TEIJIN
Human Chemistry, Human Solutions

Open-Label, Non-controlled, Single Ascending Dose Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Exploratory Efficacy of KTP-001 in Subjects with Lumbar Disc Herniation

Name of Drug: KTP-001

Protocol Number: KTP-001-CL-101

Phase: 1/2

US IND Number: [redacted]

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Amendment 4

Sponsor: Teijin America, Inc.

[redacted]

CRO:

[redacted]

Confidentiality Statement

Document History

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Amendment 4	20 October 2015
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Amendment 2	16 August 2013
Amendment 1	06 November 2012
Original protocol	10 August 2012

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1 SYNOPSIS

Protocol Title:	Open-label, non-controlled, single-ascending dose study to evaluate safety, tolerability, pharmacokinetics, and exploratory efficacy of KTP-001 in subjects with lumbar disc herniation
Sponsor:	Teijin America, Inc.
Study Phase:	Phase 1/2
Indication:	Herniated lumbar disc
Objectives:	The primary objective of this study is: • To evaluate the safety and tolerability of a single intradiscal injection of KTP-001 in subjects with a single herniated lumbar disc. The secondary objectives of this study are: • To determine the pharmacokinetics (PK) of KTP-001 in the serum of circulating blood after intradiscal injection of the study drug. • To determine the presence of anti-KTP-001 antibody in the serum of circulating blood after intradiscal injection of the study drug. The exploratory objectives of this study are: • To explore the pharmacodynamics (PD) of keratan sulfate in the serum of circulating blood after intradiscal injection of the study drug. • To assess changes in pain, neurologic examination, disability, magnetic resonance imaging (MRI) and X-ray assessments, Quality of Life (QOL), and patient global impression of change (PGI-C) scores in subjects receiving study drug.
Number of Sites:	This study will be conducted at approximately 8 sites in the United States.
Study Design:	This study is designed as an open-label, non-controlled single ascending dose study. Twenty-four subjects with a diagnosis of a single herniated lumbar disc will be divided into 4 cohorts of 6 subjects. Dose escalation will begin with a 5 µg intra-disc administration. After all subjects in the first cohort have reached the Week 13 assessment, relevant safety data will be reviewed. If adequate safety and tolerability has been demonstrated, KTP-001 dose escalation will continue in subsequent escalating doses of 15, 50, and 150 µg/disc with safety reviews conducted prior to each dose escalation.
Planned Sample Size:	Approximately 48 subjects will be screened to ensure that 24 subjects are enrolled into this study. Subjects who discontinue from the study after enrollment but prior to receiving study drug will be replaced to ensure that at least 6 subjects are treated in each of the 4 cohorts.

Subject Selection Criteria:	Subject eligibility must be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study. Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study : **Inclusion Criteria**: 1. Has had a single unilateral contained or noncontained (extruded) lumbar disc herniation at the L3-L4 or L4-L5 or L5-S1 level diagnosed by clinical symptoms and/or physical findings and confirmed by MRI. Symptom duration should be at least 6 weeks prior to screening. 2. Has radicular symptoms with a documented positive straight-leg raising or femoral stretch test consistent with the level of the disc herniation. 3. Has had at least 6 weeks of conservative therapy prior to screening. 4. Has a daily average leg pain score of ≥ 4 (using an 11-point numerical scale) on at least 3 out of the 5 days immediately prior to treatment AND on all 5 days immediately prior to treatment the daily average leg pain score is ≥ 2. 5. Has completed the subject diary for at least 4 out of the 5 days immediately prior to treatment. 6. Has an Oswestry Disability Index (ODI) of ≥ 30% at screening. 7. Is a male or female subject between 30 and 70 years of age, inclusive. 8. Has a body mass index of 18 to 35 kg/m^2. 9. Is medically healthy, other than lumbar disc herniation, with clinically insignificant screening results (including laboratory profiles, medical histories, electrocardiograms [ECGs], and physical examination) as deemed by the investigator. 10. Uses or agrees to use effective contraception methods or is a female of nonchildbearing potential (See Section 6.3). 11. Voluntarily provides written consent to participate in the study. **Exclusion Criteria**: Any subject that meets any of the following exclusion criteria will not be enrolled in this study or will be discontinued at the discretion of the investigator if he/she develops any of the following exclusion criteria during the study: 1. Has a sequestered lumbar disc herniation or intrathecal herniation confirmed by MRI. 2. Has 2 or more symptomatic lumbar disc herniations as assessed by clinical symptoms and/or physical findings and confirmed by MRI. 3. Has had previous intradiscal therapeutic intervention at the level of the current symptomatic disc herniation or has had any lumbar surgery in the past. Previous therapeutic intradiscal injections (e.g., steroids) at the level of the current symptomatic disc herniation are not permitted within 6 weeks of screening. 4. Has undergone chemonucleolysis at any level of disc herniation or has had previous exposure to study drug. 5. Has had previous epidural injections, a selective nerve root block, or a facet block within 2 weeks before screening. 6. Has had any changes in the frequency of physical therapy or the introduction of new modalities of physical therapy, acupuncture, transcutaneous electrical nerve stimulation (TENS) or any other nonpharmacologic treatment modalities within 2 weeks prior to screening.

	7. Has had any changes in dosing of pain medications or introduction of new pain medications/muscle relaxants within 1 week prior to screening. 8. Has had any changes in antidepressant treatment or "pain modulating" therapy, including gabapentin and pregabalin within 4 weeks before screening. 9. Has the presence of lumbar spine disease and/or deformity other than a lumbar disc herniation, including spondylolisthesis Grade 2 or above, clinically significant scoliosis, spinal stenosis including significant lateral recess stenosis not related to the lumbar disc herniation, vertebral compression fracture, ankylosing spondylitis, inflammatory bone or disc disease, primary or metastatic malignancy, or any other clinically significant spine disease. 10. Has symptoms of cauda equina syndrome or progressive neurologic deficit, especially motor weakness. 11. Has a concomitant neurologic disorder, such as polyneuropathy, myopathy or motor neuron disease, lumbosacral plexopathy, radiculitis, multiple sclerosis, myelopathy, spinal cord compression, prior poliomyelitis or stroke, or any other condition resulting in sensory-motor deficit in the lower extremities. 12. Has other concomitant painful condition such as fibromyalgia, rheumatoid arthritis, severe osteoarthritis of the hip and/or knee joints or other painful condition that may interfere with pain assessments in the study. 13. Has a history of and/or clinical evidence of peripheral vascular disease. 14. Has the presence of an apophyseal ring in the vertebral disc as confirmed by X-ray 15. Is pregnant, breastfeeding, or has a positive serum pregnancy test at screening or a positive urine pregnancy test prior to receiving the study drug. 16. Has a history or presence of significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or psychiatric disease. 17. Has a history or presence of cancer within 5 years of screening, with the exception of localized basal cell skin cancer 18. Has a history of heavy alcohol consumption (defined as more than 2 standard alcohol beverages per day for males or more than 1 standard alcohol beverage per day for a woman, or more than 5 standard alcohol beverages on 1 occasion more than 5 times in the last 30 days for either gender) or drug abuse within the past 2 years or has a positive urine drug screen prior to enrollment (except for prescription medications). 19. Is a current, active smoker or is unable to abstain from tobacco use for 2 weeks prior to study injection. 20. Has a history of multiple drug allergies (2 or more classes of drugs), food allergies or other life-threatening allergies deemed significant by the principal investigator. 21. Has used or is using systemic steroids within 2 weeks prior to screening (not including inhalation, ophthalmic, and topical steroids). 22. Is taking anticoagulants including (but not limited to) warfarin, heparin/low molecular weight heparins, thrombin inhibitors, factor Xa inhibitors; or has any condition/treatment associated with coagulopathy/bleeding tendency. 23. Is receiving workers' compensation or other disability benefits or has a

	pending disability claim or litigation related to a back condition/disc herniation. 24. Has participated in any clinical study within 30 days prior to screening. 25. Has a positive screen for hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), or anti-human immunodeficiency virus (HIV), or has any active, clinically significant infection. 26. Has an elevation of aspartate aminotransferase (AST) and/or alanine aminotransaminase (ALT) ≥ 2 X upper limit of normal (ULN), or a total bilirubin > ULN, or a creatinine ≥ 1.5 X ULN, or any other clinically significant laboratory abnormalities that, in the investigator's judgment, would preclude the subject from participation in the study. 27. Has any clinically significant ECG abnormalities at screening. 28. Has any contraindication to undergo an MRI or has declared inability to tolerate an MRI. 29. Has any condition that would, in the investigator's opinion, limit the subject's ability to complete the study.
Duration of Study:	After a single intradiscal injection of study drug, subjects will be confined to the study facility for the first 24 hours and will be asked to participate in this study for at least 24 months (2 years).
Study Drug:	KTP-001 1.0 mg/vial will be provided as a lyophilized powder in 2.0 mL glass vials. Each vial contains 1.0 mg of KTP-001 drug substance, which will be reconstituted with 0.5 mL of sterile water for injection and then diluted with a buffer solution to administer the required injection dose per 1.0 mL.
Dose and Route of Administration:	A single intradiscal injection of doses 5, 15, 50, and 150 µg/disc of KTP-001 will be administered intradiscally under fluoroscopic or computer tomography (CT) visualization and guidance after a local anesthetic is administered. The final injection volume per subject will be 1.0 mL. Use of an imaging dye is not permitted for the intradiscal injection.
Response Criteria:	**Safety** Measures of safety and tolerability will include vital signs, 12-lead ECGs, determination of adverse events (AEs), clinical laboratory (hematology, serum chemistry, coagulation, urinalysis), MRI, X-ray (morphological assessment), and physical and neurologic examinations. Blood samples for measures of serum anti-KTP-001 antibody will be drawn pre-dose (just prior to administration of study drug) and at the 1-, 2-, 4-, 6-, and 13-week visits post-dose or early termination visit. ***Data and Safety Monitoring Board (DSMB):*** Escalation to a higher dose in a cohort will be permitted only if adequate safety and tolerability have been demonstrated at the previous lower dose. An independent Data and Safety Monitoring Board (DSMB) will determine whether to proceed to the next dose level as planned by evaluating safety measures, including AEs and clinical laboratory values. This evaluation will be conducted at the 13-week follow-up visit for all subjects in each dose cohort.

	Halting Rules: If any of the following AEs occur in any subject, further recruitment will be held until the event is assessed by the DSMB and a recommendation is made regarding continuation of the study and/or escalation to the next dose cohort: • Neurologic deficit consistent with cauda equina syndrome or myelopathy • Exacerbation of radicular symptoms associated with onset of a new motor deficit in one or both legs following administration of study drug • Modic changes consistent with significant endplate edema or sclerosis compared to baseline, as determined by an expert spine radiologist • Loss of height of the disc of > 30% relative to the baseline and defined as the average of anterior and posterior disc height evaluated by X-ray • Evidence by X-ray of lumbar segmental instability at the treated segment defined as either: o Anterior translation of the posterior edge of the superior vertebral body relative to the posterior edge of the inferior vertebral body increase from baseline greater than 3 mm is considered strong evidence of instability o Sagittal rotation change from extension to flexion of >5° (as measured by the Dupuis method) is weak evidence of instability, and without observed translation as defined above, will require further evaluation before it would be considered a halting event NOTE: if the subject's condition does not permit the acquisition of flexion and extension films, instability will be evaluated solely on the basis of translation on the lateral view, as described above • Destructive cartilage endplate changes as confirmed by MRI.
	Efficacy (exploratory) The following measures of efficacy after administration of study drug will be explored in this study: • Lower back pain and leg pain (measured by 11-point numerical pain scale) at baseline, on Day 1 pre-dose, at 2, 4, 6, and 24 hours post-dose, at all post-dose visits (Weeks 1, 2, 4, 6 and 13, Months 6, 9, 12, 18, 24 or early termination visit). • Use and amount of any pain medications (including extra acetaminophen) added to the subject's baseline pain regimen within the first 13 weeks post-dose. • Spinal flexion and tension (measured by straight-leg raising or femoral stretch test) at 6 and 13 weeks after injection of study drug or early termination visit. • Improvement in functional ability measured by ODI at 6 and 13 weeks after injection of study drug or early termination visit. • Improvements in QOL as measured by the Short Form (SF)-12 Health Survey at 6 and 13 weeks after injection of study drug or early termination visit. • Improvements in symptom severity as measured by the PGI-C scale at 6 and 13 weeks after injection of study drug or early termination visit.

	Pharmacokinetics Blood samples for measures of serum concentrations of KTP-001 will be drawn pre-dose (just prior to administration of study drug), at 2, 4, 6, and 24 hours post-dose, and at the 1-, 2-, 4-, 6-, and 13-week follow-up visits or early termination visit. **Pharmacodynamics (exploratory)** Blood samples for measures of serum concentrations of keratan sulfate will be drawn pre-dose (just prior to administration of study drug), at 6 and 24 hours post-dose, and at the 1-, 2-, 4-, 6-, and 13-week follow-up visits or early termination visit.
Statistical Analysis:	All statistical analyses will be conducted using SAS software, version 9.1.2 or higher (SAS® Institute, Cary, NC). Additional analyses of study endpoints will be detailed in the statistical analysis plan. **Analysis populations** The following 5 analysis populations will be defined in this study. *Intent-to-Treat Population*: The Intent-to-Treat population will be defined as any subject who is enrolled into the study and whether or not he/she receives study drug. *Full Analysis Set*: The Full Analysis Set population will be defined as any subject who is enrolled into the study, receives study drug and has at least 1 efficacy evaluation after receiving study drug. *Per Protocol Set:* The Per Protocol Set will be defined as any subject who is enrolled into the study, receives study drug as planned, has at least 1 efficacy evaluation after receiving study drug, completes the Week 13 visit, and has no significant protocol violations. *Safety Population*: The Safety population will be defined as any subject who is enrolled into the study and receives study drug. *PK Evaluable Population*: The PK population will be defined as any subject enrolled into the study, receives study drug, and has at least 1 evaluable PK sample.

	Safety endpoints and analysis: The following safety endpoints will be analyzed and presented using descriptive statistics (n, mean, median, minimum, maximum, standard deviation [SD], percentage of analysis population, and confidence interval [CI]): • Adverse events, serious adverse events (SAEs), deaths, or discontinuations due to AEs (including subjects who have lumbar surgery) that occur after administration of study drug. Adverse events will be coded using the Medical Dictionary for Regulatory Activities. • Change and shifts from baseline in vital signs (including heart rate, systolic and diastolic blood pressures, respiratory rate, and body temperature), 12-lead ECGs (including heart rate, rhythm, PR, RR, PQ, and QT intervals, QTc [Bazett's and Fridericia's], and QRS), and clinical laboratory tests (including hematology, serum chemistry, coagulation, and urinalysis). • Change from baseline in MRI and X-ray (including morphological assessment). • Change from baseline in neurologic assessments, including positive straight-leg raising or femoral stretch test, alteration of deep tendon reflexes (knee and ankle), sensory, or motor deficits in the lower extremities. • Clinically significant change from baseline in physical examinations. • Number of subjects who experienced any AEs defined as a halting rule. • Serum anti-KTP-001 antibody analysis [redacted]. **Pharmacokinetic analysis:** Serum concentrations of KTP-001 will be determined [redacted] A noncompartmental analysis will include determination of the following parameters using WinNonlin® Professional Network Edition, version 5.2 or higher, Pharsight Corp, Palo Alto, CA: • Maximum observed serum concentration (C_{max}) • Time to C_{max} (t_{max}) • Area under the concentration-time curve from time zero to time (t) (AUC_t). **Exploratory efficacy endpoints and analysis:** The following efficacy endpoints will be analyzed and presented using descriptive statistics (n, mean, median, minimum, maximum, SD, percentage of analysis population, and CI): • Change from baseline in lower back pain and leg pain (numerical pain scale) at 6 and 13 weeks • Number of subjects requiring 1) additional pain medication (and amounts) added to the subject's baseline pain regimen within the first 13 weeks post-dose, 2) an epidural injection, a selective nerve root block, or a facet block after receiving study drug, 3) surgical intervention for lumbar disc herniation • Change from baseline in spinal flexion and tension signs (straight-leg

	raising or femoral stretch test) on the affected side at 6 and 13 weeks • Change from baseline in ODI at 6 and 13 weeks • Change from baseline in SF-12 at 6 and 13 weeks • Change from baseline in the PGI-C at 6 and 13 weeks. **Exploratory PD analysis:** The following exploratory PD endpoint will be analyzed and presented using descriptive statistics (n, mean, median, minimum, maximum, SD, percentage of analysis population, and CI): • Change from baseline in serum concentrations of keratan sulfate at every time point.

