[redacted]

Sponsor:	Scilex Pharmaceuticals, Inc.
Protocol Number:	SP-102 02

STATISTICAL ANALYSIS PLAN - TABLES, FIGURES AND LISTINGS SHELL APPROVAL

Study name: Corticosteroid Lumbar Epidural Analgesia for Radiculopathy (C.L.E.A.R.)
Protocol Number: SP-102 02

Statistical Analysis Plan (SAP) Version being approved: SCI_SP102-02_3198_SAP_v2.0_20AUG2021

Tables, Figures and Listings (TFL) Shell version being approved: SCI_SP102-02_3198_Table_Shells_v2.0_20AUG2021
SCI_SP102-02_3198_Listing_Shells_v2.0_20AUG2021
SCI_SP102-02_3198_Figure_Shells_v2.0_20AUG2021

The above SAP / TFL Shell has been reviewed and approved by Worldwide:

Name of Author: [redacted]

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Date: [redacted]

Name of Reviewer: [redacted]

Position: [redacted]

Signature: [redacted]

Date: [redacted]

The above SAP / TFL Shell has been reviewed and approved by the Sponsor:

Name of Sponsor Clinical Lead: [redacted]

Position: [redacted]

Signature: [redacted]

Date: [redacted]

Statistical Analysis Plan

Corticosteroid Lumbar Epidural Analgesia for Radiculopathy (C.L.E.A.R.)

Protocol Number: SP-102-02

Version 2.0

Issue Date: 20-AUG-2021

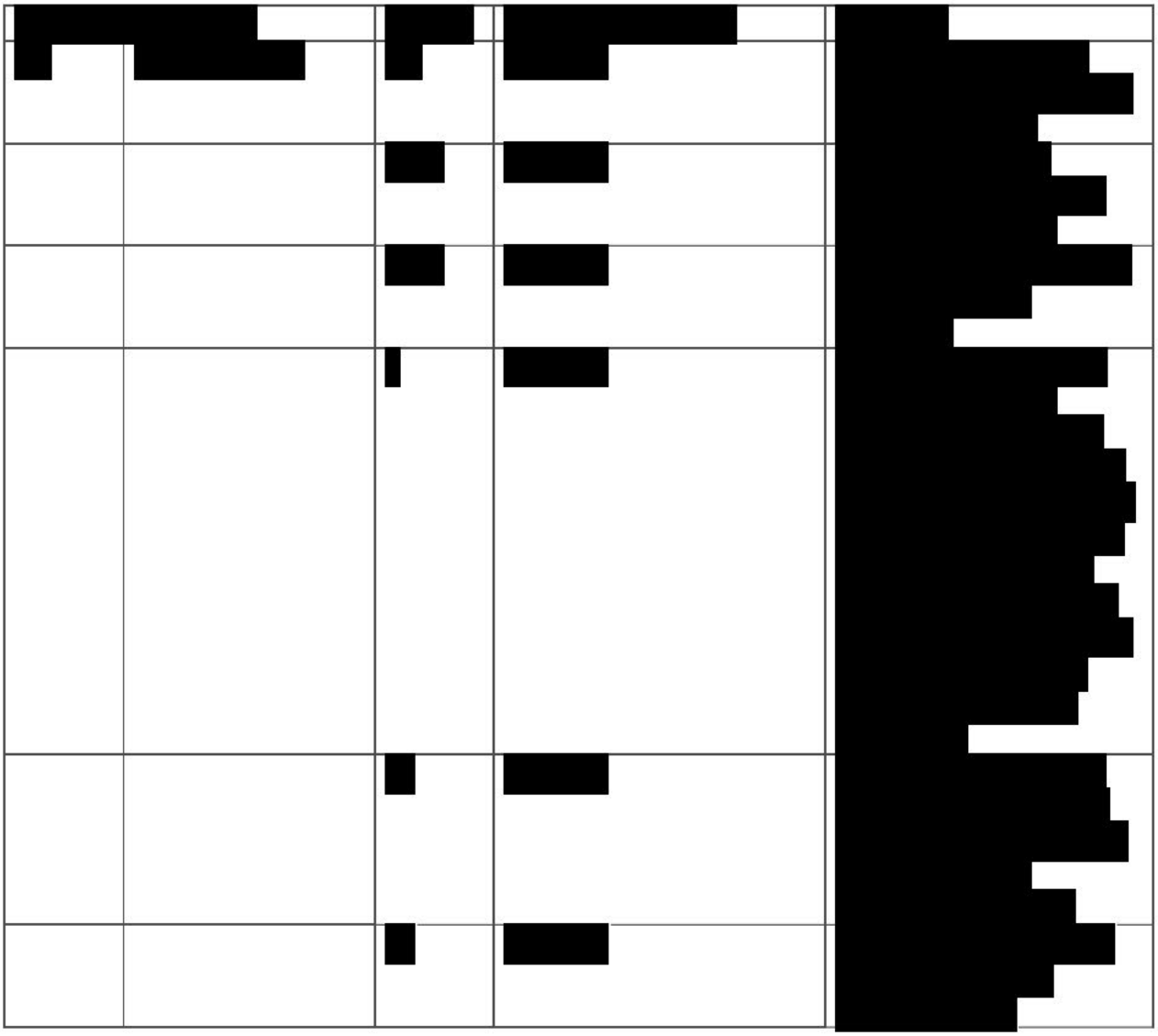
Previous Version

Version 1.0, Issue Date 04-NOV-2020

Author:

[redacted]

SAP Amendments before database lock



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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AICC	corrected Akaike's information criterion
ALT	alanine aminotransferase (serum glutamic-pyruvic transaminase)
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BPI-SF	Brief Pain Inventory-Short Form
bpm	beats per minute
CDISC	Clinical Data Interchange Standards Consortium
CGIC	Clinical Global Impression of Change
CI	Confidence Interval
C.L.E.A.R.	Corticosteroid Lumbar Epidural Analgesia for Radiculopathy
CS	clinically significant
CSR	clinical study report
DB	double-blind
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	Case Report Form
EOS	end of study
ET	early termination
g	gram(s)
HIV	human immunodeficiency virus
[redacted]	[redacted]
IP	independent programming
IPr	investigational product

Abbreviation	Definition
IWRS	interactive web recognition system
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat (data population)
mg	milligram
mmHg	millimeters of mercury
MMRM	mixed model for repeated measures
NCS	not clinically significant
NPRS	Numeric Pain Rating Scale
ODI	Oswestry Disability Index
OL	open-label
PBO	placebo
PGIC	Patient Global Impression of Change
PP	Per protocol
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment emergent adverse event
TF	transforaminal(ly)
WBC	white blood cells
[redacted]	[redacted]

2 INTRODUCTION

This document details the planned statistical analyses for the Scilex Pharmaceuticals, Inc., protocol "SP-102-02" study titled "Corticosteroid Lumbar Epidural Analgesia for Radiculopathy (C.L.E.A.R.)". Scilex Pharmaceuticals, Inc. is the new name of Semnur Pharmaceuticals, Inc. Previous study documents include "Semnur"; however, due to the merger, this document and any other documents that are yet to be finalized, approved, and signed will include "Scilex".

The proposed analyses are based on the contents of the final version (Version 4.0) of the protocol (dated 24-MAY-2018).

This is a double-blind (DB), randomized, placebo-controlled, multicenter study in subjects with lumbosacral radicular pain evaluating the safety and efficacy of a single SP-102 injection administered transforaminally (TF) compared to a single placebo injection administered intramuscularly (IM), followed by an open-label (OL) safety extension, evaluating an optional repeat SP-102 TF injection, if indicated, administered 4 to 20 weeks later. Subjects will be followed for 24 weeks following the initial treatment ("index injection").

Eligible subjects will be randomly assigned (in a 1:1 ratio) on Day (D) 1 to receive a single dose of an SP-102 TF or placebo injection [redacted] This first injection is referred to as the "index injection". An appropriately trained physician, hereafter called the Injection Physician, administering the double-blind investigational product (IPr) and other assisting staff (eg, nurse) will, therefore, not be blinded to the treatment assignment, while the rest of study staff involved in assessments and collection of data will remain blinded. Procedures will be in place at each site to ensure blinding, minimizing personnel involved with injection, and guarantee sequestration of imaging data acquired at the time of injection.

Each subject will have the option of receiving 1 supplemental OL TF injection of SP-102 ("repeat injection"). To qualify for the repeat injection, subjects must meet Repeat Injection Inclusion Criteria, Numeric Pain Rating Scale (NPRS) average pain score in the affected leg, and investigator judgment. The repeat injection may be administered between Weeks 4 and 20. Eligible subjects will receive OL SP-102 repeat injection regardless of their initial treatment assignment (SP-102 or placebo).

In case of inadequate control of radicular pain, up to 3 g of acetaminophen as rescue medication will be allowed per day. The subject should be instructed to avoid use of acetaminophen in the 6

hours prior to recording an NPRS score. Doses of rescue medication and time taken will be collected in the eDiaries until Week 12 and thereafter as a concomitant medication.

The subject will complete the eDiary twice daily approximately 12 hours apart (±2 hours) to record their NPRS scores for pain in the previous 12 hours for 12 weeks following index injection. Thereafter, NPRS scores will be recorded at clinic visits.

All subjects will be seen at the clinic on Day 15, and every 4 weeks (ie, Week 4 [Day 29], Week 8 [Day 57], Week 12 [Day 85], Week 16 [Day113], Week 20 [Day 141], and Week 24 [Day 169]) after the DB index injection for up to 24 weeks. Subjects receiving the OL repeat SP-102 injection will also be seen at the clinic 14 days after the repeat injection and continue the double-blind planned visits as well. Subjects will also be contacted by telephone by the site staff 2 days after each IPr injection to discuss their progress, any medications they are taking, and if they have had any adverse events (AEs).

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to:

- Evaluate the analgesic effect on average leg pain (as measured by the NPRS in the affected leg) following a single TF injection of SP-102 compared to an [redacted] injection of placebo over 4 weeks.

3.2 Secondary Objectives

The secondary objectives of the study are to:

- Evaluate degree of disability over time as measured by the Oswestry Disability Index (ODI).
- Characterize the change of the subject's radiculopathy symptoms and overall condition using Pain*DETECT*, Brief Pain Inventory-Short Form (BPI-SF), Clinical Global Impression of Change (CGIC), and Patient Global Impression of Change (PGIC).
- Evaluate the safety of a single and repeat SP-102 TF injection.

4 ENDPOINTS

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change from Baseline (D1) to Week 4 in the mean NPRS average pain score in the affected leg.

[redacted]

4.2 Secondary Efficacy Endpoints

The key secondary efficacy endpoint is:

- The change in ODI total score from Baseline (D1) to Week 4.

4.3 Other secondary endpoints

Other secondary endpoints are:

- PGIC at Week 2, Week 4, Week 8, and Week 12.
- The time to repeat injection of SP-102 from index injection.
- Proportion of subjects receiving repeat injection.
- The mean change from Baseline (D1) to Week 2, Week 4, Week 8, and Week 12 in the mean NPRS average pain score in the affected leg.
- The mean change from Baseline (D1) to Week 2, Week 4, Week 8, and Week 12 in the mean NPRS worst pain in the affected leg.
- The mean change from Baseline (D1) to Week 2, Week 4, Week 8, and Week 12 in the mean NPRS current pain score in the affected leg.
- The mean change from Baseline (D1) in the ODI total score to Week 12.
- The mean change in Pain*DETECT* from Baseline (D1) to Week 4 and Week 12.
- The mean change in BPI-SF score from Baseline (D1) to Week 4 and Week 12.

- Proportion of subjects achieving a response of 30%, 50%, and 75% reductions from Baseline (D1) in mean NPRS average pain score in the affected leg at Week 2 and Week 4.
- The mean change from Baseline (D1) to Week 2, Week 4, Week 8, and Week 12 in the mean NPRS average pain score in the lower back.
- CGIC at Week 2, Week 4, Week 8, and Week 12.
- Cumulative use of rescue medication (mg of acetaminophen)
- Time to first rescue medication dose.
- Proportion of subjects requiring rescue medications.
- Percent of rescue medication free days.
- The mean change from Baseline (D1) to Week 4 in the mean morning (AM) NPRS average pain score in the affected leg.
- The mean change from Baseline (D1) to Week 4 in the mean evening (PM) NPRS average pain score in the affected leg.

4.4 Safety Endpoints

- Adverse Events
- Change from Baseline (D1) in laboratory parameters
- Change from Baseline (D1) in vital signs
- Change from Baseline (D1) in neurological examination

5 SAMPLE SIZE

[redacted]

6 RANDOMIZATION

Using an Interactive Web Response System (IWRS), on D1, the site staff or research pharmacist will contact the IWRS after the Investigator has confirmed that the subject fulfills all the inclusion/exclusion criteria. The IWRS will assign a randomization number to the subject, which will be used to link the subject to a treatment arm. The research pharmacist will prepare the appropriate IP and deliver it to study staff in preparation for injection.

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

7 PLANNED ANALYSES

No statistical analysis plan (SAP) prepared in advance of the data can be absolutely definitive and the final clinical study report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

7.1 Analysis and Reporting Periods

Baseline, efficacy, and safety data will be summarized for the following analysis periods:

- Primary analysis period which includes data from baseline through 4 weeks of treatment
- Secondary analysis period which includes data from baseline to end of study (Week 24)

Also, there are two reporting periods in this study in which for each reporting period, data are summarized for both the primary and secondary analysis periods. These reporting periods are as follows:

- Primary analysis:
  This is the final inferential analysis of all efficacy endpoints, along with analysis of the safety endpoints up to Week12, which will be performed after all subjects complete the 12-week assessments and all data are cleaned. [redacted]

[redacted] For data that are collected on an ongoing basis throughout the study (eg adverse events, concomitant medications), the subject's actual Week 12 visit date will be used as a cutoff for the data in the primary analysis. For subjects who did not complete Week 12 and withdrew early, the cutoff for the data would be the earliest of the subject's projected Day 85 and discontinuation date.

- Full analysis:
  After the subjects in the OL safety extension portion of the study complete the study up to Week 24, the database will be locked, and the corresponding analysis tables produced for the primary analysis will be updated with the descriptive statistics of the Week 16, Week 20, and Week 24 data added.

Thus, exactly the same set of outputs will be produced for the primary analysis and full analysis.

7.2 Analysis Population

7.2.1 Screened Population

This consists of subjects that signed the informed consent form and were assigned a user subject number.

7.2.2 Safety Analysis Population

This is defined as all randomized subjects who received an index injection (study drug). For safety analyses, subjects will be grouped based upon the treatment received (even if different from what they were randomized to).

