Official Title:	**A Prospective, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of a Single Injection of Rexlemestrocel-L Alone or Combined With Hyaluronic Acid (HA) in Subjects With Chronic Low Back Pain**
NCT Number:	NCT02412735
Document Date:	Protocol Version 7.0: 17 December 2018

A Prospective, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of a Single Injection of rexlemestrocel-L Alone or Combined with Hyaluronic Acid (HA) in Subjects with Chronic Low Back Pain

STUDY PROTOCOL

Protocol Number: MSB-DR003
Clinical Development: Phase 3
Version: 7.0
IND Number: 14638
Protocol Date: 17 December 2018

Sponsor: Mesoblast, Ltd. c/o Mesoblast, Inc.
505 Fifth Avenue, 3rd Floor
New York, NY 10017

Sponsor Authorized Representatives:

[redacted]
Mesoblast, Inc.

Confidentiality Statement

INVESTIGATOR'S SIGNATURE

Study Title: A Prospective, Multicenter, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of rexlemestrocel-L Alone or Combined with Hyaluronic Acid (HA) in Subjects with Chronic Low Back Pain

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s)

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance and to make those records available for inspection.

I will ensure that an IRB/EC completed the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB/EC all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB/EC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Agreement Signature:

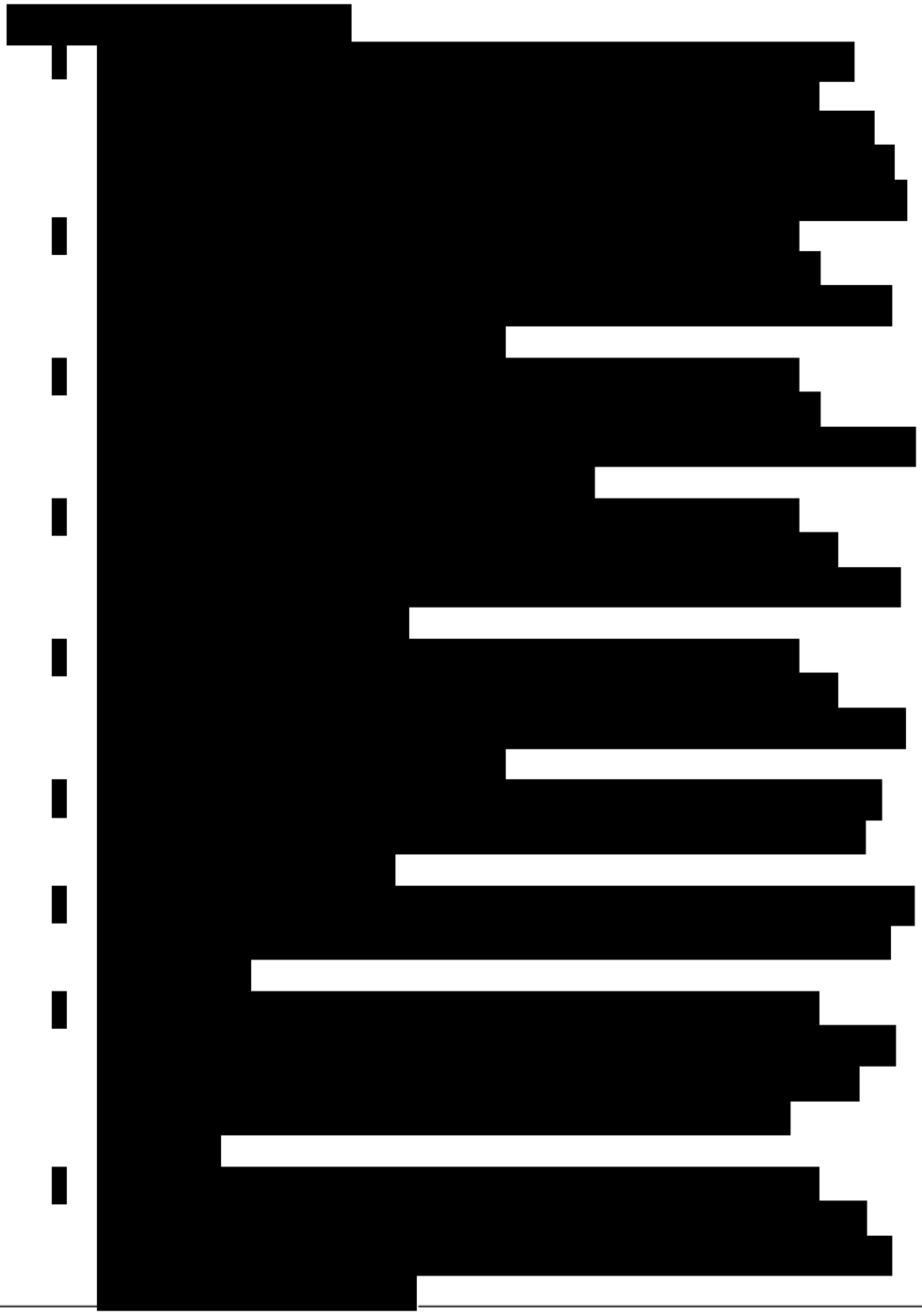
_____	_____	_____
Principal Investigator (Please print)	Principal Investigator (Signature)	Date

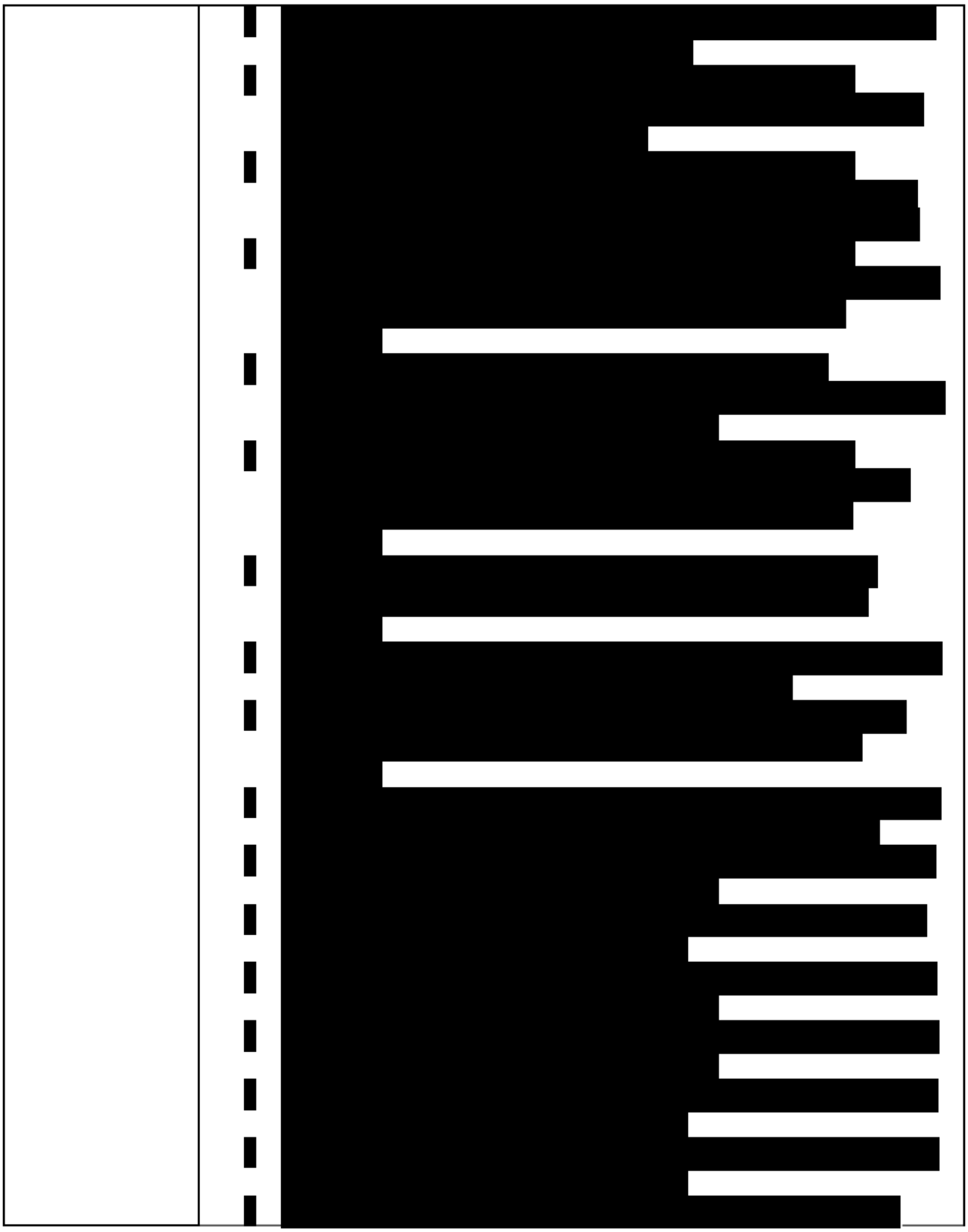
PROTOCOL SYNOPSIS

Protocol Title	A Prospective, Multicenter, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of rexlemestrocel-L alone or Combined with Hyaluronic Acid (HA) in Subjects with Chronic Low Back Pain
Sponsor	Mesoblast, Ltd.
Study Phase	Phase 3
Investigators and Clinical Sites	Up to 45 study centers from the United States, Australia, and potentially the European Union (EU)
Indication	Treatment of chronic low back pain (> 6 months duration) not adequately controlled by conservative measures and associated with moderate radiographic degenerative changes of a disc.
Objectives	**Primary Efficacy Objective:** • To determine Overall Treatment Success of rexlemestrocel-L alone or rexlemestrocel-L+HA at 12 *AND* 24 months based on a composite responder analysis of low back pain Visual Analog Scale (VAS) score, Oswestry Disability Index (ODI) score and no post-treatment interventions at the treated level. **Secondary Efficacy Objectives:** • To evaluate the effectiveness of rexlemestrocel-L alone or rexlemestrocel-L+HA in reducing chronic low back pain by performing a Pain Responder analysis at 12 *AND* 24 months post-treatment • To evaluate the effectiveness of rexlemestrocel-L alone or rexlemestrocel-L+HA in improving function by performing a Functional Responder analysis at 12 *AND* 24 months post-treatment • To evaluate the Treatment Success at 24 months of rexlemestrocel-L alone or rexlemestrocel-L+HA based upon a composite responder analysis of low back pain Visual Analogue Scale (VAS) score, Oswestry Disability Index (ODI) score and no post-treatment interventions at the treated level. • To evaluate the effectiveness of rexlemestrocel-L alone or rexlemestrocel-L+HA in reducing chronic low back pain based on incidence of subjects with minimal to no low back pain and no post-treatment interventions at the treated level at 24 months post-treatment (Minimal Pain Responder analysis) • To evaluate the effectiveness of rexlemestrocel-L alone or rexlemestrocel-L+HA in improving function based on incidence of subjects with minimal disability and no post-treatment

interventions at the treated level at 24 months post-treatment (Minimal Disability Responder analysis).

- To evaluate the effectiveness of rexlemestrocel-L alone or rexlemestrocel-L+HA in extending the time to additional interventions at the treated level over 24 months post-treatment.





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Primary Safety Objective:
To evaluate the safety of a single injection of rexlemestrocel-L alone or rexlemestrocel-L+HA injected into a lumbar intervertebral disc through 24 months post-treatment.

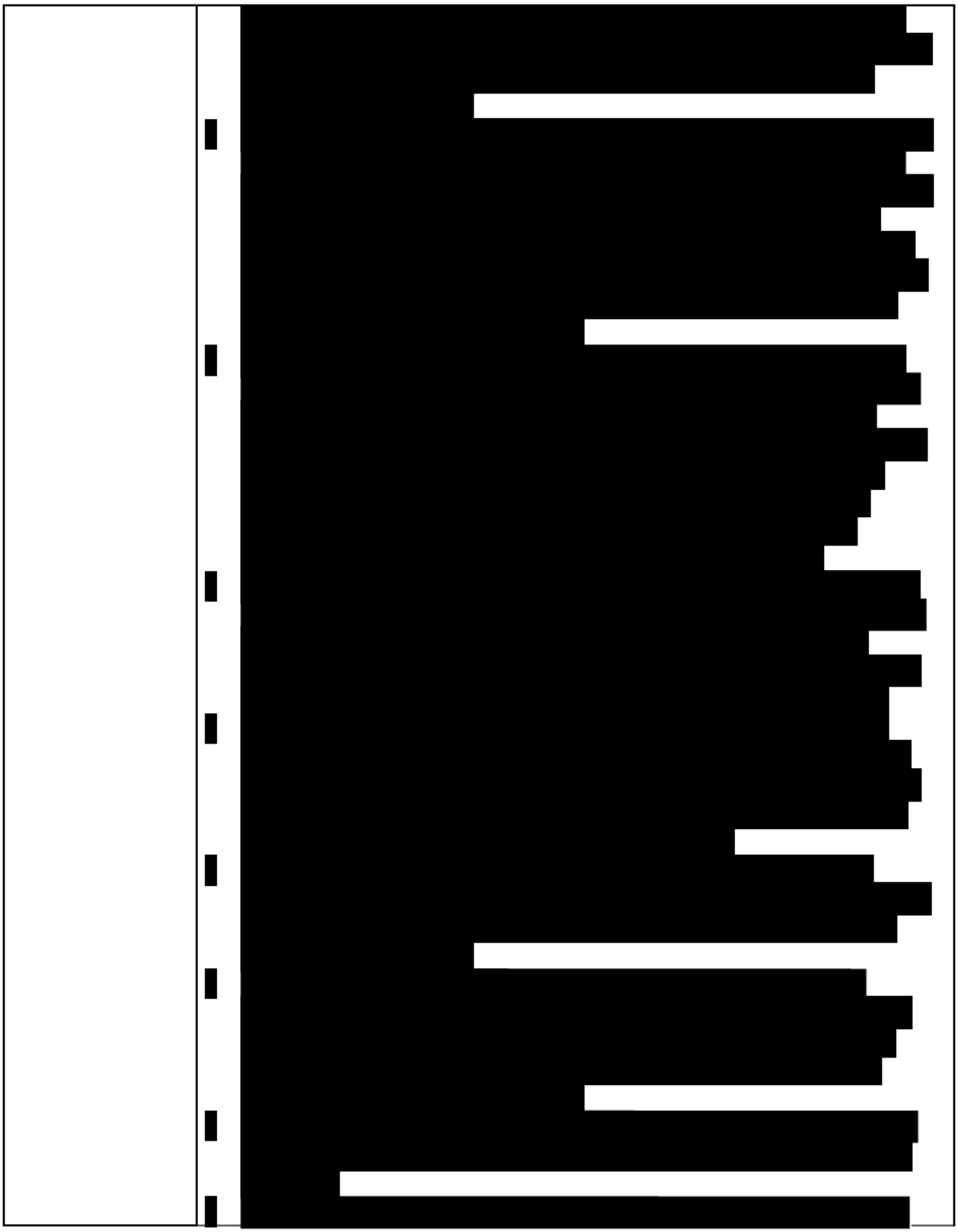
[redacted]

	[redacted]
Study Design	• Prospective • Multicenter • Double Blind • Placebo (defined as saline) controlled • Randomization, [redacted] with the randomization ratio of 1:1:1 between a. Treatment Arm 1: approximately 6 million rexlemestrocel-L cells alone b. Treatment Arm 2: approximately 6 million rexlemestrocel-L cells + HA c. Treatment Arm 3: saline • Subjects will be followed for approximately 36 months post-treatment and evaluated at baseline, treatment day (Day 0), 1, 3, 6, 12, 18, 24 and 36 months post-treatment. The primary endpoint for evaluation of safety and effectiveness will be conducted at 24 months. Longer-term safety and effectiveness assessments will be conducted at 36 months. • ***It is strongly recommended that there be no changes (increase or decrease) from or additions to baseline pain medications (opioids, NSAIDs, aniline analgesics, etc.) through at least the 24 month primary endpoint follow-up.*** This is designed to minimize possible confounding treatment effects due to alterations in pain medications. Furthermore, it is suggested that subjects do not schedule any medical procedures which would require an adjustment in pain medications during the 2 weeks prior to any study visit. Subjects not taking opioids at baseline should similarly refrain from starting opioid treatment. However, should a significant increase in pain from baseline occur, the subject should be provided appropriate pain relief. • ***Surgical and injection interventions should be avoided through at least the 24 month primary endpoint follow-up.*** Surgical and injection interventions should only be undertaken if the subject's pain, measured by VAS, and function, measured by ODI, is not improved compared to the baseline values since an intervention could confound the efficacy assessments and could classify a subject as a treatment failure.

	• ***Primary efficacy and safety evaluations will be performed through the 24 month follow-up visit*** • Study conduct and all safety will be supervised by an independent Data Safety Monitoring Board (DSMB) • Post-treatment interventions at the treated level and relationship of adverse events to treatment procedure or product will be adjudicated by a blinded and independent Treatment Events Committee (TEC).
Analysis set	Approximately 360 subjects, with the randomization ratio of 1:1:1, with a history of chronic (> 6 months) low back pain not adequately controlled by conservative measures for 6 months associated with moderate radiographic degenerative changes of a disc in the lumbar spine from L1 to S1.
Efficacy Endpoints	**Primary Efficacy Endpoint:** **Overall Treatment Success at both 12 *AND* 24 months**: Measured as subjects meeting each of the following criteria at both 12 *AND* 24 months post-treatment: • at least a 50% reduction from baseline in low back pain VAS score (average pain over 24 hours); *AND* • at least a 15 point decrease from baseline in ODI score; *AND* • no interventions at the treated level **Secondary Efficacy Endpoints:** 1. **Pain Responder at both 12 *AND* 24 months**: Measured as subjects meeting at least a 50% decrease from baseline in low back pain VAS score (average pain over 24 hours) at both Study Visit 6 (12 months post-treatment) and Study Visit 8 (24 months post-treatment) with no adjudicated post-treatment intervention through Study Visit 8. 2. **Functional Responder at both 12 *AND* 24 months**: Measured as subjects meeting at least a 15-point decrease from baseline in ODI at both Study Visit 6 (12 months post-treatment) and Study Visit 8 (24 months post-treatment) with no adjudicated post-treatment intervention through Study Visit 8. 3. **Treatment Success at 24 months:** Measured as subjects meeting each of the following criteria at Study Visit 8 (24 months post-treatment): o at least a 50% reduction from baseline in low back pain VAS score (average pain over 24 hours); AND o at least a 15 point decrease from baseline ODI score; AND o no interventions at the treated level **4. Minimal Pain Responder at 24 Months:** Measured as subjects meeting low back pain VAS score (average pain over 24 hours) of

20mm or less at Study Visit 8 (24 months post-treatment) with no adjudicated post-treatment intervention through Study Visit 8.

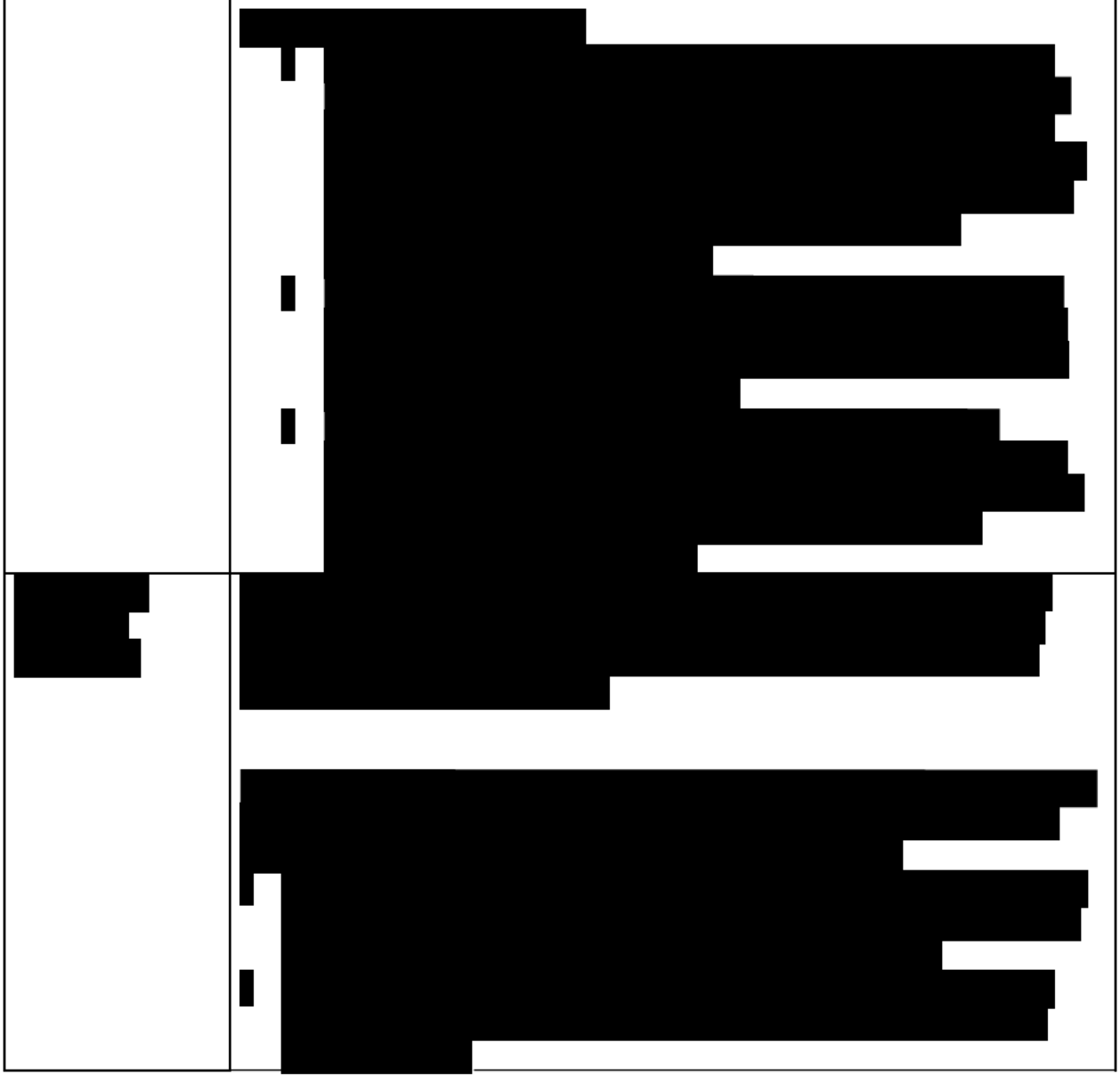
5. **Minimal Disability Responder at 24 Months:** Measured as subjects having an ODI score of 20% or less at Study Visit 8 (24 months post-treatment) with no adjudicated post-treatment intervention through Study Visit 8.
6. **Time to first intervention over 24 months:** Measured as time to first post-treatment intervention at the treated level through 24 months post-treatment.



[redacted]	[redacted]
[redacted]	[redacted]
Safety Endpoints	**Primary Safety Endpoint** Evaluation of overall safety, which includes the following: • Subject reported AEs and SAEs from baseline through 24 months post-treatment • Laboratory tests (hematology, serum chemistry, inflammatory

markers and antibody analysis). Abnormal results will be assessed relative to normative ranges and shift tables from baseline through 24 months post-treatment

- Reported events from radiographic imaging from baseline through 24 months post-treatment
- Post-treatment interventions at the treated disc through 24 months post-treatment
- Vital signs (heart rate, blood pressure and temperature)
- Physical examinations (abbreviated)
- Neurological examinations (motor, sensory, reflex).



	[redacted]
Randomization Stratification	Subjects will be stratified at randomization according to 1. Study site 2. Opioid user vs opioid non-user based on the opioid information entered in to the e-diary during baseline a) **Opioid Non-user:** subjects who did not take any opioids during the e-diary pain medication data collection period. b) **Opioid user:** subjects who did take an opioid during the e-diary pain medication data collection period. [redacted]
Inclusion Criteria	Subjects who meet the following criteria will be included in the study: 1. Male and female subjects 18 years of age and older 2. If female of childbearing potential, subject is non-pregnant, non-nursing, and agrees to use highly effective methods of contraception for a minimum of 24 months post-treatment (if a subject becomes pregnant during the study, the subject will remain in the study and only the requirement for radiation (X-ray or MRI) should be removed) 3. Signed informed consent and country-appropriate privacy forms (e.g., HIPAA forms in the US) indicating subject is willing to undergo treatment and willing to be available for each examination scheduled over the study duration 4. Have documented diagnosis of moderate radiographic degeneration of an intervertebral disc from L1 to S1, with a disc suspected of causing CLBP [redacted]

	[redacted] Chronic low back pain associated with moderate radiographic degeneration at a lumbar disc is defined as the following (subject must meet all of the listed conditions): a. Chronic low back pain for at least 6 months b. Have failed 6 months of conservative back pain care. (Conservative treatment regimens may include any or all of the following: initial rest, medications [e.g., anti-inflammatory, analgesics, narcotics/opioids, muscle relaxants], massage, acupuncture, chiropractic manipulations, activity modification, home-directed lumbar exercise program, and non-invasive pain control treatments or procedures) c. Have at a minimum undergone supervised physical therapy, such as daily walking routines, therapeutic exercises, and back education programs specifically for the treatment of low back pain ***AND*** taken a pain medication for back pain (e.g. NSAID and/or opioid medication). d. Change from normal disc morphology of the index disc as defined by radiographic evaluation by the core imaging evaluation provider. Radiographs must show all of the following: i. A modified Pfirrmann score of 3, 4, 5 or 6 on MRI at the index disc as determined by radiographic core lab ii. Modic Grade II changes or less on MRI at the index disc as determined by radiographic core lab iii. With or without contained disc protrusion at the index disc on MRI as determined by radiographic core lab e. Low back pain of at least 40mm and not more than 90mm of 100mm on low back pain VAS (average pain over 24 hours) f. Leg pain ≤20mm in both legs on a 100mm VAS scale g. ODI score of at least 30 and no more than 90 on a 100 point scale.
Exclusion Criteria	Subjects will be excluded from participating in the study if they meet any of the following exclusion criteria: 1. Female subjects who are pregnant or nursing, or women planning to become pregnant in the first 24 months post-treatment (if a subject becomes pregnant during the study, the subject will remain in the study and only the requirement for radiation (X-Ray, MRI) should be removed) 2. Extreme obesity, as defined by NIH Clinical Guidelines Body Mass Index (BMI > 40) 3. Have undergone a surgical procedure (e.g. discectomy, intradiscal electrothermal therapy, intradiscal radiofrequency, artificial disc replacement, interbody fusion) on the disc at the index or adjacent level 4. Osteoporosis, as defined by dual-energy X-ray absorptiometry

	(DEXA) scan. A DEXA T-score of ≤ -2.5 will exclude the subject. Only the following at-risk subjects will be required to undergo a DEXA scan at screening: a. Female subjects with a Simple Calculated Osteoporosis Risk Estimation (SCORE) of ≥6 and male subjects with a Male Osteoporosis Risk Estimation Score (MORES) of ≥6 b. Females ≥50 years of age or who are post-menopausal or post-hysterectomy with oophorectomy c. Subjects taking bisphosphonate medications for the treatment of osteoporosis d. Subjects with a history of chronic, high-dose steroid use (oral and/or inhaled). High-dose steroid use is defined as: i. Daily, chronic use of oral steroids of ≥5 mg/day ii. Daily, chronic use of inhaled corticosteroids (at least twice per day) iii. Use of short-term (less than 10 days) oral steroids at a daily dose >20mg prednisone (or equivalent) within 1 month of study procedure 5. Any lumbar intradiscal injection, including steroids, into the index or adjacent discs prior to treatment injection, with the exception of the following injections performed at least 2 weeks prior to study treatment: a. Contrast medium (discography or other diagnostic injection) b. NSAIDs c. Nerve-blocking anesthetics (e.g., lidocaine, bupivacaine) d. Antibiotics e. Saline 6. Have undergone a procedure affecting the structure/biomechanics of the index disc level (e.g., posterolateral fusion) 7. Epidural steroid injections within 8 weeks prior to treatment injection 8. Have received chronic (more than 7 consecutive days) treatment with systemic corticosteroids at a dose equivalent to prednisone ≥ 10 mg/day within 14 days prior to injection procedure 9. Have a known history of hypersensitivity or anaphylactic reaction to murine or bovine products or dimethyl sulfoxide (DMSO) 10. Have a known history of hypersensitivity or anaphylactic reaction to hyaluronic acid (HA) 11. Active malignancy or tumor as source of symptoms or history of malignancy within the 5 years prior to enrolment on study, except history of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or squamous cell carcinoma of the cervix

	if fully excised and with clear margins 12. Currently participating in another investigational trial and/or plans to participate in any other allogeneic stem cell/progenitor cell therapy trial within 36 months after study treatment 13. Have been a recipient of prior allogeneic stem cell/progenitor cell therapy for any indication or autologous stem cell/progenitor cell therapy or other biological intervention to repair the index intervertebral disc 14. An average baseline morphine equivalent dose (MED) of >75mg/day as determined by e-diary entries during the screening period 15. Taking systemic immunosuppressants 16. Current infection or prior history of spinal infection at the index level (e.g., discitis, septic arthritis, epidural abscess) or an active systemic infection 17. Pain catastrophizers, defined as having a score of 30 or more on the Pain Catastrophizing Scale 18. A medical condition, serious intercurrent illness, or extenuating circumstance that would preclude participation in the study or potentially decrease survival or interfere with ambulation or rehabilitation. Examples of conditions that should be excluded are as follows: • history of transient ischemic attack [TIA] • history of stroke • uncontrolled diabetes • autoimmune disease (only if it interferes with ambulation or rehabilitation) • muscular dystrophy • rheumatoid arthritis • active liver disease • upper motor neuron disease • myelopathy • disorders of bone metabolism (osteomalacia or Paget's disease) 19. Cauda equina syndrome 20. Subjects involved in spinal litigation, including workman's compensation, unless litigation is complete 21. Currently incarcerated (prisoners) 22. Are transient or has a severe alcohol or substance abuse problem defined as answering yes to 6 or more symptoms on the DSM-5 alcohol or substance/opioid questionnaires. 23. Unable to complete all required e-diary entries, assessments and follow-up according to the protocol

	24. A history of mental illness/incompetence. Mental illness/incompetence is defined as meeting the following criteria on the DSM-5 Self-Rated Level 1 Cross Cutting Symptom Measure – Adult questionnaire a. Domain 1, Depression - A response of 4 on either question b. Domain 6, Suicidal Ideation - A response of 4 on the question c. Domain 7, Psychosis - A response of 1 to 4 on either question d. Domain 9, Memory - A response of 4 on the question 25. Have a serious intercurrent medical condition or any other conditions or social situations that would impair the ability to give informed consent or unacceptably reduce protocol compliance or safety of the study treatment 26. Body habitus precluding adequate fluoroscopic visualization for the procedure or the procedure is physically impossible due to inability to inject the nucleus pulposus 27. Presence of ferromagnetic implants that would disallow MRI of the index disc 28. Presence of neurologic deficit on any component of the lumbar neurological exam at baseline (i.e., motor, sensory, or reflex portion of the exam) 29. A positive screen for human immunodeficiency virus (HIV) by antibodies or nucleic acid test 30. Clinically significant nerve pain (e.g., chronic radiculopathy or neuropathy) 31. Clinically significant sacroiliac joint pain based on the Appropriate Use Criteria established by the Spine Intervention Society including a targeted, pre-specified physical examination, and, if deemed medically necessary, confirmed by anesthetic injection. If a previously performed anesthetic injection to confirm SI joint pain was performed up to 6 months prior to injection (with documentation indicating that the SI joint pain is not the source of the subject's pain), this does not need to be repeated at screening 32. Compressive pathology due to stenosis or disc protrusion on MRI with associated clinical symptoms defined as leg pain VAS>20mm out of 100mm or neurologic deficit on neurologic exam 33. Disc extrusion with a maximum dimension greater or equal to twice the posterior height of the disc, or disc sequestration in the lumbar spine on MRI as determined by radiographic core lab 34. This criterion left blank on purpose