1.1 Schedule of Assessments and Procedures

Study Procedures	Screening	Pre-dose	Post-dose													
		Confinement [a]					Clinic Visits									
	Day -21 to Day 1	Day 1					1 wk	2 wk	4 wk	6 wk	13 wk (EOS) [b]	6 mth	9 mth	12 mth	18 mth	24 mth (EOS)[c]
		0 hr	2 hr	4 hr	6 hr	24 hr										
			±15 min			±1 hr	±2 days			±5 days		±1 wk		±2 wk	±4 wk	
Screening																
Informed Consent	X															
Inclusion/Exclusion	X	X														
Demographics	X															
Medical History	X															
Height (cm)	X															
Safety Assessments																
Concomitant/Prior Medications	X	X					X	X	X	X	X	X	X	X	X	X
MRI	X										X	X		X	X	X
X-ray	X										X	X		X	X	X
Weight (kg)	X	X				X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X			X	X	X	X	X	X	X	X	X	X	X
Neurologic Examination	X	X	X			X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG [d]	X					X					X					
Clinical Laboratory Tests [e]	X					X	X	X			X					
Serum Pregnancy Test	X										X					
Urine Pregnancy Test [f]		X														
Urine Drug Screen	X															
HBsAg, anti-HCV, anti-HIV	X															
Adverse Events		◄----------														----------►
Investigational Product Administration																
Investigational Product Administration [g]		X														

Study Procedures	Screening	Pre-dose	Post-dose													
		Confinement [a]					Clinic Visits									
	Day -21 to Day 1	Day 1					1 wk	2 wk	4 wk	6 wk	13 wk (EOS) [b]	6 mth	9 mth	12 mth	18 mth	24 mth (EOS)[c]
		0 hr	2 hr	4 hr	6 hr	24 hr										
			±15 min			±1 hr	±2 days			±5 days		±1 wk		±2 wk	±4 wk	
PK and PD Sampling																
Blood Sampling for anti-KTP-001 Antibody		X					X	X	X	X	X					
Blood Sampling for KTP-001		X	X	X	X	X	X	X	X	X	X					
Blood Sampling for keratan sulfate		X			X	X	X	X	X	X	X					
Efficacy Assessments (exploratory)																
Dispense Study Diary	X	X				X	X	X	X	X						
Collect and Review Study Diary		X				X	X	X	X	X	X					
Current Lower Back Pain and Leg Pain	X	X	X	X	X	X	X	X	X	X	X	X [h]	X [h]	X [h]		
Spinal Flexion/Tension	X	X				X	X	X	X	X	X	X	X	X		
ODI	X	X				X	X	X	X	X	X	X	X	X		
SF-12	X	X				X	X	X	X	X	X	X	X	X		
PGI-C	X	X				X	X	X	X	X	X	X	X	X		

Abbreviations: PGI-C=Patient Global Impression of Improvement; ODI=Oswestry Disability Index; SF-12=Short Form 12 (QOL assessment); PK=pharmacokinetics; PD=pharmacodynamics; MRI= magnetic resonance imaging; ECG= electrocardiogram; HBsAg=hepatitis B surface antigen, HCV=hepatitis C, HIV=human immunodeficiency virus; hr = hour(s); mth = month(s); wk = week(s)

a. 24 hours hospitalization after the intradiscal injection is performed. Discharge is based on data up to 24 hours.

b. The same procedures as described in Section 11.13 will be used for early termination prior to Week 13.

c. The same procedures as described in Section 11.12 will be used for early termination between Week 13 and Month 24.

d. Follow-up ECG(s) will be obtained if any significant abnormalities are detected after dose administration to document resolution and as clinically indicated.

e. Hematology, coagulation, serum chemistry, and urinalysis.

f. Urine pregnancy tests will also be completed whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated as per request of the ethical board or if required by local regulations.

Study Procedures	Screening	Pre-dose	Post-dose											
		Confinement [a]					Clinic Visits							
	Day -21 to Day 1	Day 1					1 wk	2 wk	4 wk	6 wk	13 wk (EOS) [b]	6 mth	9 mth	12 mth	18 mth	24 mth (EOS)[c]
		0 hr	2 hr	4 hr	6 hr	24 hr										
			±15 min			±1 hr	±2 days			±5 days		±1 wk		±2 wk	±4 wk	

g. Investigational product will be given intradiscal by injection under fluoroscopic or CT visualization and guidance and confirmed by MRI.

h. Performed at the time of the clinical visit only.

2 GENERAL INFORMATION

2.1 Study Administrative Structure

Protocol Title: Open-Label, Non-Controlled, Single Ascending Dose Study to Evaluate Safety, Tolerability, Pharmacokinetics and Exploratory Efficacy of KTP-001 in Subjects with Lumbar Disc Herniation

Sponsor:	Teijin America, Inc.
Sponsor's Responsible Medical Officer:	[redacted]
Sponsor's Contact:	[redacted]
Investigator and Clinical Study Center:	This study will be conducted at approximately 8 sites in the United States
Medical Monitor:	[redacted]
Clinical Laboratory:	[redacted]
Pharmacokinetic Analytical Laboratory:	[redacted]
Anti-KTP-001 Antibody Analytical Laboratory:	[redacted]
Pharmacodynamic Analytical Laboratory:	[redacted]
Clinical Research Organization:	[redacted]

2.2 List of Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransaminase
AP	Anterior-posterior
AST	Aspartate aminotransferase
AUC_t	Area under the serum concentration-time curve from time zero to time t
BLQ	Below the limit of quantification
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence interval
C_{max}	Maximum observed concentration
CRF	Case report form
CT	Computerized tomography
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
FDA	US Food and Drug Administration
FIH	First in human
GCP	Good Clinical Practice
H.E.	Hematoxylin and Eosin
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	Halting rules
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IU	International unit
LOAEL	Lowest observed adverse effect level
MedDRA	Medical Dictionary for Drug Regulatory Activities
µg	Microgram
MMP	Matrix metalloproteinase

MRI	Magnetic Resonance Imaging
N, n	Number of subjects/subjects in a sample from a population or analysis group
NSAID	Nonsteroidal anti-inflammatory drug
NOAEL	No observed adverse effect level
ODI	Oswestry Disability Index
PD	Pharmacodynamics
PGI-C	Patient global impression of change
PK	Pharmacokinetics
QOL	Quality of life
QRS	Principal deflection in ECG
QT	ECG interval
QT_c	QT interval corrected heart rate
RBC	Red blood cell
SAE	Serious adverse event
SD	Standard deviation
SF-12	Short form-12 (QOL scale)
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SOC	Standard of care
TEAE	Treatment-emergent AE
TENS	Transcutaneous electrical nerve stimulation
t_{max}	Time at which the maximum concentration was observed
ULN	Upper limit of normal
WBC	White blood cell count

3 INTRODUCTION AND BACKGROUND

3.1 Introduction

Teijin is developing recombinant human Matrix metalloproteinase 7 (MMP-7, code name: KTP-001) for chemonucleolysis therapy for the relief of herniated disc, characterized by a protrusion or prolapse of the nucleus pulpous through the annulus fibrosus, which in turn presses against a nerve, and causes lower back pain and/or leg pain.

The prevalence of lumbar disc herniation is approximately 1% of the population [1]. Patients with severe neurological deficits such as cauda equina syndrome will have surgery immediately. Of the remaining patients who opt for conservative therapy, approximately 10 to 54% will not be satisfied with the treatment [2-6]. Currently, when conservative therapy does not provide sufficient relief, the physician has 3 options: to continue with conservative therapy; administer epidural steroid injections/selective nerve root blocks or intradiscal therapies; or perform surgery.

Surgery eliminates nerve impingement directly and often achieves immediate relief. However, this technique is invasive and has risk related to the operation such as muscle, ligament, bone and nerve root damage. Intradiscal therapies such as percutaneous nucleotomy, percutaneous laser disc decompression or intradiscal electrothermal annuloplasty are less invasive compared with surgery, but the patient has to be carefully selected because the hernia type to which this technique is applicable is strictly defined. Therefore, it is desirable to develop a novel treatment that is efficacious, safe and applicable to broad types of hernia.

Chemonucleolysis is a procedure that dissolves the matrix in the herniated disc by the intradiscal injection of an enzyme. The technique is very simple and less invasive than current surgery and is expected to contribute to shortened hospital stays. No drug for chemonucleolysis is currently available in the US. A novel and promising agent that can be used for chemonucleolysis is desired.

Proteoglycans are the main solid components of the nucleus pulposus. MMP-7 enzymatically cleaves aggrecan, the major proteoglycan of the disc [7-8]. MMP-7 is significantly expressed in surgical samples of human herniated discs and degrades *in vitro* and *in vivo* proteoglycans. MMP-7 is an endogenous protease that results in the natural resorption of a herniated disc [9-10]. From a theoretical standpoint, recombinant human MMP-7 should be ideal for the purpose of chemonucleolysis because of its lack of antigenicity in humans and its substrate selectivity toward proteoglycans.

Based on the scientific background above, Teijin and Kaketsuken intend to develop recombinant human MMP-7 as a novel therapeutic agent for lumbar disc herniation. Kaketsuken has established the manufacturing process for pharmaceutical grade recombinant human MMP-7 (KTP-001) [redacted] Teijin has completed extensive

nonclinical studies to support this first-in human (FIH) study in subjects with lumbar disc herniation.

3.2 Description of Investigational Product

KTP-001 is a recombinant human MMP-7 [redacted]
KTP-001 is supplied as a lyophilized powder, which is reconstituted using 0.5 mL of sterile water before injection.

3.3 Nonclinical Studies

Complete information for this compound may be found in the Investigator's Brochure (IB). Summaries of nonclinical drug development studies are presented below to support the rationale for the proposed study design and doses selected for clinical evaluation.

3.3.1 Primary Pharmacology

Because KTP-001 digests proteoglycan (including aggrecan), the proteoglycan content of the nucleus pulposus was selected as a marker in the nonclinical development program to evaluate the effects of KTP-001 on nonherniated lumbar discs in animals. [redacted]

The proteoglycan content of the nucleus pulposus was determined by the intensity of alcian blue staining; the breakdown of aggrecan in the nucleus pulposus by KTP-001 was assessed by measures of the serum concentrations of keratan sulfate, and a decrease of disc height was assessed using disc height index.

[redacted]

3.3.2 Safety Pharmacology

Safety pharmacology studies conducted [redacted]

[redacted]

3.3.3 Pharmacokinetics

The nonclinical development program for KTP-001 includes distribution, metabolism and excretion of study drug and its metabolite in the intervertebral discs and in the serum of animals.

[redacted]

3.3.4 Anti-KTP Antibody Production

Anti-KTP-001 antibody production [redacted] was determined [redacted]. [redacted] Consequently, the risk of KTP-001 immunogenicity is considered to be low at the administered doses.

3.3.5 Toxicology Studies

3.3.5.1 Single Dose Toxicity

In single dose toxicology studies conducted [redacted]

3.3.5.2 Repeated Dose Toxicity

In repeated dose toxicology studies conducted [redacted]

3.3.5.3 Developmental and Reproductive Toxicity

Single intravenous doses of KTP-001 at doses of up to [redacted] were given [redacted]

3.3.5.4 Intradiscal Single Dose Local Tolerance

Intradiscal single dose local tolerance studies [redacted] were performed.

[redacted]

[redacted]

3.3.5.5 Epidural Single Dose Local Tolerance

The epidural single dose studies [redacted] were performed [redacted]

3.3.5.6 Intrathecal Single Dose Local Tolerance

The intrathecal single dose study [redacted] was performed [redacted]

3.3.5.7 Subcutaneous and Intramuscular Single Dose Local Toxicity

[redacted]

3.4 Clinical Studies

The safety, tolerability, pharmacokinetics (PK), and exploratory efficacy of KTP-001 will be evaluated in an open-label, non-controlled, single ascending dose study in subjects with lumbar disc herniation. This study will be the FIH study.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Objectives

4.1.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of a single intradiscal injection of KTP-001 in subjects with a single herniated lumbar disc.

4.1.2 Secondary Objectives

The secondary objectives of this study are:

- To determine the PK of KTP-001 in the serum of circulating blood after intradiscal injection of study drug.
- To determine the presence of anti-KTP-001 antibody in the serum of circulating blood after intradiscal injection of study drug.

4.1.3 Exploratory Objectives

The exploratory objectives of this study are:

- To determine the pharmacodynamics (PD) of keratan sulfate in the serum of circulating blood after intradiscal injection of study drug.
- To assess changes in pain, neurologic examination, magnetic resonance imaging (MRI) and X-ray assessments, disability, quality of life (QOL), and patient global impression of change (PGI-C) scores in subjects receiving study drug.

5 STUDY DESIGN

5.1 Design Summary

Study KTP-001-CL-101 is an open-label, non-controlled single ascending dose study of KTP-001 in male and female subjects between the ages of 30 and 70 with a single herniated lumbar disc. After obtaining informed consent, subjects will be evaluated during a screening period of no more than 3 weeks (21 days). The following procedures will be performed at the screening visit: collection of subject baseline demographics, medical history (including the symptoms associated with herniated lumbar disc), prior medications, height, weight, a full physical and neurologic examination (including straight-leg raising and femoral stretch test), and collection of vital signs, 12-lead ECG, and clinical laboratory tests (hematology, serum chemistry, coagulation, urinalysis, and urine drug screen). A serum pregnancy test will be conducted for female subjects of childbearing potential. The following baseline exploratory efficacy measures will be assessed: lower back and leg pain using a numerical scale (using a subject diary for 5 consecutive days prior to treatment), spinal flexion/tension using straight-leg raising and femoral stretch test, MRI assessment, lumbar spine X-ray assessment, the severity of disability using the Oswestry Disability Index (ODI), QOL using the Short Form-12 (SF-12) questionnaire, and symptom severity as measured by the PGI-C scale. A pain assessment diary will be administered and collected between screening and treatment on Day 1.

Subjects that meet all screening requirements and inclusion criteria and none of the exclusion criteria will be enrolled into 1 of 4 study cohorts and receive KTP-001. Following administration of study drug, subjects will be confined to the study unit for 24 hours to collect data for safety and efficacy measures and collect blood samples for the following purposes: safety, PK evaluation, and exploratory PD (keratan sulfate), including anti-KTP-001 antibody.

Subjects enrolled in Cohort 1 will have pre-dose assessments of concomitant medications, weight, physical and neurologic examinations, and vital signs. Female subjects will have a urine pregnancy test, and all subjects in the cohort will have blood samples taken for PK and PD analyses. Efficacy assessments will be repeated. Subjects in this cohort will receive a 5 μg/disc dose of KTP-001 by intradiscal injection. Subjects will be observed for 24 hours after injection to facilitate post-procedural monitoring and collection of additional PK samples. Subjects will return to the clinic for visits at Weeks 1, 2, 4, 6, and 13, and at Months 6, 9, 12 (1 year), Month 18 (1.5 years), and Month 24 (2 years) for safety, and exploratory efficacy assessments (including X-ray and MRI at Week 13 and Months 6, 12, 18, and 24). Subjects will be provided a study diary to record their level of leg and lower back pain on a daily basis up to Week 13. Thirteen weeks after all subjects in Cohort 1 have received study drug, safety measures will be evaluated by a Data and Safety Monitoring Board (DSMB) to determine whether to escalate

KTP-001 administration to the next dose level. This evaluation will be conducted after the 13-week follow-up visit for all subjects in each dose cohort.

If escalation is appropriate as determined by the DSMB (see Section 5.1.2), then the Cohort 2 subjects will receive KTP-001 15 µg/disc, Cohort 3 subjects will receive 50 µg/disc of KTP-001, and Cohort 4 subjects will receive 150 µg/disc of KTP-001 by intradiscal injection (Figure 5.1). All safety, PK, and exploratory efficacy assessments will be performed for the subjects in the subsequent cohorts as were performed for Cohort 1.