7.2.3 Modified Intent-to-Treat (mITT) Population

This will be the primary population for efficacy analyses and will include all subjects who were randomized and received drug delivery injection (for index injection only) in correct anatomic location. [redacted]

7.2.4 Per Protocol Population

This will include all subjects in the mITT population who do not have a major protocol deviation. Major protocol deviations will be reviewed and determined prior to unblinding. The Per Protocol (PP) population will be determined prior to treatment unblinding and will be used for supportive sensitivity analyses.

Subjects excluded from the analysis populations and the reason for their exclusion will be listed in Appendix 16.2.

7.2.5 Completed Subject

For the purposes of analysis, there are 3 types of completers in this trial:

- A Primary Efficacy Endpoint Completer is defined as one who receives an index injection and who has enough data to calculate data for the primary analysis period (i.e. first four weeks) regardless if Week 4 visit was completed. [redacted]
- A 12-week Completer is defined as one who receives an index injection and completes the study through Week 12.
- A 24-week Completer is defined as one who receives an index injection and completes the study through Week 24.

A subject does not necessarily have to complete all visits up to Week 12, or Week 24 to be considered as a 12-week Completer or 24-week Completer respectively. As long as the Week 12 or Week 24 visits are completed, the subject will be considered as a 12-week Completer or 24-week Completer respectively.

7.3 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

[redacted]

7.3.1 Race

If more than one race category has been selected for a subject, these race categories will be combined into a single category labeled "Multiple Race" in the summary tables. The listings will reflect the original selected categories.

7.3.2 Baseline

Except otherwise specified, baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first dose of SP-102 TF or placebo [redacted] injection on D1. Baseline calculations for variables collected in the diary are described in the efficacy analyses section.

7.3.3 Duration/Study Day/Time

Study day will be calculated as the number of days from first dose of SP-102 TF or placebo [redacted] injection.

- date of event – date of first dose of SP-102 TF or placebo [redacted] + 1, for events on or after first dose
- date of event – date of first dose of SP-102 TF or placebo [redacted], for events before first dose.

For all time to event analyses, subjects not reporting the specified endpoint will be censored at the time that the subjects were last known not to have experienced the endpoint. The last visit is a censoring event, and events that occur after the last visit will be disregarded in the statistical analysis. For all endpoints not encompassing death, all deaths will be treated as censoring events. In complex cases where the censoring time of the subject is uncertain, the case will be reviewed

by the Worldwide Clinical Trials (WCT) statistician and a censoring time will be assigned before database lock.

7.3.4 Conventions for Missing and Partial Dates

All rules explained below for partial/missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).

All dates presented in the individual subject listings will be as recorded on the eCRF (i.e., not completed as per the below rules).

7.3.5 Missing/Partial Start/Stop Date of Adverse Events and Concomitant Medications

Missing and partial start and stop date will be imputed for analysis purposes as follows:

Partial or missing stop date will be imputed as follows:

- If the stop date is completely missing and the event has resolved or the subject has stopped taking the concomitant medication, the stop date will be imputed as the date of the subject's last clinic visit in the study.
- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the subject's last clinic visit in the study if in the same year.
- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the subject's last clinic visit in which case the date of subject's last clinic visit in the study will be used instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the index injection or the event/concomitant medication is ongoing, the start date will be imputed as the date of the index injection.
- If the stop date occurs before the index injection, the start date of the event/concomitant medication will be imputed as the subject's screening date or the stop date of the event/concomitant medication whichever the earlier.

Partial start date (year present, but month and day missing)

- If the stop date occurs on or after the index injection or the event/concomitant medication is ongoing, and the year is the same as the year of index injection the start date will be imputed as the date of the index injection. If the year is different from the year of index injection "01-Jan" will be used.

- If the stop date occurs before the index injection, the start date of the event/concomitant medication will be imputed as the "01-Jan" of the same year.

Partial start date (month and year present, but day missing)

- If the stop date occurs on or after the index injection or the event/concomitant medication is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in same month as the index injection in which case the date of index injection will be used.
- If the stop date occurs before the index injection, the start date will be imputed as the first day of the month and year of the partial stop date.

7.3.6 Inexact Values

In the case where a laboratory parameter has result recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be used for analysis purposes.

7.3.7 Electrocardiogram Data

If more than one value is recorded at a time point for electrocardiogram (ECG) data recorded on a continuous scale, the integer of the mean value will be recorded. For overall interpretation if more than one value is recorded, the most severe (worst case) of the respective readings will be taken.

7.3.8 Unscheduled Visits

Only scheduled post-baseline laboratory and vital signs values will be tabulated. Post-baseline repeat/unscheduled (except for repeat injection visits) assessments will be disregarded, although these post-baseline assessments will be listed in the relevant appendices to the CSR.

Repeat injection visits maybe captured as unscheduled visits. All assessments carried out during a repeat injection visit will be included in the analysis.

7.3.9 Early Termination Assessments

Early Termination (ET) assessment for post-baseline efficacy, laboratory or vital sign data will be mapped to the End of Study (Week 24) visit.

7.3.10 Randomization Strata

As described in Section 6, randomization is stratified by study site. Furthermore, protocol indicates that analysis will include adjustment for study site. There are approximately 45 study sites and it is likely that some of these study sites will have small number of subjects that are

included in the mITT population and thus could lead to unreliable treatment effects estimates and p-values. With this, the study sites will be pooled by state and then by region. However, if a state has significantly large number of subjects (eg almost double) compared to the other regions, it will be considered as one of the final pooled sites. The resulting final pooled sites (referred to as 'site' from here on) are as follows:

[redacted]

7.4 Conventions

All data listings, summaries, figures and statistical analyses will be generated using SAS version 9.4 or higher[1].

Subjects will be randomized to 1 of 2 treatment groups (SP-102 or placebo) and will receive 1 injection at Baseline (D1). After 4 weeks, an additional injection of SP-102 may be administered to all subjects regardless of the treatment they were originally randomized to. Because of this, baseline, efficacy, and safety variables will be summarized in two ways.

The first will summarize data for the 2 randomized treatment groups for the primary analysis period. Subjects will be analyzed in either the SP-102 or placebo treatment groups. Baseline summaries and data for this first 4 weeks will be summarized using the following treatment columns. Only baseline data will have the overall column.

SP-102	Placebo	Overall

The second will classify subjects into 1 of 4 groups and will summarize data for the secondary analysis period. These 4 groups include the following:

- Subjects who receive only 1 SP-102 injection
- Subjects who receive 2 SP-102 injections

- Subjects who receive only 1 placebo injection
- Subjects who receive 1 placebo injection and 1 SP-102 injection

The 4 treatment groups will be used in the summary and analyses involving the secondary analysis period (randomization through end of study).

These 4 groups may be combined for additional analyses (eg, combine into one group any subject who received an injection of SP-102 at any point in time). [redacted]

SP-102/SP-102	PBO/SP-102	SP-102/none	PBO/none	Overall

Overall columns are to be included within the table shells as follows:

Data	Column labels
Demography	Treatment and overall
Baseline	Treatment and overall
Disposition	Treatment and overall
Prior Medications	Treatment and overall
Concomitant Medications	Treatment and overall
Efficacy	Treatment
AEs	Treatment
Other safety	Treatment

Listings will be sorted in the following order: treatment group, subject, parameter, and visit unless otherwise stated. All data will be listed. Subjects who were not randomized will be displayed after the randomized treatment groups.

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum. For all tabulations of changes from

baseline data, the lower and upper 95% confidence limits for the mean for the individual treatments will be given.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the subject population unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

7.4.1 Decimal Places

Decimal places for derived data described in Section 7.2 will be determined by the scale of measurement unless otherwise stated. No decimal places will be displayed if the smallest calculated value is ≥100; 1 decimal place will be displayed when the smallest value is within the interval (10, 100), with 10 being inclusive; 2 decimal places will be displayed when the smallest value is within (1, 10), with 1 being inclusive; and so on for even smaller scales of measurement.

If derived data such as number of days or total score is an integer, then it will be presented with zero decimal places.

Means, medians and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g. standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

P-Values will be quoted to 3 decimal places. P-values <0.001 will be presented as p<0.001. If this value is less than 0.05, 0.01 or 0.001, attention will be drawn to this fact using the conventional "*", "**" or "***" annotation, respectively.

7.5 Subject Disposition

Subject disposition will be summarized as follows:

- The number of subjects randomized, and number in each analysis population (Safety, mITT, and Per Protocol) will be summarized by treatment group and overall based on all randomized subjects for both the primary and secondary analysis periods.
- The number of subjects screened, who failed screening and the reasons for failure will be summarized using the Screened Population.
- The number of early termination and the reasons for termination will be tabulated by treatment group and overall for each analysis period for the Safety Analysis Population.

- The number of subjects who are Primary Efficacy Endpoint Completers, 12-Week Completers, and 24week Completers will be summarized by treatment group and overall for the Safety Analysis Population.

7.6 Protocol Deviations

Protocol deviations will be collected by study site and grouped into different categories, such as those who:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted].

Major protocol violations that impact the primary efficacy analysis may lead to exclusion from the PP population. Protocol deviation categories will be summarized for the safety analysis population by treatment group and overall. Protocol deviations will be summarized separately for the primary and secondary analysis periods.

A listing of protocol deviations will be provided within Appendix 16.2.

7.7 Baseline Comparability

The comparability of treatment groups with respect to subject demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed.

Standard continuous or categorical variable summaries will be presented by treatment group based on the Safety Analysis Population.

Baseline demographic data will be summarized using the Safety Analysis Population for both the primary and secondary analysis periods. This will include age in years, gender, fertility status (childbearing potential, post-menopausal, surgically sterile), ethnicity, race, height, weight, and BMI.

7.8 Medical History

Summary table of previous and ongoing conditions at screening will be presented by treatment group and overall for the Safety Analysis Population. Conditions will be presented by Medical

Dictionary of Regulated Activities (MedDRA) version 23.1 (or a more up-to-date version by the time of database lock) primary system organ class and preferred term. Listings of all medical history will be presented.

7.9 Prior and Concomitant Medications

Summary tables will be produced for prior and concomitant medications presented by treatment group and overall for the Safety Analysis Population. Prior medications are defined as all medications that started and stopped before the date of first dose of study drug. Prior medications will be summarized by the planned treatment for the first injection (SP-102, Placebo).

Concomitant medication refers to all drugs and therapies that started prior to, on, or after the first dose of the study medication and ended on or after the date of the first dose of the study medication, or are ongoing at end of study. Medications are coded using WHODDE B3 Global - Sep 2019 Concomitant medications will be summarized using Anatomical Therapeutic Chemical [ATC] Level 2. Listings of all prior and concomitant medications will be presented. Concomitant medications will be summarized for each post randomization treatment period as follows:

- First four weeks: summarizes all drugs and therapies taken within first 4 weeks after first dose of study medication. This will be tabulated using the two treatment groups: SP-102, Placebo.
- Entire treatment period: summarizes all drugs and therapies that started prior to, on, or after the first dose of the study medication and ended on or after the date of the first dose of the study medication. This will be tabulated using the treatment group with four arms: SP-102/SP-102, PBO/SP-102, SP-102/none, PBO/none.
- Through 12 weeks: summarizes all drugs and therapies taken within first 12 weeks after first dose of study medication. This will be tabulated using the treatment group with four arms: SP-102/SP-102, PBO/SP-102, SP-102/none, PBO/none, and by exposure to SP-102, that is, Exposed vs. Not Exposed to SP-102. The Exposed group will include the subjects that have received SP-102 for index injection and/or have repeat injection while Non-Exposed group will include the subjects that have received Placebo for index injection and do not have repeat injection

7.10 Exposure to Study Drug

The number of randomized subjects that received index injection, that received repeat injection, and that received any injection will be summarized by treatment group.

7.11 Treatment Compliance

Compliance will not be calculated but the listing of study drug administration will be provided.

7.12 Efficacy Analyses

All statistical tests will be performed using a two-tailed 5% overall significance level, unless otherwise stated. All comparisons between treatments will be reported with 95% confidence intervals (CI) for the difference. Pain profiles through the first four weeks will be presented by the treatment received for the first injection (SP-102, Placebo). Moreover, pain profiles through 12 weeks will be presented by treatment received for second injection (SP-102/SP-102, PBO/SP-102, SP-102/none, PBO/none). Also, the 'site' indicated in this section refers to the final pooled sites as described in Section 7.2.10.

7.12.1 Primary Endpoint

The primary efficacy endpoint is the mean change from Baseline (D1) to Week 4 in the mean NPRS average pain score in the affected leg.

The null and alternative hypotheses are:

[redacted]

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. Twice daily: in the morning and evening (approximately 12 hours apart), the subject will use the NPRS to record their average and worst pain in the past 12 hours. [redacted] After the Screening Visit, the NPRS will be collected twice daily using the eDiary through Week 12; thereafter, the NPRS will be collected at clinic visits only.

[redacted]

[redacted]

7.12.2 Primary Efficacy Analysis

[redacted]

The primary comparison will use a linear contrast of the least squares (LS) means comparing the mean weekly mean scores up to Week 4 (average of Weeks 1, 2, 3, and 4 change from baseline LS means estimated from the model).

For each type of pain score collected, NPRS scores will be summarized on a weekly basis (Weeks 1, 2, 3, and 4). The LS means, its corresponding standard errors and 95% CI will be presented for all four weeks. The same will be presented for the mean LS mean corresponding to the mean weekly mean scores across all four weeks. The estimate of the LS mean treatment difference, its standard error, and 95% CI will be presented for the average LS mean across all four visits.

The SAS code anticipated to be used for the analysis of the primary efficacy endpoint is as follows:

[redacted]

7.12.3 Sensitivity Analysis

The following sensitivity analysis will be applied;

1. The primary analysis will be re-run for the PP Population.

2. The primary analysis model will be re-run but will include sex, duration of leg pain, prior opioid use for current episode of pain (yes/no) as additional factors in the model. Prior opioid use for current episode of pain will be determined by reviewing all the subject's medications and checking if there is any medication with opioid (using the ATC3 codes as listed below) and comparing the medication's start date and end date to the current episode date, that is, for the subject to be classified as having a prior opioid use for current episode of pain ('yes'), the current episode date should be within the medication's start date and end date:

- N02A (Opioids)
- A07D (Antipropulsives)
- R05D (Cough suppressants, excl. combinations with expectorants)
- R05F (Cough suppressants and expectorants, combinations)

Duration of leg pain is the number of months from start date of current episode of lumbosacral radicular pain to D1. That is,

[D1 visit date – start date of current episode of lumbosacral radicular pain + 1] / 30.

[redacted]

[redacted]

The following SAS codes will be used to implement the placebo-based pattern mixture imputation.

[redacted]

[redacted]

The imputed data sets will be analyzed with the same MMRM model employed in the primary analysis and then summarized using PROC MIANALYZE.

7.12.4 Key Secondary Endpoints

The key secondary efficacy endpoint is the change in ODI total score from Baseline (D1) to Week 4.

