Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel Group, Multicenter Study to Evaluate the Safety and Efficacy of SP-103 in Subjects with Moderate to Severe Acute Lower Back Pain
NCT Number:	NCT05096494
Document Date:	17 December 2021

Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel Group, Multicenter Study to Evaluate the Safety and Efficacy of SP-103 in Subjects with Moderate to Severe Acute Lower Back Pain
Protocol Number:	SP-103-02
Clinical Phase:	2
Protocol Version and Date:	Version 2.0, 17 December 2021
US Investigational New Drug Number:	CBI
Sponsor:	Scilex Pharmaceuticals Inc. 960 San Antonio Road, Suite 100 Palo Alto, CA 94303

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SIGNATURE PAGE

Protocol Title: A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel Group, Multicenter Study to Evaluate the Safety and Efficacy of SP-103 in Subjects with Moderate to Severe Acute Lower Back Pain.

The undersigned have reviewed the format and content of this protocol and have approved the clinical study protocol. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with Declaration of Helsinki and accepted GCP principles per International Conference on Harmonisation, and to abide by the terms of this protocol.

Any modifications of the clinical study protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.



Investigator Agreement:

I have read the clinical study protocol and agree to conduct the study as outlined herein.

_____

Signature and Date

Name (print): _____

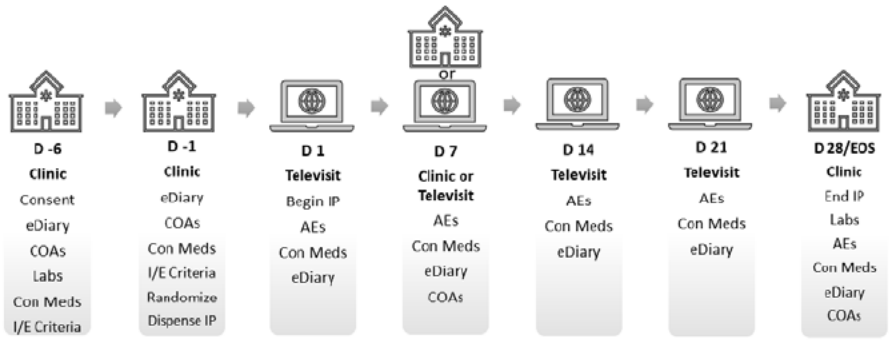
SUMMARY OF CHANGES: PROTOCOL VERSION 1.0 TO 2.0

- CBI

SYNOPSIS

Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel Group, Multicenter Study to Evaluate the Safety and Efficacy of SP-103 in Subjects with Moderate to Severe Acute Lower Back Pain
Protocol Number:	SP-103-02
Investigational Product:	SP-103 CBI
Phase of Development:	2
Investigator(s)/Study Center(s):	This study will be conducted at up to 10 study sites in the United States (US).
Planned Sample Size:	Approximately 80 subjects will be randomized in this study. The sample size goal of this study is for 70 subjects to complete first week (D7) of the study.
Objectives:	The primary objectives of this study are to: • Evaluate the safety and tolerability of SP-103. • Evaluate the analgesic effect of SP-103 in the treatment of acute lower back pain (LBP) The secondary objectives of the study are to: • Evaluate degree of disability over time. • Evaluate global impression of change. • Evaluate cumulative use of rescue medication. • Characterize the change of the subject's LBP symptoms. • Evaluate subject adhesion self-assessment of the topical system. • Evaluate muscle spasms. • Evaluate treatment satisfaction with Pain Treatment Satisfaction Scale (PTSS). The exploratory objective is to: • Assess the impact on treatment response of the psychological features of subjects with LBP using the Multidimensional Psychological Questionnaires (MPsQ).
Study Design:	This is a Phase 2, randomized, double-blind, placebo-controlled, parallel group, multicenter study to evaluate the safety and efficacy of SP-103 in subjects with moderate to severe acute LBP. **Screening Visit (D-6 ± 2 days):** After providing informed consent, each subject will complete a Screening Visit. The Screening Visit will include collection of blood and urine samples for clinical laboratory tests, drug screen, and pregnancy test (for women of child-bearing potential). A physical exam, height, weight, vital signs, electrocardiogram (ECG), and clinical rating scales will be done. Subjects will receive accurate pain reporting training, training on the use of a handheld electronic clinical outcome assessment device (eDiary), training on how a clinical research alliance with study staff differs from a clinical practice alliance, and concomitant and rescue medication requirements for the study. Subjects will record their worst, average, current at rest, and current on movement pain in their lower back in the last 24 hours using the numeric pain rating scale (NPRS) in the eDiary. Subjects meeting all the study inclusion criteria and none of the exclusion criteria at the Screening Visit, will be

	asked to discontinue all prohibited therapies, and will be provided with rescue medication and an eDiary to begin reporting daily pain scores. Subjects will be asked to return to for a Baseline Visit between 3 and 7 days after the Screening Visit. During the screening period, subject's medical eligibility will be also reviewed and confirmed by the study Medical Monitor. Subjects can progress to Baseline (D-1) only after medical eligibility approval is provided. **Baseline Visit (D-1):** Three to 7 days after the Screening Visit, subjects will return for a Baseline Visit to verify eDiary compliance, collect urine samples for a drug screen and pregnancy test (for women of child-bearing potential), and complete baseline clinical rating scales. If subjects meet all the study inclusion criteria and none of the exclusion criteria at the Baseline Visit, they will be allowed to proceed to randomization. **Randomization (D-1):** Subjects may only proceed to randomization after all eligibility criteria have been confirmed by site staff at the Baseline Visit. Each subject will be randomly (1:1) assigned to receive SP-103 or placebo. The randomization schedule will be stratified by baseline pain intensity (moderate [NPRS 4-6] or severe [NPRS 7-9]) and sex. Prior to receiving investigational product (IP), randomized subjects will be instructed to complete the Multidimensional Psychological Questionnaire (MPsQ). The MPsQ questionnaires have been designed to specifically measure participant personality characteristics associated with the placebo response. Modules of the MPsQ questionnaire (BAS-MPsQ, HBB-MPsQ, STT-MPsQ and PDS-MPsQ) are self-reported by each subject and each item is rated on a 5-point scale ranging from 1 (strongly disagree) to 5 (strongly agree). Randomized subjects will then be provided with sufficient IP for the 28-day Treatment Period. Study staff will map the site of IP application for subjects based on area of maximum pain, train them on the proper application of IP, and confirm each subject's understanding of protocol requirements through the End of Study visit. **Treatment Period (D1-D28):** Randomized subjects will proceed into the Treatment Period. Subjects are expected to apply IP for 12 hours per study day (i.e., starting at 8AM ± 2 hours to evening), D1 through D28, and to record the time of IP applications and removals in the eDiary. Subjects will capture daily NPRS scores and topical adhesions assessments in the eDiary each evening prior the removal of IP. Subjects experiencing a lack of efficacy are to remain on study and continue treatment. Subjects will remotely report to the study site on D1, D7, D14, and D21 for a televisit evaluation by the Investigator or designee. D7 may optionally be completed in the clinic based on site and/or subject preference. **End of Study (D28):** On D28, subjects will return to the study site to complete the End of Study visit. Subjects will return any unused IP and unused rescue medication for drug accountability. The visit will include collection of blood and urine samples for clinical laboratory tests, drug screen, and pregnancy test (for women of child-bearing potential). A physical exam, vital signs, ECG, and clinical rating scales will be done, including an assessment of treatment satisfaction (PTSS). The eDiary will be returned to the study site. Any subject ending their study participation early between randomization and the last day of treatment (D28) will be encouraged to complete the EOS Visit and will be considered an Early Terminator. **Rescue Medication**

	CBI **Concomitant Medication** The use of medicated creams, patches, ointments, or gels containing lidocaine, capsaicin, methyl salicylate or menthol, tetrahydrocannabinol (THC) or cannabidiol (CBD)-containing products, the Qutenza® capsaicin patch, steroids, opioids, anti-epileptics, antidepressants, benzodiazepines, muscle relaxants, gabapentinoids, or any other analgesics intended to treat LBP are not permitted from the time of consent to the end of study participation. Subjects on non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesics, except rescue acetaminophen, for treating LBP must agree to discontinue use from the time of consent through the end of study participation and rely on rescue medication for inadequate control of LBP. Non-pharmacological therapy intended to treat LBP such as tapes (e.g., KT tape®), heat therapy (e.g., heat packs/pads, sauna, hot tub), cold therapy (e.g., ice pack), and neurostimulators are not to be used from the time of consent to the end of study participation.
Study Schematic	
Subject Selection Criteria:	**Inclusion Criteria:** Subjects must meet all the Inclusion Criteria and none of the Exclusion Criteria in order to proceed to randomization: 1. Able and willing to read, write, and understand the English language and provide English-language written informed consent prior to beginning any study procedures. 2. Male or female, age 18 to 75 years (inclusive) at the Screening Visit. 3. CBI CBI

7. CBI [redacted]

11. If a woman of childbearing potential (WOCBP), agrees to use an effective method of birth control during the study. CBI [redacted]

14. Reviewed all study-specific educational materials and has, in the opinion of the Investigator, the cognitive abilities to understand and appropriately complete all study-mandated procedures.

Exclusion Criteria:

Subjects meeting any of the following Exclusion Criteria should not continue with any other study procedures and will be considered a screen failure:

1. A body mass index (BMI) ≥40 kg/m^2 (without rounding) at the Screening Visit.
2. Significant pain unrelated to LBP which, in the Investigator's and/or Sponsor's opinion, would significantly compromise assessment of LBP.
3. Has LBP due to any of the following pathologies: infection, neoplasia, severe metabolic or structural disease of spine, lumbar radiculopathy, osteoporosis, hip dysplasia, inflammatory arthritis, ankylosing spondylitis, Paget's disease, cauda equina syndrome, gout, pseudogout, fibromyalgia, active post-surgical pain, or pain over neurostimulator battery site.
4. Has LBP caused by major trauma.
5. Has had history of lower back surgery.
6. Has excess hair that cannot be clipped (shaving/waxing is not permitted to the area), excess tattoo(s), or other dermatological conditions in the topical system application area that may interfere, in the opinion of the Investigator, with administration, efficacy, and safety evaluations.
7. Use of Qutenza on the back within 3 months prior to the Screening Visit.
8. Use of opioids for ≥4 days per week during the 28 days prior to the Screening Visit.

	9. Unwilling to discontinue all opioids, NSAIDs, other analgesics, or non-pharmacological therapy intended to treat LBP such as tapes (e.g., KT tape®), heated heat therapy (e.g., heat packs/pads, sauna, hot tub), or cold therapy (e.g., ice pack) for the duration of the trial. 10. Unwilling to maintain the same regimen of physical activities throughout study participation. 11. Anxiety or depression based on the Hospital Anxiety and Depression Scale (HADS) scores ≥15 at Screening Visit, or has a major psychiatric disorder not controlled with medication that would interfere with clinical pain scores or participation in the trial. 12. Alcohol dependence, illicit drug use based on urine screen (including recreational or medical use of THC-containing substances, or non-prescribed use of controlled drug substances), or drug addiction within 1 year of the Screening Visit. 13. Current COVID-19 infection, if tested according to local requirements. 14. Clinically significant abnormalities which, in the opinion of the Investigator, may compromise subject safety such as but not limited to:  15. Significant motor impairment, sensory deficits, pain in lower extremities, and/or new onset of bowel/bladder impairment based on history and neurological examination at the Screening Visit. 16. History of fibromyalgia or diagnosis of fibromyalgia based on American College of Rheumatology 2016 criteria: a. Pain in at least 4 of 5 regions. b. Symptoms present for longer than 3 months. c. Widespread Pain Index (WPI) >7 and Symptom Severity Score (SSS) >5 OR WPI=4 to 6 and SSS >9. 17. History of malignancy or evidence of malignancy, lymphoproliferative, or neoplastic disease except for successfully treated basal or squamous cell carcinoma of the skin or cervical intraepithelial neoplasia within 5 years of the Screening Visit. 18. If female, is lactating/breastfeeding, plans to breastfeed, or plans to become pregnant while participating in the study. 19. Known history of any clinically significant or unstable medical condition, any other disorder, condition or circumstance (including secondary gain) which in the opinion of the Investigator has the potential to prevent study completion and/or to have a confounding effect on outcome assessments. 20. Has a serious illness that resulted in hospitalization in the 28 days preceding the Screening Visit.

	21. History of Myocardial Infarction within the last 6 months, New York Heart Association (NYHA) Class III or higher congestive heart failure, and any clinically significant ECG abnormality or arrhythmias. 22. CBI [redacted] 23. Use of opioid and non-opioid analgesics for indications other than back pain. 24. Use of any investigational drug and/or device within 28 days prior to the Screening Visit or is scheduled to receive an investigational drug other than blinded study drug while participating in the study. 25. CBI [redacted]. 26. Is an employee, family member, or student of the Investigator or clinical site. Screen-failed subjects may rescreen with prior sponsor approval.
Study Drug(s):	**SP-103** (CBI [redacted]). Each active topical system is 10 cm × 14 cm. SP-103 topical system will be applied to a defined area of clean, dry, intact, healthy normal skin on the area of most tenderness, applied in the morning at 8 AM (± 2 hours) and worn for 12 hours (± 2 hours). **Placebo** Each placebo topical system is 10 cm × 14 cm. Each placebo topical system is comprised of the same formulation and structural components as the active SP-103 (with the exclusion of the drug). The placebo topical system will be applied to a defined area of clean, dry, intact, healthy normal skin on the area of most tenderness, applied in the morning at 8AM (± 2 hours) and worn for 12 hours (± 2 hours). **Rescue Medication** 500 mg acetaminophen tablets (up to 3 g daily) will be recorded by e-Diary in real time with current pain at rest and current pain on movement NPRS scores being collected just prior to taking a rescue tablet. One 500 mg tablet should be taken at a time. If pain persists, subjects will be advised to take the following tablet no earlier than one hour since the previous one.
Duration of Treatment:	Each subject will participate in the study for approximately 35 days which consists of a Screening Visit (D-6), Baseline Visit (D-1), D7, D14, D21 and D28.

