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Protocol for treating lumbar spinal canal stenosis with a combination of ultrapurified, allogenic bone marrow-derived mesenchymal stem cells and in situ-forming gel: a multicentre, prospective, double-blind randomised controlled trial

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ABSTRACT

Introduction In patients with combined lumbar spinal canal stenosis (LSCS), a herniated intervertebral disc (IVD) that compresses the dura mater and nerve roots is surgically treated with discectomy after laminoplasty. However, defects in the IVD after discectomy may lead to inadequate tissue healing and predispose patients to the development of IVD degeneration. Ultrapurified stem cells (rapidly expanding clones (RECs)), combined with an in situ-forming bioresorbable gel (dMD-001), have been developed to fill IVD defects and prevent IVD degeneration after discectomy. We aim to investigate the safety and efficacy of a new treatment method in which a combination of REC and dMD-001 is implanted into the IVD of patients with combined LSCS.

Methods and analysis This is a multicentre, prospective, double-blind randomised controlled trial. Forty-five participants aged 20–75 years diagnosed with combined LSCS will be assessed for eligibility. After performing laminoplasty and discectomy, participants will be randomised 1:1:1 into the combination of REC and dMD-001 (REC-dMD-001) group, the dMD-001 group or the laminoplasty and discectomy alone (control) group. The primary outcomes of the trial will be the safety and effectiveness of the procedure. The effectiveness will be assessed using visual analogue scale scores of back pain and leg pain as well as MRI-based estimations of morphological and compositional quality of the IVD tissue. Secondary outcomes will include self-assessed clinical scores and other MRI-based estimations of compositional quality of the IVD tissue. All evaluations will be performed at baseline and at 1, 4, 12, 24 and 48 weeks after surgery.

Ethics and dissemination This study was approved by the ethics committees of the institutions involved. We plan to conduct dissemination of the outcome data by presenting our data at national and international conferences, as well as through formal publication in a peer-reviewed journal.

Trial registration number jRCT2013210076.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This multicentre, prospective, double-blind randomised study is designed to minimise the risk of bias.
⇒ The size of the incision in the intervertebral disc will be standardised.
⇒ We have included an extensive range of secondary and exploratory outcomes to expand the existing methodological designs in this field.
⇒ A small sample size has been selected to evaluate safety and effectiveness and to provide a rationale for a larger validation trial.

INTRODUCTION

Intervertebral discs (IVDs) are the soft tissues that make up the spinal column together with the vertebrae and consist of the nucleus pulposus (NP) at the centre and the surrounding annulus fibrosus (AF). The regeneration capacity of IVD is limited due to poor nutritional supply and low cell density.[1] Since the elasticity of the IVD decreases with age, stress on the intervertebral joints and the posterior elements of the spine increases, resulting in thickening of the yellow ligament and the formation of osteophytes at the facet joint that compresses the dura mater and nerve roots. This disease, called lumbar spinal canal stenosis (LSCS), causes low back pain (LBP) and lower extremity pain. It has a high incidence in the middle-aged and older adults over the age of 50 years. The most common form of surgical management of LSCS without spinal instability involves

decompression of the spinal canal via laminectomy or laminoplasty.[2–4] In the USA, the estimated annual adjusted rate of LSCS surgery is 135.5 per 100 000 Medicare beneficiaries, resulting in a hospital bill of US$1.65 billion.[4] The LSCS surgery is economically favourable than many health interventions.[5] In addition, combined LSCS may be complicated by IVD herniation.[6]

Discectomy is the conventional surgical procedure involving the removal of IVD materials compressing the nerve root to relieve symptoms of IVD herniation.[7 8] However, the defect within IVD produced by discectomy may not readily heal, which may predispose patients to further IVD degeneration.[1] Consequently, the potential for developing severe disabling discogenic pain in addition to reherniation remains, which can necessitate additional surgery.[8–10] The prevalence of reherniation was reportedly 5%—26% of approximately 500 000 lumbar discectomies per year.[7–10]

