to the disc and adjacent tissues. In this sense, it has the potential to decrease the likelihood of subsequent disc failures and resulting radiculopathy. However, there is no clinical evidence at this time confirming the adequacy of IDSD load support to resist the degenerative process. The limitations of this early-stage feasibility study begin with the small sample size, which could lead to overestimation of the treatment effects. As a single-arm study, there is no direct assessment of placebo effects or direct comparison to a known standard of care. Completion of the current 50-participant Australian study, as well as larger, controlled follow-on studies, will be required before this treatment can be taken to market. Other limitations include uncertain compliance by the study participants in reporting analgesic use.

Conclusion

Early clinical results for an injectable genipin-based nano-tethering device confirm that joint-stabilizing effects demonstrated in ex vivo experiments can be achieved in a clinical setting, while also demonstrating clinically meaningful improvements in pain and disability scores in at least 80% of patients from 2 weeks to 2 years post-treatment. For the more severely unstable joints, IDSD significantly reduced the instability score from a mean pretreatment level of 2.4 standard deviations above the mean for an asymptomatic population to the asymptomatic mean.

Seventy-five percent of "high-demand" (weight >85 kg) participants experienced a loss of treatment effect between 3 and 12 months after the procedure, while no participants weighing 85 kg or less experienced a similar drop-off. The mean improvement in pain scores at 12 months for the moderate-demand cohort was more than twice the reduction for those weighing more than 85 kg. Owing to the demonstrated ability to double the number of genipin nano-tethers and associated mechanical effects with a second round of IDSD treatment, the authors recommend evaluating the efficacy of a second treatment for higher-demand patients with discogenic back pain in future clinical trials. The conclusions from this study should be tempered with the recognition that it is an initial feasibility study with a small sample size.

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Disclosure

Dr Thomas Hedman reports personal fees from Intralink-Spine, Inc.; personal fees from Spinal Simplicity LLC; and grants and personal fees from Orthopeutics, LP, during the conduct of the study; as well as inventor's royalties from the University of Southern California, outside the submitted work. In addition, Dr Thomas Hedman has multiple US and foreign patents licensed to Spinal Simplicity, and owns a small number of stocks in Spinal Simplicity LLC via Spinal Simplicity's acquisition of Intralink-Spine and Orthopeutics in 2022. Dr Timothy Deer reports personal fees, consultancy, and research from Abbott; personal fees, consultancy, stock options, and research from Vertos; personal fees, consultancy, and stock options from SpineThera; personal fees, consultancy, stock options, and research from Saluda; personal fees, consultancy and stock options from Nalu; personal fees, consultancy, and stock options from Cornerloc; personal fees, consultancy, and common stock from Ethos; personal fees, consultancy, stock options, and research from SPR Therapeutic; personal fees from Medtronic; personal fees, consultancy, and research from Boston Scientific; personal fees, consultancy, stock options, and research from PainTeq; personal fees from Tissue Tech; personal fees, consultancy, and stock options from Spinal Simplicity; personal fees from Biotronik; research from Mainstay; and research from Avanos, outside the submitted work. In addition, Dr Timothy Deer has a patent pending with Abbott for DRG Leads. The authors report no other conflicts of interest in this work.

References

1. Buckwalter JA. Aging and degeneration of the human intervertebral disc. *Spine*. 1995;20:1307–1314. doi:10.1097/00007632-199506000-00022
2. Urban JP, Roberts S. Degeneration of the intervertebral disc. *Arthritis Res Ther*. 2003;5:120–130. doi:10.1186/ar629
3. Iatridis JC, Laible JP, Krag MH. Influence of fixed charge density magnitude and distribution on the intervertebral disc: applications of a poroelastic and chemical electric (PEACE) model. *J Biomech Eng*. 2003;125:12–24. doi:10.1115/1.1537190
4. Adams MA, Freeman BJC, Morrison HP, et al. Mechanical initiation of intervertebral disc degeneration. *Spine*. 2000;25(13):1625–1636. doi:10.1097/00007632-200007010-00005
5. Adams MA, Roughley PJ. What is intervertebral disc degeneration, and what causes it? *Spine*. 2006;31:2151–2161. doi:10.1097/01.brs.0000231761.73859.2c
6. Maniadakis N, Gray A. The economic burden of back pain in the UK. *Pain*. 2000;84:95–103. doi:10.1016/S0304-3959(99)00187-6
7. Druss BG, Marcus SC, Olfson M, et al. The most expensive medical conditions in America. *Health Aff*. 2002;21:105–111. doi:10.1377/hlthaff.21.4.105
8. Schlenk RP, Stewart T, Benzel EC. The biomechanics of iatrogenic spinal destabilization and implant failure. *Neurosurg Focus*. 2003;15:E2. doi:10.3171/foc.2003.15.3.2
9. Balague F, Mannion AF, Pellise F, et al. Non-specific low back pain. *Lancet*. 2012;379:482–491. doi:10.1016/S0140-6736(11)60610-7
10. Zhao F, Pollintine P, Hole BD, et al. Discogenic origins of spinal instability. *Spine*. 2005;30:2621–30.13. doi:10.1097/01.brs.0000188203.71182.c0
11. Butler D, Trafimow JH, Andersson GB, et al. Discs degenerate before facets. *Spine*. 1990;15:111–113. doi:10.1097/00007632-199002000-00012
12. Buckwalter JA, Woo SL, Goldberg VM, et al. Soft-tissue aging and musculoskeletal function. *J Bone Joint Surg Am*. 1993;75:1533–1548. doi:10.2106/00004623-199310000-00015