	35. Modified Pfirrmann score of 7 or 8 at any lumbar level (L1-S1) on MRI evaluation as determined by radiographic core lab 36. Symptomatic involvement of more than one lumbar disc [redacted] (i.e. more than one level with concordant pain upon provocative discography, if performed) 37. Symptomatic central vertebral canal stenosis as defined by neurogenic claudication 38. Spondylolisthesis or retrolisthesis Grade 2 and above (>25% of the AP dimension of the superior endplate of the inferior vertebra) at the index or adjacent level(s) on radiographic evaluation as determined by radiographic core lab or Spondylolysis at the index or adjacent level(s) 39. Lumbar spondylitis or other undifferentiated spondyloarthropathy affecting the index disc 40. Spinal deformity defined as lumbar scoliosis with a Cobb angle of the lumbar spine greater than 15 degrees on radiographic evaluation as determined by radiographic core lab 41. Any fracture of the spine at the index or adjacent levels that has not healed, or clinically compromised vertebral bodies at the index level due to current or past trauma, e.g., sustained pathological fracture or multiple fractures of vertebrae 42. Facet pain at the index level or adjacent segments as determined by a diagnostic medial branch block (a facet block injection is not acceptable for making this determination) to rule out facet joint involvement. If a previously performed medial branch block was performed up to 6 months prior to injection (with documentation indicating that the facet joint is not the source of the subject's pain), this does not need to be repeated at screening. 43. Have not completed a minimum of 10 out of 14 daily e-diary entries of pain medication use (e.g. NSAID, aniline analgesics and opioid use) prior to screening injection procedures (i.e., diagnostic disc injection to confirm intact annulus, discography, medial branch block and SI joint injection, if deemed necessary). If a historical screening injection procedure is used, the e-diary pain medication usage collection should be completed at least 14 days after the screening injection procedure. 44. Full thickness annular tears in the index level as determined by free flowing contrast media through the annulus fibrosis. Injection of contrast media into the index level must take place at least 2 weeks prior to the treatment injection. If a previously performed discography with contrast was performed up to 6 months prior to injection (with documentation indicating no full

	tear of the disc), this does not need to be repeated at screening.
Number of Treatment Arms	Subjects will be randomly assigned to 1 of 3 treatment arms, with the 1:1:1 chance of receiving rexlemestrocel-L alone, rexlemestrocel-L + HA, or saline control.
Investigational Treatment	**rexlemestrocel-L alone** Subjects enrolled in the "rexlemestrocel-L alone" arm will receive 1 injection of approximately 6 million rexlemestrocel-L cells in freeze media mixed in a 1:1 by-volume ratio with saline. A vial with 2mL of thawed rexlemestrocel-L cells and freeze media will be mixed with 2mL of saline. Two milliliters of the resulting mixture will be injected via pressure manometer syringe into the nucleus pulposus of the index level. **rexlemestrocel-L + HA** Subjects enrolled in the "rexlemestrocel-L + HA" arm will receive 1 injection of approximately 6 million rexlemestrocel-L cells in freeze media mixed in a 1:1 by-volume ratio with 1% hyaluronic acid (HA) solution. A vial with 2mL of thawed rexlemestrocel-L cells and freeze media will be mixed with 2mL of 1% HA solution. Two milliliters of the resulting mixture will be injected via pressure manometer syringe into the nucleus pulposus of the index level.
Control Treatment	**Saline** Subjects enrolled in the control arm will receive a saline injection. Two milliliters of thawed saline from one vial will be mixed with 2mL of thawed saline from another vial of saline. Two milliliters of the resulting saline mixture will be injected via pressure manometer syringe into the nucleus pulposus of the index level.
Blinding	Due to the appearance, configuration, and storage conditions of rexlemestrocel-L, saline, and HA, it is not possible to blind treatment. A separate study-specific blinding plan is provided. A blinding plan has been developed to ensure that the blind has been maintained throughout the study and bias is not introduced into the study. Specific methods to maintain the blind are detailed in the blinding plan. In order to maintain the blind, each site will have an unblinded designee(s) (identified by the investigator) who receives all investigational and control product, performs accountability, properly stores it in a secure location, and prepares the injection. Additionally, the health care professional who is performing the study treatment injection will be unblinded. The unblinded health care professional who is performing the study treatment injection will perform all required procedures and evaluations associated with the treatment injection, including neurological exam prior to discharge, but will not be involved with any subject care or assessment beyond the subject's discharge following the injection procedure. All other site personnel, specifically those administering subject assessments and

	care, will be blinded to the treatment as will the subjects, radiographic evaluators, and members of the study team, with the following exceptions: unblinded CRAs (responsible for IP reconciliation) and unblinded statistician(s) (responsible for providing data for the interim analyses and DSMB data). Prior to the treatment administration visit, both blinded and unblinded personnel can perform screening activities. **Importantly, all unblinded study site personnel will be specifically instructed to refrain from discussing any potentially unblinding information with either the subject or any blinded site, sponsor, or CRO personnel involved in the trial.** Independent blinded radiologists will be evaluating radiographic images for key inclusion/exclusion criteria to maintain consistency and for post-treatment radiographic endpoints. The DSMB will be unblinded in order to assess the safety of investigational product (IP). The TEC performing adjudication of post-treatment interventions at the treated disc and relationship of adverse events to the product or procedure will be blinded to treatment assignment. When the unblinded statistical analyses are conducted at the primary safety and efficacy evaluation (the 24-month safety and efficacy evaluation period), study subjects, as well as site personnel responsible for subject care and assessment, radiographic reviewers and TEC members, will continue to be blinded until completion of the study at 36 months post-treatment. An unblinded statistician will conduct the specified interim analyses and only the information prescribed in the SAP will be provided so as to maintain the blind.
Duration of Treatment	This is a one-time treatment administration.
Follow up Schedule	All subjects will be followed for 36 months post-treatment. Subjects will be evaluated at baseline, treatment day (Day 0), as well as Study Visits 3, 4, 5, 6, 7, 8, and 9 (corresponding to 1, 3, 6, 12, 18, 24, and 36 months post-treatment). **The primary analysis of safety and efficacy will be assessed at Visit 8 (24 months post-treatment).** A longer-term follow-up of safety and efficacy will be assessed at Visit 9 (36 months post-treatment).
Data & Safety	A DSMB will meet on a regular basis and ad-hoc, as needed, to review

Monitoring Board	safety, enrollment progress, and any other pertinent information. The DSMB will consist of an independent multi-disciplinary group. Based on its findings, the DSMB will make recommendations regarding study continuation, enrollment and/or study modification(s).
Post-Treatment Interventions	***Surgical and injection interventions should be avoided through at least the 24 month primary endpoint follow-up.*** Surgical and injection interventions should only be undertaken if the subject's pain, measured by VAS, and function, measured by ODI, are not improved compared to the baseline values since an intervention could confound the efficacy assessments and would classify a subject as a treatment failure. For any subjects who are planning any post-treatment intervention during the course of the study, every effort should be made to schedule an "unscheduled visit" within a 30-day time window prior to the intervention. During this visit, all assessments and activities regularly performed at Visits 3-9 will be performed, with the exception of imaging assessments, hematology, chemistry panel, Flow Class I and II % PRA with specificity testing and DSA. If the subject's originally planned assessment timepoint falls within 30 days prior to the post-treatment intervention, the unscheduled visit will not be necessary. As one of the criteria defining some of the primary endpoints and responder analyses, any post-treatment interventions should be reported in a consistent manner. In order to identify all potential interventions at the treated level and maintain standardized classification of these interventions, the TEC will be used. The TEC will perform ongoing independent blinded adjudication of post-treatment interventions.
Interim Analyses	Interim analyses may be performed during the course of the trial. These will be conducted by external independent statistician(s) who will be unblinded to study data. All blinded personnel and subjects will remain blinded to the results of the analyses. The integrity of the study database will be maintained as well, and no bias will be introduced to the evaluations in the study due to the conduct of these interim analyses. [redacted] All subjects, independent reviewers and blinded personnel interacting with subjects will remain blinded through the completion of the study.
Statistical Analysis	**General Considerations** The statistical analysis plan (SAP) will be finalized and submitted to the appropriate health authorities prior to the first interim analysis. The primary unblinded statistical analyses will be conducted by the sponsor or

authorized representative after all enrolled study subjects who remain active in the trial at the time of their 24 month study visit have completed this milestone event. All interim analyses will be conducted by the unblinded statistician and all blinded personnel will remain blinded to the results other than the specified output of each analysis.

The primary efficacy objective of the study is to demonstrate that either rexlemestrocel-L alone or rexlemestrocel-L + HA has a higher rate of treatment success — defined as a 50% reduction in low back pain VAS score, 15 point decrease in ODI score, and no interventions at the index level — compared to the saline control arm at 12 *AND* 24 months post-treatment. The significance level for the Primary Efficacy Endpoint is adjusted for multiple comparisons of each active arm to the control group. The family-wise type I error rate will be controlled below 0.025. Additional details, including the adjusted threshold for success, are provided in the SAP.

For all secondary endpoints, a gatekeeping strategy will be used maintain the overall type 1 error at overall one-sided 0.025. For all other exploratory efficacy endpoints, a two-sided significance level of 0.05 will be used for comparison between each active arm and the control group.

Sample Size and Randomization

Approximately 360 subjects will be enrolled in a randomization ratio of 1:1:1, with each subject assigned to the rexlemestrocel-L alone, rexlemestrocel-L + HA, or saline control group. Randomization will be stratified by study site and opioid use at baseline (opioid users vs opioid non-users).

[redacted]

[redacted]

[redacted]

Analysis Sets

All Enrolled Subjects Analysis Set
All subjects who signed the informed consent are included in the All Enrolled analysis set. The All Enrolled Subjects analysis set will be used for summarizing subject disposition.

Intent-to-Treat (ITT) Analysis Set
The ITT analysis set includes all subjects who are randomized, regardless of whether or not the subject is treated, or post-treatment measurements are performed. In these analyses, subjects will be assigned to treatment according to randomization (not actual treatment received). The ITT analysis set will be used for summarizing demographics, baseline characteristics, surgical procedures and treatment exposure. The ITT analysis set will be used as the primary analysis set for all primary and secondary efficacy analyses. As sensitivity, the efficacy analyses will also be performed on the Full Analysis Set, the As Treated and the Per Protocol analysis sets, as defined herein.

Full Analysis Set [FAS]
The FAS analysis set includes all subjects who are randomized and treated or randomized with an attempt to administer treatment (i.e. subjects taken to procedure room to receive treatment whether administered or not). In these analyses, subjects will be analyzed according to the treatment to which they were randomized (not actual treatment received). Subjects that were randomized but dropped out prior to attempting treatment will be omitted from the FAS analysis set.

As Treated Analysis Set
The As Treated analysis set includes all subjects randomized, analyzed according to the treatment that was actually administered.

Per Protocol (PP) Analysis Set

	The per-protocol (PP) analysis set will contain all subjects in the ITT who received treatment to which they were randomized, had at least 1 post-treatment efficacy measurement (VAS and ODI), and did not experience any major protocol deviations. Protocol deviations will be determined for all randomized subjects mainly from the clinical database and Clinical Trial Management System (CTMS) following clinical and/or medical review of subject data for relevant findings that might have an impact on the definition of the PP analysis set/ major protocol violations. Protocol deviations that occur during the study will be adjudicated by the sponsor (or designee) and categorized by severity. Protocol deviations will be classified as minor or major during a blinded review of the data prior to the lock of the database for analysis. If relevant deviations are identified, they will be designated as major protocol violations. Safety Analysis Set The safety analysis set will contain all subjects who were randomized and received treatment, and subjects will be classified according to the actual treatment received. Safety analysis set will be used for the safety analyses. If there is any doubt whether a subject was treated or not, they will be assumed treated (randomized treatment) for the purposes of analysis. **Demographic and Other Baseline Characteristics** Demographics and baseline characteristics will be summarized by treatment arm for the ITT and PP analysis sets, as well as presented in data listings. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum). In order to assess baseline comparability, treatment groups will be compared for all continuous variables using an ANOVA between individual treatment and control groups. Categorical variables will be summarized using counts and percentages for each category. Treatment groups will be compared for all non-missing categorical variables using a Chi-Square test of association. Missing categories will be presented if necessary, but excluded from any tests of association. **Statistical Methods** Primary efficacy analysis

The Primary Efficacy Endpoint for overall treatment success (responder vs non-responder) at 12 *AND* 24 months will be summarized for each treatment arm by numbers and percentages. Each active treatment arm will be compared to the saline control group using a Bayesian test of superiority using non-informative Beta (0.5, 0.5) priors for each arm.

Secondary and Other Efficacy Analyses

The same Bayesian methodology used for the primary analysis will also be used for the secondary endpoints. The Bonferroni-adjusted posterior probability threshold of 0.9875 will apply to any subsequent secondary analyses performed.

As part of the gatekeeper strategy, the evaluation will be carried out in a hierarchical fashion following the order given below. Specifically, if the primary endpoint objective is met, the secondary outcomes will be evaluated hierarchically within each arm using the posterior probability threshold of 0.9875 for each comparison, sequentially. Once a key secondary endpoint is not met at this threshold within an arm, all subsequent comparisons in that arm will be considered exploratory.

1. **Pain Responder at both 12 *AND* 24 months**: Measured as subjects meeting at least a 50% decrease from baseline in low back pain VAS score (average pain over 24 hours) at both Study Visit 6 (12 months post-treatment) and Study Visit 8 (24 months post-treatment) with no adjudicated post-treatment intervention through Study Visit 8.
2. **Functional Responder at both 12 *AND* 24 months**: Measured as subjects meeting at least a 15-point decrease from baseline in ODI at both Study Visit 6 (12 months post-treatment) and Study Visit 8 (24 months post-treatment) with no adjudicated post-treatment intervention through Study Visit 8.
3. **Treatment Success at 24 months:** Measured as subjects meeting each of the following criteria at Study Visit 8 (24 months post-treatment):
    a. at least a 50% reduction from baseline in low back pain VAS score (average pain over 24 hours); AND
    b. at least a 15 point decrease from baseline ODI score; AND
    c. no interventions at the treated level
4. **Minimal Pain Responder at 24 Months:** Measured as subjects meeting low back pain VAS score (average pain over 24 hours) of 20mm or less at Study Visit 8 (24 months post-treatment) with no adjudicated post-treatment intervention through Study Visit 8.
5. **Minimal Disability Responder at 24 Months:** Measured as

subjects having an ODI score of 20% or less at Study Visit 8 (24 months post-treatment) with no adjudicated post-treatment intervention through Study Visit 8.

6. **Time to first intervention over 24 months:** Measured as time to first post-treatment intervention at the treated level through 24 months post-treatment.

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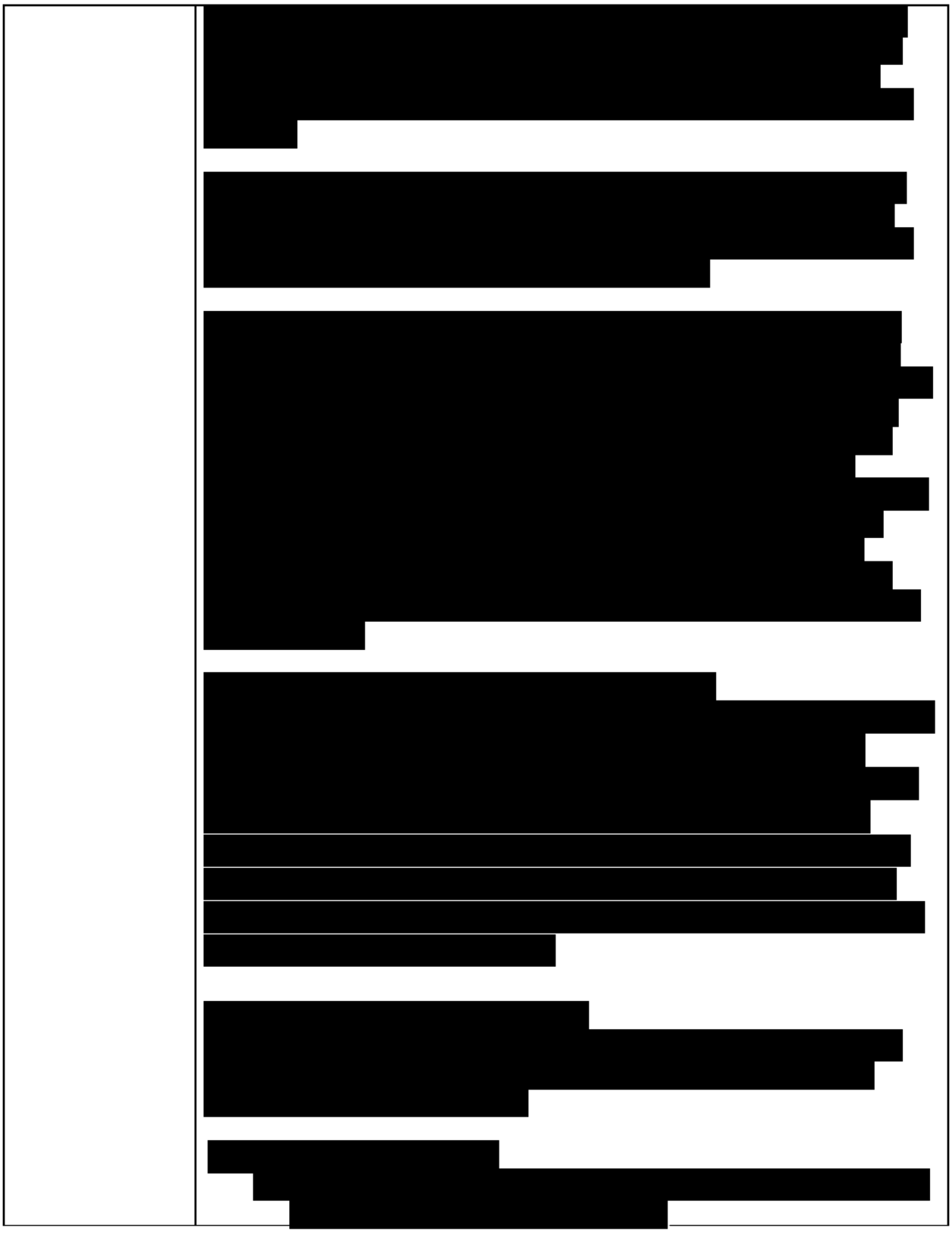

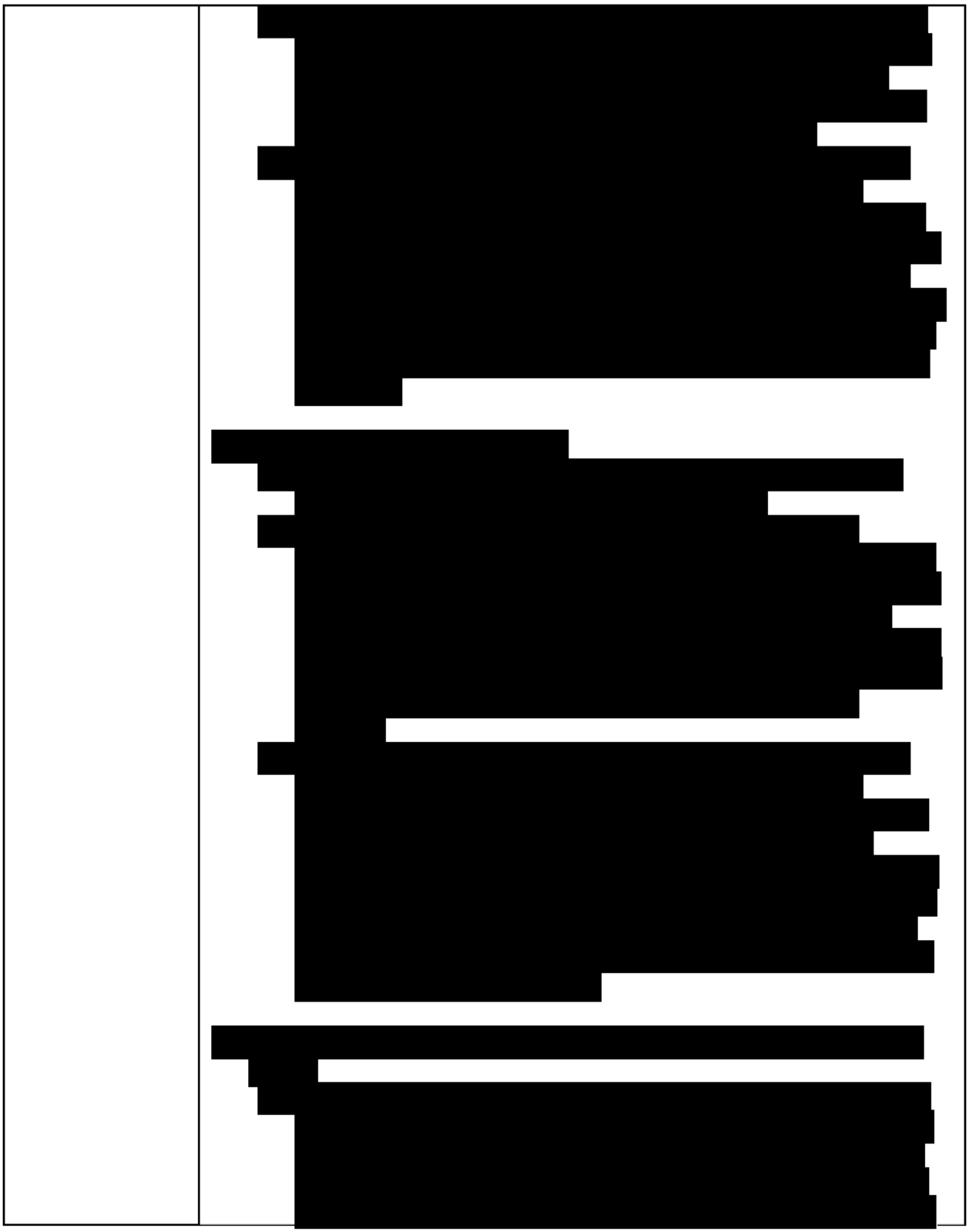

Primary Safety analyses

The Safety Analysis Set will be used for summary and analysis of the safety endpoints.

Descriptive statistics will be used for the summary of safety parameters – the number and percentage will be used for the incidences of AE/SAEs, deaths, early discontinuation due to AEs, and post-treatment interventions. The AE/SAE severity and relationship with the study procedure and treatment will be summarized and presented.

Actual and change from baseline by visit (for quantitative measurements), for parameters with continuous results, will be summarized presenting the number of subjects, mean, standard deviation, median, minimum and maximum. The shift table (cross-tabulation) for the changes from baseline to each visit (low/normal/high) for the laboratory parameters will also be also provided.
For parameters with discrete results, frequency distributions and shift from baseline will be displayed.

Incidence of abnormal values according to normal range will be tabulated using counts and percentages of subjects with at least one abnormally low or high value or as 'low/high' (if the subject has both during the study), per lab parameter through 24 months post-treatment separately.

Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements) will be presented as a cross-tabulation of low/normal/high values at baseline to those of the worst value through 24 months post-treatment separately by treatment group for each parameter.

[redacted]

Handling of Early Terminators or Missing Data

For the responder analyses, including the primary efficacy endpoint, as well as pain and function responder analyses, subjects will be classified as having attained success (responder) or not attained success (non-responder).

The Primary Efficacy Endpoint requires a subject to meet clinically significant improvements in both pain and function at both 12 and 24 months, as well as not undergo any post-treatment intervention at the treated level through 24 months, to be considered a success.

If in-clinic assessments for Study Visits 6 and 8 (corresponding to 12 and 24 months) are unavailable, the data will be considered missing. If a scheduled in-clinic visit is missed, the site should contact the subject to determine if any interventions that would classify the subject as a treatment failure have occurred since their last visit. If any interventions are reported, the site should collect all the information required if the intervention had been reported at an in-clinic visit. All intervention information collected remotely must be documented in a source document and/or worksheet.

If a subject receives a post-treatment intervention at the treated level on or

	prior to the date of Study Visit 8 (24 months), this subject will be considered a non-responder regardless if there is any missing data. For example, a subject that has a post-treatment intervention at the treated level at the time of Study Visit 4 (3 months) would be considered a non-responder regardless of whether there are Visit 6 or Visit 8 data available for analysis, as they would have already failed one of the criteria to be considered a responder. If a subject has data available at both Study Visit 6 (12 months) and Study Visit 8 (24 months), with no post-treatment intervention at the treated level as of the date of Study Visit 8, that subject will be determined either a responder or non-responder based upon whether or not the subjects meets the pain and functional improvement criteria at both study visits. Any subject that is missing one or more components in an endpoint (e.g. VAS in the primary endpoint) at a visit will be considered a non-responder at that visit if any available component of the endpoint indicates that the subject is a non-responder (even if all components of the endpoint are not available). If none of the available components impose non-response, the outcome will be considered missing and will be handled according to the proposed methodology described below. Assumptions regarding responder analyses include the following: • If the subject does not meet the criteria of either pain or function at either Visit 6 or Visit 8, the subject will be considered a non-responder. • If the subject meets the pain and function improvement criteria at both Visit 6 and Visit 8, and has no post-treatment intervention as of the date of Visit 8, the subject will be considered a responder. • Any subject that is a non-responder on one of the two primary study visits (Visit 6 or Visit 8) but has a missing outcome for the other study visit is deemed a non-responder and not considered to have a missing outcome for the primary analysis. • If a subject does not have a minimum of a visit at 3-months (Study Visit 4) they will be considered a non-responder. • Any subject that has a minimum of 3-months data (Study Visit 4) but is missing one or both of the two primary study visits, will have their outcome multiply imputed based on their available information. Separate models will be constructed for o Subjects that are missing one of the two primary study visits (Visit 6 or Visit 8) but not both; o Subjects that are missing both of the primary study visits.

	A detailed description of the statistical methodology for multiple imputation of missing data for responder analyses can be found in the SAP. For subjects who have a post-treatment interventional procedure at the treated level, the analyses of continuous and categorical efficacy variables will include only data collected before the post-treatment adjudicated intervention. MMRM will be used for the analysis of over time of quantitative variables and missing data will not be imputed. <u>Examination of Subgroups</u> Pre-specified subgroup analyses based on both the ITT and PP analysis sets for the primary and secondary efficacy variables will be performed for key demographic and baseline variables, as described in the SAP.

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GLOSSARY OF ABBREVIATIONS

ACR	Albumin-to-creatinine ratio
ADA	American Diabetes Association
AE	Adverse event
AESI	Adverse events of special interest
ALT [SGPT]	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
A/P	Anterior/posterior
AST [SGOT]	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BMI	Body mass index
BOCF	Baseline observation carried forward
BP	Blood pressure
BUN	Blood urea nitrogen
cABC	Chondroitinase ABC
CCS	Composite clinical success
CFR	Code of Federal Regulations
CI	Confidence interval
CK	Creatine kinase
CLBP	Chronic Low(er) Back Pain
CMH	Cochran Mantel Haenszel (test)
CRF	Case report form
CRT	Cardiac Resynchronization Therapy
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DAS28	Disease Activity Score in 28 Joints
DBP	Diastolic blood pressure
DCS	Data collection specification
DDD	Degenerative disc disease
DEXA	Dual-energy X-ray absorptiometry (scan)
DLCO	Diffusing capacity for carbon monoxide
DCSI	Development Core Safety Information (document)
DMC	Data Monitoring Committee
DMSO	Dimethyl sulfoxide
DSMB	Data Safety Monitoring Board
EAC	Events Adjudication Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form(s)

GLOSSARY OF ABBREVIATIONS

EDC	Electronic data capture
EEA	European Economic Area
EOT	End of Treatment
eGFR	Estimated glomerular filtration rate
eform	Electronic form (page)
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
γ-GT	Gamma-glutamyl transpeptidase
GCP	Good clinical practice
GFR	Glomerular filtration rate
HA	Hyaluronic acid
HbA1c	Glycosylated hemoglobin
Hct	Hematocrit
HDL	High density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HLA	Human leukocyte antigen
HR	Heart Rate
hsCRP	High sensitivity C-reactive protein
IB	Investigator's Brochure
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL	Interleukin
IP	Investigational product
IND	Investigational New Drug
INN	International Non-Proprietary Name
iPCQ	iMTA Productivity and Cost Questionnaire
IRB	Institutional Review Board
ISF	Investigator's Study File
ITT	Intent to treat
IVD	Intervertebral disc
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LOCF	Last Observation Carried Forward
MED	Morphine equivalent dose
MPC	Mesenchymal precursor cells
MDRD	Modification of Diet in Renal Disease
mITT	Modified intent-to-treat

GLOSSARY OF ABBREVIATIONS

MedDRA	Medical Dictionary for Regulatory Activities
MORES	Male Osteoporosis Risk Estimation Score
MPC	Mesenchymal precursor cell
MRI	Magnetic resonance imaging
MSC	Mesenchymal stem cells
MTX	Methotrexate
NIH	National Institutes of Health
NSAID	Non-Steroidal Anti-inflammatory Drugs
NYHA	New York Heart Association
PFT	Pulmonary Function Testing
PHI	Personal health information
PP	Per protocol analysis set
PRA	Panel reactive antibody
PRP	Platelet-rich plasma
PT/INR	Prothrombin time/International normalized ratio
QSI	QMA® Stability Index
RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
RBC	Red blood cell
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SAT	Self-assessment of Treatment (Questionnaire)
SBP	Systolic blood pressure
SEM	Standard Error of Mean
SMBG	Self-monitored blood glucose
SMT	Study Management Team
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2DM	Type 2 Diabetes Mellitus
TG	Triglycerides
TEC	Treatment Events Committee
TNF-α	Tumor necrosis factor-α
TPDR	Translation per degree rotation
ULN	Upper limit of normal
WBC	White blood cell

1. BACKGROUND

1.1 Degenerative Disc Disease and Low Back Pain

The degenerative process in the disc, unlike many other tissues begins as early as the second decade of life. [1-6] Degeneration of the intervertebral disc(s), commonly referred to as Degenerative Disc Disease, is consistent with advancing age, and in many cases is also associated with pain (particularly in the lumbar spine)[7] and biomechanical instability. [8-14] Currently, it is unknown what factors serve as an initiating event of painful degeneration, but genetic predisposition, smoking, infection, abnormal biomechanical loading, decreased nutrient transport across the vertebral endplates and ageing are implicated. [3,15,16]

Degenerative changes are believed to begin in the nucleus pulposus with cellular loss causing an imbalance in the anabolic to catabolic processes leading to net proteoglycan breakdown and the associated diminished water binding capacity. [10,15,17] This places abnormal compressive forces on the annulus fibrosus that cause damage resulting in cracks, tears and fissures. [9,12-14,18]

It has been hypothesized that an event secondary to a structural deficit, such as injury or leakage of nucleus pulposus material through annular fissures, is likely to result in recruitment of immune cells to the disc, which then triggers pain generation. [15] This is consistent with a theory that low back pain is associated with inflammation in the disc. [8,10,11, 15,16,19] As the annulus fibrosus begins to have more cracks and fissures, the inflammatory mediators come into contact with the nerves in the outer portion of the annulus potentially causing pain. [8,10,11, 15,16,19] This causes infiltration of immune cells, blood vessels and nerve fibers further into the disc in an attempt to repair the disc. However, this attempted reparative process further exposes the disc to increasing inflammatory mediators. [8,10,11, 15,16,19] The inflammatory mediators interact in a complex way to induce, enhance and propagate persistent pain. [19] Eventually, the degradative cascade causes the native cells to undergo phenotypic changes, senescence and apoptosis, which further reduces any anabolic capability of the disc. [8,10,11, 15,16]

The resultant low back pain from disc degeneration represents a substantial social and economic burden to the community as well as adding to one's long-term physical disability and reduced quality of life. It is estimated that as much as 80% of the analysis set experiences at least one significant episode of low back pain during life and approximately 2.5% of the working analysis set will take some sick leave during the year as a result of low back pain. The direct costs of low back pain in modern western countries has been estimated at billions of dollars, most of which is spent on consulting general practitioners, physical therapists and other conservative practitioners. [20,21] Total indirect expenditure, including surgical management, may be ten times higher. [22]

1.2 Current Treatment Options for Low Back Pain

For most patients with low back pain, symptoms resolve with over-the-counter (OTC) medication(s), rest and activity modification. However for approximately 10% of patients, low back pain becomes chronic, which is defined as lasting 3 months or more in duration. For these patients, current treatments include:

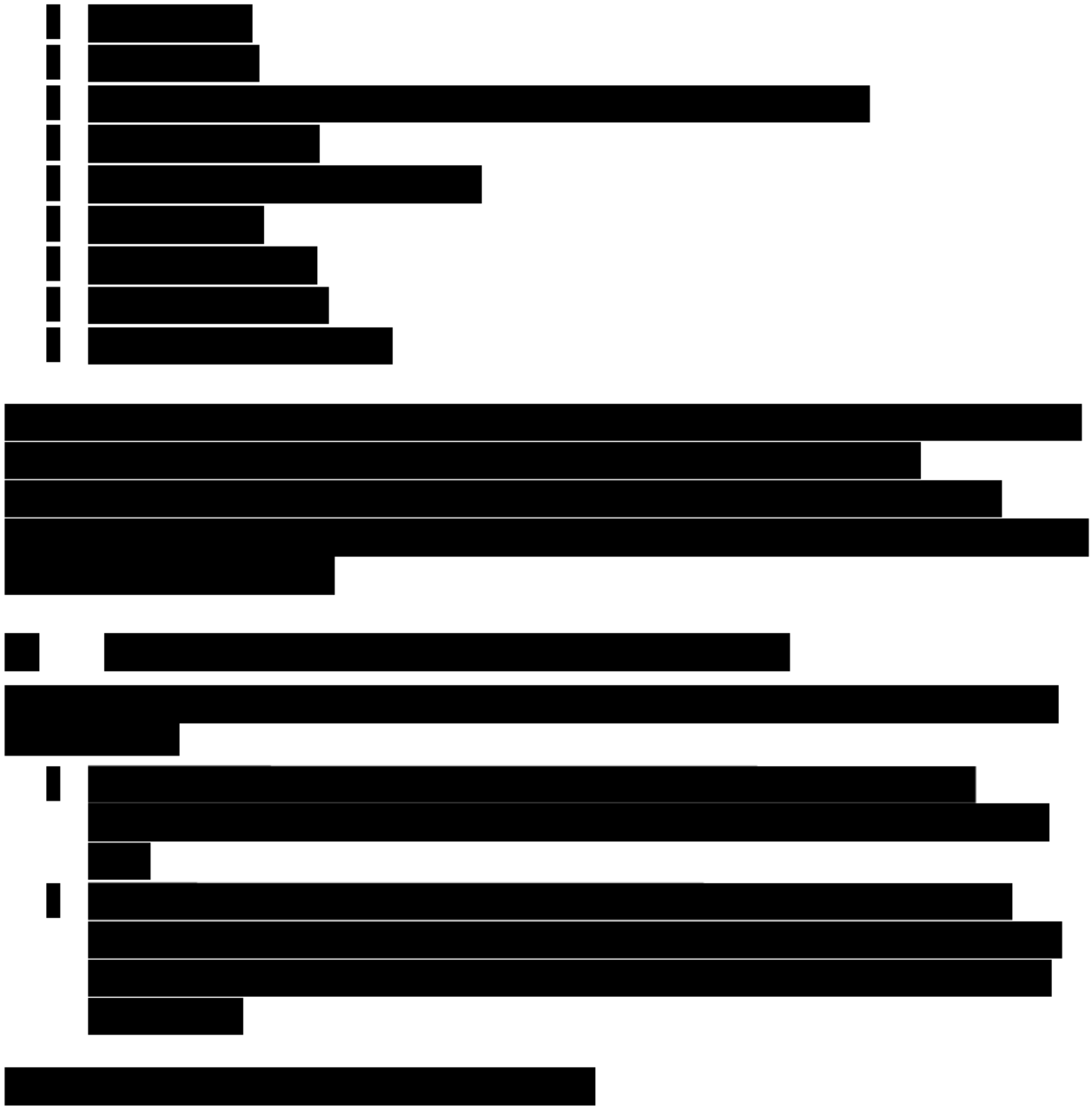
- Conservative treatments: non-steroidal anti-inflammatory drugs (NSAIDs), aniline analgesics, physical therapy, and alternative therapies (including chiropractic treatments, acupuncture, serotonin-norepinephrine reuptake inhibitors, and anticonvulsants)
- Opioids: short-acting combination opioid analgesics, long-acting opioids
- Interventional therapy: epidural steroid injections (ESI), intrathecal pumps, surgically implanted spinal cord stimulation
- Surgery: spinal fusion, artificial disc implantation.

