



STATISTICAL ANALYSIS PLAN



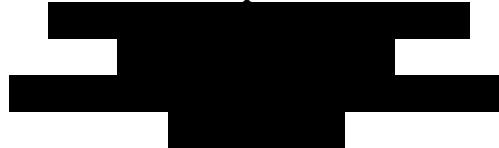
Date: 06-May-2021

A randomized, controlled, single-blinded, within-subject (split-face), multicenter, prospective clinical study to evaluate the effectiveness and safety of using the dermal filler RHA® [REDACTED] injected with a cannula or with a needle for the treatment of moderate to severe nasolabial folds

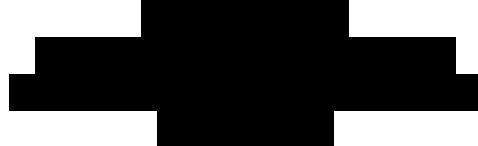
Study Sponsor

TEOXANE SA
Rue de Lyon 105
CH - 1203 Genève, Switzerland
+41 (0) 22.344.96.36

US Sponsor



Clinical Research Organization



Confidentiality Statement

The information contained in this document is provided in confidence. It is understood that this information will not be disclosed to others without prior agreement with the Sponsor.



SAP APPROVAL SIGNATURE PAGE

The following individuals approve this version of the [REDACTED] Statistical Analysis Plan.

Sponsor – TEOXANE SA:

[REDACTED], Clinical Program Manager DATE

Clinical Research Organization - [REDACTED]

[REDACTED] DATE

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1. INTRODUCTION

This statistical analysis plan (SAP) gives a comprehensive and detailed description of statistical techniques to be used for [REDACTED]. The purpose of this SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches for the analysis of study data prior to database lock. This SAP provides additional details concerning the statistical analyses outlined in the protocol. Whenever differences exist in descriptions or explanations provided in the protocol and SAP, the SAP prevails.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association and the Royal Statistical Society, for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc analyses not identified in this SAP may be performed to further examine study data. Any post hoc or unplanned analysis performed will be clearly identified as such in the final CSR.

1.1 Background

Hyaluronic acid (HA) is a long-chain, repeated dimer, N-acetyl glucosamine and D-glucuronic acid polymer and is a major component of the extracellular matrix. Due to its natural viscoelastic and hydrogel properties, HA is widely used as matrix in tissue regeneration and particularly in dermal defect reconstruction.

RHA® [REDACTED] dermal filler is a device containing colorless, biodegradable, sterile, biocompatible, crosslinked HA of non-animal origin (i.e., bacterial fermentation using *Streptococcus zooepidemicus*). Crosslinking is performed using 1,4-butanediol diglycidyl ether (BDDE) to form a gel. RHA® [REDACTED] contains 0.3% w/w of lidocaine hydrochloride, a drug substance widely used for its anesthetic properties (i.e., it blocks the origin and transmission of nervous influx at the point of injection by stabilizing the neuronal membrane).

[REDACTED]

[REDACTED]

1.2 Rationale for Study

[REDACTED]

[REDACTED]

1.3 Hypothesis

RHA® [REDACTED] injected in NLFs with a small cannula is non-inferior to RHA® [REDACTED] injected in the NLFs with a needle for the correction of moderate to severe NLFs as determined by the NLF-WSRS (validated NLF Wrinkle Severity Rating Scale) at [REDACTED] from last treatment.

A change from Baseline in the NLF-WSRS of ≥ 1 -grade will be considered clinically meaningful, and the non-inferiority margin for change in NLF-WSRS between needle and cannula will be 0.5 grade. The formal hypothesis set to be tested is as follows:

$$H_0: \mu_{\Delta(\text{needle} - \text{cannula})} \geq 0.5$$

$$H_a: \mu_{\Delta(\text{needle} - \text{cannula})} < 0.5$$

where $\mu_{\Delta(\text{needle} - \text{cannula})}$ represents the mean difference in change from Baseline between needle and cannula.