Main Parameters of Efficacy:	Efficacy assessments include:
	• NPRS.
	  ○ Recorded in the eDiary daily, in the evening, every 24 hours (± 2 hours):
	  ▪ The worst LBP NPRS score.
	  ▪ The average LBP NPRS score.
	  ▪ The current at rest LBP NPRS score.
	  ▪ The current on movement pain LBP NPRS score.
	  ○ Recorded in the eDiary each time rescue medication is taken:

	▪ The current at rest LBP NPRS score. ▪ The current on movement LBP NPRS score. • Oswestry Disability Index (ODI). • Patient Global Impression of Change (PGIC). • Pain*DETECT*. • EuroQoL-5 Dimension (EQ-5D) scale. • Brief Pain Inventory Short Form (BPI-SF). • Clinician Global Impression of Change (CGIC). • Clinical Impression of Change – Muscle Spasms (CIC-MS). • Patient Impression of Change – Muscle Spasms (PIC-MS). • Use of rescue medication (acetaminophen) as captured in the eDiary. • Pain Treatment Satisfaction Scale (PTSS).
Main Parameters of Safety:	• Adverse events (AEs) including: o Treatment-emergent adverse events (TEAEs). o Serious adverse events (SAEs). o Treatment-emergent serious adverse events (TESAEs). o Adverse events of special interest (AESIs). o TEAEs leading to discontinuation. • Physical examination. • Vital signs (temperature, blood pressure and pulse). • Laboratory parameters (serum chemistry, hematology, and urinalysis). • ECG. • Topical system adhesion assessment.
Efficacy Endpoints:	The primary efficacy endpoint is: • The average LBP NPRS Summed Pain Intensity Difference (SPID) D1-D7. Key secondary endpoints are: • The mean ODI total score at D7. • The PGIC response at D7. Secondary endpoints are: • The average LBP NPRS SPID D1-D28. • The worst LBP NPRS SPID D1-D28. • The current on movement pain LBP NPRS SPID D1-D28. • The current at rest LBP NPRS SPID D1-D28. • The mean ODI total score at D28. • The PGIC response at D28. • The mean Pain*DETECT* score at D7 and D28. • The mean EQ-5D VAS score at D7 and D28. • The mean BPI-SF score at D7 and D28. • The CGIC response at D7 and D28. • Cumulative use of rescue medication (milligrams of acetaminophen) over 7 and over 28 days of treatment. • The PTSS at D7 and D28.

	• The CIC-MS at D28. • The PIC-MS at D28. Exploratory endpoints are: • Time to resolution of pain (Average pain by NPRS <2 over two consecutive days) • Placebell©™ composite covariate (placebo score) calculated for each participant by integrating participant personality characteristics (captured with MPsQ questionnaires) and other pertinent baseline features.
Safety Endpoints:	• AEs including: o TEAEs. o SAEs. o TESAEs. o AESIs. o TEAEs leading to discontinuation. • Change from Screening in physical examinations. • Change from Baseline in vital signs. • Change from Screening in laboratory parameters. • Change from Screening ECG assessments. • Topical system adhesion assessment. • Skin irritation assessment.
Statistical Analyses:	Approximately 80 subjects will be randomized using a 1:1 allocation to treatment sequence. The primary objectives of the study are to assess safety and tolerability of SP-103 and to provide treatment effect estimates that can be used to power future studies. As such sample size considerations are based on prevalence of uncommon AEs. Given that 40 subjects in the trial will receive SP-103, there is a 33% chance of observing at least one instance of an uncommon AE to occur in only 1 in 100 subjects. Chances are 87% of observing a more common AE expected to occur in 1 in every 20 subjects. A total sample size of 80 subjects is sufficient to observe more common AEs and possibly uncommon AEs and to also provide efficacy information to plan future studies. The Modified Intent-to-Treat (mITT) population will be the primary population for efficacy analyses and will include all randomized subjects who receive any amount of study drug. The Intent-to-Treat population will include all randomized subjects and will be used for sensitivity analyses. The Per Protocol population will include all subjects in the mITT who do not have a major protocol deviation. Major protocol deviations will be determined prior to treatment unblinding and will be used for sensitivity analyses. The Safety population will be the primary population for safety analyses and will include all subjects who receive any amount of study drug. The primary efficacy endpoint is SPID D1-D7 (calculated as a time-weighted average) and will be analyzed to compare the efficacy of SP-103 and placebo, using the mITT population. The primary efficacy analysis will be performed using an analysis of covariance (ANCOVA) model, which includes treatment group, baseline severity level (moderate or severe), and sex as the factors and baseline pain intensity as the covariate. The least squares (LS) mean and 95% confidence interval for each treatment, the LS mean difference between treatment groups, and the associated p-value and 95% confidence interval for the mean difference will be computed from the ANCOVA model. Sensitivity analyses will be performed using

	different methods for any missing data and using different analysis sets (e.g., Per Protocol). Other efficacy variables will also be analyzed using similar ANCOVA models, mixed models for repeated measures (MMRM), Cochran-Mantel-Haenszel tests, and logistic regression models. While all tests will be performed using 2-sided tests at the alpha=0.05 level, no adjustment for multiplicity will be applied for this exploratory study. The focus of interpreting the results will be based on effect size estimates and corresponding confidence intervals. Safety summaries without statistical testing will be provided for summaries of TEAEs, SAEs, TESAEs, AESIs, TEAEs leading to discontinuation, physical examinations, clinical laboratory evaluations, vital sign measurements, topical system adhesion scores, skin assessment scores, and ECG assessments.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
α	alpha
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event(s) of special interest
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANCOVA	analysis of covariance
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC_{0-t}	area under the concentration-time curve from time-zero to time post-dose
BAS-MPsQ	first module of MPsQ
BMI	body mass index
BP	blood pressure
BPI-SF	Brief Pain Inventory-Short Form
bpm	beats per minute
C	Celsius
CBD	cannabidiol
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
CGIC	Clinical Global Impression of Change
CGIS	Clinical Global Impression of Severity
CIC-MS	Clinical Impression of Change – Muscle Spasms
CIS-MS	Clinical Impression of Severity – Muscle Spasms
C_{max}	maximum concentration
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COA	Clinical Outcomes Assessment(s)
CPIM	Critical Path Innovation Meeting
CRA	clinical research associate
CV	coefficient of variation
D	day
DAL	Daily Acetaminophen Log
DDE	direct data entry
DRC	Data Review Committee
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
eCRF	electronic case report form
EOS	end of study
EQ-5D	EuroQoL-5 Dimension scale
EQ-VAS	EuroQoL visual analog scale
ET	early termination

Abbreviation	Definition
F	Fahrenheit
FDA	Food and Drug Administration
g	gram
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GX	glycinexylidide
HADS	Hospital Anxiety and Depression Scale
HBB-MPsQ	second module of MPsQ
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IND	Investigational New Drug
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
LBP	lower back pain
LFT	liver function tests
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MEGX	monoethylglycinexylidide
mg	microgram
mg	milligram
min	minutes
mITT	Modified Intent-to-Treat (dataset)
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
MMRM	mixed models for repeated measures
MPsQ	Multidimensional Psychological Questionnaire
NPRS	Numeric Pain Rating Scale
NSAID	nonsteroidal anti-inflammatory drug(s)
NYHA	New York Heart Association
ODI	Oswestry Disability Index
PABA	para-amino benzoic acid
PDS-MPsQ	third module of MPsQ
PET	polyethylene terephthalate

Abbreviation	Definition
PGIC	Patient Global Impression of Change
PHN	post-herpetic neuralgia
PIC-MS	Patient Impression of Change – Muscle Spasms
PID	pain intensity difference
PK	pharmacokinetic
po	given by mouth
PRN	pro re neta (as needed)
PTSS	Pain Treatment Satisfaction Scale
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDTM	Study Data Tabulation Model
SOP	standard operating procedure
SPID	summed pain intensity difference
SSS	Symptom Severity Score
STT-MPsQ	fourth module of MPsQ
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event
THC	tetrahydrocannabinol
T_{max}	time to maximum concentration
US	United States
WBC	white blood cells
WOCBP	woman of childbearing potential
CBI	[redacted]
WPI	Widespread Pain Index

1 INTRODUCTION

1.1 SP-103 Background

Lower back pain (LBP) is a common condition that effects about 80% of adults at some time during their lifetime.[1] Topical analgesic products are often used off-label as part of the arsenal to treat LBP. Prescription topical systems or over-the-counter patches and creams containing local anesthetic lidocaine have shown benefits in treating neuropathic and nociceptive LBP, where large size patches can be easily applied to the area around the spine. However, no formulations containing local anesthetics have been approved by the Food and Drug Administration (FDA) for such an indication, and the general perception is that while such treatment options are safe, they are not strong enough to provide adequate pain control and, therefore, are often used as adjuvant therapies.



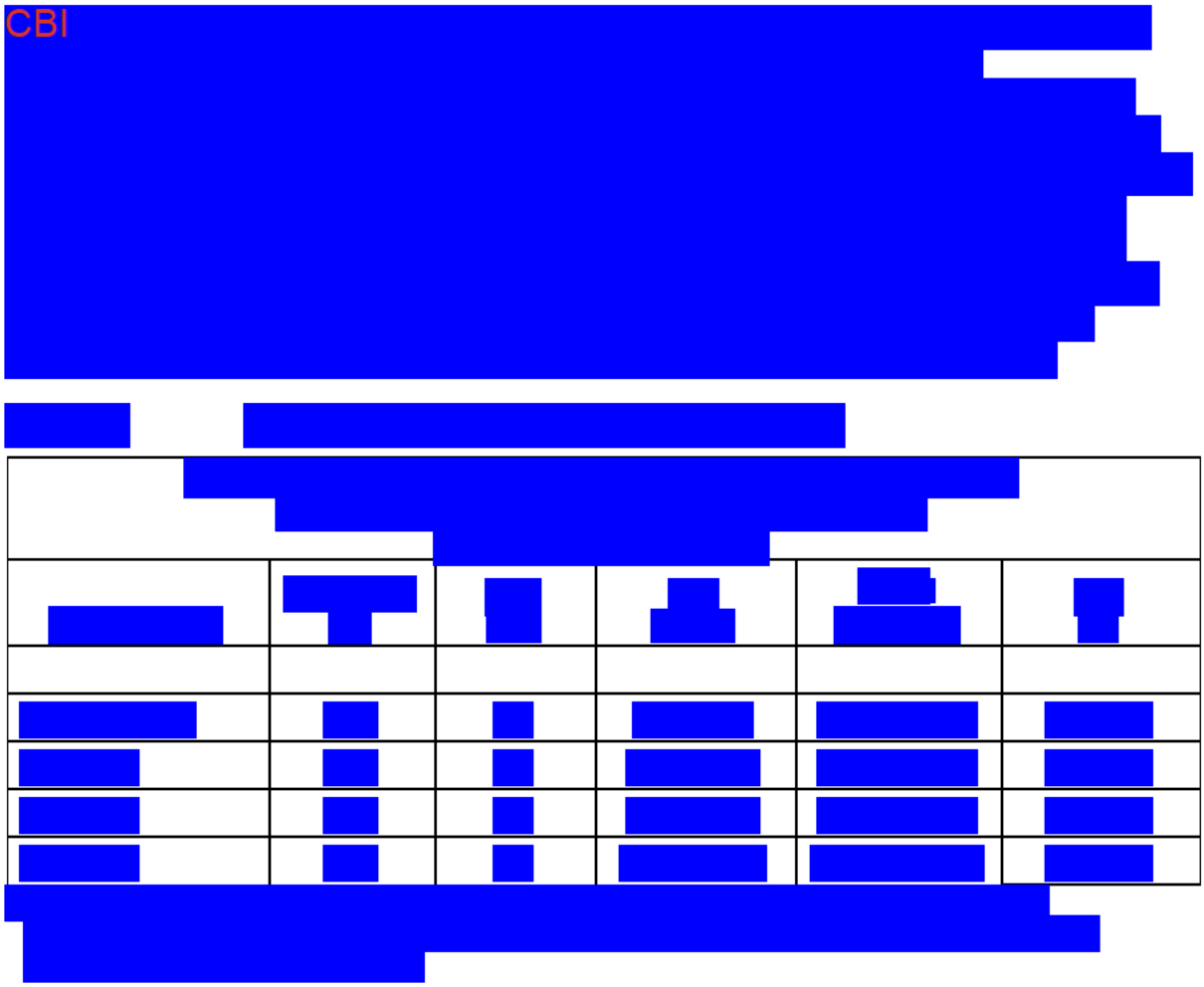
1.1.1 Pharmacodynamics



1.1.2 Pharmacokinetics

1.1.2.1 Absorption

CBI







1.2 Clinical Studies



1.3 Study Rationale

The proposed clinical use of SP-103 is for the treatment of acute LBP. For the purpose of product registration with FDA and other global regional medicinal agencies, the current trial is being performed to investigate safety and efficacy of SP-103 in a multicenter, randomized, double-blind, placebo-controlled, parallel-group study design.

1.4 Dose Rationale



CBI [redacted]

1.5 Study Endpoint Rationale

CBI [redacted]

1.6 Risks and Benefits for Subjects

SP-103 is a high-dose strength lidocaine topical system. Other topical lidocaine products are currently used off-label to treat musculoskeletal LBP. Higher drug load with higher level of delivered drug may produce greater pain relief in this patient population. Superior adhesive qualities of SP-103 patches are expected to contribute to better treatment compliance, reliable drug delivery and therefore provide a meaningful benefit to patients.

CBI [redacted]

The purpose of SP-103 system is to deliver sufficient drug concentration locally to the area of pain, while avoiding high systemic exposures associated with toxicity risks.

If a subject experiences symptoms of toxicity (Section 4.1.5), application of SP-103 topical system should be immediately discontinued.

1.6.1 Contraindications

SP-103 is contraindicated in patients with a known history of sensitivity CBI [redacted]

See the IB for SP-103 Lidocaine Topical System for more information.[2]

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objectives of this study are to:

- Evaluate the safety and tolerability of SP-103.
- Evaluate the analgesic effect of SP-103 in the treatment of acute lower back pain.