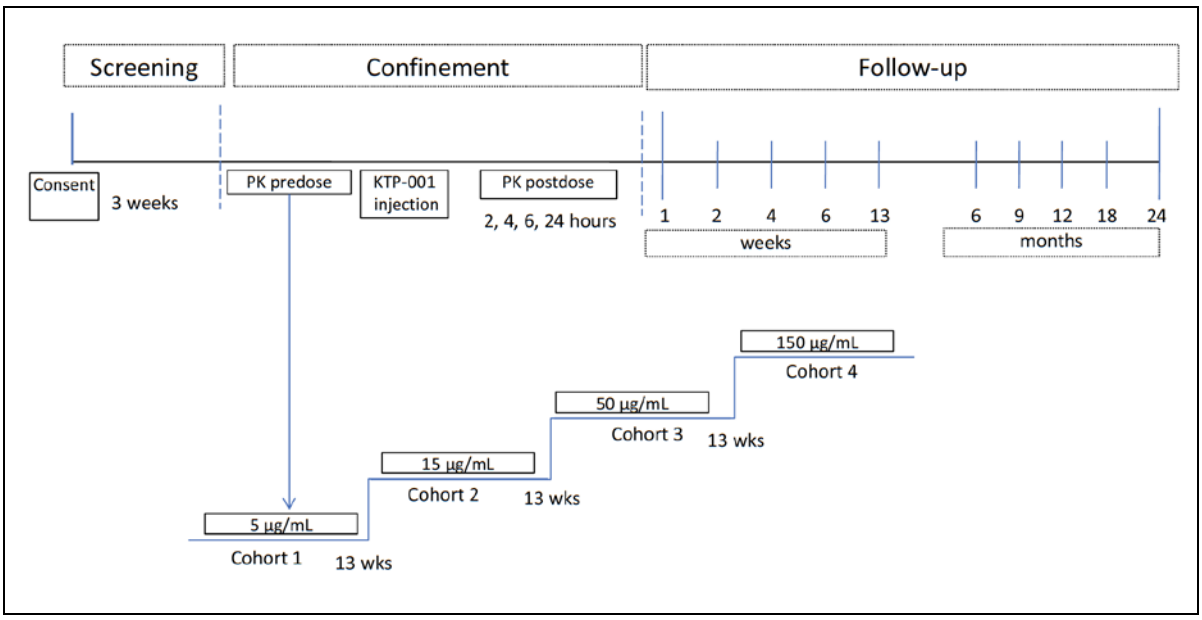

Figure 5.1 KTP-001-CL-101 Study Design

5.1.1 Treatments Administered

The proposed clinical dose concentrations for this FIH study are 5 µg/disc (Cohort 1), 15 µg/disc (Cohort 2), 50 µg/disc (Cohort 3), and 150 µg/disc (Cohort 4). Single doses of the proposed clinical dose concentrations will be administered intradiscally at the level of lumbar disc herniation by injection under fluoroscopic or computerized tomography (CT) visualization and guidance to 24 male and female human subjects between the ages of 30 and 70 with a single herniated lumbar disc as confirmed by MRI.

5.1.2 Dose Escalation

Escalation to a higher dose in a cohort will be permitted only if adequate safety and tolerability have been demonstrated at the previous lower dose level after review by the DSMB. The responsibilities of the DSMB are to monitor the safety and welfare of the study subjects by reviewing the data from the study at regular intervals and determining whether it is safe to continue the study according to the protocol. The DSMB will have the authority to recommend

stopping the study early or modifying the study design for safety concerns. Details regarding DSMB membership, dose escalation criteria, schedule and format of meetings, format for presentation of data, access to interim data, and other information relevant to the operations of the committee will be described in a separate DSMB charter. The DSMB will conduct a safety review at the 13-week follow-up visit for all subjects in each dose cohort.

5.1.3 Halting Rules

The AEs or imaging abnormalities described below will be defined in this study as a halting rule (HR). If a HR occurs in any subject during the dose escalation phase of the study, further recruitment and dosing of the current study cohort will be held until the event is assessed by the DSMB. The DSMB will make a recommendation regarding continuation of the study and/or escalation to the next dose cohort when one of the following events occurs:

- Neurologic deficit consistent with cauda equina syndrome or myelopathy
- Exacerbation of radicular symptoms associated with onset of a new motor deficit in one or both legs following administration of study drug
- Modic changes consistent with significant endplate edema or sclerosis compared to baseline, as determined by an expert spine radiologist
- Loss of height of the disc of > 30% relative to the baseline and defined as the average of anterior and posterior disc height evaluated by X-ray
- Evidence by X-ray of lumbar segmental instability at the treated segment defined as either:
    - Anterior translation of the posterior edge of the superior vertebral body relative to the posterior edge of the inferior vertebral body increase from baseline greater than 3mm is considered strong evidence of instability
    - Sagittal rotation change from extension to flexion of >5° (as measured by the Dupuis method)[11] is weak evidence of instability, and without observed translation as defined above, will require further evaluation before it would be considered a halting event

      NOTE: if the subject's condition does not permit the acquisition of flexion and extension films, instability will be evaluated solely on the basis of translation on the lateral view, as described above
- Destructive cartilage endplate changes as confirmed by MRI.

Once the last 13-week follow up period after the last dose cohort has occurred, any future instances of these events will be reported as AESI, but will not be treated as a HR. Further details on the role of the DSMB to evaluate study conduct will be provided in a separate DSMB charter.

5.1.4 Duration of Study

Subjects will be enrolled in this study for up to 24 months. After 24 hours of confinement, the subject will return to the clinic for visits at Weeks 1, 2, 4, 6, and 13, and at Months 6, 9, 12, 18, and 24 for safety and exploratory efficacy assessments.

5.2 Discussion of Study Design

Because intradiscal injection is too invasive to be performed on healthy volunteers, this study will be conducted with patients with documented herniated lumbar discs. Due to the chronic pain caused by herniated lumbar discs, concomitant medications to control pain are necessary for this subject population.

Calculations for the starting dose in this FIH study is based on nonclinical studies and described in Section 7.3. Based on these findings, the DSMB will review all relevant safety data after the Week 13 visit to guide subsequent dosage escalation, as appropriate. Further details on dose escalation criteria will be provided in a separate DSMB charter.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study. Subjects must fully meet the following inclusion criteria and none of the exclusion criteria in order to enroll in the study. In keeping with regulatory requirements, [redacted] does not grant protocol waivers to inclusion/exclusion criteria and does not contract to review or approve any protocol waivers. Any waiver granted by the Sponsor will be treated as a protocol deviation (Section 11.17).

6.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Has had a single unilateral contained or noncontained (extruded) lumbar disc herniation at the L3-L4 or L4-L5 or L5-S1 level diagnosed by clinical symptoms and/or physical findings and confirmed by MRI. Symptom duration should be at least 6 weeks prior to screening.
2. Has radicular symptoms with a documented positive straight-leg raising or femoral stretch test consistent with the level of the disc herniation.
3. Has had at least 6 weeks of conservative therapy prior to screening.
4. Has a daily average leg pain score of ≥ 4 (using an 11-point numerical scale) on at least 3 out of the 5 days immediately prior to treatment AND on all 5 days immediately prior to treatment the daily average leg pain score is ≥ 2.
5. Has completed the subject diary for at least 4 out of the 5 days immediately prior to treatment.
6. Has an ODI of $\geq 30\%$ at screening.
7. Is a male or female subject between 30 and 70 years of age, inclusive.
8. Has a body mass index of 18 to 35 kg/m^2.
9. Is medically healthy, other than lumbar disc herniation, with clinically insignificant screening results (including laboratory profiles, medical histories, electrocardiograms [ECGs], and physical examination) as deemed by the investigator.
10. Uses or agrees to use effective contraception methods or is a female of nonchildbearing potential (See Section 6.3).

11. Voluntarily provides written consent to participate in the study.

6.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the exclusion criteria, or will be discontinued at the discretion of the investigator if he/she develops any of the following exclusion criteria during the study:

1. Has a sequestered lumbar disc herniation or intrathecal herniation confirmed by MRI.
2. Has 2 or more symptomatic lumbar disc herniations as assessed by clinical symptoms and/or physical findings and confirmed by MRI.
3. Has had previous intradiscal therapeutic intervention at the level of the current symptomatic disc herniation or has had any lumbar surgery in the past. Previous therapeutic intradiscal injections (e.g., steroids) at the level of the current symptomatic disc herniation are not permitted within 6 weeks of screening.
4. Has undergone chemonucleolysis at any level of disc herniation or has had previous exposure to study drug.
5. Has had previous epidural injections, a selective nerve root block, or a facet block within 2 weeks before screening.
6. Has had any changes in the frequency of physical therapy or the introduction of new modalities of physical therapy, acupuncture, transcutaneous electrical nerve stimulation (TENS) or any other nonpharmacologic treatment modalities within 2 weeks prior to screening.
7. Has had any changes in dosing of pain medications or introduction of new pain medications/muscle relaxants within 1 week prior to screening.
8. Has had any changes in antidepressant treatment or “pain modulating” therapy, including gabapentin and pregabalin within 4 weeks before screening.

9. Has the presence of lumbar spine disease and/or deformity other than a lumbar disc herniation, including spondylolisthesis Grade 2 or above, clinically significant scoliosis, spinal stenosis including significant lateral recess stenosis not related to the lumbar disc herniation, vertebral compression fracture, ankylosing spondylitis, inflammatory bone or disc disease, primary or metastatic malignancy, or any other clinically significant spine disease.
10. Has symptoms of cauda equina syndrome or progressive neurologic deficit, especially motor weakness.
11. Has a concomitant neurologic disorder, such as polyneuropathy, myopathy or motor neuron disease, lumbosacral plexopathy, radiculitis, multiple sclerosis, myelopathy, spinal cord compression, prior poliomyelitis or stroke, or any other condition resulting in sensory-motor deficit in the lower extremities.
12. Has other concomitant painful condition such as fibromyalgia, rheumatoid arthritis, severe osteoarthritis of the hip and/or knee joints or other painful condition that may interfere with pain assessments in the study.
13. Has a history of and/or clinical evidence of peripheral vascular disease.
14. Has the presence of an apophyseal ring in the vertebral disc as confirmed by X-ray.
15. Is pregnant, breastfeeding, or has a positive serum pregnancy test at screening or a positive urine pregnancy test prior to receiving the study drug.
16. Has a history or presence of significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or psychiatric disease.
17. Has a history or presence of cancer within 5 years of screening, with the exception of localized basal cell skin cancer.
18. Has a history of heavy alcohol consumption (defined as more than 2 standard alcohol beverages per day for males or more than 1 standard alcohol beverage per day for a woman, or more than 5 standard alcohol beverages on one occasion more than 5 times in the last 30 days for either gender) or drug abuse within the past 2 years or has a positive urine drug screen prior to enrollment (except for prescription medications).

19. Is a current, active smoker or is unable to abstain from tobacco use for 2 weeks prior to study injection.
20. Has a history of multiple drug allergies (2 or more classes of drugs), food allergies or other life-threatening allergies deemed significant by the principal investigator.
21. Has used or is using systemic steroids within 2 weeks prior to screening (not including inhalation, ophthalmic, and topical steroids).
22. Is taking anticoagulants including (but not limited to) warfarin, heparin/low molecular weight heparins, thrombin inhibitors, factor Xa inhibitors; or has any condition/treatment associated with coagulopathy/bleeding tendency.
23. Is receiving workers' compensation or other disability benefits or has a pending disability claim or litigation related to a back condition/disc herniation.
24. Has participated in any clinical study within 30 days prior to screening.
25. Has a positive screen for hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), or anti-human immunodeficiency virus (HIV), or has any active, clinically significant infection.
26. Has an elevation of aspartate aminotransferase (AST) and/or alanine aminotransaminase (ALT) ≥ 2 X upper limit of normal (ULN), or a total bilirubin > ULN, or a creatinine ≥ 1.5 X ULN, or any other clinically significant laboratory abnormalities that, in the investigator's judgment, would preclude the subject from participation in the study.
27. Has any clinically significant ECG abnormalities at screening.
28. Has any contraindication to undergo an MRI or has declared inability to tolerate an MRI.
29. Has any condition that would, in the investigator's opinion, limit the subject's ability to complete the study.

6.3 Women of Nonchildbearing Potential and Acceptable Forms of Contraception

Women of nonchildbearing potential are defined as any female who is postmenopausal or posthysterectomy (medical documentation of hysterectomy must be available to the investigator). Postmenopause is defined as meeting 1 of the following conditions:

- Amenorrhea ≥ 12 consecutive months without another cause and ≥ 50 years of age

- Women younger than 50 years of age who have not menstruated for ≥ 12 consecutive months (or with irregular menstrual periods) AND have a documented serum follicle stimulating hormone level > 35 mIU/mL

Women who are of childbearing potential must be using 1 or more of the following contraceptive methods during the study:

- Oral or other hormonal contraceptives: vaginal products, skin patches, or implanted or injectable products
- Mechanical product such as an intrauterine device
- Double-barrier method: diaphragm or condoms with spermicides
- Practicing abstinence or who has a sterile (e.g., vasectomy) partner

6.4 Prior and Concomitant Therapy

All medications (prescription and over-the-counter, vitamin and mineral supplements, and herbs) and all therapies for disc herniation (including but not limited to physical therapy, acupuncture, epidural injections/selective nerve root block) taken or received by the participant within 1 month of screening and throughout study participation will be documented on the concomitant medication case report form (CRF) and will include: start and stop dates, dose and route of administration, and indication. Medications taken for a surgical procedure should also be included.

6.5 Restrictions on Concomitant Therapies or Procedures During the Study

6.5.1 Pain Management During First 13 Weeks Post-dose

Subjects will be allowed to continue their pre-study pain regimen. However, introduction of a new analgesic or dose escalation of an already used analgesic will be disallowed with the exception of temporary use to treat a documented adverse event (AE) if required and at discretion of the investigator, and only for the duration of the event. Beyond treatment for an AE, acetaminophen will be the only allowed as rescue medication in the study and use will be captured as a secondary outcome measure. The maximum total daily dose of acetaminophen (rescue plus any other combination analgesic containing acetaminophen) must not exceed 4 grams.

6.5.2 Pain Medications

A summary of allowed pain medication by study phase is provided in Appendix A. The following restrictions on pain medications are to be followed during the first 13 weeks post-dose and do not apply beyond the Week 13 visit.

1. Initiation of treatment or change in the dose regimen is disallowed for antidepressants, anticonvulsants, or any prescription or over the counter pain modulating drugs from screening to 13 weeks post-dose. If subjects are on a stable dose of any of the above medications for at least 4 weeks prior to screening, the same dose regimen should be continued through 13 weeks post-dose.
2. Initiation of treatment or dose escalation of muscle relaxants or sedatives/hypnotics is disallowed. A stable dose regimen if initiated at least 1 week prior to screening may be continued unchanged through 13 weeks post-dose. However, temporary use of a new muscle relaxant or sedative/hypnotic or dose increase of already used muscle relaxant or sedative/hypnotic will be allowed for treatment of a documented AE, for the duration of the event only. If clinically indicated, dose reduction or discontinuation of treatment is also permitted.
3. Epidural steroid injections/selective nerve root block/facet block are allowed if medically necessary within the first 13 weeks post-dose and beyond. However, the indication for the procedure (e.g., intractable lower back pain/worsening of lower back pain) must be documented as an AE (or SAE if it meets the SAE criteria defined in Section 9.9.7). Subjects who require a surgical intervention for treatment of disc herniation will be discontinued from the study.
4. Opioid and nonopioid analgesics (including topical analgesics) used for pain management on a stable dose at least 1 week prior to screening may be continued at the same or lower dose during the first 13 weeks post-dose. No dose escalation and no new opioid or nonopioid analgesics will be allowed except for acetaminophen. However, as described in Section 6.5.1, temporary use of a new analgesic or dose increase of an already administered analgesic will be allowed to treat a documented AE, for the duration of the event only. Daily doses of all analgesics including rescue doses of acetaminophen will be recorded by the subjects in the provided diaries.
5. Systemic steroids are disallowed during the first 13 weeks post-dose, except for temporary use to treat a documented AE, for the duration of event only. Topical, ophthalmic and inhalation steroids are allowed.
6. Subjects treated with a nonsteroidal anti-inflammatory drug (NSAID) should have their treatment discontinued at least 10 days prior to the study procedure. The NSAIDs may be restarted 24 hours post-dose. Use of an alternative analgesic during that period of time will be allowed at the discretion of investigator.
7. Therapeutic intradiscal interventions including intradiscal injections, other than the study injection are not permitted in the study.

