16. Appendices

16.1. Study Information

16.1.9. Documentation of Statistical Methods

Statistical Analysis Plan, version 2.0, 09 October 2019

STATISTICAL ANALYSIS PLAN

STUDY TITLE:

A Phase I, Double-blind, Randomized, Placebo-controlled, Single Dose-escalation Study to Evaluate the Tolerability and Safety of Cytisine in Adult Smokers

Protocol Code:	ACH-CYT-08
Type:	Interventional, Phase I
EudraCT No.:	2018-003344-22
SAP Version:	2.0
Date:	09OCT2019
Supersedes version:	
Date:	20MAY2019
Protocol Version	5.0
Sponsor:	Achieve Life Sciences, Inc. 520 Pike Street, Suite 2250 Seattle, Washington, USA 98101 Phone: 604 736 3678 Fax: 604 736 3687
Clinical Pharmacology Unit:	[redacted]

1. SIGNATURE PAGES

1.1. Clinical Pharmacology Unit's Representatives

[redacted]

1.2. Sponsor's Representatives

[redacted]

.....
Date

16-OCT-2019
Date

.....
Date

1.2. Sponsor's Representatives

[redacted]

17 Oct 2019
Date

.....
Date

17OCT2019
Date

SUMMARY OF CHANGES OF THIS VERSION 2.0) VERSUS PREVIOUS VERSION (1.0)

Version 1.0 of this SAP was not implemented, as the study protocol was amended prior to database lock and final statistical analysis to include 3 additional dose cohorts. Version 2.0 of this SAP has incorporated analysis for dose cohorts 7 (24 mg), 8 (27 mg) and 9 (30 mg). No modifications to analysis plans have been made other than removing analysis of cotinine and 3-OH cotinine, as testing will not be conducted, per the Sponsor.

2. CONTENTS AND ABBREVIATIONS

2.1. Table of Contents

2.2. List of Abbreviations

ADAE	Analysis Data Adverse Events
ADaM	Analysis Data Model
ADEG	Analysis Data Electrocardiogram
ADaMIG	Analysis Data Model Implementation Guide
ADLB	Analysis Data Laboratory
ADPC	Analysis Data Pharmacokinetic Concentrations
ADPP	Analysis Data Pharmacokinetic Parameters
ADSL	Analysis Dataset, Subject-Level
ADVS	Analysis Data Vital Signs
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
A_{mean}	Arithmetic mean
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Class
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
C_{max}	Maximum Observed Plasma Concentration
CO	Carbon Monoxide
CPK	Creatine Phosphokinase
CR	Clinically Relevant
Cr_{CL}	Creatinine Clearance
CSR	Clinical Study Report
CV%	Coefficient of Variation
DBP	Diastolic Blood Pressure
DSM	Data Safety Monitor
ECG	Electrocardiogram
GGT	Gamma-Glutamyltransferase
GLP	Good Laboratory Practice
G_{mean}	Geometric mean
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
INR	International Normalized Ratio
LC-MS/MS	Liquid Chromatography with Tandem Mass Spectrometry
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
NCR	Not Clinically Relevant
NMR	Nicotine Metabolite Ratio
PI	Principal Investigator
PT	MedDRA Preferred Term
RBC	Red Blood Cell

RDW-CV	Coefficient Variation of the Red Cell Distribution Width
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	MedDRA System Organ Class
TEAE	Treatment-Emergent Adverse Events
TFLs	Tables, figures and listings
T_{max}	Time of Occurrence of Maximum Observed Plasma Concentration
ULOQ	Upper Limit of Quantification
WBC	White Blood Cell

3. INTRODUCTION

This Statistical Analysis Plan (SAP) presents the details of the analysis and presentation of the safety and pharmacokinetic (PK) results for Clinical Study ACH-CYT-08.

The analyses described are based on the Clinical Study Protocol (CSP) version 5.0, dated 07MAY2019 [1].

This SAP will be finalized and approved by the Achieve Life Sciences (Achieve) and [redacted]s representatives prior to the planned database lock and unblinding of study treatment assignment code. Any deviations from this SAP will be described in detail and justified in the Clinical Study Report (CSR). If additional analyses are required to complement the analyses planned in the SAP, they may be performed and will be identified in the Clinical Study Report (CSR).

3.1. Summary of Changes from Protocol or Its Amendments

There are no changes from the protocol or its amendments.

3.2. Reporting and Deliverables

The CSR will be written using the Achieve's template. Tables, Figures and Listings (TFLs) will be prepared as described in the TFL shells within this SAP. In-text Tables and Figures will be included in the main body of the CSR. After review by the Sponsor, the TFLs will be finalized.

Before performing the analysis, all data collected will be integrated into a common repository, using SAS 9.4 (SAS Institute Inc, Cary, NC, USA). Derived analysis datasets will be generated in accordance to CDISC. ADaM compliant datasets will be delivered to the Sponsor.

4. STUDY OBJECTIVES

4.1. Primary

To assess the tolerability and safety of cytisine as a single oral dose.

4.2. Secondary

To define the C_{max} levels associated to the occurrence of dose-limiting adverse events.

5. STUDY DESIGN OVERVIEW

5.1. Study Design

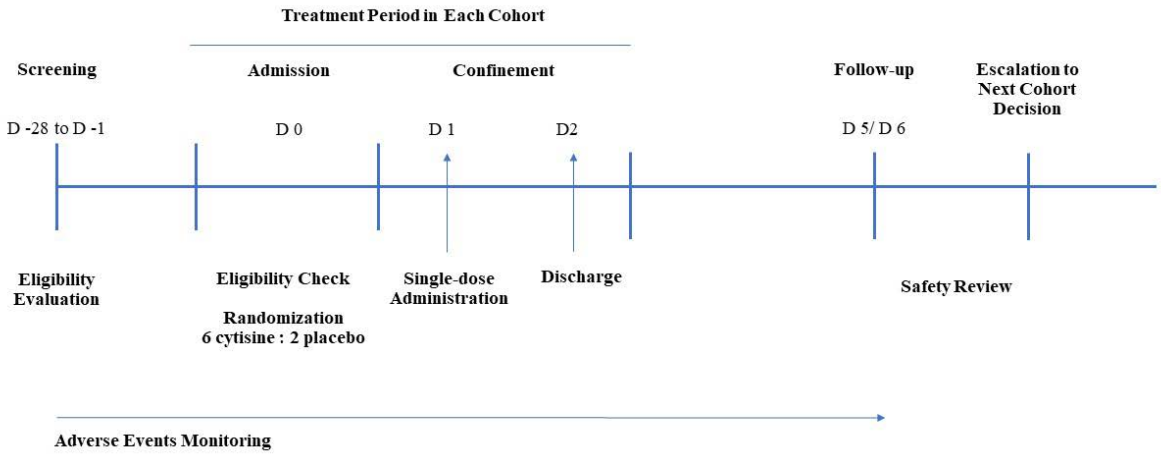
This was a single-center, double-blind, randomized, placebo-controlled, single dose-escalation, Phase 1 clinical study conducted in male or female adults who were in good general health and were current daily cigarette smokers, under fasting conditions.

Nine dose levels were pre-planned under version 5.0 of Protocol ACH-CYT-08: 6 mg, 9 mg, 12 mg, 15 mg, 18 mg, 21 mg, 24 mg, 27 mg and 30 mg. The starting dose was 6 mg cytisine (single oral dose) in Cohort 1. The study was escalated up to the cytisine dose of 30 mg in Cohort 9 without showing any of the predefined stopping criteria. Within each dose level, subjects were randomly assigned to receive a single oral dose of cytisine or placebo in a 3:1 ratio (6 cytisine:2 placebo).

Upon completion of a cohort, a safety review was performed by the Principal Investigator (PI) and two independent Data Safety Monitors (DSMs) on unblinded data. The PI and DSMs conjointly decided whether dose escalation into the next cohort was to be allowed.

Table 1 presents an overview of study design.

Figure 1. Study Diagram:



5.2. Number of Subjects

The study protocol defined a sample size of 8 subjects per cohort, which is consistent with standard practice in early-phase clinical trials with similar study objectives.

Considering that 9 cohorts were pre-planned, a total of 72 subjects was estimated for enrollment.

5.3. Number of Clinical Sites

This was a single center clinical trial.

5.4. Method of Assigning Subjects to Treatments

Using SAS® 9.4, a computer-generated block-wise randomization list adequate for placebo-controlled studies was prepared by the Programming & Biostatistics Department of [redacted]. At each cohort, 6 subjects were randomly assigned to receive cytisine and 2 subjects randomized to receive placebo.

Upon confirmation that all eligibility criteria are met on Day 0, subjects were sequentially assigned a randomization number. The randomization number was provided to the unblinded Pharmacist on site and defined the treatment to which subjects were allocated (test or placebo) per the randomization list.

6. STUDY VARIABLES

6.1. Safety variables

- Drug exposure
- Adverse events:
  - Reported Term
  - MedDRA SOC coding
  - MedDRA PT coding
  - Start date
  - Start time
  - End date
  - End time
  - Seriousness
  - Severity:
    - Mild
    - Moderate
    - Severe
  - Relationship (causality):
    - not related
    - unlikely
    - possible
    - probable
    - definite
  - Action taken
  - Outcome
- Clinical laboratory evaluations:
  - Biochemistry:
    - aspartate aminotransferase (AST)
    - alanine aminotransferase (ALT)

  - gamma-glutamyltransferase (GGT)
  - lactate dehydrogenase (LDH)
  - alkaline phosphatase (ALP)
  - creatine phosphokinase (CPK)
  - creatinine
  - estimated creatinine clearance (CR_{CL})
  - urea
  - sodium
  - potassium
  - calcium
  - glucose
  - total cholesterol
  - triglycerides
  - albumin
  - total protein
  - uric acid
  - direct bilirubin
  - indirect bilirubin
  - total bilirubin
- Hematology:
  - hemoglobin
  - hematocrit
  - hypochromic red blood cell
  - red blood cell (RBC) count
  - mean corpuscular volume (MCV)
  - mean corpuscular hemoglobin (MCH)
  - mean corpuscular hemoglobin concentration (MCHC)
  - coefficient variation of the red cell distribution width (RDW-CV)
  - total white blood cell (WBC) count
  - neutrophils
  - eosinophils
  - lymphocytes
  - monocytes
  - basophils
  - platelet count
- Coagulation:
  - prothrombin rate
  - prothrombin time - international normalized ratio (INR)
  - activated partial thromboplastin time (aPTT)
- Urinalysis:
  - pH
  - specific gravity
  - protein
  - hemoglobin
  - glucose
  - ketones
  - bilirubin
  - nitrites

  - urobilinogen
  - microscopy
- Drugs of abuse test:
  - cannabinoids
  - opiates
  - cocaine
  - amphetamines
  - benzodiazepines
- Serum beta-human chorionic gonadotropin (beta-hCG) pregnancy test
- Urine beta-hCG pregnancy test
- Ethanol breath test

– Vital signs:
  - Systolic blood pressure (SBP)
  - Diastolic blood pressure (DBP)
  - Pulse rate
  - Body temperature
– Physical examination
– 12-lead Electrocardiogram (ECG)
– CO

6.2. Pharmacodynamic variables

None.

6.3. Pharmacokinetic Variables

- Plasma concentrations of cytisine
- Maximum observed plasma concentration post dose, directly obtained from the observed cytisine concentration versus time profile (C_{max})
- Time of occurrence of C_{max} (T_{max})

7. DATA REVIEW / TRANSFORMATION

7.1. Data Management

Data handling will be conducted in accordance with the Clinical Data Management section of the CSP and the Data Management Plan developed by [redacted] for this study.

7.2. Acceptance of Data

TFLs may start being programmed prior to, or during, the course of the trial. However, the programming of analysis datasets (ADS) and TFLs will only be finished and quality-controlled after database soft lock and unblinding of the data. Only audited cytisine plasma concentration data released by the Bioanalytical Laboratory will be used

for programming the final pharmacokinetic ADS and TFLs.

7.3. Data Transformation (CDISC)

Before performing the statistical analysis, all data collected (multiple sources) will be integrated into a common repository, using SAS® 9.4.

For standardization and regulatory submission purposes, all data will be transformed according to Clinical Data Interchange Standards Consortium (CDISC):

- Study Data Tabulation Model (SDTM) version 1.4 or later;
- Study Data Tabulation Model Implementation Guide (SDTMIG) version 3.2 or later;
- The following analysis datasets will be generated (Analysis Data Model [ADaM] version 2.1; Analysis Data Model Implementation Guide [ADaMIG], version 1.1) to support the results and ease the programming activities during the statistical analysis:
    - Subject-Level Analysis Dataset (ADSL)
    - Analysis Data Adverse Events (ADAE)
    - Analysis Data Electrocardiogram (ADEG)
    - Analysis Data Vital Signs (ADVS)
    - Analysis Data Laboratory (ADLB)
    - Analysis Data Pharmacokinetic Concentrations (ADPC)
    - Analysis Data Pharmacokinetic Parameters (ADPP)

8. STATISTICAL METHODS

The statistical analysis and TFLs will be done using SAS® for version 9.4.

PK parameters for cytisine (C_{max} and T_{max}) will be estimated using non-compartmental analysis (NCA) in Phoenix® WinNonlin® version 8.1 (Pharsight Corp., Mountain View, CA).

Summaries of demographics, baseline characteristics and safety endpoints will be provided for the Safety Analysis Set, defined as all subjects who received a single dose of cytisine or placebo.

Unless otherwise indicated, numerical variables will be summarized using: number of observations (n), arithmetic mean, standard deviation, coefficient of variation (CV%), median and range (minimum and maximum). Categorical variables will be summarized with number of subjects and percentage within a treatment (dose level). Descriptive statistics will be presented with the same precision as the original data, i.e, the same number of decimals or significant digits. T_{max} is stated with the same number of significant digits as the actual sampling time. Baseline for post-dose assessments is defined as the last observation recorded before dose. Summaries will be provided for each dose level/treatment (Placebo; 6.0 mg cytisine; 9.0 mg cytisine, etc.). Unless otherwise indicated, no statistical comparisons between the cohorts are planned.

Unscheduled measurements will be listed in the individual data listings. With the

exception of baseline or unscheduled measurements performed due to an error at the scheduled measurement (e.g. equipment failure), unscheduled measurements will be excluded from the descriptive statistical analysis.

No imputation of missing data will be done, except for missing dates and/or times required for the calculation of AEs' time to onset and duration (e.g. see Section 8.7.1) and for plasma concentrations below the lower limit of quantification (LLOQ) (see Section 8.8).

Assessments for trends in dose-limiting adverse events or C_{max} levels in relationship to BMI categories/levels and baseline Nicotine Metabolite Ratio (NMR) may be explored.

8.1. Analysis Sets

8.1.1. Screening Analysis Set

The Screening Analysis Set is defined as all subjects who give written informed consent and have entered screening. Analyses will be restricted to presentation of baseline data and reasons for non-participation as contrasted to those enrolled and received study drug.

8.1.2. Safety Analysis Set

The Safety Analysis Set is defined as all enrolled subjects who were administered the single dose of study drug.

8.1.3. Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set is defined as all subjects who received a dose of cytisine and have evaluable pharmacokinetic data.

8.2. Subject Disposition

The number and percentage of subjects who meet study analysis set requirements will be presented, along with number and percentage of subjects who prematurely withdrew. Reasons for withdrawal will be included.

8.3. Demographic and Other Baseline Characteristics

Subjects demographic data (except date of birth) and other baseline characteristics will be collected at screening and will be listed and summarized descriptively for all subjects by treatment and overall. The data in the summary will include age (years), sex, race, height (cm), weight (kg) and body mass index (BMI, kg/m^2).

8.4. Medical and Smoking History

Medical history will be collected at screening and coded using the MedDRA dictionary version 21.1 or higher. Coding includes system organ class (SOC) and preferred term

(PT). Medical history events will be listed for all subjects. Frequencies of medical history events will be presented by SOC and PT, by treatment and overall.

Smoking history will be collected at screening and will be listed and summarized descriptively for all subjects by treatment and overall. The data in the summary will include duration (years) of smoking, average number of cigarettes smoked per day during the last 30 days, whether subject ever attempted to quit smoking (Yes, No). In addition, the following will be summarized for subjects who had ever attempted to quit smoking: number of previous quit attempts, time (months) since most recent quit attempt and smoking cessation treatments used. The summary of smoking cessation treatments will report the number and percentage of subjects that used each treatment, as well as the number (%) of subjects that used any prior nicotine replacement therapy (i.e., used nicotine gum or nicotine patch or nicotine nasal spray or nicotine inhaler).

Expired CO level (ppm) will be measured at screening. These data will be listed for all subjects and summarized for all subjects by treatment and overall.

8.5. Dosing

Study product administration dates and times will be listed.

8.6. Protocol Deviations

Protocol deviations will be listed.

8.7. Safety Assessments

8.7.1. Adverse Events

Clinically significant abnormalities will be reported as AEs. Adverse events will be coded using the MedDRA dictionary version 21.1 or higher. Coding includes system organ class (SOC) and preferred term (PT). The following information recorded or computed is used for the description of the AEs: reported Term; SOC and PT by MedDRA coding; start date, start time, end date and end time; seriousness; severity (intensity); relationship (causality); action taken; outcome. AE duration and time to AE onset will be derived and presented in the subject data listings.

TEAEs will be presented by dose level. TEAEs are defined as AEs not present prior to administration of investigational product, or AEs present before administration of investigational product that worsen after the subject received the investigational product. A separate listing of SAEs will be presented, if applicable. Frequencies of TEAEs will be presented by SOC and PT, by Test product and placebo and overall.

TEAEs of which the relationship to the test drug was classified as ‘possible’, ‘probable’ and ‘definite’ will be regarded as “related”, while TEAEs that are classified as ‘not related’ or ‘unlikely’ will be regarded as “not related”.

Frequencies of TEAEs will also be reported by severity class (Mild, Moderate, or

Severe) and by investigational product and dose, for all causalities and for "related" events.

8.7.2. Laboratory Data

Individual laboratory test data will be listed. A listing of the values outside the pre-specified ranges will be flagged ("H" - high or "L" - low) and classified regarding clinical relevance.

A decision regarding whether a result outside the reference range is of clinical significance or not was made by the clinical investigator and reported and annotated accordingly. Clinically significant abnormalities occurring during the study will be recorded as AEs.

The reference ranges for the site's laboratory parameters will also be entered in the database and filed in the Investigator site file.

8.7.3. Vital Signs

Continuous vital signs monitoring (heart rate, respiratory rate and pulse oximetry) will be performed from pre-dose up to 6 hours post-dose. No listing of these data will be provided. Clinically relevant abnormalities during the period of continuous monitoring will be reported as AEs.

Vital signs (systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate and body temperature) will be assessed at the following time points: Day 1 pre-dose, again at approximately 2, 4 and 6 hours post-dose on Day 1, and at discharge on Day 2.

Individual vital signs results will be listed. Out of range values will be flagged ("H" - high or "L" - low) and classified regarding clinical relevance. Clinically relevant abnormalities will be reported as AEs.

Table 2. Vital Signs: Reference Values

	Reference Values
SBP (mmHg)	$90 \leq$ SBP ≤ 120 mmHg
DBP (mmHg)	$60 \leq$ DBP ≤ 90 mmHg
Heart Rate (beats/min)	60 to 100 beats/min
Body Temperature (ºC)	35.5 to 37.5 ºC

8.7.4. Electrocardiograms

The ECG results will be listed per subject as "normal" or "abnormal".
All abnormalities will be classified in terms of clinical relevance (CR, NCR). Clinically relevant abnormalities will be reported as AEs.

8.7.5. Physical Examinations

Clinically relevant changes from screening in physical examination will be reported as AEs.

8.7.6. Previous and Concomitant Medications

All other medications used will be listed as concomitant medications.

Previous/Concomitant medications will be coded according Anatomical Therapeutic Chemical (ATC) classification system.

8.8. Plasma Concentrations

[redacted] will carry out the determination of plasma levels of cytisine in accordance with the applicable principles of Good Laboratory Practices (GLP), using a previously validated LC-MS/MS analytical method. The pre-planned lower limit of quantification (LLOQ) is 1 ng/mL and the upper limit of quantification (ULOQ) is 400 ng/mL.

Individual (per subject) and mean plasma concentration versus time profiles will be presented for both linear and semi-logarithmic scales. Graphic presentation of individual data will be based on actual blood sampling time, except for pre-dose sampling time which will be assumed as t0.

Descriptive statistics (number of subjects, geometric mean, arithmetic mean, SD, CV%, median, minimum and maximum) of the plasma concentrations will be presented for each time point. Concentrations below the LLOQ will be taken as missing for the calculation of geometric mean and replaced by zero for calculation of the remaining summary statistics.

The pre-dose blood samples were to be collected within 30 minutes prior to dosing. The post-dose blood samples were to be collected within +/-2 minutes from the scheduled sampling time. The clock time was to be recorded and reported for all blood draws and all subjects. A deviation greater than +/-2 minutes will be reported as a protocol deviation and its cause will be recorded.

8.9. Pharmacokinetic Parameters

Pharmacokinetic parameters will be estimated from the plasma concentration versus time profiles for all subjects in the pharmacokinetic analysis set.

Pharmacokinetic parameter C_{max} will be calculated as the maximum observed plasma concentration (ng/mL) and T_{max} will be the time to occurrence of maximum plasma concentration (h).
Individual PK parameters and descriptive statistics (number of subjects, arithmetic and geometric mean, SD, CV%, median, minimum value, and maximum value) will be presented by Cytisine Dose Level. For C_{max} the 90% CI of the mean will also be

estimated. If for more than ⅓ of the subjects no reliable PK parameter could be determined, only the minimum and maximum values will be presented for that parameter and all other descriptive statistics will be omitted. Missing PK parameter data will not be imputed.