2.2 Secondary Objectives

The secondary objectives of the study are to:

- Evaluate degree of disability over time.
- Evaluate global impression of change.
- Evaluate cumulative use of rescue medication.
- Characterize the change of the subject's LBP symptoms.
- Evaluate subject adhesion self-assessment of the topical system.
- Evaluate muscle spasms.
- Evaluate treatment satisfaction with Pain Treatment Satisfaction Scale (PTSS).

2.3 Exploratory Objectives

The exploratory objective is to:

- Assess the impact on treatment response of the psychological features of subjects with LBP using the Multidimensional Psychological Questionnaires (MPsQ).

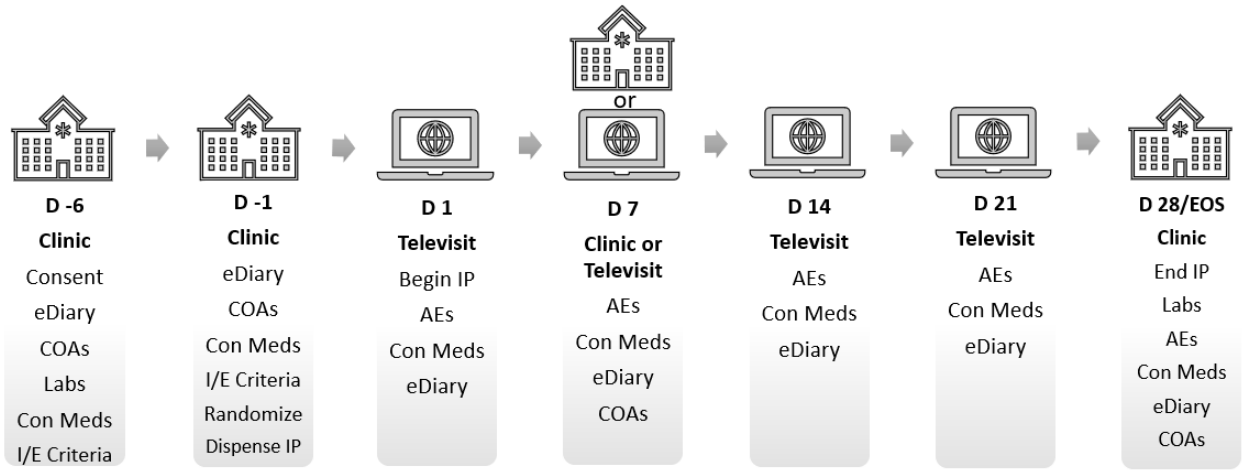
3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel group, multicenter study to evaluate the safety and efficacy of SP-103 in subjects with moderate to severe acute LBP.

The study is depicted in Figure 3.1.

Figure 3.1 Study Schematic



Screening Visit (D-6 ±2 days):

After providing informed consent, each subject will complete a Screening Visit. The Screening Visit will include collection of blood and urine samples for clinical laboratory tests, drug screen, and pregnancy test (for women of child-bearing potential). A physical exam, height, weight, vital signs, electrocardiogram (ECG), and clinical rating scales will be done. Subjects will receive accurate pain reporting training, training on the use of a handheld electronic clinical outcome assessment device (eDiary), training on how a clinical research alliance with study staff differs from a clinical practice alliance, and concomitant and rescue medication requirements for the study. Subjects will record their worst, average, current at rest, and current on movement pain in their lower back in the last 24 hours using the numeric pain rating scale (NPRS) in the eDiary. Subjects meeting all the study inclusion criteria and none of the exclusion criteria at the Screening Visit, will be asked to discontinue all prohibited therapies, and will be provided with rescue medication and an eDiary to begin reporting daily pain scores. Subjects will be asked to return to for a Baseline Visit between 3 and 7 days after the Screening Visit. During the screening period, subject's medical eligibility will be also reviewed and confirmed by the study Medical Monitor. Subjects can progress to Baseline (D-1) only after medical eligibility approval is provided.

Baseline Visit (D-1):

Baseline

Three to 7 days after the Screening Visit, subjects will return for a Baseline Visit to verify eDiary compliance, collect urine samples for a drug screen and pregnancy test (for women of child-bearing potential), and complete baseline clinical rating scales. If subjects meet all the study inclusion criteria and none of the exclusion criteria at the Baseline Visit, they will be allowed to proceed to randomization.

Randomization

Subjects may only proceed to randomization after all eligibility criteria have been confirmed by site staff at the Baseline Visit. Each subject will be randomly (1:1) assigned to receive SP-103 or placebo. The randomization schedule will be stratified by baseline pain intensity (moderate (NPRS 4-6) or severe [NPRS 7-9)]) and sex.

Prior to receiving investigational product (IP), randomized subjects will be instructed to complete the Multidimensional Psychological Questionnaires (MPsQ), that have been designed to specifically measure participant personality characteristics associated with the placebo response. Modules of the MPsQs (BAS-MPsQ, HBB-MPsQ, STT-MPsQ and PDS-MPsQ) are self-reported by each subject and each item is rated on a 5-point scale ranging from 1 (strongly disagree) to 5 (strongly agree).

Randomized subjects will then be provided with sufficient IP for the 28-day Treatment Period. Study staff will map the site of IP application for subjects based on area of maximum pain, train them on the proper application of IP, and confirm each subject's understanding of protocol requirements through the End of Study visit.

Treatment Period (D1-D28):

Randomized subjects will proceed into the Treatment Period. Subjects are expected to apply IP for 12 hours per study day (i.e., starting at 8AM ± 2 hours to evening), D1 through D28, and to record the time of IP applications and removals in the eDiary. Subjects will capture daily NPRS scores and topical adhesions assessments in the eDiary each evening prior the removal of IP. Subjects experiencing a lack of efficacy are to remain on study and continue treatment. Subjects will remotely report to the study site on D1, D7, D14, and D21 for a televisit evaluation by the Investigator or designee. D7 may optionally be completed in the clinic based on site and/or subject preference.

End of Study (D28):

On D28, subjects will return to the study site to complete the End of Study visit. Subjects will return any unused IP and unused rescue medication for drug accountability. The visit will include collection of blood and urine samples for clinical laboratory tests, drug screen, and pregnancy test (for women of child-bearing potential). A physical (including neurological) exam, vital signs, ECG, and clinical rating scales will be done, including an assessment of treatment satisfaction (PTSS). The eDiary will be returned to the study site.

Any subject ending their study participation early between randomization and the last day of treatment with the topical system (D28) will be encouraged to complete the EOS Visit and will be considered an Early Terminator.

3.2 Study Duration

Each subject will participate in the study for approximately 34 days which consists of a Screening Visit (D-6), Baseline Visit (D-1), D7, D14, D21 and D28.

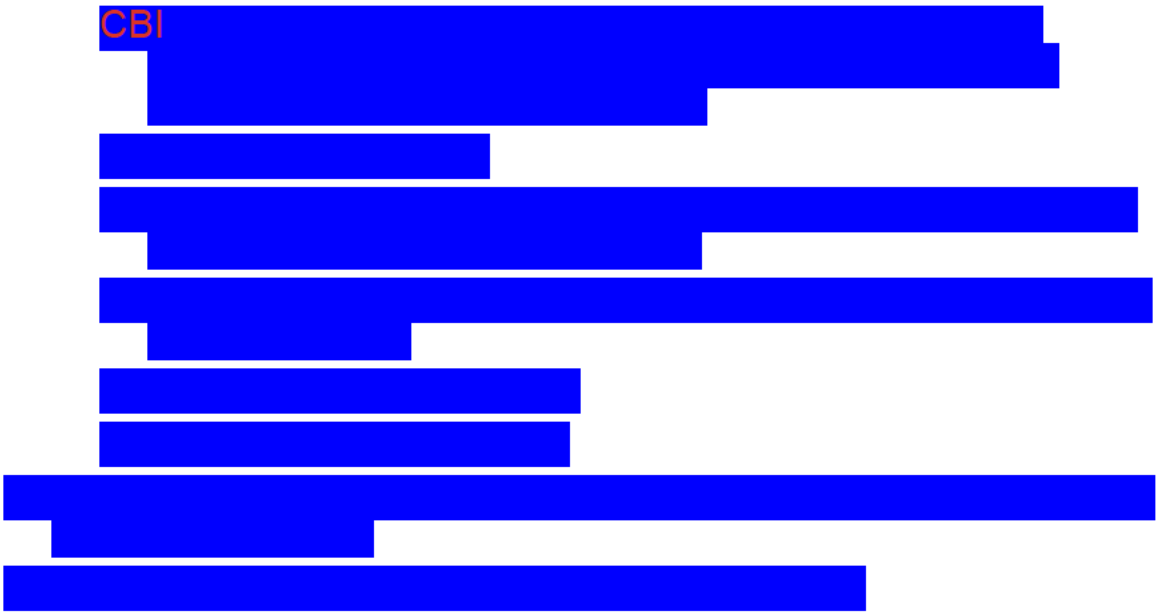
3.3 Selection of Study Population

Subject entry criteria are detailed in the following sections.

3.3.1 Inclusion Criteria

Subjects meeting all the following inclusion criteria should be considered for enrollment in the study. Subjects must meet all the Inclusion Criteria and none of the Exclusion Criteria in order to proceed to randomization:

1. Able and willing to read, write, and understand the English language and provide English-language written informed consent prior to beginning any study procedures.
2. Male or female, age 18 to 75 years (inclusive) at the Screening Visit.
3. CBI [redacted]
11. If a woman of childbearing potential (WOCBP), agrees to use an effective method of birth control during the study. CBI [redacted]



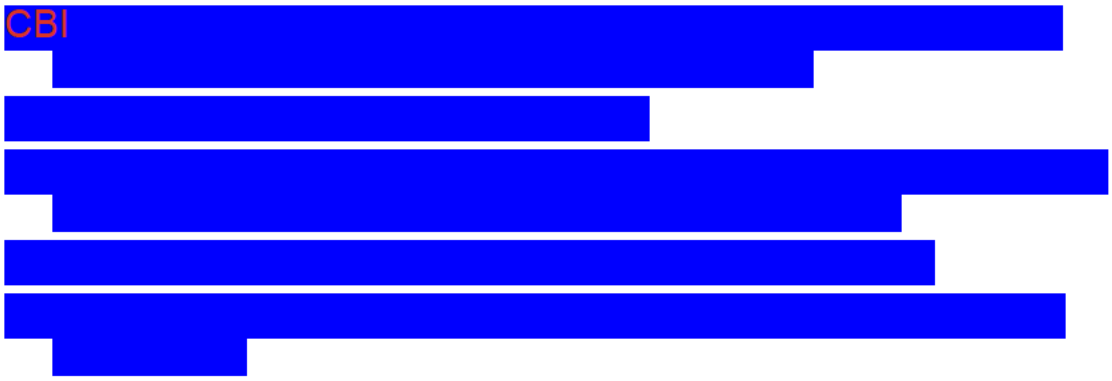
14. Reviewed all study-specific educational materials and has, in the opinion of the Investigator, the cognitive abilities to understand and appropriately complete all study-mandated procedures.

3.3.2 Exclusion Criteria

Subjects meeting any of the following Exclusion Criteria should not continue with any other study procedures and will be considered a screen failure:

1. A body mass index (BMI) ≥40 kg/m^2 (without rounding) at the Screening Visit (Appendix B).
2. Significant pain unrelated to LBP which, in the Investigator's and/or Sponsor's opinion, would significantly compromise assessment of LBP.
3. Has LBP due to any of the following pathologies: infection, neoplasia, severe metabolic or structural disease of spine, lumbar radiculopathy, osteoporosis, hip dysplasia, inflammatory arthritis, ankylosing spondylitis, Paget's disease, cauda equina syndrome, gout, pseudogout, fibromyalgia, active post-surgical pain, or pain over neurostimulator battery site.
4. Has LBP caused by major trauma.
5. Has had history of lower back surgery.
6. Has excess hair that cannot be clipped (shaving/waxing is not permitted to the area), excess tattoo(s), or other dermatological conditions in the topical system application area that may interfere, in the opinion of the Investigator, with administration, efficacy, and safety evaluations.
7. Use of Qutenza on the back within 3 months prior to the Screening Visit.
8. Use of opioids for ≥4 days per week during the 28 days prior to the Screening Visit.

9. Unwilling to discontinue all opioids, NSAIDs, other analgesics, or non-pharmacological therapy intended to treat LBP such as tapes (e.g., KT tape®), heat therapy (e.g., heat packs/pads, sauna, hot tub), or cold therapy (e.g., ice pack) for the duration of the trial.
10. Unwilling to maintain the same regimen of physical activities throughout study participation.
11. Anxiety or depression based on the Hospital Anxiety and Depression Scale (HADS, Appendix O) scores ≥15 at Screening Visit, or has a major psychiatric disorder not controlled with medication that would interfere with clinical pain scores or participation in the trial.
12. Alcohol dependence, illicit drug use based on urine screen (including recreational or medical use of THC-containing substances, or non-prescribed use of controlled drug substances), or drug addiction within 1 year of the Screening Visit.
13. Current COVID-19 infection, if tested according to local requirements.
14. Clinically significant abnormalities which, in the opinion of the Investigator, may compromise subject safety such as but not limited to:



15. Significant motor impairment, sensory deficits, pain in lower extremities, and/or new onset of bowel/bladder impairment based on history and neurological examination at the Screening Visit.
16. History of fibromyalgia or diagnosis of fibromyalgia based on American College of Rheumatology 2016 criteria (Appendix A):
    a. Pain in at least 4 of 5 regions.
    b. Symptoms present for longer than 3 months.
    c. Widespread Pain Index (WPI) >7 and Symptom Severity Score (SSS) >5 OR WPI=4 to 6 and SSS >9.
17. History of malignancy or evidence of malignancy, lymphoproliferative, or neoplastic disease except for successfully treated basal or squamous cell carcinoma of the skin or cervical intraepithelial neoplasia within 5 years of the Screening Visit.
18. If female, is lactating/breastfeeding, plans to breastfeed, or plans to become pregnant while participating in the study.