6.5.3 Antiplatelet therapy

It is recommended that antiplatelet therapy be withheld prior to the study procedure for the duration of time consistent with the type of antiplatelet drug and local standard of care (on average 7 to 10 days). It may be restarted 24 hours after the procedure. A low dose aspirin (e.g., 81 mg) for cardiovascular protection may be continued at the discretion of the investigator.

6.5.4 Disallowed Treatments

Initiation of acupuncture, TENS, physical therapy modalities, biofeedback or psychotherapy are disallowed. Continuation of the same therapy modalities/frequency as received prior to screening is allowed (if prior therapy has been stable for at least 2 weeks prior to screening). Reduced frequency of treatments and discontinuation of prior therapy is allowed. The above restrictions do not apply beyond the Week 13 visit.

6.5.5 Tobacco and Alcohol Use

Subjects are prohibited from using any tobacco products from 2 weeks prior to the study injection through 2 weeks post-dose. Consumption of alcohol should be limited to that defined in the exclusion criteria.

6.6 Subject Withdrawal and Discontinuation

Subjects are free to discontinue the study at any time, for any reason, and without prejudice to further treatment. The investigator may remove a subject if, in the investigator's judgment, continued participation would pose unacceptable risk to the subject or to the integrity of the study data.

Subjects must discontinue from the study for any of the following reasons:

- The subject experiences an intercurrent illness that in the opinion of the investigator indicates continued participation in the study is not in the subject's best interest
- The subject is unable or unwilling to comply with the protocol
- The subject withdraws informed consent
- The subject is lost to follow-up
- The subject requires lumbar spine surgery
- A female subject tests positive for pregnancy

All procedures for early termination must be completed (Section 11.13). Subjects who are withdrawn prior to administration of study drug will be replaced to ensure a total of 6 evaluable subjects in each study cohort.

6.7 Early Termination of Study

The study may be terminated at any time by the Sponsor if serious side effects occur, if the investigator does not adhere to the protocol, or if, in the Sponsor's judgment, there are no further benefits to be achieved from the study. In addition, the study may be terminated at any time at the Sponsor's discretion. In the event that the clinical development of the study drug is discontinued, Teijin America, Inc. shall inform all investigators/institutions and regulatory authorities.

7 STUDY DRUG

7.1 Description of Investigational Product

The active ingredient of KTP-001 is recombinant human MMP-7 [redacted] KTP-001 is a lyophilized powder for reconstitution provided in a sterile glass vial. Each vial contains 1.0 mg of KTP-001 drug substance in a 2 mL USP Type 1 glass vial to be reconstituted with 0.5 mL of sterile water for injection. Further details regarding the study drug are provided in the IB, and details on drug preparation for intradiscal injection will be provided in the Pharmacy Manual.

7.2 Treatments

The study procedure should be performed under sterile conditions in an ambulatory surgical center, or special-procedure ambulatory radiology suite, or an operating room. The staff of treatment facility must be appropriately trained and prepared to respond to medical emergencies including the remote possibility of systemic allergic reaction.

A single intradiscal injection of 5, 15, 50, or 150 µg/disc of KTP-001 will be administered intradiscally using a two-needle technique under fluoroscopic or CT visualization and guidance. The procedure will be performed under local anesthesia as per investigator's standard of care. Light sedation will be allowed as per local standard of care. However, the subject must remain awake and able to cooperate during the procedure. The injection volume per subject will be 1.0 mL. Use of an imaging dye is not permitted for the intradiscal injection. A prophylactic antibiotic may be used as per local standard of care.

The intradiscal injection procedure is detailed in Appendix B.

7.2.1 Local Anesthetic and Chemonucleolysis Procedures

Details on local anesthetic and chemonucleolysis procedures will be provided in the Study Manual.

7.3 Dose Rationale

The disc volume where KTP-001 will be injected is a closed space as demonstrated in numerous animal studies, and therefore, the volume of the nucleus pulposus in animals and humans was used to calculate dose levels. [redacted]

[redacted]

7.4 Method of Assigning Subjects to Treatment Groups

Approximately 48 subjects will be screened to ensure that 24 subjects are enrolled into this study. After the first cohort of 6 subjects, the remaining subjects will be enrolled into the 3 subsequent cohorts and receive the KTP-001 dose as assigned for that cohort. Subjects who discontinue from the study after enrollment but prior to receiving study drug will be replaced to ensure that at least 6 subjects are treated in each of the 4 cohorts.

7.5 Measurements of Treatment Compliance

Subjects will receive a single dose of study drug by intradiscal injection. The injection will be performed under fluoroscopic or CT guidance and documented by X-ray or CT scan, as well as in the CRF by the investigator. No other measures of treatment compliance will be used.

7.6 Investigational Product Storage and Accountability

7.6.1 Storage Conditions

The investigator will ensure that all drug supplies are kept in a secure, temperature controlled, locked area with access limited to those authorized by the investigator.

A minimum/maximum daily temperature log must be maintained.

All study drugs will be stored at 2 to 8 °C (35 to 46 °F). Any temperature excursion outside the storage temperature must be notified to [redacted] immediately.

7.6.2 Drug Accountability

The investigator must ensure that all drug supplies are kept in a secure locked area with access limited to those authorized by the investigator. The investigator must maintain accurate records of the receipt of all study drug shipped by Sponsor or their designee, including but not limited to the date received, lot number, expiration date, amount received, and the disposition date and place of all study materials. Current dispensing records will also be maintained including the date and amount of study drug dispensed and the subject receiving the drug. All unused study drug not required by regulations to be held by the clinical facility must be returned to Sponsor or their representative immediately after the study is completed. Unused needles, syringe, etc. should be disposed of per the pharmacy manual or site procedure.

7.7 Packaging and Labeling

KTP-001 is a white powder provided in a sterile 2 mL USP Type 1 glass vial. After reconstitution in 0.5 mL of sterile water for injection, it appears as a clear and colorless solution.

KTP-001 product labels will comply with FDA regulations for investigational products.

7.8 Preparation of Investigational Product

KTP-001 will be provided to the study sites as lyophilized powder in 2 mL glass vials. Each vial contains 1.0 mg of KTP-001 drug substance, which is to be reconstituted with 0.5 mL of sterile water for injection. Each vial is to be reconstituted with 0.5 mL of sterile water for injection.

Further details regarding preparation of the study drug will be provided in the Pharmacy Manual.

8 EFFICACY ASSESSMENTS

The following efficacy measures are all exploratory in nature and all analyses will be presented using descriptive statistics. For all measures, the baseline value is defined as the last assessment result collected prior to the first dose of study medication. Unless otherwise noted, the endpoint for all efficacy measures will be changes from baseline at 6 and 13 weeks post-dose.

8.1 Lower Back or Leg Pain

Lower back and leg pain will be assessed using an 11-point numerical rating scale in response to the questions provided in Appendix C at screening, for 5 consecutive days prior to Day 1, pre-dose, at 2, 4, 6, and 24 hours post-dose, and then daily until the Week 13 visit. A numerical rating scale is considered to be a valid and reliable means of measuring pain in subjects with chronic pain conditions [14].

8.2 Use of Rescue Medication or Surgical Intervention

The number of subjects and amount of rescue medication will be recorded and summarized when any of the following occurs: extra pain medication is administered that is in addition to the baseline pain regimen defined at screening prior to treatment, an epidural injection or a selective nerve root block within 13 weeks after receiving study drug, or surgical intervention for lumber disc herniation.

8.3 Spinal Flexion and Tension

Spinal flexion and tension will be measured using the straight-leg raising or femoral stretch test at baseline, on Day 1 pre-dose, at 24 hours post-dose, and at all post-dose visits. Details on administering the straight-leg or femoral stretch test are provided in Appendix D.

8.4 Functional Ability

The degree to which lower back or leg pain interferes with the subject's ability to manage everyday tasks will be measured using the ODI (version 2.1A) and is provided in Appendix E.

The ODI is a patient self-scored questionnaire in use since 1980. The ODI is a validated tool to measure how functional level is restricted by disability, and can also be used to determine improvement in functional levels as a result of treatment. The improvement or lack of improvement in functional level is determined as a change from baseline in the score.

The ODI measures 10 areas of daily function: pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and travelling. The items are scored from 0 to 5, with 0 being the best functional level and 5 being the worst functional level. A percentage is then derived from these responses (patient score/total possible score x 100 = %) and recorded as that day's ODI. Scores are then grouped into levels of disability:

0% - 20% = minimal disability

20% - 40% = moderate disability

40% - 60% = severe disability

60% - 80% = crippled

80% - 100% = bed bound

The ODI will be administered at baseline, on Day 1 pre-dose, at 24 hours post-dose, and at all post-dose visits.

8.5 Quality of Life

Quality of life will be evaluated using the SF-12 form (version 2.0). The SF-12 asks 12 questions to measure functional health and well-being from the subject's point of view across 8 health domains. Subjects provide a response to each question using a 5-point Likert scale and the resulting score provides a measurement of the subject's health compared with the general population or compared with prior scores. The SF-12 is provided in Appendix F.

The SF-12 will be administered at baseline, on Day 1 pre-dose, at 24 hours post-dose, and at all post-dose visits. The endpoint for QOL will be changes from baseline at 6 and 13 weeks post-dose.

8.6 Global Impression of Change or Improvement

Global impression of improvement as measured by the PGI-C (Appendix G) is a single question survey that will be administered at baseline, on Day 1 pre-dose, at 24 hours post-dose, and at all post-dose visits. The endpoint for global impression of change or improvement will be changes from baseline at 6 and 13 weeks post-dose.

8.7 Appropriateness of Efficacy Measures

The efficacy measures for this study are exploratory in nature and were chosen based on prior experience with the patient population.

8.8 Magnetic Resonance Imaging Assessment

Magnetic resonance evaluation on the modification/shrinkage of the treated herniated disc size, the improvement of the stenosis of spinal canal, and the reduction of associated lateral neural foramen compression will be performed at Week 13, and at Months 6, 12, 18, and 24 (or early termination). The correlation between imaging findings and symptoms (e.g., pain score or ODI score) will be conducted after database lock as part of the report analysis. The herniated disc size will be assessed quantitatively while the compression of lateral neural formation and spinal canal stenosis will be evaluated qualitatively by an independent radiological reviewer.

9 SAFETY ASSESSMENTS

Unless otherwise noted, the endpoint for all safety assessments is changes from baseline.

9.1 Vital Signs

Vital signs (heart rate, systolic and diastolic blood pressures, respiratory rate, and body temperature) will be measured at screening, pre-dose and post-dose at specified times on Day 1, at each follow-up visit during the study, and at the end of study visit or upon discontinuation from the study as specified in the Schedule of Assessments (Section 11).

9.2 Clinical Laboratory Tests

Samples will be obtained for the clinical laboratory tests at defined in Appendix H outlined in the Schedule of Assessments (Section 11) at screening, at specified times during the study.

A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

For any laboratory test value outside the reference range that the investigator considers clinically significant, the investigator will:

- Repeat the test to verify the out-of-range value.
- Follow the out-of-range value to a satisfactory clinical resolution.
- Record as an AE any laboratory test value that (1) is confirmed and the investigator considers clinically significant; or (2) that requires a subject to be discontinued from the study; or (3) that requires a subject to receive treatment.

9.3 Electrocardiograms

A standard 12-lead ECG will be obtained at screening, and at 24 hours and 13 weeks post-dose.

Additional ECGs may be obtained if clinically indicated. Follow-up ECGs will be obtained if any significant abnormalities are detected after dose administration to document resolution and as clinically indicated. Any additional relevant data obtained by the investigator during the course of this study will be supplied to the Sponsor.

9.4 Physical Examination

A complete physical examination, including height and weight, will be performed at screening. Physical examinations and weight assessments will be performed during the visits specified in Schedule of Assessments (Section 11). Any findings or absence of findings relative to each subject's physical examination will be carefully documented in the subject's CRF.

9.5 Anti-KTP-001 Antibodies

Blood samples for measures of serum anti-KTP-001 antibody will be drawn pre-dose (just prior to administration of study drug) and at the 1-, 2-, 4- , 6-, and 13-week visits post-dose or early termination visit. The DSMB must be notified if antibodies are detected and the DSMB will advise on how to proceed. The investigators and relevant Institutional Review Board (IRB) will be notified about the DSMB decision.

9.6 Magnetic Resonance and X-ray Imaging Acquisition and Evaluation

Imaging examination, including lumbar spine MRI and X-ray, will be acquired as outlined in the Schedule of Assessments (Section 11) at screening, Week 13 (±5 days), Month 6 (±1 week), Month 12 (±2 weeks), Month 18 (±4 weeks), and Month 24 (±4 weeks), or upon subject discontinuation. For subjects with contraindication for MR during the study, the alternative imaging modality is a lumbar spine CT.

The MRI lumbar spine protocol includes sagittal fast (or turbo) spin echo T2-weighted, sagittal spin echo T1-weighted, sagittal STIR (Short Tau Inversion Recovery) images, axial fast spin echo T2-weighted with and without fat suppression, and axial spin echo T1-weighted images [15]. Axial diffusion-weighted images, axial and/or coronal Short Tau Inversion Recovery images are optional and upon the discretion of on-site radiologists. Unenhanced lumbar MR imaging is generally adequate for the imaging examination, unless contrast enhancement is specifically requested by the investigator or radiologist (e.g., for suspected infection). If gadolinium is administered, both sagittal and axial contrast-enhanced T1-weighted images with fat saturation will be required. If a hematoma is suspected at a post-procedure examination, an axial T2*-weighted image should be added.

Both sagittal and axial images should include the area of clinical interest. Axial images should be obtained through the relevant lumbar disc and adjacent spine treated by chemonucleolytic procedure (e.g., L3-4, or L4-5 or L5-S1). Axial slice orientation should be set up in parallel with the treated disc and be consistent through each time point. Additional axial images may be placed at the level/location in which occurrence of adverse effect is suspected. Slice thickness of equal or less than 5.0 mm is required for sagittal images with a gap less than 1.0 mm, while slice thickness of equal or less than 3.0 mm for axial images without gap.

9.6.1 Lumbar (or lumbosacral) Spine X-ray Examination Requirements

An anterior-posterior (AP) position and lateral neutral position views of the lumbar spine are required. The flexion-extension views are optional when the patients have radicular symptom with the restriction of flexion.

9.6.2 Safety Evaluation of MRI and X-ray

Evaluation of both X-rays and MRI images will be performed by an independent radiological reviewer who shall be a spine imaging specialist. The X-ray safety evaluation will include assessment of disc height and segmental instability as defined in the halting rules in Section 5.1.3.

The MR safety evaluation will focus on assessment of Modic changes at Week 13 according to the halting rules (HRs) described in Section 5.1.3. The reviewer will also assess for evidence of hematoma/hemorrhage, infection, discitis, and any other complications that may contribute to AE reporting. Qualitative information will also be collected by the independent radiological reviewer on the size of the herniated disc, the degree of spinal canal stenosis, and compression of the nerve root in the lateral neural foramen.

Additional evaluations will be performed at Months 6, 12, 18, and 24. Lumbar spinal MR examination may be ordered upon discretion of the investigator if there is an emergency indication to conduct an examination.

9.7 Neurologic Examination

A neurological examination will be performed on at screening, on Day 1 at pre-dose, 2 hours post-dose, 24 hours post-dose, and at all consecutive visits. The neurological examination will include sensory and motor examination of both lower extremities, Babinski's sign (Appendix I), deep tendon reflexes, and the straight-leg raising test and femoral stretch test (Appendix D). The results of the neurological examination will be summarized by the investigator as unchanged, improved, or worsened, and documented in the CRF. Changes from baseline on this evaluation will be considered the neurologic safety endpoint.

9.8 Halting Rules

The number of subjects with AEs defined as HRs will be described and evaluated.

9.9 Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product during the course of a clinical investigation. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not thought to be related to the study drug. Adverse events of special interest (AESI) are defined in Section 9.9.3.

