Teijin America, Inc.
Clinical Study Protocol KTP-001-CL-101
Phase 1/2

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

STATISTICAL ANALYSIS PLAN

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Study 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**

Protocol Date: **Version 4.1 Amendment 4 – 20 October 2015**

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Reviewed at Teijin America, Inc. by:

[redacted] President

Date

REVISION HISTORY

Date	Version	Description	Author
03May2018	1.0	Baseline version	[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransaminase
ATC	Anatomical therapeutic chemical classification
AUCt	Area under the serum concentration-time curve from time zero to time t
BLQ	Below the limit of quantification
BP	Blood pressure
CI	Confidence interval
CM	Concomitant Medication
C_{max}	Maximum observed concentration
CRF	Case report form
CT	Computerized tomography
DSMB	Data and Safety Monitoring Board
eCRF	Electronic case report form
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
FIH	First in human
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	Halting rules
ICH	International Conference on Harmonisation
ICF	Informed consent form
IRB	Internal review board
LLQ	Lower limit of quantification
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	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
QTc	QT interval corrected heart rate
SAE	Serious adverse event
SAP	Statistical analysis plan

LIST OF ABBREVIATIONS

Abbreviation	Term
SD	Standard deviation
SF-12	Short form-12 (QOL scale)
SGPT	Serum glutamic-pyruvic transaminase
TEAE	Treatment-emergent AE
t_{max}	Time at which the maximum concentration was observed
WHO	World Health Organization

1.0 INTRODUCTION

The purpose of this document is to provide further details about the statistical analysis methods specified in the study protocol KTP-001-CL-101: a Phase 1/2, 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. This statistical analysis plan (SAP) has been based on International Conference on Harmonisation (ICH) E3 and E9 guidelines and in reference to protocol version 4.1 amendment 4 dated 20October2015. The statistical analysis plan covers statistical analysis, tabulations and listings of safety and efficacy data.

Any major deviations from the methods specified in this document and the protocol will be discussed and documented.

2.0 STUDY OBJECTIVES

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.

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.

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.

3.0 STUDY DESIGN

3.1 Study Design and Population

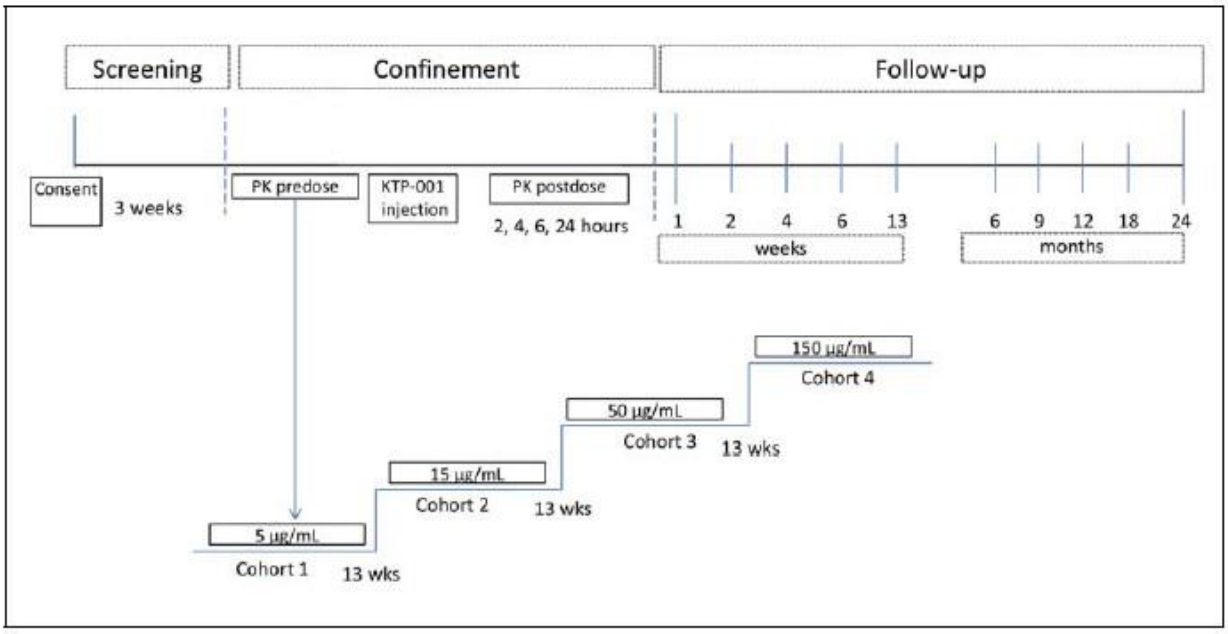
Study KTP-001-CL-101 is an open-label, non-controlled single ascending dose study of KTP-001 in male and female subjects between the ages of 30 and 70 with a single herniated lumbar disc. After obtaining informed consent, subjects will be evaluated during a screening period of no more than 3 weeks (21 days). The screening procedures will be performed at the screening visit as per the appendix 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 Cohorts 1, 2, and 3. The DSMB will conduct a safety review at the 13-week follow-up visit for all subjects in each dose cohort.