1.4 Study Objectives

The study is designed to achieve the following objectives:

1. Demonstrate the non-inferiority of RHA[®] [REDACTED] injected in the NLFs with a cannula versus the control (RHA[®] [REDACTED] injected in NLF with a needle) [REDACTED] from last treatment for the correction of moderate to severe NLFs. Assessment of non-inferiority will be based on the change from Baseline in NLF-WSRS [REDACTED] as rated by the Blinded Live Evaluator (BLE) at each investigative site.
2. Evaluate the safety of RHA[®] [REDACTED] injected in NLF with a cannula versus the control up to [REDACTED] from last treatment.

2. OVERVIEW OF STUDY DESIGN

2.1 Study Design

This is a randomized, controlled, single-blinded, within-subject (split-face), multicenter, prospective study to investigate whether RHA[®] [REDACTED] injected in NLFs with a small cannula [REDACTED] [REDACTED] is non-inferior to RHA[®] [REDACTED] injected in NLFs with a needle [REDACTED] for the correction of moderate to severe NLFs as determined by the Blinded Live Evaluator (BLE) using the NLF-WSRS (validated NLF Wrinkle Severity Rating Scale) [REDACTED] following last [REDACTED].

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2.2 Study Design Rationale

2.2.1 Study Population

[REDACTED]