Subjects will be monitored throughout the study for AEs, from the ICF signing until the last study visit unless the AE is considered related to the study drug/procedure, in which case the AE will be followed until resolution. Action taken will be categorized as none, study drug not given (for events occurring prior to study drug dosing), required concomitant medication, required procedure, or other. Event outcome at resolution or time of last follow-up will be recorded as event resolved, resolved with sequelae, ongoing, or death. Adverse events that are identified at

the last assessment visit (or the early termination visit) as specified in the protocol must be recorded on the AE CRF with the status of the AE noted, and the AE must be followed until resolution. All events that are ongoing at this time will be recorded as ongoing on the CRF. The procedures specified in Section 9.9.8 are to be followed for reporting SAEs.

9.9.1 Assessing Severity

The severity of an AE will be graded according to the following definitions:

- Mild: The subject experiences awareness of symptoms but these are easily tolerated or managed without specific treatment
- Moderate: The subject experiences discomfort enough to cause interference with usual activity, and/or the condition requires specific treatment
- Severe: The subject is incapacitated with inability to work or do usual activity, and/or the event requires significant treatment measures.

Note: it is important to distinguish between a severe AE and an SAE. Severity is a measure of intensity, whereas seriousness is classified by the criteria based on regulatory definitions as described in Section 9.9.7. An AE of severe intensity need not necessarily be classified as serious (e.g., a severe incapacitating migraine headache).

9.9.2 Assessing Causality

The relationship of the event to the study drug should be determined by the investigator according to the following criteria:

- Not related: The event is most likely produced by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs, and does not follow a known response pattern to the study drug, or the temporal relationship of the event to administration of study drug makes a causal relationship unlikely
- Possibly related: The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study drug, but could have been produced by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs
- Probably related: The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study drug, and cannot be reasonably explained by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs.

9.9.3 Adverse Events of Special Interest

The following AEs will be considered an AESI that must be reported to [redacted] within 24 hours of the investigative site becoming aware of the event.

1. MRI or X-ray findings of Modic changes, reduction of disc height, or evidence of lumbar instability as defined in Section 5.1.3, or any other acute MRI or X-ray changes from baseline images deemed significant by the central reader/spine imaging specialist.
2. Exacerbation of back or leg pain meeting at least 1 of the following criteria:
   a) increase in average daily leg or back pain score by ≥ 3 to 6 or above on the numerical rating scale for at least 5 days out of a week
   b) increase in average daily pain level associated with a new onset of focal neurological symptoms such as numbness and/or tingling or weakness lasting for > 5 days.
3. New onset of neurological symptoms associated with objective changes on neurological examination (weakness, sensory deficit, changes in deep tendon reflexes) whether or not associated with increase in pain level.
4. Any deterioration of subject's condition that in the investigator's judgment requires:
   a) emergency MRI
   b) epidural steroid injection/selective nerve root block, facet block, or surgical intervention.

Any AESI meeting seriousness criteria for SAE reporting must be reported as an SAE as defined in Section 9.9.8.

9.9.4 Following Adverse Events

All (both serious and nonserious) AEs must be followed until they are resolved or stabilized, or until all attempts to determine resolution of the event are exhausted. The investigator should use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events.

9.9.5 Discontinuation due to Adverse Events

Any subject who experiences an AE may be withdrawn at any time from the study at the discretion of the investigator. Subjects withdrawn from the study due to an AE, whether serious or nonserious, must be followed by the investigator until the clinical outcome of the AE is determined. The AE(s) should be noted on the appropriate CRFs and the subject's progress should be followed until the AE is resolved. The medical monitor must be notified.

9.9.6 Pregnancy

Subjects must be instructed to inform the study investigator immediately if they or their female partner become pregnant during the study.

The investigator must report any pregnancy to the medical monitor within 1 business day of becoming aware of it and to the [redacted] SAE hotline per procedure. The pregnant female subject must be discontinued from the study. An uncomplicated pregnancy will not be considered an AE or SAE, but it will be documented on an AE CRF page. All pregnancies will be followed through birth.

Pregnancies are captured if they occur in female subjects from the time of first signed consent for study participation until last visit. Female subjects with a positive pregnancy test at screening or pre-dose time point will be considered a screen failure.

Any congenital abnormalities in the offspring of a subject who received study drug will be reported as an SAE. Any complications of pregnancy or elective termination due to a medical reason will be reported as an AE and follow as such. A spontaneous abortion is considered an SAE. The outcome of any pregnancy and the presence or absence of any congenital abnormality will be recorded in the source documentation and reported to the medical monitor and Sponsor.

9.9.7 Serious Adverse Events

The investigator is responsible for determining whether an AE meets the definition of an SAE. An SAE is any AE occurring from ICF signing through final study visit, at any dose, that results in any of the following outcomes:

- Death
- A life-threatening event, defined as an event in which the subject was at risk of death at the time of the event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect in a child or fetus of a subject exposed to the study drug
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Note: SAEs require immediate reporting to the medical monitor. See Section 9.9.8 for details.

9.9.8 Reporting Serious Adverse Events

In the event of any SAE reported or observed during the study, whether or not attributable to the study drug, site personnel will report it immediately by telephone the SAE hotline at [redacted] per the SAE study-specific procedure. Site personnel will follow up with a written report within 24 hours as indicated below.

[redacted] SAE hotline telephone: [redacted]

This telephone report must be followed within 24 hours by a FAX transmission of a completed SAE Report Form to the number indicated below:

Fax: [redacted]

Serious AE Report Forms will be provided to the investigational site to assist in collecting, organizing, and reporting SAEs and follow-up information.

All SAEs should be followed to their resolution, with documentation provided to [redacted] on a follow-up SAE Report Form.

9.10 Appropriateness of Safety Assessments

Safety evaluations selected for this study are typical of those for this subject population and utilize widely accepted measures.

The measures of safety to be used in this study are routine clinical and laboratory procedures.

10 PHARMACOKINETIC ASSESSMENTS

10.1 Drug Concentration Measurements

Serum concentrations of KTP-001 will be determined [redacted]

10.2 Pharmacokinetic Parameters

Pharmacokinetic variables will be calculated from the serum concentration data using noncompartmental methods (WinNonlin® Professional Network Edition, version 5.2 or higher, Pharsight Corp, Palo Alto, CA) and actual sampling times.

The following PK parameters will be determined:

C_{max} Maximum observed serum concentration

t_{max} The time that C_{max} was observed

AUC_t Area under the concentration-time curve from time zero to time (t)

10.3 Pharmacodynamic Parameters (Exploratory)

Blood samples for serum concentrations of keratan sulfate will be determined [redacted]

The following exploratory PD endpoint will be analyzed and presented using descriptive statistics (n, mean, median, minimum, maximum, SD, percentage of analysis population, and CI):

- Change from baseline in serum concentrations of keratan sulfate at every time point.

11 METHODOLOGY/STUDY VISITS

11.1 Screening Procedures (Day -21 to Day 1)

The investigator will inform each prospective subject of the nature of the study, explain the potential risks, and obtain written informed consent from the subject prior to performing any study-related procedures and prior to the administration of study drug or check-in to the clinical site.

Screening evaluations will consist of the following:

- Assessment of eligibility
- Collect subject demographic information
- Review medical and surgical history
- Review concomitant and prior medications
- MRI and X-ray
- Physical examination including measurement of height and weight without shoes
- Neurologic examination
- Vital signs (including blood pressure [BP], pulse, respiratory rate, and temperature)
- 12-lead ECG
- Urine drug screen
- Clinical laboratory tests including hematology, coagulation, serum chemistry, and urinalysis
- Serum pregnancy test for women of childbearing potential (result must be negative to continue to be eligible)
- Serology (HBsAg, anti-HCV, and anti-HIV)
- Assess current lower back and leg pain using the 11-point numerical rating scale
- Assess Spinal Flexion/Tension (Straight-leg Raising/Femoral Stretch Test)
- Dispense Study Diary
- ODI, SF-12, PGI-C

Subjects will be instructed not to take any medications without the approval of the investigator. The results of the screening evaluation must meet the inclusion/exclusion criteria for the subject to continue in the study.

11.2 Visit 1 (Day 1)

11.2.1 Pre-dose

- Admit to study unit. The subject will be hospitalized for 24 hours after intradiscal injection of the study drug and will be discharged once all procedures are completed and the investigator determines the subject is safe to be discharged.
- Review concomitant and prior medications
- Physical examination including measurement of weight without shoes
- Neurologic examination
- Vital signs (including BP, pulse, respiratory rate, and temperature)
- Urine pregnancy test for women of childbearing potential (result must be negative to continue to be eligible)
- Collect and review Study Diary
- Dispense Study Diary
- Review AEs
- Assess current lower back and leg pain using the 11-point numerical rating scale
- Assess Spinal Flexion/Tension (Straight-leg Raising/Femoral Stretch Test)
- Assess ODI, SF-12, and PGI-C
- Administer study drug
- Draw blood samples for measurement of anti-KTP-001 antibody
- Draw blood samples for measurement of KTP-001
- Draw blood samples for measurement of serum keratan sulfate

11.2.2 At 2 hours post-dose (±15 minutes)

- Physical examination
- Neurologic examination
- Vital signs (including BP, pulse, respiratory rate, and temperature)
- Draw blood samples for measurement of KTP-001
- Assess current lower back and leg pain using the 11-point numerical rating scale
- Review AEs

11.2.3 At 4 hours post-dose (±15 minutes)

- Vital signs (including BP, pulse, respiratory rate, and temperature)
- Draw blood samples for measurement of KTP-001
- Assess current lower back and leg pain using the 11-point numerical rating scale
- Review AEs

11.2.4 At 6 hours post-dose (±15 minutes)

- Vital signs (including BP, pulse, respiratory rate, and temperature)
- Draw blood samples for measurement of KTP-001
- Draw blood samples for measurement of serum keratan sulfate
- Assess current lower back and leg pain using the 11-point numerical rating scale
- Review AEs

11.2.5 At 24 hours post-dose (±1 hour)

- Physical examination including measurement of weight without shoes
- Neurologic examination
- Vital signs (including BP, pulse, respiratory rate, and temperature)
- 12-lead ECG
- Clinical laboratory tests including hematology, coagulation, serum chemistry, and urinalysis
- Draw blood samples for measurement of KTP-001
- Draw blood samples for measurement of serum keratan sulfate
- Assess current lower back and leg pain using the 11-point numerical rating scale
- Assess Spinal Flexion/Tension (Straight-leg Raising/Femoral Stretch Test)
- Assess ODI, SF-12, and PGI-C
- Collect and review Study Diary
- Dispense Study Diary
- Review AEs

11.3 Visit 2 (1 Week ±2 days)

- Review concomitant and prior medications
- Physical examination including measurement of weight without shoes
- Neurologic examination
- Vital signs (including BP, pulse, respiratory rate, and temperature)
- Clinical laboratory tests including hematology, coagulation, serum chemistry, and urinalysis
- Draw blood samples for measurement of anti-KTP-001 antibody
- Draw blood samples for measurement of KTP-001
- Draw blood samples for measurement of serum keratan sulfate
- Assess current lower back and leg pain using the 11-point numerical rating scale
- Assess Spinal Flexion/Tension (Straight-leg Raising/Femoral Stretch Test)
- Assess ODI, SF-12, and PGI-C
- Collect and review Study Diary
- Dispense Study Diary
- Review AEs

11.4 Visit 3 (2 Weeks ±2 days)

- Review concomitant and prior medications
- Physical examination including measurement of weight without shoes
- Neurologic examination
- Vital signs (including BP, pulse, respiratory rate, and temperature)
- Clinical laboratory tests including hematology, coagulation, serum chemistry, and urinalysis
- Draw blood samples for measurement of anti-KTP-001 antibody
- Draw blood samples for measurement of KTP-001
- Draw blood samples for measurement of serum keratan sulfate
- Assess current lower back and leg pain using the 11-point numerical rating scale
- Assess Spinal Flexion/Tension (Straight-leg Raising/Femoral Stretch Test)
- Assess ODI, SF-12, and PGI-C
- Collect and review Study Diary

- Dispense Study Diary
- Review AEs

11.5 Visit 4 (4 Weeks ±2 days)

- Review concomitant and prior medications
- Physical examination including measurement of weight without shoes
- Neurologic examination
- Vital signs (including BP, pulse, respiratory rate, and temperature)
- Draw blood samples for measurement of anti-KTP-001 antibody
- Draw blood samples for measurement of KTP-001
- Draw blood samples for measurement of serum keratan sulfate
- Assess current lower back and leg pain using the 11-point numerical rating scale
- Assess Spinal Flexion/Tension (Straight-leg Raising/Femoral Stretch Test)
- Assess ODI, SF-12, and PGI-C
- Collect and review Study Diary
- Dispense Study Diary
- Review AEs

11.6 Visit 5 (6 Weeks ±5 days)

- Review concomitant and prior medications
- Physical examination including measurement of weight without shoes
- Neurologic examination
- Vital signs (including BP, pulse, respiratory rate, and temperature)
- Draw blood samples for measurement of anti-KTP-001 antibody
- Draw blood samples for measurement of KTP-001
- Draw blood samples for measurement of serum keratan sulfate
- Assess current lower back and leg pain using the 11-point numerical rating scale
- Assess Spinal Flexion/Tension (Straight-leg Raising/Femoral Stretch Test)
- Assess ODI, SF-12, and PGI-C
- Collect and review Study Diary

- Dispense Study Diary
- Assess adverse events

11.7 Visit 6 (13 Weeks ±5 days)

- Review concomitant and prior medications
- MRI and X-ray
- Physical examination including measurement of weight without shoes
- Neurologic examination
- Vital signs (including BP, pulse, respiratory rate, and temperature)
- 12-lead ECG
- Serum pregnancy test for women of childbearing potential (result must be negative to continue to be eligible)
- Clinical laboratory tests including hematology, coagulation, serum chemistry, and urinalysis
- Draw blood samples for measurement of anti-KTP-001 antibody
- Draw blood samples for measurement of KTP-001
- Draw blood samples for measurement of serum keratan sulfate
- Assess current lower back and leg pain using the 11-point numerical rating scale
- Assess Spinal Flexion/Tension (Straight-leg Raising/Femoral Stretch Test)
- Assess ODI, SF-12, and PGI-C
- Collect and review Study Diary
- Review AEs

11.8 Visit 7 (6 Months/26 Weeks ±1 week)

- Review concomitant and prior medications
- MRI and X-ray
- Physical examination including measurement of weight without shoes
- Neurologic examination
- Vital signs (including BP, pulse, respiratory rate, and temperature)
- Assess current lower back and leg pain using the 11-point numerical rating scale
- Assess Spinal Flexion/Tension (Straight-leg Raising/Femoral Stretch Test)

- Assess ODI, SF-12, and PGI-C
- Review AEs

11.9 Visit 8 (9 Months/39 Weeks ± 1 week)

- Review concomitant and prior medications
- Physical examination including measurement of weight without shoes
- Neurologic examination
- Vital signs (including BP, pulse, respiratory rate, and temperature)
- Assess current lower back and leg pain using the 11-point numerical rating scale
- Assess Spinal Flexion/Tension (Straight-leg Raising/Femoral Stretch Test)
- Assess ODI, SF-12, and PGI-C
- Review AEs

11.10 Visits 9 (12 Months/52 Weeks ±2 weeks)

- Review concomitant and prior medications
- MRI and X-ray
- Physical examination including measurement of weight without shoes
- Neurologic examination
- Vital signs (including BP, pulse, respiratory rate, and temperature)
- Assess current lower back and leg pain using the 11-point numerical rating scale
- Assess Spinal Flexion/Tension (Straight-leg Raising/Femoral Stretch Test)
- Assess ODI, SF-12, and PGI-C
- Review AEs

11.11 Visit 10 (18 months/78 Weeks ±4 weeks)

- Review concomitant and prior medications
- MRI and X-ray
- Physical examination including measurement of weight without shoes
- Neurologic examination
- Vital signs (including BP, pulse, respiratory rate, and temperature)
- Review AEs

11.12 End of Study Visit (24 Months/104 Weeks ±4 weeks)

- Review concomitant and prior medications
- MRI and X-ray
- Physical examination including measurement of weight without shoes
- Neurologic examination
- Vital signs (including BP, pulse, respiratory rate, and temperature)
- Review AEs

11.13 Early Termination Before Week 13

Same procedures as those outlined for Visit 6 (Week 13) in Section 11.7.

11.14 Early Termination Between Week 13 and Month 24/Week 104

Same procedures as those outlined for the End of Study visit in Section 11.12.