Integration of a next-generation surgical procedure could prevent further IVD degeneration following the discectomy procedure and might improve long-term surgical outcomes.[1] We previously developed an in situ-forming sodium alginate gel (dMD-001), which can be filled into the defect in the IVD after discectomy in patients with lumbar IVD herniation and induces tissue repair of the defective disc,[11 12] and conducted a clinical trial.[13] This material gelates within 5 min in situ via calcium ion-mediated crosslinking without resulting in material protrusion after discectomy.[11 12] However, it is thought that there is a limit to the treatment of gel alone in middle-aged and elderly patients with reduced self-tissue repair capacity; therefore, the participants in the previous clinical trials were limited to those under 50 years of age.[13]

A clinical trial of local injection of allogenic bone marrow-derived mesenchymal stem cells (BMSCs) into the IVD found it safe and effective for the treatment of discogenic LBP.[14] However, conventional BMSCs are simply prepared from bone marrow mononuclear cells that adhere to a culture dish and known issues such as quality deterioration during mass culture and difficulty in ensuring quality identity.[15–19] To overcome these limitations, we developed highly purified, allogenic human BMSCs (known as rapidly expanding clones (RECs)).[19–23] RECs are ultrapure BMSCs produced by direct separation from bone marrow using two types of antibodies (CD90 and CD271) and a cell sorter. Quality control is easy because a uniform cell population can be obtained by separation.[16]

There has been no cell therapy or filler material that can be easily inserted into the defect in the IVD after discectomy that is expected to induce IVD regeneration for the treatment of combined LSCS. The clinical significance of using dMD-001 is that it prevents the RECs from leaking out of the IVD compared with RECs used alone, resulting in RECs differentiating into NP cells and activating existing NP cells, which is expected to be effective in repairing IVD tissue after discectomy.[6 24 25] We previously demonstrated the combination of REC and dMD-001 enhances IVD regeneration after discectomy compared with dMD-001 alone in a sheep model exhibiting severe IVD degeneration.[1]

The purpose of this clinical study is to investigate the safety and efficacy of a new treatment method in which RECs are implanted into the IVD in combination with dMD-001 in patients with combined LSCS. We will conduct a randomised pilot study to prevent postdiscectomy pain and degenerative progression, to evaluate safety and efficacy and to provide a rationale for the next phase of the study, including determining if any endpoints obtained should be considered in the validation trial.

METHODS AND ANALYSIS

Study design

This is a multicentre, prospective, double-blind randomised controlled trial (RCT). Patients aged 20–75 years who are diagnosed with combined LSCS will be assessed for eligibility. The planned start date for this clinical trial is June 2022, and it is estimated to end by September 2025. The flow chart and schedule are shown in figure 1 and tables 1 and 2, respectively.

Participants and informed consent

Eligibility criteria are summarised in table 3. Both preoperative and surgical inclusion/exclusion criteria have been established for this trial. Specifically, the study will recruit participants with symptomatic combined LSCS who are unresponsive to non-operative care and considered for laminoplasty and discectomy. Clinical signs and symptoms, as well as MRI findings, must validate the diagnosis of combined LSCS. Patients who have previously undergone lumbar surgery or have spine-related systemic diseases will not be considered.[13] In addition, only patients who receive single-level laminoplasty and discectomy will be considered eligible to participate in this trial. Although incidence in younger adults below the age of 50 years is uncommon and this age group will not be included in this study, the age of 20 years is simply set to provide a lower limit of age. On completion of standard discectomy, the treating surgeon will assess the feasibility of AF reapproximation and make the final decision as to whether the patient will be officially enrolled in the study.[13] Eligible candidates will be treated at Hokkaido University Hospital, Eniwa Hospital or Hokkaido Orthopaedic Memorial Hospital, depending on where the referring orthopaedic surgeons have formal accreditation. The surgical procedure will be performed by the referring surgeons and not a single surgeon.[13] Patients who meet the inclusion criteria will be contacted by one of the investigators to confirm their willingness to participate in the trial and arrange a baseline assessment, during which written informed consent will also be obtained.[13] All patients will be informed that they can withdraw from the trial at any time.