If escalation is appropriate as determined by the DSMB, 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 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 1: KTP-001-CL-101 Study Design



Approximately 48 subjects will be screened to ensure that 24 subjects are enrolled into this study. This study will be conducted at approximately 8 sites in the United States. Subjects who discontinue from the study after enrollment but prior to receiving study drug will be replaced to 6 subjects are treated in each of the 4 cohorts.

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).

3.2 Study Treatments and Assessments

KTP-001 is the investigational medicinal product. Neither placebo nor any comparator is used. The proposed clinical dose concentrations for this first in human (FIH) study are 5 µg/disc (Cohort 1), 15 µg/disc (Cohort 2), 50 µg/disc (Cohort 3), and 150 µg/disc (Cohort 4). KTP-001 1.0 mg/vial will be provided as a lyophilized powder in 2.0 mL glass vials. The injection volume per subject will be 1.0 mL. 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. 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.

Throughout the study, patients will be assessed for the study objectives as outlined in the schedule of assessments (appendix 1).

3.3 Randomization and Blinding

The study is an open-label, non-controlled, clinical trial. There is no randomization of patients or blinding.

3.4 Sample Size Justification

No formal sample size calculation was made as no formal hypothesis testing will be performed. The sample size of 24 subjects in 4 cohorts is considered appropriate for a study of this type and was determined by practical considerations. Approximately 48 subjects will be screened to ensure that 24 subjects are enrolled into this study.

4.0 STATISTICAL CONSIDERATIONS

Statistical analyses will be performed using SAS software, version 9.3 or higher. The safety population will be used as the analysis population for the primary endpoints and all safety end points. Full analysis set and per protocol set will be used as the analysis population for secondary and exploratory efficacy endpoints.

Continuous data will be summarized using n, mean, median, standard deviation (SD), minimum value, maximum value, 95% confidence interval (CI) and, if appropriate, number of missing values. Unless noted otherwise, summaries will be produced by visit (where applicable) and cohort. Summaries by visit will be based on nominal reporting. If more than one value is reported at a scheduled visit, the value collected closest to the intended visit date will be used. In the case of a tie, the latest version will be summarized.

Categorical data will be summarized using n, percentages. Percentages will be calculated based on the number of non-missing values. The number of missing values will be presented as a separate category with no percentage, if 1 or more patients are missing data for the summary. Otherwise, all categories will be presented (even if no patients are counted in the category). Counts of zero in any category will be presented with percentage as (0%).

Precision of summary statistics:

- Integer – Sample size (n, N) and number of missing responses (if displayed).
- One additional decimal place than reported/collected on the case report form (CRF) – mean, median, confidence interval.
- Two additional decimal places than reported/collected on the CRF – standard deviation.
- Same number of decimal places as reported/collected on the CRF – minimum, maximum.
- Percentages – one decimal place.

All data will be presented on listings in order of dosing cohort, patient, assessment date/time and assessment (in order collected on eCRF, unless specified otherwise). For display purposes, cohort labels will be ordered from smallest to largest. Dates will be presented in the format DDMMMYYYY. Times will be displayed in 24-hour clock format. Numbering of tables, figures and listings will follow ICH E3 guidelines.