11.15 Withdrawal Procedures

In the event of a subject's withdrawal, the investigator will promptly notify the medical monitor and will make every effort to complete the end-of-study assessments. All withdrawn subjects will be followed until resolution of any AEs or until the unresolved AEs are judged by the investigator to have stabilized.

11.16 Total Blood Volume Required for Study

Test	Number of Samples	Volume (mL)	Total (mL)
Hematology	5	3	15
Hepatitis/HIV	1	4	4
Coagulation panel	5	2.7	13.5
Serum chemistry [1]	5	4	20
PK of KTP-001	10	1.0	10
Anti-KTP-001 antibodies	6	2.0	12
Serum keratan sulfate	8	1.0	8
	Total volume for study		**82.5**

1. The 4 mL at screening and Week 13 will include testing for serum βHCG for female subjects.

A total of 15 mL will be collected from each subject for hematology assessments, 20 mL for serum chemistry assessments, 10 mL for PK analysis of KTP-001, 10 mL for analysis of anti-KTP-001 antibodies, and 8 mL for analysis of serum keratan sulfate levels. The total blood volume to be collected per subject for the entire study will be 82.5 mL.

11.17 Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or inaction of the subject, investigator, or site staff. Examples of deviations include, but are not limited to:

- Failure to adhere to study exclusion and inclusion criteria
- Failure to comply with dispensing or dosing requirements
- Use of medications, food, drink, herbal remedies, or supplements that are specifically prohibited in the protocol
- Missed or out-of-window visits
- Drug dosing not administered within the time frame specified in the protocol
- Failure to adhere to test requirements, including vital signs, laboratory tests, physical examinations, PK blood draws, medical history, etc either tests not done, incorrect tests done, or not done within the time frame specified in the protocol

- Procedural deviations such as incorrect storage of study drug, failure to update the ICF when new risks become known, failure to obtain IRB approvals for the protocol and ICF revisions

At the outset of the study, a process for defining and handling protocol deviations will be established. This will include determining which violations will be designated “key,” requiring immediate notification to the medical monitor and Sponsor. The investigator is responsible for seeing that any known protocol deviations are recorded and handled as agreed.

12 STATISTICAL CONSIDERATIONS

12.1 General Considerations

All statistical analyses will be conducted using SAS software, version 9.1.3 or higher (SAS® Institute, Cary, NC). Additional analyses of study endpoints will be detailed in the statistical analysis plan.

12.2 Sample Size Calculation

The sample size of 24 subjects in 4 cohorts is considered appropriate for a study of this type and was determined by practical considerations. No formal sample size calculation was made as no formal hypothesis testing will be performed.

12.3 Analysis Populations

The populations used for analysis will include the following:

Intent-to-Treat Population: The Intent-to-Treat population will be defined as any subject who is enrolled into the study, whether or not he/she receives study drug.

Full Analysis Set: The Full Analysis Set population will be defined as any subject who is enrolled into the study, receives study drug, and has at least 1 efficacy evaluation after receiving study drug.

Per Protocol Set: The Per Protocol Set will be defined as any subject who is enrolled into the study, receives study drug as planned, has at least 1 efficacy evaluation after receiving study drug, completes the Week 13 visit, and has no significant protocol violations.

Safety Population: The Safety Population will be defined as any subject who is enrolled into the study and receives study drug.

PK Evaluable Population: The PK Evaluable Population will be defined as any subject who is enrolled into the study, receives study drug, and has at least 1 evaluable PK serum sample.

12.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized, including age, gender, race, ethnicity, weight, height, primary diagnosis and other parameters as appropriate.

12.5 Safety Analysis

12.5.1 Vital Signs

Descriptive statistics (mean, standard deviation [SD], minimum, maximum, and n), including change from baseline (pre-dose value of the relevant treatment period) for actual values of vital sign parameters will be presented for all scheduled time points by dose level. Additionally, the

number of subjects with "substantial" increases or decreases in BP (>20 mmHg) and heart rate (>15 bpm) will be tabulated.

12.5.2 Clinical Laboratory Tests

Descriptive statistics, including change from baseline, for the actual values of laboratory parameters will be presented for all scheduled time points by dose level. For subject data listings, abnormal values outside normal ranges will be flagged.

If data permits, urinalysis (pH and specific gravity) will be summarized (mean, SD, median, minimum, maximum, and n) at each time point.

Shift tables for laboratory parameters will be generated based on changes in National Cancer Institute Common Terminology Criteria for Adverse Events grade from baseline to worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be generated to better understand the study drug safety profile.

12.5.3 Concomitant Medications

All concomitant medications collected from screening through the study period will be classified to preferred terms according to the World Health Organization drug dictionary and presented as subject data listings.

12.5.4 Electrocardiograms

Descriptive statistics (mean, SD, minimum, maximum, and n) from the 12-lead ECG assessment will be summarized at each time point when the ECG evaluation is performed.

12.5.5 Physical Examinations

The physical examination will include descriptive statistical summaries of all abnormalities recorded.

12.5.6 Neurologic Examinations

Neurological examination results will be summarized by visit and listed by subject.

12.5.7 Adverse Events

All AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). The frequency of AEs will be tabulated by preferred term and system organ class. The maximum intensity and frequency of AEs will be summarized by treatment.

A treatment-emergent AE (TEAE) is defined as an AE that was not present prior to treatment with study drug, but appeared following treatment or was present at treatment initiation but worsened in severity during treatment. An AE that was present at treatment initiation but

resolved and then reappeared while the subject was on treatment will be considered a TEAE (regardless of the intensity of the AE when the treatment was initiated).

All TEAEs will be tabulated according to MedDRA by system organ class, high level terms and preferred terms and will include the following categories:

- TEAEs
- Drug-related TEAEs
- Severe or higher TEAEs
- Severe or higher drug-related TEAEs
- SAEs

Deaths and SAEs will be displayed in a subject data listing.

12.5.8 Imaging Data

MRI and X-ray data will be displayed in subject data listings.

12.5.9 Additional Safety Analyses

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of the study drug.

12.6 Procedures for Handling Missing Data

All available safety and efficacy data will be included in data listings and tabulations. No imputation of values for missing data will be performed. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

12.7 Efficacy Analysis

All efficacy analyses are exploratory in nature and will be presented using descriptive statistics only (n, mean, median, minimum, maximum, SD, percentage of analysis population, and confidence intervals). Post-dose change from baseline in lower back or leg pain will be tabulated by dose level in a table summary.

12.8 Pharmacokinetic Analysis

Serum concentrations will be presented descriptively by time. All derived PK parameters will be presented with individual values and descriptive statistics. Serum anti-KTP-001 antibody detection will be presented descriptively by time.

12.9 Exploratory Pharmacodynamic Analysis

Pharmacodynamic analyses are exploratory in nature and will be presented using descriptive statistics (n, mean, median, minimum, maximum, SD, percentage of analysis population, and

confidence intervals). Post-dose change from baseline in serum concentrations of keratan sulfate will be tabulated by dose level in a table summary.

12.10 Interim Analysis

An interim analysis at Month 12 will be conducted, the details of which will be described in a separate statistical analysis plan.

13 ACCESS TO SOURCE DATA/DOCUMENTS

The investigator will provide direct access to source data and documents for individuals conducting study-related monitoring, audits, IRB/Independent Ethics Committee (IEC) review, and regulatory review. The investigator must inform the study subject that his/her study-related records may be reviewed by the above individuals without violating the subject's privacy of personal health information in compliance with Health Insurance Portability and Accountability Act of 1996 regulations.

Attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and IRBs will be kept confidential by the FDA only if maintained in confidence by the clinical investigator and IRB. By signing this protocol, the investigator affirms to the Sponsor that the investigator will maintain, in confidence, information furnished to him or her by the Sponsor and will divulge such information to the IRB under an appropriate understanding of confidentiality with such board.

14 QUALITY CONTROL AND QUALITY ASSURANCE

Sponsor/[redacted] will implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements.

14.1 Conduct of Study

This study will be conducted in accordance with the provisions of the Declaration of Helsinki and all revisions thereof (Tokyo 2004), and in accordance with the FDA Code of Federal Regulations (CFR §312.50 and §312.56) and the International Conference on Harmonisation (ICH) E6 Guidelines on GCP (CPMP/ICH/135/95). Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed by an IRB or IEC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each subject will give his or her written, informed consent before any protocol-driven tests or evaluations are performed.

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB/IEC, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study and are approved by the medical monitor and/or Teijin America, Inc. Any deviation may result in the subject having to be withdrawn from the study, and may render that subject nonevaluable.

14.2 Protocol Amendments

Only the Sponsor may modify the protocol. Amendments to the protocol will be made only after consultation and agreement between the Sponsor, the medical monitor and the investigator. All amendments that have an impact on subject risk or the study objectives, or require revision of the ICF, must receive approval from the IRB/IEC prior to their implementation.

14.3 Monitoring of Study

The investigator will permit the site monitor to review study data as frequently as is deemed necessary to ensure data are being recorded in an adequate manner and protocol adherence is satisfactory.

The investigator will provide access to medical records for the monitor to verify CRF entries. The investigator is expected to cooperate with the Sponsor/designee in ensuring the study adheres to GCP requirements.

The investigator may not recruit subjects into the study until Sponsor or its designee has conducted a visit at the site to conduct a detailed review of the protocol and CRF. With agreement of the Sponsor, attendance at an investigator meeting may fulfill this requirement.

15 ETHICS

15.1 Institutional Review Board/Independent Ethics Committee Approval

15.1.1 Ethics Review Prior to Study

The investigator will ensure that the protocol and consent form are reviewed and approved by the appropriate IRB/IEC prior to the start of any study procedures. The IRB/IEC will be appropriately constituted and will perform its functions in accordance with FDA regulations, ICH GCP guidelines, and local requirements as applicable.

15.1.2 Ethics Review of Other Documents

In addition, the IRB will approve all protocol amendments (except for Sponsor-approved logistical or administrative changes), written informed consent documents and document updates, subject recruitment procedures, written information to be provided to the subjects, available safety information, information about payment and compensation available to subjects, the investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the IRB/IEC and regulatory authority as applicable.

15.2 Written Informed Consent

The nature and purpose of the study will be fully explained to each subject (or the subject's legally responsible guardian). The subjects must be given ample time and opportunity to inquire about details of the trial, to have questions answered to their satisfaction, and to decide whether to participate. Written informed consent must be obtained from each subject (or guardian) prior to any study procedures being performed.

16 DATA HANDLING AND RECORD KEEPING

16.1 Data Reporting and Case Report Forms

16.1.1 Data Collection and Case Report Forms

All relevant observations and data related to the study, as per the study protocol, will be recorded on electronic case report forms (eCRF). Adequate and accurate case records shall be maintained, including the evaluation of inclusion and exclusion criteria, medical history, physical examination, clinical assessments, a record of clinical safety laboratory sample collection, PK and PD sample collection if available, drug administration, AEs and final evaluation.

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting and releasing) will be generated and maintained by [redacted] Data Management with approval from Teijin.

The eCRFs must be completed for each subject who signs the ICF and undergoes screening procedures. The eCRF data entry shall be completed within 7 calendar days of clinical visit completion. eCRF completion guidelines will be provided to the sites to ensure accurate entry of data into the database. The investigator must sign and date the eCRF. The signature shall indicate that the investigator has reviewed the data and data queries recorded on eCRFs, and agrees with the content.

16.1.2 Laboratory Data

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to trial start. If a central laboratory has been selected to conduct any or all tests, it is essential all samples be analyzed at that laboratory. The investigator must maintain source documents such as laboratory reports and complete history and physical examination reports.

16.1.3 Serum concentration of KTP-001 and anti-KTP-001 antibody

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to trial start. If a central laboratory has been selected to conduct any or all tests, it is essential all samples be analyzed at that laboratory. The investigator must maintain source documents such as laboratory reports and complete history and physical examination reports.

16.1.4 Imaging Data

On-site safety and efficacy assessments will be performed by the investigator or on-site radiologist. One copy of the MRI and X-ray images will be stored on site. In addition, all scans archived in Digital Imaging and Communications in Medicine (a.k.a., DICOM) format will be

required to be sent to an independent medical imaging laboratory ([redacted]) for the purpose of independent review.

16.1.5 Retention of Source Documents

The investigator must maintain source documents such as laboratory reports, X-rays, ECGs, consultation reports, and complete history and physical examination reports.

16.2 Retention of Essential Documents

The study essential documents must be maintained as specified in the ICH guidelines for GCP and the applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Sponsor. It is the responsibility of Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

17 ADMINISTRATIVE INFORMATION

17.1 Financing and Insurance

Financing and insurance will be addressed in a separate agreement between Sponsor and the investigator.

17.2 Publication Policy

Teijin America, Inc. will retain ownership of all data. All proposed publications based on this study will be subject to Sponsor's approval requirements.

18 REFERENCES

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[15] ACR-ASNR practice guideline for the performance of magnetic resonance imaging (MRI) of the adult spine. Practice Guideline. MRI of the adult spine. Revised 2006. (http://www.acr.org/guidelines).

19 SIGNATURES

19.1 Investigator's Signature

I agree to conduct the study outlined above according to the terms and conditions of the protocol, GCP guidelines, and with applicable regulatory requirements. All information pertaining to the study will be treated in a confidential manner.