8.10. Dose-proportionality

Linear-dose proportionality of C_{max} after oral administration of Cytisine 6 mg, 9 mg, 12 mg, 15 mg, 18 mg, 21 mg, 24 mg, 27 mg and 30 mg will be assessed by using an exponential regression model that measures the degree of nonlinear proportionality. The relationship is written as a power function: $y = \alpha * dose^{\beta}$, where y denotes the pharmacokinetic parameter being analyzed (C_{max}), α is a constant and β is the proportionality constant. Linearization of this relationship gives:

$\log(y) = \log(\alpha) + \beta * \log(dose)$.

The relationship is dose proportional when $\beta = 1$ (linear pharmacokinetics) or considered to be dose dependent (non-linear pharmacokinetics) when $\beta \neq 1$. The exponent of the power function fitted to the individual C_{max} values and 95% CI will be assessed.

9. PRESENTATION OF RESULTS

9.1. Statistical Output Specification

The summary tables will be generated as Rich Text Files (*.rtf) from SAS® and compiled in a document, to be considered as Section 14 (Tables, Figures and Graphs Referred to But Not Included in the Text) of the CSR.

Tables and Figures for direct insertion in the body of the CSR, will also be generated as *.rtf files. In-text tables and figures will preferably be prepared in portrait format. Listings will preferably be prepared in landscape format.

The planned TFLs for the CSR are listed below.

9.1.1. In-text Tables and Figures

For CSR Synopsis:

Tables and/or Figures to be inserted in the synopsis of the CSR will be decided at the time of writing the CSR.

For CSR Body Text:
The planned tables and figures for CSR body text are listed below. Other relevant tables and/or figures may be presented in the final CSR body text. Thus, the placement and numbering presented is indicative and may deviate from the placement and numbering in the final CSR body text.

In-text Tables	Title
Table A	Study Flow-Chart (to be captured from the CSP)
Table B	Identity of Investigational Products
Table C	Treatment Assignment
Table D	Subjects Disposition
Table E	Major Protocol Deviations
Table F.1	Demographic Data – Safety Analysis Set
Table F.2	Smoking History – Safety Analysis Set
Table F.3	Baseline CO – Safety Analysis Set
Table G.1	Treatment Emergent Adverse Events – All Causalities
Table G.2	Treatment Emergent Adverse Events – Related
Table H	Cytisine: C_{max} and T_{max} Following Administration of Cytisine (6 mg, 9 mg, 12 mg, 15 mg, 18 mg, 21 mg, 24 mg, 27 mg and 30 mg)
Table I	Cytisine: Dose Proportionality of C_{max}

In-text Figures	Legend
Figure A	Cytisine: Arithmetic Mean Plasma Concentration Versus Time Profile Following Administration of Cytisine (6 mg, 9 mg, 12 mg, 15 mg, 18 mg, 21 mg, 24 mg, 27 mg and 30 mg) – Linear Scale.
Figure B	Cytisine: Arithmetic Mean Plasma Concentration Versus Time Profile Following Administration of Cytisine (6 mg, 9 mg, 12 mg, 15 mg, 18 mg, 21 mg, 24 mg, 27 mg and 30 mg) – Semi-Logarithmic Scale
Figure C	Cytisine: Dose Proportionality of C_{max}
Figure D	Cytisine: Boxplots of C_{max} as a Function of Dose

End-of-Text Tables	Title
14.1 DEMOGRAPHIC DATA	
14.1.1	Demographic Data – Safety Analysis Set
14.1.2	Smoking History – Safety Analysis Set (Part I)
14.1.3	Smoking History – Safety Analysis Set (Part II)
14.1.4	Smoking History – Expired CO at Screening
14.1.5	Medical History – Safety Analysis Set
14.2 SAFETY DATA	
14.2.1	**Treatment Emergent Adverse Events**
14.2.1.1	Adverse Events Leading to Discontinuation or Withdrawal
14.2.1.2	Listings of Serious Adverse Events
14.2.1.3	Summary of Treatment Emergent Adverse Events – All Causalities
14.2.1.4	Summary of Treatment Emergent Adverse Events - Related
14.2.1.5	Summary of Treatment Emergent Adverse Events by Severity –

	All Causalities
14.2.1.6	Summary of Treatment Emergent Adverse Events by Severity – Related
14.3 PHARMACOKINETIC DATA	
14.3.1	**Deviations from Blood Sampling Schedule**
14.3.1.1	Deviations from Blood Sampling Schedule
14.3.1.2	Missing Blood Samples
14.3.2	**Plasma Concentrations**
14.3.2.1	Cytisine 6 mg: Individual Data and Descriptive Statistics of Plasma Concentrations
14.3.2.2	Cytisine 9 mg: Individual Data and Descriptive Statistics of Plasma Concentrations
14.3.2.3	Cytisine 12 mg: Individual Data and Descriptive Statistics of Plasma Concentrations
14.3.2.4	Cytisine 15 mg: Individual Data and Descriptive Statistics of Plasma Concentrations
14.3.2.5	Cytisine 18 mg: Individual Data and Descriptive Statistics of Plasma Concentrations
14.3.2.6	Cytisine 21 mg: Individual Data and Descriptive Statistics of Plasma Concentrations
14.3.2.7	Cytisine 24 mg: Individual Data and Descriptive Statistics of Plasma Concentrations
14.3.2.8	Cytisine 27 mg: Individual Data and Descriptive Statistics of Plasma Concentrations
14.3.2.9	Cytisine 30 mg: Individual Data and Descriptive Statistics of Plasma Concentrations
14.3.3	**Pharmacokinetic Parameters**
14.3.3.1	Cytisine 6 mg: Individual Data and Descriptive Statistics of Pharmacokinetic Parameters
14.3.3.2	Cytisine 9 mg: Individual Data and Descriptive Statistics of Pharmacokinetic Parameters
14.3.3.3	Cytisine 12 mg: Individual Data and Descriptive Statistics of Pharmacokinetic Parameters
14.3.3.4	Cytisine 15 mg: Individual Data and Descriptive Statistics of Pharmacokinetic Parameters
14.3.3.5	Cytisine 18 mg: Individual Data and Descriptive Statistics of Pharmacokinetic Parameters
14.3.3.6	Cytisine 21 mg: Individual Data and Descriptive Statistics of Pharmacokinetic Parameters
14.3.3.7	Cytisine 24 mg: Individual Data and Descriptive Statistics of Pharmacokinetic Parameters
14.3.3.8	Cytisine 27 mg: Individual Data and Descriptive Statistics of Pharmacokinetic Parameters
14.3.3.9	Cytisine 30 mg: Individual Data and Descriptive Statistics of Pharmacokinetic Parameters

End-of-Text Figures	Title
14.3 PHARMACOKINETIC DATA	
14.3.4	**Cytisine Plasma Concentration-Time Profiles of All Subjects**
14.3.4.1	Cytisine 6 mg: Plasma Concentration-Time Profiles of All Subjects
14.3.4.2	Cytisine 9 mg: Plasma Concentration-Time Profiles of All Subjects
14.3.4.3	Cytisine 12 mg: Plasma Concentration-Time Profiles of All Subjects
14.3.4.4	Cytisine 15 mg: Plasma Concentration-Time Profiles of All Subjects
14.3.4.5	Cytisine 18 mg: Plasma Concentration-Time Profiles of All Subjects
14.3.4.6	Cytisine 21 mg: Plasma Concentration-Time Profiles of All Subjects
14.3.4.7	Cytisine 24 mg: Plasma Concentration-Time Profiles of All Subjects
14.3.4.8	Cytisine 27 mg: Plasma Concentration-Time Profiles of All Subjects
14.3.4.9	Cytisine 30 mg: Plasma Concentration-Time Profiles of All Subjects
14.3.5	**Cytisine Arithmetic Mean Plasma Concentration-Time Profiles**
14.3.5.1	Cytisine 6 mg: Arithmetic Mean Plasma Concentration Versus Time Profile – Linear Scale
14.3.5.2	Cytisine 6 mg: Arithmetic Mean Plasma Concentration Versus Time Profile – Semi-Logarithmic Scale
14.3.5.3	Cytisine 9 mg: Arithmetic Mean Plasma Concentration Versus Time Profile – Linear Scale
14.3.5.4	Cytisine 9 mg: Arithmetic Mean Plasma Concentration Versus Time Profile – Semi-Logarithmic Scale
14.3.5.5	Cytisine 12 mg: Arithmetic Mean Plasma Concentration Versus Time Profile – Linear Scale
14.3.5.6	Cytisine 12 mg: Arithmetic Mean Plasma Concentration Versus Time Profile – Semi-Logarithmic Scale
14.3.5.7	Cytisine 15 mg: Arithmetic Mean Plasma Concentration Versus Time Profile – Linear Scale
14.3.5.8	Cytisine 15 mg: Arithmetic Mean Plasma Concentration Versus Time Profile – Semi-Logarithmic Scale
14.3.5.9	Cytisine 18 mg: Arithmetic Mean Plasma Concentration Versus Time Profile – Linear Scale
14.3.5.10	Cytisine 18 mg: Arithmetic Mean Plasma Concentration Versus Time Profile – Semi-Logarithmic Scale
14.3.5.11	Cytisine 21 mg: Arithmetic Mean Plasma Concentration Versus

	Time Profile – Linear Scale
14.3.5.12	Cytisine 21 mg: Arithmetic Mean Plasma Concentration Versus Time Profile – Semi-Logarithmic Scale
14.3.5.13	Cytisine 24 mg: Arithmetic Mean Plasma Concentration Versus Time Profile – Linear Scale
14.3.5.14	Cytisine 24 mg: Arithmetic Mean Plasma Concentration Versus Time Profile – Semi-Logarithmic Scale
14.3.5.15	Cytisine 27 mg: Arithmetic Mean Plasma Concentration Versus Time Profile – Linear Scale
14.3.5.16	Cytisine 27 mg: Arithmetic Mean Plasma Concentration Versus Time Profile – Semi-Logarithmic Scale
14.3.5.17	Cytisine 30 mg: Arithmetic Mean Plasma Concentration Versus Time Profile – Linear Scale
14.3.5.18	Cytisine 30 mg: Arithmetic Mean Plasma Concentration Versus Time Profile – Semi-Logarithmic Scale

9.1.2. **List of Subject Data Listings (Section 16.2 of CSR)**
9.1.3.

The following data listings will be produced, to form Section 16.2. Subject Data Listings of the CSR:

Listing No.	**Title**
16.2 SUBJECT DATA LISTINGS	
16.2.1	**Subject Disposition**
16.2.1.1	Subject Disposition: Eligibility and Randomization
16.2.2	**Protocol Deviations**
16.2.2.1	Blood Sampling Time Deviations
16.2.2.2	Other Protocol Deviations
16.2.3	**Demographic Data and Other Baseline Data**
16.2.3.1	Demographic Data
16.2.3.2	Fertility/Contraception
16.2.3.2.1	Female Fertility/Contraception
16.2.3.2.2	Male Fertility/Contraception
16.2.3.3	Medical History at Screening
16.2.3.4	Smoking History at Screening
16.2.3.5	Expired CO at Screening
16.2.3.6	Drugs of Abuse and Ethanol
16.2.3.7	Previous Medication
16.2.4	**Compliance**
16.2.4.1	Investigational Product Administration
16.2.5	**Adverse Event Listings (Each Subject)**
16.2.5.1	Serious Adverse events (Part I)
16.2.5.2	Serious Adverse events (Part II)
16.2.5.3	Serious Adverse events (Part III)
16.2.5.4	Serious Adverse events (Part IV)
16.2.5.5	Serious Adverse events (Part V)
16.2.5.6	Treatment-Emergent Adverse Events

16.2.5.7	Non-Treatment-Emergent Adverse Events
16.2.6	**Listing Laboratory Measurements by Subject**
16.2.6.1	Normal Range of Laboratory Values
16.2.6.2	Hematology (Part I)
16.2.6.3	Hematology (Part II)
16.2.6.4	Biochemistry (Part I)
16.2.6.5	Biochemistry (Part II)
16.2.6.6	Biochemistry (Part III)
16.2.6.7	Coagulation
16.2.6.8	Urinalysis
16.2.6.9	Urine Microscopy
16.2.6.10	Pregnancy Test
16.2.6.11	Additional (Not Planned) Laboratory Safety Tests
16.2.7	**Vital Signs**
16.2.7.1	Vital Signs
16.2.8	**12-Lead ECG**
16.2.8.1	12-Lead ECG
16.2.9	**Individual Pharmacokinetic Data**
16.2.9.1	Individual Pharmacokinetic Data
16.2.9.1.1	Cytisine: Individual Drug Concentration Data
16.2.9.1.2	Cytisine: Individual Pharmacokinetic Parameters
16.2.9.2	Documentation of Non-Compartmental Analysis (NCA)
16.2.9.3	Cytisine: ACH-CYT-08 Phoenix NCA Output
16.2.10	**Concomitant Medication**
16.2.10.1	Concomitant Medication
16.4 INDIVIDUAL SUBJECT DATA LISTINGS (US Archival Listings)	

10. REFERENCES

[1] ACH-CYT-08 Clinical Study Protocol, Version 5.0, 07MAY2019.

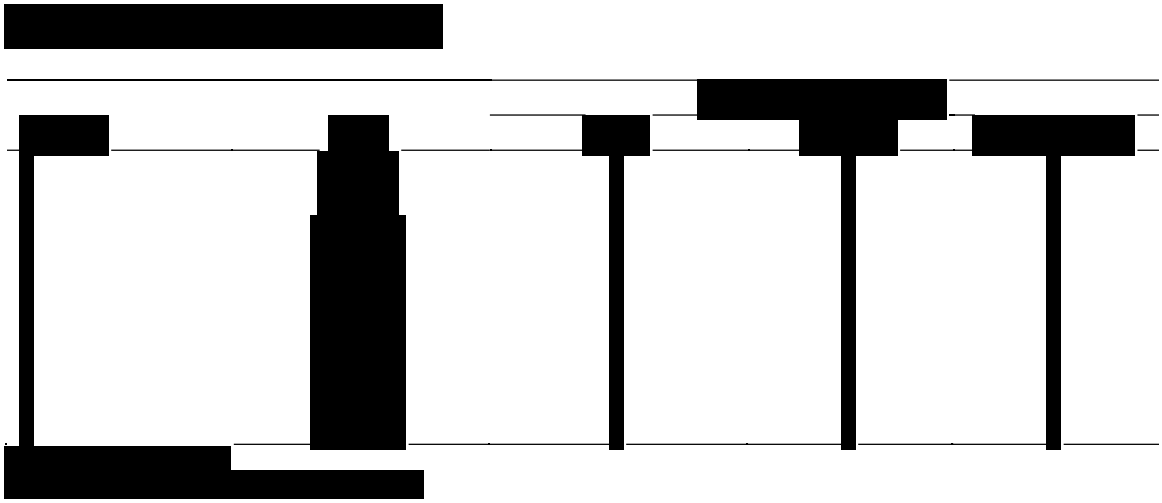
11. APPENDICES

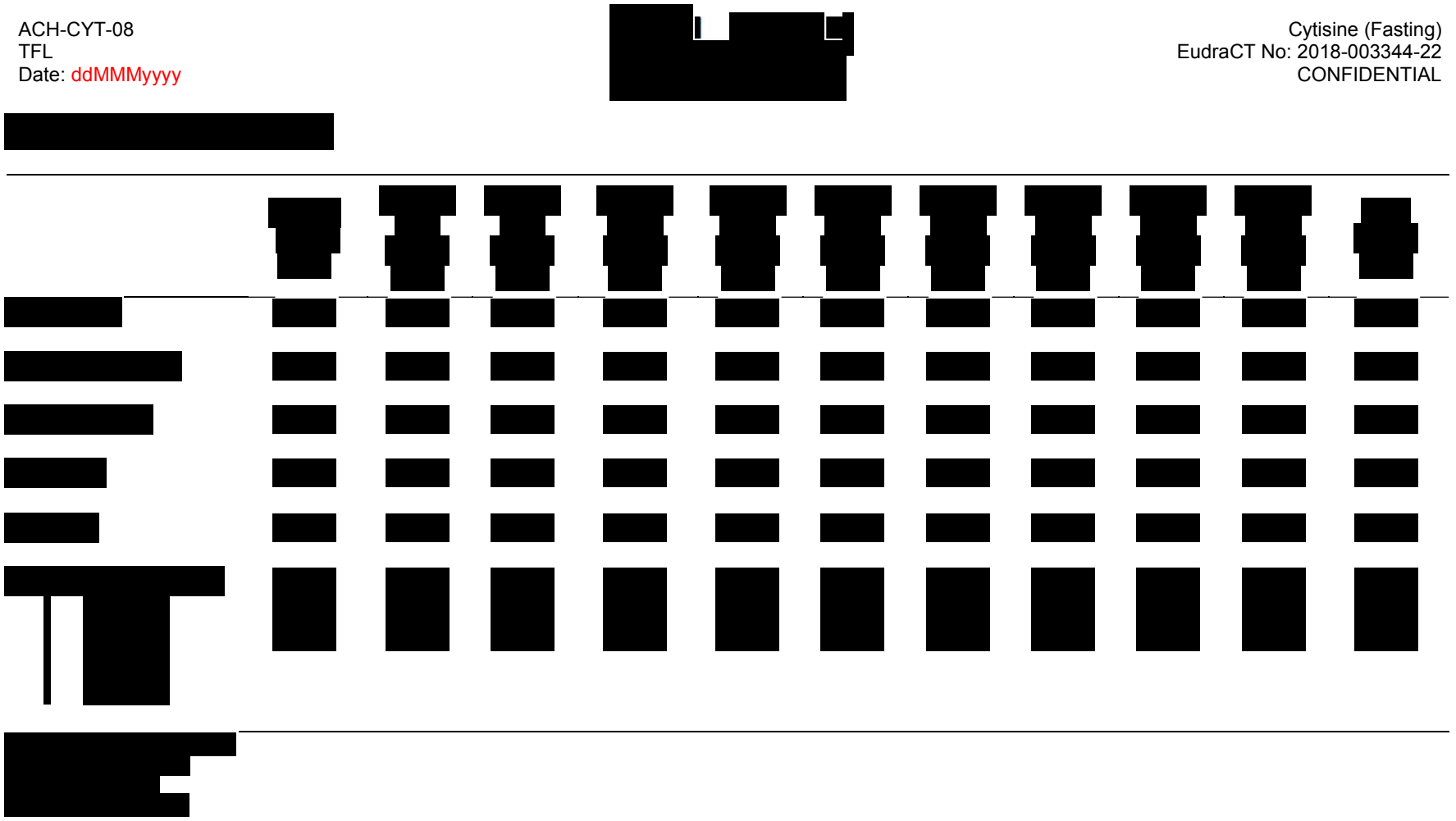
Table A. Study flow-chart

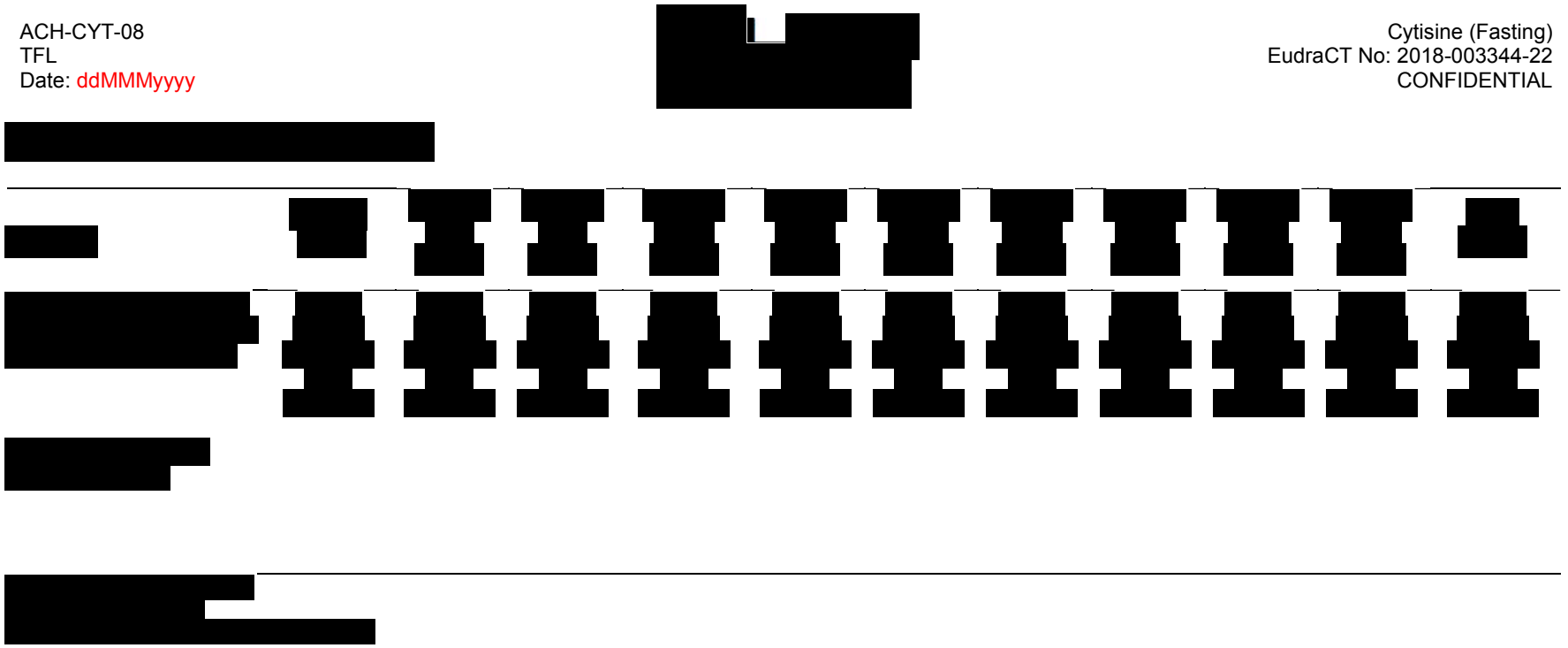
Note: To be captured from the Clinical Study Protocol and Amendments.