Conservative treatments are standard of care for acute and early chronic low back pain associated with degenerative changes of the disc. Patients with moderate to severe chronic low back pain with degenerative changes of the disc, who fail to respond to conservative treatment, typically receive short-acting combination opioid analgesics, long-acting opioids, or interventional therapies. Any of these therapies may be used in conjunction with conservative treatments. Opioids present a risk of tolerance and other safety concerns which limits their use in terms of dosage and duration, and prevents their use in certain analysis sets.

In addition, it is important to note that the rationale that underlies the use of opioids in patients with chronic low back pain assumes that these agents are effective for improving pain severity and/or functional status. However, recently this assumption has been challenged by numerous published reports which have questioned their therapeutic effectiveness. [23- 25]

For patients with long-term chronic low back pain and severe degenerative changes of the disc (black disc on MRI with 50% disc height loss), who have failed other therapies, surgery is the only choice. While some patients with CLBP and severe disc degeneration receive pain relief and functional benefit from fusion or disc replacement, some do not. Equally concerning in selecting fusion as an option is the potential for surgical complications, such as bleeding, infection, nerve damage, or non-unions (fusion failure) and altered spine biomechanics that could exacerbate degeneration at adjacent levels.
There is an unmet need for a therapy that has the ability to reduce a patient's low back pain, improve function and reverse, halt or slow the progression of degeneration of the disc. Current

therapies are only palliative and the underlying cause of pain, the degenerating disc, continues to progress until the pain is no longer manageable or reduced function causes a sufferer to elect for surgical intervention. As such, spine fusion and artificial disc replacement procedures continue to grow despite their invasiveness.



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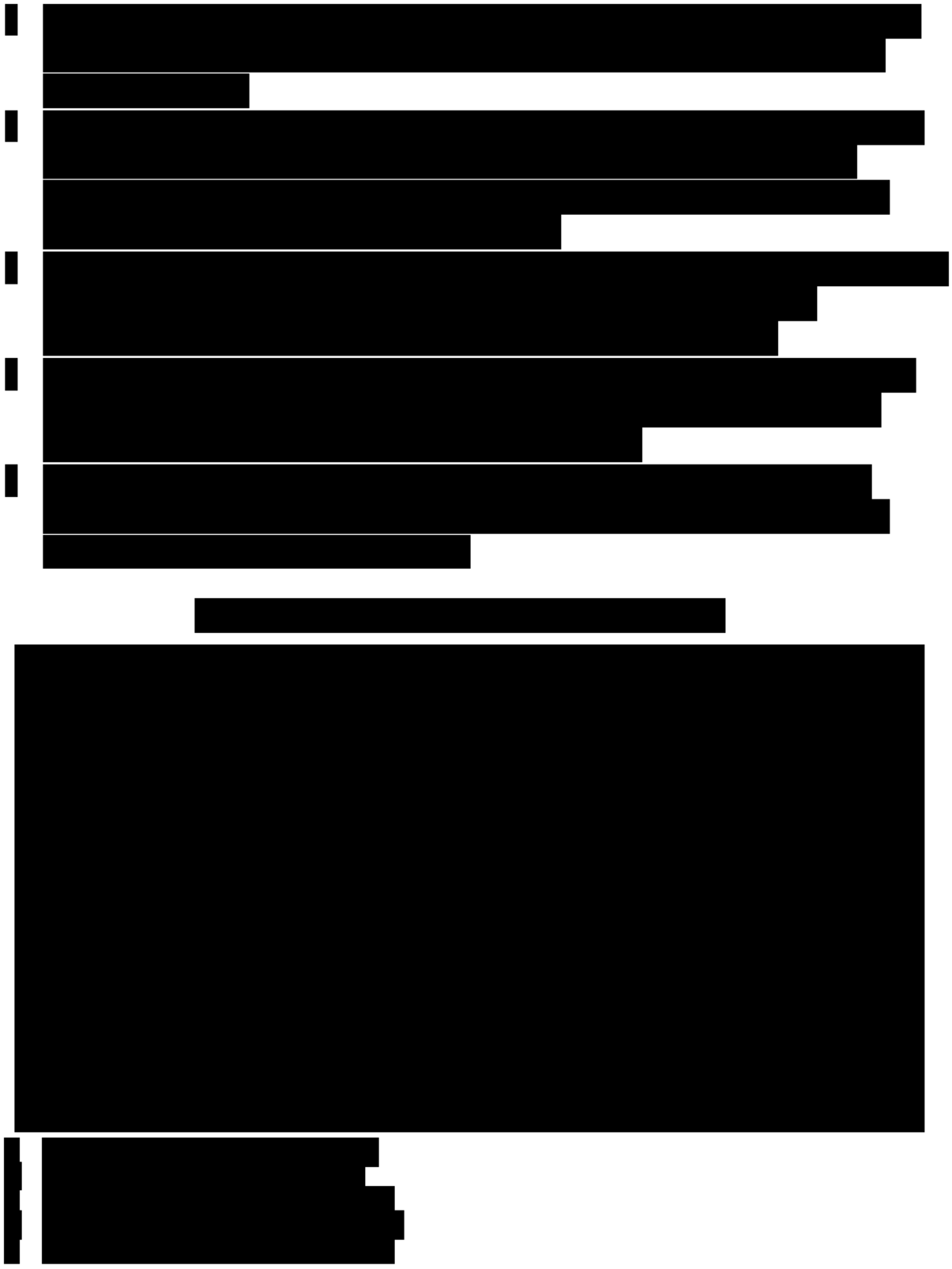

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1.6 Study Rationale

1.6.1 Rationale for the Study

As previously discussed in Section 1.2, surgical intervention is currently the only means of arresting the progression of disc degeneration and associated low back pain. Results from the Phase 1b/2 study (MSB-DR001) have shown that a single injection of rexlemestrocel-L into the degenerated lumbar disc associated with CLBP is safe and tolerable for subjects. Furthermore, clinically significant improvements in lower back pain and daily function are evident up to 24 months post-injection with rexlemestrocel-L.

Efficacy endpoints from the Phase 1b/2 study were exploratory; therefore, this subsequent Phase 3 study will serve to confirm these findings, particularly those from the Phase 1b/2 "responder analyses."

1.6.2 Rationale for Study Design

This Phase 3 study will consist of 3 treatment arms: 1) rexlemestrocel-L alone, 2) rexlemestrocel-L + HA, and 3) saline control. Results from Study MSB-DR001 study demonstrated that saline control and HA control performed similarly in terms of safety and efficacy; therefore only the saline control will be used in this study. Furthermore, the inclusion of the rexlemestrocel-L alone arm will determine a) whether or not HA has any synergistic effect when combined with rexlemestrocel-L and b) whether or not any benefit is demonstrated solely with the use of rexlemestrocel-L.

1.6.3 Rationale for Dosing Regimen and Treatment Period

The dose of rexlemestrocel-L (approximately 6 million rexlemestrocel-L cells, also referred to as "6 million rexlemestrocel-L cells") used in this study is based on that used in the Phase 1b/2a study, MSB-DR001. Efficacy and safety results were generally similar between this "low dose" and the "high-dose" of 18 million rexlemestrocel-L cells, with the high-dose offering no consistent improvement in treatment effect. For the proposed primary endpoint, the 6 million rexlemestrocel-L group had 12 subjects (44.4%) who met the primary endpoint while 11 subjects (37.9%) in the 18 million rexlemestrocel-L group met the primary endpoint. There was no significant difference between the two MPC-treated groups, though the 6 million rexlemestrocel-L group was significantly better when compared to saline (p=0.044), while the 18 million rexlemestrocel-L group did not reach statistical significance (p=0.090). The safety profiles of the two rexlemestrocel-L groups were similar; however, the 18 million rexlemestrocel-L group had a greater proportion of subjects (27%) with reports of back pain within 7 days after injection compared to 0%, 5% and 3% in the saline, HA and 6 million rexlemestrocel-L groups, respectively.

1.7 Risk/Benefit Summary

There are certain known risks associated with lumbar disc injection, expected risks with products that are used in the production of the rexlemestrocel-L, and potential risks related to allogeneic MPCs.

These risks include the following:
The administration of allogeneic MPCs may elicit immunogenic and/or inflammatory responses resulting from allogeneic exposure to the donor cells and/or manufacturing content. In a previous Phase 2 clinical study in subjects with heart failure (Study HF-AB002), 11% of exposed subjects developed donor specific anti-HLA antibodies. The incidence of anti-bovine or anti-

murine antibodies is substantially less. To date, no clinical signs or symptoms have been associated with the development of antibodies to HLA, bovine, or murine proteins.

MPCs are a STRO 3–positive subanalysis set of mesenchymal stem cells (MSCs), and thus the safety experience with MSCs may be predictive of actions with MPCs. Studies have demonstrated that human MSCs have a non-immunogenic phenotype and, by avoiding allo-recognition, represent a potentially advantageous cell type for transplantation into an allogeneic host without the need for HLA matching or immunosuppression. MPCs are highly similar to MSCs in that they not only lack HLA class II surface antigens and co-stimulatory molecules (CD86, CD80), but also exert in vitro immunomodulatory effects on T-lymphocyte activation and function.

The risks of exposure to MPCs are not fully known but there is the theoretical risk that subsequent allogeneic transplant donor selection may be limited in the presence of persistent, cross-match reactive anti-HLA antibodies. However, data from multiple exposures to other mesenchymal lineage cells suggest that this is not a clinically important issue.

Additionally, for immunoselection of the allogeneic MPCs, the technology incorporates an antibody-based sorting process using murine-derived antihuman antibody. In the cell expansion process, fetal calf serum is used. Therefore there is the risk of a hypersensitivity reaction to these murine and/or bovine products. The risk of sensitization from this formulation is unknown, but expected to be rare.

1.7.1 Reaction to Dimethyl Sulfoxide

Dimethyl sulfoxide 7.5% is used as part of the rexlemestrocel-L cryopreservation process. The therapeutic and toxic effects of DMSO include its own rapid penetration and enhanced penetration of other substances across biologic membranes, free radical scavenging, and effects on coagulation, anticholinesterase activity, and DMSO-induced histamine release by mast cells. The systemic toxicity of DMSO is considered to be low. The DMSO exposure in this therapy is minimal and is locally applied. Subjects with hypersensitivity to DMSO will be excluded from study.

1.7.2 Potential Cell Contamination

Rexlemestrocel-L is an allogeneic, immunoselected, *ex-vivo* expanded cell product which has the potential to become contaminated and subsequently cause infection in the study subject at the time of surgical implantation. This risk is greatly minimized by the use of a Good

Manufacturing Practice (GMP)-compliant production facility. Prior to the release of rexlemestrocel-L from the GMP facility, rigorous screening tests for multiple infectious agents are performed in order to ensure that no contaminated product is released for use. As with any blood or marrow-derived biological agent, infectious risks from unknown pathogens are possible.

1.7.3 Tumor Development

MPCs such as rexlemestrocel-L are living cells that have undergone *ex vivo* expansion; therefore there is a theoretical risk that these cells could directly or indirectly cause the formation of unwanted tissue growth or a tumor. Engraftment of MPCs has not been demonstrated in any preclinical or clinical setting to date. The risk of tumor development is further minimized by testing each new cell bank used in clinical trials for tumor formation potential in animals. To date, testing of these cells in animals has not revealed tumor formation or any unwanted tissue growth. To minimize the theoretical risk of tumorigenesis and taking into consideration indication specific risk-benefit, subjects with a prior history of malignancy, with the exception of certain treated cancers such as skin cancer and carcinoma in situ, are excluded.

1.7.4 Potential Inflammatory Responses

As with many cellular biologics, allogeneic MPCs may elicit immunogenic and/or inflammatory responses resulting from the allogeneic exposure to the donor cells and/or manufacturing content. To date, no clinical signs or symptoms have been associated with the development of antibodies to bovine, murine, or HLA proteins. The risks of exposure are not fully known but there is a remote potential risk that subsequent allogeneic transplant donor selection may be limited in the presence of persistent, cross-match reactive anti-HLA antibodies. Subjects will be monitored for these responses by performing antibody-screening tests for HLA at designated follow-up visits.

1.7.5 Effects on Treated and Adjacent Levels

It is unknown at this time what the long-term effects of injection of rexlemestrocel-L are. There is the potential that over the longer-term, adverse effects on the disc or adjacent vertebral bodies, such as osteolysis or Schmorl's nodes, could develop. Through 24 months, no significant adverse effects on the treated disc or surrounding structures, such as the adjacent vertebral bodies or neurologic structures, were observed in the Phase 2 clinical study.

It is unknown what if any effects injection of rexlemestrocel-L, hyaluronic acid or any other substance may have on adjacent level(s). Although, no significant changes in the adjacent levels after injection of rexlemestrocel-L with hyaluronic acid in the Phase 2 study were seen.

Adverse effects on the disc or adjacent vertebral bodies of the treated or adjacent levels could cause additional or recurrent pain and reduced function that could require treatment through medication and/or interventional procedures such as additional injections or surgery to correct the degeneration of the index or adjacent level(s).

1.7.6 Possible Effects of Cells on Fetus

Because of potential or unknown side effects of the study on the fetus, if the subject is a female of childbearing potential, the subject must have a negative pregnancy test prior to receiving study treatment. In addition, females of childbearing potential will be included in study participation provided that they use adequate contraception (hormonal or barrier method or abstinence) from the time of screening and for a period of 24 months after study treatment.

In the event that the study subject is confirmed to be pregnant during the study, the investigator must immediately notify the Clinical Research Associate and the Sponsor's Medical Monitor about the pregnancy and record it on the Pregnancy CRF. In addition, the investigator must report to the Sponsor follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. The study subject will continue to be monitored for the duration of the study.

1.7.7 Radiation Exposure

X-rays will be performed at screening, 1, 3, 6, 12, 18, 24 and 36 months post-treatment. There is also radiation exposure associated with the image amplifying during the preliminary diagnostic injection (for confirmation of full thickness annular tears) and at the time of treatment injection.

The primary risk to the subjects enrolled in this study is radiation due to the X-ray scans required for this study. The total estimated radiation dose for a subject that undergoes all study-required imaging is expected to be approximately 19.2 mSv. Based on a large study of cancer risk associated with exposure to radiation, it was estimated that the excess relative risk for cancer is 0.97 per Sv. [35] The excess relative risk of the radiation that each subject would receive from participation in this study is therefore 0.97/Sv * 19.2 mSv * 1 Sv/1000 mSv = 18.6 x 10-3. To help place the radiation risk estimate for this study into perspective, a person will be exposed to 0.03 mSv of radiation during a typical coast-to-coast round-trip airplane flight [36], and the public

is exposed to approximately 3 mSv/year from background radiation. [37] Therefore, the effective radiation dose for subjects is approximately equivalent to 6.4 years of the natural environmental background radiation for the average US citizen.
The FDA web site suggests that 10 mSv of radiation (a typical CT exam) would increase the possibility of fatal cancer by 1 chance in 2000[38] based on statistical calculations using data collected about Japanese atomic bomb survivors. There are no direct data on the risks from clinical x-rays in adult patients. The actual risk is difficult to determine since 1/4 to 1/5th of all people will die from cancer[39], with wide variations between communities and lifestyles.

The American Association of Physicists in Medicine (AAPM) states that "[r]isks of medical imaging at effective doses below 50 mSv for single procedures or 100 mSv for multiple procedures over short time periods are too low to be detectable and may be nonexistent." [40]

1.7.8 Lumbar Disc Injection/Discography Risks and Complications

The complication rate of intravertebral disc injection is comparable to the complications associated with discography. The complications associated with discography are low, and is accepted to be less than 1%.

Although very unlikely, there is the potential that insertion of the spinal needle into the disc could damage adjacent visceral and/or neurologic structures as it is passed into the disc. Additionally, it is possible that the tip of the needle may not be placed into the nucleus pulposus of the disc. This could result in the product not being able to perform its intended function or impacting surrounding structures. This could lead to continued pain and functional deficit or even a worsening of symptoms. The potential for inadvertent damaging of surrounding structures and/or misplacing the product is minimized by the use of fluoroscopy to provide real time imaging of the placement and path of the needle. Furthermore, the use of trained and experienced physicians that routinely perform intra-discal procedures such a discography further reduces the likelihood of damaging adjacent structures and/or misplacing the product upon injection.

In a retrospective analysis of 10 discography studies in which prophylactic antibiotics were not given, an infection rate of 0.25% in 4891 subjects and 0.094% in 12,770 discs was found, with the conclusion that the risk of post-discography discitis was minimal. [41] The most serious and frequently encountered complication is discitis. One subject who received an injection of 6 million cells of rexlemestrocel-L experienced procedure-related discitis in Study MSB-DR001.

The incidence of infection can be decreased with the use of double needles and styleted needles. [42,43] Many practitioners prophylactically administer broad-spectrum antibiotics as a precaution against possible discitis. [44-47]
Nerve damage may also occur but usually causes only transient symptoms. Transthecal puncture may result in post-procedural headache. Other possible complications are needle breakage, accidental intra-dural injection, intrathecal hemorrhage, meningitis, arachnoiditis, osteomyelitis, and epidural abscess.

Some publications have shown that injections in the disc do not cause injury to the disc itself.[48,49] However, some recent literature has suggested that lumbar intradiscal injections, such as in discography, can result in disc degeneration. Carragee et al.[50] performed a 10-year matched cohort study comparing progression of common degenerative findings between lumbar discs injected 10 years earlier with those same disc levels in matched subjects not exposed to discography. They found that over the 10-year follow-up period, discs that had been exposed to puncture and injection had greater progression of degenerative findings compared to control discs, greater progression of disc degeneration, increased rate of disc herniation, and greater loss of disc height and disc signal intensity.

Other potential complications from intra-discal injection and/or discography include intravascular uptake, bleeding, epidural abscess, allergic contrast reaction, subarachnoid puncture, and meningitis.[51]

Additionally, it is possible that rexlemestrocel-L and HA may leak from the intervertebral disc during or after the injection procedure. Although, the risk is very low since each subject must undergo an injection of contrast media to demonstrate that there is no full thickness tear in the disc through which injected substances may leak outside of the disc. If some or all of the rexlemestrocel-L leaks out of the intervertebral disc, it may reduce or prevent repair of the intervertebral disc and thereby potentially fail to relieve the subject's back pain. The effect of rexlemestrocel-L and/or hyaluronic on structures of the spine outside of the disc has not been studied. There is a potential risk that the rexlemestrocel-Land/or hyaluronic acid could leak out and damage nearby neurologic structures that could cause a neurologic deficit requiring surgical intervention to correct. There are no anticipated risks with saline leakage.

Hyaluronic Acid:
Hyaluronic acid is commonly used as viscosupplementation for knee osteoarthritis and is administered as an intra-articular injection in the knee. There is a low incidence of mild to moderate adverse events local to the injection site. [52] These events usually resolve within 1 to

3 days, with minimal to no treatment. The most common reactions are local knee joint pain and injection site pain. [53-58] Other common injection-related events include joint swelling/effusion, [53-55, 57,58] joint stiffness, [53,55] local skin/injection site reaction (warmth, redness, rash, echymossis, itching, bruising). [53,54,56-58] Non-local events considered possibly related to intra-articular HA injection include headache, [54,56-58] gastrointestinal complaint/nausea/vomiting, [54,56,57] back pain, [57,58] rash, dizziness, chills, hives, itching, muscle cramps, peripheral edema, malaise, [57] swelling of the face and/or extremities, redness of the face, rash, hives, and fever. [55,56]

Rare cases of allergic reactions, anaphylactic reactions, [54,56] and intra-articular infection [54] have been observed.

In addition to the established use of HA as an intra-articular injection, HA alone was administered intra-discally as a control treatment in the Phase 2 study of chronic discogenic low back pain. Of the 20 subjects treated with HA in a double-blind fashion, 3 AEs were reported that were considered possibly related to study treatment. One subject experienced mild urticarial, which subsequently resolved, and another subject experienced 2 events of back pain, 1 event of which was considered possibly related to investigational product and related to study procedure, the other of which was considered possibly related to investigational product and not related to study procedure.

1.7.9 Subsequent Surgical Interventions

Failure of the treatment to alleviate the low back pain or to address potential complications which develop subsequent to initial implantation of the product can result in use of additional pain medication or surgical intervention. Surgical intervention may include discectomy, fusion, disc replacement or other surgical intervention.

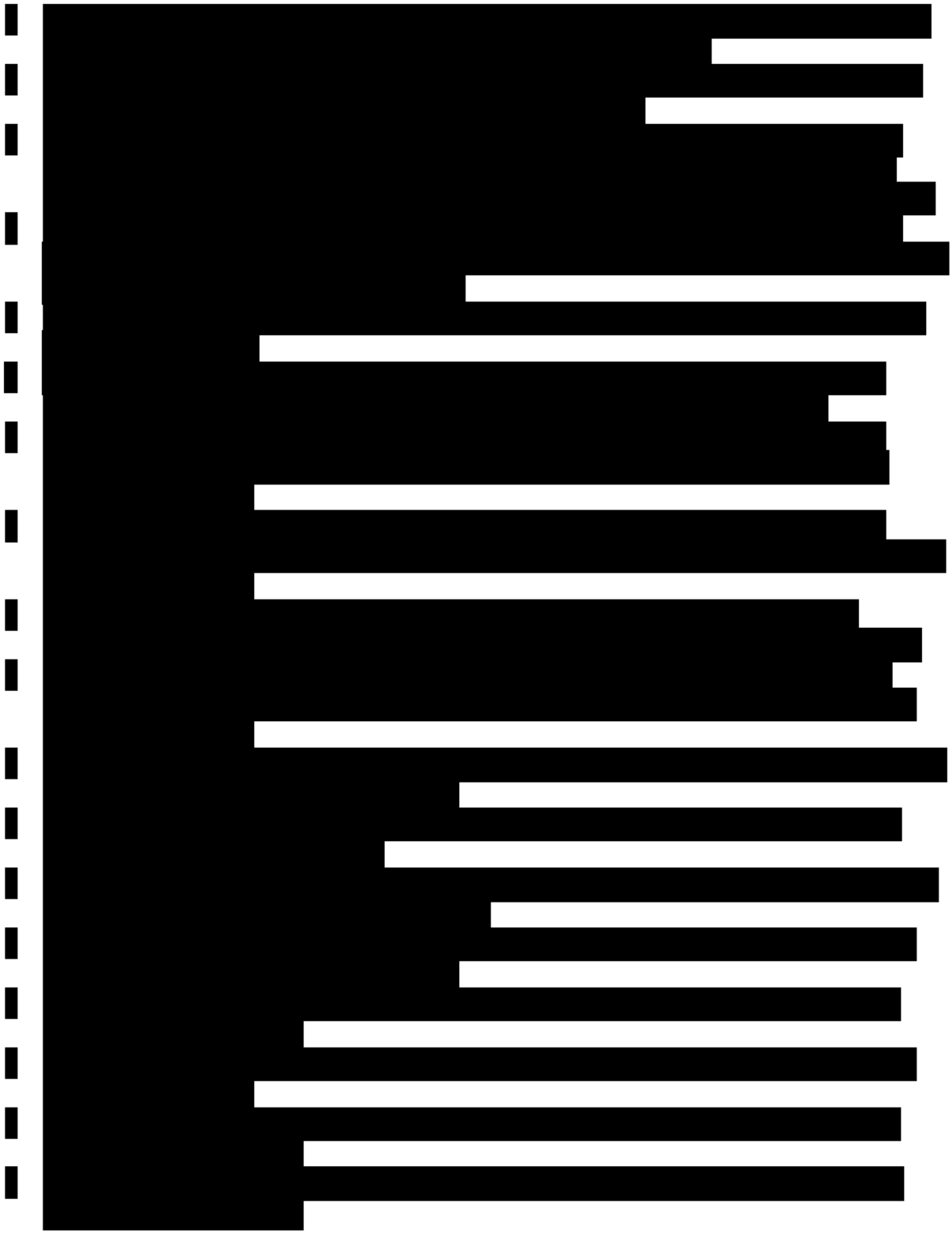
2. STUDY OBJECTIVES

2.1 Primary Efficacy Objective

To determine Overall Treatment Success of rexlemestrocel-L alone or rexlemestrocel-L+HA at 12 *AND* 24 months based on a composite responder analysis of low back pain Visual Analog Scale (VAS) score, Oswestry Disability Index (ODI) score and no post-treatment interventions at the treated level.

2.2 Secondary Efficacy Objectives

- To evaluate the effectiveness of rexlemestrocel-L alone or rexlemestrocel-L+HA in reducing chronic low back pain by performing a Pain Responder analysis at 12 *AND* 24 months post-treatment
- To evaluate the effectiveness of rexlemestrocel-L alone or rexlemestrocel-L+HA in improving function by performing a Functional Responder analysis at 12 *AND* 24 months post-treatment
- To evaluate the Treatment Success at 24 months of rexlemestrocel-L alone or rexlemestrocel-L+HA based upon a composite responder analysis of low back pain Visual Analogue Scale (VAS) score, Oswestry Disability Index (ODI) score and no post-treatment interventions at the treated level.
- To evaluate the effectiveness of rexlemestrocel-L alone or rexlemestrocel-L+HA in reducing chronic low back pain based on incidence of subjects with minimal to no low back pain and no post-treatment interventions at the treated level at 24 months post-treatment (Minimal Pain Responder analysis)
- To evaluate the effectiveness of rexlemestrocel-L alone or rexlemestrocel-L+HA in improving function based on incidence of subjects with minimal disability and no post-treatment interventions at the treated level at 24 months post-treatment (Minimal Disability Responder analysis).
- To evaluate the effectiveness of rexlemestrocel-L alone or rexlemestrocel-L+HA in extending the time to additional interventions at the treated level over 24 months post-treatment.



2.5 Primary Safety Objective

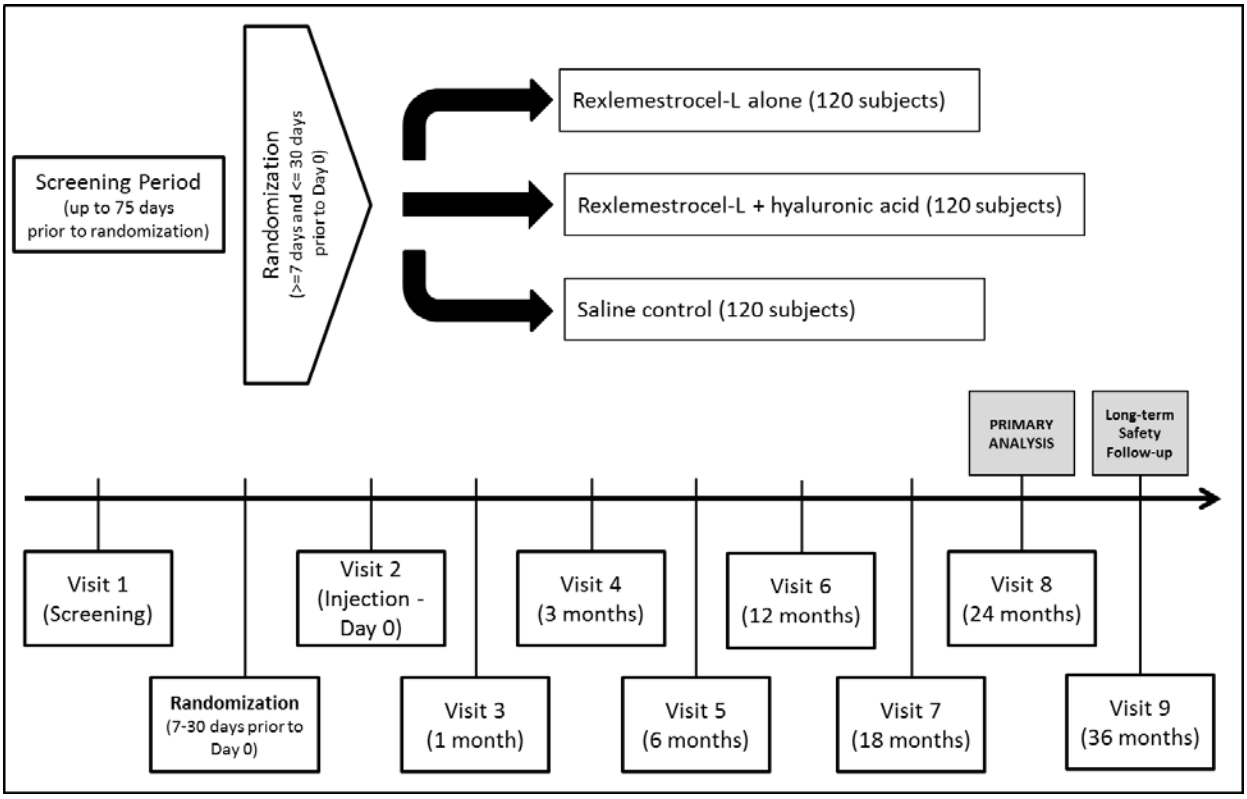
To evaluate the safety of a single injection of rexlemestrocel-L alone or rexlemestrocel-L+HA injected into a lumbar intervertebral disc through 24 months post-treatment.

[redacted]

3. STUDY DESIGN

3.1 Overview of Study Design

Figure 3: Diagram of Study Design



This is a prospective, multicenter, randomized, double-blind, placebo-controlled Phase 3 study designed to evaluate the safety and efficacy of Mesoblast's rexlemestrocel-L alone or combined with hyaluronic acid (HA) in subjects with chronic low back pain (> 6 months) not adequately controlled by conservative measures and associated with moderate radiographic degenerative changes of a disc.

Up to 45 investigational centers in the US and Australia, and potentially the EU, will participate in this trial. Approximately 360 subjects (approximately 120 subjects per treatment group) will be randomized and treated. Centers will screen subjects with a diagnosis of chronic low back pain (>6 months) unresponsive to 6 months of conservative therapy (e.g., medication, chiropractic manipulation, activity modification, physical therapy) associated with moderate radiographic degenerative changes of a disc between L1 and S1.

Each eligible subject's participation in Study MSB-DR003 will last approximately 39 months. A screening period for Study MSB-DR003 (starting from the time of subject consent) of up to 75 days will precede randomization. Screening evaluations will include those listed in Table 3.

Eligible subjects in this study will undergo injection of a single degenerated lumbar intervertebral disc with 1 of 3 treatments: rexlemestrocel-L alone (approximately 6.0 million rexlemestrocel-L cells), rexlemestrocel-L (approximately 6.0 million rexlemestrocel-L cells) + HA, or saline. The study treatment will be injected directly into the nucleus pulposus via a posterior-lateral approach under fluoroscopic guidance.

After injection of study treatment, and as a general guideline, subjects will be discharged from the facility when they are comfortable. Subjects will be given the following instructions for post-injection rehabilitation/treatment:

- Day of Procedure – Bed rest
- Day After procedure – Gentle ambulation with a gradual increase thereafter
- Days 1 to 3 – Avoid repetitive bending, stooping and lifting greater than
- 10-15 lbs.
- Return to normal daily activity when pain has subsided to their baseline.