Investigator's Signature _____

Date _____

19.2 [redacted] Clinical Research Signatures

[redacted] Clinical Research Authors

[redacted]
Director, Medical and Safety Services — Date

[redacted]
Sr Biostatistician II, Biostatistics — Date

[redacted]
Director, Medical & Scientific Affairs
[redacted] — Date

[redacted] Clinical Research Approval

[redacted]
Senior Director, Medical Writing — Date

[redacted]
Sr Biostatistician Project Director, Biostatistics — Date

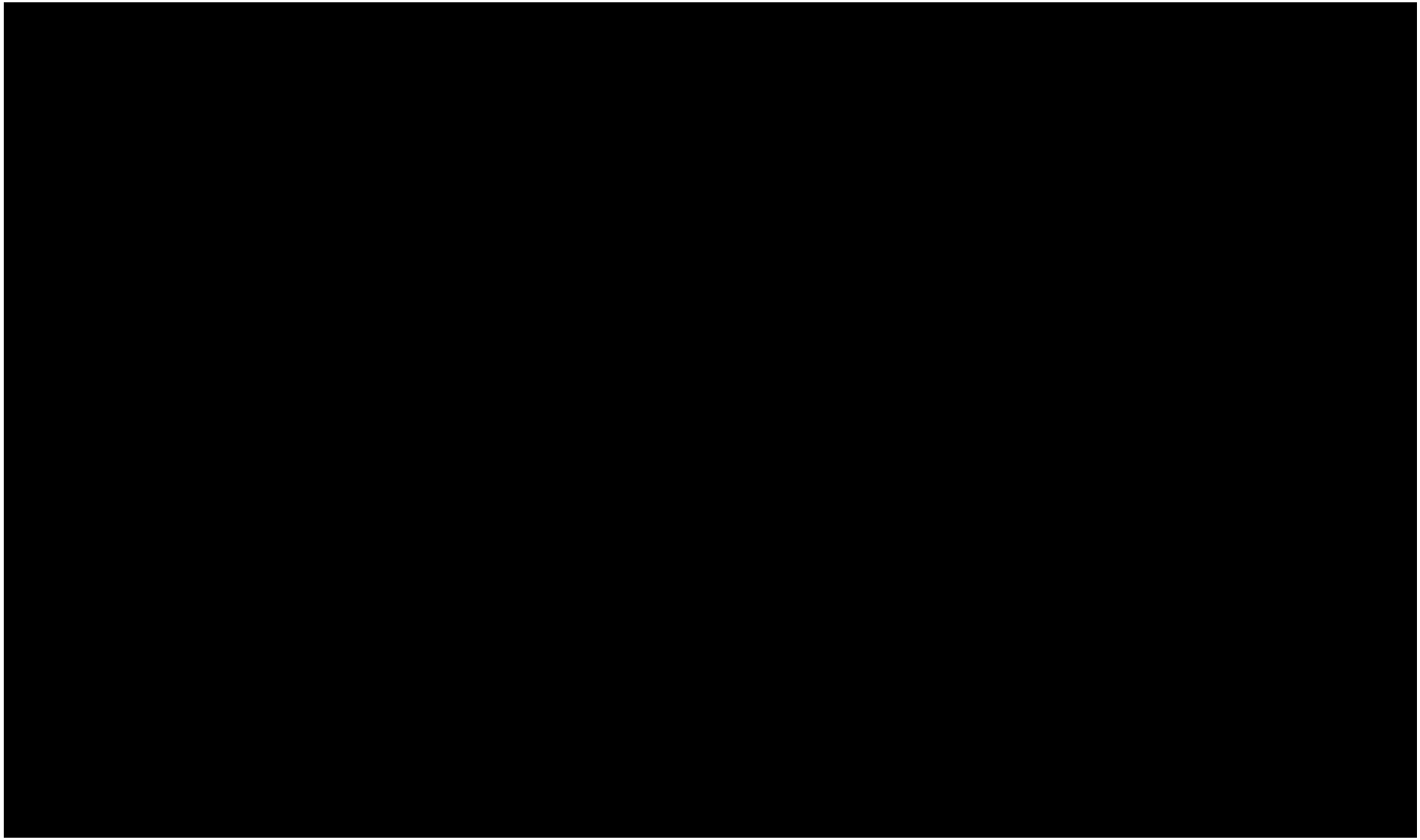
19.3 Teijin America, Inc. Signatures

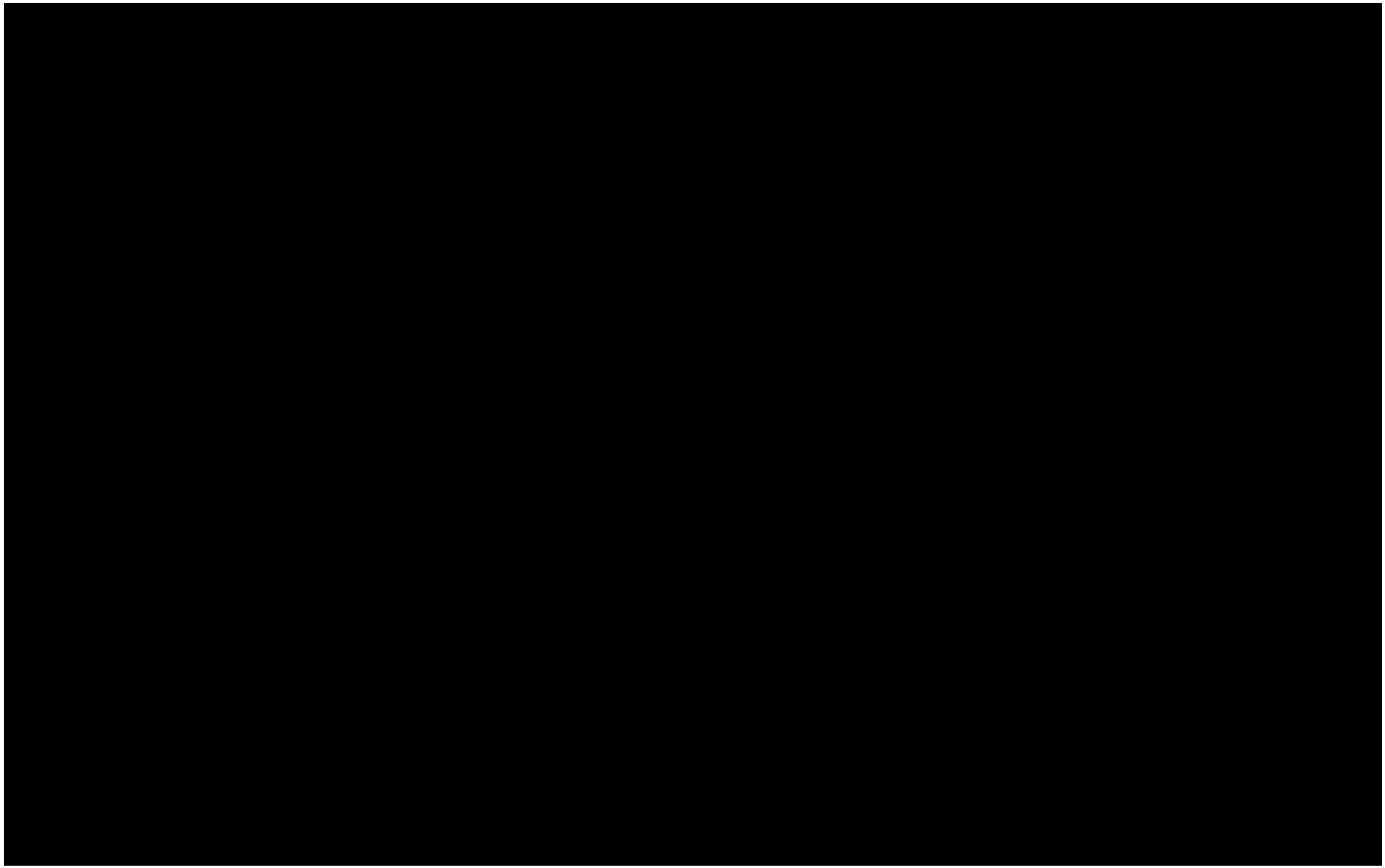
This clinical study protocol has been reviewed and approved by Teijin America, Inc.

[redacted]
President, Teijin America, Inc.

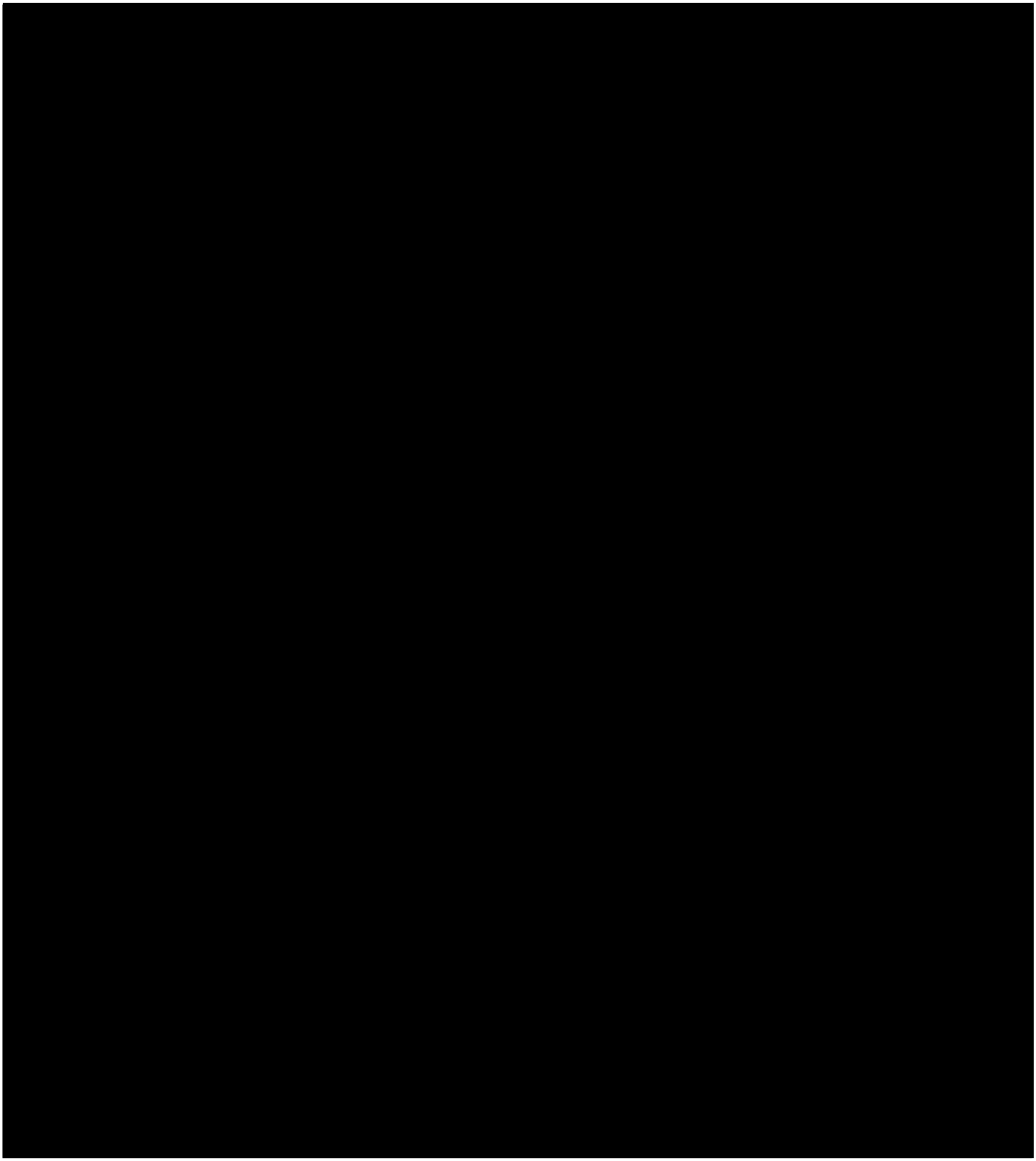
Date

APPENDIX A: PAIN MEDICATIONS

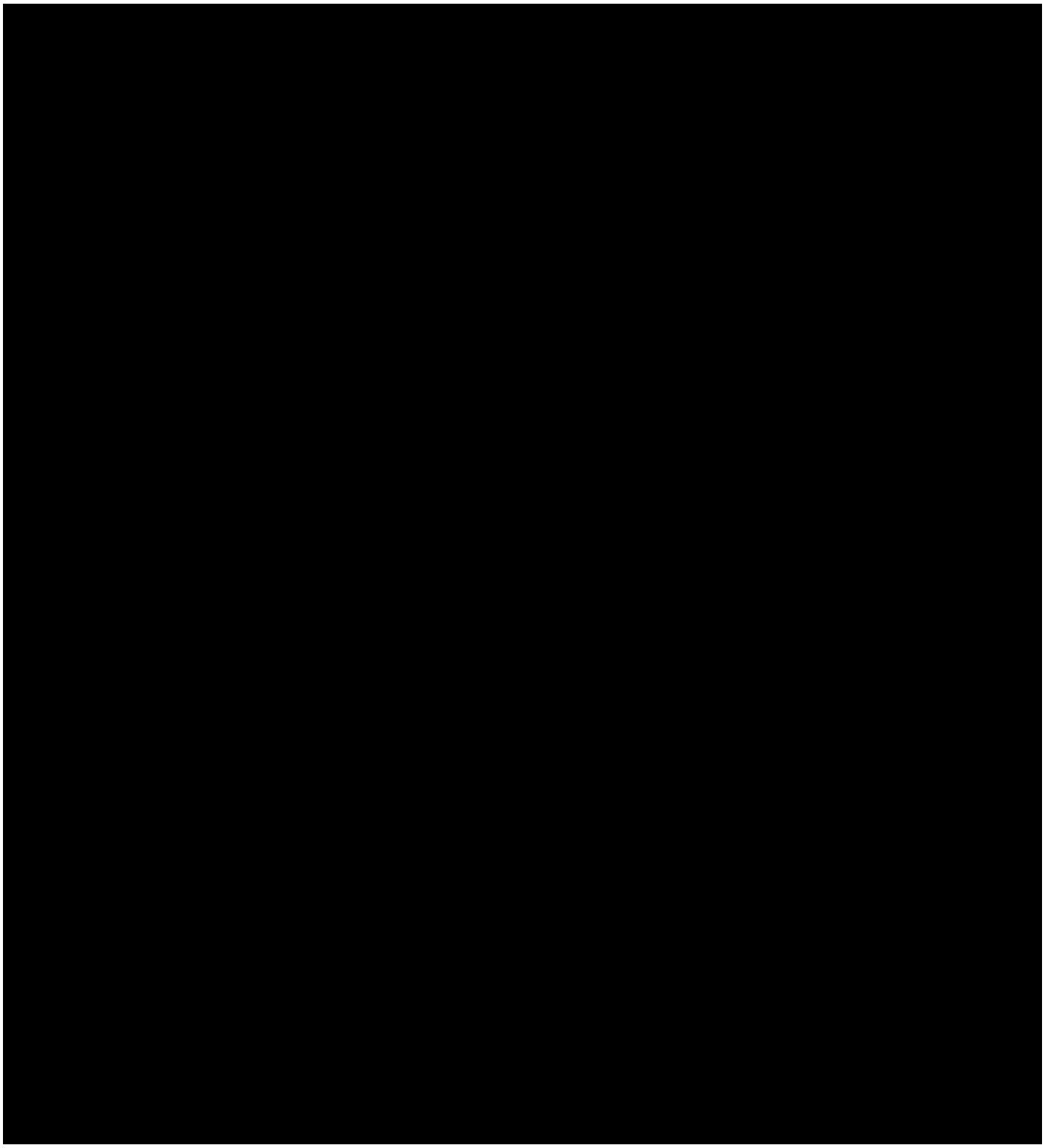




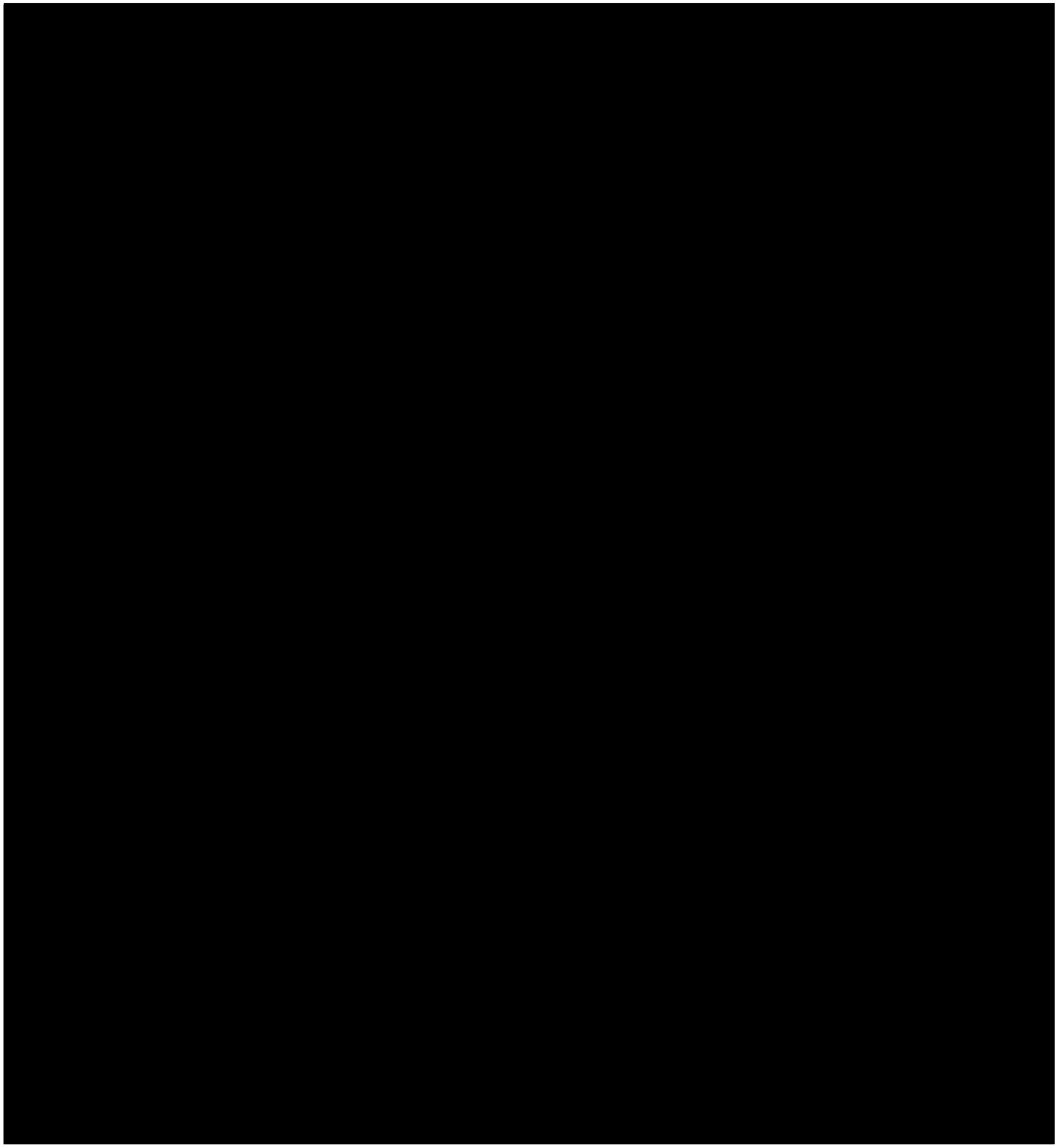
APPENDIX B: INTRADISCAL INJECTION PROCEDURE