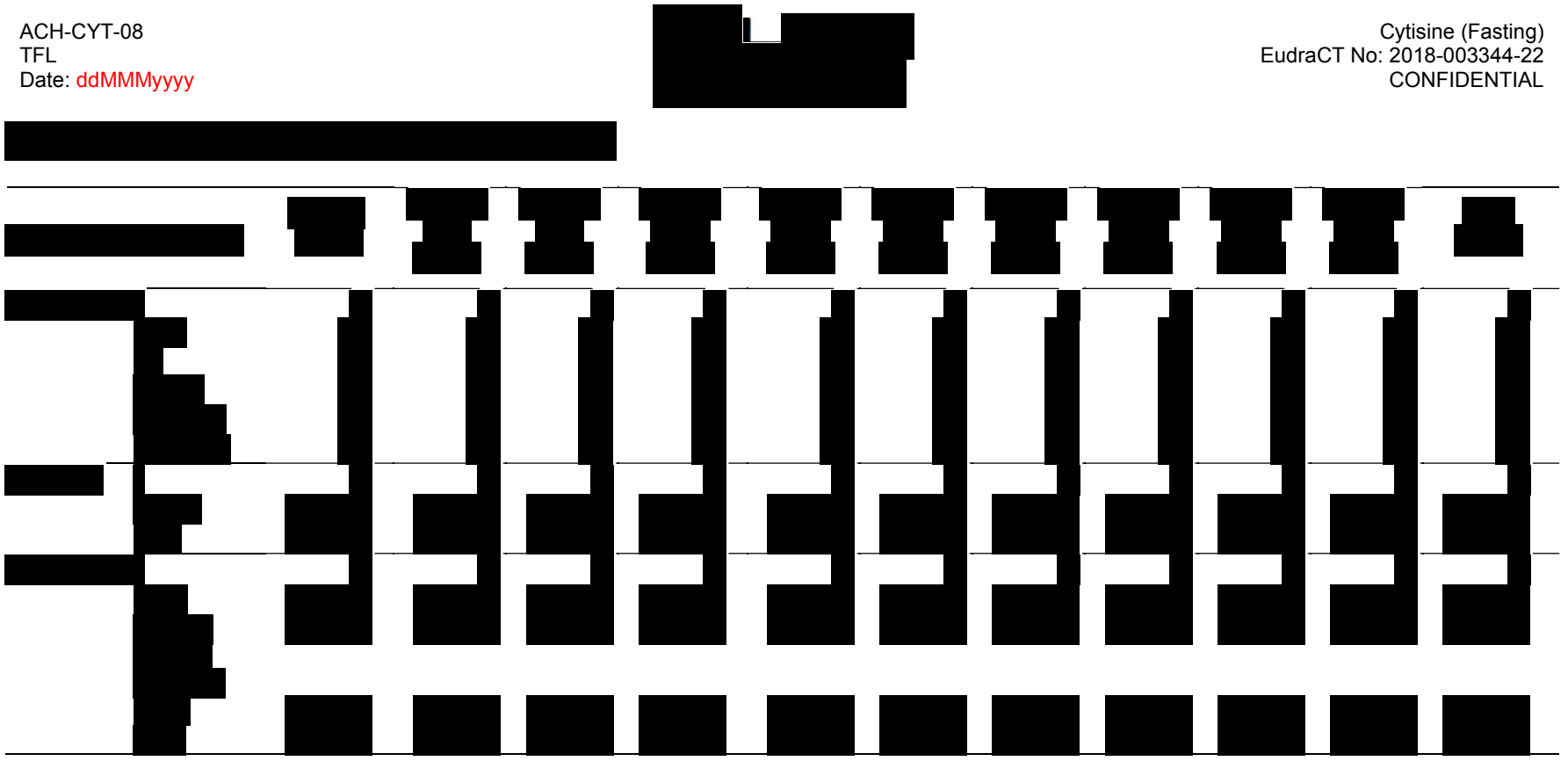
Table B. Identity of Investigational Products

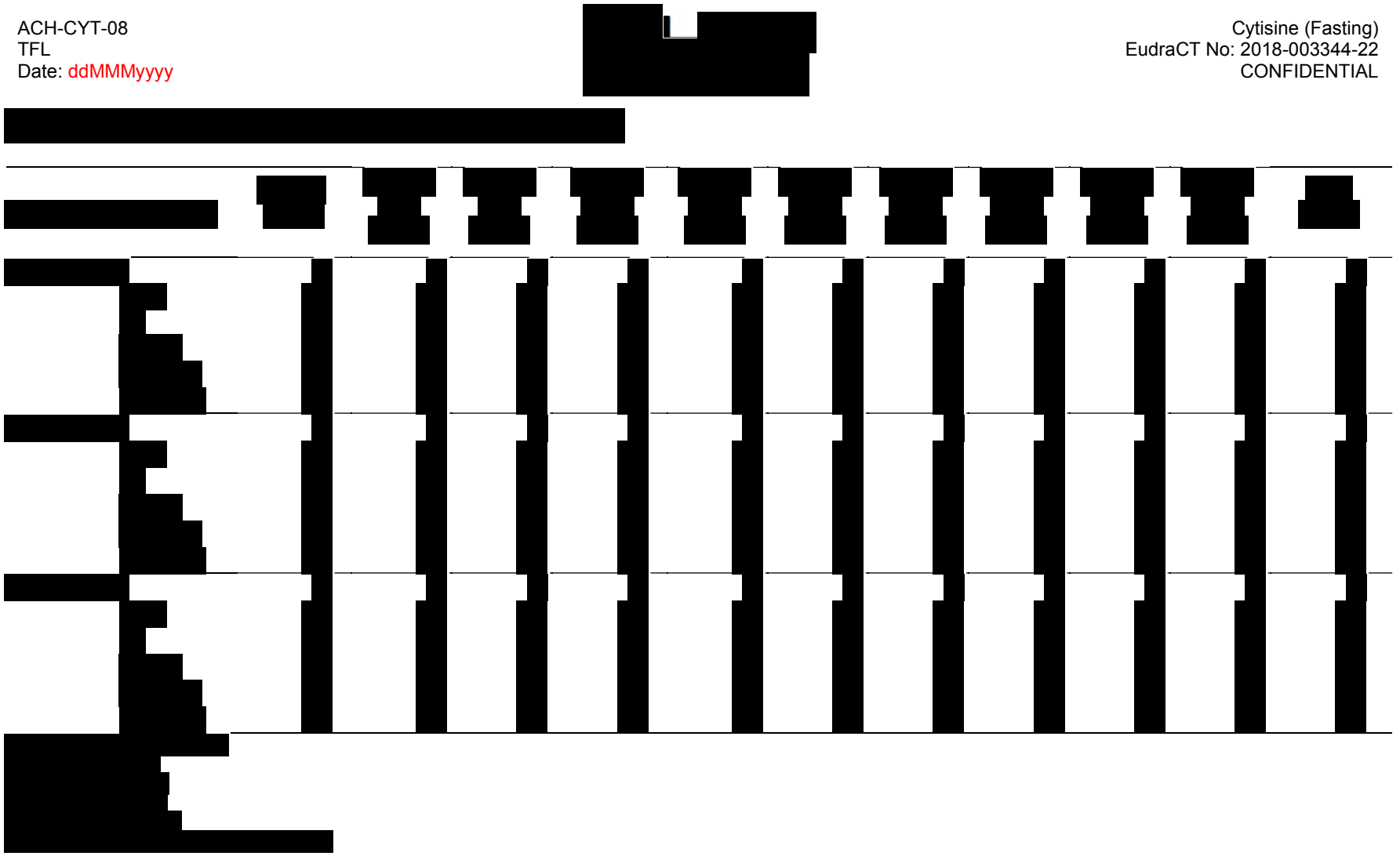
Note: To be generated by the MW.