In Study MSB-DR003, each subject will be evaluated clinically at 1, 3, 6, 12, 18, 24 and 36 months after treatment. The primary analysis of safety and efficacy will be conducted at 24 months with a longer term assessment of safety and efficacy conducted at 36 months. Clinical assessments for Study MSB-DR003 will include those listed in Table 3. X-rays will also be taken at 1, 3, 6, 12, 18, 24 and 36 months after treatment and will consist of AP and lateral radiographs as well as flexion and extension x-rays. MRI scans will be taken at 12, 18, 24 and 36 months.

Surgical and injection interventions should be avoided through at least the 24 month primary endpoint follow-up. Surgical and injection interventions should only be undertaken if the subject's pain, measured by VAS, and function, measured by ODI, is not improved compared to the baseline values since an intervention could confound the efficacy assessments and would classify a subject as a treatment failure.

If a subject intends to undergo an intervention at the treated level, subjects should be encouraged to attend an unscheduled in-clinic visit for evaluation within 30 days prior to the new intervention (if a scheduled assessment does not already occur within that timeframe). During

this visit, all assessments and activities regularly performed at Visits 3-9 will be performed, with the exception of imaging assessments, hematology, chemistry panel, Flow Class I and II % PRA with specificity testing and DSA. If the subject's originally planned assessment timepoint falls within 30 days prior to the post-treatment intervention, the unscheduled visit will not be necessary.

It is strongly recommended that there be no changes (increase or decrease) from or additions to baseline pain medications (opioids, NSAIDs, aniline analgesics etc.). This is designed to minimize possible confounding treatment effects due to alterations in pain medications. Furthermore, it is suggested that subjects do not schedule any medical procedures which would require an adjustment in pain medications during the 2 weeks prior to any study visit. Subjects not taking opioids at baseline should similarly refrain from starting opioid treatment. However, should a significant increase in pain from baseline occur, as determined by a VAS score greater than baseline, the subject should be provided appropriate pain relief. Should there be any deviation from the baseline dose, information regarding the deviation must be documented.

All patient-reported outcomes (including VAS and ODI assessments), as well as baseline use of pain medication (i.e., 2-week e-diary record), will be established during screening. All such assessments should be performed prior to the screening injection procedures: diagnostic disc injection to confirm intact annulus or discography, medial branch block and SI joint injection, if deemed necessary. However, in the case of a re-screen (see Section 4.4) or if the subject had previous diagnostic injection procedures performed prior to the screening period (but within the permitted timeframes to serve as the baseline evaluation; see Section 4.2.2), these patient-reported outcomes and e-diary entries should be completed at least 14 days following the most recent injection procedure, provided original e-diaries are not available. If an e-diary was collected during a previous screen, this may be used, provided it meets all criteria for acceptability.

Based on the opioid information entered into the e-diary during baseline, subjects will be classified into one of the following groups for stratification at randomization:

Opioid Non-User: subjects who did not take any opioids during the e-diary pain medication data collection period

Opioid User: subjects who did take an opioid during the e-diary pain medication data collection period.

[redacted]

[redacted]

Pain medication (opioid, NSAID and/or aniline analgesic) usage will also be subsequently captured each day for a 2 week period during the 30 days prior to each clinic visit, other than the 1 month visit that must be conducted within the 14 days prior to the 1 month visit using electronic diaries (e-diaries) completed by the subjects. Based on the pain medication information entered into the e-diary during the 2 weeks prior to each post-treatment visit, it will be determined if subjects have significantly increased pain medication usage from baseline.

Low back pain (average over past 24 hours and worst pain over 24 hours) and leg pain (average leg pain in left and right legs, individually over the past 24 hours) VAS and ODI evaluations will also be taken using e-diaries during the same 2 week period where pain medication usage is being collected. The VAS scores will be collected every day for the 14 day period with at least evaluations for 7 days. If more than 7 days of VAS scores are collected the last 7 days' scores will be used to calculate the average pain over a week. The ODI score must be taken at least once during the 14 day period. If more than one ODI score is collected, the most recent ODI score will be used. If a scheduled in-clinic visit is missed, the site should contact the subject to determine if any interventions that would classify the subject as a treatment failure have occurred since their last visit. If any interventions are reported, the site should collect all the information required if the intervention had been reported at an in-clinic visit. All intervention information collected remotely must be documented in a source document and/or worksheet.

Review of concomitant treatments will also be performed at each clinic visit. Subjects will be asked for all concomitant medications used since the last visit. Additionally, at each clinic visit, subjects will be asked whether they have undergone or intend to undergo any spinal interventions such as surgery (e.g., discectomy, intervertebral fusion, or disc replacement) or any injection for alleviation of pain at the treated disc (e.g., epidural corticosteroid injection, or transforaminal injection). In order to maintain standardized classification of post-treatment interventions affecting the treated disc, the TEC will be used. The TEC will perform ongoing independent blinded adjudication of post-treatment interventions. Following are procedures that should be considered interventions and consequently treatment failures for responder analyses if they occur at the treated level:

Table 2: Procedures Considered Treatment Interventions at the Treated Level

Surgical Interventions	Spine Injections
Spine fusion, interbody or posterolateral	Epidural steroid injections
Artificial Disc Replacement	Transforaminal injection of corticosteroid
Interlaminar or Spinous Process Stabilization Device Implantation	Injection of any anesthetic, analgesic, steroid or other potential pain relieving substance into the disc
Discectomy	Facet Injection of corticosteroid
Surgical Disc Decompression, including minimally invasive decompression procedures such as mild®	
Laminectomy	
Laminotomy	
Osteotomy	
Foraminotomy	
Facetectomy	
Facet Joint Ablation/Denervation/Rhizotomy	
Disc nucleoplasty	
Spinal cord stimulation	
Intradiscal Electrothermal Annuloplasty	
Intradiscal Ablation Procedures	
Intrathecal pump implantation	

The investigator, or designee, will make all evaluations for the purpose of medical care decisions. However, to minimize bias, an independent blinded radiologist(s) will review and evaluate all MRI and X-rays images as specified in Appendix 1.

A DSMB will meet on a regular basis and ad-hoc, as needed, to review safety, enrollment progress, and any other pertinent information. The DSMB will consist of an independent multidisciplinary group. Based on its findings, the DSMB will make recommendations regarding study continuation, enrollment and/or study modification(s).

The TEC will also review and adjudicate the potential relationship of adverse events to the product and/or procedure.

Interim analyses

Interim analyses may be performed during the course of the trial. The timing and details of the interim analyses are outlined in the Statistical Analysis Plan (SAP).

These will be conducted by external independent statistician(s) who will be unblinded to study data. All blinded personnel and subjects will remain blinded to the results of the analyses. The integrity of the study database will be maintained as well, and no bias will be introduced to the evaluations in the study due to the conduct of these interim analyses.

All subjects, independent reviewers and blinded personnel interacting with the subjects will remain blinded through completion of the study.

3.2 Dosing Regimen

Each treatment solution will be prepared by an unblinded designee(s) who is otherwise not involved in study participation after the treatment injection. The health care professional administering the injection will be unblinded to the treatment administered. All other study staff, as well as each study subject, will be blinded to study therapy until the end of the study.
Eligible subjects will be randomized to receive 1 of 3 treatments:

- Rexlemestrocel-L alone: One injection of approximately 6 million rexlemestrocel-L cells in freeze media mixed in a 1:1 by-volume ratio with saline. A vial with 2mL of thawed rexlemestrocel-L cells and freeze media will be mixed with 2mL of saline. Two milliliters of the resulting mixture will be injected via pressure manometer syringe into the nucleus pulposus of the index level.
- Rexlemestrocel-L + HA: One injection of approximately 6 million rexlemestrocel-L cells in freeze media mixed in a 1:1 by-volume ratio with 1% hyaluronic acid (HA) solution. A vial with 2mL of thawed rexlemestrocel-L cells and freeze media will be mixed with 2mL of 1% HA solution. Two milliliters of the resulting mixture will be injected via pressure manometer syringe into the nucleus pulposus of the index level; OR
- Saline: One injection of 2mL of thawed saline from one vial will be mixed with 2mL of thawed saline from another vial of saline. Two milliliters of the resulting saline mixture will be injected via pressure manometer syringe into the nucleus pulposus of the index level.

Treatment assignment will occur in sequential chronological order according to a central master list of random assignments. Randomization will be stratified [redacted]

3.3 Study Sites

In order to enroll approximately 360 subjects, up to 45 study centers in the US, Australia, and potentially the EU will participate.

4. STUDY ANALYSIS SET

4.1 Overview

This study will enroll approximately 360 subjects in the randomization ratio of 1:1:1. Eligible subjects will be those with a history of chronic (> 6 months) low back pain not adequately controlled by conservative measures and associated with moderate radiographic degenerative changes of a disc in the lumbar spine from L1 to S1.

4.2 Eligibility Criteria

4.2.1 Inclusion Criteria

Subjects who meet the following criteria will be included in the study:

1. Male and female subjects 18 years of age and older
2. If female of childbearing potential, subject is non-pregnant, non-nursing, and agrees to use highly effective methods of contraception for a minimum of 24 months post-treatment (if a subject becomes pregnant during the study, the subject will remain in the study and only the requirement for radiation (x-ray or MRI) should be removed)
3. Signed informed consent and country-appropriate privacy forms (e.g., HIPAA forms in the US) indicating subject is willing to undergo treatment and willing to be available for each examination scheduled over the study duration
4. Have documented diagnosis of moderate radiographic degeneration of an intervertebral disc from L1 to S1, with a disc suspected of causing CLBP [redacted] Chronic low back pain associated with moderate radiographic degeneration at a lumbar disc is defined as the following (subject must meet all of the listed conditions):
    a. Chronic low back pain for at least 6 months
    b. Have failed 6 months of conservative back pain care. (Conservative treatment regimens may include any or all of the following: initial rest, medications [e.g., anti-inflammatory, analgesics, narcotics/opioids, muscle relaxants], massage, acupuncture, chiropractic manipulations, activity modification, home-directed lumbar exercise program, and non-invasive pain control treatments or procedures)
    c. Have at a minimum undergone supervised physical therapy, such as daily walking routines, therapeutic exercises, and back education programs specifically for the

treatment of low back pain ***AND*** taken a pain medication for back pain (e.g. NSAID and/or opioid medication)

d. Change from normal disc morphology of the index disc as defined by radiographic evaluation by the core imaging evaluation provider. Radiographs must show all of the following:
    i. A modified Pfirrmann score of 3, 4, 5 or 6 on MRI at the index disc as determined by radiographic core lab
    ii. Modic Grade II changes or less on MRI at the index disc as determined by radiographic core lab
    iii. With or without contained disc protrusion at the index disc on MRI as determined by radiographic core lab
e. Low back pain of at least 40mm and not more than 90mm of 100mm on low back pain VAS (average pain over 24 hours)
f. Leg pain ≤20mm in both legs on a 100mm VAS scale
g. ODI score of at least 30 and no more than 90 on a 100 point scale.

4.2.2 Exclusion Criteria

Subjects will be excluded from participating in the study if they meet any of the following exclusion criteria:

1. Female subjects who are pregnant or nursing, or women planning to become pregnant in the first 24 months post-treatment (if a subject becomes pregnant during the study, the subject will remain in the study and only the requirement for radiation (x-ray or MRI) should be removed)
2. Extreme obesity, as defined by NIH Clinical Guidelines Body Mass Index (BMI > 40)
3. Have undergone a surgical procedure (e.g. discectomy, intradiscal electrothermal therapy, intradiscal radiofrequency, artificial disc replacement, interbody fusion) on the disc at the index or adjacent level
4. Osteoporosis, as defined by dual-energy X-ray absorptiometry (DEXA) scan. A DEXA T-score of ≤ -2.5 will exclude the subject. Only the following at-risk subjects will be required to undergo a DEXA scan at screening:
    a. Female subjects with a Simple Calculated Osteoporosis Risk Estimation (SCORE) of ≥6 and male subjects with a Male Osteoporosis Risk Estimation Score (MORES) of ≥6
    b. Females ≥50 years of age or who are post-menopausal or post-hysterectomy with oophorectomy
    c. Subjects taking bisphosphonate medications for the treatment of osteoporosis

   d. Subjects with a history of chronic, high-dose steroid use (oral and/or inhaled). High-dose steroid use is defined as:
      i. Daily, chronic use of oral steroids of ≥5 mg/day
      ii. Daily, chronic use of inhaled corticosteroids (at least twice per day)
      iii. Use of short-term (less than 10 days) oral steroids at a daily dose >20mg prednisone (or equivalent) within 1 month of study procedure
5. Any lumbar intradiscal injection, including steroids, into the index or adjacent discs prior to treatment injection, with the exception of the following injections performed at least 2 weeks prior to study treatment:
   a. Contrast medium (discography or other diagnostic injection)
   b. NSAIDs
   c. Nerve-blocking anesthetics (e.g., lidocaine, bupivacaine)
   d. Antibiotics
   e. Saline
6. Have undergone a procedure affecting the structure/biomechanics of the index disc level (e.g. posterolateral fusion)
7. Epidural steroid injections within 8 weeks prior to treatment injection
8. Have received chronic (more than 7 consecutive days) treatment with systemic corticosteroids at a dose equivalent to prednisone ≥ 10 mg/day within 14 days prior to injection procedure
9. Have a known history of hypersensitivity or anaphylactic reaction to murine or bovine products or dimethyl sulfoxide (DMSO)
10. Have a known history of hypersensitivity or anaphylactic reaction to hyaluronic acid (HA)
11. Active malignancy or tumor as source of symptoms or history of malignancy within the 5 years prior to enrolment on study, except history of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or squamous cell carcinoma of the cervix if fully excised and with clear margins
12. Currently participating in another investigational trial and/or plans to participate in any other allogeneic stem cell/progenitor cell therapy trial within 36 months after study treatment
13. Have been a recipient of prior allogeneic stem cell/progenitor cell therapy for any indication or autologous stem cell/progenitor cell therapy or other biological intervention to repair the index intervertebral disc
14. An average baseline morphine equivalent dose (MED) of >75mg/day as determined by e-diary entries during the screening period

15. Taking systemic immunosuppressants
16. Current infection or prior history of spinal infection at the index level (e.g., discitis, septic arthritis, epidural abscess) or an active systemic infection
17. Pain catastrophizers, defined as having a score of 30 or more on the Pain Catastrophizing Scale
18. A medical condition, serious intercurrent illness, or extenuating circumstance that would preclude participation in the study or potentially decrease survival or interfere with ambulation or rehabilitation. Examples of conditions that should be excluded are as follows:
    - History of transient ischemic attack (TIA)
    - History of Stroke
    - Uncontrolled diabetes
    - Autoimmune disease **(only if they interfere with ambulation or rehabilitation)**
    - Muscular dystrophy
    - Rheumatoid arthritis
    - Active liver disease
    - Upper motor neuron disease
    - Myelopathy
    - Disorders of bone metabolism (osteomalacia or Paget's disease)
19. Cauda equina syndrome
20. Subjects involved in spinal litigation, including workman's compensation, unless litigation is complete
21. Currently incarcerated (prisoners)
22. Are transient or have a severe alcohol or substance abuse problem defined as answering yes to 6 or more symptoms on the DSM-5 alcohol or substance/opioid questionnaires
23. Unable to complete all required e-diary entries, assessments and follow-up according to the protocol.
24. A history of mental illness/incompetence. Mental illness/incompetence is defined as meeting the following criteria on the DSM-5 Self-Rated Level 1 Cross Cutting Symptom Measure – Adult questionnaire
    - Domain 1, Depression – A response of 4 on either question
    - Domain 6, Suicidal Ideation – A response of 4 on the question
    - Domain 7, Psychosis – A response of 1 to 4 on either question
    - Domain 9, Memory – A response of 4 on the question

25. Have a serious intercurrent medical condition or any other conditions or social situations that would impair the ability to give informed consent or unacceptably reduce protocol compliance or safety of the study treatment.
26. Body habitus precluding adequate fluoroscopic visualization for the procedure or the procedure is physically impossible due to inability to inject the nucleus pulposus
27. Presence of ferromagnetic implants that would disallow MRI of the index disc
28. Presence of neurologic deficit on any component of the lumbar neurological exam at baseline (i.e., motor, sensory, or reflex portion of the exam)
29. A positive screen for human immunodeficiency virus (HIV) by antibodies or nucleic acid test
30. Clinically significant nerve pain (e.g., chronic radiculopathy or neuropathy)
31. Clinically significant sacroiliac joint pain based on the Appropriate Use Criteria established by the Spine Intervention Society including a targeted, pre-specified physical examination, and, if deemed medically necessary, confirmed by anesthetic injection. If a previously performed anesthetic injection to confirm SI joint pain was performed up to 6 months prior to injection (with documentation indicating that the SI joint pain is not the source of the subject's pain), this does not need to be repeated at screening.
32. Compressive pathology due to stenosis or disc protrusion on MRI with associated clinical symptoms defined as leg pain VAS > 20mm out of 100mm or neurologic deficit on neurologic exam
33. Disc extrusion with a maximum dimension greater or equal to twice the posterior height of the disc, or disc sequestration in the lumbar spine on MRI as determined by radiographic core lab
34. This criterion left blank on purpose
35. Modified Pfirrmann score of 7 or 8 at any lumbar level on MRI evaluation as determined by the core imaging provider
36. Symptomatic involvement of more than one lumbar disc [redacted] (i.e. more than one level with concordant pain upon provocative discography, if performed)
37. Symptomatic central vertebral canal stenosis as defined by neurogenic claudication
38. Spondylolisthesis or retrolisthesis Grade 2 and above (>25% of the AP dimension of the superior endplate of the inferior vertebrae) at the index or adjacent level(s) on radiographic evaluation as determined by radiographic core lab or Spondylolysis at the index or adjacent level(s).
39. Lumbar spondylitis or other undifferentiated spondyloarthropathy affecting the index disc.

40. Spinal deformity defined as lumbar scoliosis with a Cobb angle of the lumbar spine greater than 15 degrees on radiographic evaluation as determined by radiographic core lab.
41. An acute fracture of the spine at the index or adjacent levels that has not healed, or clinically compromised vertebral bodies at the index level due to current or past trauma (e.g. sustained pathological or multiple fractures of vertebrae.
42. Facet pain at the index level or adjacent segments as determined by a diagnostic medial branch block (a facet block injection is not acceptable for making this determination) to rule out facet joint involvement. If a previously performed medial branch block was performed up to 6 months prior to injection (with documentation indicating that the facet joint is not the source of the subject's pain), this does not need to be repeated at screening.
43. Have not completed a minimum of 10 out of 14 daily e-diary entries of pain medication use (e.g. NSAID, aniline analgesics and opioid use) prior to screening injection procedures (i.e., diagnostic disc injection to confirm intact annulus, discography, medial branch block and SI joint injection, if deemed necessary). If a historical screening injection procedure is used, the e-diary pain medication usage collection should be completed at least 14 days after the screening procedure.
44. Full thickness annular tears in the index level as determined by free flowing contrast media through the annulus fibrosis. Injection of contrast media into the index level must take place at least 2 weeks prior to the treatment injection. If a previously performed discography with contrast was performed up to 6 months prior to injection (with documentation indicating no full tear of the disc), this does not need to be repeated at screening.

4.3 Information to be collected for Screen Failures and Randomized Not-treated Subjects

Subjects who fail any inclusion/exclusion criteria up to the timepoint of randomization are considered screen failures. Subjects who are randomized but do not receive treatment are considered randomized not-treated subjects.

The following information must be recorded for all screen failures and randomized not-treated subjects: demography, medical history, concomitant treatment, inclusion/exclusion criteria met and not met, adverse events, if any, and reason for screen failure or withdrawal. If diagnostic injection for confirmation of full thickness annual tears was performed, information regarding the procedure will also be collected.

4.4 Re-screening

Screen failures may be re-screened **twice** at the discretion of the investigator (however, subjects who have been previously randomized cannot be re-screened). Subjects will be assigned a new study identification number upon re-screening. All screening activities will need to be repeated with the possible exception of the following, if performed within the permitted timeframe: diagnostic medial branch block; diagnostic injection to confirm intact annulus or discography; possible anesthesia injection for detection of SI joint point, anterior/posterior (AP), lateral and flexion-extension X-rays; and screening MRI. For these screening activities to be waived (i.e., not repeated), they must have been performed within the following timeframes:

Screening injection procedures:

- **Diagnostic medial branch block**: within 6 months prior to injection of study treatment (with documentation indicating no clinically significant facet pain in accordance with exclusion #42)
- **SI joint injection to determine SI joint pain (not required for all subjects):** within 6 months prior to injection of study treatment (with documentation indicating no clinically significant SI joint pain in accordance with exclusion #31)
- **Diagnostic injection to confirm intact annulus or discography**: at least 2 weeks but no longer than 6 months prior to injection of study treatment.

Imaging:

- **MRI:** within 6 months prior to injection of study treatment
- **DEXA:** within 6 months prior to injection of study treatment
- **AP, lateral and flexion-extension x-rays:** within 6 months prior to injection of study treatment and according to study-defined procedure.

Note: MRIs and X-rays should be taken on the same machine using the same settings, and in accordance with the radiographic guidelines provided, from baseline to completion of the study to minimize potential differences in results caused by use of different machines. Radiographic evaluations may vary for a given subject depending on the time of day the assessments are made. Therefore, for each subject, all radiographic evaluations of a specific type (e.g., X-ray) should be taken at the same time of day at each assessment if possible, preferably in the morning.

If the diagnostic injection to confirm an intact annulus or discography is repeated in re-screening, a neurological exam must be performed prior to the injection procedure and again after the procedure. If a recent diagnostic injection taken before the screening period serves as the

baseline evaluation for a subject, the pre-injection neurological exam may be waived, though a neurological exam will need to be performed prior to any additional invasive procedures or the treatment injection. This post-diagnostic injection neurological exam will be used as the subject's baseline neurologic status.

For subjects who are re-screened, the following patient-reported outcomes must be repeated no sooner than 2 weeks after the most recent diagnostic injection procedure to confirm an intact annulus or discography: VAS assessments (leg and low back pain), ODI questionnaire, EQ-5D, iPCQ, and e-diary collection of pain medication usage for a minimum of 10 out of 14 days.

4.5 Subject Withdrawal

Subjects will be free to withdraw from the study at any time, for any reason.

A subject also may be withdrawn/removed by the investigator, if necessary, to protect the subject's health. The investigator has the right to withdraw subjects from the study in the event of intercurrent illness, adverse events, administrative, or other reasons. Any reasons for withdrawal must be documented and explained to the subject.

It is understood, however, by all concerned, that an excessive rate of withdrawals can render the study uninterpretable. Therefore, unnecessary withdrawal of subjects should be avoided.

If for any reason a treated subject is withdrawn from study participation, the reason for and date of withdrawal from the study must be recorded. If the reason for withdrawal is an adverse event or a clinically significant abnormal laboratory test result, monitoring will continue until the event has resolved, stabilized, or until the follow-up period is complete.

4.6 Withdrawal Procedure

When a subject withdraws from the study or if a subject is withdrawn by the investigator, all assessments normally required at the completion of the study will be obtained, where possible. All details available will be reported and recorded. If the reason for removal of a subject from the study is an adverse event, intercurrent illness, surgical intervention or an abnormal laboratory value considered a clinically significant abnormality, i.e., requiring medical intervention or treatment, the specific event will also be recorded. All AEs are intended to be followed through until resolved or stabilized or until the follow-up period is complete.

Case report forms are required for all subjects who are screened. Subjects who sign an informed consent and undergo any procedures for the study, including those who are subsequently excluded or withdrawn from the study before randomization will be documented on the site's screening log. Whenever possible, all sections of the screening worksheets and relevant case report forms, up to the time of withdrawal, should be completed. If applicable, efforts should be made to obtain complete information regarding safety.

If during the course of the study a subject chooses to revoke his/her written authorization for the use and disclosure of personal health information (PHI; per HIPAA privacy ruling or other country and/or region specific law), the subject will then be withdrawn from the study as well (i.e., participation in the MSB-DR003 study is contingent upon an "active" written PHI use, collection, and disclosure authorization) and only safety data will be collected as required by applicable laws. PHI collected prior to the date that the subject revokes his/her written authorization may still be used. If a subject decides to withdraw from the study, he/she should be asked if he/she can still be contacted for further information. The outcome of that discussion should be documented in the medical records.

If a subject decides to withdraw or is withdrawn from the study, the investigator will promptly notify the blinded CRA, or designee, and the reason for and date of withdrawal from study must be recorded.

4.6.1 Lost to Follow-Up

A subject is considered to have been lost to follow-up if he/she is unable to be contacted by the investigator post-randomization. The investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls or registered letters. The end of participation for a subject lost to follow-up is the date of the last known contact (e.g., visit or telephone contact).

4.7 End of Study

The end of study is defined as the date of the last follow-up visit or the date at which the last data point occurs for the last subject.

5. INVESTIGATIONAL PRODUCT

5.1 Investigational Product Labeling

The product label will contain the elements for investigational products required by 21CFR, 312.6 and other applicable regulatory agencies.

5.2 Description of Investigational Product

5.2.1 Active Treatment

Rexlemestrocel-L cells are STRO-3 selected allogeneic MPCs, which are derived from adult bone marrow mononucleated cells that are immunoselected, culture-expanded, and subsequently cryopreserved.

rexlemestrocel-L alone
Subjects enrolled in the "rexlemestrocel-L alone" arm will receive 1 injection of approximately 6 million rexlemestrocel-L cells in freeze media mixed in a 1:1 by-volume ratio with saline. A vial with 2mL of thawed rexlemestrocel-L cells and freeze media will be mixed with 2mL of saline. Two milliliters of the resulting mixture will be injected, under fluoroscopic imaging, via pressure manometer syringe into the nucleus pulposus of the index level.

rexlemestrocel-L + HA
Subjects enrolled in the "rexlemestrocel-L + HA" arm will receive 1 injection of approximately 6 million rexlemestrocel-L cells in freeze media mixed in a 1:1 by-volume ratio with 1% hyaluronic acid (HA) solution. A vial with 2mL of thawed rexlemestrocel-L cells and freeze media will be mixed with 2mL of 1% HA solution. Two milliliters of the resulting mixture will be injected, under fluoroscopic imaging, via pressure manometer syringe into the nucleus pulposus of the index level.

5.2.2 Control Agent

Subjects enrolled in the control arm will receive a saline injection. Two milliliters of thawed saline from one vial will be mixed with 2mL of thawed saline from another vial of saline. Two milliliters of the resulting saline mixture will be injected, under fluoroscopic imaging, via pressure manometer syringe into the nucleus pulposus of the index level.

5.3 Investigational Product Storage

Rexlemestrocel-L will be shipped just prior to treatment procedures in the vapor phase of liquid nitrogen at ≤ -140°C to -196°C until it is ready for use. Additional details regarding the storage and preparation of rexlemestrocel-L are contained in the study materials provided to the site.

Hyaluronic acid will also be shipped directly to the study sites. Once received by the study sites, HA should be stored in accordance with the HA product labeling.

Saline will also be shipped in a cryopreserved container, similar to rexlemestrocel-L. In order to minimize the potential for unblinding, saline should be stored under similar conditions to that of rexlemestrocel-L.

Any IP provided by the sponsor should be stored in a secure location with limited access to the unblinded designees assigned to the study. Blinded designees should not have access to IP.

5.4 Investigational Product Preparation and Administration

5.4.1 rexlemestrocel-L

The vial, in which the rexlemestrocel-L is supplied, will be removed from a shipping container and immersed with gentle shaking in a 37°C water bath. With gentle agitation, the cells will be thawed after approximately 6-8 minutes of submersion and just before the last crystal of ice has fully melted. Once the product is thawed, a timer should be started and run until the time the product is applied to the study subject.

Warning:
If the treatment is not injected within 75 minutes from the start of thaw, product cannot be administered.

5.4.2 All Investigational Product

Refer to the Investigational Product (IP) Manual for details regarding product handling and preparation. A detailed description of the process of injecting the investigational and control materials is also included in the IP Manual.

5.4.3 Investigational Product Handling and Accountability

All investigational product accountability records including records of randomization assignment will be maintained by the unblinded qualified designee, stored in a secure location and reviewed during monitoring visits by the unblinded CRA.

If the rexlemestrocel-L alone, or rexlemestrocel-L + HA is prepared, but not used for whatever reason, the circumstances will be recorded in the accountability log/form(s) and destruction of investigational product container will occur per the site's policy once accountability by the unblinded CRA has been performed.

The final disposition of all investigational product, whether used or discarded, must be recorded. The final disposition of all unused, empty, and partially used vials will be handled in accordance with the institution's policy and the supplied study materials.

An unblinded CRA will be responsible for reconciliation of IP accountability throughout the study and at study completion.

5.5 Maintenance of the Treatment Blind

Due to the appearance, configuration, and storage conditions of rexlemestrocel-L, saline, and HA, it is not possible to blind all personnel at the investigational study site.

In order to maintain the blind, each site will have an unblinded designee(s) (identified by the investigator) who receives all investigational and control product, performs accountability, properly stores it in a secure location, and prepares the injection. Additionally, the health care professional who is performing the study treatment injection will be unblinded. The unblinded health care professional who is performing the study treatment injection will perform all required procedures and evaluations associated with the treatment injection, including neurological exam prior to discharge, but will not be involved with any subject care or assessment beyond the subject's discharge following the injection procedure. All other site personnel, specifically those administering subject assessments and care, will be blinded to the treatment as will the subjects, radiographic evaluators, and members of the study team, with the following exceptions: unblinded CRAs (responsible for IP reconciliation) and unblinded statistician(s) (responsible for providing data for the interim analysis and DSMB data). Prior to the treatment administration visit, both blinded and unblinded personnel can perform screening activities.

Care should be taken to ensure that the subject does not know which investigational product he/she is receiving. Additionally, care should be taken to ensure that blinded personnel at the site and CRO are not unblinded to treatment assignment. All unblinded study site personnel will be specifically instructed to refrain from discussing any potentially unblinding information with either the subject or any blinded site, sponsor, or CRO personnel involved in the trial. Additional information is provided in the Blinding Plan.

Independent blinded radiologists will be evaluating radiographic images for key inclusion/exclusion criteria to maintain consistency and for radiographic endpoints. Two independent and blinded radiologists will review screening radiographic images to confirm subjects meet the radiographic inclusion/exclusion criteria with a third independent and blinded radiologist will adjudicate any differences between the two initial radiologist's reviews. Follow-up evaluation of radiographic images will be performed by at least 2 blinded independent radiologists with a third radiologist to adjudicate any differences between two initial radiographic reviewers' assessments.

Any Interim analyses will be conducted by an unblinded independent statistician.

The DSMB will also be unblinded in order to assess the safety of IP.

The Treatment Events Committee (TEC), performing adjudication of post-treatment interventions and relationship of adverse events to product and/or procedure will be blinded.

When the unblinded statistical analyses are conducted at the conclusion of the primary safety and efficacy evaluation period, study subjects, as well as site personnel responsible for subject care and assessment, will continue to be blinded until the completion of the long-term safety and efficacy follow-up period (i.e., when all subjects who remain active in the study have completed their 36-month treatment visit).

5.6 Treatment Compliance

All subjects in this study will undergo an injection into a single lumbar disc with either rexlemestrocel-L in freeze media ("rexlemestrocel-L alone"), rexlemestrocel-L cells in freeze media mixed with HA ("rexlemestrocel-L + HA"), or saline.

Each qualified subject will be randomized to one of 2 active treatment arms (rexlemestrocel-L alone or with HA) or to the saline control arm. All subjects will receive a single injection with the study product injected directly into the nucleus pulposus of the index level.

Any randomized subjects who, upon re-examination just prior to the injection procedure, do not meet the inclusion criteria or withdraw consent prior to treatment, will be considered randomized not-treated and will not receive treatment.

Throughout the study, the assigned unblinded CRA will monitor compliance with the treatment assignment, review and verify all investigational product accountability records and inventory at each participating investigational center.

6. STUDY PROCEDURE

6.1 Visit Schedule and Assessments

Table 3 shows all planned assessments, which are marked with an "X" for the visits at which they are performed. Subjects should be seen for all visits on the designated days or within the given windows for those visits. The study assessment schedule outlines all procedures to be performed on subjects at the scheduled visits.

In order to minimize variability in evaluations, ideally, the same personnel should perform the same tests and assessments on all the subjects at a given trial site, if possible.

Sites are required to access the interactive web response system (IWRS) at the beginning of the screening period to obtain a screening number. Sites are also required to access IWRS at the conclusion of the screening period to register the subject status. If the subject does not meet all inclusion and exclusion criteria, the subject will be considered a screen failure. If the subject meets all inclusion and exclusion criteria, the subject must be randomized a minimum of 7 days prior to treatment (Day 0) to allow time for shipment of investigational product to the site. In addition, treatment must be administered no later than 30 days following randomization.