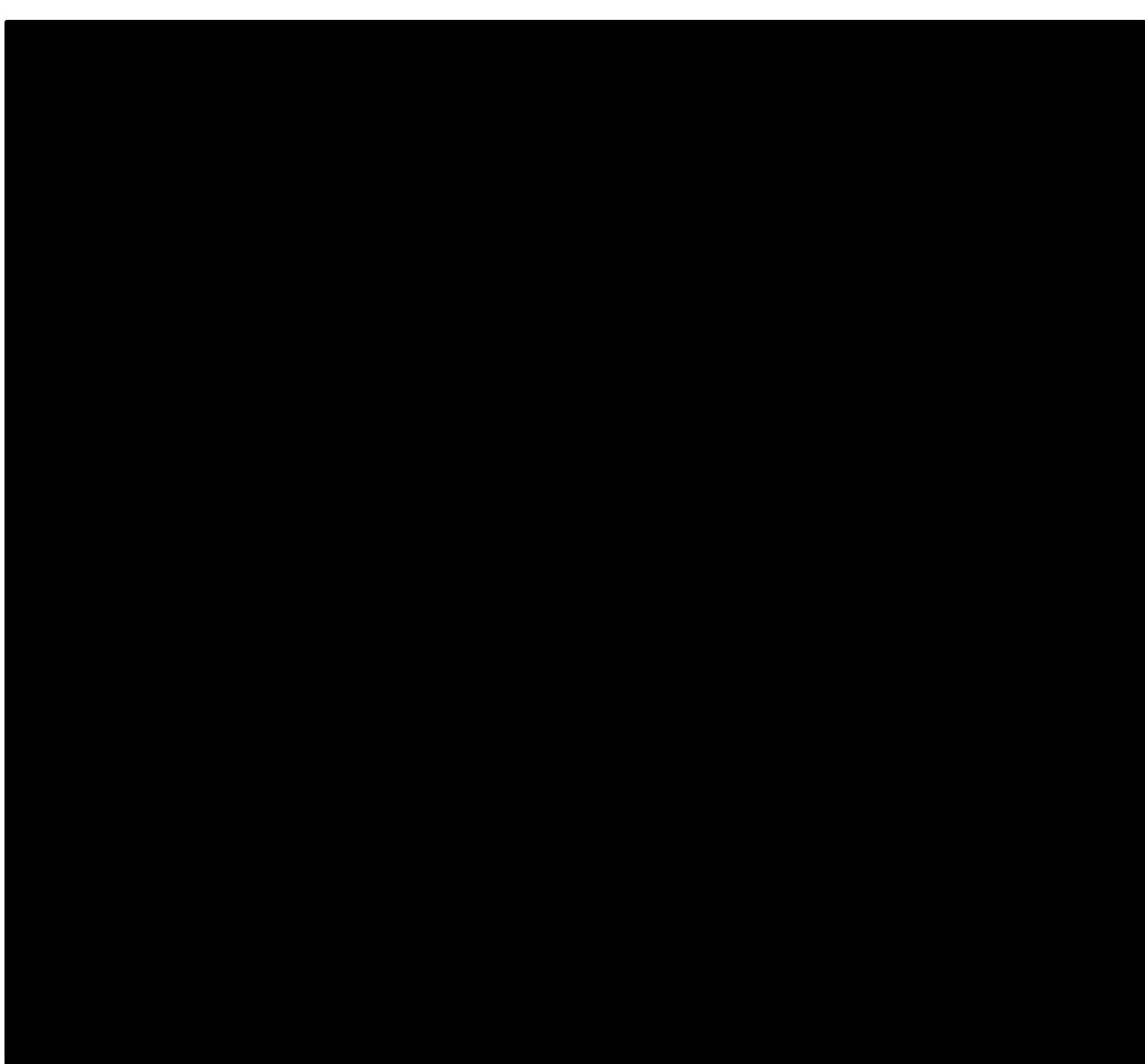
2.2.2 Primary Endpoint

The primary effectiveness endpoint will be aesthetic improvement from pre-injection as assessed by the NLF-WSRS (BLE) at [REDACTED] following last treatment (initial or touch-up). The primary hypothesis is that RHA® [REDACTED] used in conjunction with cannula is non-inferior to RHA® [REDACTED] with needle. An NLF-WSRS change from Baseline of ≥ 1 -grade will be considered clinically significant. [REDACTED]

[REDACTED]

For more information, contact the Office of the Vice President for Research and Economic Development at 319-273-2500 or research@uiowa.edu.

A 16x16 grid of black and white pixels. The top 15 rows are mostly black with scattered white blocks. The bottom row is mostly white with scattered black blocks. The grid is divided into four quadrants by thick black lines. The top-left quadrant has a large black block in the top-left corner. The top-right quadrant has a large black block in the top-right corner. The bottom-left quadrant has a large white block in the bottom-left corner. The bottom-right quadrant has a large black block in the bottom-right corner. The center of the grid is mostly white with a few black blocks. The grid is set against a light blue background.



3. TREATMENT ALLOCATION, RANDOMIZATION AND BLINDING

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4. DEVICE ADMINISTRATION

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.1 Injection of Study Devices

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

A large black rectangular redaction box covers the majority of the page content, starting below the header and ending above the footer. The redaction is irregular, with some white space visible at the top and bottom edges.

5. STUDY EVALUATIONS

5.1 Effectiveness Variables

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[REDACTED]

[REDACTED]

[REDACTED]
IE
[REDACTED]

[REDACTED]

[REDACTED]

5.2 Safety

[REDACTED]

5.2.1 Adverse Events

The Treating Investigator will assess AEs

[REDACTED]

5.2.2 Patient Common Treatment Response Diary

The study coordinator will provide subjects with instructions for daily recording of his/her observations of the CTRs of the study treatments into an electronic diary for the first 4 weeks after each treatment. The diary will be activated after treatment and will be discussed during the 3-day post-injection telephone follow-up.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

A bar chart illustrating the distribution of a variable across 15 categories. The y-axis is labeled "Category" and the x-axis is labeled "Value". The bars are black with thin white outlines. The distribution is highly right-skewed, with the highest value (category 15) being significantly larger than the others.

Category	Value
1	10
2	12
3	15
4	20
5	25
6	30
7	35
8	40
9	45
10	50
11	55
12	60
13	65
14	70
15	150

6. STATISTICAL METHODS

6.1 Analysis Populations

A horizontal bar chart consisting of five black bars with white outlines. The bars are positioned in a sequence from left to right, with heights increasing in a non-linear fashion. The first bar is the shortest, followed by a medium bar, a tall bar, a medium bar, and the longest bar on the far right.