19. Known history of any clinically significant or unstable medical condition, any other disorder, condition or circumstance (including secondary gain) which in the opinion of the Investigator has the potential to prevent study completion and/or to have a confounding effect on outcome assessments.
20. Has a serious illness that resulted in hospitalization in the 28 days preceding the Screening Visit.
21. History of Myocardial Infarction within the last 6 months, New York Heart Association (NYHA) Class III or higher congestive heart failure, and any clinically significant ECG abnormality or arrhythmias.
22. Has a hypersensitivity or allergy to the investigational compound/compound class being used in this study or any ingredients of this medication, CBI
23. Use of opioid and non-opioid analgesics for indications other than back pain.
24. Use of any investigational drug and/or device within 28 days prior to the Screening Visit or is scheduled to receive an investigational drug other than blinded study drug while participating in the study.

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26. Is an employee, family member, or student of the Investigator or clinical site.

Screen-failed subjects may rescreen with prior sponsor approval.

3.3.3 Removal of Subjects from Therapy or Assessment

A subject will be considered to have completed the study when he or she completes the D28/EOS/ET Visit. If a subject is discontinued at any time after randomization into the study but prior to completing the D28/EOS/ET Visits, the Investigator will make every effort to follow the subject and complete the D28/EOS/ET assessments.

A termination electronic case report form (eCRF) page should be completed for every subject who receives IP, whether the subject completes the study or not. The reason for any early discontinuation should be indicated on this form. The primary reason for a subject discontinuing early should be selected from the following standard categories of ET:

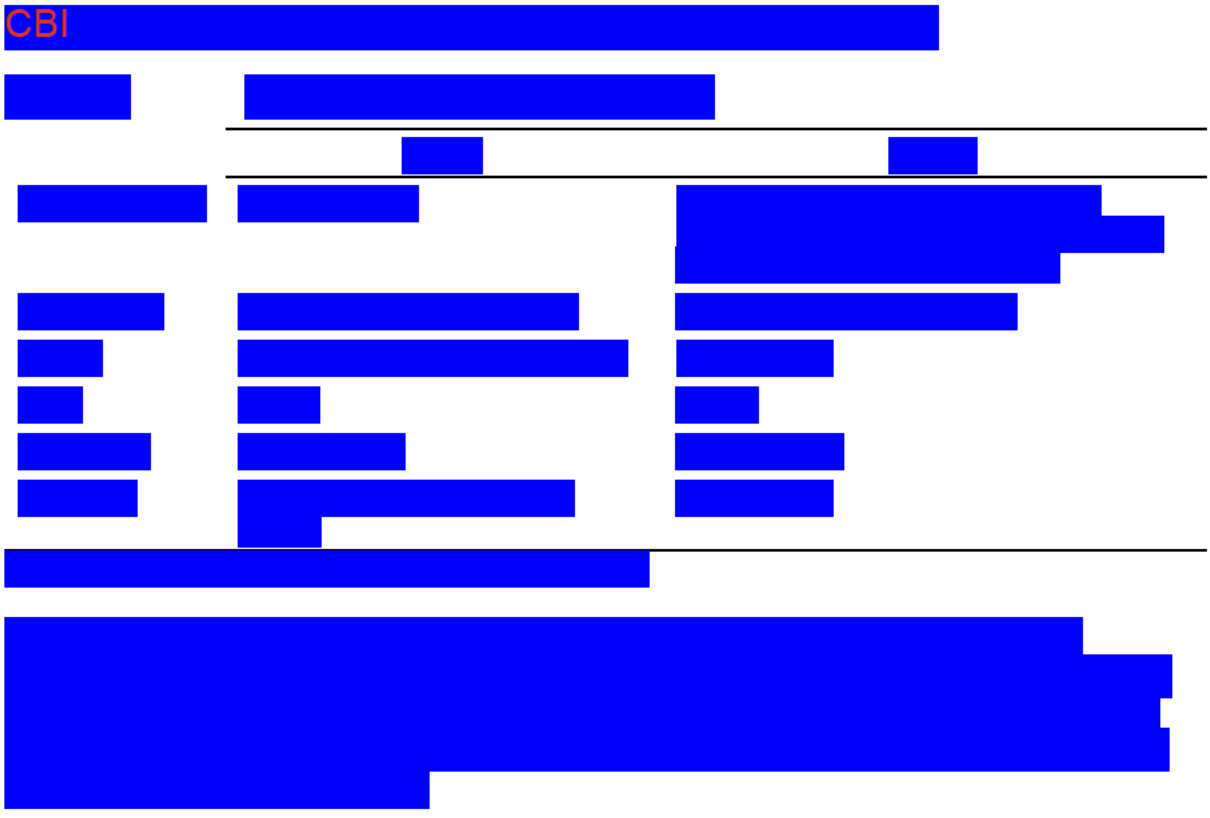
- *Medical History:* Screening or Baseline Visit outcomes resulting in clinically significant findings which, in the opinion of the Investigator, may compromise subject safety, confound study assessments, or interfere with participation in the trial.
- *Adverse Event*: Clinical or laboratory events occurred that, in the medical judgment of the Investigator for the best interest of the subject, are grounds for discontinuation.

This includes serious and nonserious adverse events (AEs) regardless of relation to the IP.

- *Death:* The subject died.
- *Withdrawal of Consent*: The subject desired to withdraw from further participation in the study in the absence of an Investigator-determined medical need to withdraw. If the subject gave a reason for withdrawing, it should be recorded in the eCRF.
- *Protocol Deviation*: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., drug noncompliance, failure to return for defined number of visits). The deviation necessitated early discontinuation from the study.
- *Lost to Follow-Up*: The subject stopped coming for visits and study personnel were unable to contact the subject.
- *Other*: The subject was discontinued for a reason other than those listed above, such as theft, loss of IP, or termination of study by Sponsor.

3.4 Treatments

3.4.1 Details of Study Treatments



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3.4.2 Dosage Schedule

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[redacted]

3.4.3 Treatment Assignment

After the subject has provided consent to participate in the study, the site staff will obtain a subject identification (ID) number. The subject ID number is to be used to identify the subject on all study documents, systems, and in the study database.

After the Investigator has confirmed that the subject fulfills all the inclusion/exclusion criteria at the Baseline Visit (D-1), the site staff will access the IRT to enter the subject into the Treatment Period where subjects will be randomized to receive SP-103 or placebo.

A subject is considered enrolled in the study only after randomization and their first dose of IP has been applied.

A randomization schedule will be employed to facilitate effective randomization. The schedule will involve a block randomization technique, randomly assigning participants within blocks based on a 1:1 allocation ratio.

3.4.4 Drug Packaging and Blinding

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[redacted]

3.4.5 Drug Inventory and Accountability

The Investigator must keep an accurate accounting of the number of IP and rescue acetaminophen units delivered to the site, dispensed to subjects, and returned to the Sponsor or other disposition during and at the completion of the study. The IP must be dispensed to subjects only by an appropriately qualified person. The IP is to be used in accordance with the protocol by subjects who are under the direct supervision of the Investigator. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all IPs and rescue acetaminophen received at the site before final disposition. At the end of the study, or as directed, all study drugs, including unused and empty containers/envelopes, may be destroyed on site or returned to the Sponsor or its designee. If destroyed on site, the destruction procedures must be reviewed and approved by the Sponsor or designee.

Drug accountability and reconciliation records will be maintained and be readily available for monitoring and auditing purposes, and will be made open to inspection by health authorities.

3.4.6 Treatment Compliance

Compliance with IP usage will be based on the daily application and removal times recorded by the subject each day in the eDiary and on the count of unused topical systems and the empty envelopes of the used topical systems returned at the last clinic visit.

3.4.7 Rescue Medication

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[redacted]



3.4.8 Prior and Concomitant Illnesses and Medications

3.4.8.1 Prior and Concomitant Illnesses

Investigators should document in the eCRF all significant illnesses that the subject has experienced within 3 months of the Screening Visit in the eCRF Medical History. Additional illnesses present at the time informed consent is given are to be regarded as concomitant illnesses. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF.

3.4.8.2 Prior and Concomitant Medications

All prescription and non-prescription medications (e.g., over-the-counter drugs and herbal supplements) that subjects report taking during the 3 months prior to the Screening Visit will be assessed and recorded in the eCRF Concomitant Medication. For each medication, documentation should list the trade or generic name, the total daily dose including units (or the dose, units and scheduled and actual frequency of administration if the medication is not taken daily), the route of administration, date(s) of administration, and the reason for use.

Concomitant medication refers to all drugs and therapies used from the time of informed consent through the D28/EOS/ET.

Changes, additions, or discontinuations to medications will be assessed and recorded in the eCRF during each study visit and at the D28/EOS/ET. All as needed (*pro re nata,* PRN) prescriptions should be converted to reflect actual number of pills and dose taken per day.

To be eligible for this study, each subject agrees that any oral, non-opioid analgesic medication regimen for indications other than LBP (e.g., neuropathic pain, cardiac

prophylaxis) will not be altered from the Screening Visit through the D28/EOS/ET Visit. The Investigator must inform the Medical Monitor (in advance, if possible) if a subject requires analgesic medications contrary to the protocol during the study.

3.4.8.3 Prohibited Medications, Substances, Treatments, and Activities

The following medications, substances, and treatments are prohibited from Screening through the D28/EOS/ET Visit:



Subjects should be encouraged to maintain the same level of physical activities and to avoid engagement in new physical therapy or chiropractic care throughout study participation.

3.4.8.4 Allowed Medications and Treatments



3.5 Assessments

Unless otherwise indicated, all assessments will be performed by the Investigator or designated study personnel and captured into eCRFs.

Remote visit assessments will be conducted via video (Televisits). The Investigator or study personnel need to have documented training on how to conduct real-time video conferencing visits (e.g., training on the use of telemedicine for remote clinical trial visits). Procedures need to be in place to maintain the study subject's privacy, as would be done for a clinical visit. If video is unavailable for a Televisit, an audio-only visit is an acceptable alternative.

During remote visits, both the Investigator and the study subject should confirm their respective identities with one another before engaging in a real-time video conference visit according to an identity verification plan. To provide the same information that would be documented during an in-clinic visit, the date of a real-time video conference visit should be documented in the eCRF and, if specified in the protocol, the time of the visit. Investigators should ask for the subject's location during a video conference visit in case a medical emergency arises during the visit.

3.6 Schedule of Assessments

The procedures to be performed throughout the study are outlined in the Schedule of Assessments (Table 3.2).

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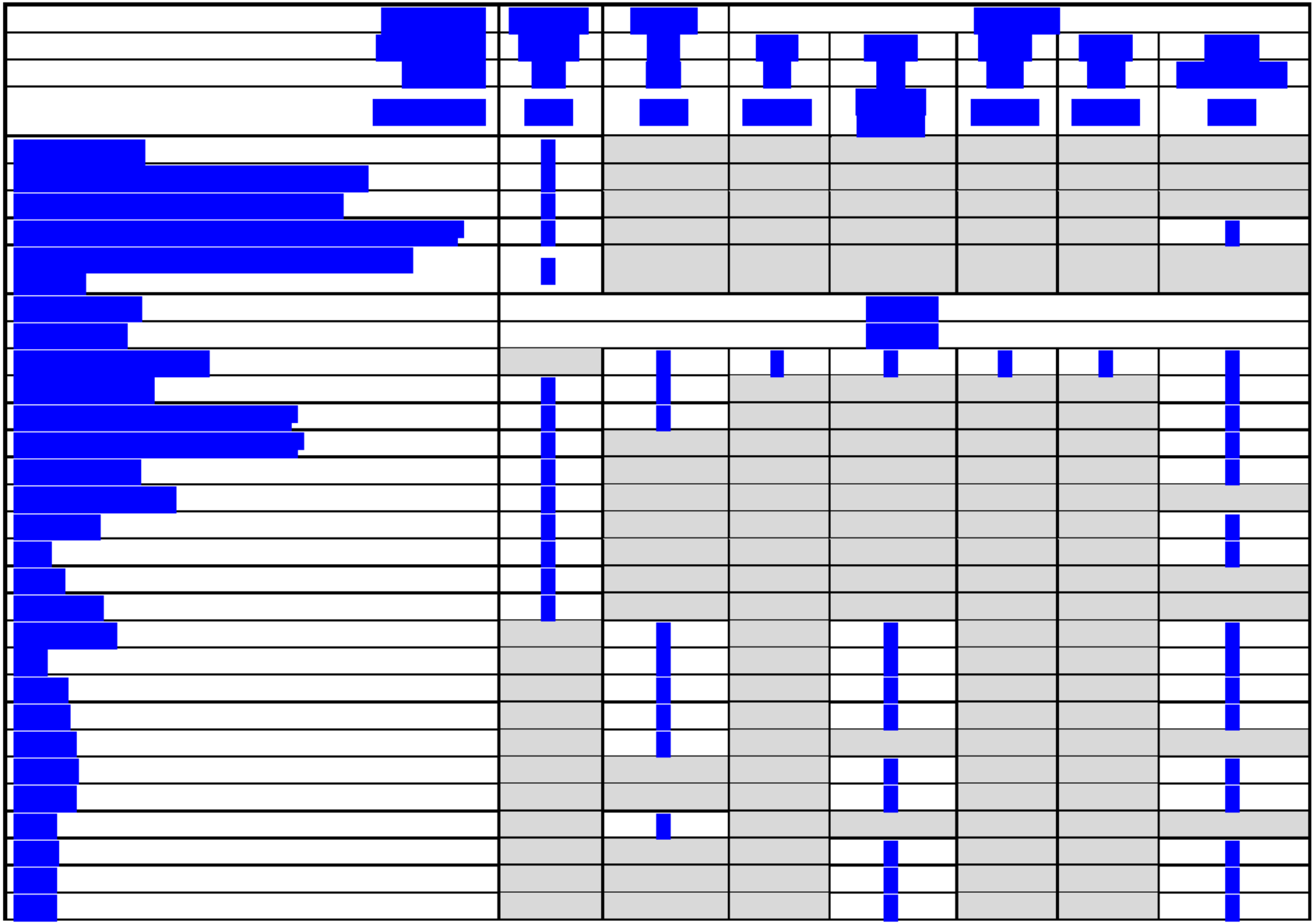

