

# **STATISTICAL ANALYSIS PLAN**

## **CLINICAL STUDY PROTOCOL**

A Randomized, Double-Masked, Parallel Group, Multicenter, Study to Evaluate Efficacy and Safety of SPARC's SDN-037 Twice Daily Compared with Vehicle for The Treatment of Inflammation and Pain Associated with Ocular Surgery.

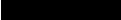
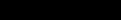
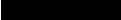
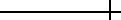
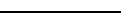
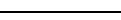
**Protocol No.** : CLR\_16\_31  
**Protocol Version** : Version 01 Amendment 03  
**Protocol Date** : 22JAN2020  
**Plan Version No.** : 1  
**Plan Version Date** : 17SEP2020

## STATISTICAL ANALYSIS PLAN

## SIGNATURE PAGE

The figure consists of a 7x4 grid of bar charts. Each bar is black with a red outline and a red tick mark at the top. The first three columns have a black background, while the fourth column has a light gray background. The bars in the fourth column are significantly taller than those in the first three columns. The bars in each row are of different heights, indicating variability over time.

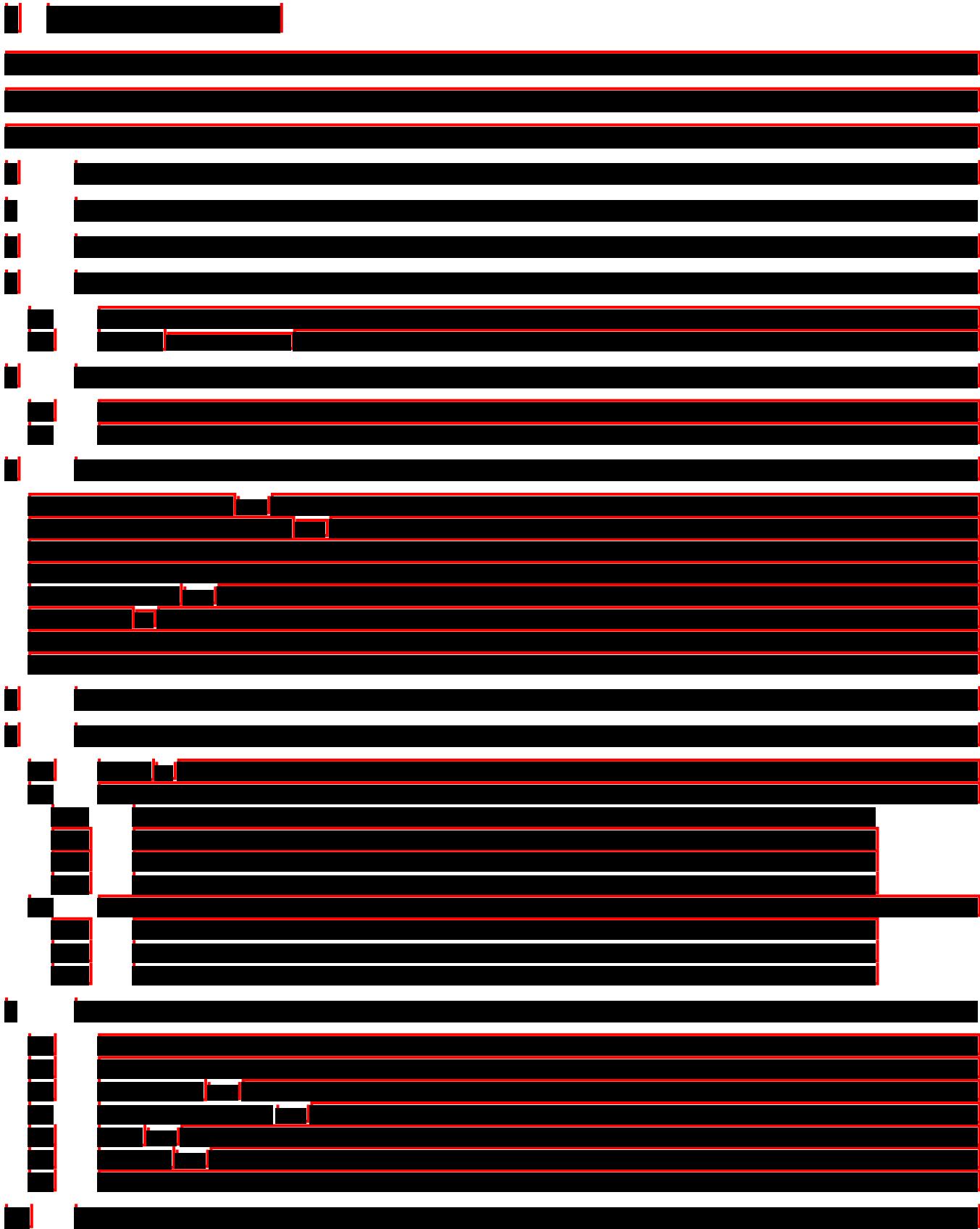
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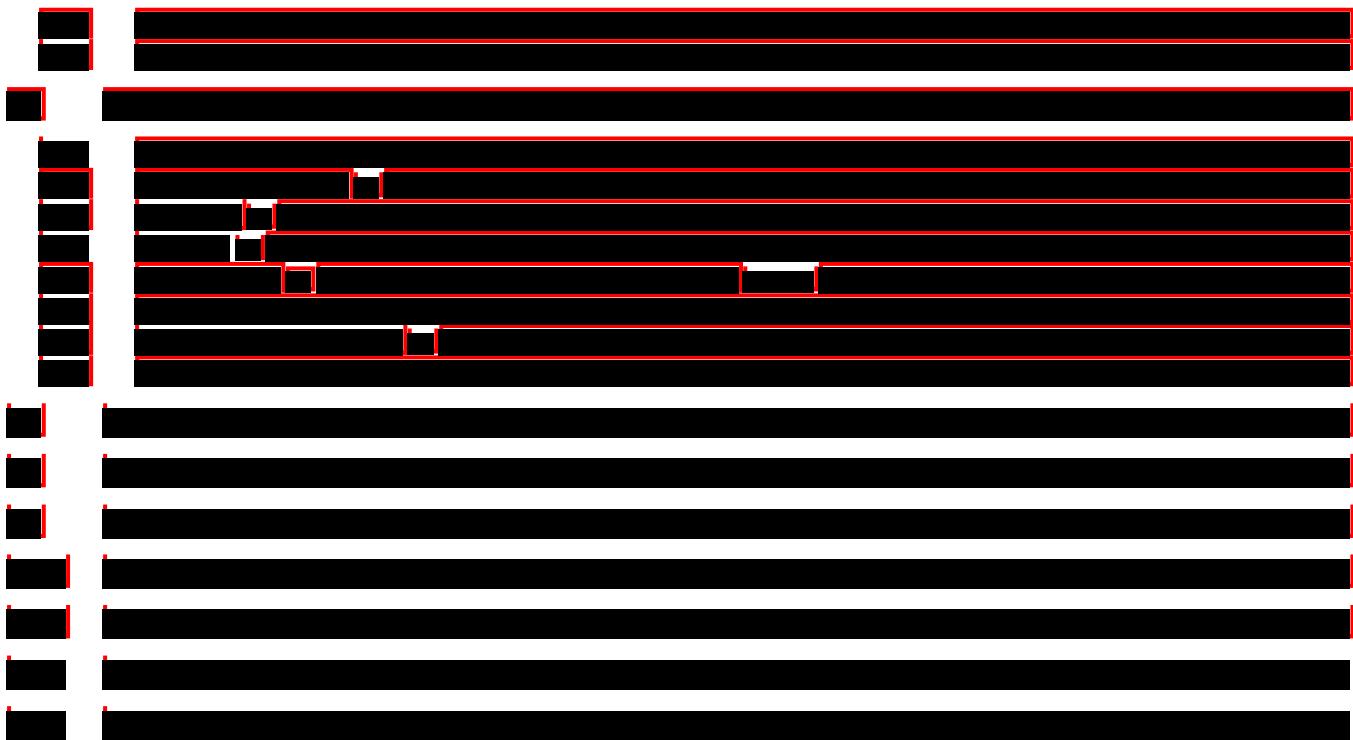
# STATISTICAL ANALYSIS PLAN

## STATISTICAL ANALYSIS PLAN DETAILS

TRIAL FULL TITLE	A Randomized, Double-Masked, Parallel Group, Multicenter, Study to Evaluate Efficacy and Safety of SPARC's SDN-037 Twice Daily Compared with Vehicle for The Treatment of Inflammation and Pain Associated with Ocular Surgery
CT IDENTIFIER	NCT03426267
SAP VERSION	1
SAP VERSION DATE	17SEP2020
TRIAL CHIEF INVESTIGATOR	MULTI-CENTER