The ODI is a widely accepted and validated measure for measuring degree of disability and estimating quality of life in a person with low back pain. The ODI is a 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 six 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 0-5 with the first statement being zero 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 (0 to 100). If a subject misses some questions, the total score of the answered questions will be divided by the total expected score (number of answered questions times 5) then multiplied by 100 (Fairbank[4]). The ODI index obtained using this algorithm is equivalent to the ODI index obtained by summing all the scores then multiplying it by 2 in the event that there are no skipped or missed questions. A subject would need to answer at least seven questions out of ten before a total score is calculated for that visit. Zero is equated with no disability and 100 is the maximum disability possible. The ODI will be obtained at the Screening, Baseline (D1), Week 4 (Day 29), Week 12 (Day 85), and Week 24 (Day 169) visits.

7.12.5 Key Secondary Analysis

Baseline ODI is defined as the last ODI assessment score prior to the first injection on D1. The change in ODI total score from baseline will be analyzed using the mITT and PP Analysis Populations. This endpoint will be analyzed using the analysis of covariance (ANCOVA) model where change from baseline in ODI score at Week 4 will be the response variable with fixed effects for treatment (two groups: SP-102 or placebo), site, Pain Catastrophizing Scale group (<30 or

≥30), and baseline ODI. The treatment group categories for this analysis will be the SP-102 and placebo groups. A summary of the observed and change from baseline ODI total score will be presented by visit and treatment group jointly for both the primary and secondary analysis periods. Listings of all 10 topic scores and total scores will be presented.

The following SAS code will be used for this key secondary analysis;

[redacted]

7.12.6 Other Secondary Endpoints and Analysis

All other secondary endpoints (outlined below) will be analyzed using the mITT and PP Analysis Population.

7.12.6.1 PGIC at Week 2, Week 4, Week 8, and Week 12.

The PGIC is a seven-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. PGIC will be collected after randomization at Weeks 2, 4, 8, 12, 16, 20, and 24. For analysis, a subject will be classified as either PGIC responder, that is, a PGIC response of 1: very much improved or 2: much improved or a PGIC non-responder, that is, all other PGIC responses (recorded as 3-7 in the scale). Subjects who do not complete the measure at the timepoint of interest will also be considered non-responders. The number and percentage of subjects reporting each of the seven PGIC response levels will also be summarized by visit and treatment. The analysis will utilize separate Chi-Square tests for Week 2 and Week 4 where the p-value of the treatment difference will be presented. Separate logistic regression models with treatment, site, and Pain Catastrophizing Scale group as factors will also be used to compare the treatment groups at each week (Week 2 and Week 4) using the two treatment groups. The odds ratio of SP-102 vs placebo at Weeks 2 and 4, and its corresponding 95% CI and p-value will be presented.

Separate Chi-Square tests and similar logistic regression analyses will be applied at Weeks 2, 4, 8, and 12 using the treatment group with four arms: SP-102/SP-102, PBO/SP-102, SP-102/none, PBO/none. The following odds ratios at Weeks 2, 4, 8, and 12 and the corresponding 95% CIs and p-values will be presented:

- SP-102/none vs. PBO/none

- SP-102/SP-102 vs. PBO/none
- SP-102/none vs. PBO/SP-102
- SP-102/SP-102 vs. PBO/SP-102

A summary of the assessments at Weeks 16, 20, and 24 will be presented.

7.12.6.2 The time (days) to repeat injection of SP-102

The time to repeat injection of SP-102 will be analyzed using survival analysis methods. Subjects that do not receive a repeat injection will be censored at 20 weeks, and subjects who discontinue the study prior to 20 weeks without receiving a repeat injection will be censored at the time of discontinuation. The Kaplan-Meier estimator will be used to estimate the quartiles of the time to repeat injection in days. A Cox proportional hazards model will be utilized to test the treatment difference in time to repeat injection while adjusting for site, and Pain Catastrophizing Scale. The response variable of the Cox model will be time to repeat injection. The treatment group categories for this analysis will be the SP-102 and placebo groups. The quartiles and their corresponding 95% CIs from the Kaplan-Meier estimation, and the hazard ratio of SP-102 to placebo with its 95% CI and p-value will be presented. A survival plot of time to repeat injection will also be presented. Listings of time to repeat injection will be presented.

7.12.6.3 Proportion of subjects receiving repeat injection.

The proportion of subjects receiving repeat injections will be compared between the two treatment groups using a Chi-Square test. The proportion of subjects receiving a repeat injection will be summarized by treatment group.

7.12.6.4 The mean change from Baseline (D1) to Week 2, Week 4, Week 8, and Week 12 in the mean NPRS average pain score in the affected leg.

Baseline and post-baseline values for this endpoint is obtained as discussed in Section 7.12.1. A similar approach in modeling the restricted maximum likelihood (REML)-based MMRM as in the primary analysis will be applied for this endpoint. Mean change from baseline to Week 2 and Week 4 will be analyzed and presented by the treatment received for the first injection (SP-102, Placebo). Mean change from baseline for the first 12 weeks (Weeks 2, 4, 8, and 12) will utilize similar MMRM model except that the outcome variable will be change from baseline in mean weekly NPRS average pain score in the affected leg at Weeks 2, 4, 8, and 12, and the fixed effects are as follows: treatment (four groups: SP-102/SP-102, PBO/SP-102, SP-102/none, PBO/none), week (2, 4, 8, 12), site, Pain Catastrophizing Scale group (<30 or ≥30), baseline averaged daily leg

pain score, and the treatment-by-week interaction. Mean change from baseline for Weeks 2, 4, 8, and 12 will be summarized by treatment received for second injection (SP-102/SP-102, PBO/SP-102, SP-102/none, PBO/none).

As part of this analysis, comparisons will test the mean LS mean differences between the following groups:

- SP-102/none vs. PBO/none
- SP-102/SP-102 vs. PBO/none
- SP-102/none vs. PBO/SP-102
- SP-102/SP-102 vs. PBO/SP-102

NPRS average scores are also collected at visits (Weeks 16, 20, and 24) after visit 12. This data will not be included in the model but will be included in the summary table.

7.12.6.5 The mean change from Baseline (D1) to Week 2, Week 4, Week 8, and Week 12 in the mean NPRS worst pain score in the affected leg.

This will be analyzed and presented using the same MMRM model described in the primary analysis but the response variable will be change from baseline in mean weekly worst NPRS score. Baseline NPRS score is the mean of at least 5 days and no more than 7 days of scores from the Screening visit until treatment randomization (D1). [redacted] The mean weekly NPRS score will be calculated for each subject for each week up to Week 12. Change from baseline in mean weekly NPRS score will be calculated by subtracting the baseline value from the weekly score. Mean change from baseline for the first 4 weeks (with overall average) will be analyzed and presented by the treatment received for the first injection (SP-102, Placebo). Mean change from baseline for the first 12 weeks (Weeks 2, 4, 8, and 12) will be analyzed and summarized by treatment received for second injection (SP-102/SP-102, PBO/SP-102, SP-102/none, PBO/none). As part of this analysis, comparisons will test the mean LS mean differences between the following groups:

- SP-102/none vs. PBO/none

- SP-102/SP-102 vs. PBO/none
- SP-102/none vs. PBO/SP-102
- SP-102/SP-102 vs. PBO/SP-102

NPRS worst pain score is also collected at visits after Week 12 (Weeks 16, 20, and 24), but this score is only collected once, that is, during the clinic visits. This data will not be included in the model but will be included in the summary table.

7.12.6.6 The mean change from Baseline (D1) to Week 2, Week 4, Week 8, and Week 12 in the mean NPRS current pain score in the affected leg

The current pain intensity "pain now" is measured at every clinic visit and used for assessment of accuracy of pain reporting and monitoring of outlier values. This endpoint will be analyzed and presented using the same MMRM model described in the primary analysis but the response variable will be change from baseline in mean NPRS current pain score at Weeks 2, 4, 8, and 12; with baseline NPRS score as the last score collected prior to the first injection on D1. Mean change from baseline to Week 2 and Week 4 will be analyzed and presented by the treatment received for the first injection (SP-102, Placebo). Mean change from baseline for the first 12 weeks (Weeks 2, 4, 8, and 12) will be analyzed and summarized by treatment received for second injection (SP-102/SP-102, PBO/SP-102, SP-102/none, PBO/none). As part of this analysis, comparisons will test the mean LS mean differences between the following groups:

- SP-102/none vs. PBO/none
- SP-102/SP-102 vs. PBO/none
- SP-102/none vs. PBO/SP-102
- SP-102/SP-102 vs. PBO/SP-102

NPRS average scores are also collected at visits (Weeks 16, 20, and 24) after visit 12. This data will not be included in the model but will be included in the summary table.

7.12.6.7 The mean change from Baseline (D1) in the ODI total score to Week 12.

The treatment group categories will be: SP-102/SP-102, PBO/SP-102, SP-102/none, PBO/none. As part of this analysis, comparisons will test the mean LS mean differences between the following groups:

- SP-102/none vs. PBO/none

- SP-102/SP-102 vs. PBO/none
- SP-102/none vs. PBO/SP-102
- SP-102/SP-102 vs. PBO/SP-102

An MMRM analysis will be applied using the four treatment groups to analyze change from baseline in ODI through Week 12 (Weeks 4 and 12). ODI at Week 24 will be summarized. The change from baseline at Weeks 4 and 12 will be the response variable with fixed effects for treatment, Week, site, Pain Catastrophizing Scale group (<30 or ≥30), baseline ODI, and treatment-by-week interaction. The following SAS code will be used for this analysis;

[redacted]

7.12.6.8 The mean change in Pain*DETECT* from Baseline (D1) to Week 4 and Week 12.

Pain*DETECT* is a 7-question validated tool to determine the prevalence of neuropathic pain in individuals with lower back pain. The 7 responses, with possible values of never (0), hardly noticed (1), slightly (2), moderately (3), strongly (4), and very strong (5), are summed for a possible score ranging from 0-35. 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) with 0, -1, 1, and 1 score assignments respectively, and whether the pain radiates to other regions of the body or not which adds 2 to the total score for a "yes" response and 0 for a missing or "no" response. Hence, the total overall scale score will range from 0 to 38. Baseline Pain*DETECT* total score is defined as the last score collected prior to the first injection on D1. Since this endpoint is summing the responses to get the total score, if a subject is missing a question aside from the question on whether the pain radiates to other regions of the body or not, the total score will not be calculated for that subject. Pain*DETECT* will be collected at Baseline (D1), Week 4, and Week 12.

Pain*DETECT* at Week 4 will be analyzed using an ANCOVA model with change from baseline at Week 4 as the response variable with fixed effects for treatment (two groups: SP102 or placebo), site, Pain Catastrophizing Scale group (<30 or ≥30), and baseline Pain*DETECT* total score.

Change from baseline to Week 12 will also be analyzed using an MMRM analysis with change from baseline to Week 12 (Weeks 4 and 12) as the response variable, with fixed effects for treatment (SP-102/SP-102, PBO/SP-102, SP-102/none, PBO/none) week, site, Pain Catastrophizing Scale group (<30 or ≥30), baseline score, and treatment-by-week interaction. As part of this analysis, comparisons will test the mean LS mean differences between the following groups:

- SP-102/none vs. PBO/none
- SP-102/SP-102 vs. PBO/none
- SP-102/none vs. PBO/SP-102
- SP-102/SP-102 vs. PBO/SP-102

Pain*DETECT* will be summarized for Week 24 by treatment (four groups).

7.12.6.9 The mean change in BPI-SF score from Baseline (D1) to Week 4 and Week 12.

The BPI-SF is a 15-item self-rating scale assessing use of medications, as well as sensory, and reactive components of pain. The BPI-SF includes items that will address components of sensory pain, including severity, location, chronicity, and degree of relief due to therapy. The BPI-SF also has items that address reactive pain components, including depression, suffering, and perceived availability of relief. The BPI-SF will be collected at Screening, Baseline (D1), Week 4 (Day 29), and Week 12 visits. Two BFI-SF scales will be derived from the BRI-SF responses: Pain Severity Score and Pain Interference Score.

Pain Severity Score = Mean of items 3-6 (pain at its worst, pain at its least, average).

Pain Interference Score = Mean of items 9A-9G (interference of pain with: general activity, mood, walking, normal work, relations, sleep, enjoyment of life).

BPI-SF at Week 4 will be analyzed using an ANCOVA model with change from baseline at Week 4 as the response variable with fixed effects for treatment (two groups: SP102 or placebo), site, Pain Catastrophizing Scale group (<30 or ≥30), and baseline score. Baseline BPI-SF scale score is defined as the last BPI-SF assessment scale score prior to first injection on Day 1.

Change from baseline to Week 12 will also be analyzed using an MMRM analysis with change from baseline to Week 12 (Weeks 4 and 12) as the response variables, with fixed effects for

treatment (SP-102/SP-102, PBO/SP-102, SP-102/none, PBO/none), week, site, Pain Catastrophizing Scale group (<30 or ≥30), baseline score, and treatment-by-week interaction. As part of this analysis, post-hoc comparisons will test the mean LS mean differences between the following groups:

- SP-102/none vs. PBO/none
- SP-102/SP-102 vs. PBO/none
- SP-102/none vs. PBO/SP-102
- SP-102/SP-102 vs. PBO/SP-102

BPI-SF scores will be summarized for Week 24 by treatment (four groups).

7.12.6.10 Proportion of subjects achieving a response of 30%, 50%, and 75% reductions from Baseline (D1) in mean NPRS average pain score in the affected leg at Week 2 and Week 4.

Responders are defined and calculated as follows:

30% responder = (Change from baseline/ baseline) x 100 ≤ -30.

50% responder = (Change from baseline/ baseline) x 100 ≤ -50.

75% responder = (Change from baseline/ baseline) x 100 ≤ -75.

Subjects that discontinue or have missing scores at Week 2 and Week 4 will be considered non-responders.

The proportion of subjects achieving a response will be analyzed for each cut off percentage (30%, 50%, and 75%) by week. This will be analyzed using a Chi-Square test where the p-value of the treatment difference will be presented. For each cutoff response percentage, a logistic regression models with treatment (two groups: SP102 or placebo), site, Pain Catastrophizing Scale group (<30 or ≥30), and baseline averaged daily leg pain score as factors will also be used to compare the treatment groups at each week. The odds ratio of SP-102 vs placebo, its corresponding 95% CI and p-value will be presented. The number and percentage of responders will be presented for each visit.

A continuous responder analysis will also be performed. The proportion of subjects achieving a reduction in pain will be plotted against the continuous cutoff ranging from 0% to 100% reduction in pain intensity from Baseline (D1) as measured by the NPRS average daily leg pain scores in the

affected leg. This analysis will be performed using data observed at Week 4 and then over the first 4 weeks (using average of the 4 weekly mean NPRS average daily leg pain scores in the affected leg to calculate the percent reduction). All subjects who withdraw early from the study within 4 weeks will be considered non-responders. Treatment groups (SP-102 and placebo) will be compared using a log rank test.