Table 3: Schedule of Assessments and Procedures[a]

Assessment	Screen/ Baseline[b] Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Unscheduled Visit [c]
	Days -105 to 0 [a]	Day 0 Treatment Injection[w] (7-30 days post-Randomization)	1 Month (± 14 Days) [a]	3 Months (± 14 Days) [a]	6 Months (± 30 Days) [a]	12 Months (± 60 Days) [a]	18 Months (± 60 Days [a]	24 Months (± 60 Days [a]	36 Months (± 60 Days [a]	
Informed consent and privacy forms (e.g., HIPAA) [d]	X	—	—	—	—					
Inclusion/exclusion criteria	X	X	—	—	—	—				
Demography and smoking history	X	—	—	—	—	—				
Medical & surgical histories	X	—	—	—	—	—				
Alcohol and Substance Abuse Questionnaire	X									
Mental Illness/Incompetence Questionnaire	X									
Pain Catastrophizer Scale	X									
SCORE or MORES assessment	X [o]									
Disease targeted, abbreviated PE [e]	X	X	X	X	X	X	X	X	X	
Neurological Examination	X [f]	X [g]	X	X	X	X	X	X	X	X
Targeted PE to rule out SI joint pain [h]	X									
Vital signs, seated, if possible	X	X [i]	X	X	X	X	X	X	X	X
Height, weight, and BMI	X	X	X	X	X	X	X	X	X	X
Hematology	X	—	X	—	—	X		X	X	
Chemistry Panel	X [j]	—	X	—	—	X		X	X	
HIV	X	—	—	—	—	—				
Pregnancy Test [k]	X	X	—	—	—	—				
Flow Class I and II % PRA with specificity testing and DSA [l]	X	—	—	—	—	X		X	X	
MRI scan [m]	X	—	—	—	—	X	X	X	X	
Flexion/extension x-ray [m]	X[n]	—	X	X	X	X	X	X	X	
AP, lateral x-rays [m]	X[n]	—	X	X	X	X	X	X	X	

Assessment	Screen/ Baseline[b] Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Unscheduled Visit [c]
	Days -105 to 0 [a]	Day 0 Treatment Injection[w] (7-30 days post-Randomization)	1 Month (± 14 Days) [a]	3 Months (± 14 Days) [a]	6 Months (± 30 Days) [a]	12 Months (± 60 Days) [a]	18 Months (± 60 Days [a]	24 Months (± 60 Days [a]	36 Months (± 60 Days [a]	
Lumbar spine DEXA [o]	X[p]									
Leg pain assessments VAS	X [q,r]	—	X	X	X	X	X	X	X	X
Low back pain assessment VAS (average and worst pain over 24 hours)	X [q,r]	—	X	X	X	X	X	X	X	X
Oswestry Disability Index (ODI) Questionnaire	X [q]	—	X	X	X	X	X	X	X	X
Self-Assessment of Treatment (SAT) Questionnaire		—	X	X	X	X	X	X	X	
EQ5D	X [q]	—	X	X	X	X	X	X	X	
iMTA Productivity and Cost Questionnaire (iPCQ)	X [q]	—	X	X	X	X	X	X	X	
Patient-reported Utilization Questionnaire	X	—	—	—	—	X	X	X	X	
Diagnostic medial branch block [s]	X	—	—	—	—	—				
Disc Injection to Confirm Intact Annulus	X [t]	—	—	—	—	—				
Discography Procedure, if required	X [bb]									
Randomization	X[u]	—	—	—	—	—				
Collection of Pharmacoeconomic Data [v]	X	—	—	—	—	X		X	X	
Treatment Injection	—	X [w]	—	—	—	—				
Subject e-Diary Reminder	X [x]	—	X [y]	X [y]	X [y]	X [y]	X	X	X	
Subject e-Diary Completion [z]	X [x]	—	X	X	X	X	X	X	X	
Concomitant treatment [aa]	X	X	X	X	X	X	X	X	X	X
AE evaluation	X	X	X	X	X	X	X	X	X	X

a. All clinic visits are calculated from Visit 2/Day 0.

b. For subjects who are re-screened, all screening assessments should be repeated with the exception of the following:
   - **Diagnostic medial branch block**: if performed within 6 months prior to injection of study treatment (with documentation indicating no clinically significant facet pain in accordance with exclusion #42)
   - **SI joint injection to determine SI joint pain (not required for all subjects)**: within 6 months prior to injection of study treatment (with documentation indicating no clinically significant SI joint pain in accordance with exclusion criteria #31)
   - **Diagnostic injection to confirm intact annulus**: if performed at least 2 weeks but no longer than 6 months prior to injection of study treatment
   - **MRI:** if performed within 6 months prior to injection of study treatment
   - **DEXA:** if performed within 6 months prior to injection of study treatment
   - **AP, lateral and flexion-extension x-rays:** if performed within 6 months prior to injection of study treatment and according to study-defined procedure

c. Low back pain VAS (average and worst pain over 24 hours), ODI, vital signs, height, weight, concomitant treatment, neurological exam and AE evaluation are required at all unscheduled visits. All other assessments may be performed at the discretion of the investigator. For any subjects who are planning a post-treatment intervention during the course of the study, every effort should be made to schedule an unplanned study visit within a 30-day time window prior to the intervention. During this pre-intervention visit, all assessments and activities regularly performed at Visits 3-9 will be performed, with the exception of imaging assessments, hematology, chemistry panel, and Flow Class I and II % PRA with specificity testing and DSA. If the subject's originally planned assessment timepoint falls within 30 days prior to the post-treatment intervention, the unplanned study visit will not be necessary.

d. Subjects will complete the informed consent process for Study MSB-DR003 at Screen/Baseline

e. Disease targeted/abbreviated PE to include but not limited to examination of the musculoskeletal system.

f. During screening, the neurological exam will be performed twice: one prior to the diagnostic injection to confirm an intact annulus and once after the diagnostic injection to assess if the injection procedure has resulted in any neurologic changes. The neurological exam prior to the diagnostic injection can be performed by the unblinded or blinded evaluator, but preferably the blinded evaluator. The post-diagnostic injection exam will be performed by the health care professional performing the injection procedure; this person may or may not be blinded.

g. Neurological exam to be performed post treatment injection, prior to discharge to assess if the injection procedure has resulted in any neurologic changes. This will be performed by the unblinded health care professional performing the injection procedure, to avoid the potential unblinding of the blinded evaluator.

h. If findings are inconclusive, the investigator may perform a diagnostic injection of anesthetic to the SI joint (Section 6.4.6).

i. To be performed prior to the procedure and then following the procedure prior to discharge.

j. Screening Chemistry Panel includes: albumin, alkaline phosphatase, ALT, AST, BUN, creatinine, hsCRP, chloride, direct bilirubin, GGT, glucose, lactic dehydrogenase, sodium, potassium, phosphorous, total bilirubin, total calcium, carbon dioxide, total cholesterol, total protein and uric acid

k. For women of child bearing potential. A serum pregnancy test will be analyzed by the central laboratory at screening. An additional urine pregnancy test will be performed prior to administration of study treatment to confirm a negative result. If the urine pregnancy test is positive, study treatment will not be administered that day, and the result will be confirmed by a serum pregnancy test.

l. Specificity testing and DSA only for those Class I or II PRA results ≥5%. Specificity testing and DSA results will be blinded until the end of the study.

m. MRIs and radiographs should be taken on the same machine using the same settings, and in accordance with the radiographic guidelines provided, from baseline to completion of the study to minimize potential differences in results caused by use of different machines. Radiographic evaluations may vary for a given subject depending on the time of day the assessments are made. Therefore, for each subject, all radiographic evaluations of a specific type (e.g., X-ray) should be taken at the same time of day at each assessment if possible, preferably in the morning. MRIs and radiographs will be evaluated by a core imaging provider for the criteria noted in the inclusion & exclusion criteria. All other radiographic evaluations at screening will be assessed by the investigator. Evaluation of the change in macromolecular content and hydration of the treated disc will be performed on a subset of subjects where T1 rho and T2 mapping capability is available.

n. Screening DEXA scans and AP, lateral and flexion-extension x-rays performed according to study-defined procedure may be performed up to 6 months prior to procedure.

o. Any female subject with a SCORE of ≥6 or male subjects with a MORES of ≥ 6 will require a lumbar spine DEXA scan to be performed. Similarly, subjects who are considered at risk, as defined in exclusion criterion #4 (Section 6.4.5), will be required to have a DEXA scan at screening, regardless of SCORE value.

p. The DEXA scan will measure bone mineral density and determine whether or not the subject is considered to have severe osteoporosis. A T-score that is within ≤ -2.5 standard deviations from the standard will exclude a potential subject from participating in this study.
q. For subjects who are re-screened, this patient-reported outcome must be performed at least 2 weeks after the most recent diagnostic injection procedure (i.e., diagnostic disc injection to confirm intact annulus, medial branch block and SI joint injection, if deemed necessary).
r. At screening, the VAS evaluation must be administered before any diagnostic injections or at least 2 weeks following any injections to relieve pain.
s. If a previously performed medial branch block on and/or SI joint injection was performed up to 6 months prior to injection (with documentation indicating no facet pain and/or SI joint pain), this does not need to be repeated at screening
t. <u>There must be at least a 2-week "washout" period following the diagnostic disc injection and prior to the injection of study treatment (i.e., any injection of contrast media into the disc must be performed at least 2 weeks prior to the rexlemestrocel-L injection procedure). If an injection of contrast media was performed within 6 months prior to the rexlemestrocel-L injection procedure and presence/absence of full thickness annular tears is documented, it will not have to be repeated.</u>
u. Must occur at least 7 days prior to treatment injection to allow for investigational product to be shipped to the site, but not more than 30 days prior to treatment injection.
v. A subject's informed consent in this study will include permission for the release of any non-study-related medical records that will provide data for pharmacoeconomic analyses. However, this is optional and will not impact a subject's participation in the study.
w. Includes recording procedural information. Treatment injection must occur no later than 30 days after randomization.
x. At a timepoint after informed consent, subjects should be instructed to complete the e-diary for 2 weeks. Subject e-diary should be completed each day for 2 weeks after signing informed consent but prior to diagnostic injection to confirm intact annulus unless a historical diagnostic injection or e-diary is used.
y. Subjects should be contacted, either automatically by IWRS or by the site, approximately 2 weeks prior to each post-treatment visit as a reminder to complete daily pain medication patient e-diaries.
z. Please see sections 6.7.2, 6.7.3, and 6.7.6 for collection details on VAS, ODI and pain medication. .
aa. Subject will be asked about all medications being taken, including pain medications (e.g., NSAIDs, opioids), tricyclic anti-depressants, membrane stabilizers/anticonvulsants, sleeping pills, muscle relaxants, etc. and other treatments (chiropractic, acupuncture, physical therapy, spinal injections, etc.) used to treat their back pain.
bb. A discography procedure may be performed to determine the index level. [redacted] a discography procedure may be required.

6.1.1 Screening Period

A subject will enter the screening period once a written informed consent has been signed by the subject. In addition, all subjects must sign a HIPAA authorization or other local regulatory agency required form as applicable for use, collection, and disclosure of PHI.

This initial screening period will not exceed 105 days (75 day screening period until randomization and a maximum of 30 days between randomization and study treatment). During the screening period it will be determined that the subject meets all inclusion and exclusion criteria. Baseline assessments will also be completed during this time. All patient-reported outcomes (including VAS and ODI assessments), as well as baseline use of pain medication (i.e., 2-week e-diary record), will be established during screening. All such assessments should be performed prior to the diagnostic disc injection to confirm intact annulus or discography, if deemed necessary. However, if the subject had received a previous diagnostic injection procedure to confirm intact annulus or discography prior to the screening period (but within the permitted timeframes to serve as the baseline evaluation; see Section 4.2.2), these patient-reported outcomes and e-diary entries must be started at least 14 days following the most recent injection procedure.

A neurological exam will be performed prior to the diagnostic injection to confirm an intact annulus or discography and again after the procedure. If a recent diagnostic injection or discography taken before the screening period serves as the baseline evaluation for a subject, the pre-injection neurological exam may be waived, though a neurological exam will need to be performed prior to any additional invasive procedures or the treatment injection. This neurological exam will be used as the subject's baseline neurologic status.

If a subject is re-screened, most patient-reported outcomes must be completed again at least 2 weeks after the most recent diagnostic injection procedure. These patient-reported outcomes include VAS assessments (leg and low back pain), ODI questionnaire, EQ-5D, and iPCQ. However, if an e-diary was collected during a previous screen, this may be used, provided it meets all criteria for a valid e-diary collection (i.e. 10 out of 14 days pain medication usage collected).

There must be at least a 2-week "washout" period following the diagnostic disc injection or discography prior to the injection of study treatment (see Section 6.4.8).

6.1.2 Randomization

Randomization must occur a minimum of 7 days prior to treatment (Day 0) to allow time for shipment of investigational product to the site. In addition, treatment must be administered no later than 30 days following randomization. Subjects will be enrolled in the study sequentially by dose via a central randomization system. Randomization will be stratified by site and by whether the subject is taking an opioid medication or not.

6.1.3 Safety and Efficacy Evaluation Period (Day 0 to 24 Months Post-treatment)

On Day 0/Treatment Administration day, each subject will receive an intradiscal injection of rexlemestrocel-L alone, rexlemestrocel-L +HA, or saline control in a 1:1:1 randomization ratio. This will commence the 24-month primary safety and efficacy period, which includes intensive safety and efficacy evaluations.

Treatment injection and post-procedure care (anesthesia, prophylactic antibiotics, blood product [i.e., packed red blood cells and platelets], rehabilitation regimens, etc.) will be performed in accordance with standard of care, as appropriate in the judgment of the investigator, and documented.

Subjects will be given the following directions for post-injection rehabilitation/treatment:

- Day of Procedure – Bed Rest
- Day After Procedure – Gentle Ambulation with gradual increase thereafter
- Days 1 to 3 – Avoid repetitive bending, stooping and lifting greater than 10-15 lbs.
- Return to normal daily activity when pain has subsided to their baseline.

After the treatment injection visit, all safety and efficacy evaluations should be completed by blinded site staff.

Subjects will attend study visits 3, 4, 5, 6, 7, and 8 (corresponding to 1, 3, 6, 12, 18 and 24 months post-treatment) to complete the primary safety and efficacy period. Subjects will return at Study Visit 9 for a 36 month long-term safety and efficacy evaluation before completing the study. Subjects may also attend unscheduled visits for safety reasons as warranted.

If, for any reason, additional medication must be prescribed, subjects should inform the study site personnel.

Subjects may call the investigator at any time during the study if they experience any problems. The investigator may decide to follow up with a telephone call and/or request an unscheduled visit.

At least 2 blinded independent radiologists with a third radiologist to adjudicate any differences between two initial radiographic reviewers' assessments will review the specified screening radiographic images to confirm subjects meet the radiographic inclusion/exclusion criteria. Follow-up evaluation of radiographic images and any screening assessments that are not inclusion/exclusion criteria will be performed by at least 2 blinded independent radiologists with a third radiologist to adjudicate any differences between two initial radiographic reviewers' assessments as specified in Appendix 1.

Study center personnel (with the exception of unblinded staff preparing and administering the investigational treatment) and subjects will remain blinded to the treatment allocation for the entire 36-month post-treatment period. Blinded radiographic evaluators will also remain blinded for the entire post-treatment study period.

Treatment allocation for the primary analysis of safety and efficacy at 24 months post-treatment will occur only for the sponsor and any authorized representative. These personnel include those members of the study team responsible for generating a summary and analysis of the data. All site personnel, specifically those administering subject assessments and care, will be blinded to treatment allocation, with the following exceptions: unblinded CRAs (responsible for IP reconciliation) and unblinded statistician(s) (responsible for providing data for the interim analysis and DSMB data).

During Study MSB-DR003, subjects may attend unscheduled visits for safety reasons if warranted.

6.2 Unscheduled Visits

Unscheduled visits may be conducted at any time for safety reasons, if deemed medically necessary by the investigator. During such visits vital signs, height, weight, VAS, ODI, concomitant treatments, neurological exam and AE evaluation will be required, while all other assessments may be performed at the investigator's discretion.

For any subjects who are planning an intervention during the course of the study, every effort should be made to schedule an "unscheduled visit" within a 30-day time window prior to the intervention. Surgical and injection interventions should be avoided through at least the 24 month primary endpoint follow-up. Surgical and injection interventions should only be undertaken if the subject's pain, measured by VAS, and function, measured by ODI, are not improved compared to the baseline values since an intervention could confound the efficacy assessments and would classify a subject as a treatment failure. During this visit, vital signs, height, weight, VAS, ODI, concomitant treatments, neurological exam and AE evaluation will be required, while all other assessments may be performed at the investigator's discretion. However, if the subject's originally scheduled visit falls within 30 days prior to the planned intervention, the unscheduled visit will not be necessary. Such visits will allow for subject-reported efficacy assessments (VAS and ODI) to be used in last observation carried forward (LOCF) analysis. Details of this analysis are provided in Section 9.9.

6.3 Missing or Delayed Study Visits

Subjects should be encouraged not to miss any visits. Any visits that are missed or not completed within the specified timeframe (or window allowance) should be documented by the site and the CRA should be notified.

If a scheduled in-clinic visit is missed, the site should contact the subject to determine if any interventions that would classify the subject as a treatment failure have occurred since their last visit. If any interventions are reported, the site should collect all the information required if the intervention had been reported at an in-clinic visit. All intervention information collected remotely must be documented in a source document and/or worksheet.

6.4 Screening Assessments

6.4.1 Subject Demographics/Other Baseline Characteristics

Demographic and baseline characteristics will be recorded during the screening period. This includes the following: demographics, including past and current smoking history, medical and surgical history including, but not limited to, surgical history of the spine (including all invasive spinal interventions) and history of packed red blood cells and platelets administration, vaccinations and pregnancies (where applicable).

Subjects will also be asked to provide medical records or access to medical information relating to any healthcare utilization that has occurred up to 12 months prior to treatment. However, this is optional and will not impact a subject's participation in the study.

6.4.2 Pre-Treatment Pain Medication Usage Collection by E-Diary

Baseline pain medication usage must be established prior to diagnostic injection procedures if performed during the screening. A minimum of 10 out of the 14 daily entries must be complete in order to establish a baseline dose. If more than 4 out of 14 daily entries are missing, subjects should be asked to continue completing the e-diary until 10 out of 14 daily entries are obtained.

Based on the opioid information entered into the e-diary during baseline, subjects will be classified into one of the following groups:

- **Opioid Non-user:** subjects who did not take any opioids during the e-diary pain medication data collection period
- **Opioid user:** subjects who did take an opioid during the e-diary pain medication data collection period.

[redacted]

6.4.3 Prohibited Concomitant Medication and Procedures

Subjects should be encouraged not to receive any of the following medications or treatments during the course of the study and/or for the times specified below:

- Chronic (at least 7 consecutive days) systemic corticosteroids at a dose equivalent to $\geq$ 10 mg/day of prednisone are prohibited from 14 days prior to the study treatment injection. Topical, nasal, and inhaled corticosteroids are permitted. Use of systemic corticosteroids post-treatment are not prohibited, but should be discouraged so that an accurate assessment of the treatment's effectiveness can be made.
- Systemic NSAIDS and local injections of NSAIDs into the treated disc and and/or adjacent vertebral discs are prohibited from 7 days prior to the study treatment injection. Use of NSAIDS post-treatment are not prohibited, but should be discouraged so that an accurate assessment of the treatment's effectiveness can be made.

- Any lumbar intradiscal injection procedure (e.g., injection methylene blue, dextrose, PRP, or glucosamine and chondroitin sulphate) at the treated disc other than discography or epidural steroid injection prior to treatment injection are prohibited. The injection of contrast medium must be done at least 2 weeks prior to study treatment procedure.
- Use of surgical procedures or intradiscal injections should be avoided through at least the 24 month primary endpoint so that an accurate assessment of the treatment's effectiveness can be made. Surgical and injection interventions should only be undertaken if the subject's pain, measured by VAS, and function, measured by ODI, is not improved compared to the baseline values since an intervention could confound the efficacy assessments and would classify the subject as a treatment failure.
- Epidural steroid injections within 8 weeks prior to study treatment. Use of epidural steroids post-treatment are not prohibited, but should be discouraged so that an accurate assessment of the treatment's effectiveness can be made.
- Other investigational therapy or device within 6 months prior to the treatment injection and/or plans to participate in any other allogeneic stem cell/progenitor cell therapy trial for the 36-months following.

6.4.4 Concomitant Treatments

Subjects may continue with all other baseline medication(s). If for any reason, a subject requires additional medication(s) or a change in the dose of existing medication(s), the medication(s), route of administration, and the reason for which it was given should be recorded. During the course of the study, a subject may decide to use over the counter medication(s). As with prescription medications, all over the counter medication(s), including herbal medications must be recorded.

Furthermore, subjects will be asked about medications and treatments to deal with their low back pain at each follow-up visit in addition to asking about potential AEs and other medications being taken.

6.4.5 Determination of Baseline Bone Mineral Density

Prior to treatment, each female subject will be screened for risk of osteoporosis using the Simple Calculated Osteoporosis Risk Estimation (SCORE) and each male subject will be screened for risk of osteoporosis using the Male Osteoporosis Risk Estimation Score (MORES). Any female subject with a SCORE of ≥6 or a male subject with a MORES score of ≥6 will require a lumbar spine DEXA scan to be performed or, alternatively, a historic T-score to be obtained, if the prior

scan was taken within 6 months prior to the estimated date of study treatment. Similarly, subjects who are considered at risk, as defined in exclusion criterion #4 (Section 6.4.5), will be required to have a DEXA scan at screening, regardless of SCORE value.

The DEXA scan will measure bone mineral density and determine whether or not the subject is considered to have osteopenia or osteoporosis. A T-score that is within ≤-2.5 standard deviations from the standard will exclude a potential subject from participating in this study.

6.4.6 Determination of Baseline SI Joint Pain

A targeted physical examination to rule out SI joint pain will be performed at screening. Clinical examination of the subject's lumbar spine and pelvis should be performed. As part of this examination, the following Laslett's Tests[59] should be performed.

Table 4: Physical Examination for Evaluation of SI Joint Pain

Test	Description (Positive Findings)
Distraction	Patient supine. Examiner applies posterolateral directed pressure to bilateral ASIS. (Reproduction of pain)
Compression	Patient side-lying. Examiner compresses pelvis with pressure applied over the iliac crest directed at the opposite iliac crest. (Reproduction of symptoms)
Thigh Thrust	Patient supine. Examiner place hip in 90 deg flexion and adduction. Examiner then applies posteriorly directed force through the femur at varying angles of abduction/adduction. (Reproduction of buttock pain)
Sacral Thrust	Patient prone. Examiner delivers an anteriorly directed thrust over the sacrum. (Reproduction of pain)
Gaenslen's	Patient supine with both legs extended. The test leg is passively brought into full knee flexion, while the opposite hip remains in extension. Overpressure is then applied to the flexed extremity. (Reproduction of pain)

Subjects who present with all of the following symptoms should be considered positive for SI joint pain:

1. Maximal tenderness at or below L5,
2. Tenderness over the posterior superior iliac spine / sacral sulcus, and
3. Three positive SI joint provocation tests (Laslett's tests).

Should the results of the targeted examination prove inconclusive, the investigator may perform a diagnostic injection of anesthetic to the SI joint in order to determine presence of SI join pain.

6.4.7 Pregnancy Tests

A serum pregnancy test will be analyzed for all females of childbearing potential at screening. Women of childbearing potential are defined as premenopausal and not surgically sterilized or postmenopausal for fewer than 2 years. A urine pregnancy test will be performed prior to administration of study treatment to confirm a negative result. If the urine pregnancy test is positive, study drug will not be administered that day, and the result will be confirmed by a serum pregnancy test.

Serum pregnancy tests will be performed at the central clinical laboratory, whereas urine pregnancy tests will be performed by qualified clinical site personnel using kits.

There must be at least a 2-week "washout" period following the diagnostic disc injection and prior to the injection of study treatment (i.e., any injection of contrast media into the disc must be performed at least 2 weeks prior to the study treatment injection procedure).

If an injection of contrast media was performed within 6 months prior to the rexlemestrocel-L injection procedure and presence/absence of full thickness annular tears is documented, it will not have to be repeated.

6.4.9 Worksheets for DSM-5 Criteria for Alcohol and Substance Abuse Disorder

Subjects will complete the Worksheets for DSM-5 Criteria for Alcohol and Substance Abuse Disorder to determine whether they may have an alcohol or substance abuse problem that could inhibit their participation in the study or accurate assessment of the effect of treatment on their low back pain. Any subject answering yes to 6 or more questions on either worksheet are excluded from the study.

6.4.10 Mental Illness/Incompetence

Subjects will complete certain portions of the DSM-5 Self Rated Level 1 Cross-Cutting Symptom Measure-Adult to determine if the subject has mental illness or incompetence that would preclude participation. Subjects will complete Domain1-Depression, Domain 6-Suicidal Ideation, Domain 7-Psychosis and Domain 9-Memory. Subjects with a response of "Severe/Nearly Every Day" (Score of 4) to any question in Domains 1, 6 and 9 are excluded from the study. Subjects with a response of "Slight Rare, Less Than a Day or Two" or greater (Score of 1-4) to any question in Domain 7 are excluded from the study.

6.4.11 Pain Catastrophizer Scale

Subjects will complete the Pain Catastrophizer Scale to determine whether they are a pain catastrophizer. Pain catastrophizers are less likely to receive benefit from any treatment for pain and should be excluded from the study. Subjects that have a score of 30 or more on the pain catastrophizing scale are excluded from the study.

6.4.12 Discography, if performed

Physicians may use a discography procedure to assist in determining what level should be treated [redacted]
Discography is not required to be performed on all subjects. [redacted]

NOTE: The diagnostic injection to determine if the annulus is intact can be performed as part of the discography procedure as long as all of the information required to be collected during the diagnostic injection is collected during the discography procedure.

6.5 Administration of Investigational Product

All subjects in this study will undergo an intervertebral lumbar injection into the target disc with 1 of 3 possible treatments:

- **"rexlemestrocel-L alone":**
  2.0 mL of rexlemestrocel-L cells in freeze media (containing approximately 6 million rexlemestrocel-L cells) mixed in a 1:1 ratio with saline
- **"rexlemestrocel-L + HA":**
  2.0 mL of rexlemestrocel-L cells in freeze media solution (containing approximately 6 million rexlemestrocel-L cells) mixed in a 1:1 ratio with 1% HA
- **saline control:**
  2.0mL saline solution.

Vital signs will be recorded prior to injection.

The treatment injection should be performed with a pressure manometer syringe provided by the sponsor.

The injection procedure MUST be stopped if any of the following occur:

- The investigator cannot accurately place the needle tip in the nucleus pulposus
- The injection pressure is greater than 100 psi
- The subject becomes hemodynamically unstable during the injection procedure.

The following information regarding the treatment procedure must be documented in source documentation:

- Procedure start and stop time, including start time of thaw
- Treatment administration stop time
- Treatment interruption information, if applicable
- Opening pressure of the treated disc
- Pressure when 2mL of treatment is injected
- Maximum injection pressure achieved
- Total volume of treatment injected
- Anesthesia type(s).

The following evaluations will be performed after procedure, but prior to discharge:

- Record vital signs
- Perform a disease targeted/abbreviated physical examination
- Perform a neurological examination (motor, sensory, reflex) to assess if the injection procedure has resulted in any neurologic changes. This will be performed by the unblinded health care professional performing the injection procedure, to avoid the potential unblinding of the blinded evaluator. The neurologic exam should be performed after the treatment injection but prior to discharge.
- Prescribe post-injection rehabilitation/treatment and record any prescriptions for post-procedure pain
- Record concomitant medications
- Record adverse events.

All injection and post-procedure care (anesthesia, prophylactic antibiotics, rehabilitation regimens, etc.) will be performed in accordance with standard of care.

Subjects will be given the following directions for post-injection rehabilitation/treatment:

- Day of Procedure – Bed Rest
- Day After Procedure – Gentle Ambulation with gradual increase thereafter
- Days 1 to 3 – Avoid repetitive bending, stooping and lifting greater than 10-15 lbs.
- Return to normal daily activity when pain has subsided to their baseline.

Discharge instructions will include, as needed, prescriptions for pain management. Subjects should be encouraged to remain on the medication they were taking prior to treatment for the first 24 months following treatment. Following study treatment, each subject should adhere to the prescribed post-injection rehabilitation/treatment. Additional guidance can be found in the IP Manual.

The injection procedure is deemed to be completed upon discharge of the subject. After discharge of the subject, the unblinded health care professional should have no involvement in assessing the subject for the protocol or making treatment decisions for the subject.

6.6 Safety Assessments

Measurement of all safety parameters should be performed as described in Table 3. Adverse event reporting is discussed in detail in Section 7.

Standardized instructions for determining all other safety parameters are provided in the following sections.

6.6.1 Prior and Concomitant Medication and Treatment

Concomitant medications will be recorded at all study visits. All pharmacologic (including, but not limited to opioids, NSAIDs, aniline analgesics, tricyclic antidepressants and membrane stabilizers/anticonvulsants) and non-pharmacologic treatment used by study subjects within 6 months prior to screening should be recorded. Any dose modification of concomitant medications should be checked at each visit and recorded. Pain medication, specifically opioids and non-opioids (e.g. NSAIDS and aniline analgesics), usage will also be recorded by the subject into an e-diary to determine actual pain medication usage over a 2-week period during screening and prior to each in-clinic visit.

All subjects will be asked to enter pain medication (e.g. opioid, NSAID and aniline analgesics) usage information into an e-diary during screening. For baseline assessment of pain medication use, subjects should complete pain medication e-diaries for 2 weeks prior to any screening injection procedures (i.e., diagnostic disc injection to confirm intact annulus or discography, medial branch block and SI joint injection, if deemed necessary). If a subject had received a previous diagnostic injection procedure to confirm intact annulus or discography prior to the screening period (but within the permitted timeframes to serve as the baseline evaluation; see Section 4.2.2), the 14-day e-diary must be started at least 14 days after that injection procedure. If more than 4 out of 14 daily entries are missing, the subjects should be asked to continue completing the e-diary until 10 out of 14 daily entries are obtained. Following study treatment, subjects should complete the pain medication e-diary every day for a 2 week period during the 30 days prior to each clinic visit, other than the 1 month visit that must be conducted within the 14 days prior to the 1 month visit using electronic diaries (e-diaries) completed by the subjects. At each clinic visit at least 10 of 14 daily entries should be available. The site is to review the pain medication reported and log the visit within the subject's e-diary to close the reporting for that visit.

6.6.2 Post-treatment Interventions at the Treated Level

Surgical and injection interventions should be avoided through at least the 24 month primary endpoint follow-up. Surgical and injection interventions should only be undertaken if the subject's pain, measured by VAS, and function, measured by ODI, is not improved compared to the baseline values since an intervention could confound the efficacy assessments and would classify a subject as a treatment failure.

Records of secondary interventions during the post-treatment period are collected in this study for use in efficacy and safety analyses. As a safety measure, subjects requiring post-treatment interventions may be monitored for newly occurring AEs, and other concomitant treatments received in the same period of time. Post-treatment interventions will be adjudicated by a blinded and independent TEC. Following are procedures that should be considered interventions and consequently treatment failures for responder analyses if they occur at the treated level:

Surgical Interventions

- Spine fusion, interbody or posterolateral
- Artificial Disc Replacement
- Interlaminar or Spinous Process Stabilization Device Implantation

- Discectomy
- Surgical Disc Decompression, including minimally invasive decompression procedures such as mild®
- Laminectomy
- Laminotomy
- Osteotomy
- Foraminotomy
- Facetectomy
- Facet Joint Ablation/Denervation/Rhizotomy
- Disc nucleoplasty
- Spinal cord stimulation
- Intradiscal Electrothermal Annuloplasty
- Intradiscal Ablation Procedures
- Intrathecal pump implantation.

Spine Injections

- Epidural steroid injections
- Transforaminal injection of corticosteroid
- Injection of any anesthetic, analgesic, steroid or other potential pain relieving substance into the disc
- Facet Injection of corticosteroid.

For any subjects who are planning a post-treatment intervention during the course of the study, every effort should be made to schedule an "unscheduled visit" within a 30-day time window prior to the intervention. However, if the subject's originally scheduled visit falls within 30 days prior to the planned intervention, the unscheduled visit will not be necessary.

6.6.3 Neurological Examination

Neurological examination will be performed at screening and at each scheduled study visit thereafter. During screening, the neurological exam will be performed twice: once at any time during the screening period prior to the diagnostic injection to confirm an intact annulus or discography, and once after the diagnostic injection, prior to discharge, to assess if the injection procedure has resulted in any neurologic changes. If a historical diagnostic injection to confirm an intact annulus is used, the neurologic exam prior to the injection can be waived. In this case, the neurological exam will be performed during the screening period and will be used as the subject's baseline neurological exam for inclusion/exclusion determination as well as comparing to follow-up visits for any changes from baseline. The neurological exam prior to the diagnostic injection to confirm an intact annulus or discography, as well as the neurologic exam prior to the treatment injection, will be performed by either the unblinded or blinded evaluator, but preferably by the blinded evaluator who is to perform neurological exams from Visit 3 through the duration of the study. The post-diagnostic injection exam will be performed by the health care professional performing the injection procedure; this person may or may not be blinded.

Additionally, a neurological examination is to be performed after the treatment injection at Visit 2, prior to discharge, to assess if the injection procedure has resulted in any neurologic changes. This examination is to be performed by the unblinded health care professional performing the injection procedure to avoid the potential unblinding of the blinded evaluator.

The neurologic exam should include an assessment of lumbar-associated motor function, reflexes and sensory functions at L1-S1 and will assist in determination of adverse events.

The neurological evaluation must be conducted by the investigator or by a qualified medical practitioner delegated by the investigator. The components of the exam are:

Motor (Muscle Strength)

Each of the following assessments will be performed on the left and right side:

- Hip flexion
- Knee flexion
- Knee extension
- Ankle dorsiflexion
- Ankle plantar flexion
- Great toe dorsiflexion.