Unscheduled measurements will be excluded from the descriptive statistical analysis. However, unscheduled measurements that were performed immediately after the scheduled measurement, in case of a previous measurement error (e.g. equipment failure), will not be excluded from the analysis. In these cases, the original erroneous measurement will be excluded from the analysis and the unscheduled visit substituted. All the unscheduled measurements will be included in the listing.

Unless otherwise stated, the baseline value is defined as the as the last assessment result collected prior to the first dose of study medication.

5.0 ANALYSIS POPULATION

The populations used for analysis will include intent-to-treat population, full analysis set, per protocol set and safety population. The primary objective endpoints analysis and safety endpoints will be performed based on safety population. Full analysis set and per protocol set will be used as the analysis population for secondary and exploratory efficacy endpoints. Baseline characteristics analysis will be performed on intent-to-treat population.

Intent-to-Treat Population

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

Full Analysis Set

The full analysis set is defined as any subject who is enrolled into the study, received study drug, and has at least 1 efficacy evaluation after receiving study drug.

Per Protocol Set

The per protocol set is defined as any subject who is enrolled into the study, received 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. Significant protocol violation list will be documented in a separate file.

Safety Population

The safety population is defined as any subject who is enrolled into the study and received study drug.

6.0 METHODS OF ANALYSES AND PRESENTATIONS

The following sub-sections would be considered for logical presentation of study data.

6.1 Subject Disposition

The number of subjects screened, screen failure, enrolled, study completion status will be summarized. Subjects who discontinued from the study will be summarized and listed by their primary reason for discontinuation. Inclusion/exclusion criteria evaluation will also be listed. Analysis populations will be summarized. Subject disposition will be summarized by dosing cohort.

6.2 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 Internal Consent Form (ICF) when new risks become known, failure to obtain Internal Review Board (IRB) approvals for the protocol and ICF revisions.

Protocol deviations will be identified by the project team prior to database lock. A summary of major protocol deviations will be provided by cohort. All protocol deviations will be listed. Intent-to-treat population will be used as an analysis population for this analysis.

6.3 Demographic and Baseline Characteristics

Demographic data and subjects' baseline characteristics at screening will be summarized and listed using descriptive summary statistics for intent-to-treat population. The demographic information of age, gender, ethnicity and race will be summarized by cohort. Apart from that, additional information's of height, weight, primary diagnosis and other parameters such as anatomical location of the intervertebral disc (e.g. L5-S1), Location of herniation (e.g. anterior), etc. as appropriate will also be summarized. All demographic and baseline characteristics will be listed in full.

6.4 Medical History

An analysis of the medical history (including the symptoms associated with herniated lumbar disc) will be performed at screening. A summary table of medical history conditions by body system and preferred term will be presented by cohort. The table will be sorted in alphabetical order by body system and in decreasing frequency of preferred terms based on total number of reports within each body system. The frequency and percentage of subjects who present at least 1 occurrence of the medical history or concurrent condition will be presented. Medical history will be coded using the most recent version available of the Medical Dictionary for Regulatory Activities (MedDRA). All medical history will be listed. The medical history will be analyzed using intent-to-treat population.

6.5 Prior and Concomitant Medication

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 included on the concomitant medication. Medications taken for a surgical procedure should also be included.

Prior medication is defined as any medication starting and ending before the first study dose.

Prior and Concomitant medications will be classified using the latest version of World Health Organization Drug Dictionary (WHO drug) and will be summarized by the number and percentage of subjects by anatomical therapeutic chemical classification (ATC) level 2 and preferred term. The table will be sorted in alphabetical order by ATC level 2 and in decreasing frequency of preferred terms based on total number of reports within each ATC level. All prior/concomitant medication will be listed.

Concomitant procedures/therapy, rescue medication details also will be summarized by cohort and listed same as mentioned above. Intent-to-treat population will be used as an analysis population.

6.6 Study Drug Treatment Compliance

Subjects received a single dose of study drug by intradiscal injection. The injection will be performed under fluoroscopic or computerized tomography (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. Study drug administration details will be listed for safety population, full analysis set and per protocol population separately.