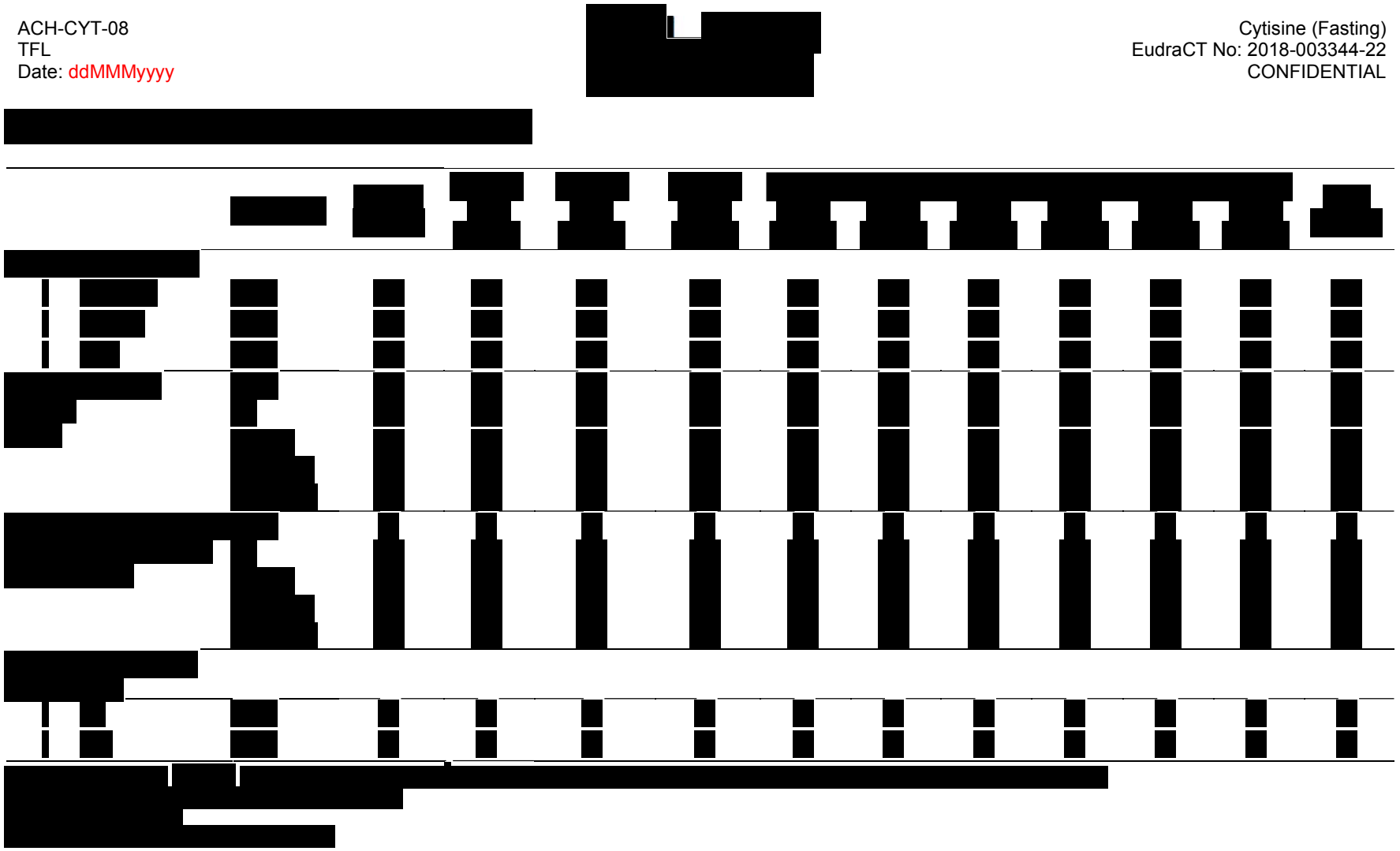


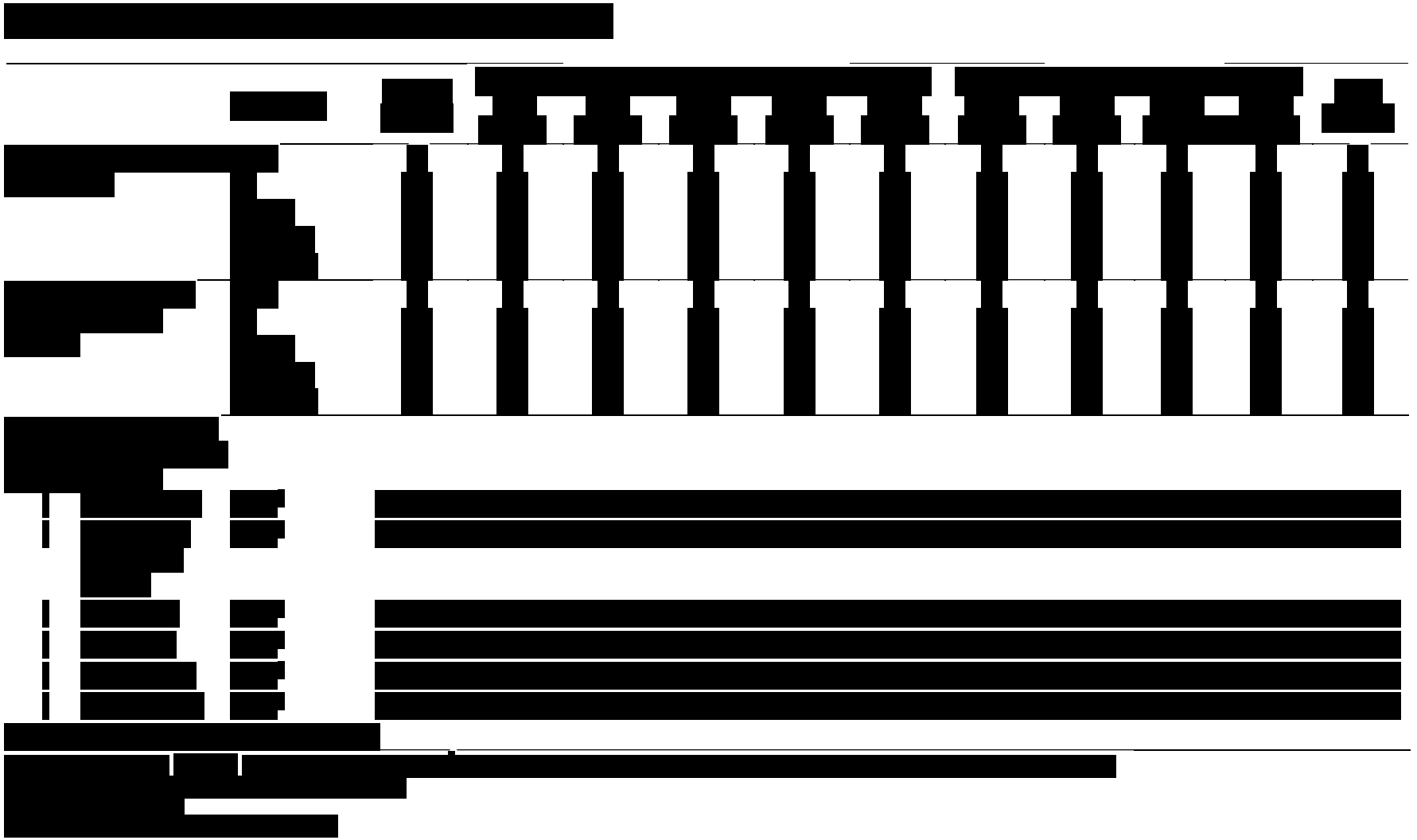


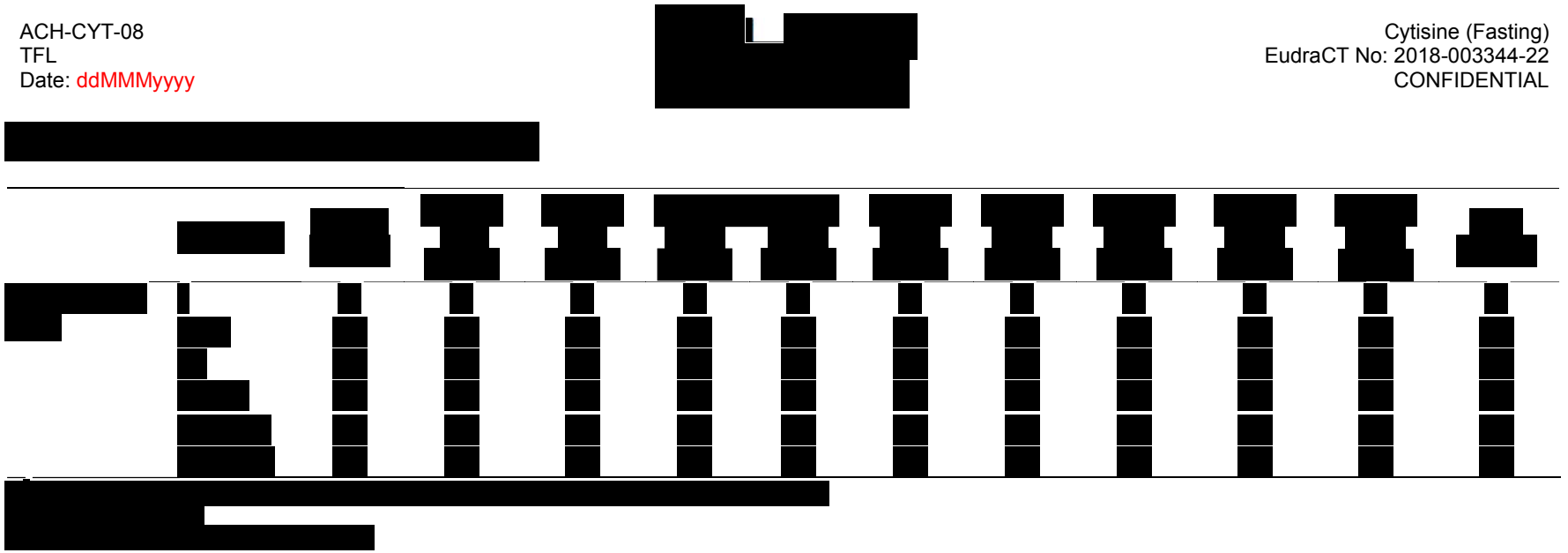


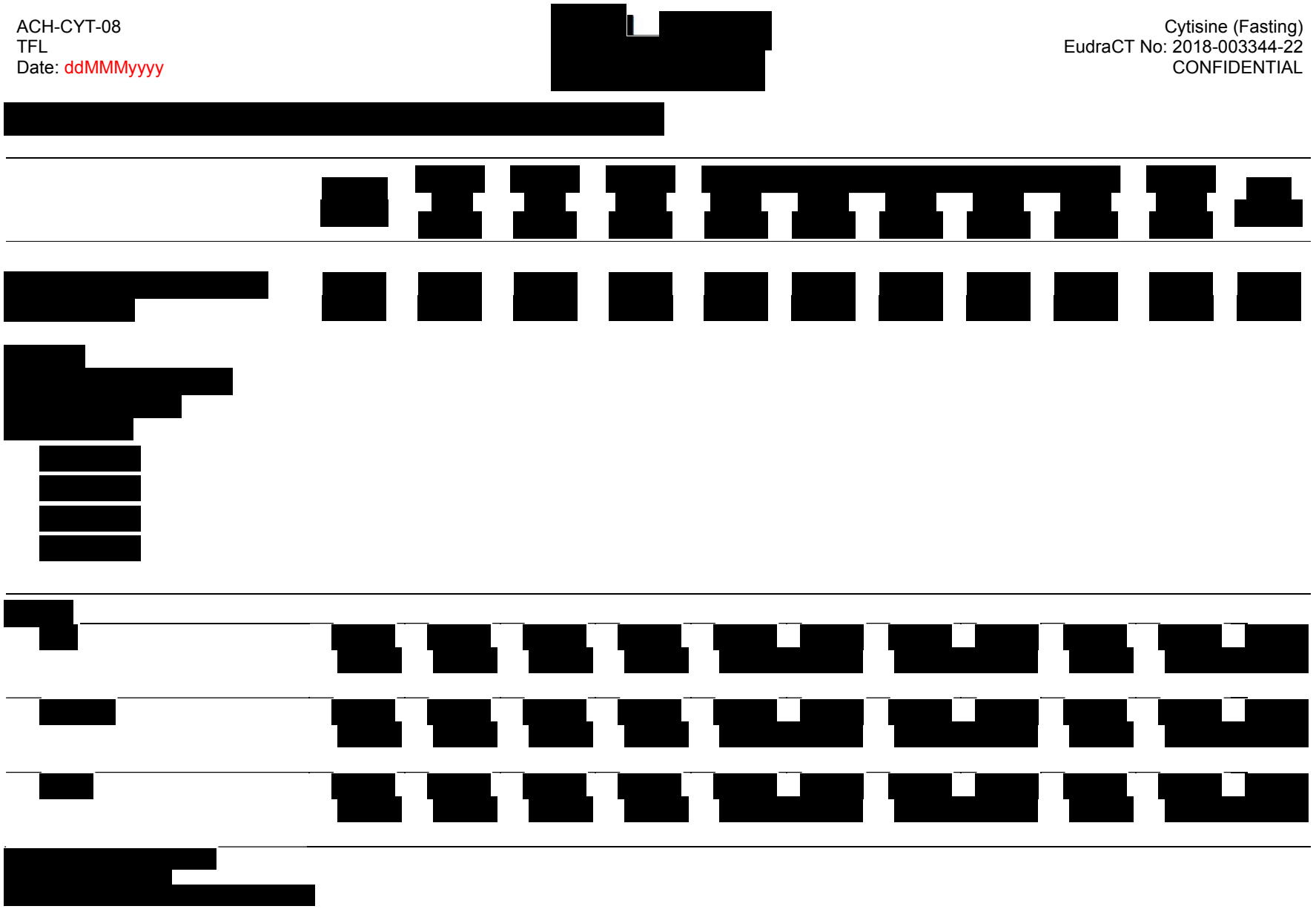


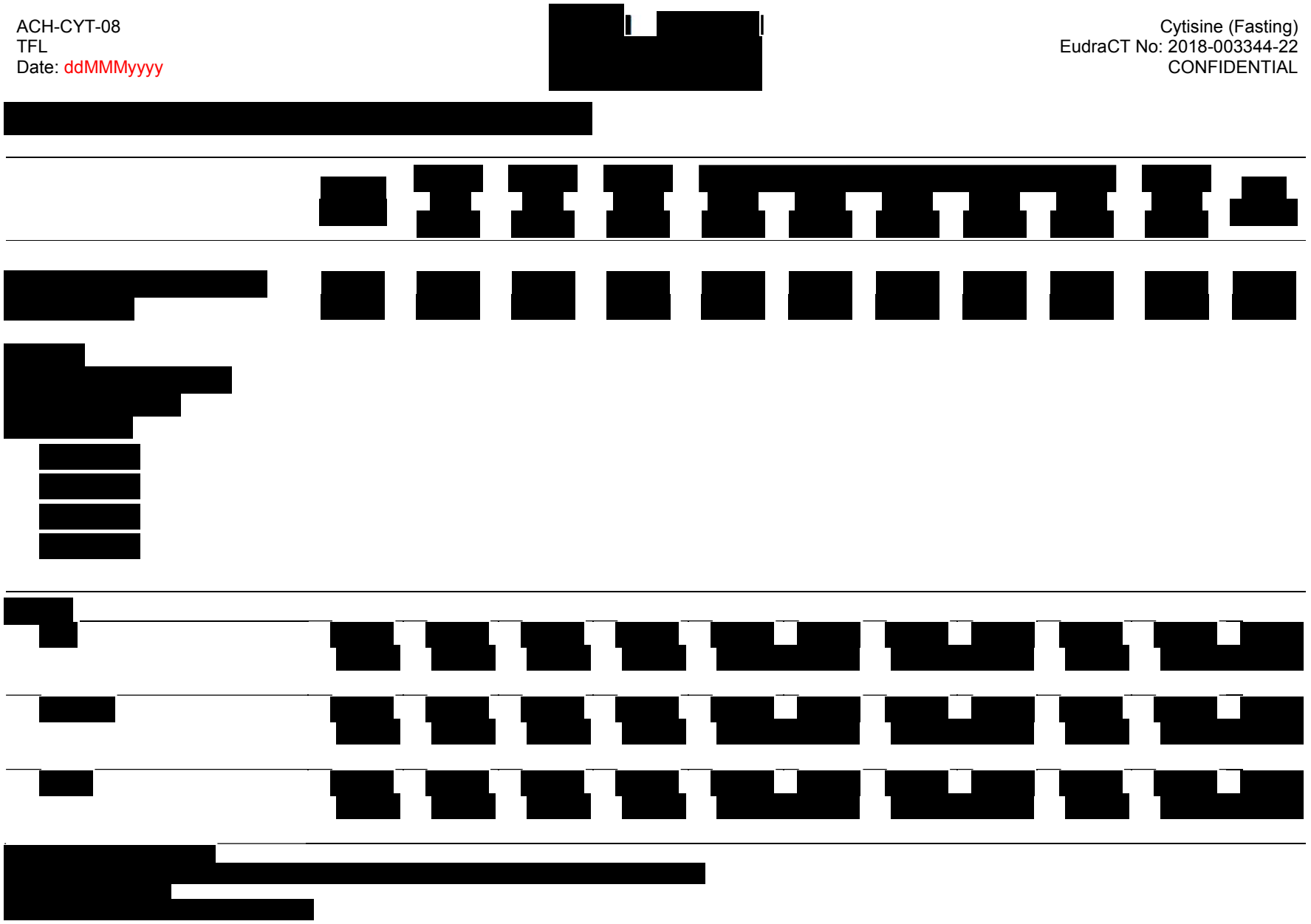


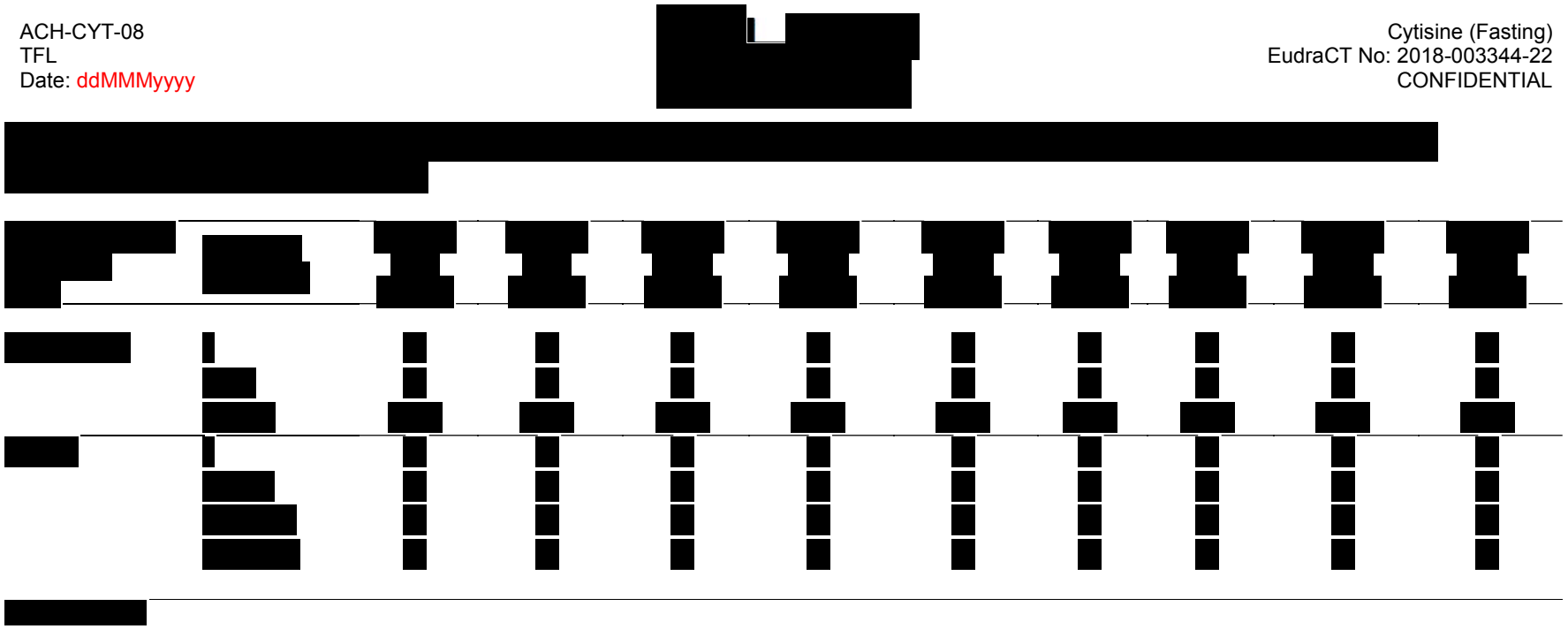












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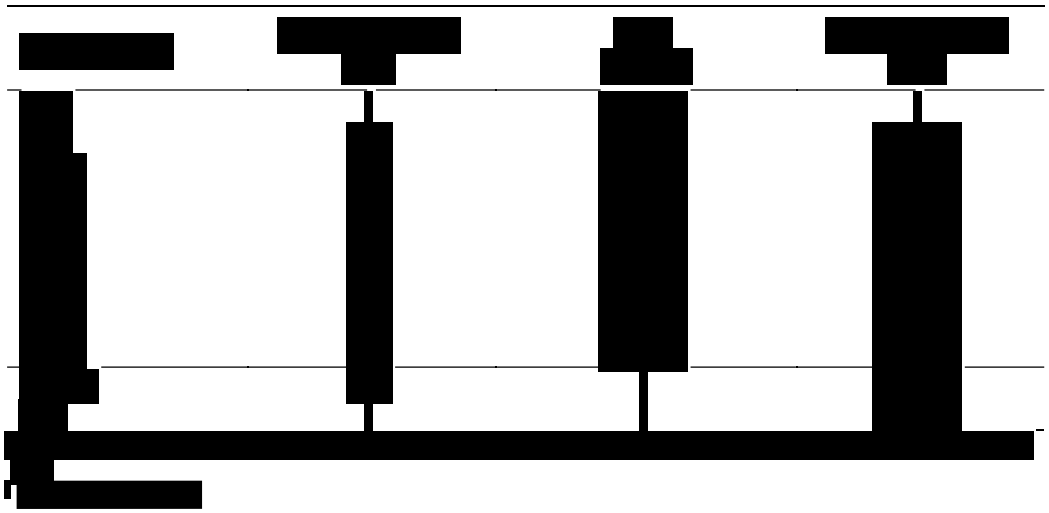

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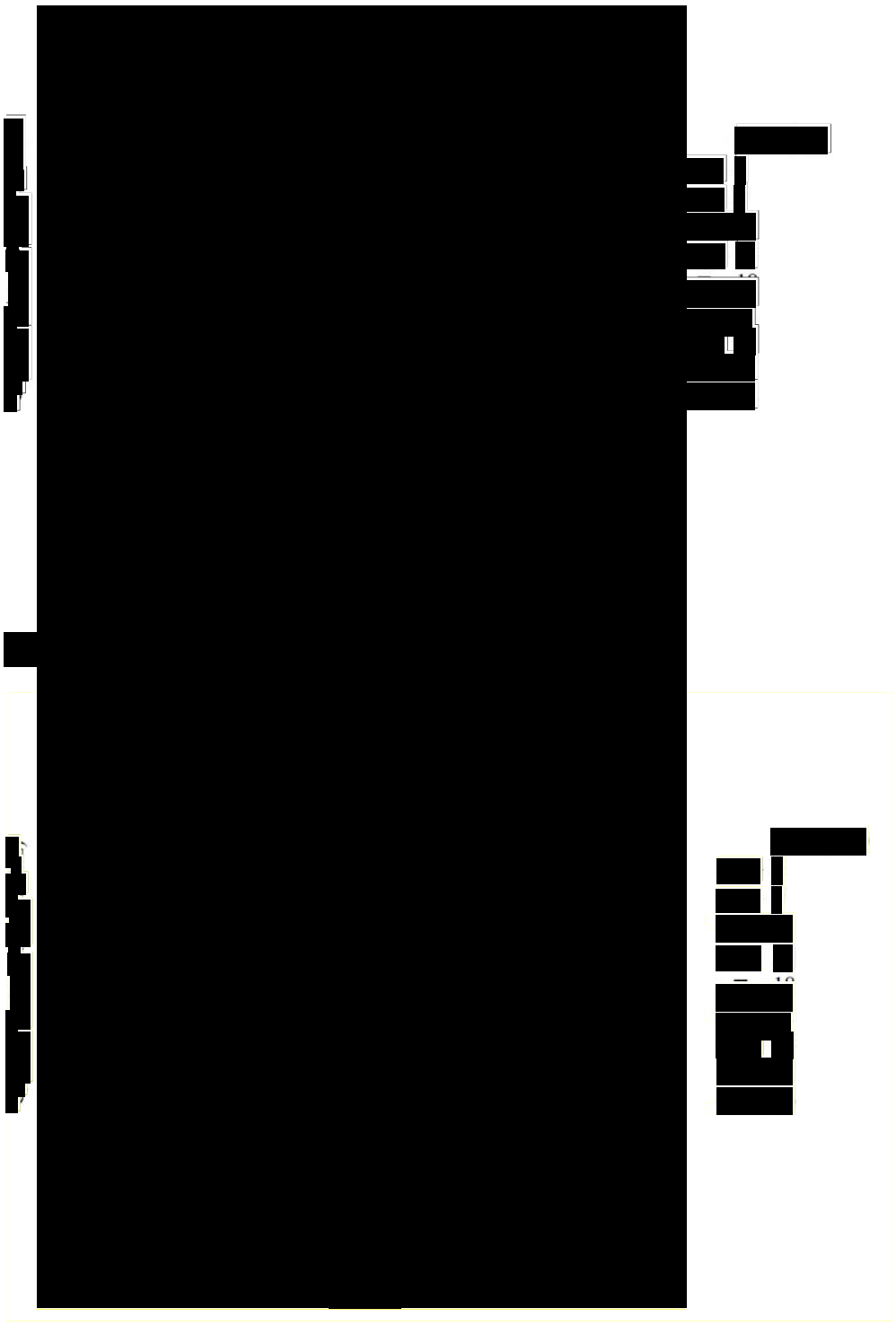

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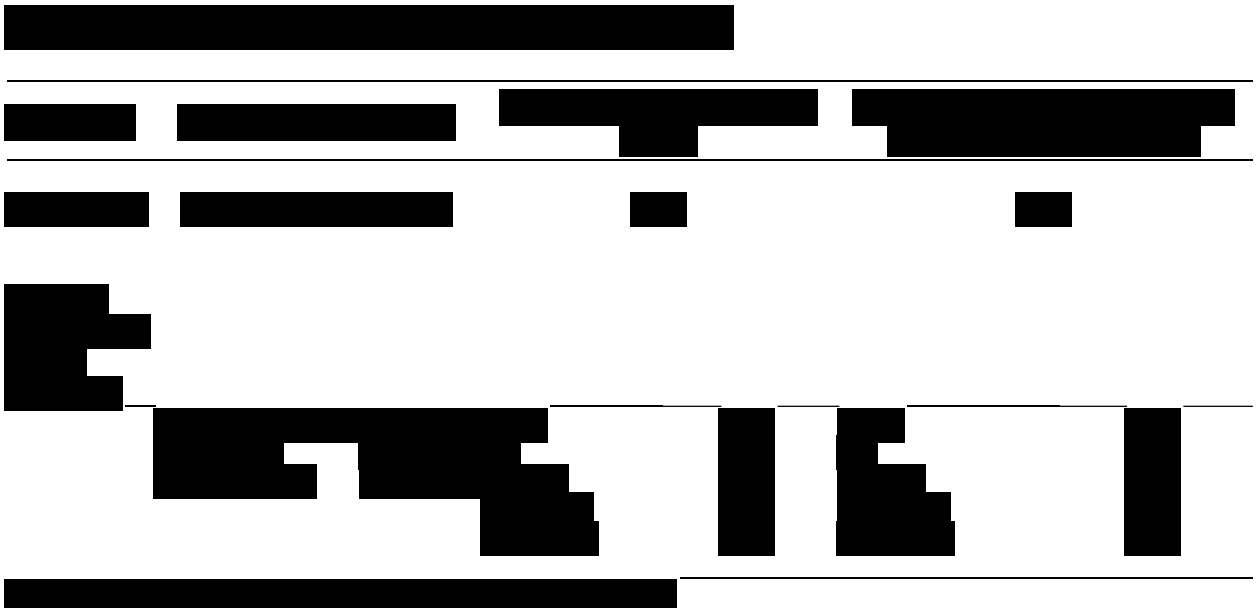