# STATISTICAL ANALYSIS PLAN



# STATISTICAL ANALYSIS PLAN

## 2 ABBREVIATIONS AND DEFINITIONS

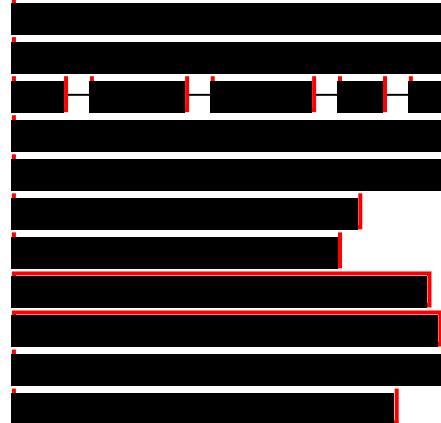
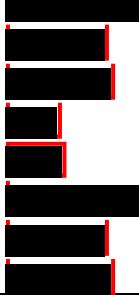
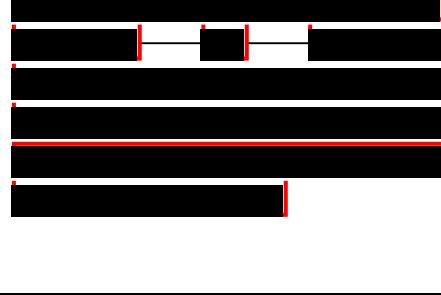
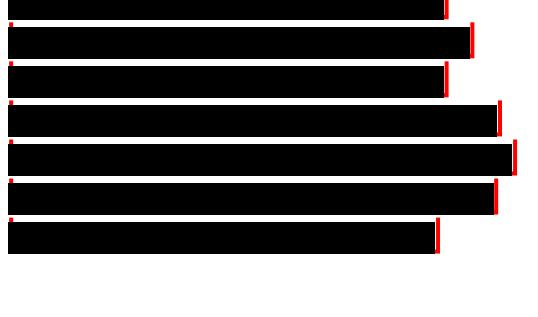
ACC	Anterior Chamber Cell
ACF	Anterior Chamber Flare
AE	Adverse Event
BCVA	Best Corrected Visual Acuity
BID	Twice a day (bis in die)
BSCVA	Best-Spectacle Corrected Visual Acuity
CI	Confidence Interval
CRO	Contract Research Organization
eCRF	electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug
IOP	Intraocular Pressure
IOL	Intra Ocular Lens
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
ITT	Modified Intent-To-Treat
LAR	Legally Acceptable Representative
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
OPD	(in-)Office Physician Dispensing
PP	Per Protocol
PT	Preferred Term
RLD	Reference Listed Drug
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class

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SPARC	Sun Pharma Advanced Research Company, Ltd.
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
VAS	Visual Analog Scale
WHO-DD	World Health Organization Drug Dictionary
w/v	Weight/Volume

## 3 SUMMARY OF LIST OF CHANGES FROM PROTOCOL


# STATISTICAL ANALYSIS PLAN

# STATISTICAL ANALYSIS PLAN

## 4 INTRODUCTION

### 4.1 Preface

Sun Pharma Advanced Research Company Ltd. (SPARC) has developed a novel topical ophthalmic formulation of difluprednate as a [REDACTED] for the treatment of inflammation and pain associated with ocular surgery. SPARC intends to develop the ophthalmic difluprednate product at a [REDACTED] dose [REDACTED] and with a [REDACTED], [REDACTED]

### 4.2 Purpose of the analyses

These analyses will assess the efficacy and safety of topical administration of [REDACTED]

## 5 STUDY OBJECTIVES AND ENDPOINTS

### 5.1 Study Objectives

To evaluate the efficacy and safety of topical administration of [REDACTED] dose [REDACTED] after surgery followed by [REDACTED].

### 5.2 Endpoints

Efficacy:

- The primary efficacy endpoint is the proportion of subjects with an ACC grade of 0 at Day 15 [REDACTED]
- The key secondary efficacy endpoint is the proportion of subjects who achieve a pain score of 0 [REDACTED] at Day 15.



## 6 STUDY METHODS

### 6.1 General Study Design and Plan

- This study is a phase 3, randomized, multicenter, double-masked, vehicle-controlled, parallel-group clinical study.