13. Butler MF, Ng YF, Pudney PDA. Mechanism and kinetics of the crosslinking reaction between biopolymers containing primary amine groups and genipin. *J Polymer Sci Part a Polymer Chem*. 2003;41:3941–3953. doi:10.1002/pola.10960
14. Slusarewicz P, Zhu K, Hedman T. Kinetic analysis of genipin degradation in aqueous solution. *Nat Prod Commun*. 2010;5:1853–1858.
15. Mi FL, Shyu SS, Peng CK. Characterization of ring-opening polymerization of genipin and pH-dependent cross-linking reactions between chitosan and genipin. *J Polymer Sci Part a Polymer Chem*. 2005;43:1985–2000. doi:10.1002/pola.20669
16. Panjabi MM. Clinical instability and low back pain. *J Electromyogr Kin*. 2003;13:371–379. doi:10.1016/S1050-6411(03)00044-0
17. Hedman TP, Saito H, Vo C, et al. Exogenous cross-linking increases the stability of spinal motion segments. *Spine*. 2006;31:480–485. doi:10.1097/01.brs.0000224531.49174.ea
18. Popovich JM, Yau D, Chuang SY, et al. Exogenous collagen crosslinking of the intervertebral disc restores joint stability following lumbar posterior decompression surgery. *Spine*. 2011;36:939–944. doi:10.1097/BRS.0b013e3181e8b1d5
19. Kirking BC, Toungate JK, Hedman TP. The dose response relationship between intervertebral disc flexion-extension neutral zone metrics and injected genipin concentration. *J Appl Biomater Funct Mater*. 2013;11:e73–e79. doi:10.5301/JABFM.5000151
20. Slusarewicz P, Zhu K, Kirking B, et al. Optimization of protein crosslinking formulations for the treatment of degenerative disc disease. *Spine*. 2011;36:E7–13. doi:10.1097/BRS.0b013e3181cc3de9
21. Chuang SY, Odono RM, Hedman TP. Effects of exogenous crosslinking on in vitro tensile and compressive moduli of lumbar intervertebral discs. *Clin Biomech*. 2007;22:14–20. doi:10.1016/j.clinbiomech.2006.08.001
22. Hedman TP, Chen WP, Lin LC, et al. Effects of collagen crosslink augmentation on mechanism of compressive load sharing in intervertebral discs. *J Med Biol Eng*. 2017;37:94–101. doi:10.1007/s40846-016-0207-z
23. Kirking B, Hedman T, Criscione J. Changes in the interfacial shear resistance of disc annulus fibrosus from genipin crosslinking. *J Biomech*. 2014;47:293–296. doi:10.1016/j.jbiomech.2013.10.019
24. Toungate J, Hedman TP, Slusarewicz P. Consecutive applications of protein crosslinking reagents to intervertebral disc annulus fibrosus results in a cumulative increase in crosslinking. *J Clin Eng*. 2014;39:90–95. doi:10.1097/JCE.0000000000000024
25. Weiler PJ, King GJ, Gertzbein SD. Analysis of sagittal plane instability of the lumbar spine in vivo. *Spine*. 1990;15:1300–1306. doi:10.1097/00007632-199012000-00012
26. Hipp JA, Guyer RD, Zigler JE, Ohnmeiss DD, Wharton ND. Development of a novel radiographic measure of lumbar instability and validation using the facet fluid sign. *Int J Spine Surg*. 2015;9:37. doi:10.14444/2037
27. Staub BN, Holman PJ, Reitman CA, Hipp J. Sagittal plane lumbar intervertebral motion during seated flexion-extension radiographs of 658 asymptomatic nondegenerated levels. *J Neurosurg Spine*. 2015;23(6):731–738. doi:10.3171/2015.3.SPINE14898
28. Manchikanti L, Pampati V, Benyamin RM, et al. Analysis of efficacy differences between caudal and lumbar interlaminar epidural injections in chronic lumbar axial discogenic pain: local anesthetic alone vs. local combined with steroids. *Int J Med Sci*. 2015;12:214–222.
29. Fischgrund JS, Rhyne A, Franke J, et al. Intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: a prospective randomized double-blind sham-controlled multi-center study. *Eur Spine J*. 2018;27:1146–1156. doi:10.1007/s00586-018-5496-1
30. Siepe CJ, Heider F, Haas E, et al. Influence of lumbar intervertebral disc degeneration on the outcome of total lumbar disc replacement: a prospective clinical, histological, X-ray and MRI investigation. *Eur Spine J*. 2012;21:2287–2299. doi:10.1007/s00586-012-2342-8
31. Laird RA, Gilbert J, Kent P, Keating JL. Comparing lumbo-pelvic kinematics in people with and without back pain – a systematic review and meta-analysis. *BMC Musculoskelet Disord*. 2014;15:229. doi:10.1186/1471-2474-15-229
32. Hansen BB, Bendix T, Grindsted J, et al. Effect of lumbar disc degeneration and low-back pain on the lumbar lordosis in supine and standing: a cross-sectional MRI study. *Spine*. 2015;40:1690–1696. doi:10.1097/BRS.0000000000001120