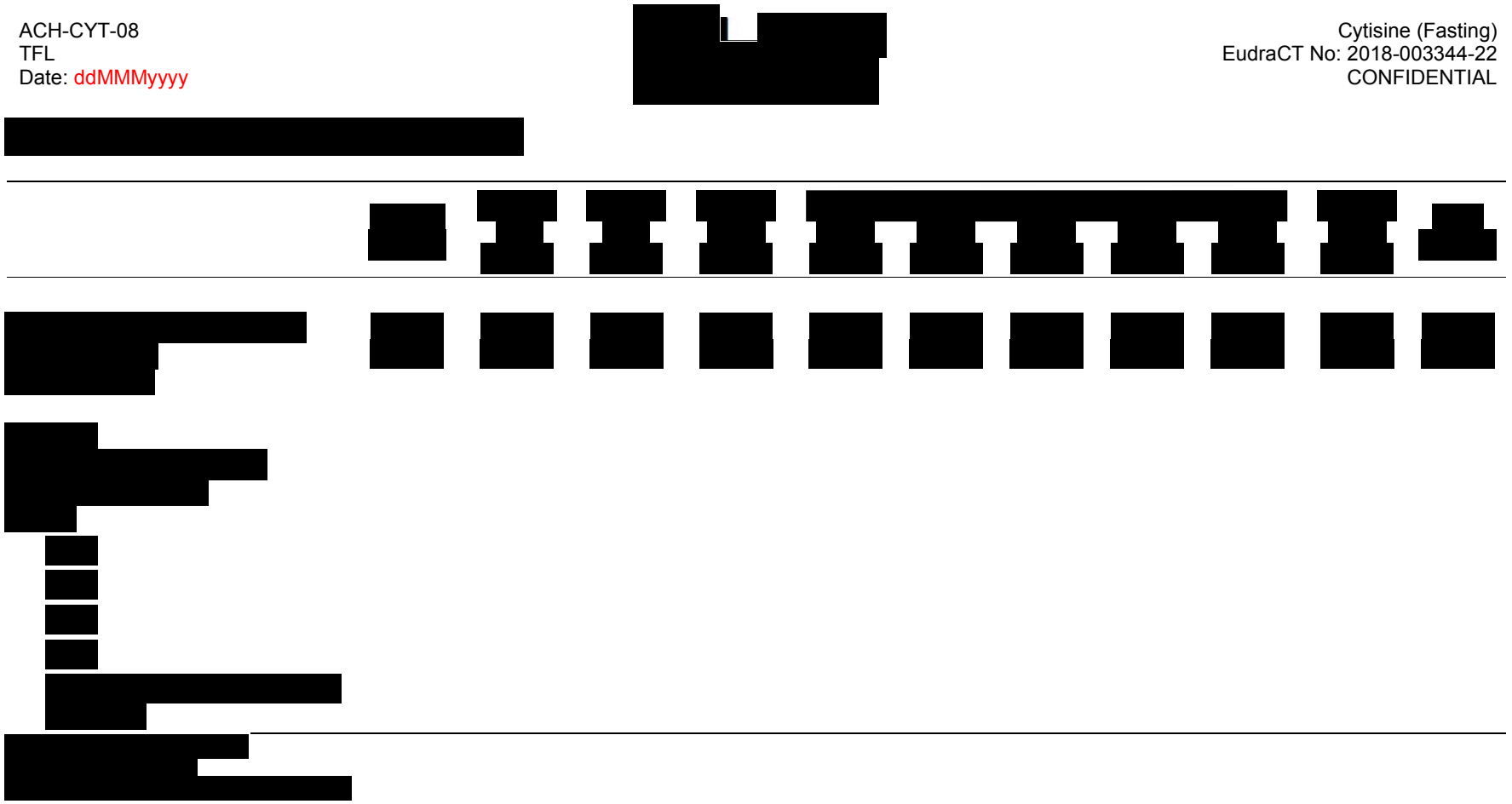

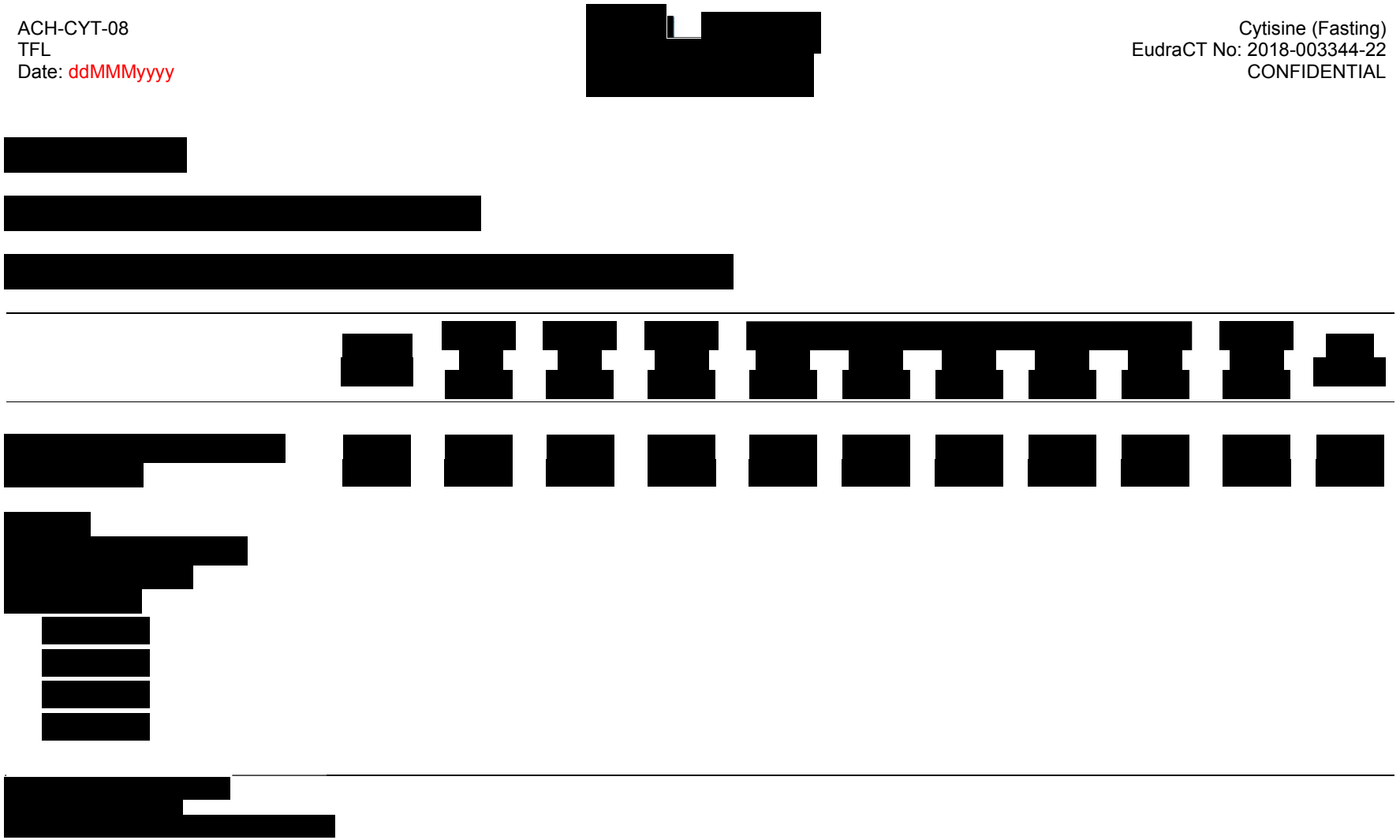

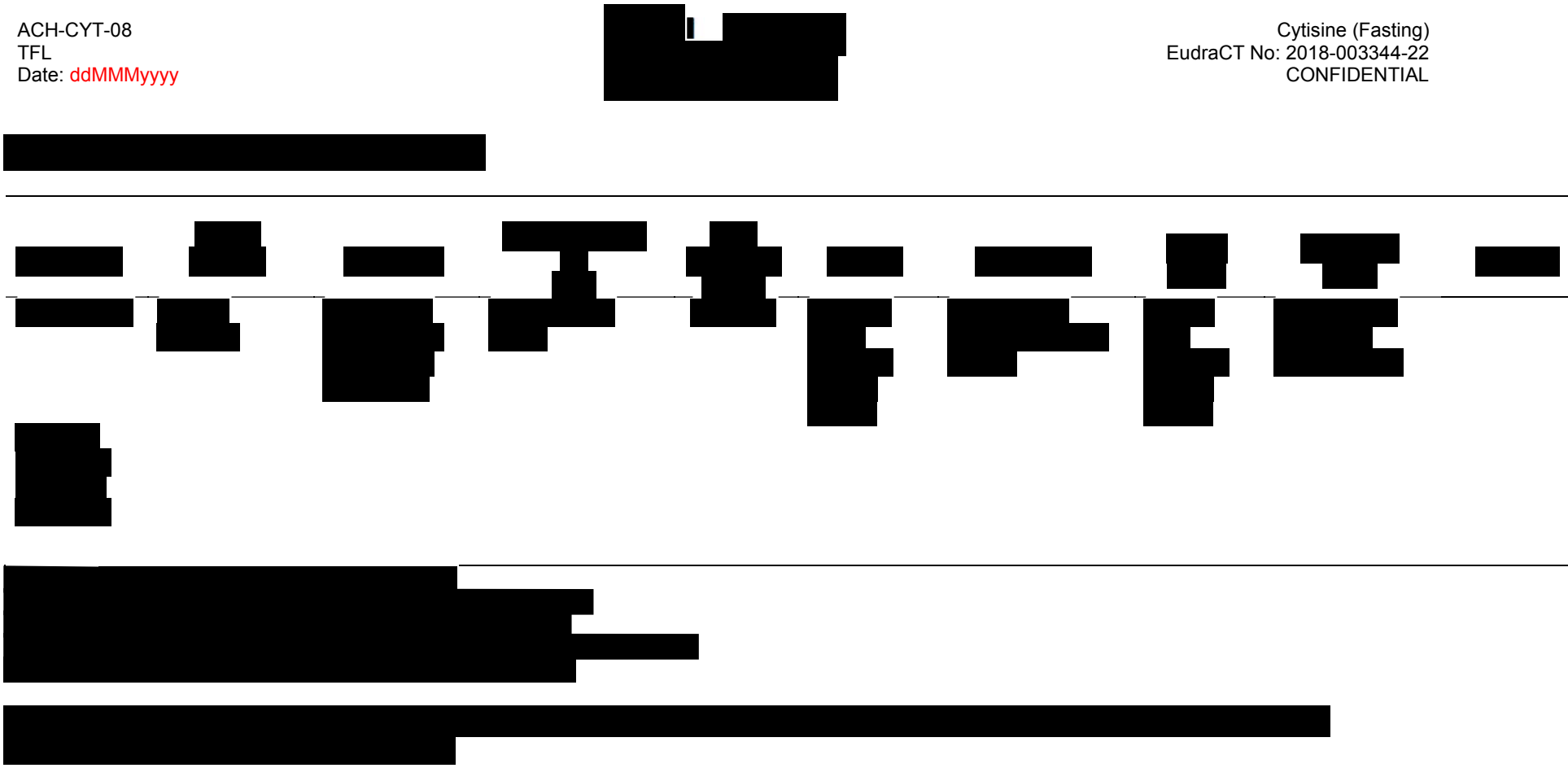

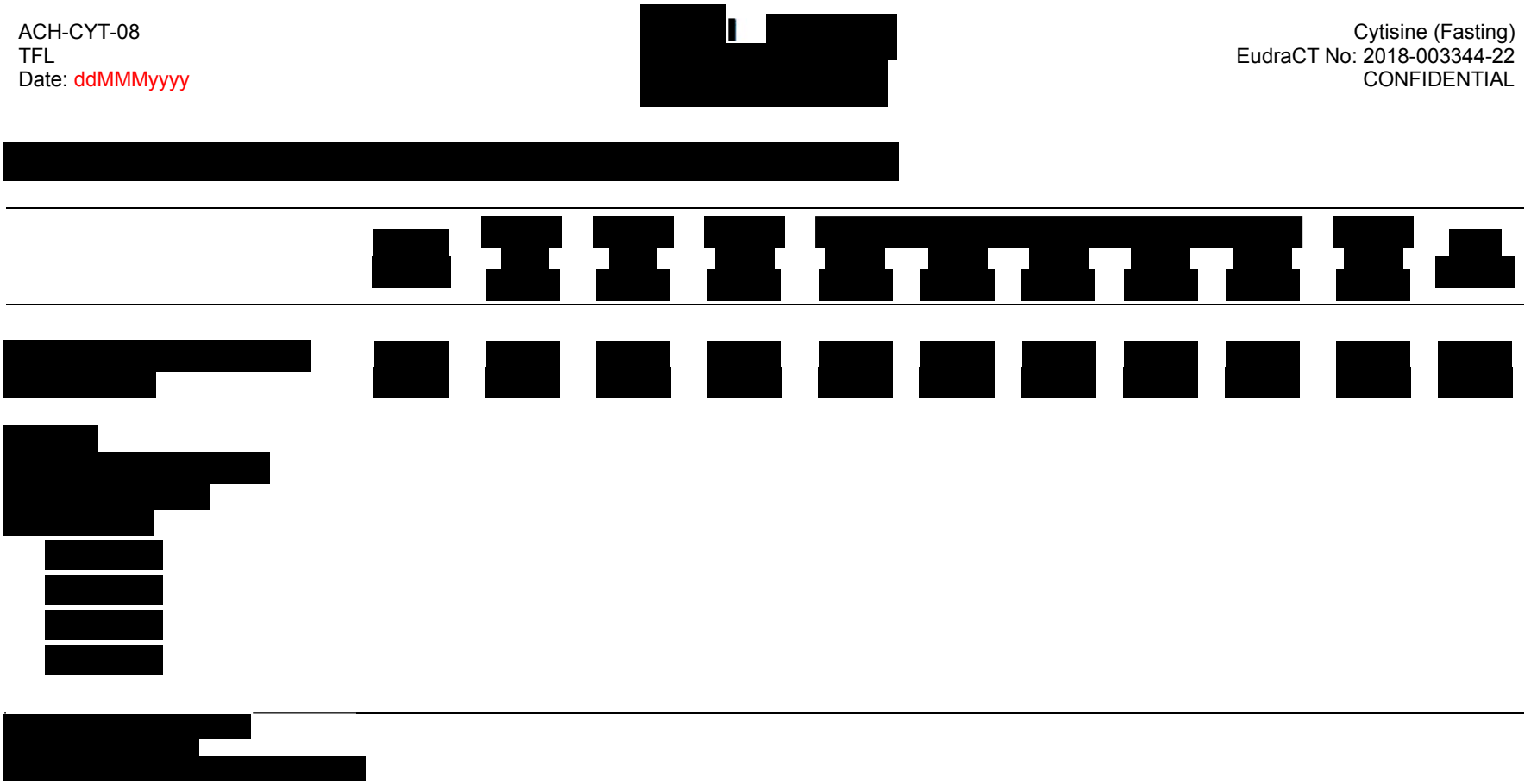

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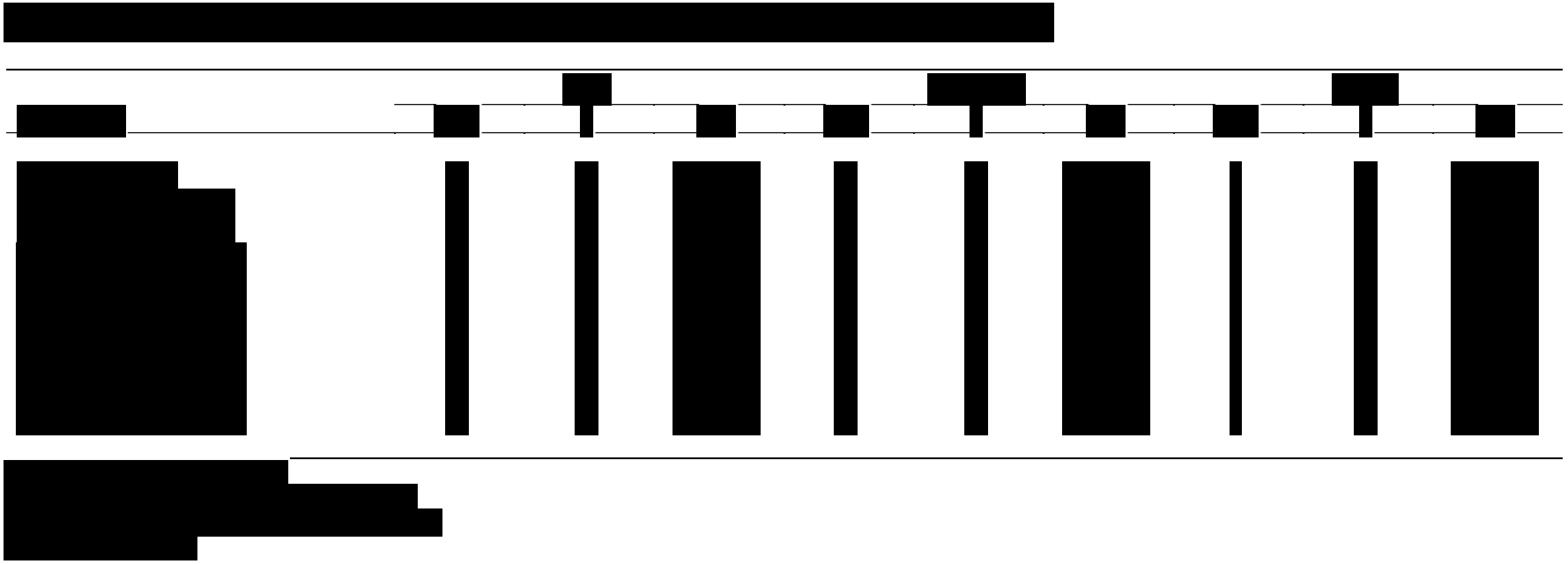

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14.3. PHARMACOKINETIC DATA

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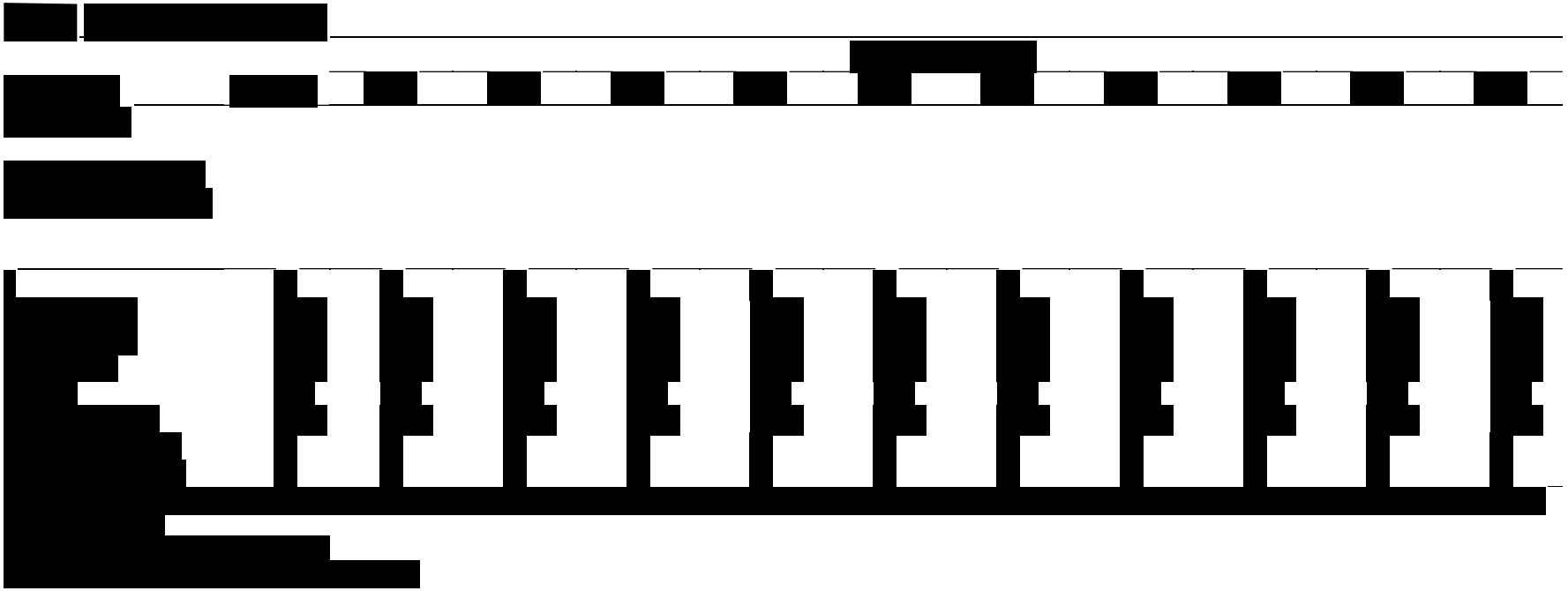

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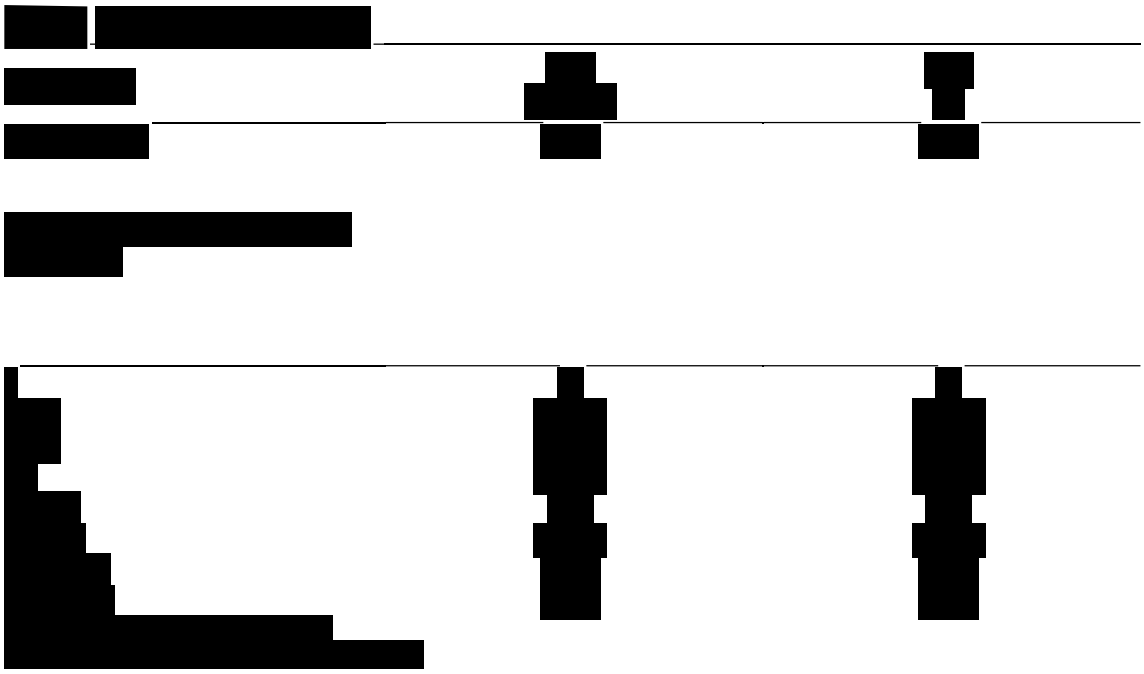

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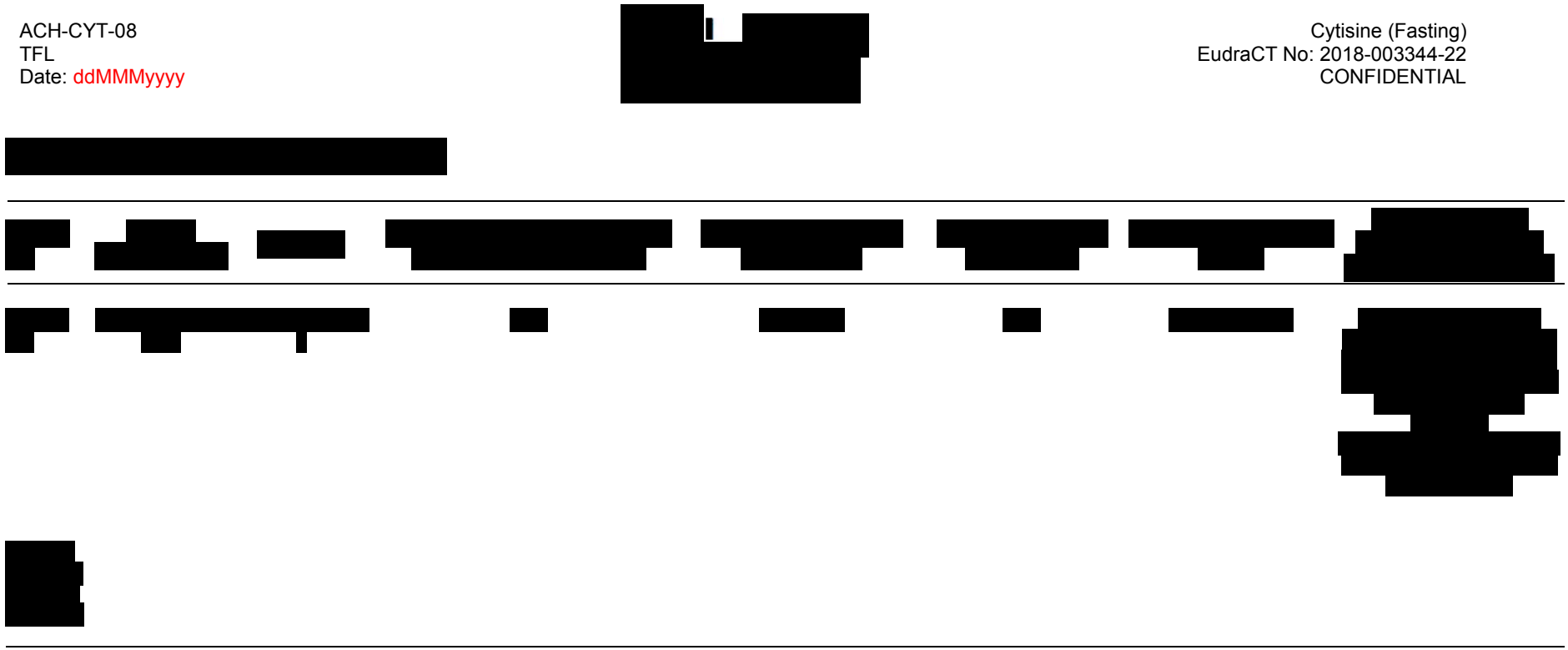

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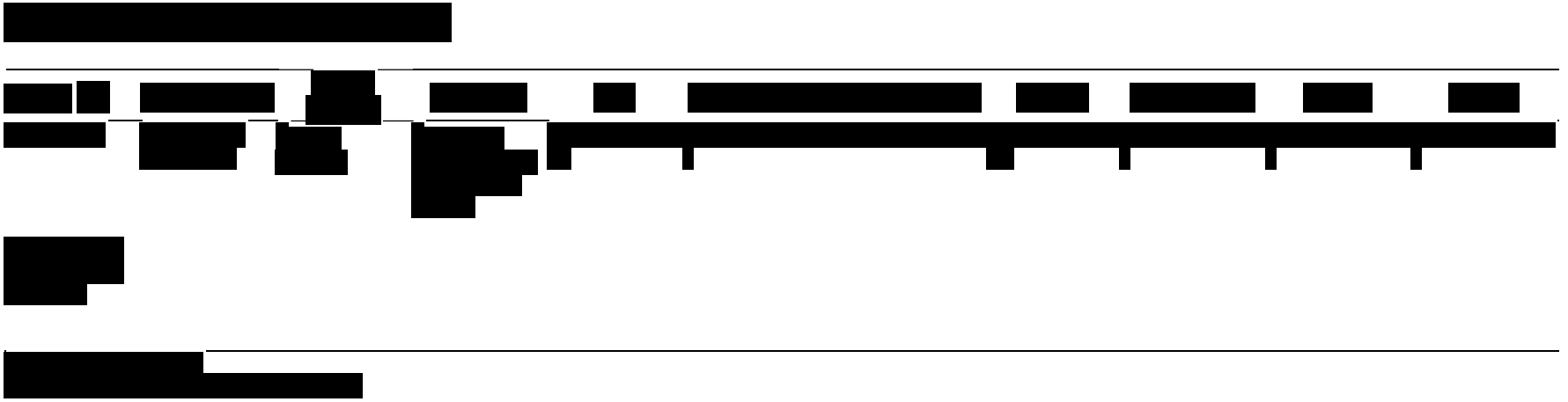