# STATISTICAL ANALYSIS PLAN

- **Type of control:** [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]
- **Level and method of blinding:** [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]
- **Method of treatment assignment:** Subjects who qualify via inclusion and exclusion criteria will be [REDACTED] assigned to study treatment groups [REDACTED].
- [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]
- [REDACTED]  
[REDACTED]
- [REDACTED]  
[REDACTED]
- [REDACTED]  
[REDACTED]

## 6.2 Inclusion-Exclusion Criteria and General Study Population

- **INCLUSION CRITERIA**
  1. Be male or female, of 18 years of age or older  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]
  5. Able to self-instill the IP or have a caregiver available to instill all doses of the IP, as instructed.

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6. Females of childbearing potential must not be pregnant (as confirmed by a negative urine pregnancy test) [REDACTED]

7. Be able and willing to follow study instructions and complete all required visits

- EXCLUSION CRITERIA

1. Any known allergy or hypersensitivity to difluprednate therapy

11. Any active corneal pathology noted in the study eye

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14. Currently suffering from alcohol and/or drug abuse

[REDACTED]	[REDACTED]

[REDACTED]

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## 6.4 Study Termination

The study may be stopped at any time by the sponsor, the investigator and/or the IRB with appropriate notification.

If the study is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). [REDACTED]

## STATISTICAL ANALYSIS PLAN

A horizontal bar composed of five segments. The first four segments are black and of equal length, arranged side-by-side. The fifth segment is a single red pixel located at the far right end of the bar.

Redacted content.

A 10x6 grid of black bars with red end caps, representing a sparse matrix. The bars are positioned such that they overlap in a non-contiguous manner across the columns, indicating non-zero elements in specific rows and columns. The red caps at the ends of the bars mark the boundaries of the non-zero elements.

## STATISTICAL ANALYSIS PLAN

A 10x10 grid of black rectangles with red outlines. The grid is composed of 100 cells in total. The pattern of black and white cells follows a specific rule: a cell is black if its row index plus its column index is even, and white if it is odd. This results in a checkerboard-like pattern where black cells are at (0,0), (1,1), (2,2), (3,3), (4,4), (5,5), (6,6), (7,7), (8,8), (9,9) and white cells are at (0,1), (1,0), (2,1), (3,0), (4,1), (5,0), (6,1), (7,0), (8,1), (9,0).

Term	Percentage
GMOs	100
Organic	75
Natural	75
Artificial	75
Organic	100
Natural	100
Artificial	100
Organic	100
Natural	100
Artificial	100
Organic	100
Natural	100
Artificial	100
Organic	100
Natural	100
Artificial	100

## STATISTICAL ANALYSIS PLAN

A horizontal bar chart with four bars. The first three bars are black and of equal length, representing the mean. The fourth bar is red and shorter, representing the standard deviation.

A horizontal bar chart consisting of four solid black bars of increasing height from left to right. The first bar is the shortest, followed by a slightly taller one, then a medium one, and the fourth bar is the longest. A small red dot is positioned at the far right end of the fourth bar.

Cancer Type	Percentage
Lung	~10%
Stomach	~25%
Liver	~35%
Esophagus	~40%
Pancreas	~45%

10.1002/anie.201907002

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Figure 10: The five possible configurations of the two black squares in the 10th row of the 1000th column of the 1000th matrix. The red dots indicate the positions of the two black squares. The first and last configurations are the only ones that are possible in the 1000th column of the 1000th matrix.

A horizontal row of four black rectangular bars. Each bar has a small red square at its top-left corner. The bars are evenly spaced and extend across the width of the row.

# STATISTICAL ANALYSIS PLAN

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]

[REDACTED]

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

# STATISTICAL ANALYSIS PLAN

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

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

[REDACTED]	[REDACTED]