7.12.6.11 The mean change from Baseline (D1) to Week 2, Week 4, Week 8, and Week 12 in mean NPRS average pain score in the lower back.

The average pain score in the lower back is measured at every clinic visit. This endpoint will be analyzed and presented using the same MMRM model described in the primary analysis but the response variable will be change from baseline in mean NPRS average pain score in the lower back at Weeks 2, 4, 8, and 12; with baseline NPRS score as the last score collected prior to the first injection on D1. Mean change from baseline for the first 4 weeks (Week 2 and Week 4) will be analyzed and presented by the treatment received for the first injection (SP-102, Placebo). Mean change from baseline for the first 12 weeks (Weeks 2, 4, 8, and 12) will also be analyzed and summarized by treatment received for second injection (SP-102/SP-102, PBO/SP-102, SP-102/none, PBO/none). As part of this analysis, comparisons will test the mean LS mean differences between the following groups:

- SP-102/none vs. PBO/none
- SP-102/SP-102 vs. PBO/none
- SP-102/none vs. PBO/SP-102
- SP-102/SP-102 vs. PBO/SP-102

NPRS average scores are also collected at visits (Weeks 16, 20, and 24) after visit 12. This data will not be included in the model but will be included in the summary table.

7.12.6.12 CGIC at Week 2, Week 4, Week 8, and Week 12.

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. CGIC will be collected after randomization at Weeks 2, 4, 8, 12, 16, 20, and 24. For analysis, a subject will be classified as either CGIC responder, that is, a CGIC response of 1: very much improved or 2: much improved or a CGIC non-responder, that is, all other CGIC responses (recorded as 3-7 in the scale). Subjects who do not complete the measure at the timepoint of interest will also be considered non-responders. The number and percentage of subjects reporting each of the seven

CGIC response levels will also be summarized by visit and treatment. Analyses will utilize separate Chi-Square tests for Week 2 and Week 4 where the p-value of the treatment difference will be presented. Separate logistic regression models with treatment, site, and Pain Catastrophizing Scale group (<30 or ≥30) as factors will also be used to compare the treatment groups for Week 2 and Week 4 using the 2 treatment groups. The odds ratio of SP-102 vs placebo at Weeks 2 and 4, and its corresponding 95% CI and p-value will be presented. Listings of CGIC will also be provided.

Separate Chi-Square tests and similar logistic regression analyses will be applied at Weeks 2, 4, 8, and 12 using the treatment group with four arms: SP-102/SP-102, PBO/SP-102, SP-102/none, PBO/none. The following odds ratios at Weeks 2, 4, 8, and 12 and the corresponding 95% CIs and p-values will be presented:

- SP-102/none vs. PBO/none
- SP-102/SP-102 vs. PBO/none
- SP-102/none vs. PBO/SP-102
- SP-102/SP-102 vs. PBO/SP-102

A summary of the assessments at Weeks 16, 20, and 24 will be presented.

7.12.6.13 Cumulative use of rescue medication (mg of acetaminophen)

In this study, acetaminophen is the permitted and study-provided rescue medication. For subjects that withdraw early, their missing weekly values after withdrawal will be imputed using the average weekly score for the respective treatment group. If the subject has partial records of rescue medication on the week of subject's withdrawal, the rescue medication use on that week will be imputed as follows:

[partial record of rescue medication on the withdrawal week * (7/number of days in the withdrawal week with partial record)].

Cumulative use of rescue medication at Week 4 will be obtained as the rescue medication use during the first four weeks relative to the index injection, that is, up to the subject's Day 29 in the study. It will be analyzed using an analysis of variance (ANOVA) model with cumulative use from baseline to Week 4 as the response variable with fixed effects for treatment (two groups: SP102 or placebo), site, and Pain Catastrophizing Scale group (<30 or ≥30). The same ANOVA model will

be applied on only subjects that complete 4 Weeks and output will be presented using the two treatment groups.

Cumulative use of rescue medication at Week 12 will be obtained as the rescue medication use during the first 12 weeks relative to the index injection, that is, up to subject's Day 85 in the study. It will also be analyzed using an ANOVA model with cumulative use from baseline to Week 12 as the response variable with fixed effects using the four treatment (SP-102/SP-102, PBO/SP-102, SP-102/none, PBO/none) variable, site, and Pain Catastrophizing Scale group (<30 or ≥30). The same ANOVA model will be applied on only subjects that complete 12 Weeks and output will be presented using the four treatment groups.

7.12.6.14 Time to first rescue medication dose

The time to first rescue medication dose, in days, will be analyzed like the time to event endpoint in Section 7.11.6.2. Time to first rescue medication dose will be analyzed separately for the first 4 weeks (two groups), and the first 12 weeks (four groups). For both analysis periods, time to first rescue medication dose will be calculated relative to the date of index injection. For the primary analysis period (first 4 weeks), subjects who do not use rescue medications for the first 4 weeks will be censored at Day 29th while subjects who discontinue the study prior to the subject's Day 29th in the study will be censored at the time of discontinuation. Similarly, for the secondary analysis period, subjects who do not use rescue medication for the first 12 weeks will be censored at Day 85th while subjects who discontinue the study prior to the subject's Day 85th in the study will be censored at the time of discontinuation.

7.12.6.15 Proportion of subjects requiring rescue medication

The proportion of subjects requiring rescue medications will be compared across treatment arms using a Chi-Square test. This endpoint will be analyzed separately for the first 4 weeks (two groups), and the first 12 weeks (four groups).

7.12.6.16 Percent of rescue medication free days.

The percent of rescue medication free days will be calculated for the primary efficacy endpoint completers as:

$$\frac{\text{Number of days without rescue medication from baseline to subject's Day 29th in the study}}{28} \times 100$$

For subjects that withdrew from the study prior to the subject's Day 29th in the study, the percent of rescue medication free days will be calculated as:

$$\frac{\text{Number of days without rescue medication from baseline to Early Termination Date}}{\textit{Number of days from baseline to Early Termination Date}} \text{ x } 100$$

This will be analyzed for the primary analysis period. A one-way ANOVA model will be used to test the difference between SP-102 and the placebo arms.

7.12.6.17 The mean change from Baseline (D1) to Week 2, Week 4, Week 8, and Week 12 in the mean morning (AM) NPRS average pain score in the affected leg

This will be analyzed and presented using the same MMRM model described in the primary analysis, but the response variable will be change from baseline in mean weekly morning (AM) NPRS average pain score. Baseline morning NPRS average pain score is the mean of at least 5 days and no more than 7 days of morning NPRS average pain scores from the Screening visit until treatment randomization (D1). The mean weekly morning NPRS average pain score will be calculated by taking the average of the daily morning NPRS average pain scores of the seven days prior to that week. Post-baseline mean weekly morning NPRS average pain scores will be calculated as long as a week has at least 3 days with morning NPRS average pain score. If there are less than three days with morning NPRS average pain score, the mean weekly morning NPRS score will be set to missing. The mean weekly morning NPRS score will be calculated for each subject for each week up to Week 12. Change from baseline in mean weekly morning NPRS score will be calculated by subtracting the baseline value from the weekly morning NPRS score. Mean change from baseline for the first 4 weeks (with overall average) will be analyzed and presented by the treatment received for the first injection (SP-102, Placebo). Mean change from baseline for the first 12 weeks (Weeks 2, 4, 8, and 12) will be analyzed and summarized by treatment received for second injection (SP-102/SP-102, PBO/SP-102, SP-102/none, PBO/none). As part of this analysis, comparisons will test the mean LS mean differences between the following groups;

- SP-102/none vs. PBO/none
- SP-102/SP-102 vs. PBO/none
- SP-102/none vs. PBO/SP-102
- SP-102/SP-102 vs. PBO/SP-102

7.12.6.18 The mean change from Baseline (D1) to Week 2, Week 4, Week 8, and Week 12 in the mean evening (PM) NPRS average pain score in the affected leg

This will be analyzed and presented using the same MMRM model described in the primary analysis, but the response variable will be change from baseline in mean weekly evening (PM) NPRS average pain score. Baseline evening NPRS average pain score is the mean of at least 5 days and no more than 7 days of evening NPRS average pain scores from the Screening visit until treatment randomization (D1). The mean weekly evening NPRS average pain score will be calculated by taking the average of the daily evening NPRS average pain scores of the seven days prior to that week. Post-baseline mean weekly evening NPRS average pain scores will be calculated as long as a week has at least 3 days with evening NPRS average pain score. If there are less than three days with evening NPRS average pain score, the mean weekly evening NPRS score will be set to missing. The mean weekly evening NPRS score will be calculated for each subject for each week up to Week 12. Change from baseline in mean weekly evening NPRS score will be calculated by subtracting the baseline value from the weekly evening NPRS score. Mean change from baseline for the first 4 weeks (with overall average) will be analyzed and presented by the treatment received for the first injection (SP-102, Placebo). Mean change from baseline for the first 12 weeks (Weeks 2, 4, 8, and 12) will be analyzed and summarized by treatment received for second injection (SP-102/SP-102, PBO/SP-102, SP-102/none, PBO/none). As part of this analysis, comparisons will test the mean LS mean differences between the following groups;

- SP-102/none vs. PBO/none
- SP-102/SP-102 vs. PBO/none
- SP-102/none vs. PBO/SP-102
- SP-102/SP-102 vs. PBO/SP-102

7.12.6.19 Multiplicity

To control for multiplicity, a sequential testing procedure will be used on the key secondary and other secondary endpoints. Thus, if the primary endpoint is statistically significant, then the key secondary endpoint can be tested. Then if the key secondary endpoint is statistically significant, then the next secondary endpoint can be tested. This will continue until all endpoints have been tested, or until non-significance is observed for an endpoint. The ordering of the tests will follow the order the endpoints listed below:

[redacted]

[redacted]

7.12.6.20 Placebo Responder Analysis

An analysis predicting the placebo response may be performed. Full details will be provided in a separate SAP.

7.13 Safety Analyses

The safety analyses will be presented in two ways:

1) by the two treatment groups received in the first four weeks for the primary analysis period
2) by the four treatment groups for the data up to 24 weeks for the secondary analysis period

All safety analyses will be done in the Safety Analysis Population.

7.13.1 Adverse Events

Adverse events will be recorded using MedDRA v23.1 or a more up-to-date version by the time of database lock. A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has an onset on or after the first dose of SP-102 or placebo
- Any pre-existing AE that has worsened in severity on or after the first dose of SP-102 or placebo.

A treatment-related TEAE is any study medication related TEAE and/or study procedure related TEAE.

A study medication treatment-related AE is defined as one of the following; possibly related, probably related, or definitely related to the study drug. If an AE has a missing relationship to study medication it is assumed to be related to the study drug for analysis purposes.

A study procedure treatment-related AE is defined as an AE related to the study procedure.

The intensity/standard toxicity grade of an AE is defined as an AE being Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), or Grade 4 (Life-Threatening).

Severe intensity (Grade 3) will be assumed for an AE with missing intensity.

The summary of TEAEs 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.

TEAEs will be assigned to one of the two treatments (SP-102 or Placebo). AEs starting while on Placebo but before the repeat injection will be assigned to Placebo. AEs starting on or after the repeat injection of SP-102 will be assigned to SP-102. Any pre-existing TEAE that started during the Placebo use and that has worsened in severity on or after the repeat injection of SP-102 will be assigned to SP-102.

Any TEAEs will be summarized by treatment, for each post-randomization treatment period:

- Entire treatment period
- Occurring after the randomization injection, but prior to a second injection (of SP-102)
- Occurring after the second injection (of SP-102)

The following incidence (number and percent of subjects reporting the AE at least once during the study) of TEAEs tables will be presented:

- Overall incidence and the number of TEAEs, related TEAEs, serious adverse events (SAEs), related SAEs, TEAEs leading to withdrawal, and TEAEs leading to death.
- TEAE by system organ class and preferred term, incidence and number of events
- Study medication-related TEAE by system organ class and preferred term, incidence and number of events
- Study procedure-related TEAE by system organ class and preferred term, incidence and number of events
- Serious TEAE by system organ class and preferred term, incidence and number of events
- Serious study medication-related TEAE by system organ class and preferred term, incidence and number of events
- Serious study procedure-related TEAE by system organ class and preferred term, incidence and number of events
- TEAE by system organ class, preferred term and intensity, incidence
- Serious TEAE by system organ class, preferred term and intensity, incidence
- Treatment-related TEAE by system organ class, preferred term and intensity, incidence

- TEAEs leading to early termination of the study by system organ class and preferred term, incidence
- Listing of Serious TEAEs (presented in the Table section of the appendices)
- Listing of Deaths (presented in the Table section of the appendices)

Additionally, an overall summary of the incidence and the number of TEAEs, related TEAEs, SAEs, related SAEs, TEAEs leading to withdrawal, and TEAEs leading to death through 12 weeks, and a summary of incidence and number of events of TEAEs by system organ class and preferred term through 12 weeks will be presented as follows:

- by four groups (SP-102/SP-102, PBO/SP-102, SP-102/none, and PBO/none)
- by treatment (Placebo, SP-102) but only for the subjects in the PBO/SP-102 group
- by exposure to SP-102, that is, Exposed vs. Not Exposed to SP-102; the Exposed group will include the subjects that have received SP-102 for the index injection and/or have a repeat injection while Non-Exposed group will include the subjects that have received Placebo for the index injection and do not have repeat injection

All AEs will be listed.

7.13.2 Laboratory Data

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment group and visit for each hematology (hemoglobin, hematocrit, red blood cell count, white blood cell (WBC) count (with differential [lymphocytes, neutrophils, eosinophils, basophils, and monocytes]), platelet count, hemoglobin A1c, activated partial thromboplastin time, prothrombin time and international normalization ratio), urinalysis (color, turbidity, specific gravity, pH, glucose, protein, ketones, urobilinogen, bilirubin, blood nitrate, leukocyte esterase, and microscopic examination) and serum chemistry (albumin, alanine aminotransferase [ALT], alkaline phosphatase, aspartate aminotransferase [AST], direct bilirubin, total bilirubin, blood urea nitrogen, calcium, chloride, creatine kinase, creatinine, gamma-glutamyl transferase, glucose, lactate dehydrogenase, potassium, sodium, uric acid) parameter. Each measurement (continuous data) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Laboratory data will be summarized for the secondary analysis period.

Shift tables in relation to the normal range from baseline to each follow-up visit will be presented.

All other laboratory tests will be listed only. This includes troponin I, troponin T, lipid panel, plasma cortisol, human immunodeficiency virus (HIV), hepatitis B, hepatitis C, and serum

pregnancy test (females of childbearing potential only), cortisol, urine drug screen, and urine pregnancy test.

A listing of abnormal laboratory measurements defined as any out of normal range laboratory values recorded throughout the study will be presented.