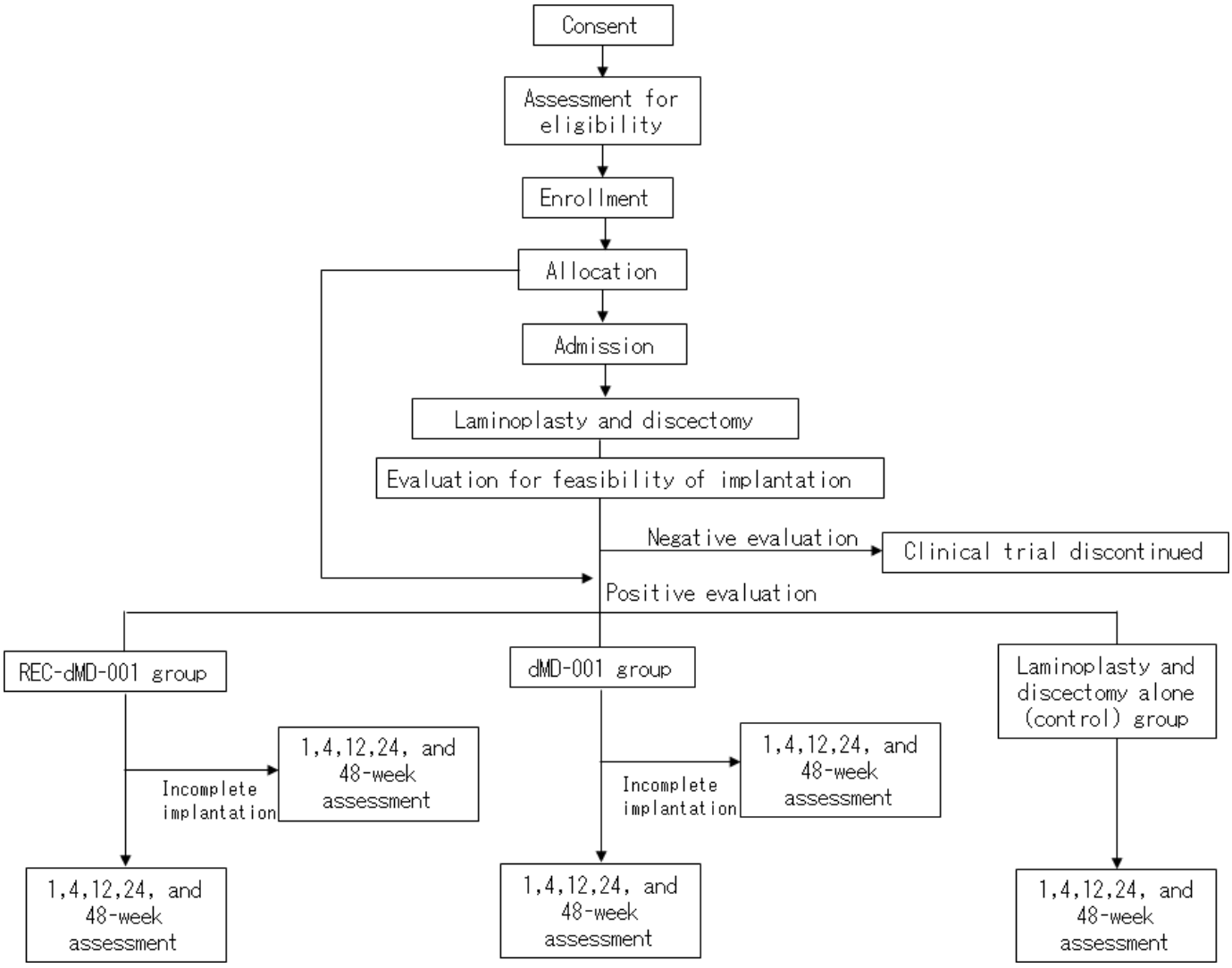

Figure 1 Study flow chart. REC, rapidly expanding clone.