6.2 Primary Effectiveness Endpoint

The primary endpoint of NLF-WSRS change from Baseline █ as rated by the BLE will be analyzed in a non-inferiority statistical model using the PP population with a 0.5 margin for the difference between cannula and needle. A sensitivity analysis will be done using the ITT population. Expressing the difference between treatment groups as the mean of change from Baseline in RHA®█ injected with needle minus change from Baseline in RHA®█ injected with cannula, the one-sided 97.5% confidence limit must be < 0.5 to conclude non-inferiority. A paired t-test will be used to calculate the confidence interval to account for dependence. The formal hypothesis set to be tested is:

$$H_0: \mu_{\Delta(\text{needle} - \text{cannula})} \geq 0.5$$

$$H_a: \mu_{\Delta(\text{needle} - \text{cannula})} < 0.5$$

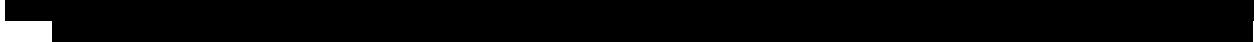
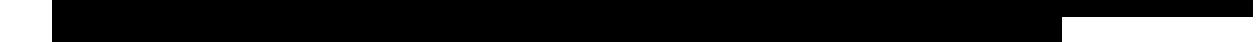
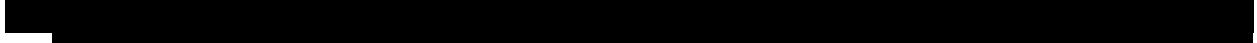
where $\mu_{\Delta(\text{needle} - \text{cannula})}$ represents the mean difference in change from Baseline between needle and cannula.

6.3 Secondary Effectiveness Endpoints

All statistical inference tests will be performed at the same significance level (α) of 0.05. For categorical and continuous variables, the two groups will be compared using two-sided parametric or non-parametric tests for paired data, as appropriate. For continuous variables, the Shapiro-Wilk test will be used to assess normality. If data are normally distributed, testing will be conducted using the Student t-test, while testing will be conducted with the Wilcoxon signed-rank test if not normally distributed.

6.4 Safety Endpoints

The SAFT Population will be used to summarize the safety of the study devices and will consist of all treated subjects. The primary safety analysis is the calculation of the incidence of CTRs and adverse events in the study period. Point estimates for all CTRs, AEs and SAEs will be presented and two-sided exact 95% confidence intervals will be calculated for the overall incidence of AEs and SAEs. Tables will be generated which summarize AEs by investigator assessments of both relationship to treatment and severity.



6.4.1 Safety (SAFT) Population

[REDACTED]

6.5 Sample Size Considerations

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6.6 General Considerations

Data will be listed by treatment group and subject number. Safety and efficacy data will be summarized by treatment group. Descriptive statistics will consist of mean, standard deviation, median, minimum/maximum for **continuous variables** (quantitative), and frequency and percent for **discrete variables** (qualitative), and 95% CIs will be provided for select data. Missing values will be presented for all variables.

All programs for data output and analyses will be written in SAS version 9.4 or higher (SAS Institute, Inc., Cary, NC).

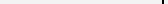
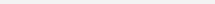
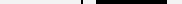
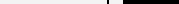
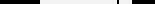
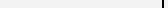
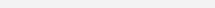
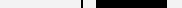
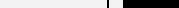
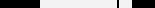
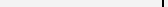
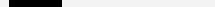
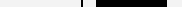
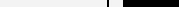
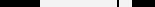
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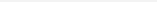
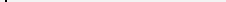
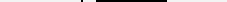
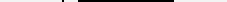
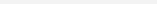
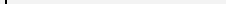
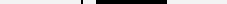
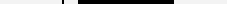


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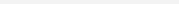
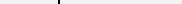
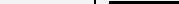
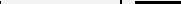
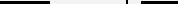
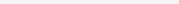
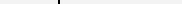
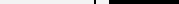
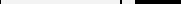
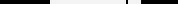
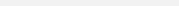
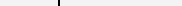
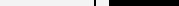
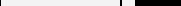
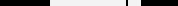
For more information, contact the Office of the Vice President for Research and Economic Development at 319-335-1111 or research@uiowa.edu.

[REDACTED]

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Wilcoxon signed-rank test

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[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] test
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] Wilcoxon signed-rank test
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TEOXANE SA

11. *What is the primary purpose of the following statement?*

11. **What is the primary purpose of the *Journal of Clinical Endocrinology and Metabolism*?**