7.13.3 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by treatment group, visit, and timepoint within visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (Heart Rate) [bpm]

Vital signs data will be summarized separately for both the primary and the secondary analysis periods. Vital sign values will be categorized into the following potential clinical concern categories if applicable, and then summarized.

Vital Sign	Potential Clinical Concern Categories
Systolic blood pressure	≥160 mmHg
Diastolic blood pressure	≥100 mmHg
Pulse rate (Heart Rate)	<60 or >100 bpm

All vital sign measurements including the position of the subject when the measurement was taken will be listed.

7.13.4 Electrocardiogram Data

Descriptive statistics for observed values in the following ECG variables at the screening visit will be tabulated:

- Pulse Rate (Heart rate) [bpm]
- PR interval (ms)
- RR interval (ms)
- QRS duration (ms)
- QT interval (ms)
- QTc interval (ms) [Bazett's formula - QTcB]
- QTc interval (ms) [Fridericia's formula - QTcF]

All ECG measurements and the position of the subject when the measurement was taken will be listed.

7.13.5 Physical Examination

The body systems within the physical examination data at Screening will be summarized by treatment group and finding (Normal, Abnormal NCS, Abnormal CS). Details of clinically significant findings will be listed.

7.13.6 Neurological Examination

Neurological examination will include evaluation of mental status (awareness of person, place, and time), cranial nerves, motor function and balance, sensory exam (ability to feel) and reflexes. Specific neurological examination demonstrating findings of radiculopathy, including straight leg raise test will be performed as part of this evaluation, according to the checklist (see Appendix A of the protocol).

Shift tables in relation to finding (Normal, Abnormal) from baseline to each follow-up visit will be presented for the General Neurological Exam results. Details of any abnormalities will be listed.

8 INTERIM ANALYSIS

No interim analyses are planned.

9 DATA SAFETY MONITORING BOARD ANALYSIS

No data safety monitoring board (DSMB) analyses are planned.

10 POST-HOC ANALYSIS

Sensitivity Analyses to assess impact of COVID-19 on study endpoints might be considered and will be done as post-hoc analyses.

11 CHANGES TO PLANNED PROTOCOL ANALYSIS

The following are changes to the planned protocol analysis:

- [redacted]

[redacted]

- A Screened Population, which consists of subjects that signed the informed consent form and were assigned a user subject number, was added.
- A 12-week Completer, defined as one who receives an injection of study drug and completes the study through Week 12, is added as another type of completer in this trial.
- The following endpoints were updated:
  1. "Week 4" was added to the endpoint "The mean change from Baseline (Day 1) to Week 2, Week 8, and Week 12 NPRS mean average pain score in the affected leg". The updated endpoint is "The mean change from Baseline (Day 1) to Week 2, Week 4, Week 8, and Week 12 NPRS mean average pain score in the affected leg".
  2. "during the first 4 weeks" was removed from the endpoint "Proportion of subjects requiring rescue medications during the first 4 weeks". The updated endpoint is "Proportion of subjects requiring rescue medications".
- Percent of rescue medication free days, mean change from Baseline (D1) to Week 4 in the mean morning (AM) NPRS average pain score in the affected leg, and mean change from Baseline (D1) to Week 4 in the mean evening (PM) NPRS average pain score in the affected leg were added as endpoints.
- Ordering of the endpoints to be tested for controlling for multiplicity has changed. PGIC which was 13th in the order of endpoints in the protocol was moved to third in order. That is, PGIC will be tested next if the key secondary endpoint is statistically significant.
- [redacted]
- An overall summary of the incidence and the number of TEAEs, related TEAEs, SAEs, related SAEs, TEAEs leading to withdrawal, and TEAEs leading to death through 12 weeks and a summary of incidence and number of events of TEAEs by system organ class and preferred term will also be summarized as follows:
  - by four groups (SP-102/SP-102, PBO/SP-102, SP-102/none, and PBO/none)
  - by treatment (Placebo, SP-102) but only for the subjects in the PBO/SP-102 group
  - by exposure to SP-102, that is, Exposed vs. Not Exposed to SP-102; the Exposed group will include the subjects that have received SP-102 for the index injection

and/or have a repeat injection while Non-Exposed group will include the subjects that have received Placebo for the index injection and do not have repeat injection

- The Primary Efficacy Endpoint Completer definition was changed from "as one who receives an injection of study drug and completes the study though W4" to "as one who receives an index injection and who has enough data to calculate data for the primary analysis period (i.e. first four weeks) regardless if Week 4 visit was completed or not"

12 REFERENCES

1. SAS Institute Inc. The SAS System, Version 9.4. Cary, NC, SAS Institute Inc. 2012.
2. Yuan, Y. (2014). Sensitivity Analysis in Multiple Imputation for Missing Data. *SAS Global Forum 2014 Conference*. Retrieved from http://support.sas.com/resources/papers/proceedings14/SAS270-2014.pdf
3. Li, L. (2019). SAS® V9. 4 MNAR statement for multiple imputations for missing not at random in longitudinal clinical trials. *PharmaSUG 2019 Conference*. Retrieved from https://www.pharmasug.org/proceedings/2019/ST/PharmaSUG-2019-ST-103.pdf
4. Fairbank JC, Pynsent PB. The Oswestry Disability Index. Spine 2000 Nov 15;25(22):2940-52

13 LIST OF TABLES, FIGURES AND LISTINGS

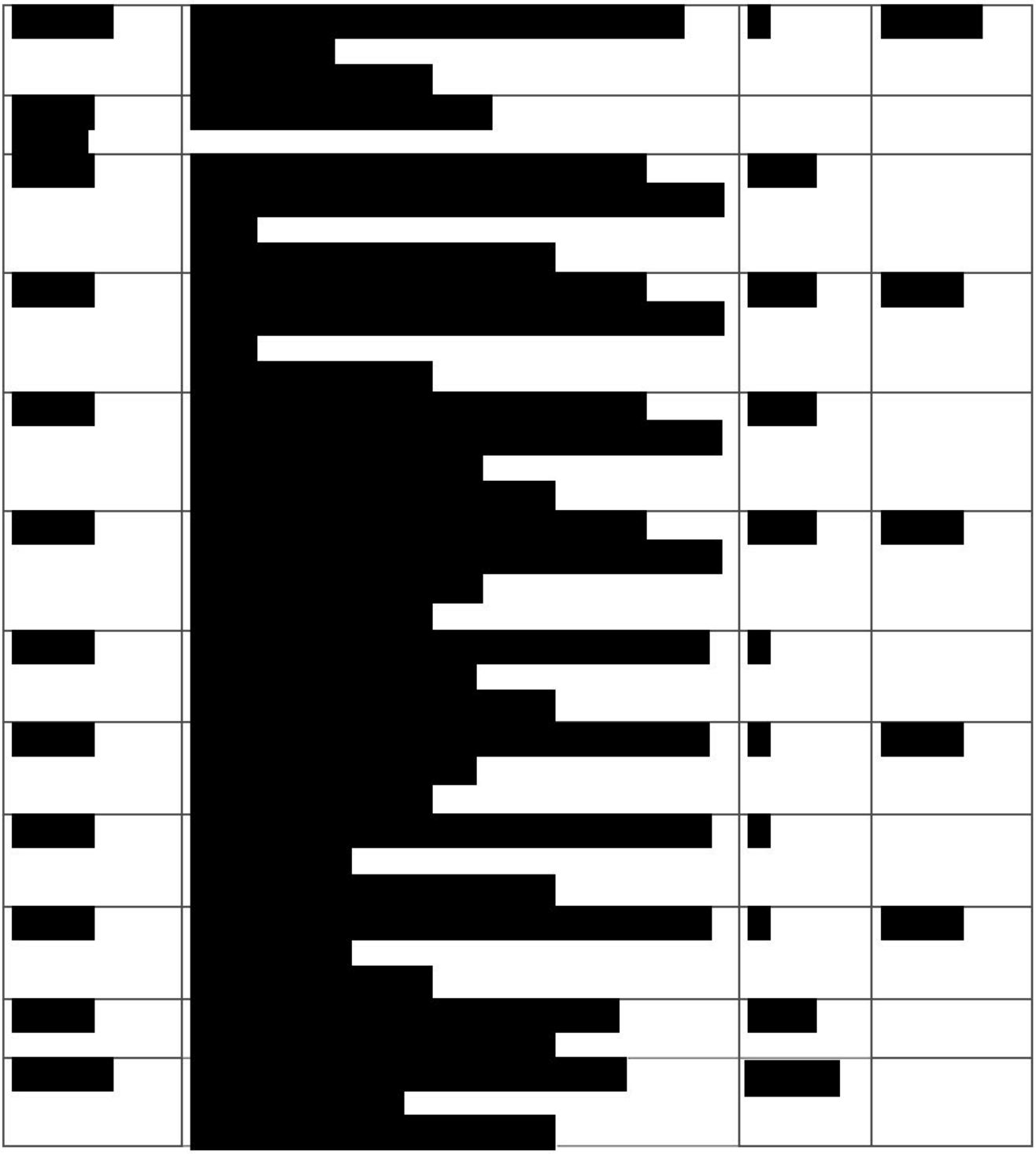
The following table includes details of the tables, figures and listings to be included within each section of the eCTD. The eCTD section is shown in bold. The following validation methods maybe used

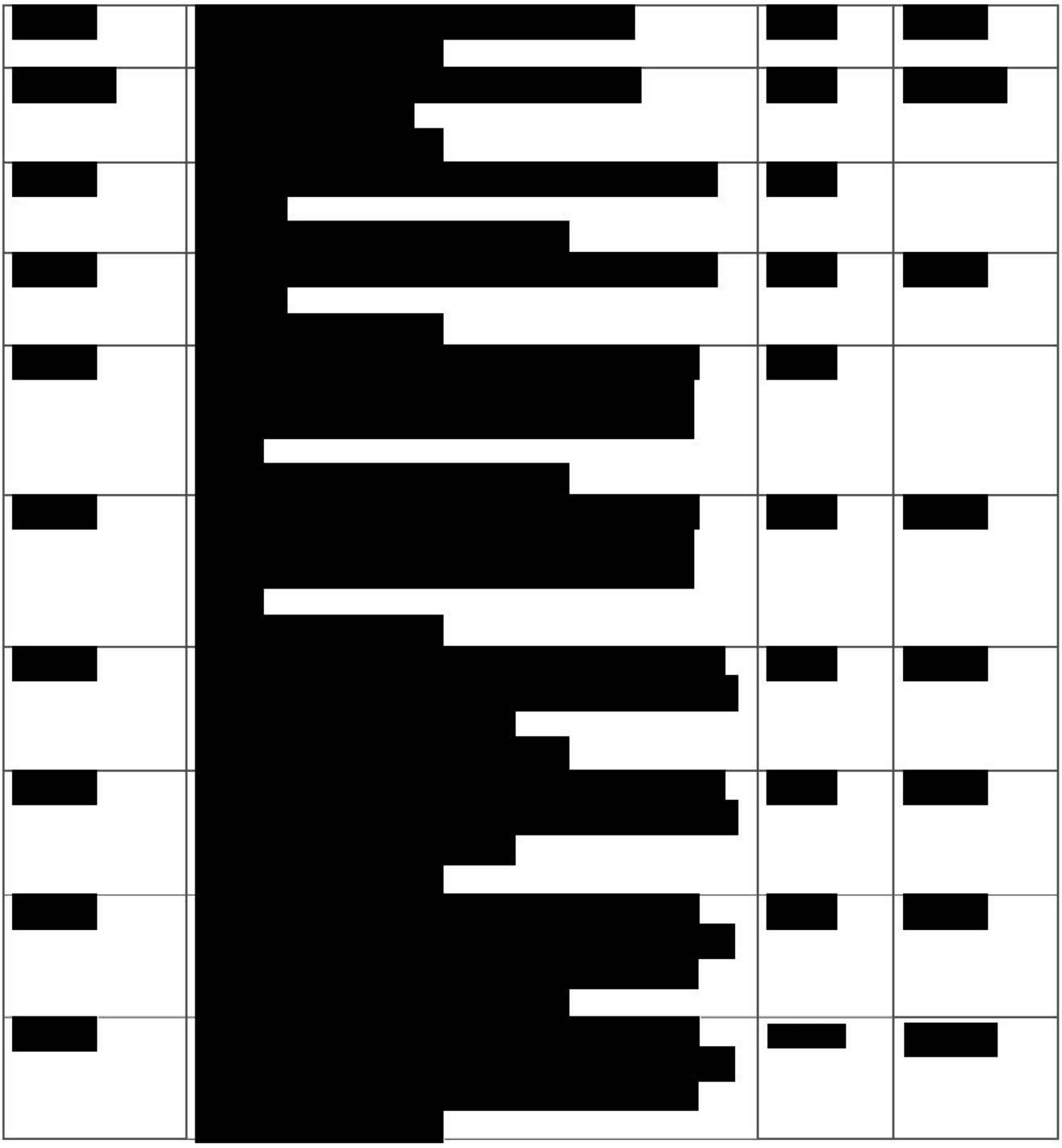
- Independent programming of numbers and manual review of format (IP)
- Independent programming by statistician of numbers and manual review of format (Stat IP)
- Manual review (MR)
- Code review (CR)