Randomisation and blinding

On enrolment, treatment groups will be randomly assigned at the data centre. A minimisation method[26] will be used to ensure that there is no significant bias in the following ranges: (1) the number of patients enrolled in each group, (2) age and (3) preoperative visual analogue scale (VAS) score of lower extremity. After performing laminoplasty and discectomy, participants will be randomised 1:1:1 to receive treatment in the combination of REC and dMD-001 (REC-dMD-001) group, the dMD-001 group or the laminoplasty and discectomy alone (control) group. The details of the random assignment will not be given to the investigator.

In order to ensure blinding, surgeons and evaluators will be completely separated. In addition, monitors will be divided based on whether they are blinded or non-blinded, and all parties will be blinded except for the investigators who will be the surgeons at the investigational sites, operating room staff, investigational product managers, allocators, non-blinded collaborators and non-blinded monitors. The investigational product manager will dispense the investigational product under unblinded conditions. In addition, the unblinded monitor will monitor the study product delivery and other unblinded study records. Furthermore, information that impairs the blinding of surgical records to the investigational product will not be disclosed to the investigator who conducts the evaluation, the cooperating investigator or the participant until the key opening.

In case of medical emergencies where the identification of the investigational product is judged to be extremely important to minimise adverse health effects to the participant, the principal investigator may request the opening of the emergency key code in accordance with the 'Procedure for Opening the Key Code' provided separately.

Intervention

Laminoplasty and discectomy

All participants will undergo decompression of the spinal canal via laminoplasty and discectomy for combined LSCS. These open procedures will be conducted using standard retractors, with or without the use of an operating microscope or loupes. Laminoplasty is performed

Table 1 Schedule of trial enrolment, intervention, assessment and follow-up

	Study period						
	Enrolment	Operation	Postoperation				
Time point (week)	**−1**	**0**	**1**	**4**	**12**	**24**	**48**
Enrolment							
Eligibility screening	X	X					
Obtaining informed consent	X						
Randomisation	X						
Assessment							
Allergy test for sodium alginate (skin prick testing)	X						
Recording demographic characteristics	X						
Physical examination/vital signs evaluation	X		X	X	X	X	X
Laboratory tests	X		X	X	X	X	X
Visual analogue scale scoring for back pain and leg pain	X		X	X	X	X	X
Japanese Orthopaedic Association (JOA) scoring	X		X	X	X	X	X
36-item Short Form Health Survey	X		X	X	X	X	X
Oswestry Disability Index evaluation	X		X	X	X	X	X
Rolland-Morris Disability Questionnaire	X		X	X	X	X	X
JOA Back Pain Evaluation Questionnaire	X		X	X	X	X	X
Zurich Claudication Questionnaire	X		X	X	X	X	X
Radiographic evaluation	X	X					
MRI evaluation	X					X	X
Reporting adverse events	◄	———	———	———	———	———	►
Recording medical/drug use history	◄	———	———	———	———	———	►

Table 2 Laboratory tests

Survey item	Survey period
(Haematological examination) Red cell count, white cell count, haemoglobin, haematocrit, platelet count, white blood cell fraction, haemoprecipitation, date of specimen collection	Preobservation period (within 28 days before registration,* the day before surgery) Follow-up period (1, 4, 12, 24 and 48 weeks)
(Blood biochemical tests) AST, ALT, ALP, γ-GTP, total bilirubin, total protein, albumin, urea nitrogen, creatinine, total cholesterol, sodium, potassium, crawl, CRP, specimen collection date	
(Immunological markers) IgA, IgE, IgG, sample collection date	
(Urinalysis) Urine protein, urine sugar, date of specimen collection	
(Pregnancy urine test)† Pregnancy test results, date of specimen collection and reason if not performed	

*Test results performed within 28 days prior to registration will be made available even before consent is given.
†The study will be conducted in female participants of childbearing potential. However, this will not apply to participants who are at least 6 months postmenopausal or who have had a previous hysterectomy.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GTP, glutamyl transpeptidase; Ig, immunoglobulin.

from the midline to the lateral pars interarticularis and facets. After resection of the spinous processes and superficial dorsal lamina, central decompression is performed with removal of the ligamentum flavum. Partial medial facetectomies are performed to decompress the lateral recess and expose the neuroforamina and nerve roots (figure 2).[27 28]