6.7 Data Endpoints and Analyses

The primary objective endpoints analysis and safety endpoints will be performed based on safety population. Full analysis set and per protocol set will be used as the analysis population for secondary and exploratory efficacy endpoints. All the results will be summarized by cohort. Descriptive summary statistics mentioned in the section 4.0 will be used for the analysis. Comprehensive listings of all data will be presented.

6.7.1 Analysis of Primary Endpoint - Safety

Primary endpoint of this study is safety and tolerability. The following are the primary safety endpoints:

- Adverse events (AE)
- Serious adverse events (SAE)
- Deaths or discontinuations due to AEs (including subjects who have lumbar surgery) that occur after administration of study drug.
- Change and shifts from baseline in vital signs of
    - Heart rate
    - Systolic/Diastolic blood pressure
    - Respiratory rate
    - Body temperature
- Tabulation of number of subjects with "substantial" increases or decreases in BP (>20 mmHg) and heart rate (>15 bpm)
- 12-lead Electrocardiograms (ECGs)
    - Heart rate
    - Rhythm
    - PR
    - RR
    - PQ
    - QT intervals
    - QTc [Bazett's and Fridericia's]
    - QRS
- Clinical laboratory tests
    - Hematology
    - Serum chemistry
    - Coagulation
    - Urinalysis
- Data from MRI and X-ray (including morphological assessment)
- Data from neurologic assessments
    - Positive straight-leg raising or femoral stretch test

- Alteration of deep tendon reflexes (knee and ankle)
- Sensory, or motor deficits in the lower extremities.

- Abnormalities in physical examinations
- Number of subjects who experienced any AEs defined as a halting rule
- Serum anti-KTP-001 antibody analysis by electrochemiluminescence

6.7.1.1 Adverse events

Adverse events (AEs) will be collected from the time of first dose until the last study visit or premature discontinuation of the study drug KTP-001. All (both serious and non-serious) AEs must be followed until they are resolved or stabilized, or until all attempts to determine resolution of the event are exhausted.

All AEs will be coded using the latest version of MedDRA. The frequency of AEs will be tabulated by system organ class and preferred term. 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 and preferred terms. Adverse events table will be summarized for

- Overall summary of adverse events, it includes number of treatment-emergent adverse events, subjects with any TEAE, subjects with any TE- serious adverse events (SAE), subjects with TEAEs leading to discontinuation, subjects with any related TEAE, subjects with any severe TEAE
- Summary of adverse events by system organ class and preferred terms
- Summary of SAEs by system organ class and preferred terms
- Deaths or discontinuations due to AEs (including subjects who have lumbar surgery) that occur after administration of study drug by system organ class and preferred terms.
- Summary of TEAEs by system organ class and preferred terms
- Summary of drug-related TEAEs by system organ class and preferred terms
- Summary of severe TEAEs by system organ class and preferred terms
- Summary of drug-related TEAEs by system organ class and preferred terms
- Adverse events of special interest (AESI) by system organ class and preferred terms

The following AEs will be considered an AESI

1. MRI or X-ray findings of Modic changes, reduction of disc height, or evidence of lumbar instability as defined in Appendix 4, 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.

All AEs, SAEs and deaths will be listed.

6.7.1.2 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 cohort. Additionally, the number of subjects with "substantial" increases or decreases in BP (>20 mmHg) and heart rate (>15 bpm) will be tabulated as shift table. It includes heart rate, systolic and diastolic blood pressures, respiratory rate, and body temperature. Vital signs details will be listed.

6.7.1.3 12-Lead electrocardiograms

Descriptive statistics (mean, standard deviation [SD], minimum, maximum, and n), including change from baseline (pre-dose value of the relevant treatment period) for 12-Lead Electrocardiograms parameters of heart rate, rhythm, PR, RR, PQ, and QT intervals, QTc [Bazett's and Fridericia's], and QRS will be presented for all scheduled time points by cohort. ECG results will be listed.

6.7.1.4 Clinical laboratory tests

Descriptive statistics (mean, standard deviation [SD], minimum, maximum, and n), including change from baseline (pre-dose value of the relevant treatment period) for laboratory parameters of hematology, serum chemistry, coagulation, and urinalysis will be presented for all scheduled time points by cohort. Laboratory test results will be listed and 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 AE grade from baseline to worst post-baseline value.