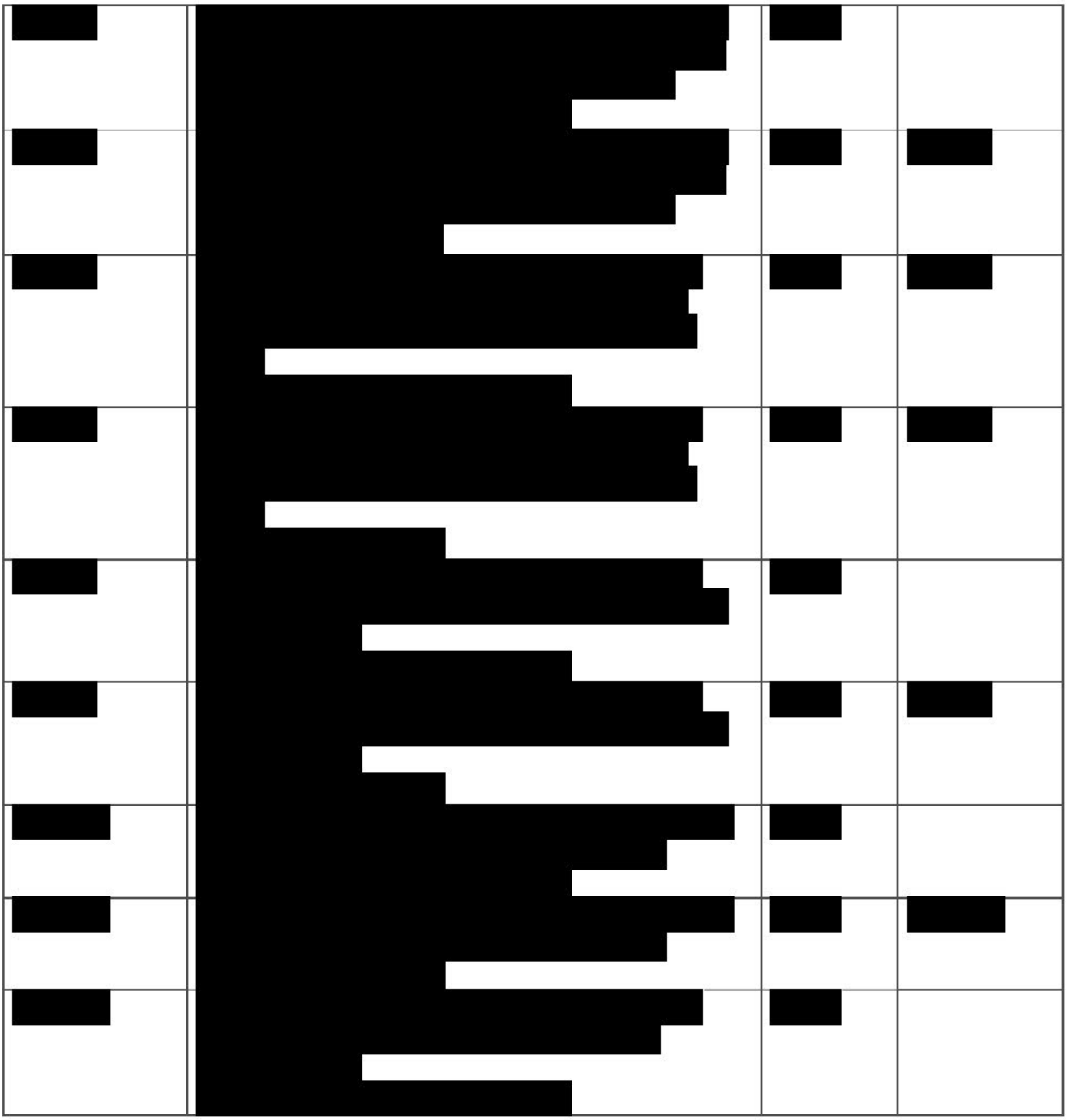
These sets of outputs will be produced twice:

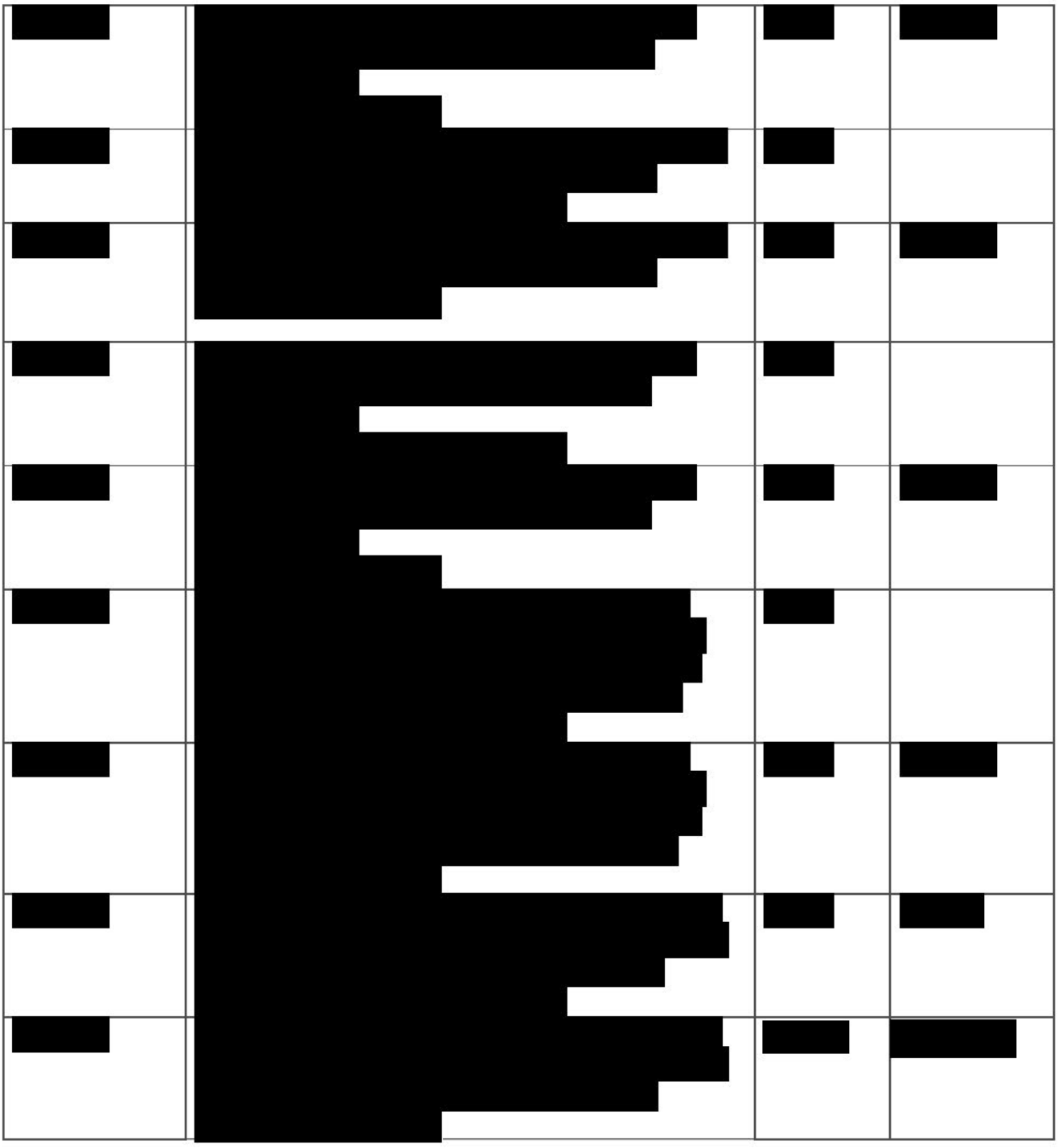
- one for the primary analysis (which will occur after all subjects complete the 12-week assessments) AND
- another for the full analysis (which will occur after the subjects in the OL safety extension portion of the study complete the study up to Week 24)