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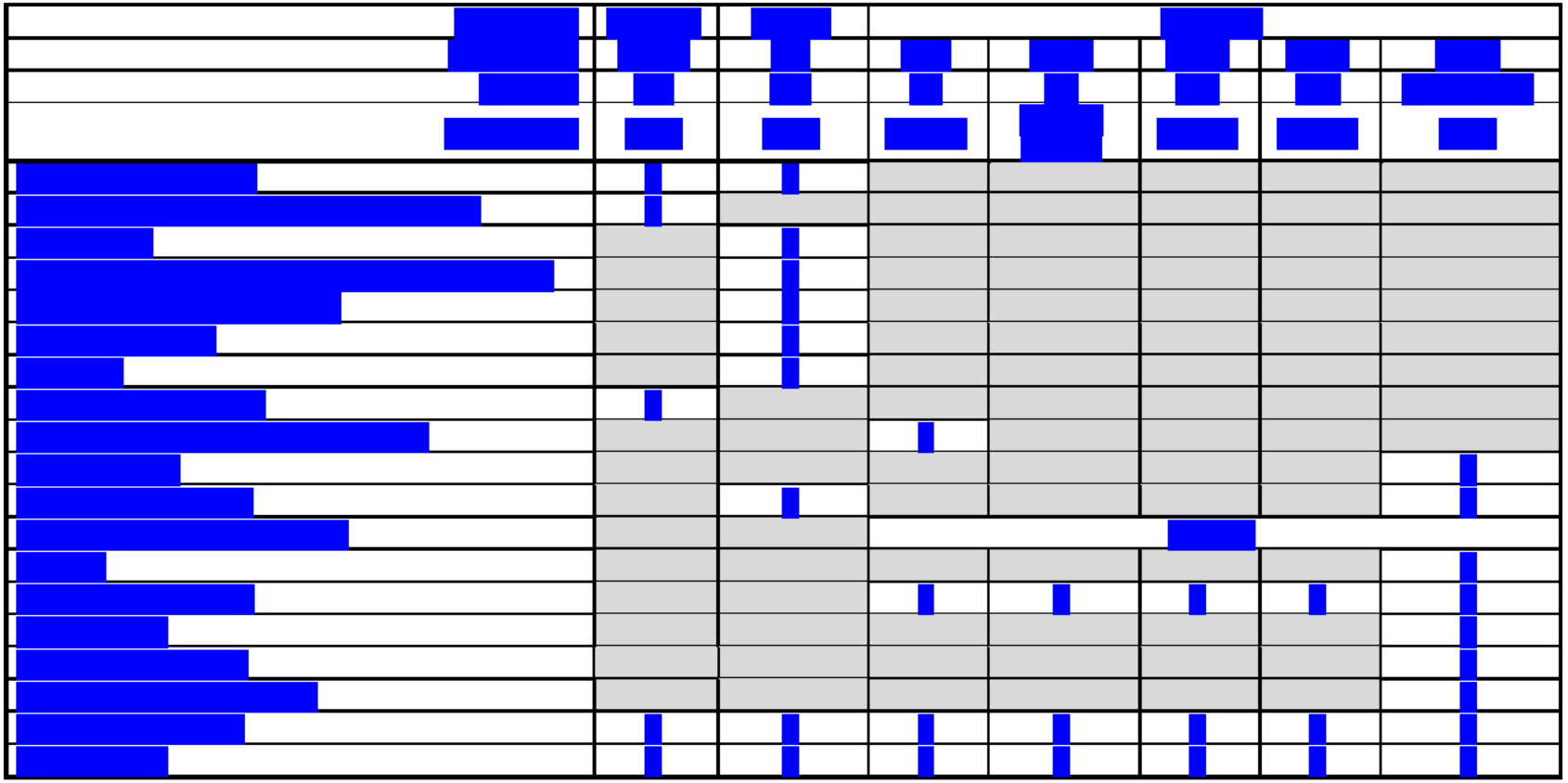

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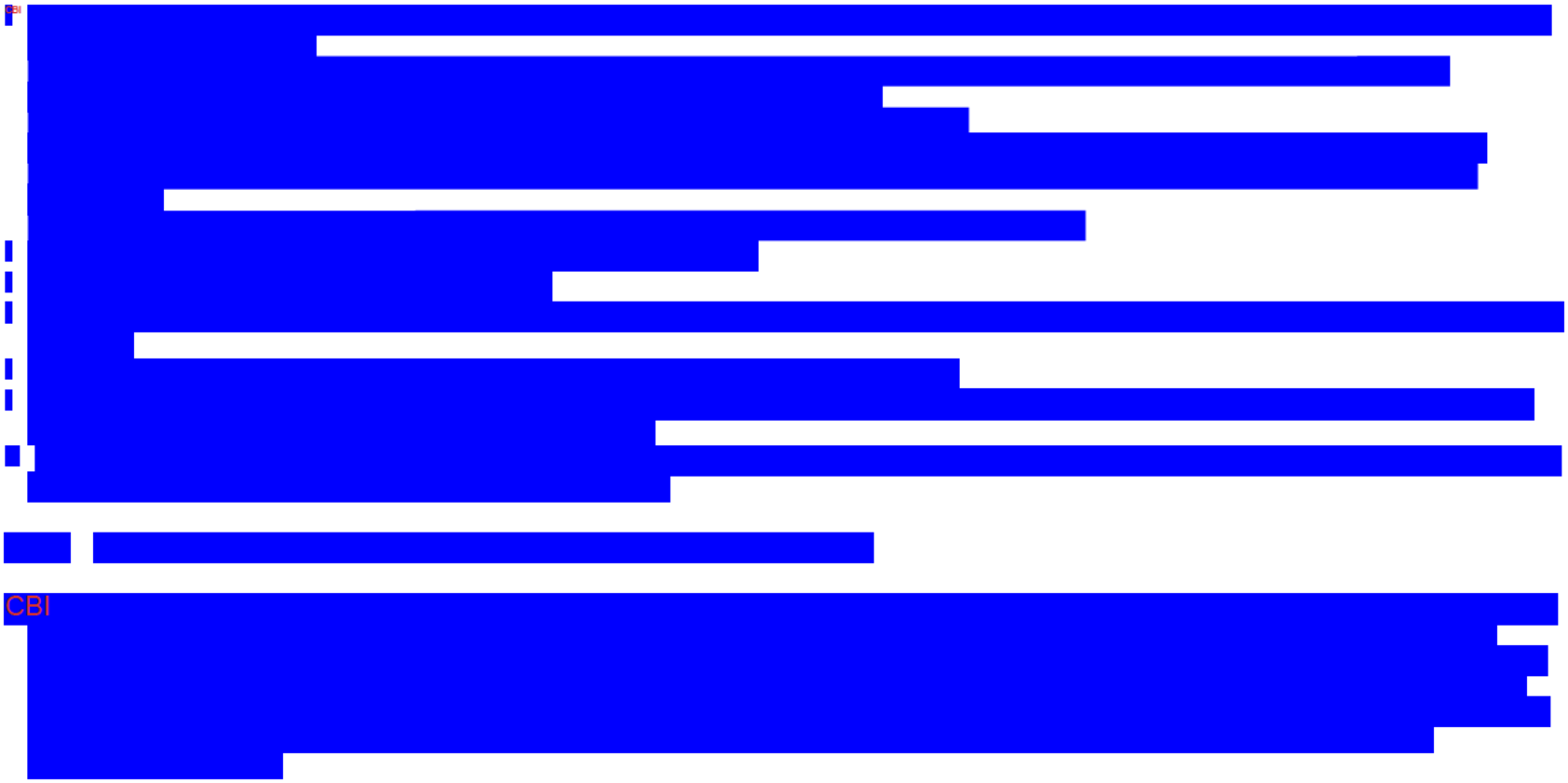

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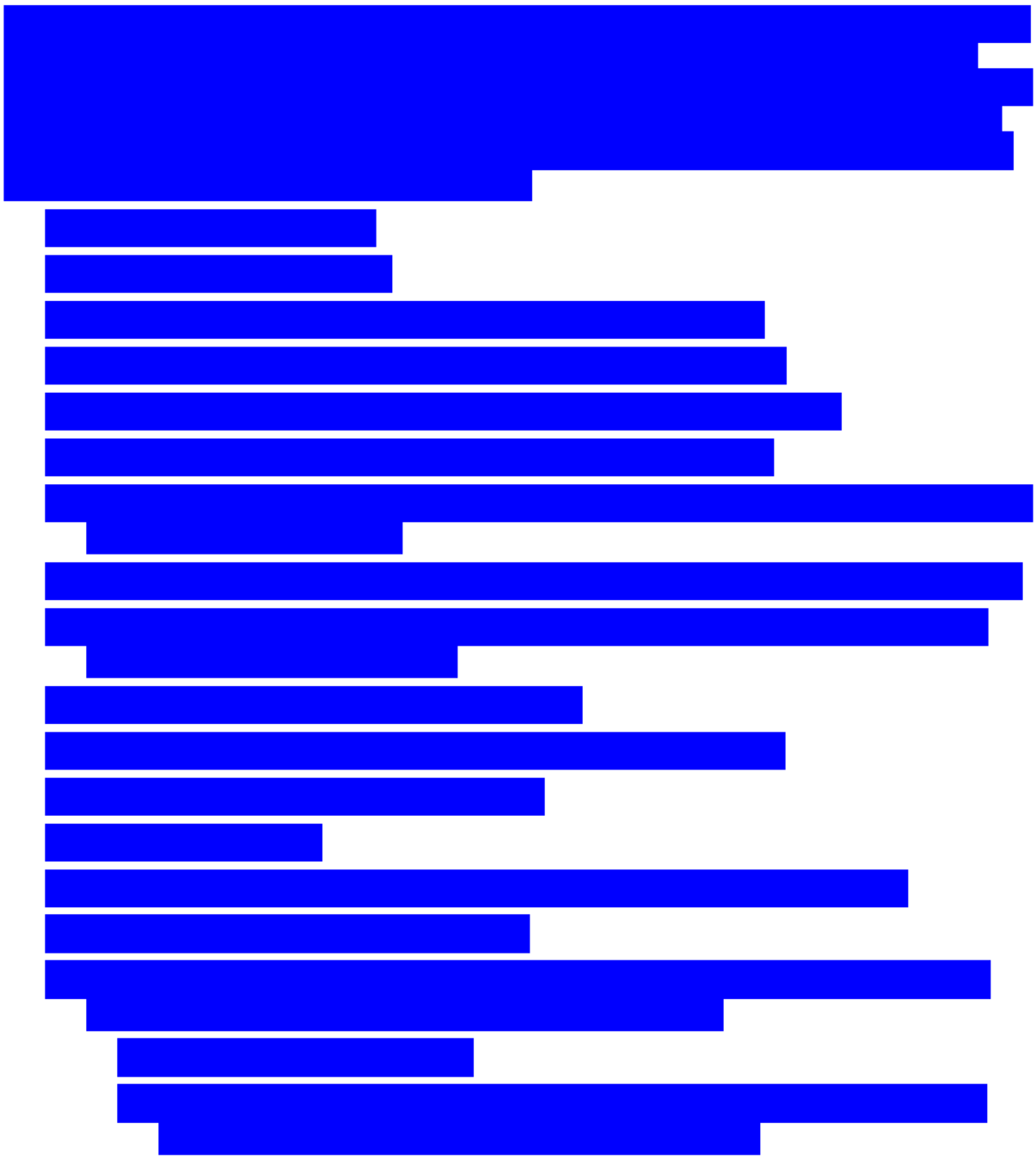
3.6.1 Study Procedures

The procedures to be performed throughout the study are outlined in the Schedule of Assessments (Table 3.2).

3.6.1.1 Screening/Baseline/Randomization

The assessments during the Screening and Baseline Visits will determine subjects' eligibility for randomization (enrollment) in the study.

3.6.1.1.1 CBI



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3.6.1.1.2 Baseline Visit & Randomization (Day -1)

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3.6.1.2 Treatment Period

3.6.1.2.1 Day 1, Televisit

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3.6.1.2.2 Day 7, Clinic or Televisit

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3.6.1.2.3 Day 14, Televisit

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3.6.1.2.4 Day 21, Televisit

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3.6.1.2.5 Day 28/EOS/ET, Clinic Visit

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3.6.2 Unscheduled Visit

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3.6.3 Assessments for Early Termination

If the subject's participation in the study is terminated prematurely for any reason after dosing, the reason for ET should be documented and the D28/EOS/ET Visit procedures should be performed.

An EOS eCRF page should be completed for every subject who receives IP, whether the subject completes the study or not. The reason for any ET should be indicated on this form. The primary reason for the ET should be selected as noted in Section 3.3.3.

3.6.4 Efficacy Assessments

Medical advisors, psychometricians, and clinical research associates (CRAs) may request to review subject evaluations occurring as part of this protocol. A site and subject rater training program and a surveillance mechanism for protocol outcome measures will be implemented and described in separate operational plans. Site raters will receive didactic scale trainings and placebo response training. A subject training video, specific to the subject reported outcome measures in this protocol and placebo response training, will be provided to all study subjects for review and completion. The data surveillance program to be implemented will be specific to identified data flags, to be reviewed on a regular basis by a reviewer (blinded to treatment arm) for identification of potential scoring anomalies and variability. If clinically significant anomalies are detected on subject-rated scales, sites and/or subjects may be requested to perform retraining.

3.6.4.1 Numeric Pain Rating Scale

The NPRS (Appendix E) is an 11-point scale (0 to 10-point scale where 0 is no pain and 10 is worst pain imaginable) that allows the subject to rate the severity of their pain intensity at various points in time.[5] The subject will use the NPRS to record their worst, average, current at rest, and current on movement pain in the past 24 hours every evening prior to removing the topical system. Current pain at rest and current pain on movement is to be collected every time rescue medication is recorded in the DAL. Current pain on movement is the pain a subject experiences when bending forward at a 90 degree angle from a standing position.

3.6.4.2 Oswestry Disability Index

The ODI (Appendix F) is a validated questionnaire that was first published in 1980 but it was updated in 2000.[6,7] The ODI is currently the gold standard for measuring degree of disability and estimating quality of life in a person with low back pain. The ODI is questionnaire completed by the subject which contains 10 topics concerning intensity of pain, lifting, ability to care for oneself, ability to walk, ability to sit, sexual function, ability to stand, social life, sleep quality, and ability to travel. Each topic category is followed by 6 statements describing different potential scenarios in the subject's life relating to the topic. The subject then checks the statement which most closely resembles their situation. Each question is scored on a scale of 0 to 5 with the first statement being 0 and indicating the least amount of disability, and the last statement is scored 5 indicating most severe disability. The scores for all questions answered are summed, then multiplied by 2 to obtain the index (range 0 to 100). Zero is equated with no disability, and 100 is the maximum disability possible.