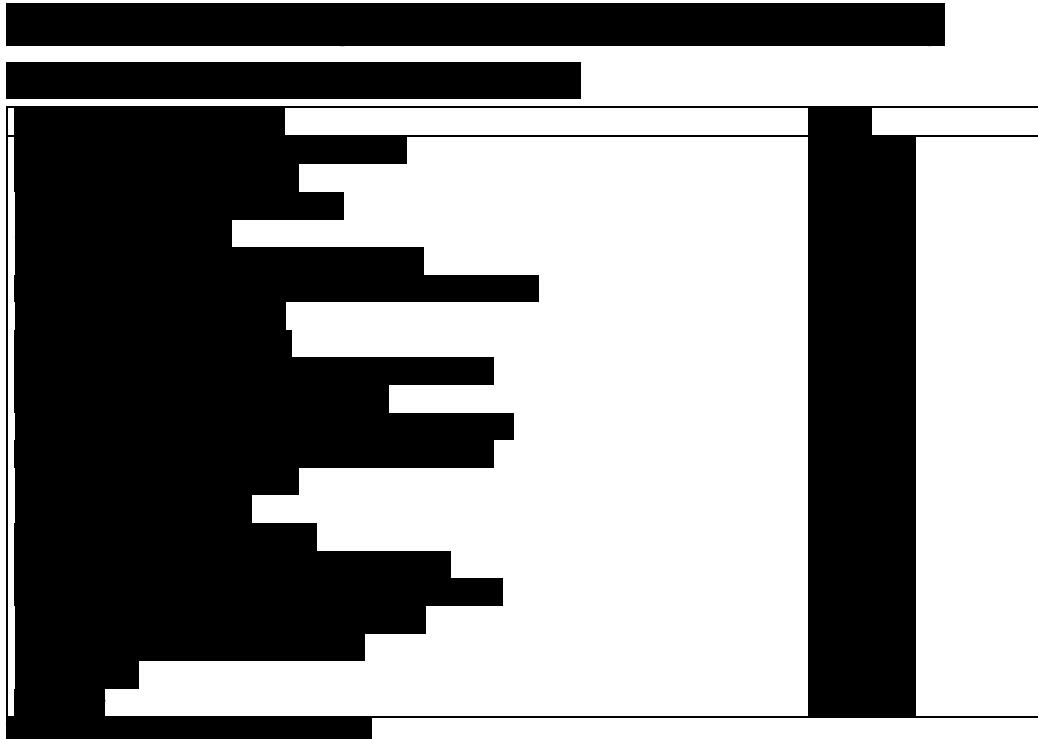
Black rectangular redaction box.

A 7x7 grid of 49 black bars of varying widths and heights, arranged in a pattern that tapers towards the center. The bars are positioned such that they overlap and create a central white space. The widths of the bars range from 1 to 7 pixels, and their heights range from 1 to 7 pixels. The bars are placed in a staggered, non-overlapping manner within each row and column, creating a complex geometric pattern.