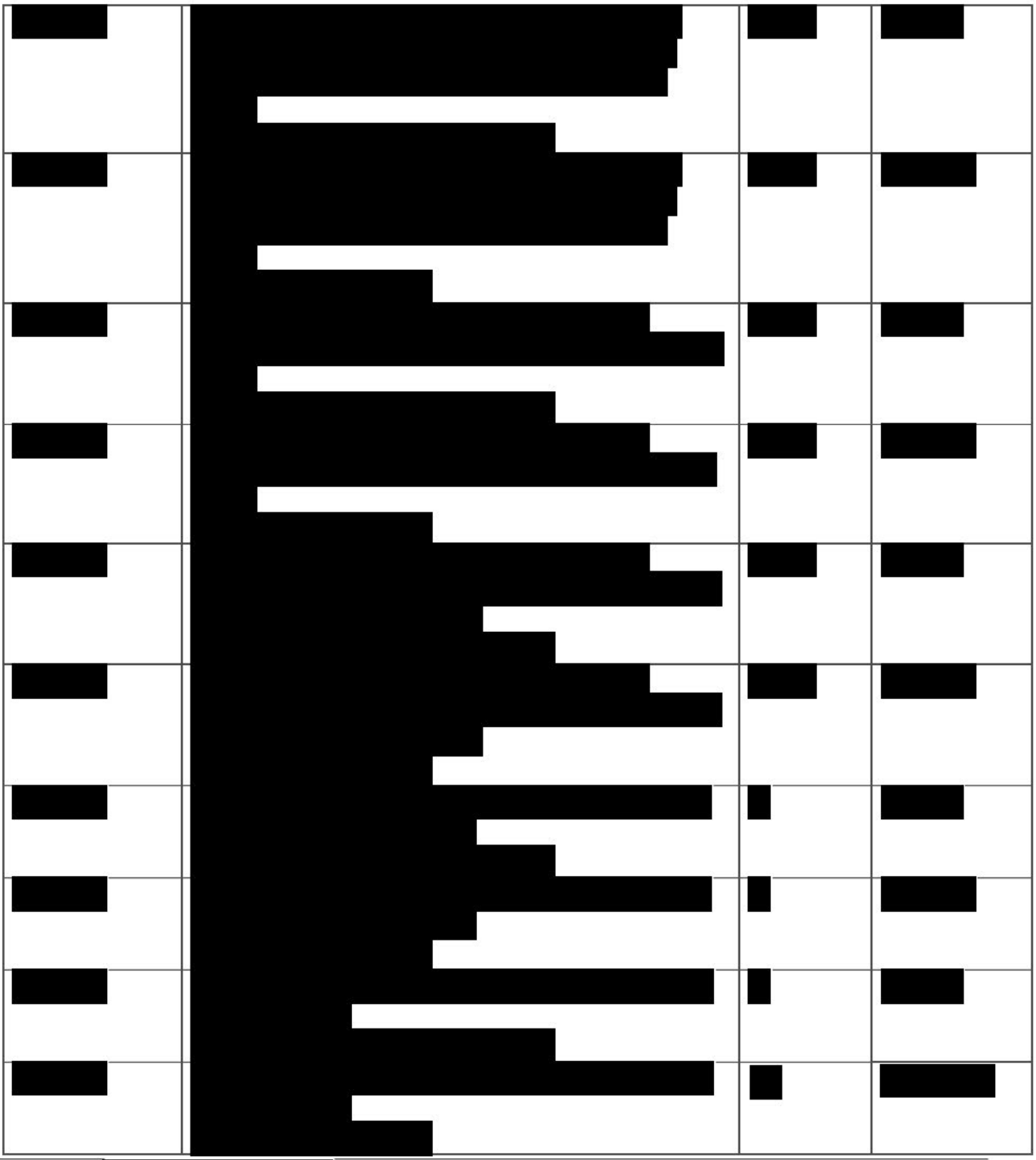
List of Tables

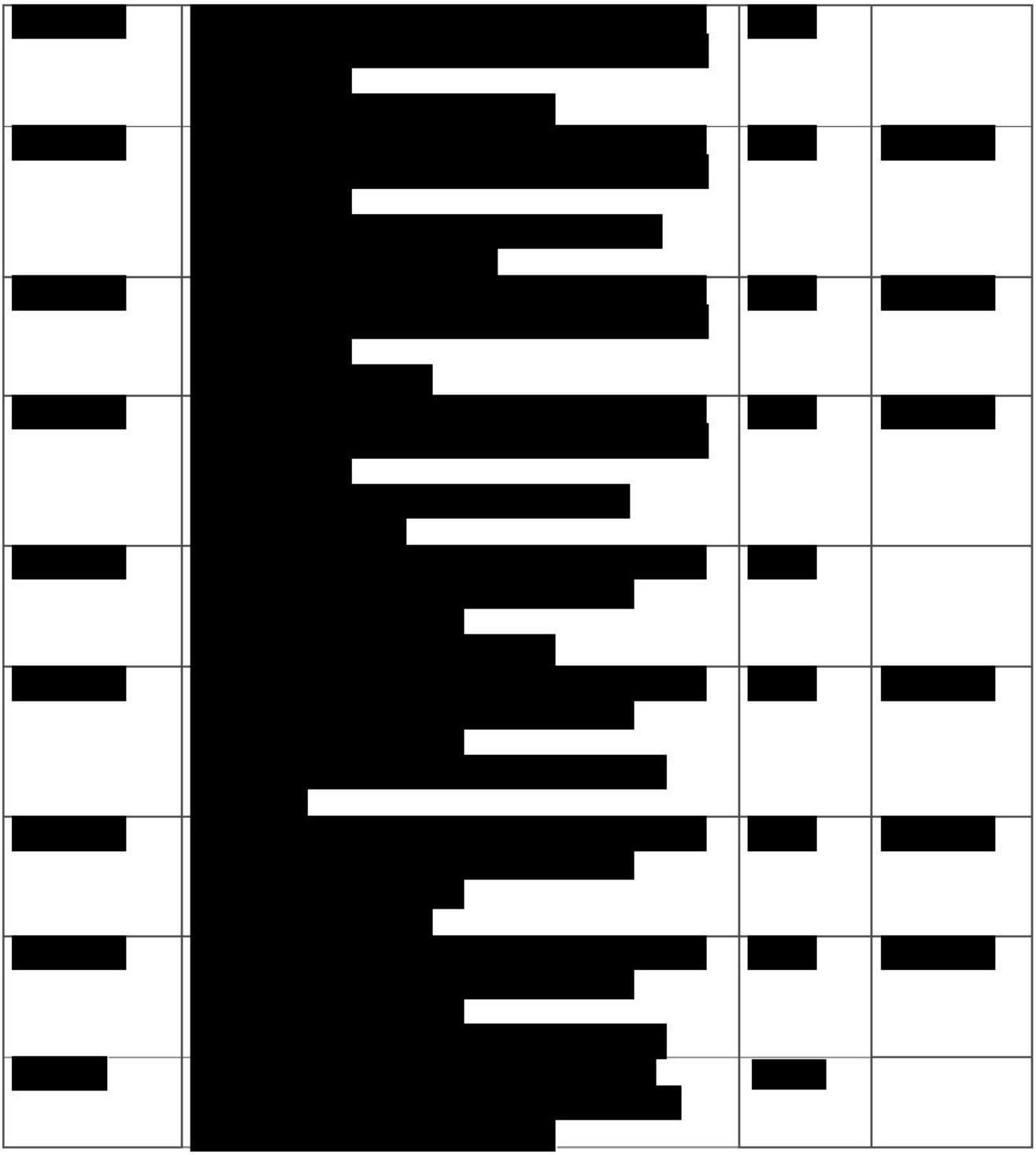


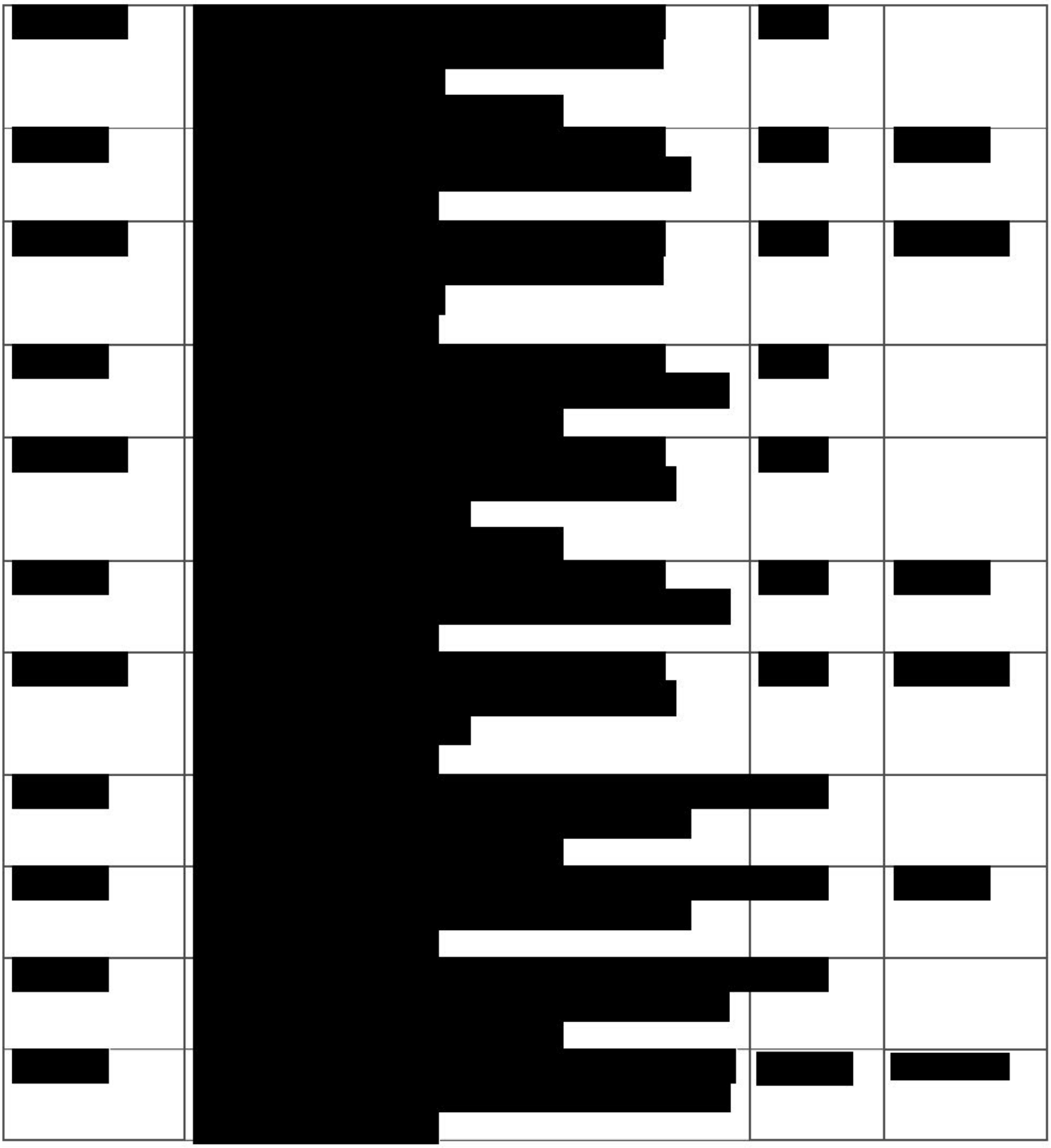


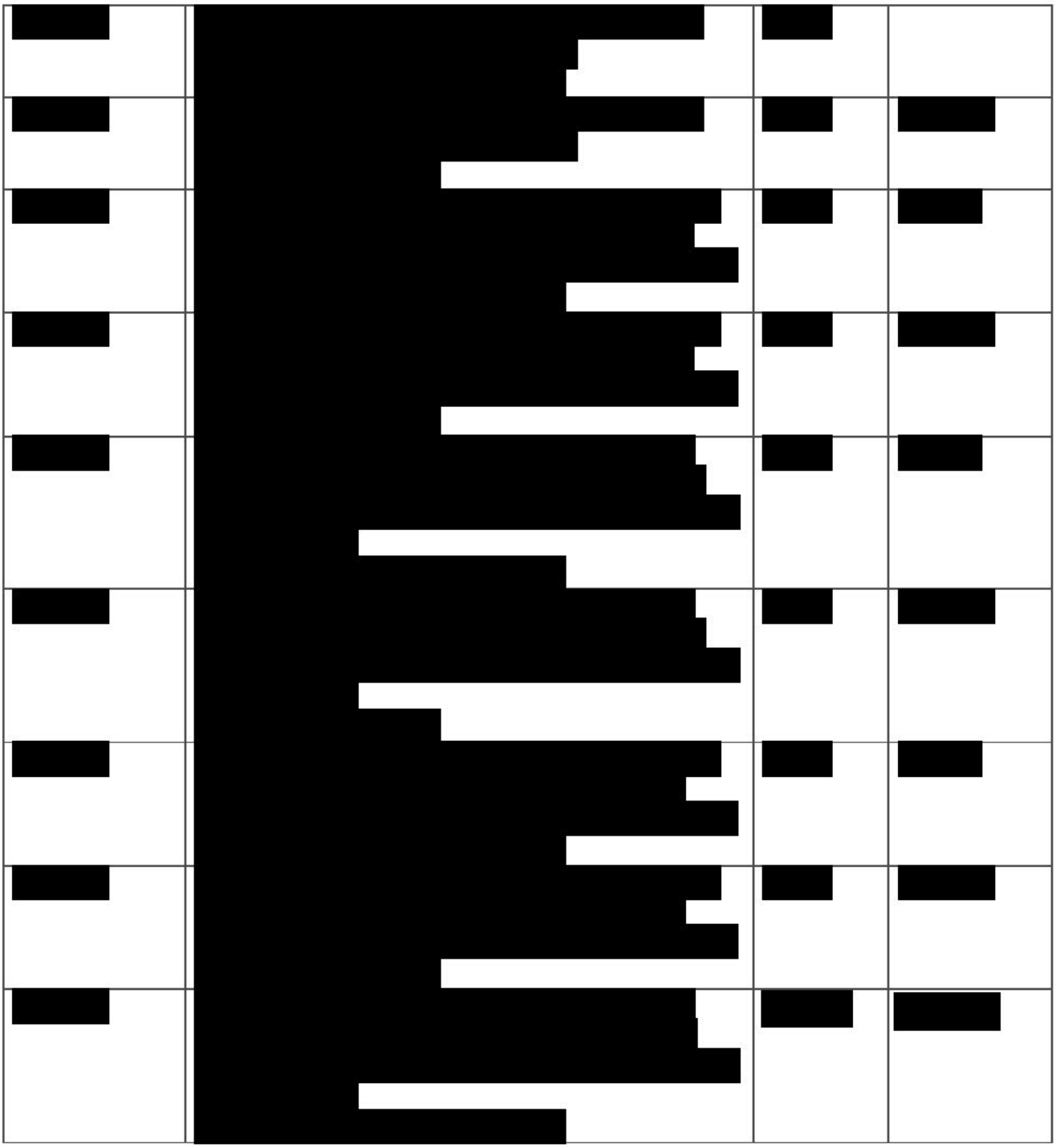


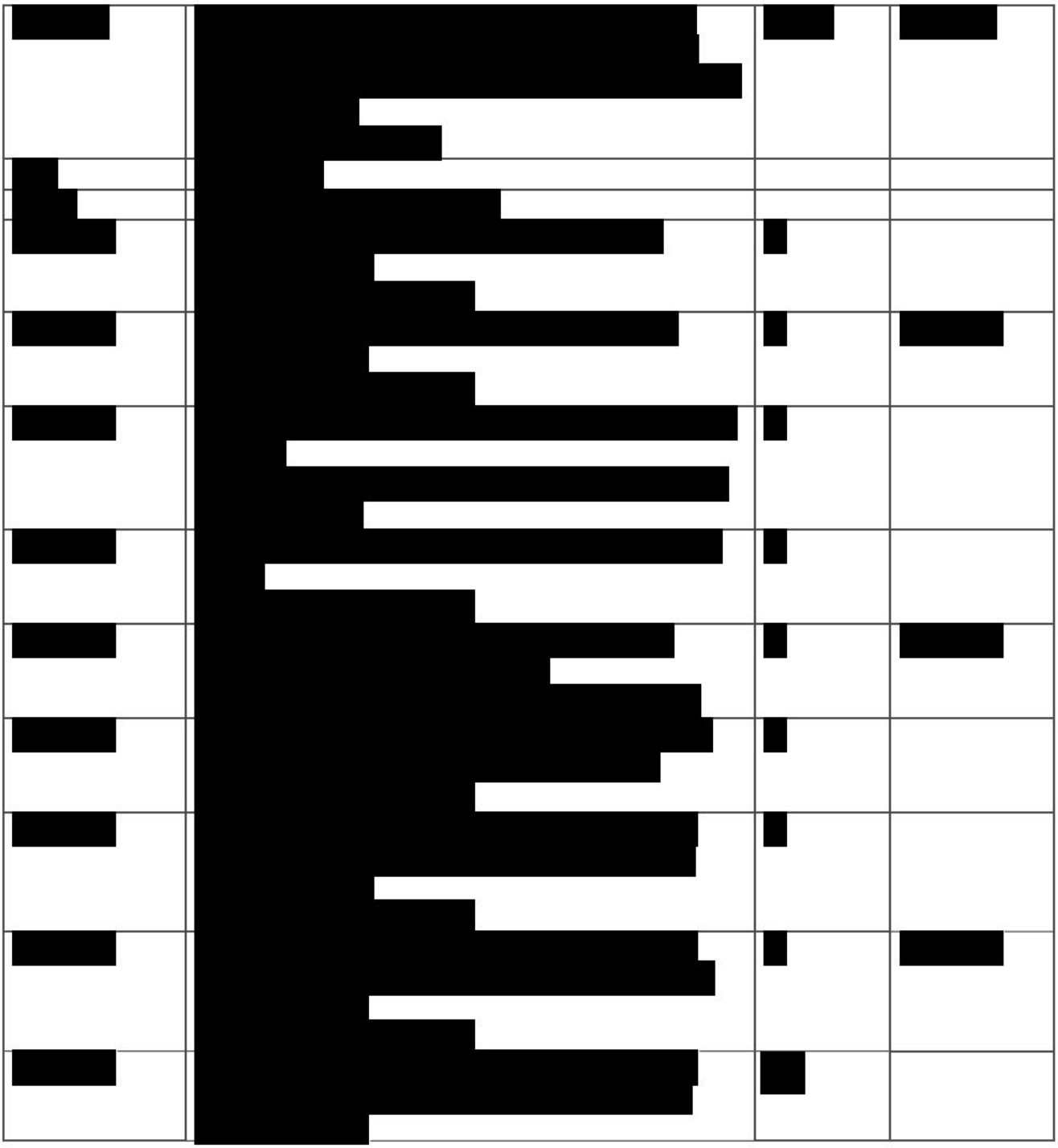


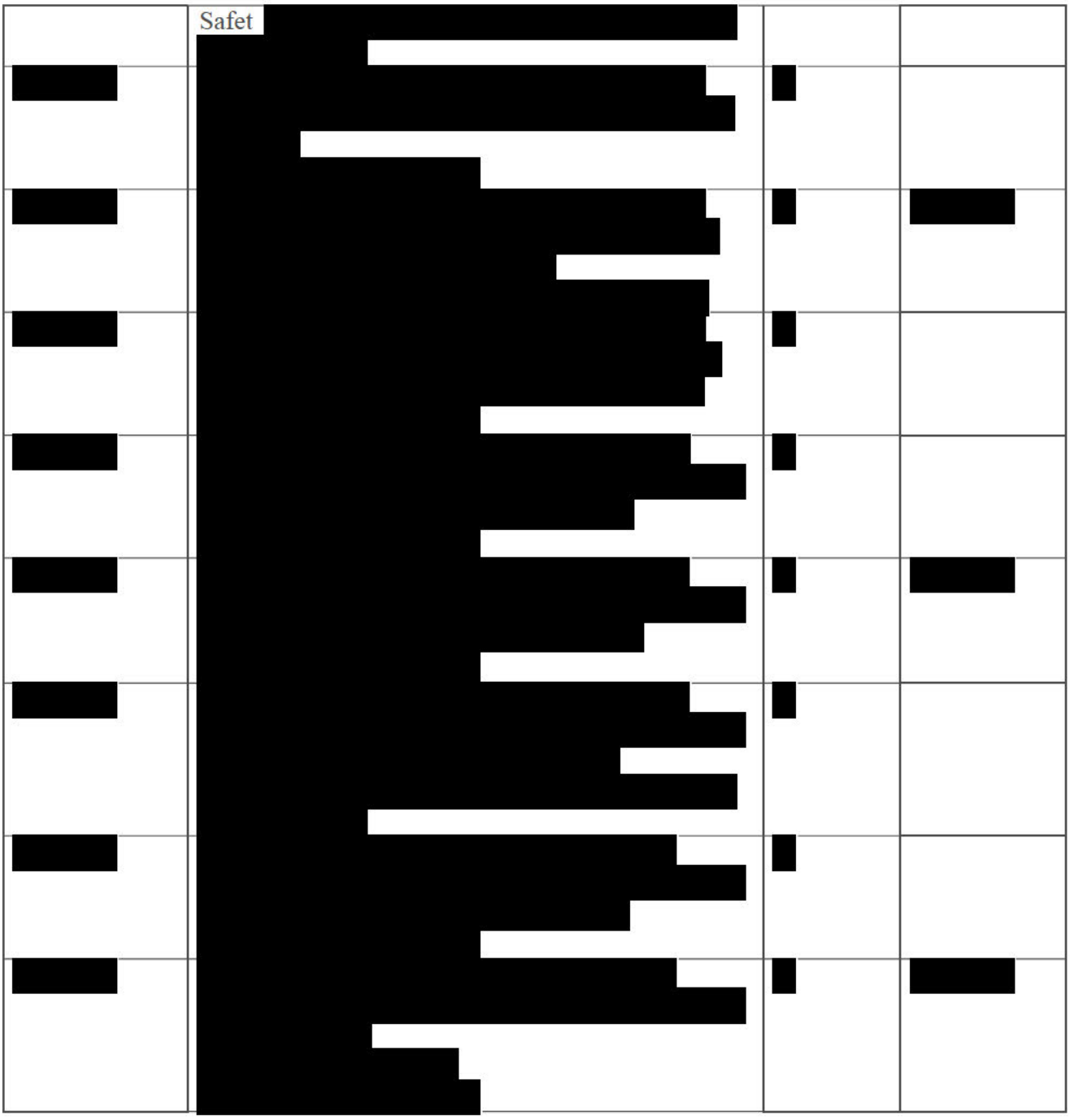