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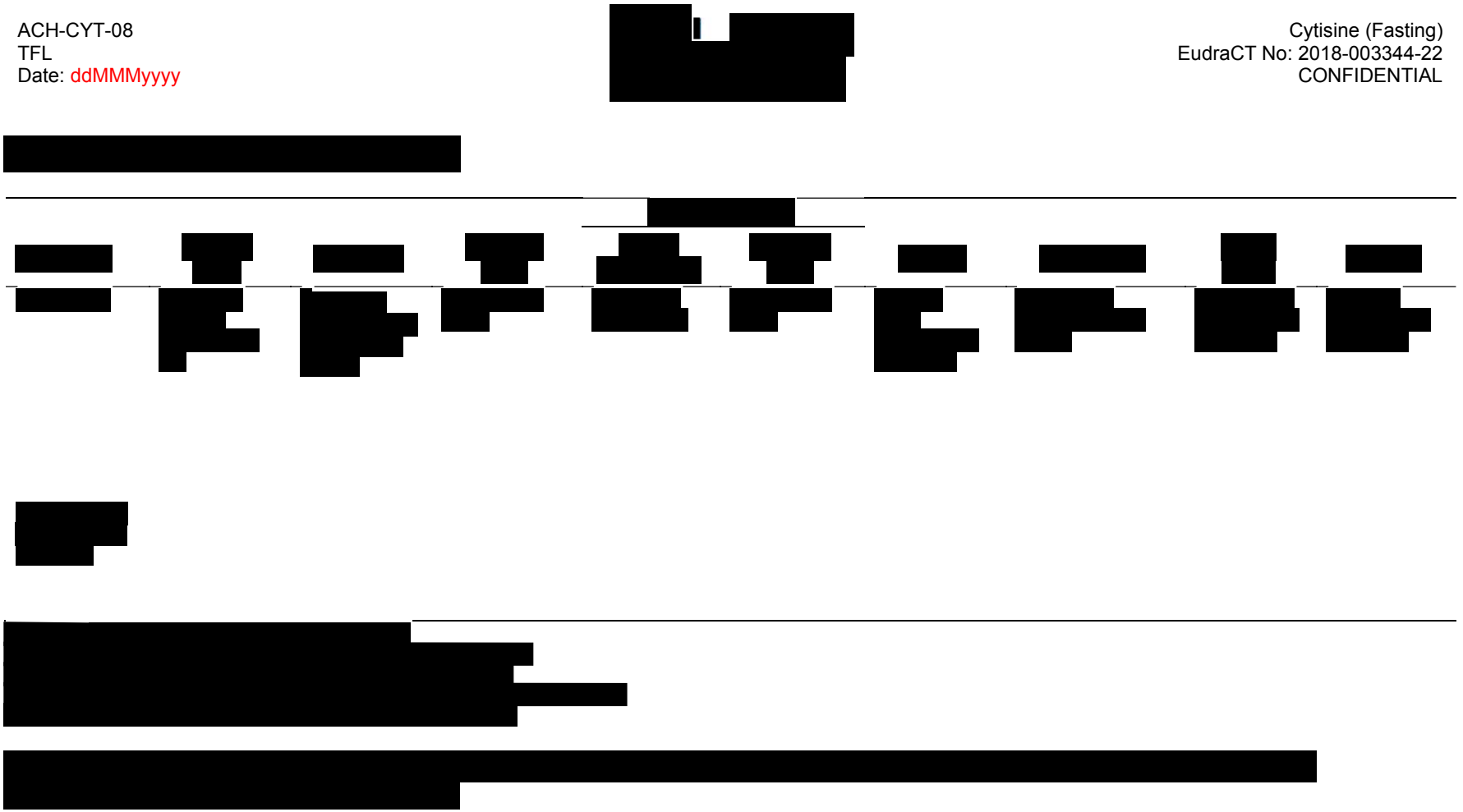

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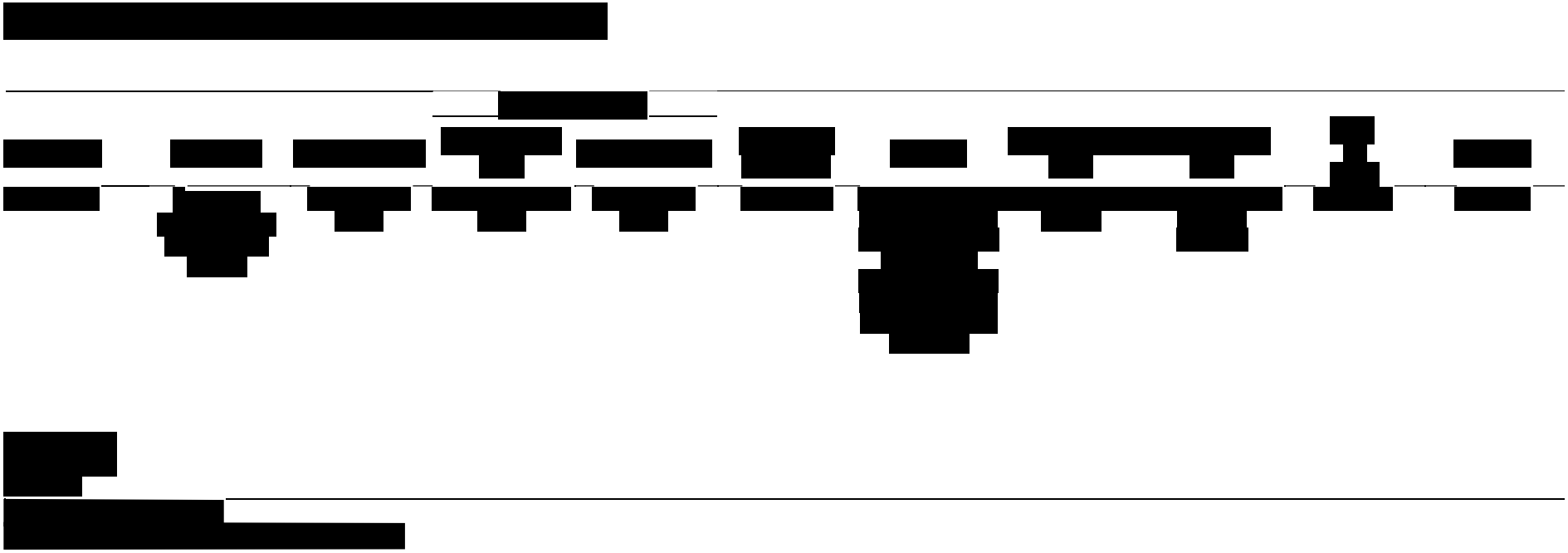

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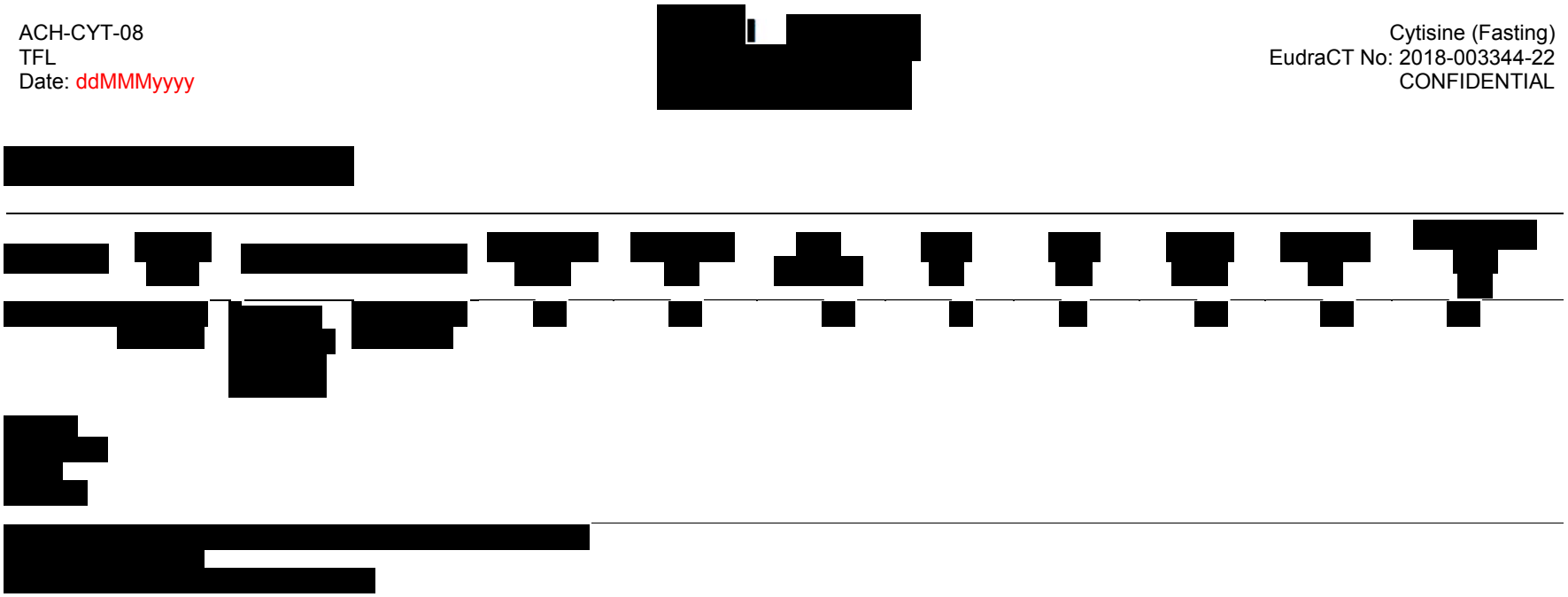

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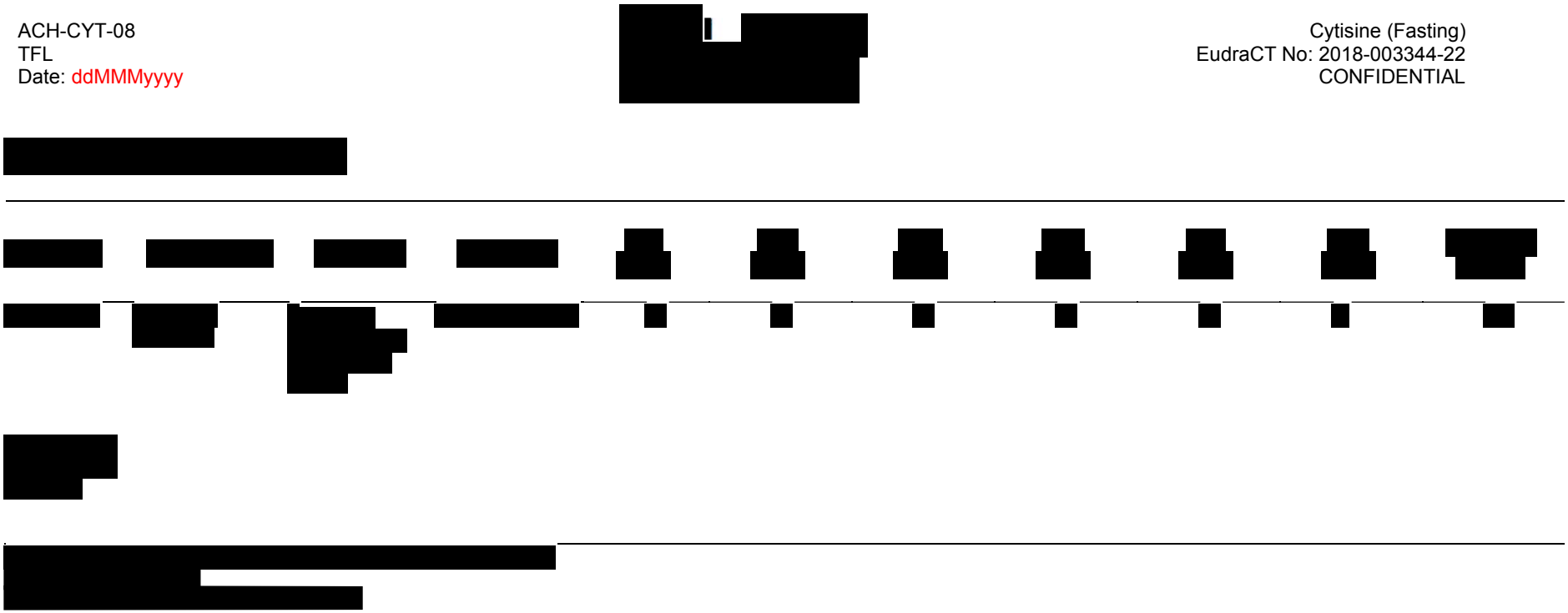

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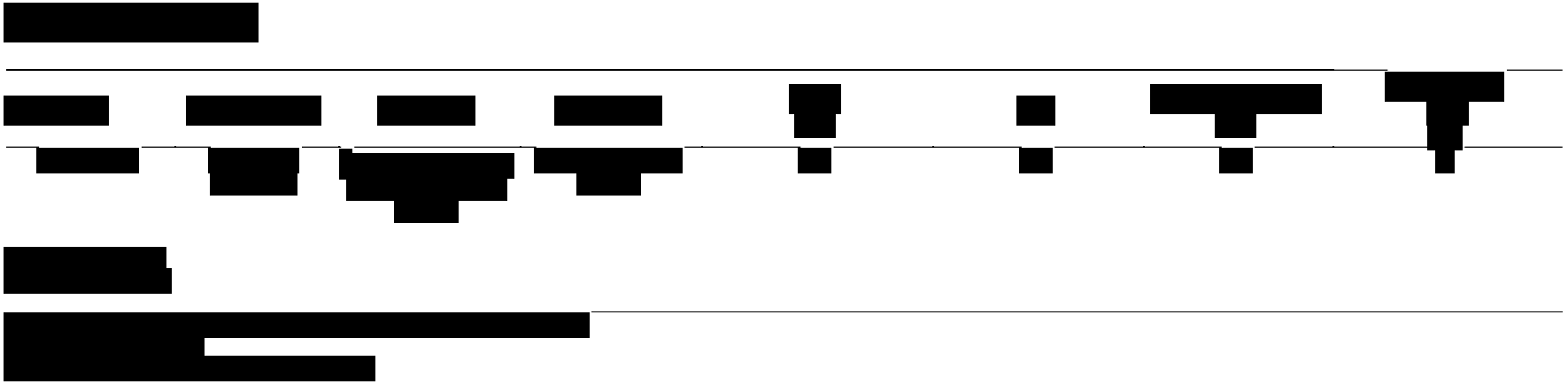

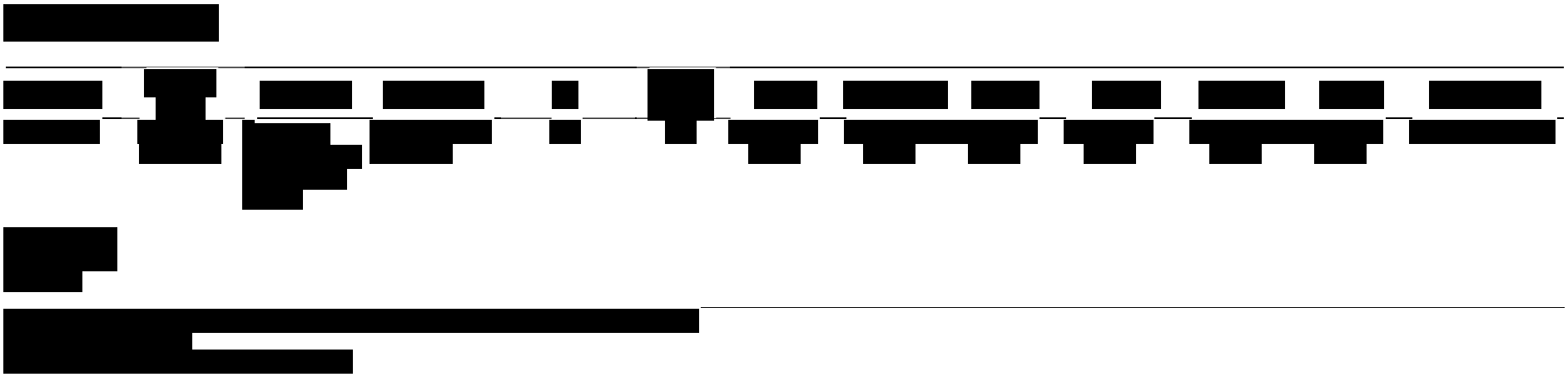

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12. ANNEXES

[1] Data Blind Review Process Minutes – 10OCT2019.

[2] List of Dosed Subjects.

Annex 2: Data Blind Review Process Minute

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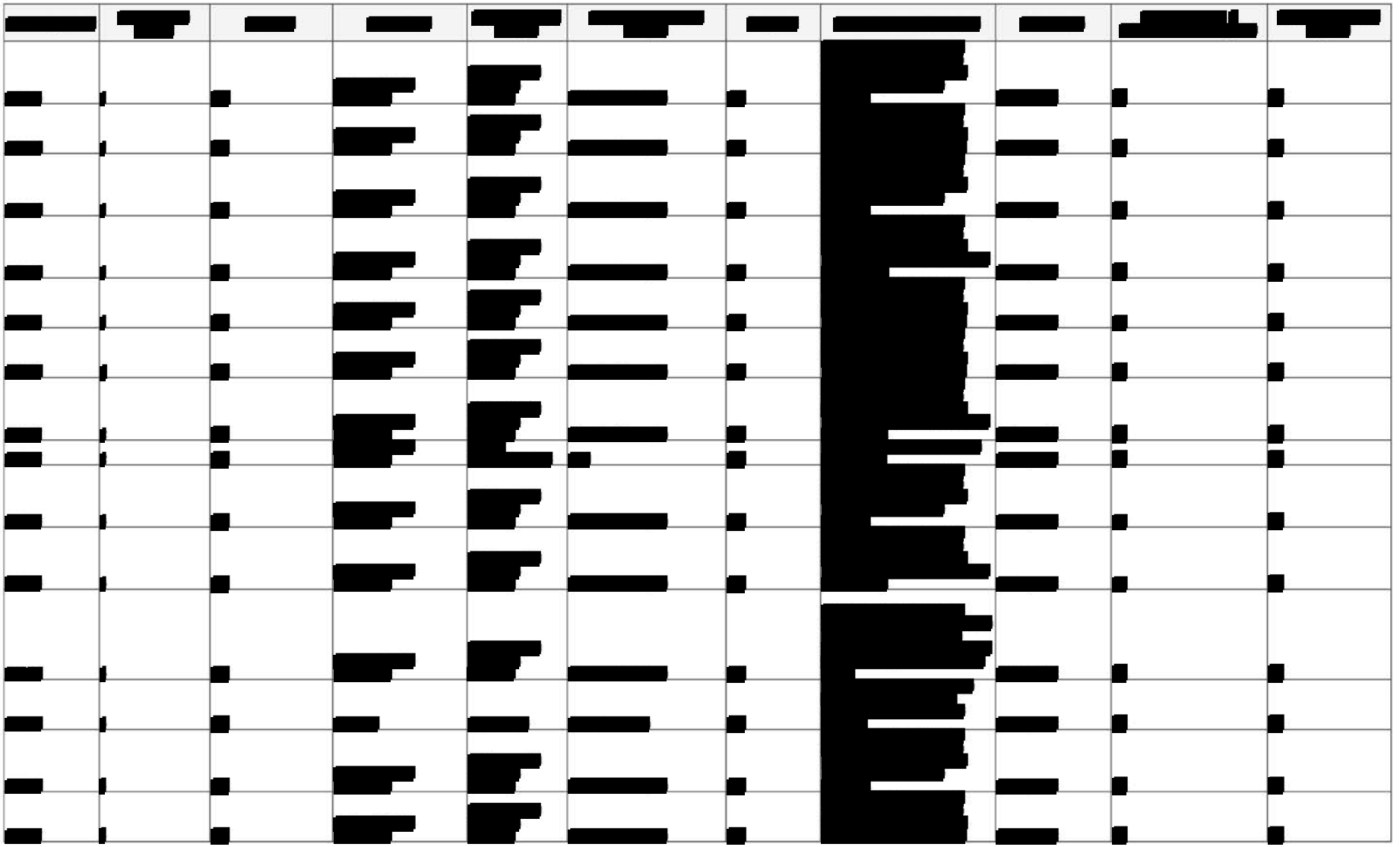