6.7.1.5 MRI and X-ray data

The results of independently evaluated imaging assessments will be provided [redacted]. Absolute and change from baseline in MRI and X-ray (including morphological assessment) results will be analyzed for all scheduled time points and cohort using descriptive statistics. MRI and X-ray data will be displayed in subject data listings.

6.7.1.6 Neurologic assessments

Neurological examination results and change from baseline will be summarized for all scheduled time points by cohort. Information includes: deep tendon reflexes (patellar [or knee], Achilles [or ankle] as normal, decreased, absent, increased or clonus and Babinski's Sign as present, plantar flexion or no response); muscle strength (hip flexion, knee flexion, knee extension, ankle dorsiflexion/long toe extension, ankle plantar flexion as normal, decreased to resistance, against gravity only/no resistance, or no movement); sensory exam to pin-prick (anterior knee, medial malleolus, dorsum of the foot, anterior toes 1-3 and anterior toes 4-5 and lateral malleolus as normal, decreased/abnormal or absent) and overall clinical impression since baseline (as improved, remain unchanged or worsened). Positive straight-leg raising or femoral stretch test will also be summarized. A data listing of neurological evaluations will be provided.

6.7.1.7 Physical examinations

The number of patients reporting abnormalities for physical examination will be tabulated for all scheduled time points using counts and percentages for each body system. Physical examination results will be displayed in the subject data listings.

6.7.1.8 Halting rules

The number of subjects with AEs defined as halting rules (HRs) will be described and evaluated. Halting rule is explained in the appendix 4.

6.7.2 Analysis of Exploratory Efficacy Endpoints

Exploratory efficacy endpoints analyses will be performed on the full analysis set and per protocol set and all analyses will be presented using descriptive statistics as mentioned in the section 4. For all measures other than the daily pain, the baseline value is defined as the last assessment result collected prior to the first dose of study medication. For daily pain assessments, the baseline value is defined as the average of the results of 5 consecutive days prior to the first dose of study medication.

The following are the primary exploratory efficacy endpoints:

- Change from baseline in lower back pain or leg pain (numerical pain scale for each sub categories as mentioned below) at 6 and 13 weeks

  - Leg average daily pain
  - Leg worst daily pain
  - Low back average daily pain
  - Low back worst daily pain
  - Current leg pain
  - Current low back pain
- Number of subjects requiring:
  - Additional pain medication (and amounts) added to the subject's baseline pain regimen within the first 13 weeks post-dose
  - An epidural injection, a selective nerve root block, or a facet block after receiving study drug,
  - 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

Pharmacodynamic Parameters

- Serum concentrations of keratan sulfate at every time point.

Lower back or leg pain

Lower back and leg pain assessed using an 11-point numerical rating scale. Visit value and change from baseline average daily, worst daily and current lower back pain or leg pain (numerical pain scale) at 6 and 13 weeks will be summarized by cohort. Visit value and change from baseline for other visits also summarized in a separate table. Listing will be provided for lower back and leg pain data [1]. Line graphs of baseline and post-baseline values for each pain categories will be graphically displayed for each subject by cohort.

Use of rescue medication or surgical intervention

The number of subjects used rescue medications and list of rescue medication will be summarized by cohort and it will be listed. Summarization includes additional pain medication (and amounts) added to the subject's baseline pain regimen within the first 13 weeks post-dose, an epidural injection, a selective nerve root block, or a facet block after receiving study drug and surgical intervention for lumbar disc herniation.

Spinal flexion and tension

Spinal flexion and tension 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. Visit value and change from baseline (i.e. percentage 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 will be summarized by cohort. Rest of the time point details will be summarized same as mentioned above as a separate table. Listing will be provided for the spinal flexion and tension data.

Functional ability

The Oswestry disability index (ODI) is a patient self-scored questionnaire and 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 ODI will be administered at baseline, on day 1 pre-dose, at 24 hours post-dose, and at all post-dose visits. The improvement or lack of improvement in functional level is determined as a change from baseline in the score. Visit value and change from baseline in ODI at 6 and 13 weeks will be summarized by cohort. Rest of the time point details will be also summarized. Listing will be provided.