Subjects will receive a grade for each assessment performed (e.g., a grade for the left-sided hip flexion and a grade for the right-sided hip flexion). The grading system is as follows:

0 = no movement
1 = trace of muscle contraction
2 = active movement without gravity
3 = active movement against gravity
4 = active movement against resistance

A subject who receives a grade of 4 for all assessments will be considered a success for the motor exam. All other subjects will be considered failures for the motor exam. A failed baseline motor exam at any location would exclude the subject.

Sensory Exam of Dermatome Distribution:

Using a pinwheel, the clinician will evaluate both left and right dermatomes at each of the following levels:

- Hip Girdle and Groin Area (L1)
- Mid-anterior Thigh (L2)
- Medial Femoral Condyle (L3)
- Medial Malleolus (L4)
- Dorsum 3rd MTP Joint (L5)
- Lateral Heel (S1).

Subjects will be assessed as pass/fail for the sensory exam. A subject who experiences sensation in response to the pinwheel stimulus at each of the dermatomes will be considered a success for the sensory exam; all other subjects will be considered failures for the sensory exam. A failed baseline sensory exam at any dermatome would exclude the subject

Patellar and Ankle Reflex Exam:

- Patellar: subject is seated on a table with legs hanging at the knee. The clinician administers a patellar reflex response test 3 times on both the left and right side.
- Ankle: subject is seated similar to the patellar reflex exam. The clinician dorsiflexes the ankle to put tension on the Achilles tendon, then administers an ankle reflex response test 3 times on both the left and right sides.

If a subject experiences at least one reflex response for both the left and right side on both the patellar and ankle reflex response exams, that subject will be considered a success for the reflex exam. All other subjects will be considered as failures for the reflex exam. A failed baseline reflex exam for either patellar or ankle reflex would exclude the subject.

Subjects will also be asked if they have experienced other neurological symptoms and will be observed for foot drop or other gait disturbances. Affirmative responses or positive observations should be reported as adverse events.

6.6.4 Disease-targeted, Abbreviated Physical Examination

A disease targeted/abbreviated physical examination including, but not limited to, examination of the musculoskeletal system will be performed at screening. Abbreviated, symptom-driven physical examinations noting any adverse changes or new adverse findings since baseline as adverse events will be performed at each subsequent evaluation through the course of the study (Day 0 and 1, 3, 6, 12, 18, 24 and 36 months post-treatment). Exams must be performed by qualified healthcare personnel.

6.6.5 Vital Signs

Vital signs will be recorded at screening, at Day 0 pre- and post-treatment, and at 1, 3, 6, 12, 18, 24 and 36 months post-treatment.

Vital signs will include sitting (if possible) blood pressure, heart rate per minute and oral temperature.

On the day of the treatment injection, these should be performed prior to the procedure and then following the procedure, prior to discharge. Vital sign measurements will be taken at every visit.

6.6.6 Height and Weight

Height, weight, and BMI measurements will be performed at screening, at Day 0 and 1, 3, 6, 12, 18, 24 and 36 months post-treatment.

6.6.7 MRI Scans and X-rays

MRI scans will be performed at screening and at 12, 18, 24 and 36 months post treatment. Flexion/extension X-rays and AP, lateral X-rays will be performed at screening, 1, 3, 6, 12, 18, 24 and 36 months. MRIs and X-ray scans should be taken on the same machine using the same settings, and in accordance with the radiographic guidelines provided, from baseline to completion of the study to minimize potential differences in results caused by use of different machines. Radiographic evaluations may vary for a given subject depending on the time of day the assessments are made. Therefore, for each subject, all radiographic evaluations of a specific type (e.g., X-ray or MRI) should be taken at the same time of day at each assessment if possible, preferably in the morning.

Radiographic images (MRI and X-rays) will be sent to the imaging core lab for blinded, independent radiographic evaluation. Review of radiographic images will be conducted by two blinded independent radiologists with a third reviewer to adjudicate any differences between the reviewers. Review of the radiographic images for the criteria specified in the inclusion/exclusion to be conducted by the radiographic core lab will be conducted by two reviewers with a third reviewer to adjudicate any differences. The MRI and X-ray scans will be used for efficacy assessments. Investigators should also evaluate images for potential safety issues, such as disc herniation, worsening disc morphology, heterotopic ossification (osteophytes), annular tears/fissures and/or changes in bony structures. The radiographic evaluations to be conducted are included in Appendix 1.

Investigators will review the radiographic imaging provided on-site or locally, as well as any associated reports. The investigator should document his or her review, including any clinically significant findings. In addition, radiographic imaging reports for screening will be made available to the investigator from the core imaging provider. Investigators should review such reports and maintain documentation of the review and any clinically significant findings. Radiographic imaging and reports should be kept as part of the subject's medical record.

As differences in readings between investigators and the core imaging provider are expected, reconciliation between imaging assessments will not be necessary. Throughout the course of the study, radiographic efficacy endpoints will be based on results from the core imaging provider. The investigator reviews will be used to determine any potential safety issues (including AEs).

Section 6.7.4 provides further discussion of the radiographic efficacy endpoints.

6.6.8 Visual Analog Scale for Leg Pain Assessment

Right and left leg pain, as assessed by VAS (average pain over 24 hours), will be assessed at all visits, with the exception of Day 0. Right and left leg pain will be assessed separately. Though low back pain VAS scores will be used for efficacy assessments in this study, leg pain VAS scores will be used only for eligibility into the study and for safety assessments. A more detailed discussion of low back pain VAS assessment is provided in Section 6.7.2.

6.6.9 Laboratory Evaluations

Clinical laboratory tests will be performed according to the schedule indicated in Table 3. Specific laboratory parameters are displayed in Table 5.

Table 5: Laboratory Parameters

Chemistry	Hematology	Special
Albumin	Hematocrit	hCG (urine)
Alkaline phosphatase (AP)	Hemoglobin	HIV
ALT (SGPT)	Red Blood Cells	anti-HLA class I and II antibody: Flow Class I and II % PRA (Specificity and DSA only for those Class I or II PRA results ≥5%)
AST (SGOT)	Platelets	hsCRP
CO2	White Blood Cells	Serum pregnancy test (beta hCG)
Blood urea nitrogen (BUN)	Neutrophils	
Calcium	Lymphocytes	
Chloride	Monocytes	
Creatinine	Eosinophils	
Direct Bilirubin	Basophils	
Total Bilirubin		
Glucose (non-fasting)		
Phosphorus		
Lactic dehydrogenase (LDH)		
Potassium		
Total Cholesterol		
Sodium		
Total protein		
GGT		
Uric Acid		

Any changes in clinical laboratory results deemed by the investigator to be clinically significant (see Section 7.5) or that qualifies as an adverse event should be documented.
All analyses, with the exception of urine pregnancy, will be performed at the central clinical laboratories.

Specificity testing and DSA results will be blinded until the end of the follow-up period.

6.7 Efficacy Assessments

Measurement of all efficacy parameters should be performed as described in Table 3. Standardized instructions for determining these parameters are provided in the following sections.

6.7.1 Post-treatment Interventions Affecting the Treated Disc

Post-treatment interventions over the 36-month post-treatment period are collected in this study for use in efficacy analyses as well as safety analyses. As these post-treatment interventions are used for all responder analyses, such interventions should be reported in a consistent manner. In order to maintain standardized classification of these interventions, a TEC will be used. (Section 12.2) provides greater detail regarding the TEC.

6.7.2 Visual Analog Scale for Low Back Pain Evaluation

Measuring pain intensity with a VAS is a useful and widely recognized tool in describing spine subjects. [60] Pain intensity is recorded on a horizontal 100 mm VAS and measured as the distance in millimeters from the left origin of the horizontal VAS line and the point indicated by the subject as representing his/her level of pain.

A horizontal 100 mm visual analog scale (VAS) anchored on the left with the words “No Pain” and on the right with the words “Worst Possible Pain”, will be used to measure low back, right and left leg pain intensity. Scores are obtained by measuring the distance in millimeters from the left origin of the line (0) to the point indicated with a slash placed by the subject to indicate the subject’s level of pain.

During the course of this study low back pain (average pain over 24 hours and worst pain over 24 hours) will be measured using a 100 mm VAS at the following visits: screening, 1, 3, 6, 12, 18, 24 and 36 months post-treatment. This will be an assessment of average pain and worst pain

over the previous 24 hours (see Appendix 2). At screening, the VAS evaluation must be administered at least 2 weeks following any injections to relieve pain.
Prior to administering the VAS, subjects will be instructed on its completion.

Subjects will be asked to complete the VAS directly on the corresponding worksheet completed during the in-clinic follow-up visits, which will serve as source documentation for this measurement. The in-clinic VAS assessments are considered the primary data source for VAS evaluations. However, the study source documents should reflect the date when each subject successfully completes the VAS or if there are any issues with VAS administration. The results of the VAS will be then transferred to the eCRF by the site using a validated method.

Under no circumstances should the worksheets containing the VAS be photocopied as photocopying may impact the length of the VAS line(s) and corresponding measurements.

Low back (average over past 24 hours and worst pain over 24 hours) and leg pain (average leg pain in left and right legs, individually over the past 24 hours) VAS evaluations will also be taken using e-diaries during the same 14 day period where pain medication usage is being collected. The VAS scores will be collected every day for the 14 day period with at least evaluations for 7 days. If more than 7 days of VAS scores are collected the last 7 days' scores will be used to calculate the average pain over a week.

Note: Low back and/or leg pain may generally be considered an adverse event and used in the evaluation of treatment safety. In this study, however, low back pain is also evaluated as an efficacy endpoint. Section 7.3 provides further details on how AEs of low back pain are defined.

6.7.3 Oswestry Disability Index

The ODI was first developed in 1976 as a specific outcomes tool for patients suffering from back pain. The validity, consistency and reproducibility of the ODI have been extensively tested and reviewed by Roland and Fairbank, 2000.[60] The questionnaire scores 10 aspects of the patient's home and work life and analgesic use. The disability index is then calculated as a percentage with a high percentage indicating a high level of disability. The ODI has been generally adopted since the mid-1980s to monitor the progress of patients suffering from back pain.

Improvements in functional mobility in this study will be based on the results of the ODI administered at screening, 1, 3, 6, 12, 18, 24 and 36 months post-treatment. Prior to

administering the ODI, subjects should be instructed on its completion. A qualified member of the clinic's staff should review the completed ODI to ensure that all questions have been covered and answered appropriately and that subjects use standard procedures for making corrections (see Appendix 3).

The questionnaire will be completed by the subject on the corresponding questionnaire forms at their in-clinic follow-up visit, which will serve as source documentation for this measurement. The in-clinic ODI assessment is considered the primary data source for ODI evaluations. The source documents should reflect the date when each questionnaire was successfully completed and any issues with its administration. The results of the questionnaire will be then transferred to the eCRF by the site.

An ODI evaluation will also be taken using e-diaries during the same 14 day period where pain medication usage is being collected. The ODI score must be taken at least once during the 14 day period. If more than one ODI score is collected, the most recent ODI score will be used.

6.7.4 Radiographic Evaluations

Plain radiographs and MR images will be used to assess the treated disc (see Appendix 1). All radiographic imaging will be sent to the imaging core lab for blinded, independent radiographic evaluation. Radiographic images will be assessed by two blinded and independent radiologists with a third reviewer to adjudicate any differences between the two reviewers.

Radiographic images will be made available to the investigator. Investigators should review these images, and any clinically significant findings, as well as the review itself, should be documented in the source.

During screening, the core imaging lab will assess the provided radiographic imaging (x-ray and MRI). The specified screening review assessments will be conducted by two blinded and independent radiologists with a third blinded and independent radiographic reviewer to adjudicate any differences between the two initial reviewers. The core lab will provide the investigator/site a report detailing the following:

- Modified Pfirrmann score at all lumbar levels
- Modic changes at all lumbar levels
- Absence or presence of disc protrusion, extrusion and/or sequestration at each lumbar level

- Absence or presence of spondylolisthesis/retrolisthesis of Grade 2 or more at each lumbar level
- Absence or presence of lumbar scoliosis of greater than a Cobb angle of 15 degrees in the lumbar spine.

The site will use the report provided by the core radiographic lab to determine whether the subject can be included in the study according to the inclusion/exclusion criteria (See Section 4.2) [redacted]

MRI will be used specifically to assess change in the qualitative status of the intervertebral disc according to the Modified Pfirrmann scoring system. Each treated disc, as well as adjacent discs, will be evaluated for improvement from screening. The evaluation of modified Pfirrmann improvement will be made at screening and 12, 18, 24 and 36 months post-treatment. These evaluations will be performed by the core imaging provider. MRI will also be used for evaluation of the change in macromolecular content and hydration of the treated disc by using T1 rho and T2 mapping at facilities with this capability from baseline to 12, 18, 24 and 36 months post-treatment on a subset of subjects.

A/P and lateral X-rays of treated and adjacent levels will be collected at screening and 1, 3, 6, 12, 18, 24 and 36 months post-treatment. These images will be used to determine the height of the treated disc and any changes from baseline.

Flexion/extension X-rays will also be taken at screening and 1, 3, 6, 12, 18, 24 and 36 months post-treatment and will be used to determine spinal stability. The stability metric used in this study will be the QMA® Stability Index (abbreviated QSI, with units of standard deviations from mean). QSI is based on the translation per degree of rotation (abbreviated TPDR with units of % endplate width/degree) normalized per lumbar level. QSI is further defined in Appendix 1.

Radiographic evaluations may vary for a given subject depending on the time of day the assessments are made. Therefore, for each subject, all radiographic evaluations of a specific type (e.g., X-ray or MRI) should be taken at the same time of day at each assessment if possible, preferably in the morning.

For this study, the definition of a composite clinical stability success (CSS), relative to disc stability, is defined as QSI < 0 (determined by flexion and extension spine radiographs and indicating an improvement in disc stability compared to baseline) and at least a 50% reduction from baseline in low back pain VAS score (average pain over 24 hours) with no intervention at the treated level compared to baseline.

6.7.5 iPCQ, SAT, EQ5D, and Patient-reported Utilization Questionnaires

The iPCQ and EQ-5D questionnaires will be administered at each study visit: screening, 1, 3, 6, 12, 18, 24 and 36 months after treatment. The SAT will not be performed at screening, but at all post-treatment visits: 1, 3, 6, 12, 18, 24 and 36 months post-treatment. The Patient-reported Utilization Questionnaire will be administered at screening and 12, 18, 24 and 36 months.

iMTA Productivity and Cost Questionnaire (iPCQ)
The iPCQ is a measure of indirect costs arising outside the scope of the healthcare system, also known as productivity costs, that derive from health problems. The questionnaire consists of 3 modules focusing lost productivity due to absenteeism, presenteeism, and unpaid work (see Appendix 4).

Self-assessment of Treatment (SAT) Questionnaire
The SAT questionnaire is comprised of 5 items that assess subject-reported improvement and satisfaction with treatment (see
Appendix 5).

EuroQoL EQ-5D
The EQ-5D is a standardized measure of health outcomes (see Appendix 6).

Patient-reported Utilization Questionnaire
This questionnaire is used as a tool for assessing direct healthcare costs related to back pain associated with DDD. The questionnaire requires subjects to provide a 12 month retrospective of relevant healthcare usage (see Appendix 7).

6.7.6 Post-Treatment Pain Medication Usage Collected by E-Diary

For collection of post-treatment pain medication use, subjects should be contacted by either IWRS or by the site, approximately 2 weeks prior to each post-treatment visit as a reminder to complete daily pain medication e-diaries for 2 weeks during the 30 days prior to each follow-up

visit other than for the 1 month visit that must be collected during the 14 days prior to the scheduled visit. At least 10 daily entries out of a possible 14 should be available at each study visit. Otherwise, absence of more than 4 entries will be considered a protocol deviation. Based on the opioid information entered into the e-diary during the 2 weeks prior to each post-treatment visit, it will be determined if subjects have shifted from baseline. Category shifts in opioid usage will be defined as:

[redacted]

It is strongly recommended that there be no changes (increase or decrease) from or additions to baseline pain medications (opioids, NSAIDs, aniline analgesics, etc.) for at least the 24 month primary efficacy and safety follow-up period.

This is designed to minimize possible confounding treatment effects of alterations in pain medications. Furthermore, it is suggested that subjects do not schedule any medical procedures during the 2 weeks prior to any study visit which would require an adjustment in pain medications. However, should a significant increase in pain from baseline occur, the subject

should be provided appropriate pain relief and an adverse event documented. Should there be any deviation from the baseline dose, information regarding the deviation must be documented.

7. SAFETY GUIDANCE

7.1 Definitions

7.1.1 Adverse Event

According to the International Conference of Harmonization [ICH] guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.
An AE can therefore be any of the following:

- Unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration or abnormality in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening procedures such as biopsies etc.).

Adverse events will be captured following signing of the informed consent form. Pre-existing conditions (i.e., medical history) which **worsen** during a study are to be reported as AEs.

7.1.2 Serious Adverse Event (Reportable to the Sponsor within 24 Hours)

An SAE is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the subject at immediate risk of death). This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death
- Requires or prolongs inpatient hospitalization

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the subject's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to investigational product
- Significant medical event in the investigator's judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

Any AE that is defined as serious and which occurs during the course of the study, regardless of the treatment arm must be reported within 24 hours of the investigator becoming aware of the event.

7.1.3 Severity

A clinical determination will be made of the severity of an AE. The terms "severe" and "serious" are not synonymous. Severity is a description of the intensity of the manifestation of the AE and is distinct from seriousness, which implies a subject outcome. Severity will be assessed according the following scale:

Mild	Discomfort noticed but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect daily activity
Severe	Inability to work or perform normal daily activity

7.2 Relationship of Adverse Event to Study Treatment or Study Procedure

A determination will be made of the relationship between an AE and the treatment received. A causal relationship is present if a determination is made that there is a *reasonable possibility* that the AE may have been caused by the study treatment and/or study procedure. In general, a causal relationship will be assigned when evidence exists to support the causal relationship. When assessing a potential relationship between the study treatment and/or study procedure and an AE, the following parameters should be considered:

- Temporal relationship between study treatment and/or protocol-specified procedures and the AE
- The biological plausibility that the study treatment and/or procedure caused the event
- Any underlying/concurrent illness in the subject
- Concomitant medications the subject may have received

- How commonly the event occurs in the study analysis set independent of treatment.

Examples of evidence to suggest a causal relationship between the study treatment and/or study procedure and the AE include the following:

- A single occurrence of an event that is uncommon and known to be strongly associated with investigational product exposure or study procedure (e.g., angioedema, discitis, hepatic injury, Stevens-Johnson Syndrome).
- One or more occurrences of an event that is not commonly associated with investigational product exposure or study procedure, but is otherwise uncommon in the analysis set exposed to the drug (e.g., tendon rupture).

Low back pain within 14 days of the treatment procedure is expected.

7.3 Adverse Events of Special Interest – Back Pain

Low back pain may generally be considered an adverse event and used in the evaluation of treatment safety. In this study, however, low back pain is also evaluated as an efficacy endpoint. Pain data provided on the low back pain VAS will not routinely be considered an adverse event in this study. If a subject reports an adverse event of low back pain, the following information will be collected from the subject:

1. Whether or not the pain is of increased intensity from baseline
2. Whether or not there is an increased frequency of pain, regardless of intensity, as compared to baseline
3. Whether or not the pain is in a different location in the lower back as compared to baseline
4. Whether the symptoms required an unscheduled visit
5. The subject's assessment of the cause of the event, if any specific cause is suspected.

A back pain AE should be reported if the subject answers yes to questions 1-4 above. If a back pain AE is reported, the subject's assessment of the cause of the event should also be recorded if any specific cause is suspected.

7.4 Treatment and Follow-up of AEs and SAEs

AEs and SAEs, especially those for which there is an established relationship to investigational product, should be followed up until they have returned to baseline status, stabilized, or the follow-up period is complete.

If after the follow-up period, return to baseline status or stabilization cannot be established an explanation should be recorded on the eCRF.

7.5 Laboratory Test Abnormalities

Laboratory test results will appear on electronically produced laboratory reports directly from the central laboratory. Local laboratory results should be recorded on the eCRF, if applicable.

Any laboratory result fulfilling the criteria for an AE or SAE should be recorded on the eCRF and reported to the designated responsible parties in safety accordingly. The preference is to report a diagnosis rather than the laboratory value as the adverse event. However, if a diagnosis has not been confirmed, a clinically significant laboratory value should be reported including a modifier (e.g., worsening, increased, decreased) until a final diagnosis can be reported.

Any treatment-emergent clinically significant abnormal laboratory result is defined as meeting one or more of the following conditions:

- Accompanied by clinical symptoms
- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).

This applies to any protocol and non-protocol specified safety and efficacy laboratory result from tests performed after informed consent form signature, which fall outside the laboratory reference range and are considered clinically significant by the investigator. This does not apply to any abnormal laboratory result which falls outside the laboratory reference range but which does not meet the criteria for clinical significance (these will be analyzed and reported as laboratory abnormalities).

In the event of clinically significant abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established, it should be recorded on the eCRF.

7.6 Unblinding

The study blind should not be broken except in a medical emergency and only where knowledge of the test material received would affect the treatment. In an emergency, the investigator can obtain treatment assignment of any subject at their study center by contacting the medical monitor. If an emergency un-blinding becomes necessary, the investigator should notify the CRA or medical monitor, as soon as possible.

In the event treatment assignment needs to be provided to any blinded member of the sponsor study team, it must be done in accordance with the pre-specified blinding plan to ensure that bias is not introduced.

Importantly, all unblinded individuals will be specifically instructed to refrain from discussing any potentially unblinding information with either the subject or any blinded site, sponsor, or CRO personnel involved in the trial.

8. REPORTING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.1 Reporting of Serious Adverse Events [Immediately Reportable]

All SAEs (as described in Section 7) that occur after the subject has signed informed consent (including the protocol-defined follow up period), regardless of judged relationship to investigational product, or after the study period, if considered serious and related to investigational product or to the subject's participation in the study, must be reported to the sponsor or designee within 24 hours of the investigator's knowledge of the event. All subjects with an SAE must be followed up and the outcomes reported until the event has returned to baseline status or stabilized. In the event of an SAE, the investigator must immediately notify sponsor or designee. SAE reporting will originate in the electronic data capture (EDC) system and an email will be sent to the designated responsible parties in safety.

The paper SAE form is in place as a back-up in the rare event that EDC is not accessible to the reporter of the SAE:

- [redacted]
- Provide copy of all relevant source documents, including medical history, hospital records and discharge summaries, and concomitant medications pages, as appropriate.

All SAEs that are considered unexpected, according to the Investigator's Brochure (IB), and related to the investigational medicinal product will be reported by the sponsor or its designee as an expedited 15-day report to the regulatory authorities as applicable and to all participating investigators.

Fatal or life-threatening suspected adverse reactions that are considered unexpected according to the IB and related to investigational product will be reported by the Sponsor or its designee to the regulatory authorities as applicable, and to all participating investigators as an expedited 7-day report.

Each investigator must notify the IRB/EC responsible for reviewing the study at their site of all 15-day or 7-day safety reports required by local regulations or IRB/EC requirements and shall provide the sponsor or its designee with written confirmation of said IRB/EC notification.

This study will comply with all local regulatory requirements and adhere to the full requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2.

8.2 Procedures for Reporting Pregnancies

All pregnancies that occur during the study are to be reported within 24 hours to the individual identified in the clinical study personnel contact information section of this protocol, and the investigator must provide sponsor or designee, by facsimile, a signed pregnancy tracking form. If a subject becomes pregnant during the study, the subject will remain in the study and only the requirement for radiation (x-ray or MRI) should be removed. All subjects who become pregnant will be monitored to the completion or termination of the pregnancy, including perinatal and neonatal outcome. Monitoring of the subject should continue until conclusion of the pregnancy. If the pregnancy is associated with an SAE (e.g., hemorrhage, spontaneous abortion), in addition to the Pregnancy Form, a separate SAE form must be provided as described in Section 8.1.

If a subject becomes pregnant during the study, the subject will remain in the study and only the requirement for radiation (x-ray or MRI) should be removed.

8.3 Expedited Reporting to Health Authorities, Investigators, IRBs, and ECs

The sponsor will promptly evaluate all SAEs and non-serious AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety

findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the sponsor will assess the expectedness of these events using the current Investigator's Brochure.

The sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the sponsor as needed.

9. STATISTICAL CONSIDERATIONS

9.1 General Considerations

The statistical analysis plan (SAP) will be finalized and submitted to the appropriate health authorities before any interim analysis or unblinding occurs. The primary unblinded statistical analyses will be conducted by the sponsor or authorized representative after all enrolled study subjects who remain active in the trial at the time of their 24 month study visit have completed this milestone event.

Interim analyses may be performed during the course of the trial. These will be conducted by external independent statistician(s) who will be unblinded to study data. All blinded personnel and subjects will remain blinded to the results of the analyses. The integrity of the study database will be maintained as well, and no bias will be introduced to the evaluations in the study due to the conduct of these interim analyses.

The details of interim analyses are outlined in the Statistical Analysis Plan (SAP). All subjects, independent reviewers and blinded personnel interacting with subjects will remain blinded through the completion of the study.

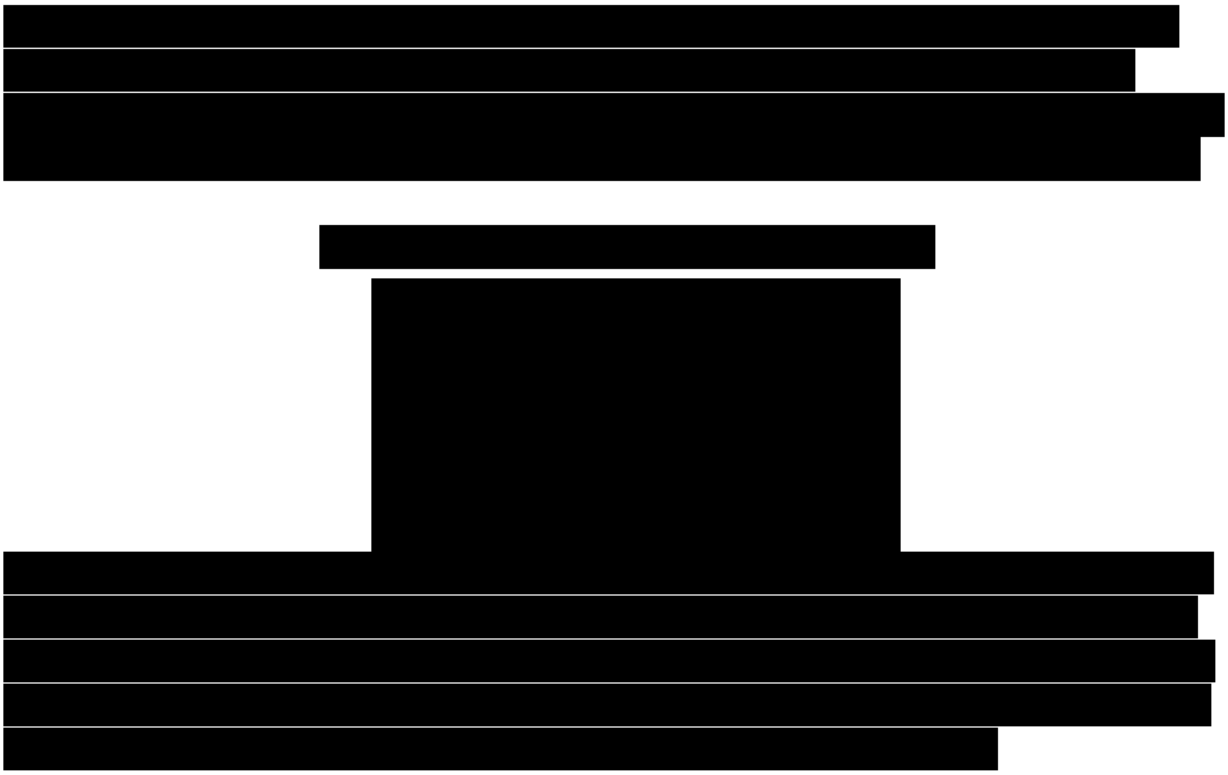
The primary efficacy objective of the study is to demonstrate that either rexlemestrocel-L alone or rexlemestrocel-L + HA has a higher rate of treatment success—defined as 50% reduction in low back pain VAS score, 15 point decrease in ODI score, and no interventions at the treated disc—compared to the saline control arm at 12 *AND* 24 months post-treatment. The significance level for the Primary Efficacy Endpoint is adjusted for multiple comparisons of each active

treatment arm to the control group. The family-wise type I error rate will be controlled below one-sided 0.025. Additional details, including the adjusted threshold for primary analysis success, will be finalized in the SAP.

For secondary endpoints, a gatekeeping strategy will be used to maintain the overall type 1 error at overall one-sided 0.025. For all other exploratory efficacy endpoints, the significance level of two-sided 0.05 will be used for comparison between each active arm and the control group.

9.2 Sample Size and Randomization

Approximately 360 subjects will be enrolled in a randomization ratio of 1:1:1, with each subject assigned to the rexlemestrocel-L alone, rexlemestrocel-L + HA, or saline control group. Randomization will be stratified by study site and opioid use at baseline (opioid users vs. opioid non-users).



9.3 Analysis Analysis sets

The classification of subjects into each of the following analysis analysis sets will be determined prior to database lock for the 24-month data analysis and prior to the 36 month longer-term follow-up analysis.

9.3.1 All Enrolled Subjects Analysis Set

All subjects who signed the informed consent are included in the All Enrolled analysis set. The All Enrolled Subjects analysis set will be used for summarizing subject disposition.

9.3.2 Intent-to-Treat (ITT) Analysis Set

The ITT analysis set includes all subjects who are randomized, regardless of whether or not the subject is treated, or post-treatment measurements are performed. In these analyses, subjects will be assigned to treatment according to randomization (not actual treatment received). The ITT analysis set will be used for summarizing demographics, baseline characteristics, surgical procedures and treatment exposure. The ITT analysis set will be used as the primary analysis set for all primary and secondary efficacy analyses. As sensitivity, the efficacy analyses will also be performed on the Full Analysis Set, the As Treated and the Per Protocol analysis sets, as defined herein.

9.3.3 Full Analysis Set (FAS)

The FAS analysis set includes all subjects who are randomized and treated or randomized with an attempt to administer treatment (i.e. subjects taken to procedure room to receive treatment whether administered or not). In these analyses, subjects will be analyzed according to the treatment to which they were randomized (not actual treatment received). Subjects that were randomized but dropped out prior to attempting treatment will be omitted from the FAS analysis set.

9.3.4 As Treated Analysis Set

The As Treated analysis set includes all subjects randomized, analyzed according to the treatment that was actually administered.

9.3.5 Per Protocol (PP) Analysis Set

The per-protocol (PP) analysis set will contain all subjects in the ITT who received treatment to which they were randomized, had at least 1 post-treatment efficacy measurement (VAS and ODI), and did not experience any major protocol deviations.

Protocol deviations will be determined for all randomized subjects mainly from the clinical database and Clinical Trial Management System (CTMS) following clinical and/or medical review of subject data for relevant findings that might have an impact on the definition of the PP analysis set/ major protocol violations. Protocol deviations that occur during the study will be adjudicated by the sponsor (or designee) and categorized by severity. Protocol deviations will be classified as minor or major during a blinded review of the data prior to the lock of the database for analysis. If relevant deviations are identified, they will be designated as major protocol violations.

9.3.6 Safety Analysis Set

The safety analysis set will contain all subjects who were randomized and received treatment, and subjects will be classified according to the actual treatment received. Safety analysis set will be used for the safety analyses.

If there is any doubt whether a subject was treated or not, they will be assumed treated (randomized treatment) for the purposes of analysis.

9.4 Efficacy Endpoints

The efficacy endpoints to be assessed include:

9.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be a composite responder analysis for Overall Treatment Success at both Study Visit 6 (12 months post-treatment) AND Study Visit 8 (24 months post-treatment), based on pain, function and post-treatment interventions:

- at least a 50% reduction from baseline in low back pain VAS score (average pain over 24 hours, in-clinic assessment); *AND*
- at least a 15 point decrease from baseline in ODI score (in-clinic assessment; *AND*
- no interventions at the treated level.