All procedures will involve an AF incision of 5 mm × 5 mm.[13] Because patients with large annular defects following discectomy are at increased risk for symptomatic recurrence and reoperation and incision size may affect postoperative outcomes,[29] the size of the incision will be standardised. In patients with a transligamentous extrusion-type or sequestration-type herniated disc, the AF opening will be measured and reported.[13] The technique used for discectomy will be at the discretion of the surgeon.[13 30] It will not be a limited discectomy. The surgeon will aim to remove as much disc material as possible. Although the surgeons' preference may confound the outcomes, this represents an acceptable limitation that has been allowed to facilitate the recruitment of participants.[13] Instead, the mass of the disc material will be recorded and its effects will be analysed.

Stopping criteria before REC-dMD-001 or dMD-001 implantation[13]:

Table 3 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Candidate for laminoplasty following lumbar discectomy for combined LSCS.	1. Previous surgery involving a lumbar level.
2. Radiographic findings corroborating symptoms of combined LSCS.	2. Prior or planned spinal fusion involving a lumbar level.
3. Condition unresponsive to six consecutive weeks of therapy or experiencing acute/uncontrolled leg pain, defined as a score >80 on the 100 mm VAS, in which higher scores represent worse pain.	3. Local kyphosis involving the affected disc level, evident on plain radiography of the lumbar spine in the flexion, neutral or extension position.
4. Single-level combined LSCS.	4. Intradiscal air pattern at the affected level.
5. Persistent and predominant leg pain (score >40 on the 100 mm VAS).	5. Spondylolisthesis or retrolisthesis above grade 1 at the affected level.
6. Age between 20 and 75 years (inclusive).	6. IVD (height obtained by averaging the anterior and posterior heights of the IVD to be operated in the lumbar X-ray image in the neutral position) less than or equal to an average half of the adjacent caudal disc height.
7. Willingness to provide written informed consent, fill in all necessary questionnaires and return for follow-up.	7. History of treatment with condoliase.
	8. Severe hypersensitivity to serum albumin or antibiotics.
	9. Acute local or systemic infection.
	10. Active malignancy or other similar comorbidities.
	11. Current drug or alcohol dependency.
	12. Current significant emotional disturbance.
	13. Current fracture, tumour and/or deformity of the lumbar spine.
	14. Current or planned pregnancy.
	15. Currently enrolled in other research that could confound the results of the present trial.
	16. Presence of a metal implant or any other contraindication to MRI.
	17. Allergy to sodium alginate revealed on skin prick testing.
	18. Any other reason judged by an investigator or clinical trial doctor that renders the candidate unsuitable for this clinical trial.

IVD, intervertebral disc; LSCS, lumbar spinal canal stenosis; VAS, visual analogue scale.

1. The AF incision for discectomy exceeds 5 mm × 5 mm (ie, the diameter of the incision exceeds 5 mm).
2. The treating surgeon judges that AF reapproximation is not feasible or there is some other reason rendering the patient unsuitable for the implantation.

If either of the above stopping criteria is satisfied, no implantation will be conducted after standard discectomy and the patient will be excluded from the trial.

Implantation of REC-dMD-001 or dMD-001

Both RECs and dMD-001 are manufactured based on good manufacturing practice-compliant levels by PuREC (Izumo, Japan) and Mochida Pharma (Tokyo, Japan), respectively. Frozen RECs are thawed in a warm bath at 37°C prior to implantation, collected after centrifugation (110×g for 10 min at 4°C) and mixed with the dMD-001 solution to make a final concentration of 1×10^6 cells/mL.