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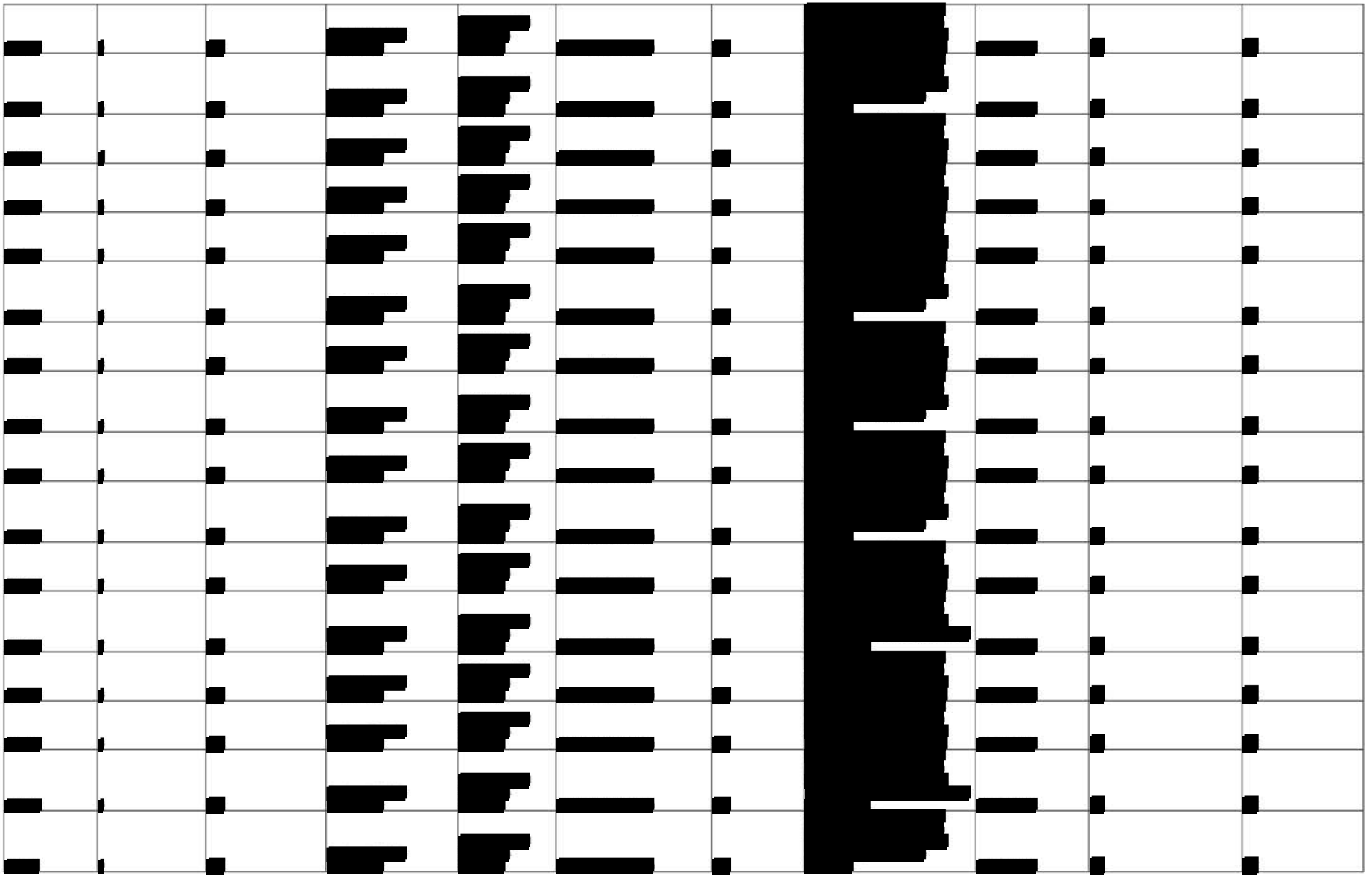