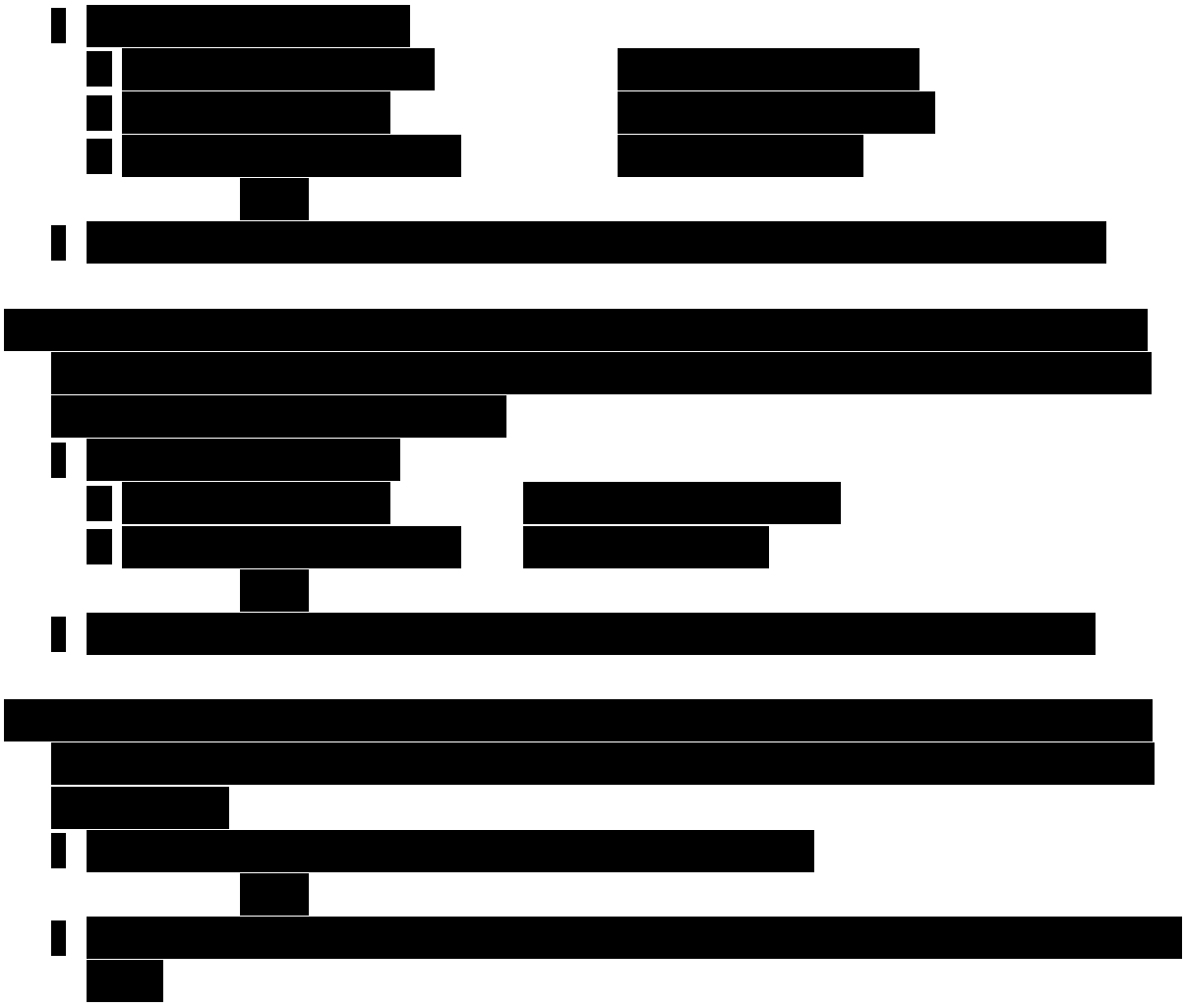
9.4.2 Secondary Efficacy Endpoints

If the primary analysis yields a significant result, then analyses will be performed on the following secondary efficacy endpoints in sequential order to control type I error:

1. **Pain Responder at both 12 *AND* 24 months**: Measured as subjects meeting at least a 50% decrease from baseline in low back pain VAS score (average pain over 24 hours) at both Study Visit 6 (12 months post-treatment) and Study Visit 8 (24 months post-treatment) with no adjudicated post-treatment intervention through Study Visit 8.
2. **Functional Responder at both 12 *AND* 24 months**: Measured as subjects meeting at least a 15-point decrease from baseline in ODI at both Study Visit 6 (12 months post-treatment) and Study Visit 8 (24 months post-treatment) with no adjudicated post-treatment intervention through Study Visit 8.
3. **Treatment Success at 24 months:** Measured as subjects meeting each of the following criteria at Study Visit 8 (24 months post-treatment):
    a. at least a 50% reduction from baseline in low back pain VAS score (average pain over 24 hours); AND
    b. at least a 15 point decrease from baseline ODI score; AND
    c. no interventions at the treated level
4. **Minimal Pain Responder at 24 Months:** Measured as subjects meeting low back pain VAS score (average pain over 24 hours) of 20mm or less at Study Visit 8 (24 months post-treatment) with no adjudicated post-treatment intervention through Study Visit 8.
5. **Minimal Disability Responder at 24 Months:** Measured as subjects having an ODI score of 20% or less at Study Visit 8 (24 months post-treatment) with no adjudicated post-treatment intervention through Study Visit 8.
6. **Time to first intervention over 24 months:** Measured as time to first post-treatment intervention at the treated level through 24 months post-treatment.

[redacted]

[redacted]



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9.6 Statistical Methods

9.6.1 Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment arm for the ITT and PP analysis sets, as well as presented in data listings.

Continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum). In order to assess baseline comparability, treatment groups will be compared for all continuous variables using an ANOVA between individual treatment and control groups.

Categorical variables will be summarized using counts and percentages for each category. Treatment groups will be compared for all non-missing categorical variables using a Chi-Square test of association. Missing categories will be presented if necessary, but excluded from any tests of association.

Demographic data will include:

- Sex
- Age
- Race (White, Hispanic-White, Hispanic non-white, Black or African American, American Indian/Alaska Native, Asian, Native Hawaiian or Pacific Islander, Other)
- Smoking status (Never Smoked, Current Smoker, and Previous Smoker).

General baseline characteristics will include weight, height, and BMI, and baseline characteristics of the index level, as assessed by independent radiologist and will be listed and summarized based on the following assessments collected at the screening visit:

- Medical history, including history of disc disease (DDD) at the index level (duration of low back/limb pain)
- Spinal surgery history
- Medication history
- VAS, ODI, iPCQ, EQ-5D questionnaire

- Disc degeneration, Modified Pfirrmann score, herniation presence and score, average disc height
- Opioid user or opioid non-user at baseline.

General medical history will be listed and summarized, as well as medication history. Spinal surgery history and disease-specific history will be listed only.

9.6.2 Primary Efficacy Analysis

The Primary Efficacy Endpoint for overall treatment success (responder vs non-responder) at 12 *AND* 24 months will be summarized for each treatment by numbers and percentages. Each active treatment arm will be compared to the saline control group using a Bayesian test of superiority using non-informative Beta (0.5, 0.5) priors for each arm. An arm will be considered superior to the saline arm if there is sufficiently high posterior probability that the response rate of that arm is higher than the saline control arm. The posterior probability threshold is Bonferonni-adjusted to account for multiple comparisons. The value of the posterior probability threshold for success will be discussed in the study statistical analysis plan (SAP).

The rationale for using a Bayesian approach for the primary analysis is that we are already using Bayesian methodology for multiple imputation of missing data (see Section 9.9). Keeping the Bayesian methodology for the primary analysis ensures a consistent framework that naturally synthesizes the multiply imputed outcomes into the posterior distribution. In this way, the uncertainty due to missing data is naturally incorporated into the inference, without the cumbersome necessity of combining p-values as in a frequentist framework.
The methods for handling missing data are discussed in Section 9.9.

9.6.3 Secondary and Other Efficacy Analyses

The same Bayesian methodology used for the primary analysis will also be used for the secondary endpoints. The Bonferroni-adjusted posterior probability threshold of 0.9875 will apply to any subsequent secondary analyses performed.

As part of the gatekeeper strategy, the evaluation will be carried out in a hierarchical fashion following the order given below. Specifically, if the primary endpoint objective is met, the secondary outcomes will be evaluated hierarchically within each arm using the posterior probability threshold of 0.9875 for each comparison, sequentially. Once a key secondary endpoint is not met at this threshold within an arm, all subsequent comparisons in that arm will be considered exploratory.

1. **Pain Responder at both 12 *AND* 24 months**: Measured as subjects meeting at least a 50% decrease from baseline in low back pain VAS score (average pain over 24 hours) at both Study Visit 6 (12 months post-treatment) and Study Visit 8 (24 months post-treatment) with no adjudicated post-treatment intervention through Study Visit 8.
2. **Functional Responder at both 12 *AND* 24 months**: Measured as subjects meeting at least a 15-point decrease from baseline in ODI at both Study Visit 6 (12 months post-treatment) and Study Visit 8 (24 months post-treatment) with no adjudicated post-treatment intervention through Study Visit 8.
3. **Treatment Success at 24 months:** Measured as subjects meeting each of the following criteria at Study Visit 8 (24 months post-treatment):
    a. at least a 50% reduction from baseline in low back pain VAS score (average pain over 24 hours); AND
    b. at least a 15 point decrease from baseline ODI score; AND
    c. no interventions at the treated level
4. **Minimal Pain Responder at 24 Months:** Measured as subjects meeting low back pain VAS score (average pain over 24 hours) of 20mm or less at Study Visit 8 (24 months post-treatment) with no adjudicated post-treatment intervention through Study Visit 8.
5. **Minimal Disability Responder at 24 Months:** Measured as subjects having an ODI score of 20% or less at Study Visit 8 (24 months post-treatment) with no adjudicated post-treatment intervention through Study Visit 8.
6. **Time to first intervention over 24 months:** Measured as time to first post-treatment intervention at the treated level through 24 months post-treatment.

[redacted]

[redacted]

For the time to first intervention (since study injection), a Kaplan-Meier analysis will be used. The overall treatment comparison and each active treatment group versus the saline control group, as well as between the two active treatment groups for time to first adjudicated intervention will be analysed using a log-rank test, stratified by study (or pooled) sites. The following Kaplan-Meier point estimates of time to first adjudicated intervention and their corresponding 95% confidence intervals (CI) will be presented: 25th percentile, median, and 75th percentile. Kaplan-Meier curves to illustrate the differences among the treatment arms will be provided. Subjects who did not receive post-treatment intervention and subjects who withdraw or are lost to follow-up will be censored at the last performed visit

[redacted]

9.7 Safety and Other Analyses

The Safety Analysis Set will be used for summary and analysis of the safety endpoints.

9.7.1 Primary Safety Endpoint

Evaluation of overall safety, which includes the following:

- Subject reported AEs and SAEs from baseline through 24 months post-treatment, including adverse events of special interest (i.e., AEs of worsening low back pain)
- Laboratory tests (hematology, serum chemistry, inflammatory markers and antibody analysis). Abnormal results will be assessed relative to normative ranges and shift tables from baseline through 24 months post-treatment
- Reported events from radiographic imaging from baseline through 24 months post-treatment, including disc height at the treated level
- Post-treatment interventions affecting the treated disc through Visit 8 (24 months post-treatment) (comparison of the proportion of subjects in each group with an adjudicated post-treatment intervention at the treated level, and the proportion of subjects in each group with an adjudicated post-treatment intervention any lumbar level)
- Vital signs (heart rate, blood pressure and temperature) and body measurements (height, weight and BMI)
- Physical examinations (abbreviated).
- Neurological examinations (motor, sensory, reflex).

Descriptive statistics will be used for the summary of safety parameters – the number and percentage will be used for the incidences of AE/SAEs, deaths, early discontinuation due to AEs, and post-treatment interventions. The AE/SAE severity and relationship with the study procedure and treatment will be summarized and presented.

The mean, standard deviation/error, minimum, median, and maximum will be used for the laboratory parameters. The shift table (cross-tabulation) for the changes from baseline (low/normal/high) for the laboratory parameters will also be also provided and the test for treatment difference.

Safety parameters of special interest (i.e., AEs of worsening low back pain) will be summarized through 24 months post-treatment by treatment arm, severity, and the time from the study injection to the start of the AEs (0 to ≤7 days, >7 days to < 3 months, ≥3 months to 24 Months).

The incidence of this special interest AE (worsening low back pain) occurring within 3 to 24 months after study treatment will be also summarized, by treatment arm, for the responders and non-responders of the Primary Efficacy Endpoint.

The actual low back pain VAS score, the changes from the baseline and the responders with at least 50% reduction of low back pain VAS score at the time which the AEs of low back pain occurs will be summarized for each treatment, and the subject data listing will be presented for clinical review and assessment. Shift tables of changes in opioid use from the baseline to the time of AE onset will be also presented.

[redacted]

[redacted]

[redacted]

9.8 Interim Analyses

Interim analyses may be performed during the course of the trial. These will be conducted by external independent statistician(s) who will be unblinded to study data. All blinded personnel and subjects will remain blinded to the results of the analyses. The integrity of the study database will be maintained as well, and no bias will be introduced to the evaluations in the study due to the conduct of these interim analyses.

The details of interim analyses are outlined in the Statistical Analysis Plan (SAP). All subjects, independent reviewers and blinded personnel interacting with subjects will remain blinded through the completion of the study.

9.9 Handling of Missing Values, Early Termination, or Non-Interpretable Data

For the responder analyses, including the primary efficacy endpoint, as well as pain and function responder analyses, subjects will be classified as having attained success (responder) or not attained success (non-responder).

The Primary Efficacy Endpoint requires a subject to meet clinically significant improvements in both pain and function at both 12 and 24 months, as well as not undergo any post-treatment intervention at the treated level through 24 months, to be considered a success.

If in-clinic assessments for Study Visits 6 and 8 (corresponding to 12 and 24 months) are unavailable, the data will be considered missing. If a scheduled in-clinic visit is missed, the site should contact the subject to determine if any interventions that would classify the subject as a treatment failure have occurred since their last visit. If any interventions are reported, the site should collect all the information required if the intervention had been reported at an in-clinic visit. All intervention information collected remotely must be documented in a source document and/or worksheet.

If a subject receives a post-treatment intervention at the treated level on or prior to the date of Study Visit 8 (24 months), this subject will be considered a non-responder regardless if there is any missing data. For example, a subject that has a post-treatment intervention at the treated level at the time of Study Visit 4 (3 months) would be considered a non-responder regardless of whether there are Visit 6 or Visit 8 data available for analysis, as they would have already failed one of the criteria to be considered a responder.

If a subject has data available at both Study Visit 6 (12 months) and Study Visit 8 (24 months), with no post-treatment intervention at the treated level as of the date of Study Visit 8, that subject will be determined either a responder or non-responder based upon whether or not the subjects meets the pain and functional improvement criteria at both study visits.

Any subject that is missing one or more components in an endpoint (e.g. VAS in the primary endpoint) at a visit will be considered a non-responder at that visit if any available component of the endpoint indicates that the subject is a non-responder (even if all components of the endpoint are not available). If none of the available components impose non-response, the outcome will be considered missing and will be handled according to the proposed methodology described below.

Assumptions regarding responder analyses include the following:

- If the subject does not meet the criteria of either pain or function at either Visit 6 or Visit 8, the subject will be considered a non-responder.
- If the subject meets the pain and function improvement criteria at both Visit 6 and Visit 8, and has no post-treatment intervention as of the date of Visit 8, the subject will be considered a responder.

- Any subject that is a non-responder on one of the two primary study visits (Visit 6 or Visit 8) but has a missing outcome for the other study visit is deemed a non-responder and not considered to have a missing outcome for the primary analysis.
- If a subject does not have a minimum of a visit at 3-months (Study Visit 4) they will be considered a non-responder.
- Any subject that has a minimum of 3-months data (Study Visit 4) but is missing one or both of the two primary study visits, will have their outcome multiply imputed based on their available information. Separate models will be constructed for
    - Subjects that are missing one of the two primary study visits (Visit 6 or Visit 8) but not both;
    - Subjects that are missing both of the primary study visits.

A detailed description of the statistical methodology for multiple imputation of missing data for responder analyses can be found in the SAP.

For subjects who have a post-treatment interventional procedure at the treated level, the analyses of continuous and categorical efficacy variables will include only data collected before the post-treatment adjudicated intervention.

MMRM will be used for the analysis of over time of quantitative variables and missing data will not be imputed.

The SAP provides additional details regarding methods for handling missing data.

9.10 Subgroups

Pre-specified subgroup analyses based on both the ITT and PP analysis sets for the primary and secondary efficacy variables will be performed for key demographic and baseline variables, as described in the SAP.

10. DATA COLLECTION, MANAGEMENT AND QUALITY ASSURANCE

All aspects of the study will be monitored by Mesoblast or authorized representatives of Mesoblast according to Good Clinical Practices (GCP) and Standard Operating Procedures (SOPs) for compliance with applicable government regulations, (i.e., Informed Consent Regulations [US 21CFR, Part 50] and Institutional Review Board regulations [US 21CFR, Part 56.103]). Access to all records, both during the trial and after trial completion, should be made available to Mesoblast at any time for review and audit to ensure the integrity of the data.

The investigator must conduct the protocol in accordance with applicable GCP regulations and guidelines; applicable Informed Consent Regulations (US 21CFR, Part 50); and in compliance with the Declaration of Helsinki. Every attempt must be made to follow the protocol and to obtain and record all data requested for each subject at the specified times. If data is not recorded per protocol, the reasons must be clearly documented on the eCRF/records.

Prior to the study, at a site initiation visit or Investigators' Meeting, a Mesoblast representative will review the protocol and study procedures and processes to include IP receipt, storage, and accountability; investigator responsibilities and staff adequacy; event reporting timelines; monitoring and audit requirements; study documentation responsibilities; subject enrollment procedures; imaging and laboratory processes; and eCRF requirements to include system training with the Investigator and site staff. Additional tasks and activities may be completed as needed for the study.

During the study all protocol-specified data will be recorded in the source documents and data will be entered on the eCRFs from the source documents. Checks will be performed by the CRA to ensure the quality, consistency, and completeness of the data. Instances of missing or un-interpretable data will be resolved with the investigator or study coordinator. Site personnel will be responsible for providing resolutions to the data queries and for correcting the eCRFs, as appropriate.

Any amendments and corrections necessary will be undertaken in both the source documents and eCRFs (as appropriate) and countersigned by the Investigator, or documented designee, stating the date of the amendment/correction. Errors must remain legible and may not be deleted with correction aids. The investigator must state his/her reason for the correction of any data.

10.1 Investigator's Files/Retention of Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories, consisting of: 1) An Investigator's Study File (ISF) and 2) subject clinical source documents.

The ISF will contain copies of all site specific essential documents to include the protocol/amendments and schedule of assessments, IRB/EC and governmental approval with correspondence, IRB/EC-approved informed consent, IP accountability, staff curriculum vitae,

and other appropriate documents/correspondence. Documents should be filed in reverse chronological order in their specified sections. If a document is not filed in its designated section, a Note to File must be generated to document the location of the document. CRAs will review the file on a regular basis to ensure that all documents are complete, current, and filed appropriately for the study. Documents will be collected and received to ensure that the ISF files are consistent with the Central Investigator File for the study. A final reconciliation of the ISF to the central investigational file will be performed at the end of the study. In addition, at the end of the study the investigator will receive the subject eCRF data, including an audit trail containing a complete record of all changes to data, query resolution correspondence, and reasons for changes, in a readable format on CD that must be kept with the ISF.

The investigator must keep written or electronic source documents for every subject participating in the study. Subject clinical source documents may include hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, special assessment reports, signed informed consent forms, and consultant letters. There is an increase in the number of sites using electronic medical records (EMR). Access to EMRs must be “Read Only” to ensure that the data integrity and/or quality of the monitoring is compromised in a way. If “Read Only” access is not possible, then the site should provide a printout of the records that has the investigator’s signature on the front page and a note that documents that the printout is a verified copy as of that date. Each page should have a date or version number, be bound by a secure staple, or have the investigator’s (or designee’s) initials and dates on each page.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee compliance with this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these documents in a sealed container(s) outside of the site in order to ensure that they can be returned sealed to the investigator in the event of a regulatory audit. Where source documents are required for continued care of subjects, appropriate copies should be made for storing outside of the site.

10.2 Source Documents and Background Data

The investigator shall provide to the sponsor, upon request, any required background data from the study documentation or clinic records. This is particularly important in cases where errors in data transcription are suspected. In cases of special problems and/or governmental queries or requests for audit inspections, it is also necessary for the sponsor to have direct access to the complete source documents, provided that subject confidentiality is protected.

10.3 Electronic Case Report Forms

Data for this study will be recorded using eCRFs. Sites will be responsible for data entry into the eCRF. In the event of discrepant data, the sponsor or designee will request clarification from the sites. The sites will resolve discrepant data electronically in the eCRF. A Mesoblast representative, or a designee, will perform final data review and external data reconciliations prior to all major milestones, including database close and lock. eCRFs and correction documentation will be maintained in the eCRF's audit trail. Records retention for the study data will be consistent with the SOPs of the sponsor or designee.

An eCRF must be completed for each screened subject. For each screen-failed subject, the reason for screen failure will be collected in the screening disposition eCRF. The entire subject casebook of data must be reviewed and electronically signed by the investigator or by an authorized delegate from the study staff. This also applies to records for those randomized-not-treated and randomized subjects who fail to complete the study. If a subject withdraws early from the study, the reason must be noted at the end of the study eCRF. If a subject is withdrawn from the study because of a treatment-limiting AE, attempts should be made to clearly document the outcome.

Sites will receive training for appropriate eCRF completion. All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or designee.
At the end of the study, the investigator will receive subject data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

10.4 Other Electronic Data

Data from the central laboratory, core imaging provider, and electronic diary vendor will be sent directly to the sponsor or designee, using SOPs to handle and process the electronic transfer of these data.

10.5 Coding of Medical Terms

Medical coding of verbatim medical terms will be performed for this study. The verbatim terms for medical history, adverse events, reason for intervention/procedure will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; English Version 17.0; Release date March 1, 2015 or more recent version). Concomitant medications, including pain medications from the subject e-diaries will be coded using the World Health Organization Drug Dictionary Enhanced (WHODDE; version March 1, 2015 release date or more recent version).

10.6 Audits and Inspections

Source documents for this trial must be made available by the investigator to appropriately qualified personnel from the sponsor's (or designee's) Quality Assurance Unit or its designees, IRBs/ECs, or to health authority inspectors, upon appropriate notification. Verification of the eCRF data must be by direct inspection of source documents.

11. MONITORING OF STUDY

The sponsor's responsible CRA (or designee) will contact and visit the investigator regularly and will be permitted, upon request, to inspect the trial records, including eCRFs and other pertinent data, provided that subject confidentiality is maintained in accordance with local requirements.

CRAs will visit the sites to review the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrollment, continued acceptability of site staff, facilities, third party vendors and equipment, address outstanding actions/issues, ensure protocol amendments and approval are acknowledged and filed appropriately, verify that laboratory test results are being assessed in a timely manner, and discuss findings with the investigator (or designee). At regular intervals, CRAs will review the ISF to establish that all essential documents are present, current, and accurately filed. The investigator (or designee) must agree to cooperate with the CRA to ensure that any problems detected in the course of these monitoring visits are resolved. CRAs will work according to the Source Documentation Plan. The CRAs will complete source document verification activities to verify that the correct version

of the informed consent form has been used to consent the subjects before any study activities began; verify that all subjects enrolled into the study are eligible for enrollment; ensure that all protocol deviations have been recorded and events are reported according to timelines and study specifications; and confirm that changes made in the data have been made by appropriate staff, that all resolved queries have been reviewed and approved by the investigator, and that the investigator has reviewed all clinical data.

A separate unblinded CRA will ensure that the investigational product is being stored, prepared, administered, and accounted for according to specifications.

A final close-out visit will be performed at the end of the study. The CRA will complete any source data verification tasks, ensure that all events have been documented, reported, and followed-up appropriately. The CRA will remind the investigator to report the end of the study to the IRB/EC. This CRA will also perform a final reconciliation of IP and ensure the return or destruction of IP. complete the reconciliation of the ISF against the CIF and collect all documents required, confirm that all biological samples are labeled, stored, and/or shipped appropriately, review with the investigator regulatory and financial responsibilities, and any miscellaneous tasks as needed.

Follow-up activities after each monitoring visit will include the dissemination of a follow-up letter to the investigator to document any issues and corrective actions. Other activities will be the follow-up of any outstanding questions, outstanding data clarification forms, pending financial issues, and confirming the submission of any unreported events.

12. STUDY COMMITTEES

12.1 Independent Data and Safety Monitoring Board (DSMB)

The DSMB is an independent multidisciplinary group (independent of both the sponsor and CRO) who collectively has experience in the management of participating subjects as well as in the conduct and monitoring of randomized clinical trials.

The DSMB will meet at regular intervals, and if needed, on an ad hoc basis. The DSMB will review enrollment progress, baseline characteristics of the study analysis set, all treatment-emergent safety reports, study findings including relevant clinical and non-clinical results, and status of therapeutic benefit. DSMB reviews will be unblinded to treatment allocation. The members of the DSMB will be notified of all SAEs.

The DSMB will recommend one of the following at each of their meetings:

- Continue the trial
- Modify the trial (amend the protocol)
- Stop enrollment in the trial.

Additional details regarding the specifics of the DSMB operations may be found in the DSMB Charter.

12.2 Treatment Events Committee

A Treatment Events Committee (TEC) will be used during the course of the study in order to perform ongoing independent adjudication, identification and classification of post-treatment interventions at the treated disc and adjudication of the relatedness of adverse events to the product and/or procedure.

Additional details regarding the specifics of the TEC operations may be found in the TEC Charter and SAP.

12.2.1 Post-treatment Interventions at the Treated Level

As one of the criteria defining some of the primary endpoints, post-treatment interventions should be reported in a consistent manner. In order to maintain standardized classification of these interventions, the TEC will be used. The TEC will evaluate all interventions after the treatment procedure to determine if an intervention has occurred at the treated level, indicating a failure of the treatment to provide symptomatic improvement ("treatment failure"). TEC Members will also have an opportunity to identify post-treatment interventions that may not have been reported previously.

Following is a list of procedures at the index level that will be considered an intervention and treatment failure for responder analyses:

Surgical Interventions

- Spine fusion, interbody or posterolateral
- Artificial Disc Replacement
- Interlaminar or Spinous Process Stabilization Device Implantation
- Discectomy
- Surgical Disc Decompression, including minimally invasive decompression procedures such as mild®
- Laminectomy
- Laminotomy
- Osteotomy
- Foraminotomy
- Facetectomy
- Facet Joint Ablation/Denervation/Rhizotomy
- Disc nucleoplasty
- Spinal cord stimulation
- Intradiscal Electrothermal Annuloplasty
- Intradiscal Ablation Procedures
- Intrathecal pump implantation.

Spine Injections

- Epidural steroid injections
- Transforaminal injection of corticosteroid
- Injection of any anesthetic, analgesic steroid or other potential pain relieving substance into the disc
- Facet Injection of corticosteroid.

13. LAWS, REGULATIONS, AND ETHICS

13.1 Local Regulations/Declaration of Helsinki

This clinical study shall be conducted in full compliance with current material and relevant laws and regulations and investigator will use best efforts to ensure such compliance. This clinical study will also be conducted in compliance with principles outlined in the "Guideline for Good Clinical Practices" ICH tripartite Guideline[61] and with the ethical principles of the "Declaration of Helsinki"[62] or with the laws and regulations of the country in which the research is conducted, including but not limited to the EU Clinical Trial Directive.[63]

13.2 Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator if local regulations permit, to obtain signed informed consent from each subject prior to the subject's participation in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. For subjects who are not qualified to or are incapable of giving legal consent, written consent must be obtained from a legally acceptable representative. In cases where both the subject and his/her legal representative are unable to read, an impartial witness must be present during the entire informed consent discussion. After the subject and representative have orally consented to participation in the trial, the witness' signature on the form would attest that the information in the consent form was accurately explained and understood. The investigator or designee must also ensure that the subject understands he/she is free to refuse to enter or withdraw from the study at any time and for any reason, that a copy of the consent would be provided to the subject, and that the process by which consent is obtained is described in the source documentation. A subject's informed consent in this study will include permission for the release of any non-study-related medical records that will provide data for pharmacoeconomic analyses. However, this is optional and will not impact a subject's participation in the study.

The eCRFs for this study will contain a section for documenting subject informed consent, which must be completed appropriately. If new safety information results in significant changes in the benefit/risk assessment, the consent form should be reviewed and updated. All subjects, including those already being treated, should be informed of the new information, provided with a copy of the revised form, and give their consent to continue in the study in accordance with the IRB/EC requirements.

Subjects will authorize the use of their protected health information during the informed consent process in accordance with the applicable privacy requirements (HIPAA, local Regulatory Agency, etc.). Subjects who deny permission to use and disclose protected health information will not be eligible to participate in the study. The Investigator will ensure that study documents forwarded to Mesoblast, and any other documents, contain no mention of subject names or other sensitive information, in accordance with local privacy requirements.

13.3 Institutional Review Board/ Ethics Committees (IRB/EC)

It is the understanding of the sponsor that this protocol and any modifications as well as appropriate consent procedures, any accompanying material provided to the subject, such as subject information sheets or descriptions of the study used to obtain informed consent and advertisements or compensation given to the subject, will be reviewed and approved by appropriate Competent Authority and IRBs/ECs.

Before initiation of the trial at each investigational site, approval from the appropriate IRB/EC must be obtained. Written approval must be obtained before the investigational product is released to the investigator.

Any extensions or renewals of IRB/EC approval must be obtained during the course of the study. If required, approvals must also be obtained for any changes to the protocol, the informed consent form, the written information provided to subjects and/or other procedures.

Any new information that may adversely affect the safety of the subjects or the conduct of the study will be reported promptly to the IRB/EC by the investigator and/or the sponsor, in accordance with applicable local requirements. Written summaries of the study status will be submitted to the IRB/EC annually, or more frequently if required by the IRB/EC. On completion of the study, the IRB/EC will be notified that the study has ended.

The Investigator must notify Mesoblast immediately if the responsible IRB/EC has been disqualified, IRB/EC approval has been suspended, or if proceedings leading to disqualification have begun.

13.4 Protocol Adherence

Investigators will ensure that due diligence is applied in order to avoid protocol deviations. Protocol waivers will not be granted; however, if the site needs to deviate from the protocol to remove a subject from an immediate safety hazard, permission is not required. When protocol deviations do occur, they should be recorded and a CRA notified. The clinical study report will provide a discussion of protocol deviations that occurred during the study.

14. CONDITIONS FOR MODIFYING THE PROTOCOL

Requests from investigators to modify the protocol for ongoing studies will be considered only by consultation between an appropriate representative of the sponsor and the investigator. Protocol modifications must be prepared by a representative of the sponsor and initially reviewed and approved by the sponsor.

All protocol modifications must be submitted to the appropriate IRB/EC for information and approval in accordance with local requirements, and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor[s], change of telephone number[s]).

15. CONDITIONS FOR TERMINATING THE STUDY

Mesoblast reserves the right to terminate the study at any or any study site at any time under the conditions specified in the Clinical Trial Agreement. Termination will be preceded by written notices and submitted a reasonable time in advance of the intended termination. The Investigator may also terminate the protocol at his or her site for reasonable cause, after providing written notice to Mesoblast a reasonable time in advance of the intended termination. Advance notice is not required by either party if the protocol is stopped due to safety concerns. If Mesoblast terminates the protocol for safety reasons, it will immediately notify the investigator by telephone and subsequently provide written instructions for termination. If the investigator elects to terminate the study at his or her site, the investigator will be responsible for returning all investigational products and study-related documents to the sponsor in a timely manner. Source documents supporting study-related data must be retained by the investigator as previously described. In the event the trial is terminated before the planned completion date, action will be taken to assure the protection of the subjects' interests.

15.1 Early Termination of Study

Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study or if, in the sponsor's judgment there are no further benefits to be achieved from the study.
- A decision on the part of Mesoblast to suspend or discontinue testing, evaluation or development of a product.

15.2 Early Termination of a Study Site

The study site may warrant suspension, closure and/or termination for the following reasons:

- Failure of the investigator to enroll subjects into the study at an acceptable rate
- Failure of the investigator to comply with pertinent regulatory authority regulations
- Submission of knowingly false information from the study site to Mesoblast, its designee(s), study monitor, or a regulatory authority
- Insufficient adherence to the protocol requirements
- At the request of the investigator.

Study termination and follow-up will be performed in compliance with the conditions set forth in 21 CFR 312.50 and 21 CFR 312.56, or applicable local regulations.

15.3 Study Stopping Rules Based on Safety Monitoring

Safety will be continuously monitored. All SAEs reported or observed during the trial, whether protocol defined or not and whether or not attributable to the IP, must be reported to Mesoblast within 24 hours of the knowledge of the occurrence.

Mesoblast will notify all regulatory authorities and investigators in an expedited manner (according to 21 CFR 312.32, Directive 2001/83/EC or specified criteria stipulated in the institutions approval) by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the IP as soon as possible but in no event later than 7 calendar days after their initial receipt of the information. All other unexpected serious adverse reactions will be reported to all regulatory authorities and investigators within 15 days of receipt of the information.

16. CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must ensure that subject anonymity is maintained and that subject identity is protected from unauthorized parties. On eCRFs or other documents submitted to the sponsor, subjects should be referenced by an identification code rather than by their names. The investigator should keep a subject enrollment log showing codes, names and addresses. The investigator should maintain documents that will not be submitted to the sponsor (e.g., subjects' written consent forms) in strict confidence.

17. PUBLICATION POLICY

Mesoblast, Inc. shall retain ownership of all data. All proposed publications based on this study must be subject to the sponsor's approval requirements.