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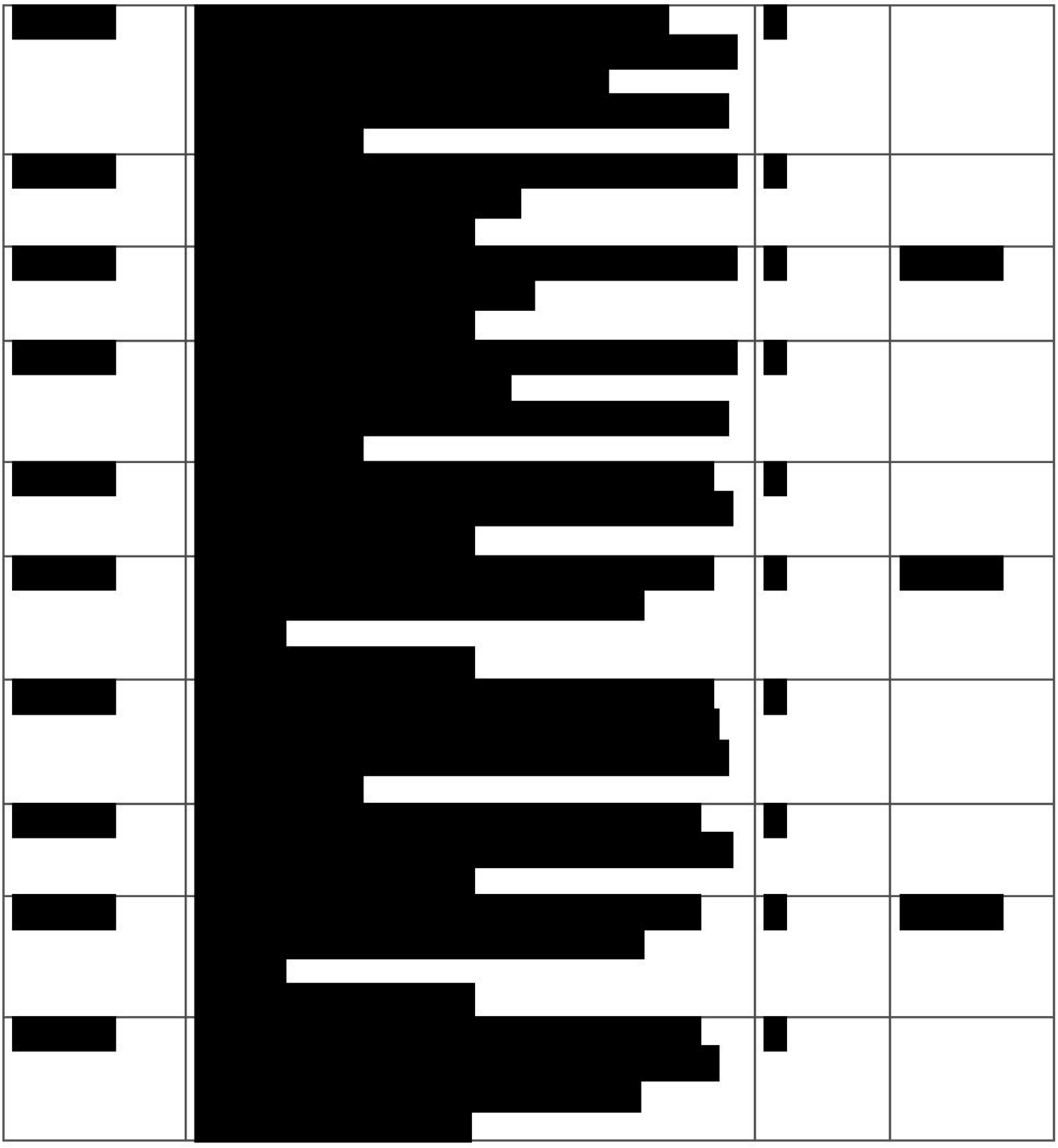

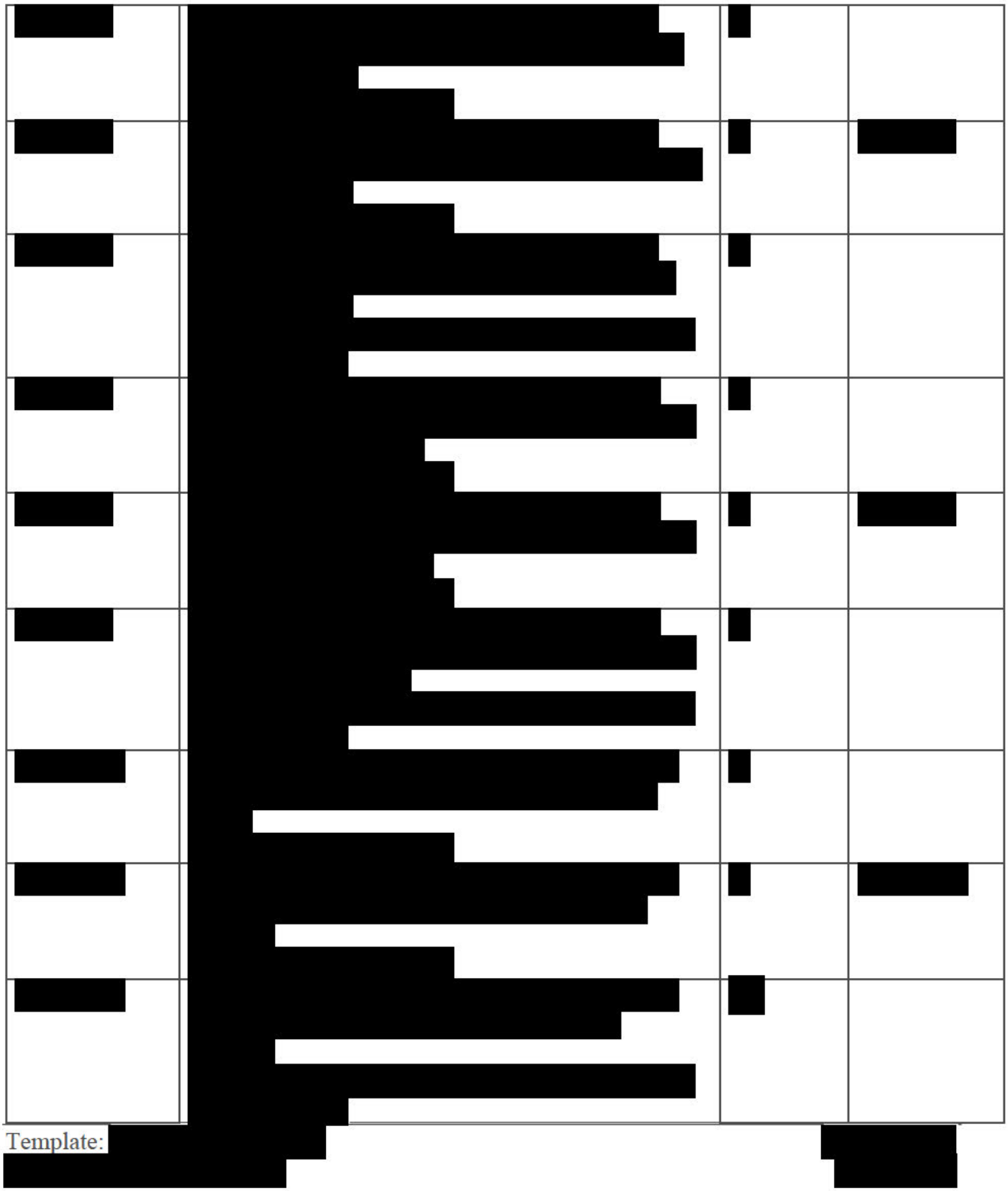


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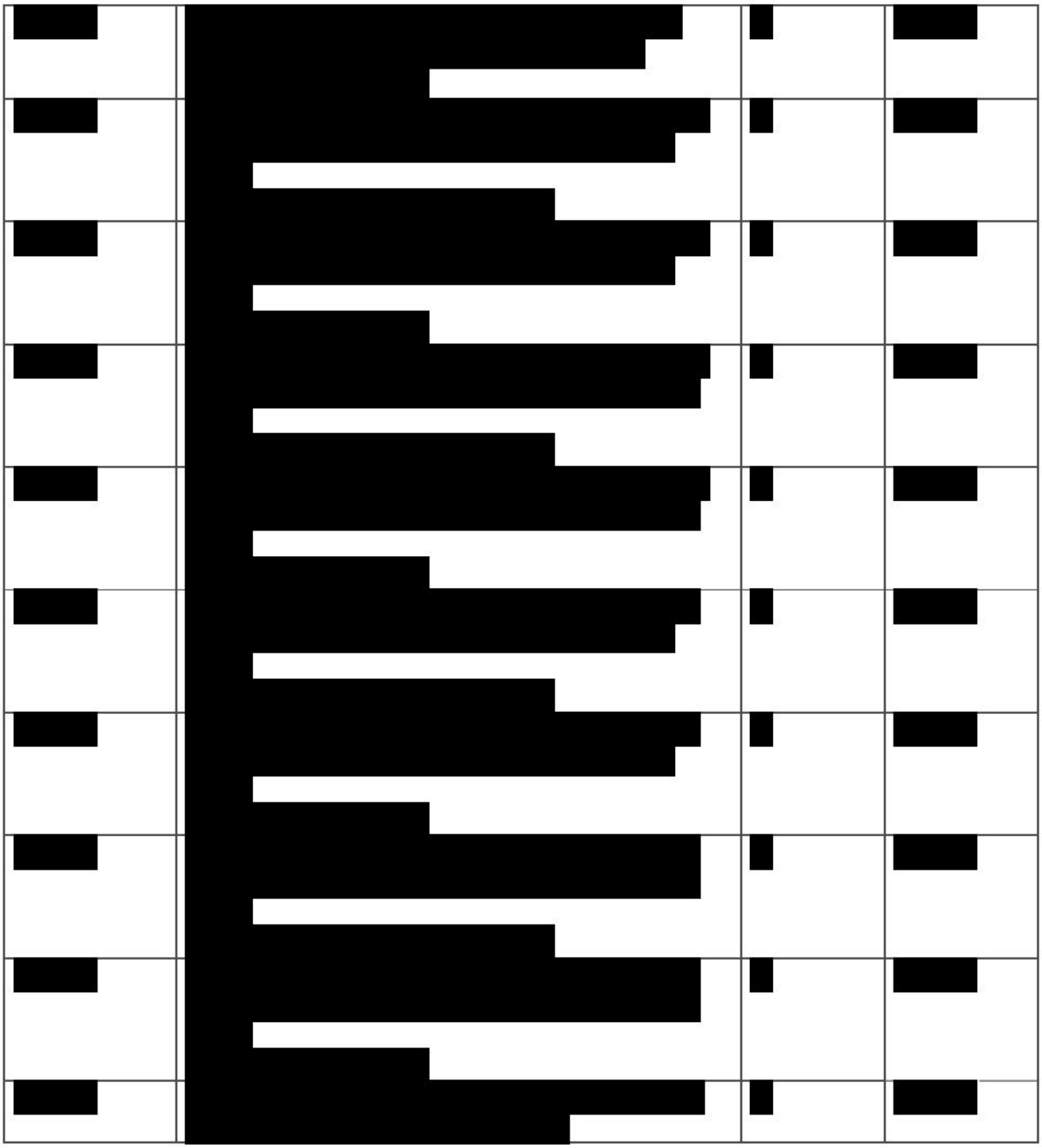

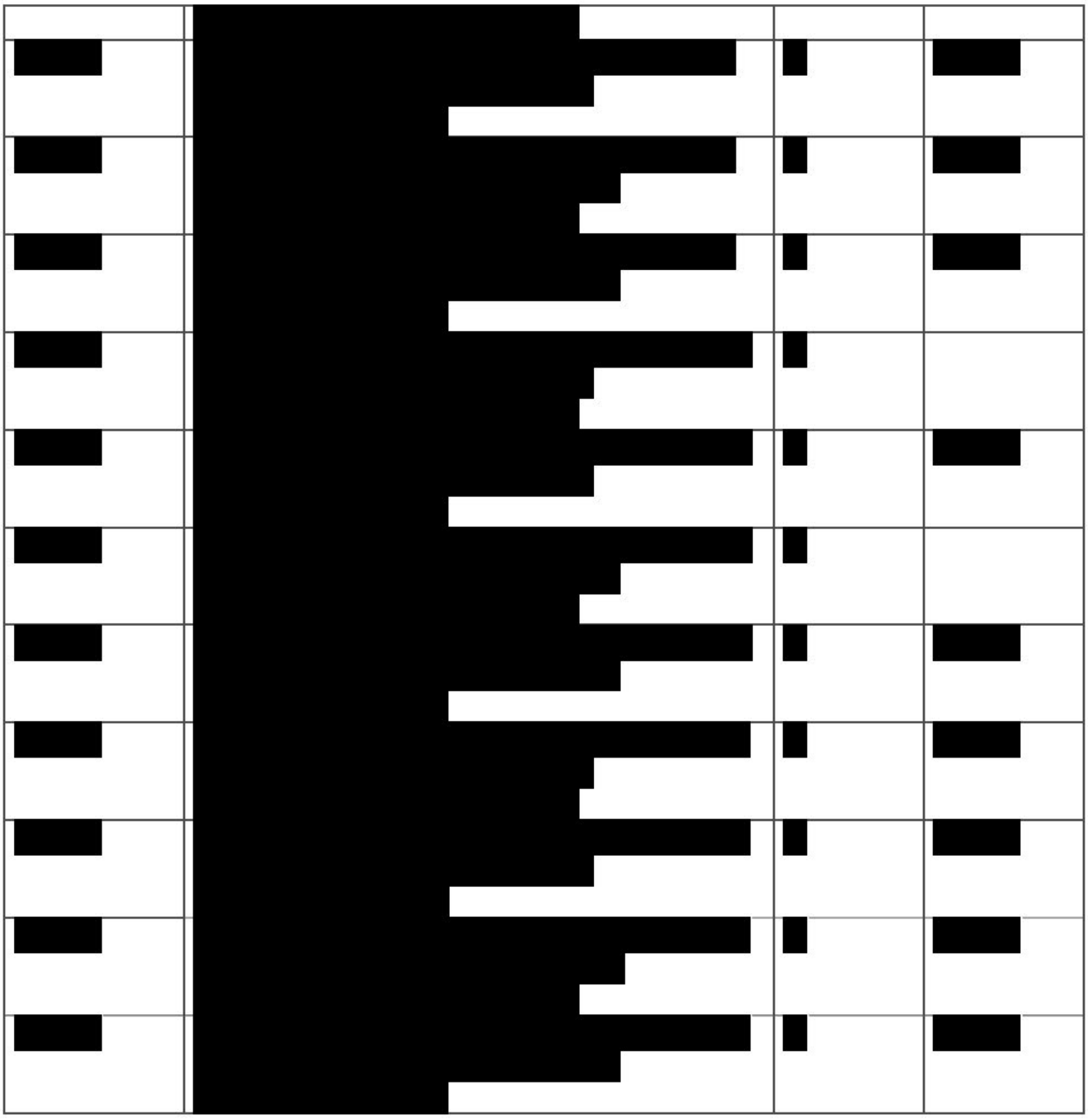

List of Listings