Score is calculated as patient score/total possible score x 100 = %. Scores will be grouped into levels of disabilities of 0% - 20% = minimal disability, 20% - 40% = moderate disability, 40% - 60% = severe disability, 60% - 80% = crippled, 80% - 100% = bed bound and it will also summarize.

Quality of life

Quality of life evaluated using the SF-12 form (version 2.0). 8 domains scores will be summarized for change from baseline in the SF-12 at 6 and 13 weeks descriptive by cohort. Quality of life results will be displayed in the subject data listings. The SF-12 will be administered at baseline, on day 1 pre-dose, at 24 hours post- dose, and at all post-dose visits. Rest of the time point details will also be summarized.

Global impression of change or improvement

Global impression of improvement as measured by the patient global impression of change (PGI-C) 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. Visit value and change from baseline in PGI-C score at 6 and 13 weeks will be summarized by cohort. Visit value and change from baseline for other visits also summarized in a separate table same as mentioned above. Listing will be provided for PGI-C score.

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). Visit value in treated herniated disc size, the improvement of the stenosis of spinal canal, and the reduction of associated lateral neural foramen compression for each visit

will be summarized by cohort and will be presented using descriptive statistics as mentioned in the section 4.

The correlation between imaging findings and symptoms (e.g., average daily, worst daily and current lower back pain or leg pain values and ODI score) will be conducted after database lock as part of the report analysis for each visit by cohorts. Spearman rank correlation coefficient and p-value will be presented. Additionally listing will also be provided.

Pharmacodynamic Parameters

Serum concentrations of keratan sulfate and change from the baseline at every time point will be summarized and corresponding listings will also be provided.

6.8 Other Safety Endpoints

Other safety endpoint includes serum pregnancy test and KTP-001 Antibody and serum concentration of KTP-001 will be summarized and listed. Other tests of urine pregnancy test, HBsAg, anti-HCV, anti-HIV, KTP-001 Antibody and serum concentration will be listed as subject data listings. Line graphs of baseline and post-baseline values will be graphically displayed for each subject by cohort.

7.0 HANDLING OF MISSING VALUES AND OUTLIERS

All available safety and efficacy data will be included in data listings and tabulations. No imputation of values for missing data will be performed.

When laboratory test results are above or below the limit of quantification (i.e proceeded by a "<" or ">" sign, for example "<xx"), the numerical value, xx, will be used for calculation in summary tables.

Missing or partially date missing for AEs/TEAE:

if due to partial dates or times it is not possible to definitively conclude that an AE is not treatment emergent, then a conservative approach will be taken whereby it will be classified as a TEAE e.g. if the first dose of study drug is "13May" and the AE starts in "May", then that AE will be classified as a TEAE, unless the AE stop date precludes this (i.e. the AE stop date is definitively prior to the first dose of study drug).

Missing or partially missing medication date and Prior or Concomitant Medication (CM) determination:

If due to partial dates it is not possible to categorize a medication as prior or concomitant, then a conservative approach will be taken whereby it will be classified as such e.g. if the first dose of study drug is "13May" and another medication is started in "May", then that medication will be classified as both previous and concomitant, unless the medication stop date precludes one of these classifications.

Missing safety data will not be replaced, except for AE and CM dates as described above.

Adverse events with missing severity will be summarized as severe. Adverse events with missing causal relationship will be summarized as related.

8.0 INTERIM ANALYSIS

No Interim analysis will be performed.

9.0 CHANGES FROM ANALYSIS METHODS PLANNED IN THE PROTOCOL

The planned protocol analysis of PK parameters and summary on counting the rescue medications were removed.

10.0 REFERENCES

1. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain.2005; 113(1-2):9-19.
2. Pierre R Dupuis, Ken Yong-Hing, J David Cassidy, William H Kirkaldy Willis. Radiological diagnosis of degenerative lumbar spinal instability. Spine 1985; 10((3): 262-76.

11.0 APPENDIX

Appendix 1: Schedule of assessment 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					
Lower Back Pain or 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.