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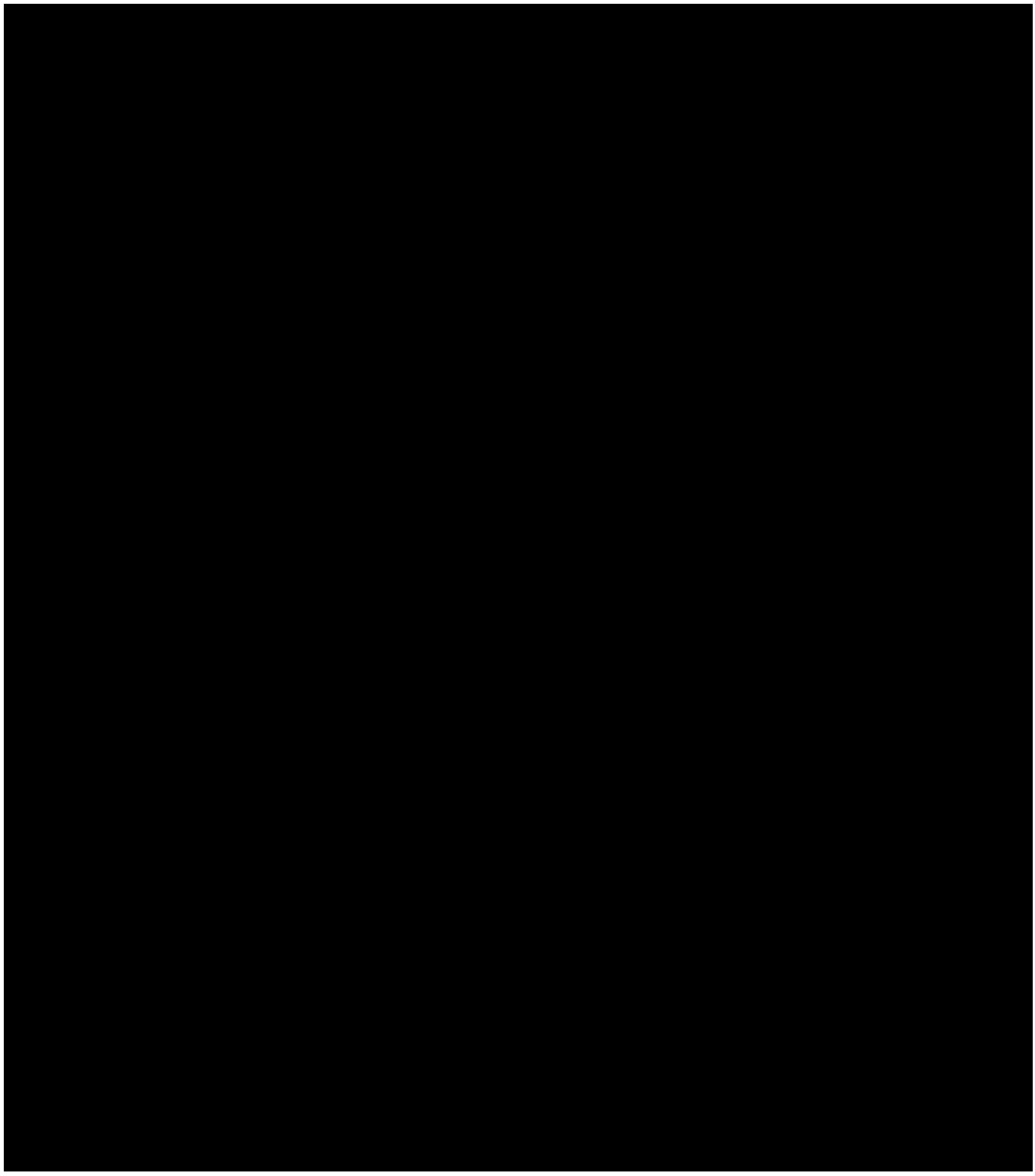
19. APPENDICES



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Appendix 2: Visual Analogue Scale (VAS): average low back pain, worst back pain, average leg pain

Appendix 2: Visual Analogue Scales (VAS)

Low Back Pain VAS – Average Pain Over 24 Hours

What was your average low back pain over the last 24 hours?

No pain — The strongest possible pain

Low Back Pain VAS – Worst Pain Over 24 Hours

What was your worst low back pain over the last 24 hours?

No pain — The strongest possible pain

Right Pain Vas – Average Pain Over 24 Hours

What was your average right leg pain over the last 24 hours?

No pain — The strongest possible pain

Left Leg Pain VAS – Average Pain Over 24 Hours

What was your average left leg pain over the last 24 hours?

No pain — The strongest possible pain

Appendix 3: Oswestry Disability Index (ODI)

Oswestry Disability Index Version 2.1a

This questionnaire is designed to give us information as to how your back (or leg) trouble affects your ability to manage in everyday life.
Please answer every section. Mark one box only in each section that most closely describes you today.

Section 1 - Pain intensity

- I have no pain at the moment.
- The pain is very mild at the moment.
- The pain is moderate at the moment.
- The pain is fairly severe at the moment.
- The pain is very severe at the moment.
- The pain is the worst imaginable at the moment.

Section 2 - Personal care (washing, dressing, etc.)

- I can look after myself normally without causing additional pain.
- I can look after myself normally but it is very painful.
- It is painful to look after myself and I am slow and careful.
- I need some help but manage most of my personal care.
- I need help every day in most aspects of my personal care.
- I do not get dressed, I wash with difficulty and stay in bed.

Section 3 - Lifting

- I can lift heavy weights without additional pain.
- I can lift heavy weights but it gives me additional pain.
- Pain prevents me from lifting heavy weights off the floor but I can manage if they are conveniently positioned, e.g. on a table.
- Pain prevents me from lifting heavy weights but I can manage light to medium weights if they are conveniently positioned.
- I can only lift very light weights.
- I cannot lift or carry anything at all.

Section 4 - Walking

- Pain does not prevent me from walking any distance.
- Pain prevents me from walking more than one mile.
- Pain prevents me from walking more than a quarter of a mile.
- Pain prevents me from walking more than 100 yards.
- I can only walk using a cane or crutches.
- I am in bed most of the time and have to crawl to the toilet.

Section 5 - Sitting

- I can sit in any chair as long as I like.
- I can sit in my favorite chair as long as I like.
- Pain prevents me from sitting for more than 1 hour.
- Pain prevents me from sitting for more than half an hour.
- Pain prevents me from sitting for more than 10 minutes.
- Pain prevents me from sitting at all.

Section 6 - Standing

- I can stand as long as I want without additional pain.
- I can stand as long as I want but it gives me additional pain.
- Pain prevents me from standing for more than 1 hour.
- Pain prevents me from standing for more than half an hour.
- Pain prevents me from standing for more than 10 minutes.
- Pain prevents me from standing at all.

Section 7 - Sleeping

- My sleep is never interrupted by pain.
- My sleep is occasionally interrupted by pain.
- Because of pain I have less than 6 hours sleep.
- Because of pain I have less than 4 hours sleep.
- Because of pain I have less than 2 hours sleep.
- Pain prevents me from sleeping at all.

Section 8 - Sex life (if applicable)

- My sex life is normal and causes no additional pain.
- My sex life is normal but causes some additional pain.
- My sex life is nearly normal but is very painful.
- My sex life is severely restricted by pain.
- My sex life is nearly non existent because of pain.
- Pain prevents me from having any sex life at all.

Section 9 - Social life

- My social life is normal and causes me no additional pain.
- My social life is normal but increases the degree of pain.
- Pain has no significant effect on my social life apart from limiting my more energetic interests, e.g. sport, etc.
- Pain has restricted my social life and I do not go out as often.
- Pain has restricted my social life to home.
- I have no social life because of pain.

Section 10 - Traveling

- I can travel anywhere without pain.
- I can travel anywhere but it gives me additional pain.
- Pain is bad but I am able to manage trips over two hours.
- Pain restricts me to trips of less than one hour.
- Pain restricts me to short necessary trips of under 30 minutes.
- Pain prevents me from traveling except to receive treatment.

Result

Your ODI = [ ]%

ODI% = Total score/5 x Number of questions answered x 100

Appendix 4: iMTA Productivity and Cost Questionnaire (iPCQ)

Please read this first!

Who is this questionnaire for?
This questionnaire is for you. There are different possibilities:

- You received this form from your (family) doctor or from (the) hospital.
- You received this form in the post with your name posted on the envelope.

You cannot fill in the form on your own?
If you are unable to fill in the form on your own, maybe someone can help you, for example a member of the family.

What is the questionnaire about?
The questionnaire is about your health and work during the last four weeks. We will start with general questions, for example about your gender and date of birth.

How long does it take to fill in the form?
It takes about 10 minutes to fill in the form.

How should you fill in the form?

- Start with the first question and follow the numbering.
- Put 1 **x** in the question box, unless the question states that you may put more than 1 **x**.
- For some of the questions you may fill in a number or otherwise on the dotted line.
- There are no wrong answers.

Do you want to change an answer?

- Cross out the old answer.
- Put an **x** in the new answer box.
- Put an arrow in front of the new answer.

~~☒ old answer~~

→ ☒ new answer

What happens to your answers?
Your answers will be used for research. Only the researchers will see your answers. That means therefore no one else.

The researchers do not write your name anywhere. And they will not tell anyone that you have participated in this research project.

We greatly appreciate that you are willing to fill in this form for us!

General questions

Question A1. What is the date while you are filling in this questionnaire?

day ☐☐ month ☐☐ year ☐☐☐☐

Question A2. What is your date of birth?

day ☐☐ month ☐☐ year ☐☐☐☐

Question A3. What is your gender?

- ☐ Male
- ☐ Female

Question A4. What is the highest degree in education that you have achieved? Look for your highest degree in education and fill in an **x** in the box.

- ☐ I never finished school or training programme
- ☐ Primary school or elementary school
- ☐ Junior vocational education
- ☐ Lower general secondary school
- ☐ Intermediate vocational education
- ☐ Higher general secondary education
- ☐ School for higher vocational education
- ☐ University
- ☐ I achieved another degree, namely……
  …….

Question A5. What do you do? Place an **x** in the box for what you usually do.

- ☐ I go to school, I am studying
- ☐ I am employed
- ☐ I am self employed
- ☐ I am a housewife, househusband

- ☐ I am unemployed
- ☐ I am unable to work, for …. %
- ☐ I am retired or on a pre-pension plan
- ☐ I do something else, namely……

Question A6. Do you have a paying job?

☐ No
☐ Yes

The following questions refer to your work. That is work that you get paid for.

You do not have a paying job? Skip to question 10. *Please first read the explanation above the question.*

Question 1. What is your occupation?

……

Question 2. How many hours a week do you work? Count only the hours that you get paid.

…….. hours

Question 3. How many days a week do you work?

…… days

Question 4. Have you missed work in the last 4 weeks as a result of being sick?

☐ No
☐ Yes, I have missed …… days.
(Only count the missed work days in the last 4 weeks)

Did you check "Yes"? Go to question 5.
Otherwise skip to question 7.

Question 5. Did you miss work earlier than the period of 4 weeks due to being sick? This is referring to one whole uninterrupted period of missed work as a result of being sick.

☐ No
☐ Yes

Did you check "Yes"? Go to question 6.
Otherwise skip to question 7.

Question 6. When did you call in sick?

day ☐☐ month ☐☐ year ☐☐☐☐

Skip to question 10. *Please first read the explanation above question 10.*

Question 7. During the last 4 weeks have there been days in which you worked but during this time were bothered by physical or psychological problems?

☐ No
☐ Yes

Did you check "Yes"? Go to question 8 and 9.
Otherwise skip to question 10. *First read the explanation above question 10*.

Question 8. How many days at work were you bothered by physical or psychological problems? (Only count the days at work in the last 4 weeks)

..... work days

Question 9. On the days that you were bothered by these problems, was it perhaps difficult to get as much work finished as you normally do? On these days how much work could you do on average? Look at the figures below. A 10 means that you were able to do as much work as you normally do. A 0 means that you were unable to do any work on these days. Circle the figure that fits best.

On these days I could not anything					I was able to do half as much as I normally do					I was able o do just as do much as I normally do
0	1	2	3	4	5	6	7	8	9	10

Explanation
Even for unpaid work, you can be bothered by physical or psychological problems. Sometimes as a result you (might) do less. For example you have trouble caring for your children or doing voluntary work. Or you are unable to run errands and pick up groceries, or to work in the garden. The following questions refer to this.

Question 10. Were there days in which you were forced to do less unpaid work because of physical or psychological problems? Only days in the last four weeks.

☐ No
☐ Yes

Did you check "Yes"? Go to question 11 and 12.
Otherwise skip to the end of the questionnaire.

Question 11. How many days did this happen? Only count the days in the last 4 weeks.

…….. Days

Question 12. Imagine that somebody, for example your partner, family member or friend helped you on these days, and he or she did all the unpaid work that you were unable to do for you. How many hours on average did that person spend doing this on these days?

On average …….. hours on these days

That was the last question.

Do you have any questions or comments?
Perhaps you have some questions or comments? Please write these here below.

……
……
……
……
……
……
……
……
……
……
……

Appendix 5: Subject Self-Assessment of Treatment (SAT)

Appendix 5: Self-Assessment of Treatment

(1) How do you assess your pain relief after treatment in this study?

□ I feel my pain is much worse (−2)

□ I feel my pain is somewhat worse (−1)

□ I feel my pain is no better and no worse (0)

□ I feel my pain is somewhat better (1)

□ I feel my pain is much better (2)

(2) How do you assess your activity level after treatment in this study?

□ I feel much less active (−2)

□ I feel somewhat less active (−1)

□ I feel no more and no less active (0)

□ I feel somewhat more active (1)

□ I feel much more active (2)

(3) How has your quality of life changed after treatment in this study?

□ I feel my quality of life is much worse (−2)

□ I feel my quality of life is somewhat worse (−1)

□ I feel my quality of life is no better and no worse (0)

□ I feel my quality of life is somewhat better (1)

□ I feel my quality of life is much better (2)

(4) Would you undergo this treatment again?*

□ No, definitely not (−2)

□ No, probably not (−1)

□ Unsure (0)

□ Yes, probably (1)

□ Yes, definitely (2)

(5) How do you compare the treatment you received in this study to previous medication or therapies for your pain?

□ Very much prefer my previous treatments to this treatment (−2)

□ Somewhat prefer my previous treatments (−1)

□ No preference (0)

□ Somewhat prefer this treatment to my previous treatment (1)

□ Very much prefer this treatment to my previous treatments (2)

*In Study C116, SAT Item 4 was administered with 3 response options: "No, absolutely not" (−2), "Unsure" (0), and "Yes, definitely" (2). The item was administered in Study C117 with 5 response levels as shown above.

Appendix 6: Euroqol-5D (EQ-5D)

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

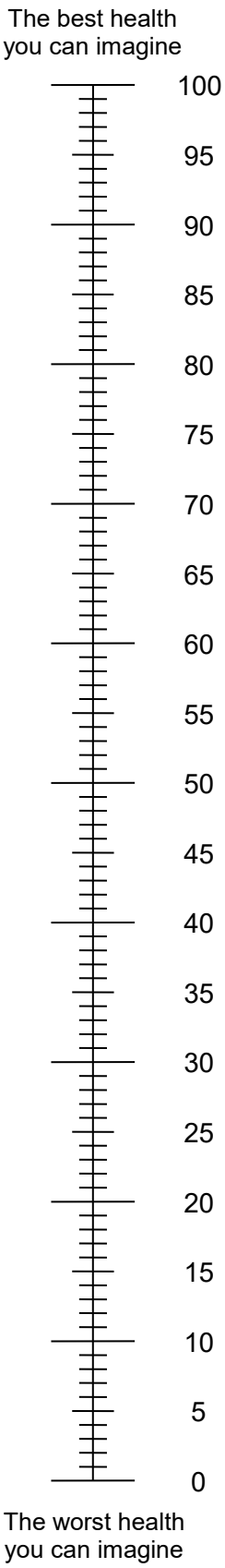
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 7: Patient-reported Utilization Questionnaire

Appendix 7: Patient Reported Utilization Questionnaires

Patient Reported Utilization Questionnaire - Baseline

1. In the past 12 months, have you seen the following health care providers or sites to discuss your back pain?

Primary care doctor

○ Yes ○ No

a. If 'Yes', how many times?
   ○ 0-1 ○ 2-3 ○ 4-5 ○ 6-7 ○ 8-9 ○ 10 or more

b. If 'Yes', was treatment recommended?
   ○ Yes ○ No ○ I don't know
   i. If 'Yes', describe treatment recommendations.

_____

Pain specialist

○ Yes ○ No

a. If 'Yes', how many times?
   ○ 0-1 ○ 2-3 ○ 4-5 ○ 6-7 ○ 8-9 ○ 10 or more

b. If 'Yes', was treatment recommended?
   ○ Yes ○ No ○ I don't know
   i. If 'Yes', describe treatment recommendations.

_____

Emergency department

○ Yes ○ No

a. If 'Yes', how many times?
   ○ 0-1 ○ 2-3 ○ 4-5 ○ 6-7 ○ 8-9 ○ 10 or more

b. If 'Yes', was treatment recommended?
   ○ Yes ○ No ○ I don't know
   i. If 'Yes', describe treatment recommendations.

_____

Hospital admission

○ Yes ○ No

a. If 'Yes', how many times?
   ○ 0-1 ○ 2-3 ○ 4-5 ○ 6-7 ○ 8-9 ○ 10 or more

b. If 'Yes', was treatment recommended?
   ○ Yes ○ No ○ I don't know
   i. If 'Yes', describe treatment recommendations.

_____

Spine Surgeon (Orthopedic Surgeon or Neurosurgeon)

○ Yes ○ No

a. If 'Yes', how many times?
   ○ 0-1 ○ 2-3 ○ 4-5 ○ 6-7 ○ 8-9 ○ 10 or more

b. If 'Yes', was treatment recommended?
   ○ Yes ○ No ○ I don't know
   i. If 'Yes', describe treatment recommendations.

_____

Acupuncturist

○ Yes ○ No

a. If 'Yes', how many times?
   i. ○ 0-1 ○ 2-3 ○ 4-5 ○ 6-7 ○ 8-9 ○ 10 or more

b. If 'Yes', was treatment recommended?
   i. ○ Yes ○ No ○ I don't know
   i. If 'Yes', describe treatment recommendations.

_____

Physical therapist

○ Yes○ No

a. If 'Yes', how many times?
   ○ 0-1 ○ 2-3 ○ 4-5 ○ 6-7 ○ 8-9 ○ 10 or more

b. If 'Yes', was treatment recommended?
   ○ Yes ○ No ○ I don't know
   i. If 'Yes', describe treatment recommendations.

Massage therapist

o Yeso No

a. If 'Yes', how many times?

o 0-1 o 2-3 o 4-5 o 6-7 o 8-9 o 10 or more

b. If 'Yes', was treatment recommended?

o Yes o No o I don't know

i. If 'Yes', describe treatment recommendations.

_____

Other (specify):_____

o Yes o No

a. If 'Yes', how many times?

o 0-1 o 2-3 o 4-5 o 6-7 o 8-9 o 10 or more

b. If 'Yes', was treatment recommended?

o Yes o No o I don't know

i. If 'Yes', describe treatment recommendations.

_____

1. In the past 12 months, were you **prescribed** any of the following medications specifically for your back pain? (Check all that apply)

o **Anti-depressants and Anti-Anxiety Medications** such as:

Generic	Brand Name
o Citalopram	Celexa
o Escitalopram	Lexapro, Cipralex
o Fluoxetine	Prozac, Sarafem; Pexeva
o Fluvoxamine	Luvox
o Paroxetine	Paxil, Paxil CR
o Sertraline	Zoloft
o Bupropion	Wellbutrin, Zyban; Aplenzin
o Desvenlafaxine	Pristiq
o Duloxetine	Cymbalta
o Levomilnac-ipran	Fetzima
o Milnacipran	Savella
o Venlafaxine	Effexor

o **General Pain medications <u>Non-prescription</u> Nonnarcotic analgesics** such as:

Generic	Brand Names
o Acetamino-phen	Tylenol
o Aspirin	
o Ibuprofen	Advil, Motrin
o Naproxen	Aleve

o **Prescriptions Non-steroidal Anti-Inflammatory Drugs** such as:

Generic	Brand Names
o Diclofenac	Cataflam, Voltaren, Zipsor
o Diflunisal	Dolobid
o Etodolac	Lodine, Lodine XL
o Fenoprofen	Nalfon
o Flurbiprofen	Ansaid
o Indomethacin	Indocin, Indocin SR, Tivorbex
o Ketoprofen	Actron, Orudis, Oruvail
o Ketorolac	Toradol, Sprix
o Meloxicam	Mobic
o Nabumetone	Relafen
o Celecoxib	Celebrex

o **Prescription Opioid Analgesic Drugs** such as:

Generic	Brand Names
o Acetaminophen with codeine	Tylenol
o Hydrocodone with acetaminophen	Vicodin
o Oxycodone sustained release	Oxycontin

o Oxycodone with acetaminophen	Percocet
o Tramadol, tramadol with acetaminophen	Ultram

- o **Muscle relaxants** such as

Generic	Brand Names
o Diazepam	Valium
o Alprazolam	Xanax

- o **Steroids** (injection or oral)

- o **Antiepileptics** such as:

Generic	Brand
o Gabapentin	Neurontin
o Pregablin	Lyrica
o Lamtrigine	Lamictal

- o **Sleep medications** such as:

Generic	Brand
o Benzodiazepines	o Valium, Halcion,
o Non-benzodiaepines	o Ambien, Sonata, Lunesta, Rozerem

- o **Other (specify):** _____
- o **Other (specify):** _____
- o **Other (specify):** _____

2. In the past 12 months, have you ever received epidural steroid injections to relieve your back pain?
   o Yes o No
   A. If 'Yes', how many injections did you receive?
      o 0-1 o 2-3 o 4-5 o 6-7 o 8-9 o 10 or more

3. In the past 12 months, have you had any of the following procedures have you had for your back pain? (Exclude those required by the study.)
   A. CT Scans
      o Yes o No
      i. If 'Yes', how many times?
         o 0-1 o 2-3 o 4-5 o 6 or more
   B. MRIs
      o Yes o No
      i. If 'Yes', how many times?
         o 0-1 o 2-3 o 4-5 o 6 or more
   C. X-Rays
      o Yes o No
      i. If 'Yes', how many times?
         o 0-1 o 2-3 o 4-5 o 6 or more

4. In the past 12 months have you discussed any other surgical disc procedures related to your back pain such as arthrodesis (fusion), disectomies (removal of bulging or herniated disc), kyphoplasties (vertebral augmentation for compression fractures), laminectomies (removal of bony covering over the back of the spinal canal) or other?
   o Yes o No o I don't know
   A. If 'Yes', did you schedule the procedure?
      o Yes o No
      i. If yes, did you have the surgical procedure?
         o Yes o No

5. In the past 12 months, have you had any of the following treatments/services for your back pain?
   A. Chiropractic Manipulation
      o Yes o No
      i. If 'Yes', how many times?

○ 0-1 ○ 2-3 ○ 4-5 ○ 6 or more

B. Physical Therapy
○ Yes ○ No
i. If 'Yes', how many times?
○ 0-1 ○ 2-3 ○ 4-5 ○ 6 or more

C. Massage Therapy
○ Yes ○ No
i. If 'Yes', how many times?
○ 0-1 ○ 2-3 ○ 4-5 ○ 6 or more

D. Acupuncture
○ Yes ○ No
i. If 'Yes', how many times?
○ 0-1 ○ 2-3 ○ 4-5 ○ 6 or more

6. In the past 12 months, have you seen a clinician for any mental health purposes?
○ Yes ○ No ○ I don't know

7. If yes to question 7, estimate how often you received these services in the past 12 months?
○ 0-1 ○ 2-3 ○ 4-5 ○ 6-7 ○ 8-9 ○ 10 or more

Patient Reported Utilization Questionnaire – Follow-up

1. In the past 12 months, have you seen the following health care providers or sites to discuss your back pain?

Primary care doctor

○ Yes ○ No

c. If 'Yes', how many times?

○ 0-1 ○ 2-3 ○ 4-5 ○ 6-7 ○ 8-9 ○ 10 or more

d. If 'Yes', was treatment recommended?

○ Yes ○ No ○ I don't know

ii. If 'Yes', describe treatment recommendations.

_____

Pain specialist

○ Yes ○ No

c. If 'Yes', how many times?

○ 0-1 ○ 2-3 ○ 4-5 ○ 6-7 ○ 8-9 ○ 10 or more

d. If 'Yes', was treatment recommended?

○ Yes ○ No ○ I don't know

i. If 'Yes', describe treatment recommendations.

_____

Emergency department

○ Yes ○ No

c. If 'Yes', how many times?

○ 0-1 ○ 2-3 ○ 4-5 ○ 6-7 ○ 8-9 ○ 10 or more

d. If 'Yes', was treatment recommended?

○ Yes ○ No ○ I don't know

ii. If 'Yes', describe treatment recommendations.

_____

Hospital admission

○ Yes ○ No

c. If 'Yes', how many times?

○ 0-1 ○ 2-3 ○ 4-5 ○ 6-7 ○ 8-9 ○ 10 or more

d. If 'Yes', was treatment recommended?

○ Yes ○ No ○ I don't know

ii. If 'Yes', describe treatment recommendations.

_____

Spine Surgeon (Orthopedic Surgeon or Neurosurgeon)

○ Yes ○ No

c. If 'Yes', how many times?

○ 0-1 ○ 2-3 ○ 4-5 ○ 6-7 ○ 8-9 ○ 10 or more

d. If 'Yes', was treatment recommended?

○ Yes ○ No ○ I don't know

ii. If 'Yes', describe treatment recommendations.

_____

Acupuncturist

○ Yes ○ No

c. If 'Yes', how many times?

i. ○ 0-1 ○ 2-3 ○ 4-5 ○ 6-7 ○ 8-9 ○ 10 or more

d. If 'Yes', was treatment recommended?

i. ○ Yes ○ No ○ I don't know

ii. If 'Yes', describe treatment recommendations.

_____

Physical therapist

○ Yes○ No

c. If 'Yes', how many times?

○ 0-1 ○ 2-3 ○ 4-5 ○ 6-7 ○ 8-9 ○ 10 or more

d. If 'Yes', was treatment recommended?

○ Yes ○ No ○ I don't know

ii. If 'Yes', describe treatment recommendations.

_____

Massage therapist

○ Yes○ No

c. If 'Yes', how many times?

o 0-1 o 2-3 o 4-5 o 6-7 o 8-9 o 10 or more

d. If 'Yes', was treatment recommended?

o Yes o No o I don't know

ii. If 'Yes', describe treatment recommendations.

_____

Other (specify):_____

o Yes o No

c. If 'Yes', how many times?

o 0-1 o 2-3 o 4-5 o 6-7 o 8-9 o 10 or more

d. If 'Yes', was treatment recommended?

o Yes o No o I don't know

ii. If 'Yes', describe treatment recommendations.

_____

2. In the past 12 months, were you **prescribed** any of the following medications specifically for your back pain? (Check all that apply)

o **Anti-depressants and Anti-Anxiety Medications** such as:

Generic	Brand Name
o Citalopram	Celexa
o Escitalopram	Lexapro, Cipralex
o Fluoxetine	Prozac, Sarafem; Pexeva
o Fluvoxamine	Luvox
o Paroxetine	Paxil, Paxil CR
o Sertraline	Zoloft
o Bupropion	Wellbutrin, Zyban; Aplenzin
o Desvenlafaxine	Pristiq
o Duloxetine	Cymbalta
o Levomilnac-ipran	Fetzima
o Milnacipran	Savella
o Venlafaxine	Effexor

o **Muscle relaxants** such as

Generic	Brand Names
o Diazepam	Valium
o Alprazolam	Xanax

o **Antiepileptics** such as:

Generic	Brand
o Gabapentin	Neurontin
o Pregablin	Lyrica
o Lamtrigine	Lamictal

o **Sleep medications** such as:

Generic	Brand
o Benzodiazepines	o Valium, Halcion,
o Non-benzodiaepines	o Ambien, Sonata, Lunesta, Rozerem

o **Other (specify):** _____

o **Other (specify):** _____

o **Other (specify):** _____

3. In the past 12 months, have you had any of the following procedures have you had for your back pain? (Exclude those required by the study.)

D. CT Scans

o Yes o No

ii. If 'Yes', how many times?

o 0-1 o 2-3 o 4-5 o 6 or more

E. MRIs

o Yes o No

ii. If 'Yes', how many times?
○ 0-1 ○ 2-3 ○ 4-5 ○ 6 or more

F. X-Rays
○ Yes ○ No

ii. If 'Yes', how many times?
○ 0-1 ○ 2-3 ○ 4-5 ○ 6 or more

4. In the past 12 months, have you had any of the following treatments/services for your back pain?

E. Chiropractic Manipulation
○ Yes ○ No

ii. If 'Yes', how many times?
○ 0-1 ○ 2-3 ○ 4-5 ○ 6 or more

F. Physical Therapy
○ Yes ○ No

ii. If 'Yes', how many times?
○ 0-1 ○ 2-3 ○ 4-5 ○ 6 or more

G. Massage Therapy
○ Yes ○ No

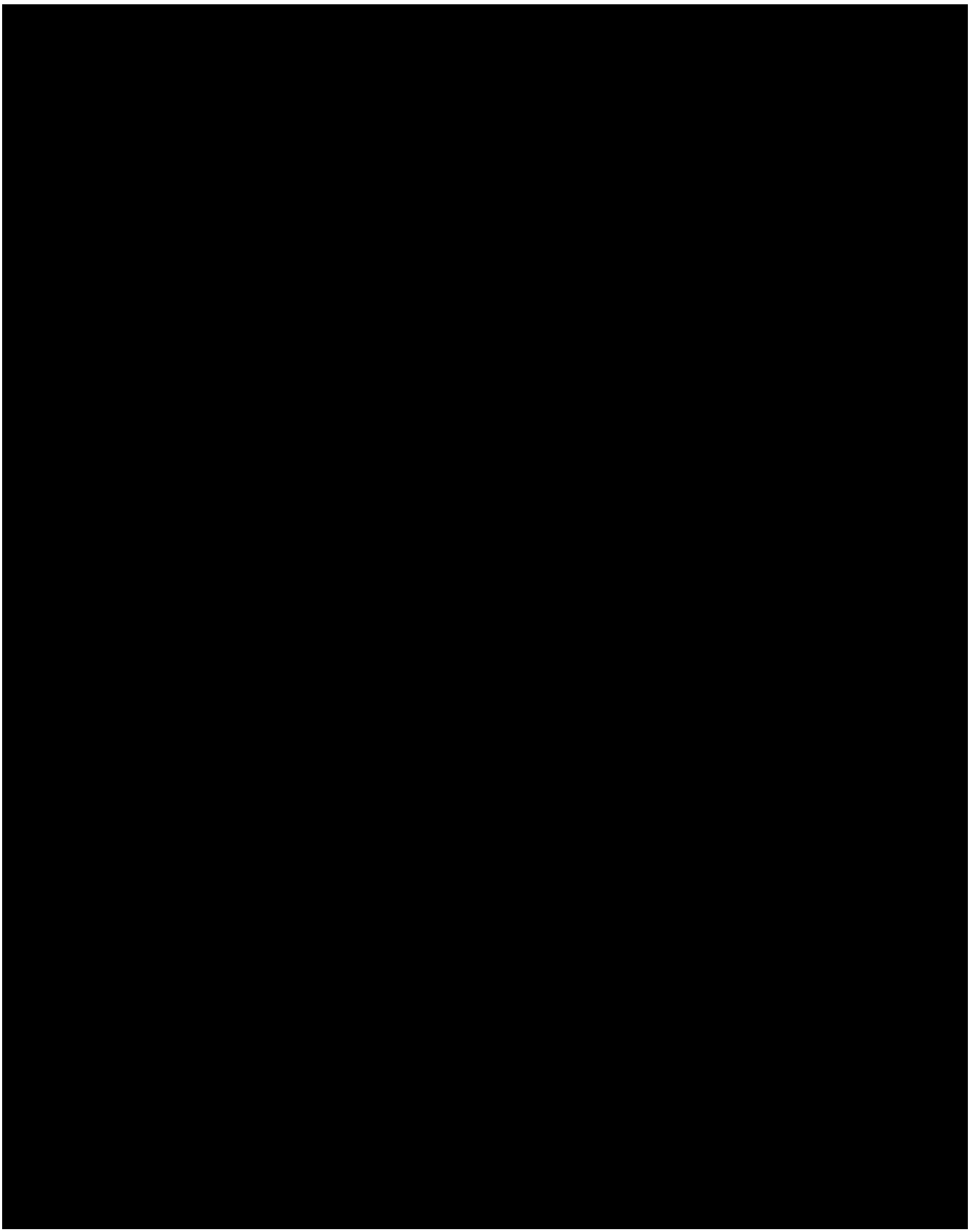
ii. If 'Yes', how many times?
○ 0-1 ○ 2-3 ○ 4-5 ○ 6 or more

H. Acupuncture
○ Yes ○ No

ii. If 'Yes', how many times?
○ 0-1 ○ 2-3 ○ 4-5 ○ 6 or more

5. In the past 12 months, have you seen a clinician for any mental health purposes?
○ Yes ○ No ○ I don't know

6. If yes to question 5, estimate how often you received these services in the past 12 months?
○ 0-1 ○ 2-3 ○ 4-5 ○ 6-7 ○ 8-9 ○ 10 or more



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