3.6.4.3 PainDETECT

Pain*DETECT* (Appendix G) is a 7-question validated tool to determine the prevalence of neuropathic pain in individuals with LBP. The 7 responses are summed for a possible score ranging from 0 to 35. In addition to the 7 questions, subjects note the course of pain (Persistent pain with slight fluctuations; Persistent pain with pain attacks, Pain attacks without pain between them; Pain attacks with pain between them) for a total, overall scale score of 0 to 38. Since its development, 4 additional questions have been added but do not contribute to scoring. They ask the patient to rate their pain now and over the last 4 weeks, and to mark on a body chart if their pain is radiating to other parts of the body.

3.6.4.4 EuroQoL-5-Dimension Scale

The EQ-5D scale (Appendix V) version was introduced by the EuroQoL Group in 1990.[8] The EQ-5D scale essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The 3-level version will be used in this study.

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. The participant is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the participant's health state.

The EQ-VAS records the participant's self-rated health on a vertical VAS, where the endpoints are labelled 'The best imaginable health state' and 'The worst imaginable health state'. The VAS can be used as a quantitative measure of health outcome that reflect the participant's own judgement.

3.6.4.5 Brief Pain Inventory - Short Form

The BPI-SF (Appendix H) a 9-item scale that assesses pain at its "worst," "least," "average," and "right now" (current pain). The pain severity domain will be derived by summing items 3 through 6. The BPI also measures how much pain has interfered with 7 daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep.

3.6.4.6 Clinical and Patient Global Impression Scales

The CGIS (Appendix I) is rated on an 8-point scale, with responses ranging from 0 (not assessed) and 1 (normal) through 7 (amongst the most severely ill subjects). The CGIS will be completed at the Baseline Visit by the physician indicating the severity of the LBP for the subject.

The CGIC (Appendix I) scores range from 0 (not assessed) and 1 (very much improved) through 7 (very much worse) as determined by the trained site rater. The PGIC (Appendix J) scores range from 1 (very much improved) through 7 (very much worse) as assessed by the

subject. The CGIC and PGIC will indicate the improvement in the subject's condition compared to the CGIS at the Baseline Visit.

3.6.4.7 Clinical and Patient Impression Scales for Muscle Spasms

The CIS-MS (Appendix K) is rated on a 6-point scale, with responses ranging from 0 (not assessed) and 1 (none) through 5 (severe [board-like hardness of the muscles]). The CIS-MS will be evaluated at the Baseline Visit by the physician using palpation to indicate the severity of the muscle spasms in the subject.

The physician will assess their CIC-MS compared to the CIS-MS at the Baseline Visit, based on physical examination, degree of muscle spasm (presence of muscle spasm assessment), reaction to palpation (presence of local pain assessment) and evaluation of the patient's reported functional assessment (limitation of activities of daily living assessment). The CIC-MS (Appendix K) scores range from 0 (not assessed) and 1 (worse) through 5 (marked improvement) as determined by the trained site rater.

The PIC-MS (Appendix L) uses a similar scale as the CIC-MS. The subject will be asked to assess the change in their muscle spasms since starting treatment using the PIC-MS.

3.6.4.8 Multidimensional Psychological Questionnaire

The placebo effect is a phenomenon that continues to severely jeopardize drug development in many indications, including profoundly impacting the development of new therapeutics to treat pain. The IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) consortium suggested addressing several factors to increase assay sensitivity in chronic pain trials: study design, patient psychology, expectations, Investigator site training, and staff-patient interactions.[9]

While training of patients to more accurately report pain symptoms is widely performed,[10] the placebo is still an issue in clinical trials. The Placebell©™ approach was developed to characterize patient personality, expectation, and staff-patient interactions according to the guidelines provided by the IMMPACT group.

The MPsQ questionnaires (BAS-MPsQ, HBB-MPsQ, STT-MPsQ and PDS-MPsQ) have been designed to specifically measure patient personality traits that are associated with the placebo response. Furthermore, a composite covariate (Placebell©™) integrating these psychological features with other pertinent baseline patient features has been developed. With this method, the Placebell©™ covariate is calculated at baseline to characterize/quantify the placebo response for each patient and to improve the statistical analysis when computing drug effect.[11] The concept of using baseline covariates has been addressed in a recent FDA draft guidance,[12] and the Placebell©™method was presented to FDA at a Critical Path Innovation Meeting (CPIM). The CPIM recommended to pursue the development of Placebell in the context of individual drug development programs.

Data from previous clinical trials in peripheral neuropathic pain and osteoarthritis indicates that the Placebell covariate may significantly reduce the variance associated with the placebo effect and consequently increase the statistical power of a clinical trial population.[13] The

administration of the MPsQ questionnaires in Scilex SP-103-02 will support the confirmation of the Placebell approach to manage the placebo response in LBP. Data generated during this study will support further application of Placebell in future clinical development of SP-103.

The MPsQ modules are self-reported by subject and each item is rated on a 5-point scale ranging from 1 (strongly disagree) to 5 (strongly agree). BAS-MPsQ (Appendix O) takes on average 18 minutes to complete; STT-MPsQ (Appendix Q), HBB-MPsQ (Appendix R) and PDS-MPsQ (Appendix S) 7 minutes each.

3.6.4.9 Pain Treatment Satisfaction Scale

The PTSS (Appendix M) is a measure of patient satisfaction for patients receiving treatment for either acute or chronic pain. The multi-item domains of the final PTSS included 39 items grouped in 5 dimensions: information (5 items); medical care (8 items); impact of current pain medication (8 items); satisfaction with pain medication which included the 2 subscales: medication characteristics (3 items) and efficacy (3 items); and side effects (12 items). The PTSS is a valid, comprehensive instrument to assess satisfaction with treatment of pain based on independent modules that have demonstrated satisfactory psychometric performance.

3.6.4.10 Rescue Medication Use

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3.6.5 Safety Assessments

3.6.5.1 Adverse Events

All AEs occurring after the subject signs the ICF through the D28/EOS/ET Visit will be recorded by site staff in the eCRF asking subjects a general question "How have you been feeling since your last visit?" as well as the specific question "Have you experienced any skin irritation since your last visit?" Any AEs occurring before the start of treatment (i.e., before the first dose of the IP) will be recorded in the medical history.

See Section 4 for AE reporting requirements.

3.6.5.2 Physical Examination

A complete physical examination, including examination of general appearance, skin, neck, eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, neurological and musculoskeletal systems, will be performed. Height (in inches without shoes) and weight (in pounds) will be recorded at Screening. Body mass index will be calculated at Screening using the chart in Appendix B.

3.6.5.3 Vital Signs

Vital signs will include temperature, systolic and diastolic BP and pulse. During the usual clinic visits, the subject is to be seated for approximately 3 mins before vital signs are recorded.

3.6.5.4 Laboratory Parameters

The following clinical laboratory tests are to be performed:

- *Hematology:* Hemoglobin, hematocrit, red blood cell count, white blood cell count (with differential [lymphocytes, neutrophils, eosinophils, basophils, and monocytes]), and platelet count.
- *Blood Chemistry:* albumin, alkaline phosphatase, AST, ALT, direct bilirubin, total bilirubin, blood urea nitrogen, calcium, chloride, creatinine, gamma-glutamyl transferase, glucose, lactate dehydrogenase, potassium, sodium, and uric acid.
- *Other tests:* HIV, hepatitis B, and hepatitis C.
- *Urine drug screen:* Includes opiates, barbiturates, benzodiazepines, tricyclic antidepressants, cannabinoids, phencyclidine, cocaine, ecstasy, and amphetamines.
- *For females of childbearing potential*: Serum and urine pregnancy test.

Laboratory samples will be analyzed by a central laboratory to ensure consistent interpretation of results. Samples are to be shipped to the central laboratory as indicated in the Laboratory Manual. In the event of an unexplained clinically noteworthy abnormal laboratory test value, the test should be repeated immediately and followed up until it has returned to the normal range and/or an adequate explanation of the abnormality is found.

3.6.5.5 Electrocardiogram

Standard 12-lead ECGs will be measured on site machines. The ECG results and clinical significance will be documented in the eCRF.

3.6.5.6 Skin Irritation Assessment

Skin irritation at the site of application will be assessed at Baseline (D -1) and on D28/EOS/ET. On D28/EOS/ET, subjects will be advised to remove the topical system after all rating scales have been administered and at least 30 minutes prior to the final skin irritation assessment. The observed skin reaction will be scored according to the scales presented in Appendix U.

When an “Other Effects” score is observed, each score should be reported as a number and also as a numerical total (i.e., numerical “Dermal Response” score + numerical “Other Effects” score). Skin irritation scores will be provided for safety and tolerability purposes only but will not be included in statistical analysis except for descriptive statistics.

3.6.5.7 Topical System Adhesion Assessment

The subject will complete a questionnaire in the eDiary daily from D1 through D28/EOS/ET to provide time of application/removal and how well the topical system adhered to the application sites (Appendix N. As instructed in the Topical System Adhesion Assessment, if subjects remove the topical system due to discomfort or pain (itching or burning), they will be asked to take a photo of the application site and describe the appearance in the eDiary.

3.6.6 Other Assessments

3.6.6.1 Hospital Anxiety and Depression Scale

HADS (Appendix O) is commonly used to determine a subject's anxiety and depression levels. The scale is comprised of 14 items rated on a scale of 0 to 3; 7 items focused on anxiety symptoms and 7 items focused on depression symptoms. The HADS will be used for inclusion criteria and completed at Screening only. A score of 11 to 14 on either the depression or anxiety subscale is indicative of moderate symptomatology. A score of ≥15 on either the depression or anxiety subscale is indicative of severe symptomatology.[5] Subjects with HADS scores ≥15 will be excluded from this study.[14]

3.6.7 Appropriateness of Measurements

All assessments to be used in this study are commonly used, standard measurements frequently seen in LBP studies.

4 ADVERSE EVENT REPORTING

4.1 Definitions and Criteria

4.1.1 Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.[15] An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product or not.

Medical interventions such as surgeries, diagnostic procedures, and therapeutic procedures are not AEs, but the action taken to treat the medical condition. They should be recorded as treatment of the AEs.

4.1.2 Serious Adverse Events

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse; malignancy tumors [histologically different from primary tumor]).

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations. An SAE is not necessarily severe; e.g., an overnight hospitalization for a diagnostic procedure must be reported as an SAE even though the occurrence is not medically serious. By the same token, a severe AE is not necessarily serious: nausea of several hours' duration may be rated as severe but may not be considered serious.

4.1.3 Unexpected Adverse Drug Reactions

An unexpected adverse drug reaction (ADR) is a reaction for which the nature or intensity is not consistent with the applicable product information.[2] Until product information is amended, expedited reporting is required for additional occurrences of the reaction. Reports that add significant information on specificity or intensity of a known, already documented SAE constitute unexpected events. For example, an event more specific, severe, or frequent than described in the IB would be considered "unexpected." Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

Guidance on reporting AEs and SAEs is described in Section 4.2.

4.1.4 Abnormal Laboratory Values

Any abnormality in a laboratory value that is new in onset or which has worsened in intensity or frequency from the baseline condition and meets 1 of the following criteria will be recorded on the AE pages of the eCRF:

- Requires therapeutic intervention or diagnostic tests.
- Leads to discontinuation of IP.
- Has accompanying or inducing symptoms or signs.
- Is judged by the Investigator as clinically significant.

4.1.5 Adverse Events of Special Interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to study drug, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such AEs may require further investigation to characterize and understand them. For this study, occurrence of the typical prodromal symptoms and signs of systemic lidocaine toxicity are considered AESIs.

These are:

- perioral numbness
- metallic taste
- headache
- dizziness
- tinnitus
- somnolence

An occurrence of at least 2 AESIs assessed by the Investigator at moderate intensity or higher will preclude the subject from receiving the next administration of IP. In addition to these AESIs, presence or absence of tachycardia (i.e., heart rate >100 beats per minute [bpm]) will be checked during vital sign collections at the clinic visits. A single occurrence of tachycardia will preclude further dosing of a subject until investigation is completed to determine the cause.

4.1.6 Assessing Intensity and Relationship

All AEs will be assessed on 2 descriptive parameters: intensity and relationship to the IP:

- Intensity refers to the severity of an event and references impact on a subject's functioning.
- Relationship refers to the likelihood that the event being assessed was caused by the IP.

Intensity

Each AE will be classified according to the following categories:

Mild:	The AE does not interfere in a significant manner with the patient's normal level of functioning.
Moderate:	The AE produces some impairment of functioning but is not hazardous to the patient's health.
Severe:	The AE produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes over several days, those changes should be recorded separately (with distinct onset dates).

Relationship

Each AE will be assessed as to its relationship to the IP, based on the following criteria. Although the attribution by the Investigator will be collected for reported events, for analytic purposes a temporal association with the use of the IP will be assumed sufficient for at least plausible association.

Investigators are required to assess the causal relationship (i.e., whether there is reasonable possibility that the study drug caused the event) using the following definitions:

Unrelated:	A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations of the event.
Possibly Related:	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the study drug, but that could also be explained by concurrent disease or other drugs or chemicals. Information on study drug causality may be lacking or unclear.
Probably Related:	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the study drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on re- administration (rechallenge) or withdrawal (dechallenge) of the study drug.
Definitely Related:	A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship definite and is clearly related to use of the IP.

When assessing the relationship to the IP, the following criteria will be considered:

- Positive rechallenge.
- Positive dechallenge (resolution upon stopping suspect the IP, in absence of other intervention or treatment).
- Known class effect.
- Biological plausibility.
- Lack of alternative explanation—concomitant drug or disease.