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

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

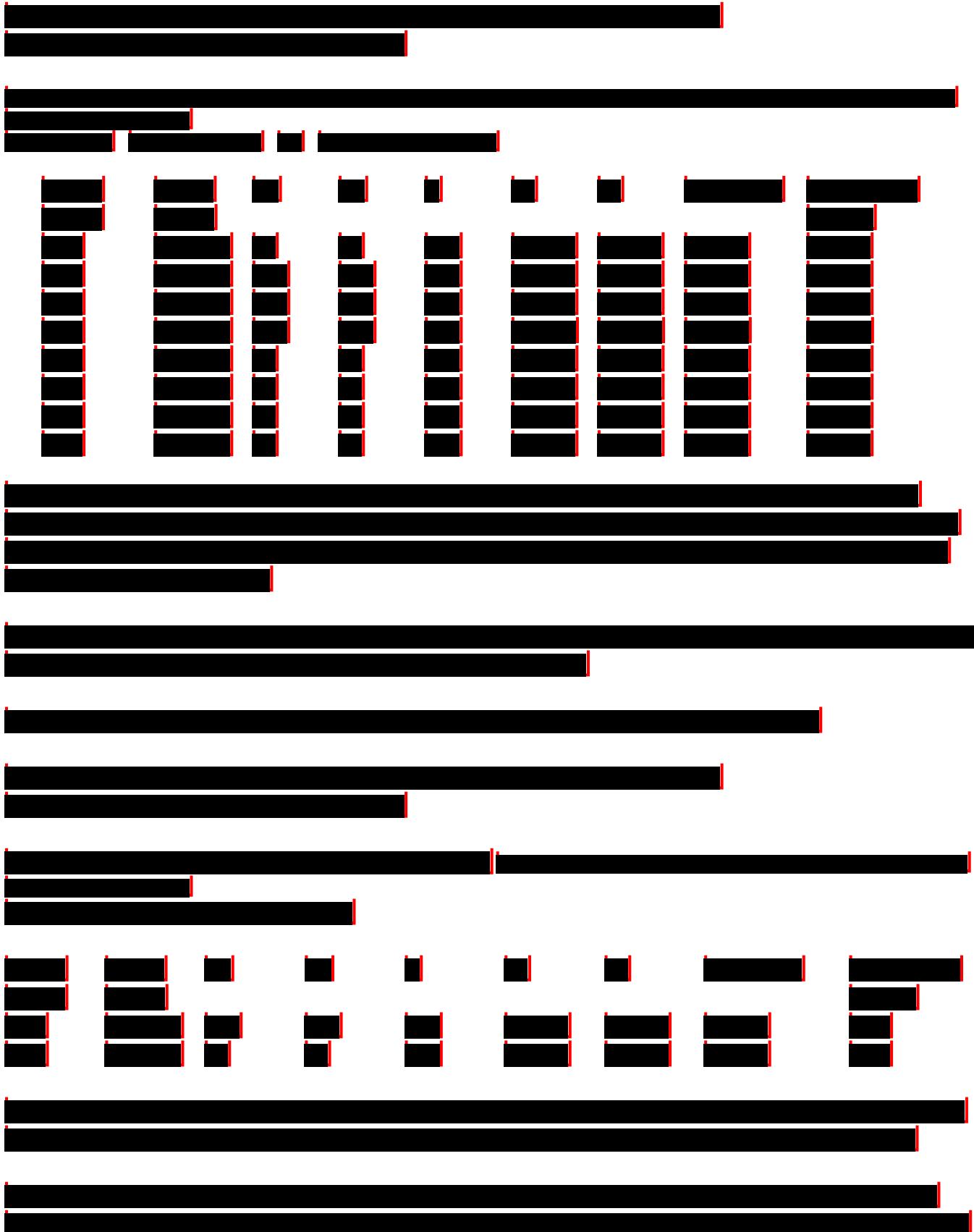
[REDACTED]	[REDACTED]

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

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

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

# STATISTICAL ANALYSIS PLAN



## STATISTICAL ANALYSIS PLAN

A horizontal bar chart showing the distribution of 1000 samples across 100 bins. The x-axis represents the bin index from 0 to 99, and the y-axis represents the frequency of samples. The distribution is highly right-skewed, with the highest frequency in bin 0 (~450 samples) and a long tail extending to bin 99 (~10 samples).

Bin Index	Frequency (approx.)
0	450
1	100
2	50
3	20
4	10
5	5
6	3
7	2
8	1
9	1
10	1
11	1
12	1
13	1
14	1
15	1
16	1
17	1
18	1
19	1
20	1
21	1
22	1
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85	1
86	1
87	1
88	1
89	1
90	1
91	1
92	1
93	1
94	1
95	1
96	1
97	1
98	1
99	1

## STATISTICAL ANALYSIS PLAN

A 10x10 grid of black bars with red end caps, representing a 10x10 matrix. The bars are arranged in a 10x10 pattern, with each bar having a red cap at both ends. The bars are of varying lengths, with some being very short and others being very long, creating a visual representation of a matrix with different values or weights.