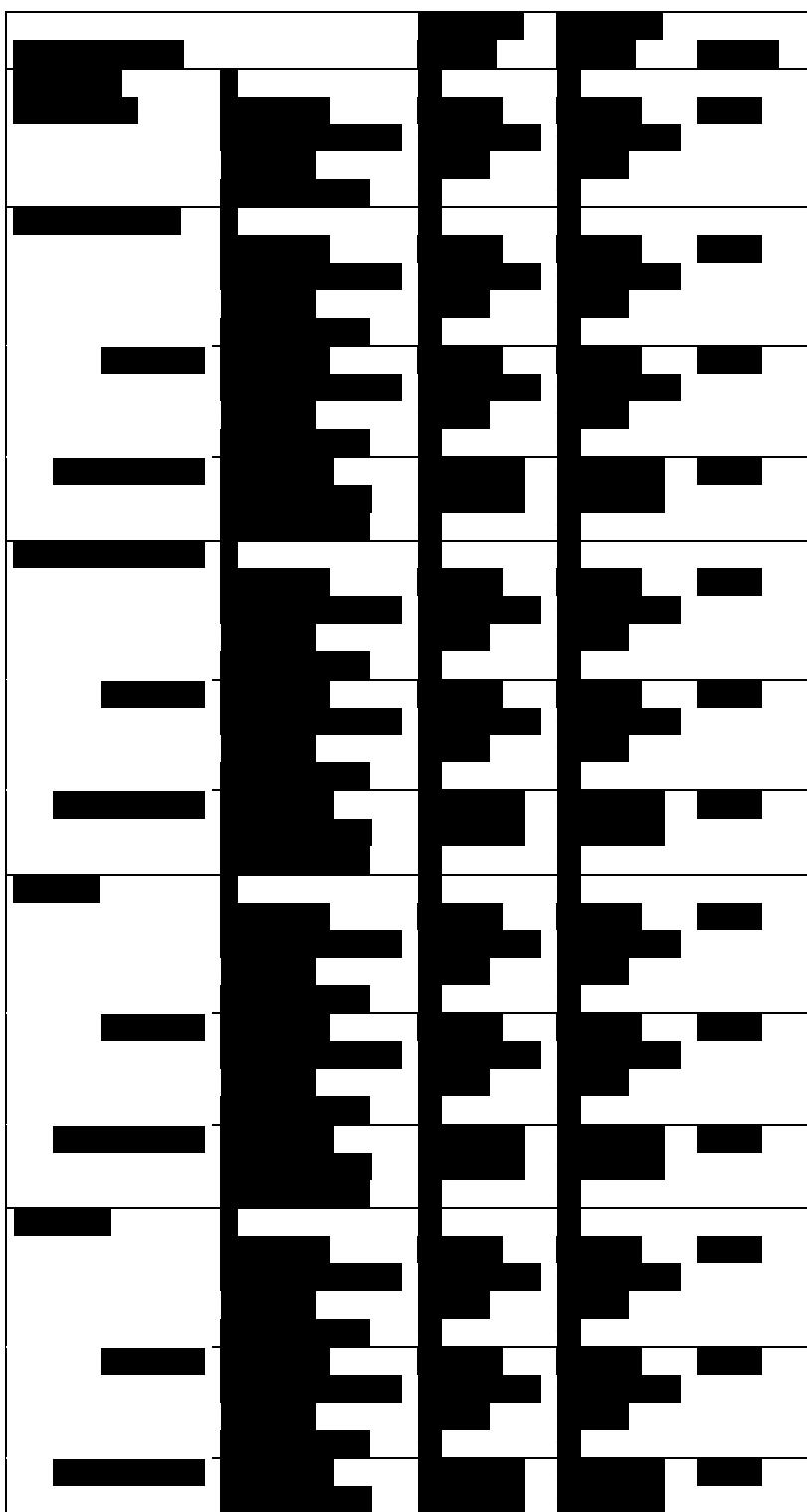
For more information, contact the Office of the Vice President for Research and the Office of the Vice President for Student Affairs.

1. **What is the primary purpose of the study?** (Please check one box)

Topic	Percentage
Healthcare	85%
Technology	78%
Finance	72%
Politics	65%
Entertainment	58%
Science	52%
Food	45%
Sports	38%
Business	32%
Art	25%



A 10x5 grid of black bars representing data points. The bars are arranged in 10 rows and 5 columns. The lengths of the bars vary, with some being very long and others very short. The grid is bounded by a thin black border.



A 6x5 grid of black bars on a white background, representing a sparse matrix. The bars are of varying lengths and are positioned in a non-overlapping manner. The grid is composed of six horizontal rows and five vertical columns. The bars are located at the intersections of the grid lines, with some cells containing multiple bars. The lengths of the bars vary, with some being very short and others being relatively long. The overall pattern is a sparse distribution of black bars across the grid.

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The figure consists of a 6x6 grid of binary images. Each image is a 2D binary matrix (black and white pixels). The sequence of images shows a pattern of black and white blocks that change over time. In the first five frames, the pattern is a sequence of horizontal black bars of increasing length from left to right, followed by a vertical column of black blocks. In the last frame, a vertical line of black blocks appears in the bottom row. The vertical line of black blocks in the last frame is a key feature for identifying the sequence.

[REDACTED]

[REDACTED]

[REDACTED]

Digitized by srujanika@gmail.com

The figure consists of two identical panels, each containing five groups of horizontal bars. Each group contains 12 bars, representing different categories. The bars are black on the left and white on the right, with a thin black border in the center. The groups are separated by thin black lines, and the entire panel is enclosed in a black frame.

ANSWER

For more information, contact the Office of the Vice President for Research and Economic Development at 515-294-4610 or research@iastate.edu.