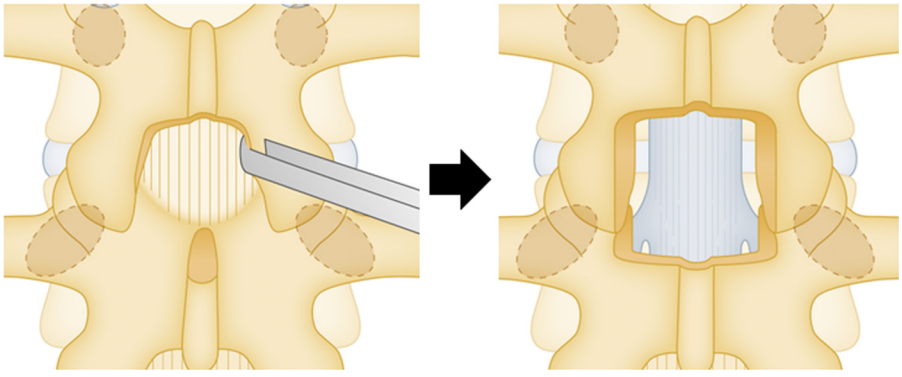

Figure 2 Illustration of laminoplasty.

Each REC-dMD-001 and dMD-001 is filled in a 2.5 mL syringe and covered with a translucent coloured surgical drape for blinding.

Following standard laminoplasty and discectomy, the treating surgeon will evaluate the feasibility of AF reapproximation. If the evaluation is positive, the IVD cavity will be implanted with the mixture of REC and dMD-001 solutions for the REC-dMD-001 group and dMD-001 solution for the dMD-001 group. Up to 2 mL of dMD-001 solution will be delivered into the IVD cavities, and 10 mL of 0.1 mol/L $CaCl_2$ solution will then be applied to the surface of the solution to gelate the alginate.[6 13] Five minutes after application of the $CaCl_2$ solution, the surgical site will be irrigated with a full dose of sterile, clinical-grade, normal saline.[13] For the control group, no additional procedures are required after laminoplasty and discectomy, and the surgical site will be irrigated and closed. All patients will receive standard postoperative care. Braces will not be used after surgery.

Stopping criteria during REC-dMD-001 or dMD-001 implantation[9]:

1. The volume of solution delivered into the IVD defect exceeds 2.0 mL.
2. The solution does not gelate on treatment with $CaCl_2$.
3. Any other reason judged by the treating surgeon that renders the participant unsuitable for the trial at this time.

If any of the above stopping criteria are satisfied, the surgical site will be irrigated with a full dose of sterile, clinical-grade, normal saline.[13] Assessment of safety after injection of the solution will be performed for up to 48 weeks after surgery.

Outcomes

Primary outcomes

The primary outcomes of this trial are the safety and effectiveness of the procedure. Adverse events occurring 48 weeks after the surgical treatment will be summarised with laboratory tests used as a safety assessment. Safety will be evaluated by the incidence of adverse events. The respective pain scores (VAS) for LBP and leg pain (for both the most painful leg and the contralateral leg)[13] and MRI imaging assessment (modified Pfirrmann classification,[31] disc height index (DHI[13])) will be conducted with a 3.0 T scanner (Ingenia Elition; Philips Healthcare, Best, the Netherlands).

The blinded investigator will evaluate back pain and leg pain (for both the most painful leg and the opposite leg), on a scale of 101 from 0 to 100 mm, before surgery and at 1, 4, 12, 24 and 48 weeks after surgery.[13] For lower extremity pain, the results of the pre-enrolment VAS score of the leg on the most painful side will be used as the baseline (primary assessment), and the VAS score for the same leg the day before surgery will be used as the baseline (secondary assessment). The transition and amount of change in the VAS score will be assessed during the follow-up period. For LBP, the VAS score at the first week of the follow-up period will be used as the baseline, and the change in the VAS score and the amount of change during the follow-up period will be evaluated. The VAS scores for LBP and lower limb pain will be evaluated separately.

For each participant, two board-certified specialists with over 10 years of experience will independently assess the treated IVD on mid-sagittal T2-weighted images according to the modified Pfirrmann grading system[31] and DHI using mid-sagittal T2-weighted images within 1 month before surgery (baseline) and 24 and 48 weeks postoperatively.[13] As DHI is the ratio of IVD height to proximal vertebral body height, both these values will be measured for the middle portion.[13] The DHI measurement using radiographic image will not be performed owing to the possibility of inaccurate measurement; this is because the measurement requires that irradiation direction of X-ray be parallel to the vertebral endplates and also depends on the patient's posture.