## STATISTICAL ANALYSIS PLAN

## ANSWER

100

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1

[REDACTED]

1

[REDACTED]

1

1

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

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## STATISTICAL ANALYSIS PLAN

A 10x10 grid of black bars with red end caps, representing a sparse matrix. The bars are arranged in a grid pattern, with each bar's length and position indicating the non-zero elements of the matrix. The red caps at the ends of the bars mark the coordinates of these non-zero elements.

## STATISTICAL ANALYSIS PLAN

## 10 EFFICACY ANALYSIS

## 10.1 Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of subjects with an ACC grade of 0 at Day 15

A 2x10 grid of black rectangles. The top row has a single red vertical bar at the center. The bottom row has a single red vertical bar at the far left.

## STATISTICAL ANALYSIS PLAN

A large grid of black bars with red highlights. The grid is composed of numerous horizontal and vertical lines. The horizontal lines are primarily black, with red highlights at their ends. The vertical lines are also black, with red highlights at their ends. The grid is set against a white background.

## STATISTICAL ANALYSIS PLAN

Redacted

Figure 1 consists of four horizontal bars representing DNA strands. The top three bars are solid black with red vertical end caps at both ends. The bottom bar is solid black with a red vertical end cap at the right end and a small black dot near the left end.

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A horizontal bar consisting of four thin white lines on a black background, with a small red square at each end.

A horizontal bar consisting of three black segments and two red segments, centered on the page.

Date of Version 17SEP2020

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# STATISTICAL ANALYSIS PLAN

## 11.5 Relationship of Treatment-Emergent Adverse Events to the IP

A summary of TEAEs by SOC, PT, and relationship to the IP will be presented by treatment group. The relationships indicate the investigator's assessment of whether or not the event was caused by the IP. The possible relationships are "Unrelated", "Unlikely", "Possibly", "Probably", and "Certainly". [REDACTED]

## 11.6 Serious Adverse Events

Serious adverse events (SAEs) will be listed by subject; SAEs will be summarized by event and treatment group.

## 11.7 Adverse Events Leading to Study Drug Withdrawal

All AEs leading to study withdrawal or study drug withdrawal will be listed and summarized.

[REDACTED]

■ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

■ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

■ [REDACTED]

## STATISTICAL ANALYSIS PLAN

The figure consists of three distinct groups of horizontal bars, each group containing 10 bars. The bars are black with a thin red outline. In the first group, the first bar is significantly shorter than the others. In the second group, the last bar is significantly shorter than the others. In the third group, the 6th bar is significantly shorter than the others. The bars are arranged in a grid-like pattern, with each group occupying a row of the grid.

## 12 REPORTING CONVENTIONS

Summary tables and listings (e.g., post text tables and individual subject data listings are prepared according to ICH Guideline E3) include a header, showing Protocol Number, Status, and sponsor; and a “footer” providing explanatory notes that indicate as a minimum:

- SAS program name and data file source
- Date of data extraction
- Date of output generation

Post text tables also include reference(s) to the subject data listing(s) that supports the summary data. The data extraction date links the output to the archived database that is locked to ensure the replication of the results.

Post text tables will be organized with respect to treatment groups for safety and efficacy. The order of presentation will be chronological for visits. A total column will appear as the last column, as applicable. The summary tables clearly indicate the number of subjects to which the data apply and unknown or not performed are distinguished from missing data.

## STATISTICAL ANALYSIS PLAN

Summary tables for medications and medical conditions are coded according the WHO Drug Dictionary and MedDRA respectively. Adverse event preferred terms and body/organ systems are coded using the MedDRA dictionary. The MedDRA dictionary can be used, as well, in the coding of signs and symptoms, medical history, physical examination abnormalities, and clinical diagnoses.

Supportive individual subject data listings, at a minimum, are sorted and presented by subject ID and treatment. Listings also include visit number, visit date, and days relative to the initiation of treatment.

[REDACTED]

## STATISTICAL ANALYSIS PLAN


A horizontal bar chart with 15 data series. The series are grouped into two categories: a left category with 5 bars and a right category with 10 bars. Each bar is black with a red vertical tick mark at its right end. The bars are separated by thin white lines.

## STATISTICAL ANALYSIS PLAN

## STATISTICAL ANALYSIS PLAN

A horizontal bar chart consisting of 10 bars. Each bar is a solid black rectangle with a thin red vertical line at its right end. The bars are arranged in a single row, with some space between them. The lengths of the bars vary, indicating different data points. The chart is set against a white background with horizontal grid lines.

# STATISTICAL ANALYSIS PLAN

[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]

## STATISTICAL ANALYSIS PLAN