4.2 Reporting Procedures and Requirements

4.2.1 Adverse Events

All AEs occurring after the subject signs the informed consent form (ICF) through the D28/EOS/ET Visit will be recorded by site staff asking subjects a general question “How have you been feeling since your last visit?” as well as the specific question “Have you

experienced any skin irritation since your last visit?" Any AEs occurring before the start of treatment (i.e., before the first dose of the IP) will be recorded in the medical history.

All AEs will be monitored and recorded on an AE eCRF, including the AE's description, start and end date, seriousness, intensity, action taken, and relationship to the IP. If AEs occur, the first concern will be the safety of the study subjects. All AEs will be followed until resolved or stable, or until a subject ends study participation (whichever comes first).

Disease progression including the worsening of signs and symptoms of disease present before starting of treatment are NOT to be considered AEs.

If the Investigator learns of an AE in a study subject within 30 days after the last scheduled visit and considers the event possibly related or related to prior study treatment, the Investigator should report it to the Sponsor.

The Investigator should report all AEs on the AE page(s) of the eCRF and source documents (if the eCRF is unavailable for direct data entry [DDE]), regardless of seriousness, intensity, and causality. Whenever possible, an AE will be reported using a diagnostic term, (e.g., "common cold" or "upper respiratory infection" rather than individual symptoms such as "runny nose, cough, mild fever") and should be described with the attributes described in Section 4.1.6.

4.2.2 Serious Adverse Events

Each AE will be assessed to determine whether it meets seriousness criteria (Section 4.1.2). If the AE is considered serious, the Investigator should report this event to CBI as outlined below and to the institutional review board (IRB) according to its standard operating procedures (SOPs).

If the Investigator detects an SAE in a study subject within 30 days after the last scheduled study visit, and considers the SAE related or possibly related to prior study treatment, the Investigator should report it to the Sponsor.

The Investigator should report all SAEs to the Sponsor on the eCRF within 24 hours of the Investigator, designee or site staff's knowledge of the event regardless of relationship to study drug.

If the site experiences a temporary disruption of the eCRF system, a back-up paper SAE Report Form will be available for site staff to complete.

- Site staff will complete the paper SAE report form and email it within 24 hours.
- Only in cases where the email system is unavailable, site staff will send the SAE by fax.

CBI



All recorded SAEs, regardless of relationship to study treatment, will be followed up until resolution, stabilization, or the subject is lost to follow-up and cannot be contacted. In circumstances where the Investigator is unable to contact the subject, the Investigator must provide a written statement to Scilex confirming that the subject is lost to follow-up. SAEs that are ongoing at the D28/EOS/ET Visit should be followed until resolved.

Additional follow-up information must be reported in the eCRF within 24 hours of awareness following Investigator (or site) awareness of the information. The Investigator should not delay reporting an SAE to obtain additional information. Additional information, when available, should be reported to CBI by the reporting procedures described above.

The Sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities per the applicable regulatory requirements.

4.3 Procedures for Documenting Pregnancy During the Study

Pregnancy is not considered an AE. Pregnancy occurring in a female subject should be reported within 24 hours of becoming aware of the event using the pregnancy eCRF. The Investigator will also: (1) notify the subject's physician that the subject may have been treated with SP-103 and (2) follow the progress of the pregnancy to term and document the outcome of the pregnancy. Pregnancy outcome information should be forwarded to SponsorCBI when available.

Any pregnancies will be followed through delivery or premature termination. If a subject becomes pregnant during the study, any complications of that pregnancy such as abortion (spontaneous or induced), premature birth, or congenital abnormality will be captured as SAEs. In the event the eCRF system is unavailable, a back-up paper Pregnancy Reporting Form will be available for site staff to complete following reporting guidelines as outlined in Section 4.2.2.

5 DATA MANAGEMENT AND STATISTICAL ANALYSIS

5.1 Study Data

To streamline and modernize this clinical investigation in accordance with FDA's Electronic Source Data in Clinical Investigations Guidance for Industry this trial promotes capturing source data in electronic form via DDE into eCRFs and subject eDiaries.[16] This real-time electronic data capture is intended to eliminate unnecessary duplication of data, reduce the possibility for transcription errors, encourage entering source data during subject visits, eliminate transcription of source data into an eCRF, facilitate remote monitoring of data, promote real-time access for data review, and facilitate the collection of accurate and complete data.

For data entered directly into eCRFs and eDiaries, the eCRF and eDiaries are source. If a paper transcription or separate electronic source step is used, then the paper or other electronic documentation should be retained and made available for monitoring. Study data in this protocol will be source verified only if paper transcription or separate electronic source precede eCRF DDE or data entry into eDiaries.

To comply with the requirement to maintain accurate case histories, clinical Investigator(s) should review and electronically sign the completed eCRF for each subject before the database is locked.

All study data will be formulated into data sets to provide transparency, traceability, and integrity of trial analysis results from the collection source. Observed study data will be mapped to the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model architecture.

5.2 Data Management Considerations

eCRFs will be employed for this study. Completed eCRFs for this study will be forwarded to the Sponsor or its representative at the end of the study. Queries will be issued for any inconsistencies, omissions, and discrepancies and will be resolved by the appropriate parties. The statistical analysis of these data will be performed by the Sponsor or its representative. All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary. Data management details will be outlined in a separate data management plan.

5.3 Statistical Considerations

A detailed Statistical Analysis Plan (SAP) will be finalized and signed before database lock and the code for all subjects is broken and before analysis of the study being carried out. Any deviations from the analyses described below will be included in the SAP, which will be included in the clinical study report.

5.3.1 Sample Size Justification



5.3.2 Definition of a Completed Subject

For the purposes of analysis, a completer is defined as a subject who applies ≥1 topical system in the Treatment Period and completes the study through the D28/EOS/ET Visit.

5.3.3 Analysis Methods

Descriptive summaries of variables by treatment will be provided where appropriate. For continuous variables, the number of non-missing values (n) and the median, mean, SD, minimum, and maximum will be tabulated by treatment. For categorical variables, the counts and proportions of each value will be tabulated by treatment.

5.3.4 Analysis Populations

The Modified Intent-to-Treat (mITT) population will be the primary population for efficacy analyses and will include all randomized subjects who receive any amount of study drug.

The Intent-to-Treat population will include all randomized subjects and will be used for sensitivity analyses.

The Per Protocol population will include all subjects in the mITT who do not have a major protocol deviation. Major protocol deviations will be determined prior to treatment unblinding and will be used for sensitivity analyses. Dosing for less than one week will be considered a major protocol deviation.

The Safety population will be the primary population for safety analyses and will include all subjects who receive any amount of study drug.

Additional analysis populations may be defined prior to database lock. Full details will be provided in the SAP.

5.3.5 Protocol Deviations

Protocol deviations should be collected by site and grouped into different categories; these include but are not limited to:

- Entered the study even though they did not satisfy the entry criteria.
- Received the wrong treatment or incorrect dose.
- Are not sufficiently compliant recording daily NPRS scores.
- Received an insufficient amount of study drug.
- Received an excluded concomitant treatment.

Major protocol deviations that impact the primary efficacy analysis may lead to exclusion from the PP population. Protocol deviations will be reviewed prior to breaking the study treatment blind to determine which protocol deviations will be considered major protocol deviations. Full details regarding these will be provided in the SAP.

5.3.6 Demographic and Baseline Characteristics

Treatment groups will be compared with respect to subject demographics and baseline characteristics and will be summarized using descriptive statistics, but no formal statistical analysis testing will be performed.

5.3.7 Efficacy Measures

All efficacy analyses will use the mITT as the primary analysis population, and all primary and secondary endpoints will additionally be analyzed with the PP population.

Efficacy variables include:

- NPRS: The NPRS is an 11-point scale (0 to 10-point scale where 0 is no pain and 10 is most severe pain) that allows the subject to rate the severity of their pain intensity at various points in time. In this study, the subject will record their score daily in the evening for their worst, average, current at rest, and current on movement pain in the lower back. For each type of pain score collected, daily NPRS scores will be used to calculate time-weighted Summed Pain Intensity Difference (SPID) scores (D1-D7 and D1-D28). The SPID will be calculated using the pain intensity difference (PID) at each follow-up time point weighted (multiplied) by the amount of time since the prior assessment. PID is calculated as the NPRS score at the baseline minus the current day NPRS score. Just prior to taking rescue medication on a given day the subject will be asked to record the current at rest pain NPRS along with the current on movement pain NPRS. The highest (most pain) NPRS score recorded at rest or on movement (including all measurements recorded prior to taking rescue medication) will be used for the NPRS score for that day. NPRS scores will also be analyzed at each visit.

- CGIC: The CGIC is an 8-point scale (0 to 7, where 0 is not assessed, 1 is very much improved, and 7 is very much worse) that allows clinicians to rate the subject's global impression of change. For analysis, the CGIC response will be grouped into 1 of 2 categories, 1) very much improved or much improved (recorded as a 1 or 2 in the scale), and 2) all other responses (recorded as 3 to 7 in the scale). The number and percentage of subjects reporting each of the 7 CGIC response levels will also be provided by visit and treatment.
- PGIC: The PGIC is a 7-point scale (1 to 7, where 1 is very much improved and 7 is very much worse) that allows patients to rate their global impression of change. For analysis, the PGIC response will be grouped into 1 of 2 categories, 1) very much improved or much improved (recorded as a 1 or 2 in the scale), and 2) all other responses (recorded as 3 to 7 in the scale). The number and percentage of subjects reporting each of the 7 PGIC response levels will also be provided by visit and treatment.
- ODI: The ODI is a measure of disability associated with low back and leg pain with 10 topics, with each topic having a response ranging from 0 to 5. The 10 responses are then summed and multiplied by 2 resulting in an ODI score ranging from 0 to 100.
- Pain*DETECT*: Pain*DETECT* is a 7-question validated tool to determine the prevalence of neuropathic pain in individuals with LBP. The 7 responses are summed for a possible score ranging from 0 to 35. In addition to the 7 questions, subjects note the course of pain (Persistent pain with slight fluctuations; Persistent pain with pain attacks, Pain attacks without pain between them; Pain attacks with pain between them; and Radiating pains marked on a body chart) for a total, overall scale score of 0 to 38.
- BPI-SF: The BPI assesses pain at its "worst," "least," "average," and "right now" (current pain). The pain severity domain will be derived by summing items 3 through 6. The BPI also measures how much pain has interfered with 7 daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. BPI pain interference is typically scored as the mean of the 7 interference items. The pain interference domain will be derived by summing items 9A through 9G.
- EQ-5D: The EQ-5D scale consists of the 5-dimension scores (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) along with the VAS score. The number and percentage of subjects reporting the responses to the 5 dimensions will be provided by visit and treatment. The VAS score will be summarized at each visit but will also be analyzed using statistical models.
- PTSS: The multi-item domains of the final PTSS included 39 items grouped in 5 dimensions: information (5 items); medical care (8 items); impact of current pain medication (8 items); satisfaction with pain medication which included the 2 subscales: medication characteristics (3 items) and efficacy (3 items); and side effects (12 items). The PTSS is a valid, comprehensive instrument to assess satisfaction with

treatment of pain based on independent modules that have demonstrated satisfactory psychometric performance.

- CIC-MS: The CIC-MS is a 6-point scale (0 to 5, where 0 is not assessed, 1 is worse, and 5 is marked improvement) that allows clinicians to rate the subject's impression of change in their muscle spasms. For analysis, the CIC-MS response will be grouped into 1 of 2 categories, 1) moderate or marked improvement (recorded as a 4 or 5 on the scale), and 2) all other responses (recorded as 1 to 3 on the scale). The number and percentage of subjects reporting each of the 6 CGIC response levels will also be provided by visit and treatment.
- PIC-MS: The PIC-MS is a 6-point scale (0 to 5, where 0 is not assessed, 1 is worse, and 5 is marked improvement) that allows patients to rate their impression of change in their muscle spasms since prior to the start of treatment. For analysis, the PIC-MS response will be grouped into 1 of 2 categories, 1) moderate or marked improvement (recorded as a 4 or 5 on the scale), and 2) all other responses (recorded as 1 to 3 on the scale). The number and percentage of subjects reporting each of the 6 PIC-MS response levels will also be provided by visit and treatment.
- Rescue Medication: In this study, acetaminophen is the permitted and study provided rescue medication. The time to first rescue medication dose and number of milligrams taken will be collected and analyzed.

5.3.7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the Summed Pain Intensity Difference (SPID) D1-D7.

The null and alternative hypotheses are:

H_0: SP-103 and placebo do not differ in their mean average LBP NPRS SPID D1-D7.

H_A: SP-103 and placebo differ in the mean average LBP NPRS SPID D1-D7.

5.3.7.2 Principal Analysis

The primary efficacy endpoint is average LBP NPRS SPID D1-D7 (calculated as a time-weighted average) and will be analyzed to compare the efficacy of SP-103 and placebo, using the mITT population. The primary efficacy analysis will be performed using an analysis of covariance (ANCOVA) model, which includes treatment group, baseline severity level (moderate or severe), and sex as the factors and baseline pain intensity as the covariate. The least squares (LS) mean and 95% confidence interval for each treatment, the LS mean difference between treatment groups, and the associated p-value and 95% confidence interval for the mean difference will be computed from the ANCOVA model. Sensitivity analyses will be performed using different methods for any missing data and using different analysis sets (e.g., Per Protocol). Full details will be provided in the SAP.

5.3.7.3 Secondary Efficacy Endpoints

Key secondary endpoints are:

- The mean ODI total score at D7.
- The PGIC response at D7.

Secondary endpoints are:

- The average LBP NPRS SPID D1-D28.
- The worst LBP NPRS SPID D1-D28.
- The current on movement pain LBP NPRS SPID D1-D28.
- The current at rest LBP NPRS SPID D1-D28.
- The mean ODI total score at D28.
- The PGIC response at D28.
- The mean Pain*DETECT* score at D7 and D28.
- The mean EQ-5D VAS score at D7 and D28.
- The mean BPI-SF score at D7 and D28.
- The CGIC response at D7 and D28.
- Cumulative use of rescue medication (milligrams of acetaminophen) over 7 and over 28 days of treatment.
- The PTSS at D7 and D28.
- The CIC-MS at D28.
- The PIC-MS at D28.

Exploratory endpoints are:

- Time to resolution of pain (Average pain by NPRS <2 over two consecutive days).