Secondary outcomes

The secondary outcomes of this trial are as follows: (1) physical function scores; (2) self-reported patient satisfaction at 1 day before surgery (baseline) and at 1, 4, 12, 24 and 48 weeks after surgery; (3) compositional quality of the IVD tissue evaluated on MRI within 1 month before surgery (baseline) and 24 and 48 weeks after surgery[13]; (4) hernia removal volume; and (5) filling volume of REC-containing sodium alginate or sodium alginate solutions.

The Japanese Orthopaedic Association (JOA) score will be used to assess functional status and the severity of clinical symptoms.[32] Health-related quality of life will be assessed using the 36-item Short Form Health Survey.[33] Overall functional outcome will be evaluated using the Oswestry Disability Index.[34] LBP-specific quality of life will be assessed using the Roland-Morris Disability Questionnaire.[35] Multidimensional evaluation of health status, including dysfunctions, disabilities and psychosocial problems associated with the lumbar spine disorder, will be assessed using the JOA Back Pain Evaluation Questionnaire.[36] The Zurich Claudication Questionnaire will be used to evaluate symptom severity, physical function and surgery satisfaction in LSCS.[37]

The use of medication in the week preceding each follow-up visit will be recorded at 1, 4, 12, 24 and 48 weeks postoperatively.

Sagittal T1ρ-weighted, T2*-weighted and diffusion-weighted images will be received after obtaining mid-sagittal T2-weighted images.[13 38–40] Each IVD will be extracted automatically on T1ρ and T2* mappings with reference to the T2 images using a software (Jim V.8; Xinapse Systems, Essex, UK), and T1ρ, T2* and apparent diffusion coefficient values of the treated IVD within the region of interest will be assessed.[13]

Hernia removal and filling volumes of REC-containing sodium alginate or sodium alginate solution will be evaluated.

Clinical events committee

Adverse events will be classified by an independent trained committee according to the study protocol.[13] The committee consists of four medical specialists (specialising in medical safety, infectious disease, stem cells and spine surgery). The adjudicating committee members will remain blinded to all treatment assignments throughout the adjudication process. As this is the first-in-human clinical study, we plan to proceed with the study while confirming the safety of each case for the first 10 cases. Then, safety will be confirmed in each of the next 10 cases.

Sample size

At this time, there are no clinical data on the combination of cells and biomaterials we will use to fill the cavity after discectomy. Therefore, it is not possible to statistically calculate a target sample size for this exploratory pilot trial based on previous references. This trial was designed to evaluate 45 patients, based on a previous exploratory clinical trial of dMD-001 implantation that was conducted on 40 patients with lumbar disc herniation over a 3-year period; this previous study found that 40 participants were sufficient for an exploratory clinical trial because it allowed them to detect probability differences with an accuracy of 95% in one or more adverse events exhibiting an incidence ratio of 7.5%.[13] We aim to evaluate key trial parameters such as preliminary indications of effectiveness and to advise of our calculation of a sample size for a full trial in the future.[13 41] Published guidelines recommend that pilot studies be undertaken to allow the testing of trial protocols under study conditions prior to evaluation in a full RCT.[13 42 43] Thus, the results of this limited phase I/II trial will also assist in determining the relevance and possible benefits of performing a significantly phase IIb or larger phase III RCT.[13 43]

Statistical methods

Data set category

The primary analysis for safety evaluation will be the safety analysis set (SAF). Population per-protocol set (PPS), which conforms to the study protocol, will be used for the analysis of primary and secondary outcomes, excluding the filling volume of REC-containing sodium alginate solution. The population of participants allocated REC-dMD-001 implantation will be used for the analysis of filling volume of REC-containing sodium alginate solution. The largest analysis population (full analysis set (FAS)) will also be analysed in the secondary analysis to examine the robustness of the conclusions.

SAF: the population of enrolled participants who meet all of the following criteria:

1. Participants deemed eligible for REC-dMD-001 or dMD-001 implantation.
2. Participants with no serious Good Clinical Practice (GCP) violations.