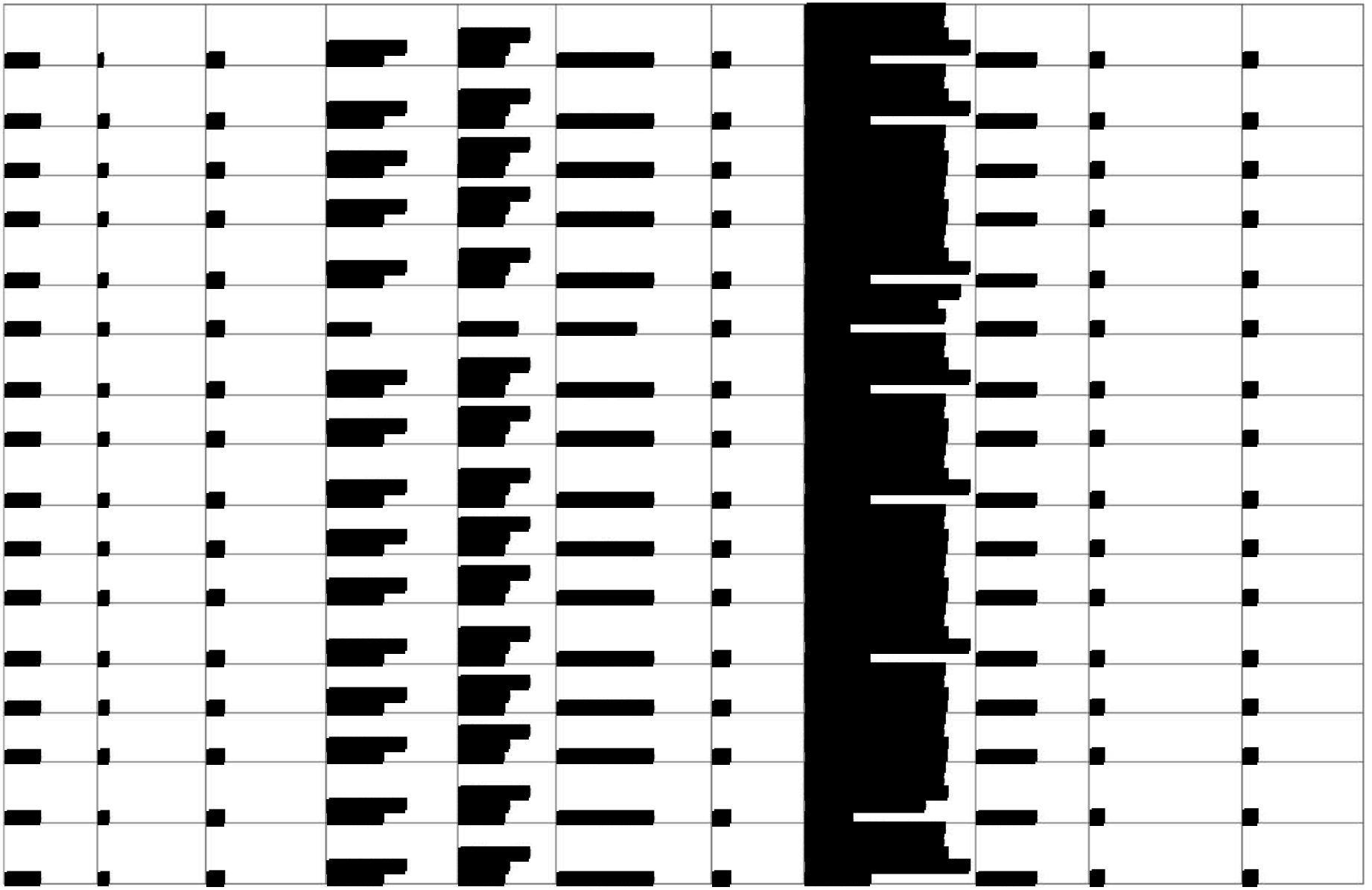

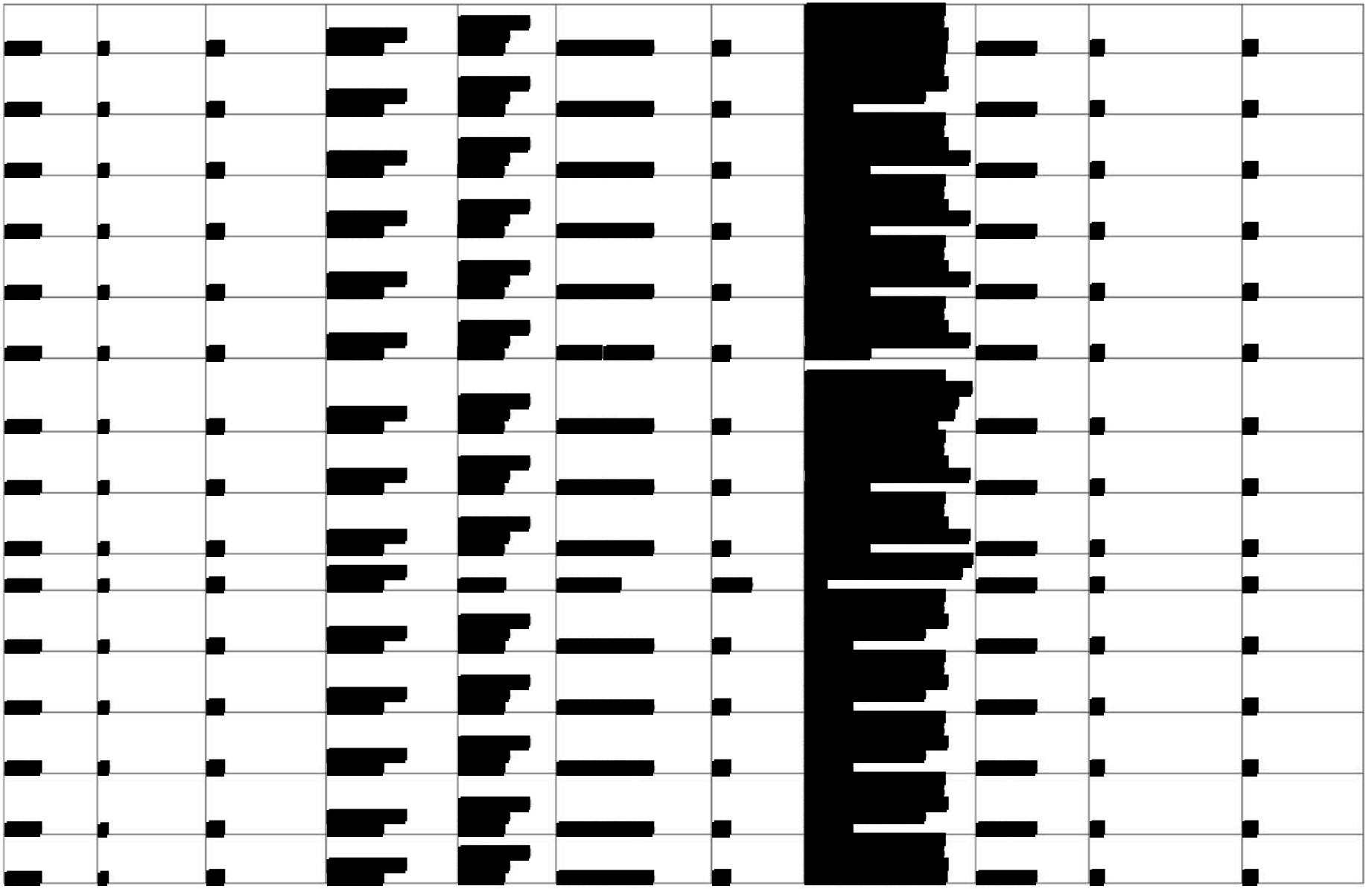

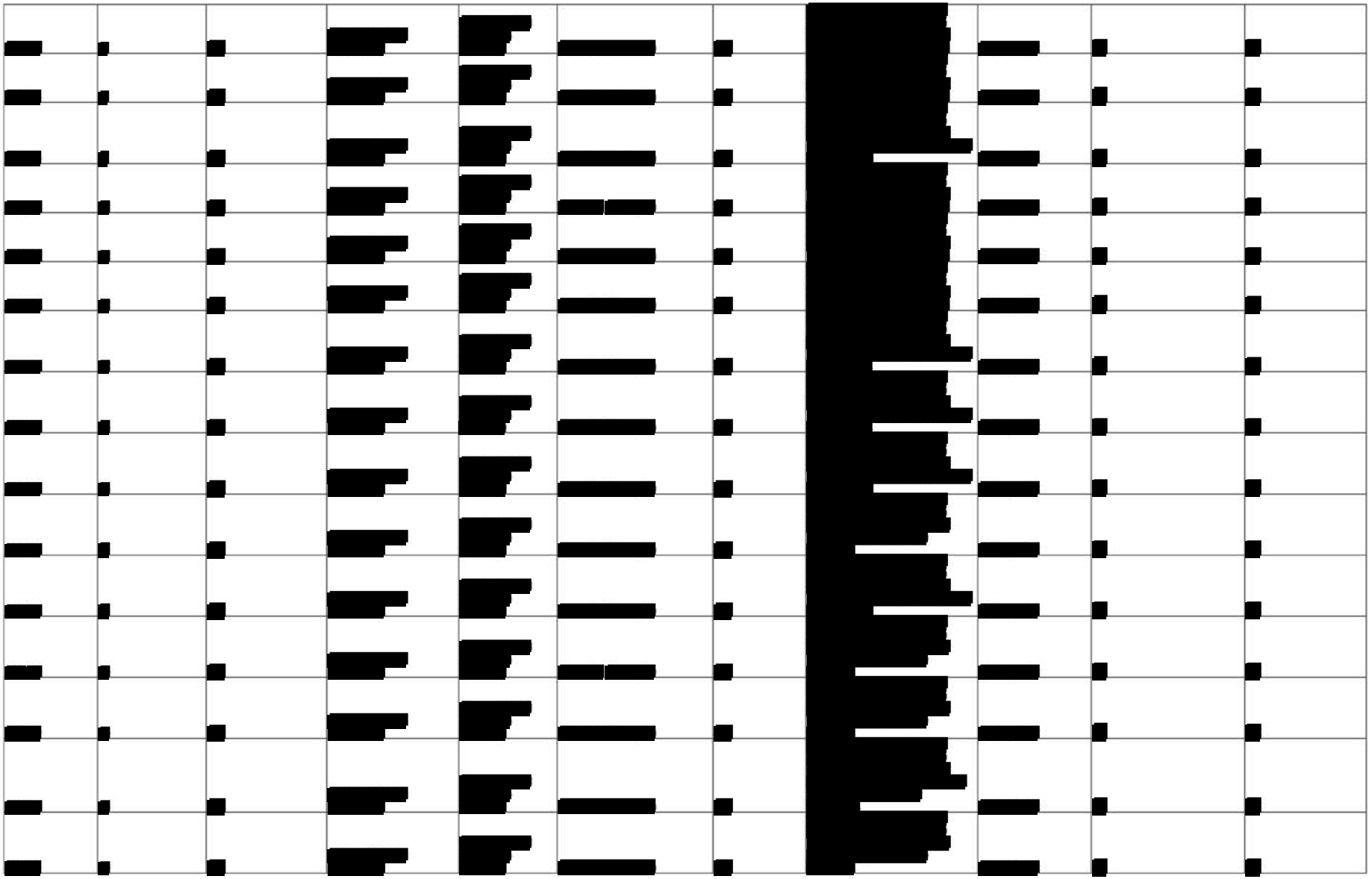

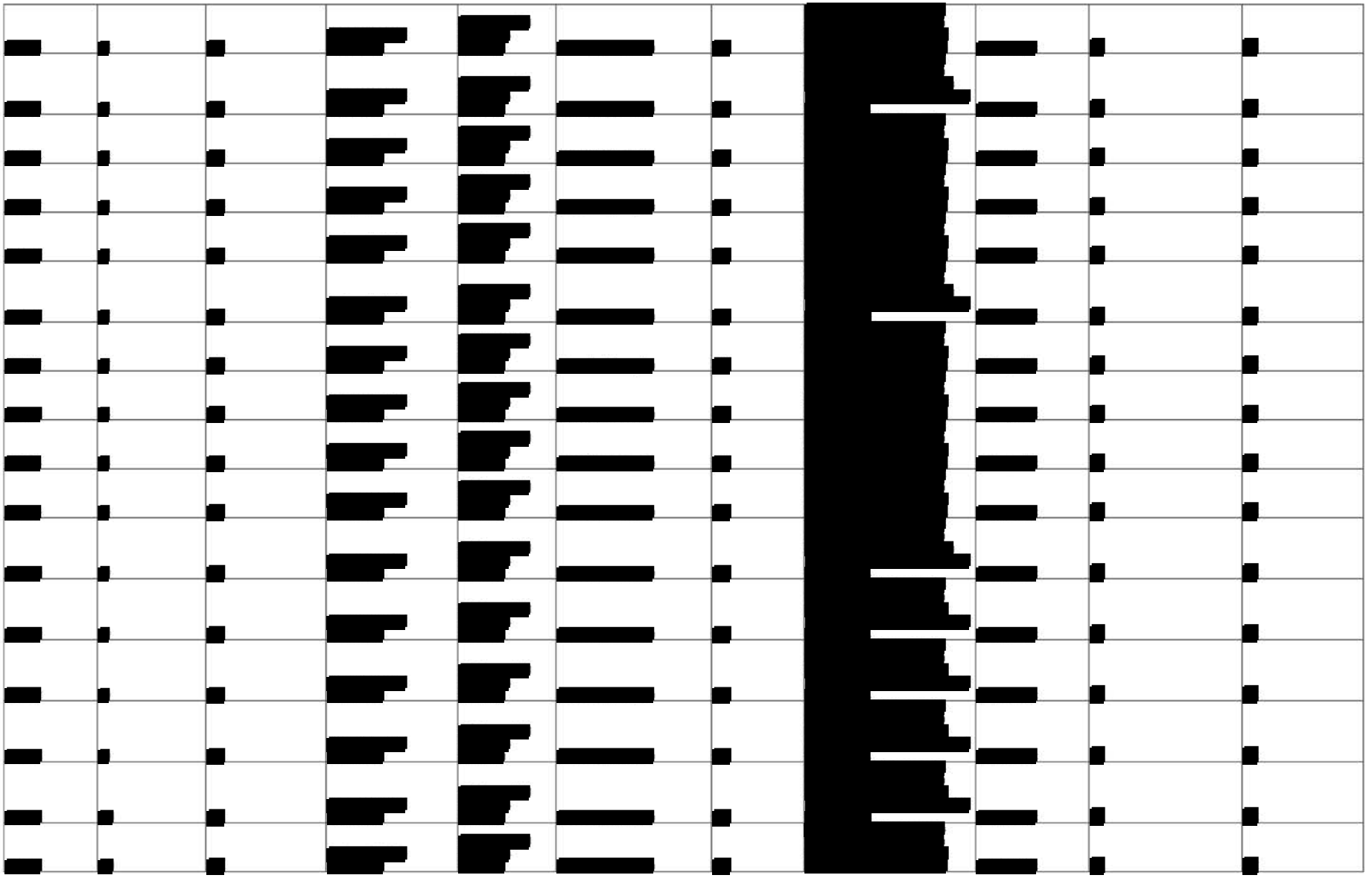

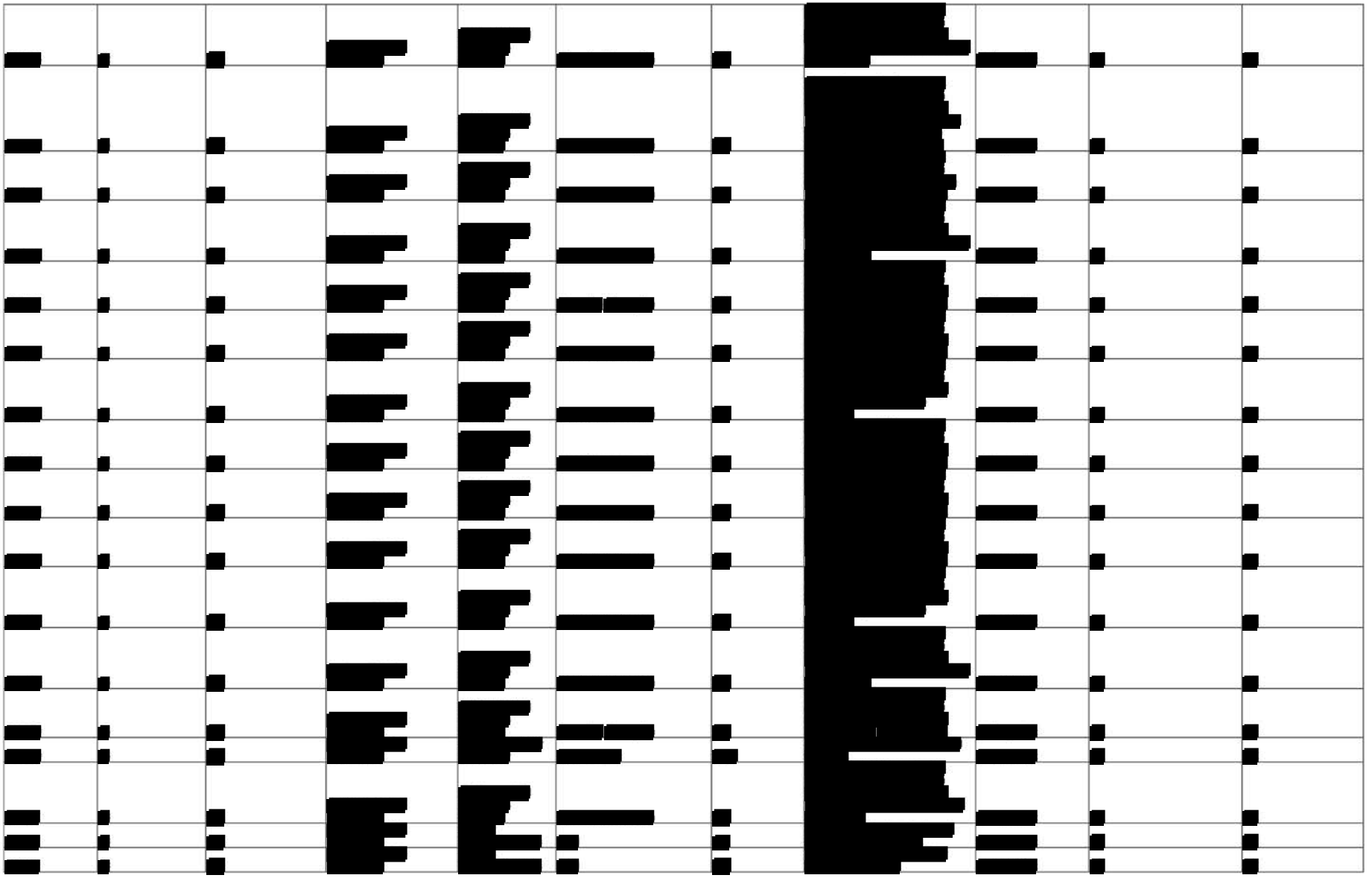

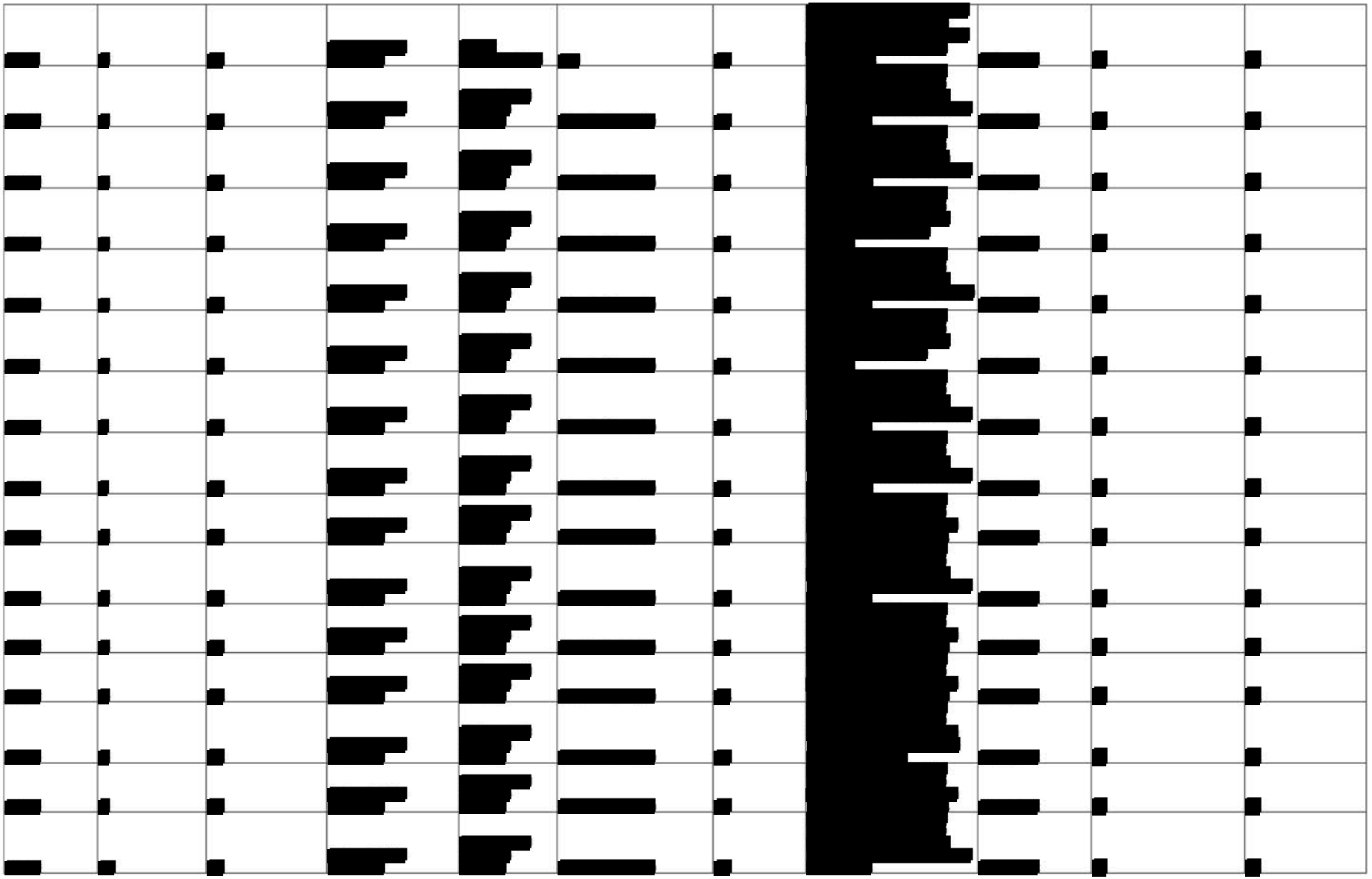

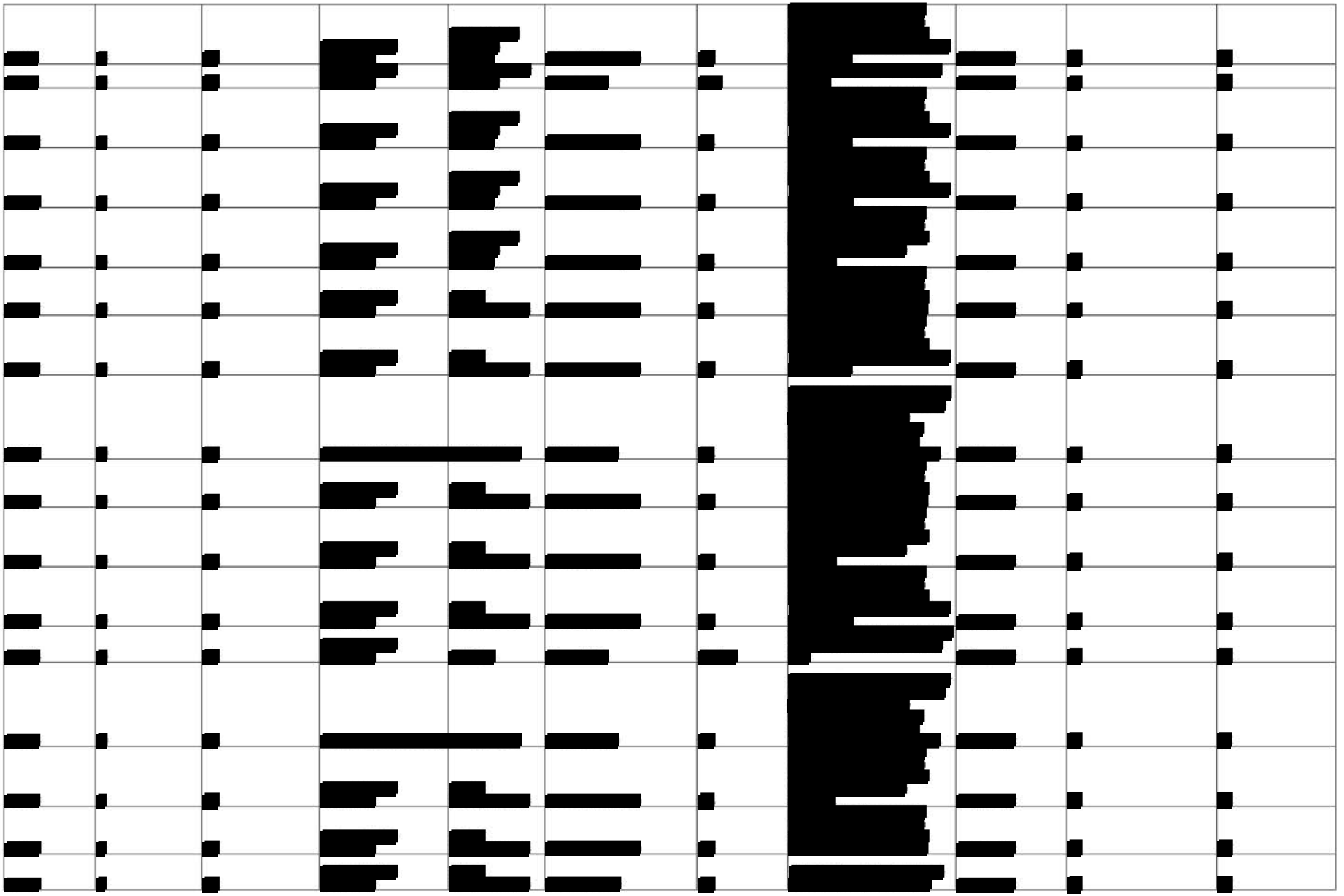

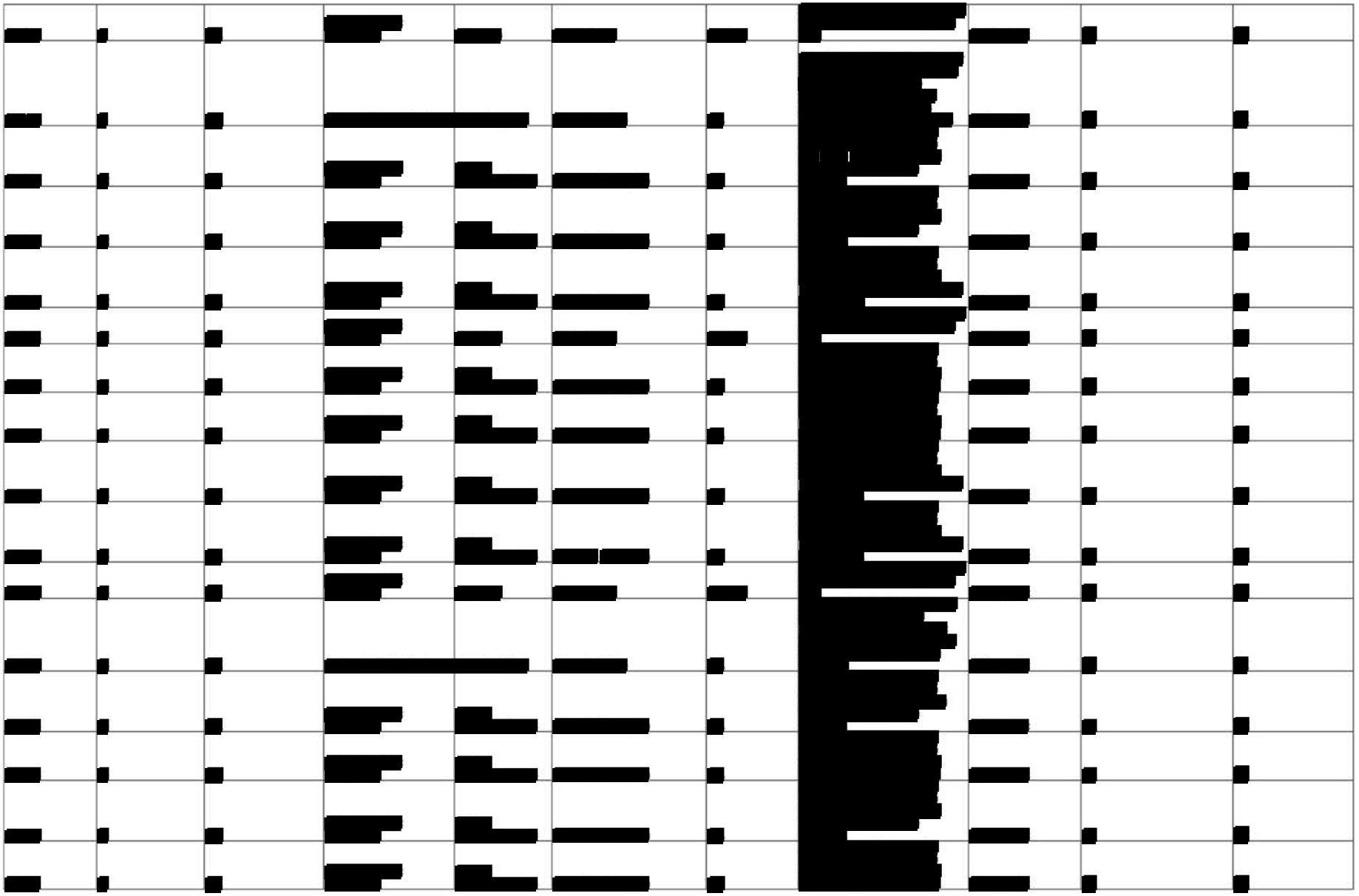

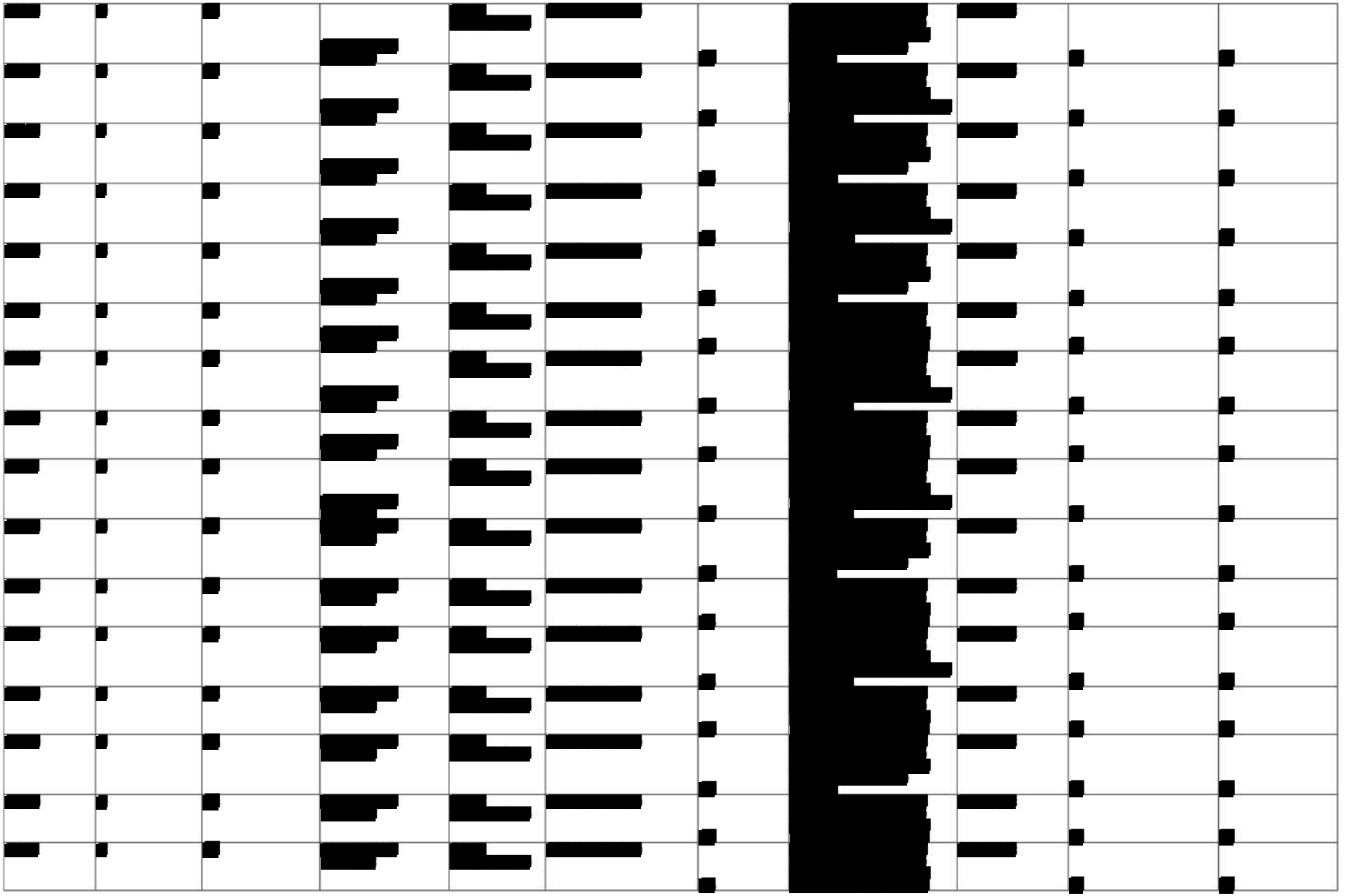

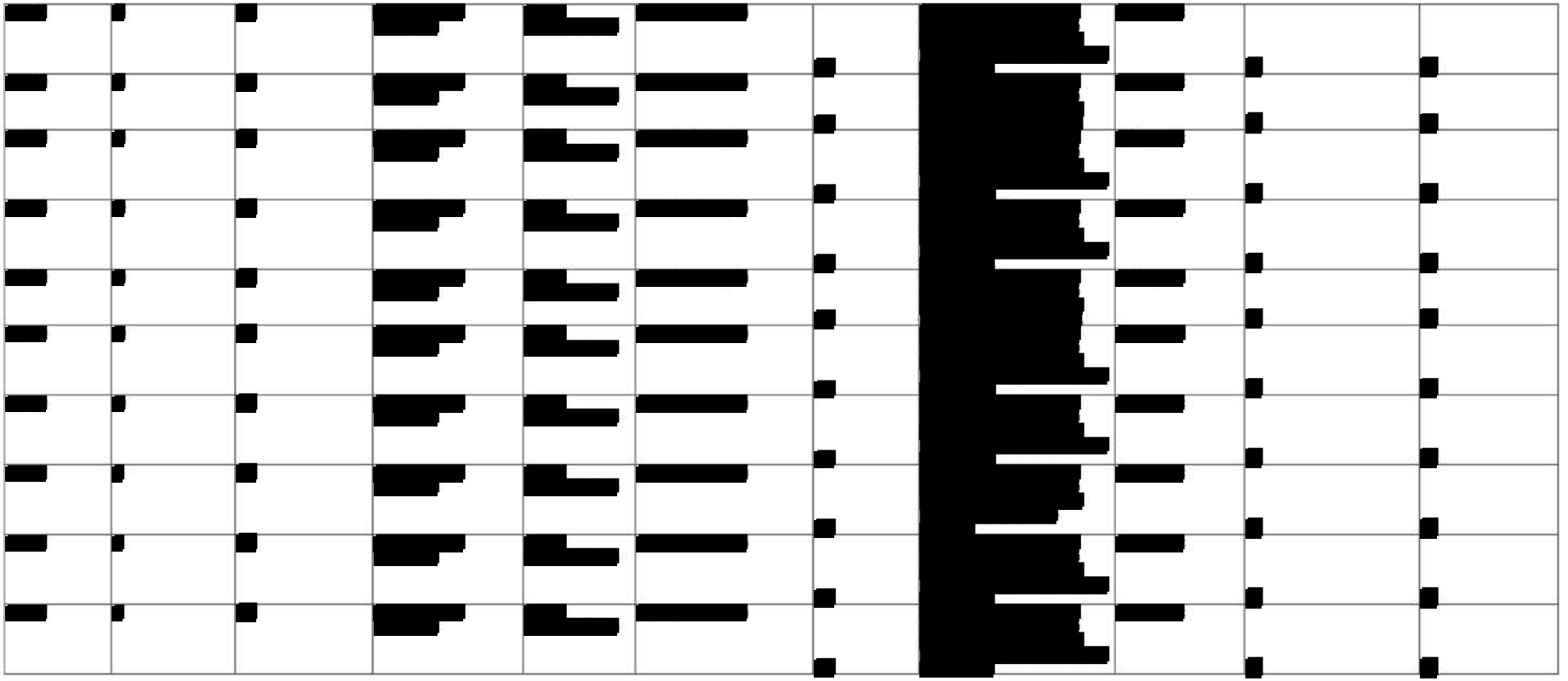

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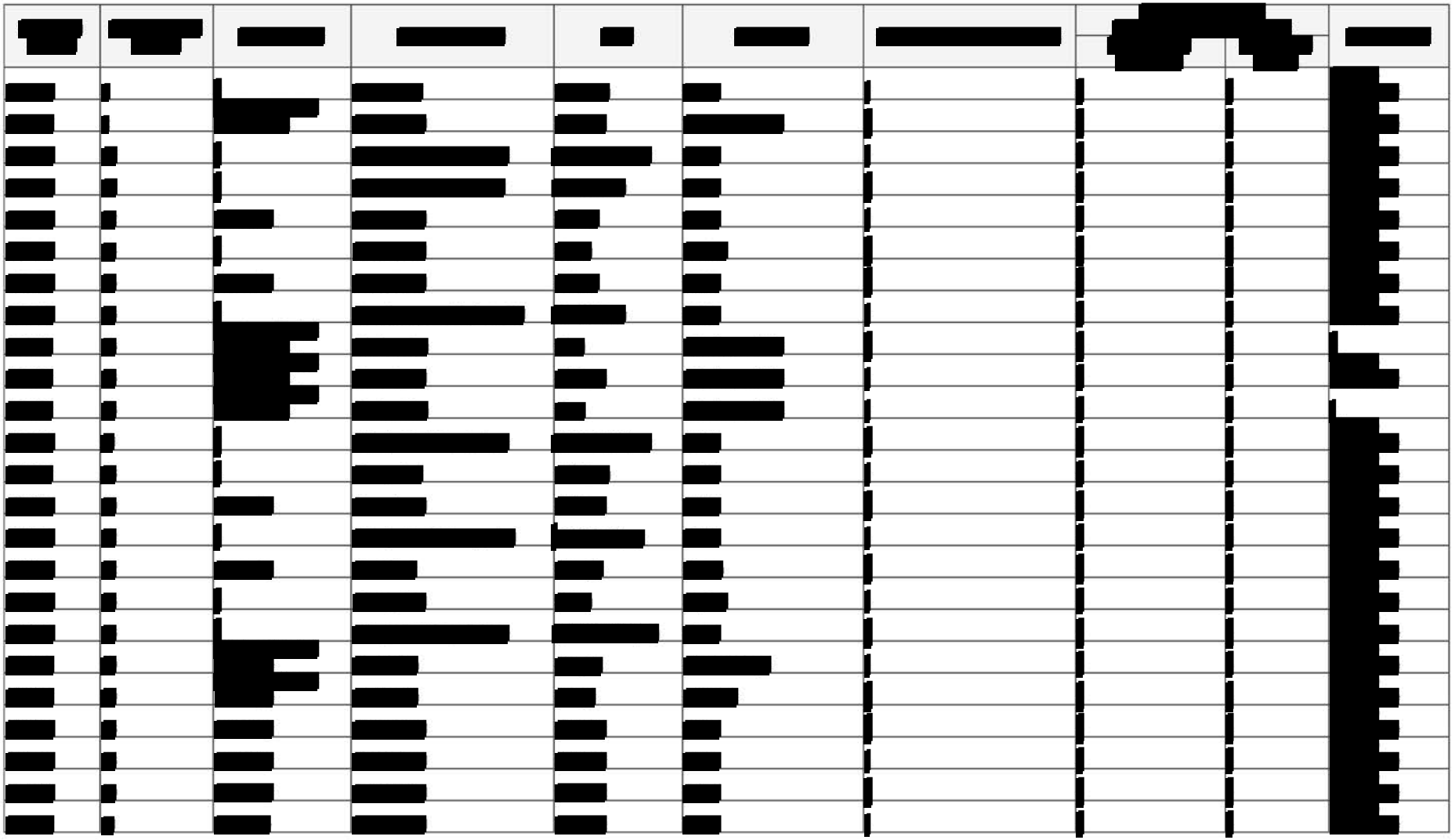

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