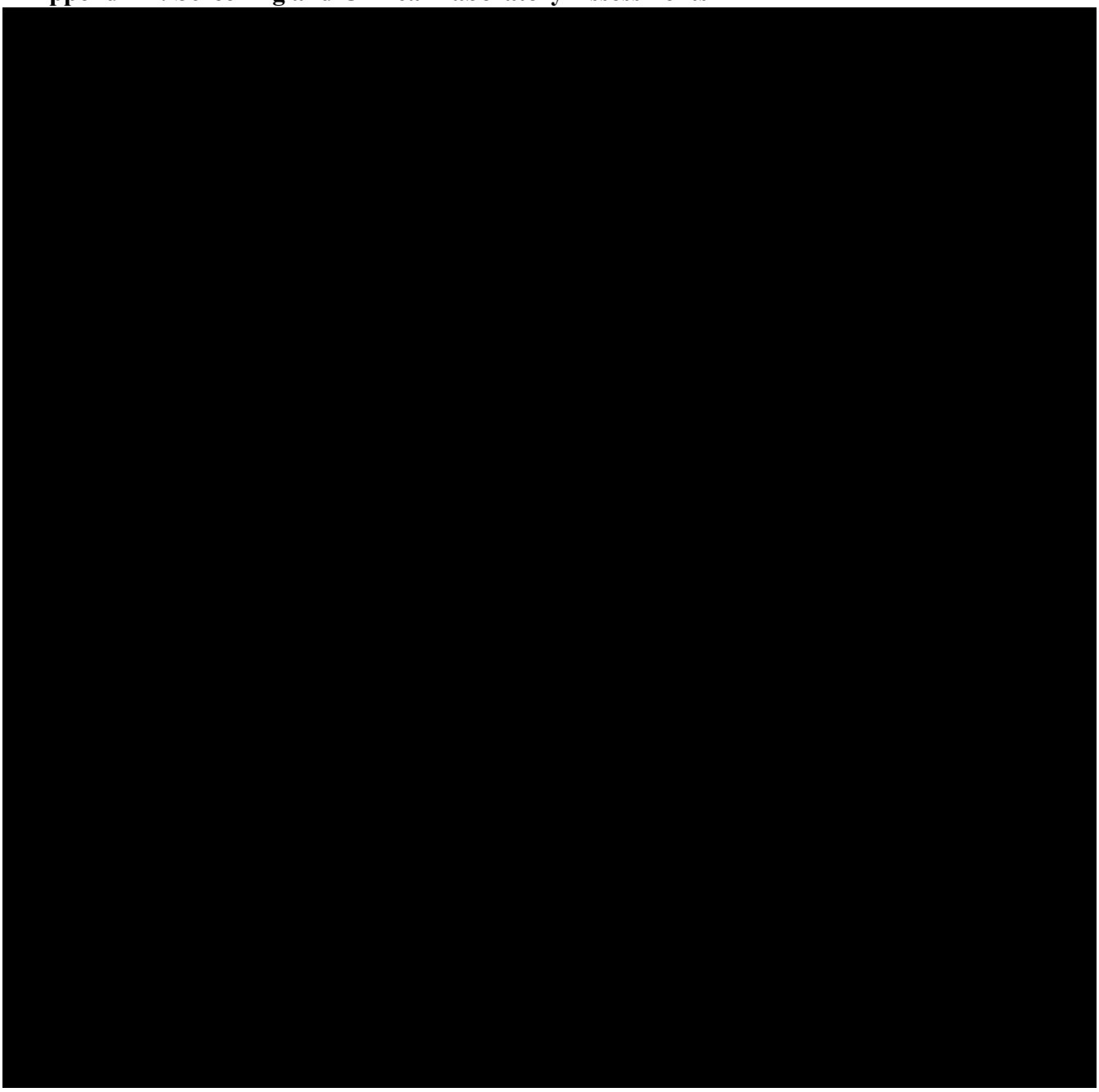
e. Hematology, coagulation, serum chemistry, and urinalysis.

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.

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.

Appendix 2: Screening and Clinical Laboratory Assessments



Appendix 3: Definition

Adverse event (AE)

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

The following AEs will be considered an AESI:

1. MRI or X-ray findings of Modic changes, reduction of disc height, or evidence of lumbar instability, 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.

Serious Adverse event (SAE)

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.

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.

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.

Appendix 4: 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 Data and Safety Monitoring Board (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) [2] 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.