PPS: the population of enrolled participants who meet all of the following criteria:

1. Participants deemed eligible for REC-dMD-001 or dMD-001 implantation.
2. If assigned to the REC-dMD-001 or dMD-001 implantation group, participants who have completed REC-dMD-001 or dMD-001 implantation.
3. Participants with at least one efficacy assessment after random assignment.
4. Participants with no serious GCP violations.
5. Participants with no serious protocol violations.

FAS: the population of enrolled participants who meet all of the following criteria:

1. Participants deemed eligible for REC-dMD-001 or dMD-001 implantation.
2. Participants with at least one efficacy assessment after random assignment.
3. Participants with no serious GCP violations.

Statistical analysis

Data will be expressed as mean number±SD and frequency (percentage), as appropriate. For safety, the names of adverse events will be replaced by the names in the Japanese version of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use International Terminology for Drugs (Japanese version of the Medical Dictionary for Regulatory Activities), and the number of participants and incidence rates will be calculated. For efficacy, summary statistics will be calculated for the VAS and the MRI assessments, and an unpaired t-test will be performed to compare the means of each group. VAS scores, MRI assessments and other secondary outcomes overtime within subjects will be compared by using the repeated measures analysis of variance, and a paired t-test with Bonferroni adjustment will be performed for multiple comparisons. The χ^2 method will be used for the statistical analysis of categorical data. A p value <0.05 will be considered statistically significant. Statistical analysis will be performed using SAS V.9.4 (SAS Institute).

Monitoring

To secure adequate study performance, on-site monitoring of the study progress and compliance with the study protocol will be independently performed including checking of consent forms and direct inspection of clinical records, and original sources.

Ethics and dissemination

This study was designed in accordance with the Declaration of Helsinki and was approved by the ethics committees of Hokkaido University Hospital (approval number: R3-11), Eniwa Hospital (approval number: 22-01) and Hokkaido Orthopaedic Memorial Hospital (approval number: 22-02), as well as by the Japanese Pharmaceuticals and Medical Devices Agency (Japan). The trial will follow the GCP guidelines issued by the Japanese Ministry of Health, Labour and Welfare. The protocol has been registered with the Japan Registry of Clinical Trials (jRCT) (trial registration number: jRCT2013210076).

Any revisions to the protocol will be documented in the jRCT. We plan to present our data in presentations at national and international conferences, as well as publish our findings in a peer-reviewed journal.

Patient and public involvement

Patients and/or the public were not involved in the design or conduct, or reporting, or dissemination plans of this research.

DISCUSSION

This is the first exploratory study to investigate the safety and key trial parameters regarding the effectiveness of a combination of BMSCs and a biomaterial after discectomy in patients with combined LSCS. The RECs combined with the dMD-001 will provide valuable insights into the treatment of IVD defect after discectomy. Although LSCS is a common pathology, it will not be difficult to recruit the patients. However, as this is the first-in-human clinical study, we plan to proceed with the study while confirming the safety of each case for the first 10 cases. Then, safety will be confirmed in each of the next 10 cases. Because of the aforementioned reasons, this study is set to run over 3 years. In addition, the patients will be continually followed up until 96 weeks postoperatively, which will constitute an observational study after this trial.

The strengths of this study include its multicentre, prospective, double-blind randomised trial design that will minimise the risk of bias throughout. Another strength is that the size of the incision in the IVD will be standardised. In addition, we have included an extensive range of secondary and exploratory outcomes to expand the existing methodological designs in this field. Conversely, it is not yet common to involve patients and the public in the design of the clinical study in Japan. In addition, the study is limited by its small sample size owing to the funds obtained; however, this size has been selected to evaluate safety and effectiveness as a precursor to provide the rationale for a larger validation trial.

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Contributors HS is the principal investigator of this study, led the design of this pilot study and filed the funding application. HS, TM, YW, YMI, KK, KKT, NY, HK, TT, NI, TA, NS and TI have all contributed to the design of the study and to the drafting of the study protocol. HS drafted the manuscript. YMI provided statistical expertise to support the study methodology. All authors approved the final version of the manuscript.

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Competing interests HS is listed as an inventor on a patent application related to this work.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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