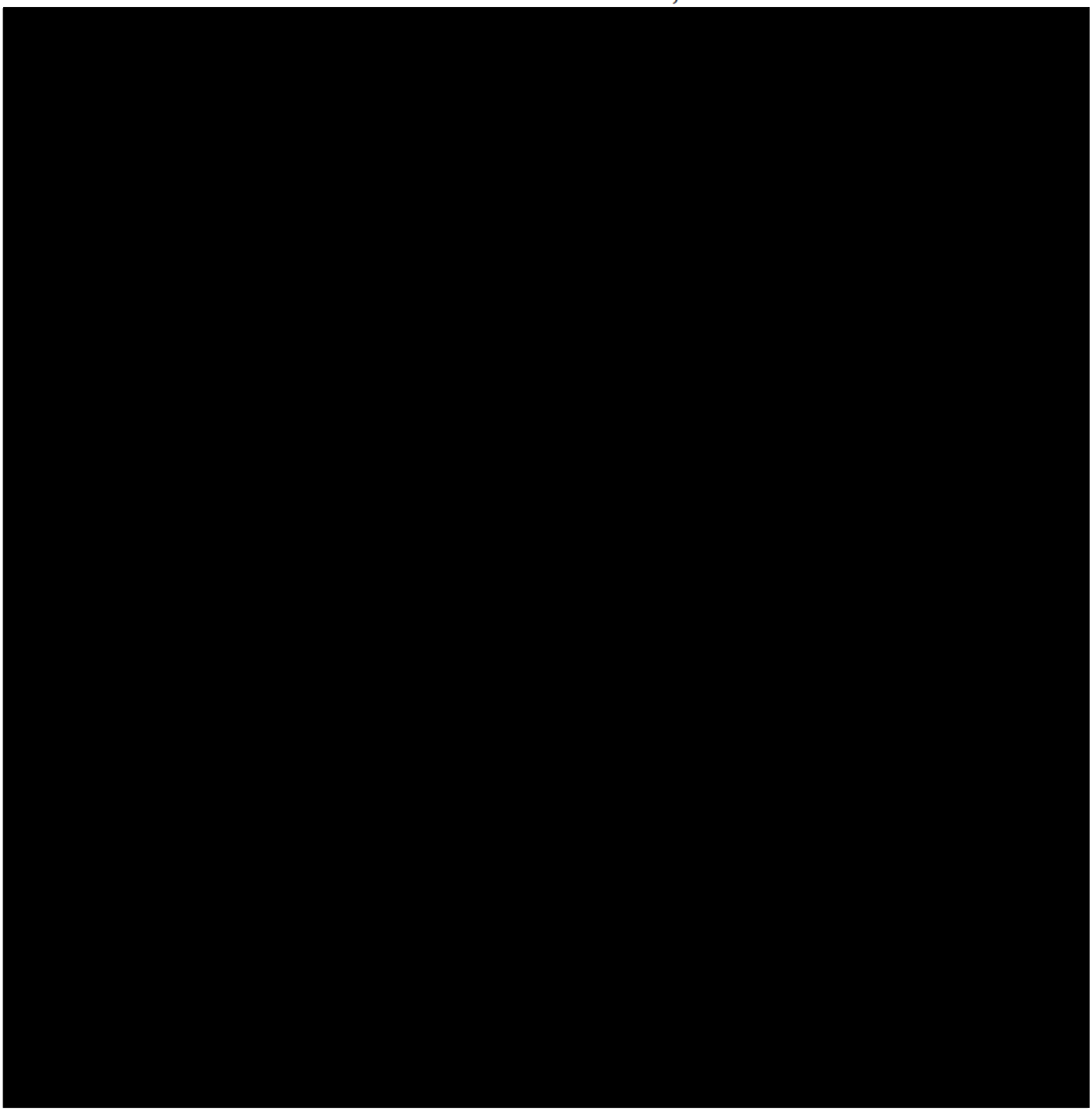
APPENDIX C: LOWER BACK OR LEG PAIN ASSESSMENT



APPENDIX D: STRAIGHT-LEG-RAISING AND FEMORAL STRETCH TESTS

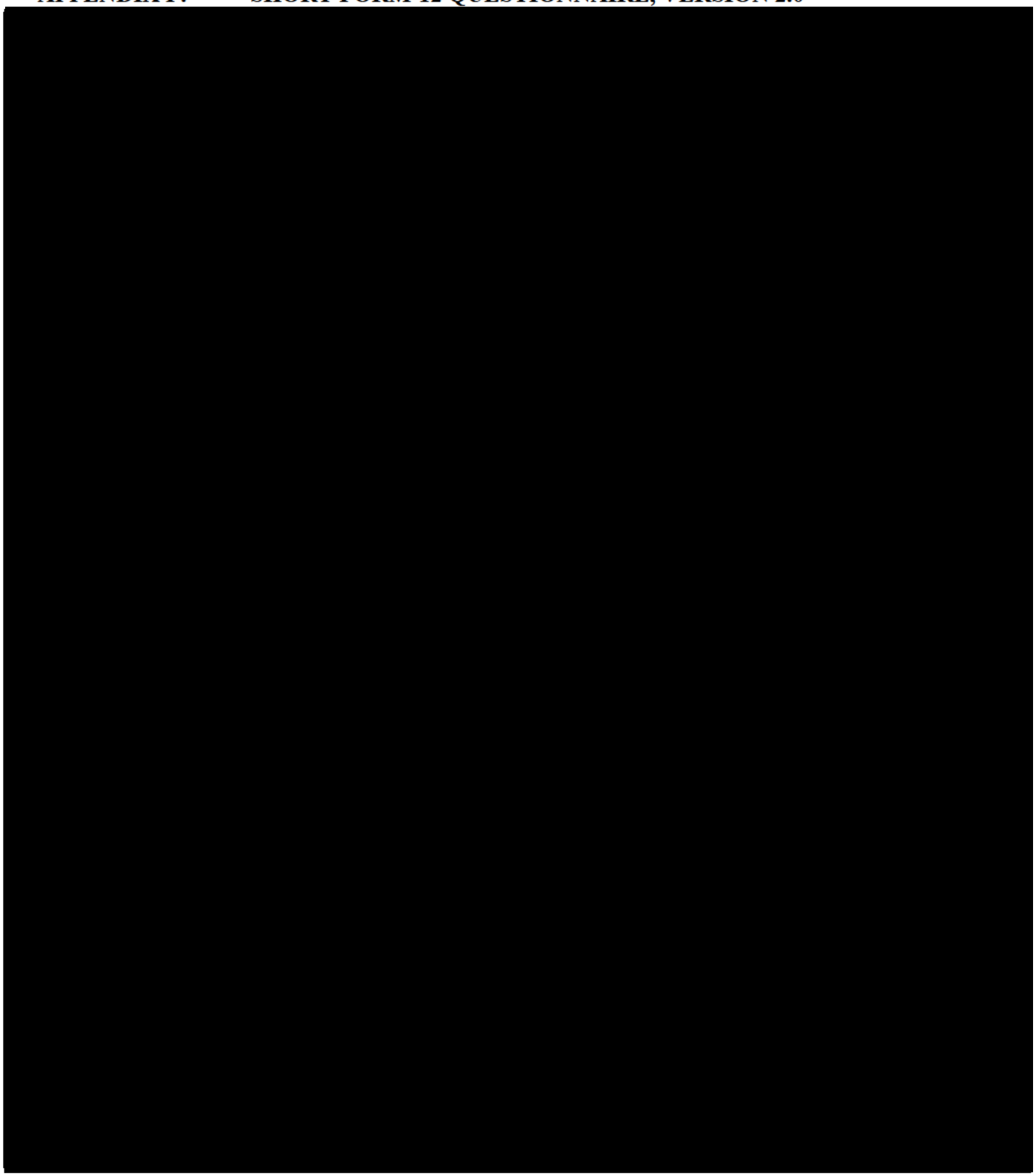


APPENDIX E: OSWESTRY DISABILITY INDEX, VERSION 2.1A

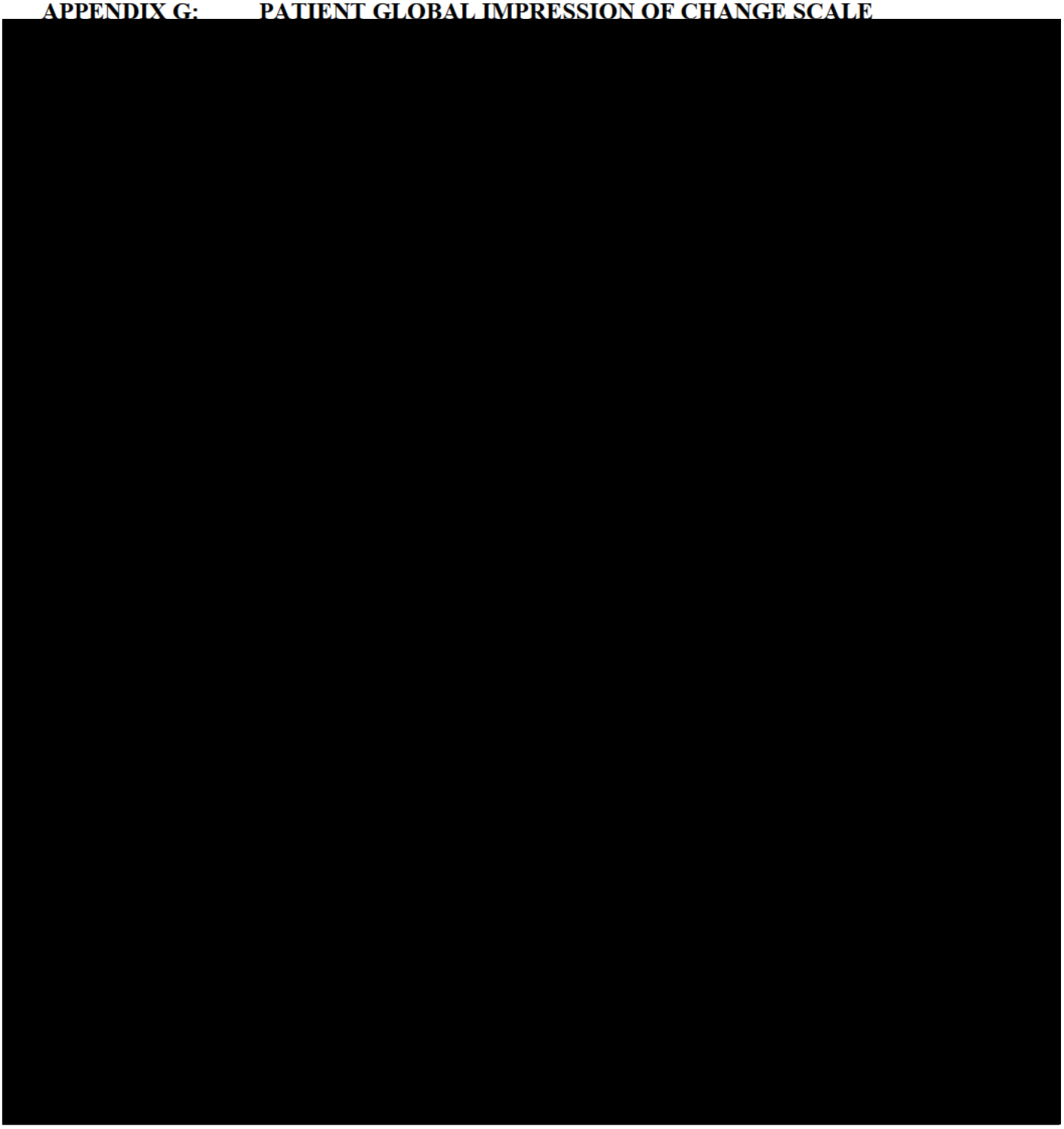


[redacted]

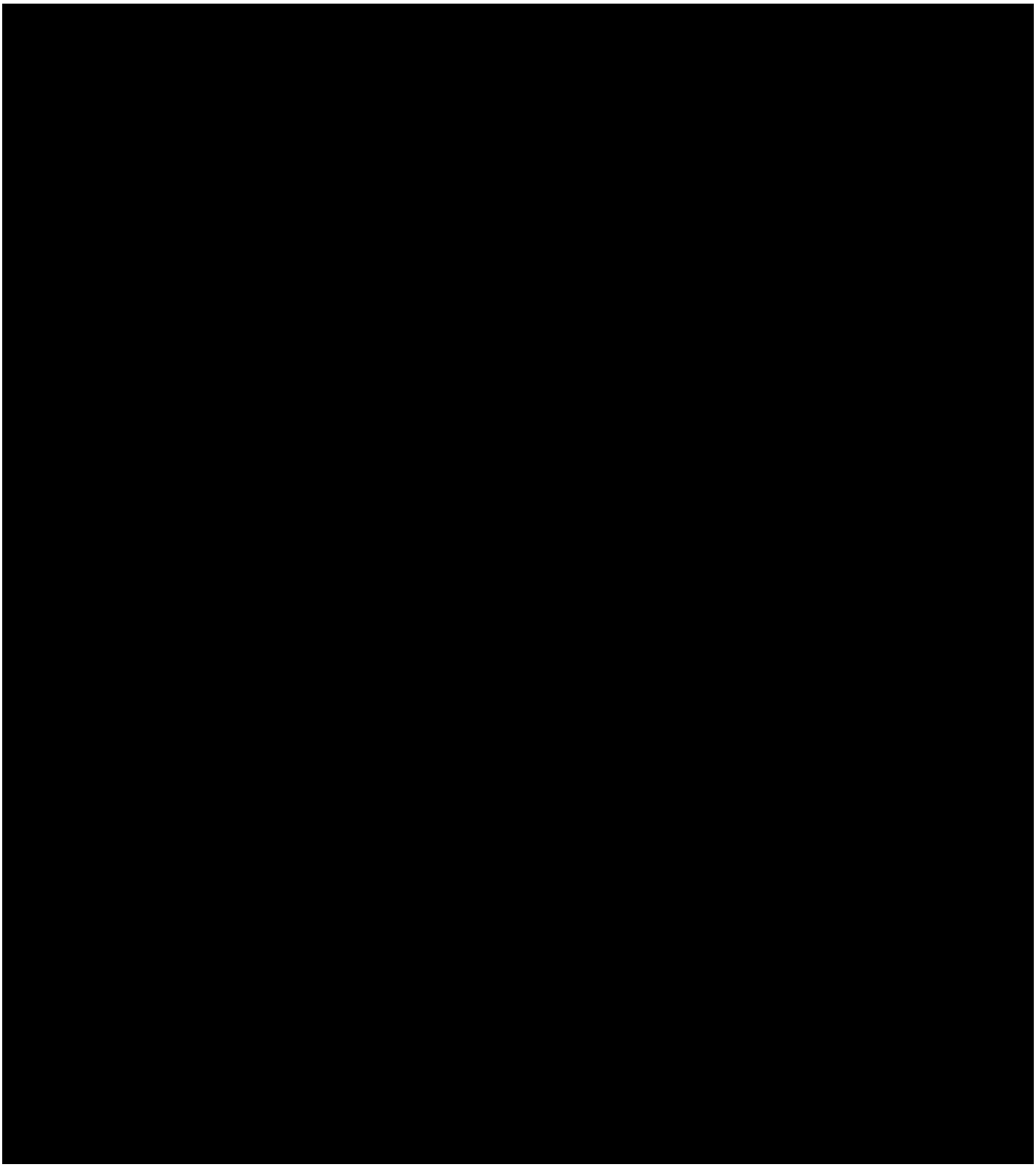
APPENDIX F: SHORT FORM-12 QUESTIONNAIRE, VERSION 2.0



APPENDIX G: PATIENT GLOBAL IMPRESSION OF CHANGE SCALE



APPENDIX H: SCREENING AND CLINICAL LABORATORY ASSESSMENTS



APPENDIX I: NEUROLOGIC EXAMINATION