For more information, contact the Office of the Vice President for Research and the Office of the Vice President for Student Affairs.

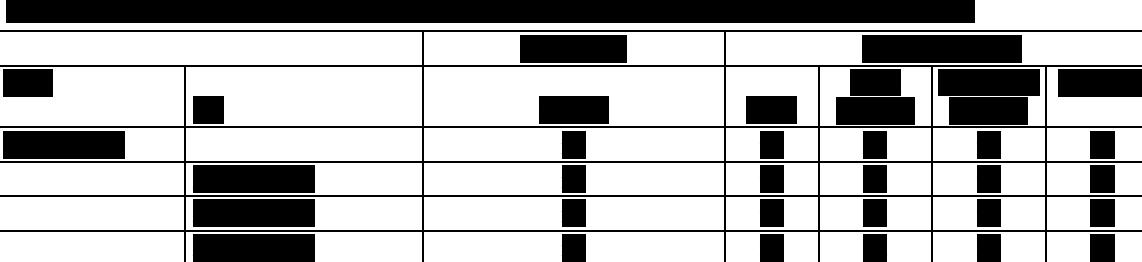
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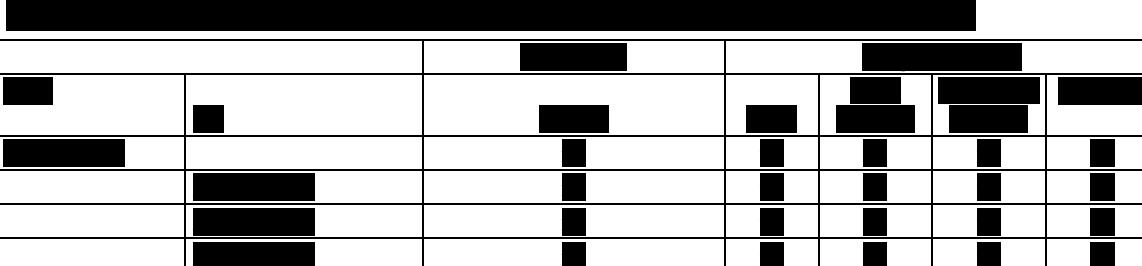








A table with 6 columns and 6 rows. The first column contains a single cell with a black square. The second column contains a single cell with a black square. The third column contains a single cell with a black square. The fourth column contains a single cell with a black square. The fifth column contains a single cell with a black square. The sixth column contains a single cell with a black square. The first row contains a single cell with a black square. The second row contains a single cell with a black square. The third row contains a single cell with a black square. The fourth row contains a single cell with a black square. The fifth row contains a single cell with a black square. The sixth row contains a single cell with a black square.



A table with 6 columns and 6 rows. The first column contains a single cell with a black square. The second column contains a single cell with a black square. The third column contains a single cell with a black square. The fourth column contains a single cell with a black square. The fifth column contains a single cell with a black square. The sixth column contains a single cell with a black square. The first row contains a single cell with a black square. The second row contains a single cell with a black square. The third row contains a single cell with a black square. The fourth row contains a single cell with a black square. The fifth row contains a single cell with a black square. The sixth row contains a single cell with a black square.

100% of the time.

[REDACTED]

For more information, contact the Office of the Vice President for Research and Economic Development at 515-294-6450 or research@iastate.edu.

A 10x10 grid of black and white bars of varying widths, arranged in a pattern that suggests a 2D barcode or a matrix code. The grid is composed of 100 individual bars, each consisting of a series of vertical black segments of different widths on a white background. The overall pattern is highly repetitive and structured.

TEOXANE SA

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This figure illustrates a 2D convolution operation. The input layer (left) consists of 10 rows and 10 columns of black bars. The output layer (right) also consists of 10 rows and 10 columns of black bars. A 3x3 kernel, highlighted in dark gray, is applied to the input. The stride is 2, and the padding is 1. The output layer has 5 rows and 5 columns of black bars, with the first row and column being entirely black. The remaining 4x4 area contains a 4x4 grid of black bars, representing the result of the convolution operation.

[REDACTED]						
[REDACTED]						
[REDACTED]						
[REDACTED]						
[REDACTED]						