Exploratory analyses may be added to the SAP prior to unblinding.

5.3.7.4 Secondary and Exploratory Efficacy Endpoint Analyses

Analysis of continuous endpoints measured at one time point will be analyzed using ANCOVA models similar to the primary efficacy endpoint analysis. Continuous endpoints measured over multiple visits will be analyzed using mixed models for repeated measures (MMRM) that include treatment, visit, and treatment-by-visit interaction terms and baseline as a covariate. Categorical endpoints will be analyzed using Cochran-Mantel-Haenszel tests and logistic regression models. Time to event variables will be summarized using Kaplan-Meier methods and log rank tests. The impact of pain duration at Screening or Baseline on efficacy endpoints may be assessed. Full details will be provided in the SAP.

The Placebell©™ technology will be applied and the Placebell©™ Covariate calculated in the SP-103-02 study to potentially reduce variance resulting from placebo response. Full details will be part of Tools4Patient SAP, which will be finalized prior to data receipt.

5.3.7.5 Multiplicity

While all tests will be performed using 2-sided tests at the alpha=0.05 level, no adjustment for multiplicity will be applied for this exploratory study. The focus of interpreting the results will be based on effect size estimates and corresponding confidence intervals.

5.3.8 Safety Analyses

Safety endpoints are:

- AEs including:
  - Treatment-emergent adverse events (TEAEs).
  - SAEs.
  - Treatment-emergent serious adverse events (TESAEs).
  - AESIs.
  - AEs leading to discontinuation.
- Change from Screening in physical examinations.
- Change from Baseline in vital signs.
- Change from Screening in laboratory parameters.
- Change from Screening ECG assessments.
- Topical system adhesion assessment.

5.3.8.1 Adverse Events

All AEs will be coded using the most current version of MedDRA.

The incidence of TEAEs (number and percent of subjects reporting the AE at least once during the study), SAEs, TESAEs, AESIs, and AEs leading to discontinuation will be summarized by treatment.

A TEAE is defined as any AE that has an onset on or after the dose of IP, or any pre-existing condition that has worsened on or after the first dose of IP.

AEs will be assigned to the period in which they first begin or worsen.

The incidence of TEAEs and treatment-related AEs will also be summarized by maximum intensity and most-related relationship to IP by MedDRA primary system organ class and preferred term. The summary will include the total number and percentage of subjects reporting an event. In counting the number of events reported, a continuous event, i.e.,

reported more than once and which did not cease, will be counted only once; non-continuous AEs reported several times by the same subject will be counted as multiple events.

5.3.8.2 Physical Examination

Changes from Screening physical examination results will be presented.

5.3.8.3 Vital Signs

Summary statistics for the absolute vital sign value and the changes from Baseline will be presented by treatment group and period for each visit, for each of the following vital signs:

- Temperature
- Systolic blood pressure (mmHg).
- Diastolic blood pressure (mmHg).
- Pulse (bpm).

Vital sign values will be categorized into the following potential clinical concern categories if applicable and summarized.

Vital Sign	**Potential Clinical Concern Categories**
Temperature	<97 °F or > 99 °F
Systolic blood pressure	≥160 mmHg
Diastolic blood pressure	≥100 mmHg
Pulse	<60 or >100 bpm

5.3.8.4 Laboratory Data

Mean changes from Screening and D28/EOS/ET for each laboratory variable will be summarized by treatment. In addition, each reading will be classified as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables for the Screening and follow-up measurements will be presented.

5.3.8.5 Electrocardiographic Data

ECG results will be summarized by visit.

5.3.8.6 Topical System Adhesion Assessment Data

Topical system adhesion assessment data will be summarized over time

5.3.9 Interim Analysis

Not applicable.

6 STUDY MANAGEMENT

6.1 Ethics and Consent

6.1.1 Regulations and Guidelines

The study will be performed in accordance with this protocol, US investigational new drug (IND) regulations (21 CFR 312), ICH guidelines for Good Clinical Practice (GCP),[15] the regulations on electronic records and electronic signature (21 CFR 11), and the most recent guidelines of the Declaration of Helsinki.[23]

6.1.2 Institutional Review Board/Independent Ethics Committees

Conduct of the study must be approved by an appropriately constituted IRB. Approval is required for the study protocol, protocol amendments, ICFs, subject information sheets, and advertising materials. No IP will be shipped to a site until written IRB authorization has been received by the Sponsor or its representative.

6.1.3 Informed Consent

For each trial subject, a written ICF will be obtained before any protocol-related activities. As part of this procedure, the Investigator or a designated representative must explain orally and in writing the nature, duration, and purpose of the study, and the action of the IP in such a manner that the subject and (if applicable) appointed guardian are aware of the potential risks, inconveniences, or adverse effects that may occur. Subjects should be informed that they may withdraw from the study at any time. They will receive all information that is required by federal regulations and ICH guidelines. The Principal Investigator or a designated representative will provide the Sponsor or its representative with a copy of the IRB-approved ICF before the start of the study.

6.2 Discontinuation of the Study by the Sponsor

The Sponsor reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. A site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated, and/or the site closed for whatever reason, all documentation and IP pertaining to the study must be returned to the Sponsor or its representative.

6.3 Study Documentation

By signing a copy of Form FDA 1572, the Principal Investigator acknowledges that he/she has received a copy of the IB on SP-103 and assures the Sponsor that he/she will comply with the protocol and the provisions stated in Form FDA 1572. No changes in this protocol can be made without the Sponsor's written approval.

6.4 Study Monitoring and Auditing

This study will be monitored for quality assurance at all stages of its development by the clinical research personnel employed by the Sponsor or its representative. Monitoring will include personal visits, remote visits, and telephone communication to assure that the investigation is conducted per the protocol, SOPs, Guidelines of GCP, and applicable regulatory requirements. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Remote and on-site review of eCRFs will include a review of forms for completeness and clarity, and consistency with electronic or paper source documents (if used) for each subject.

Medical advisors and CRAs or assistants may request to witness subject evaluations occurring as part of this protocol. The Investigator and appropriate personnel will be periodically requested to attend meetings/workshops organized by the Sponsor to assure acceptable protocol execution. The study may be subject to audit by the Sponsor or by regulatory authorities. If such an audit occurs, the Investigator must agree to allow access to required subject records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities, for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

6.5 Retention of Records

The Investigator must arrange for retention of study records at the site for 2 years after the IPs New Drug Application is approved or the IND is withdrawn, as required by FDA regulations. The Investigator should take measures to prevent accidental or premature destruction of these documents.

6.6 Use of Study Findings

By signing the study protocol, the Investigator agrees to the use of results of the study for the purposes of national and international registration. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. Reports covering clinical and biometric aspects of the study will be prepared by the Sponsor or its representative.

6.7 Publications

As a multicenter trial, the Sponsor intends to publish clinical data from all centers participating in the investigation. A publication committee selected by the Sponsor will submit draft manuscripts to all participating Investigators for their comments. In conformity with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals published by the International Committee of Medical Journal Editors, Investigators whose contribution consists solely in the collection of data will not be named individually as authors.[24] Rather, those Investigators will receive a collective authorship as the "SP-103-02 Study Group" and will be identified in a note.

Individual Investigators and/or their associates subsequently may publish additional findings of this study in scientific journals or present them at scientific meetings, if the Sponsor is given ample opportunity to review any proposed abstract, manuscript, or slide presentation before its submission. This review is required to ensure that the Sponsor is aware of all written and oral presentations of the data and does not imply any editorial review or restriction of the contents of the presentation or use.

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8 APPENDICES

Appendix A Fibromyalgia Diagnostic Criteria

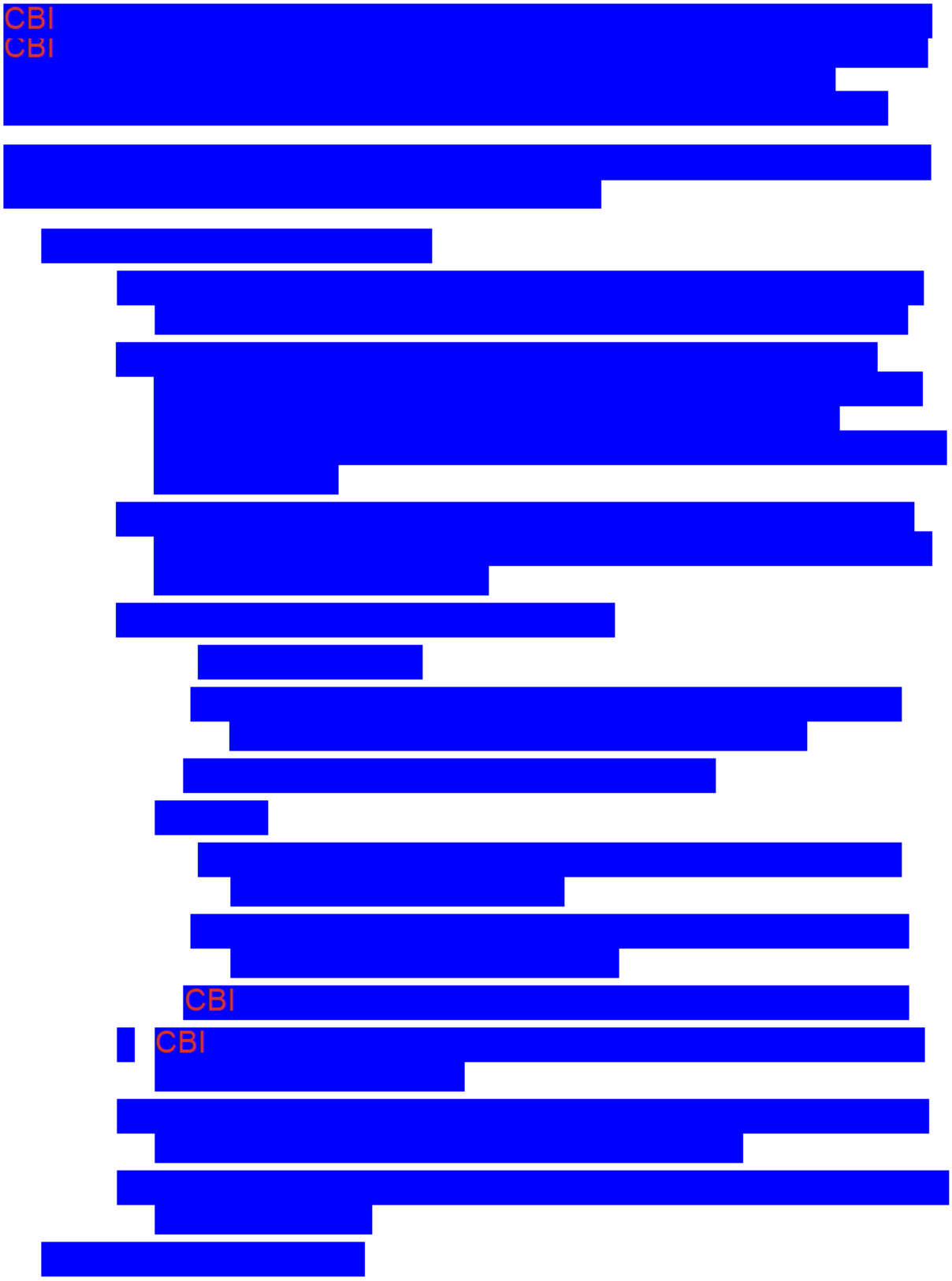
CBI

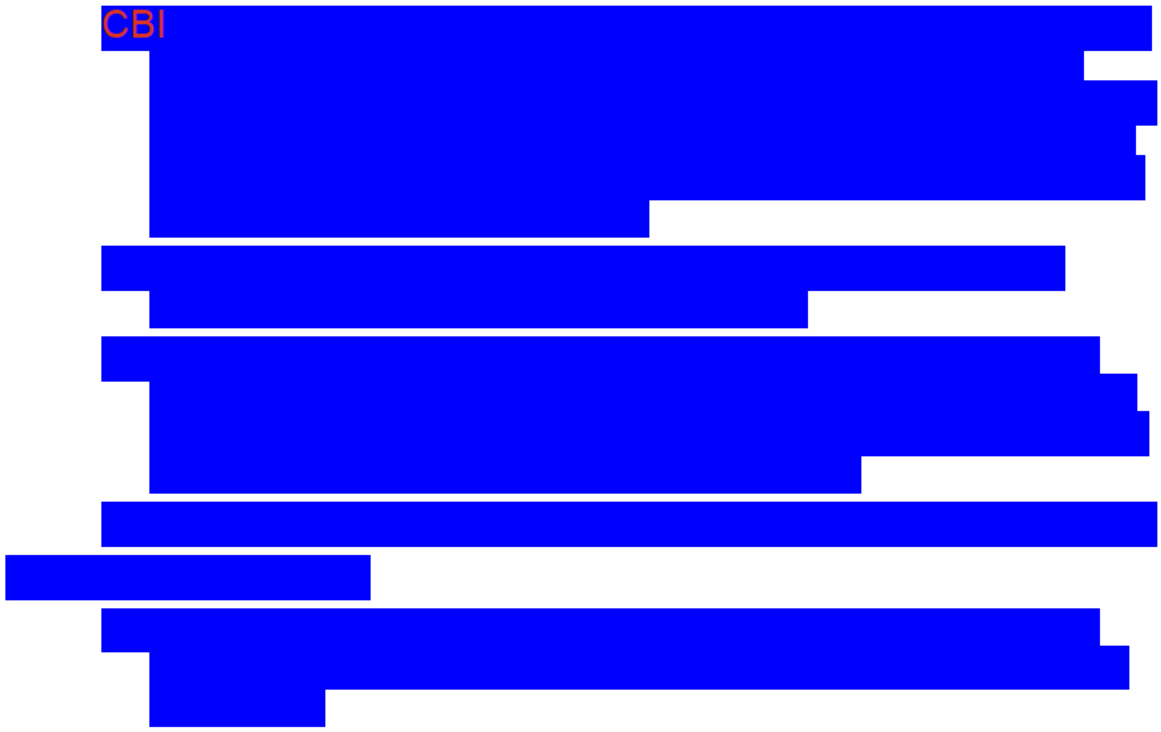
Table 3



CBI

Appendix C Clinician Instructions for Topical System Application

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