



## CLINICAL STUDY PROTOCOL

A Randomized, Multi-Center, Investigator-Masked, Parallel Group, Equivalence Study of Once Daily Brimonidine Tartrate Ophthalmic Suspension Compared with Three Times Daily Alphagan® P in Subjects with Open Angle Glaucoma or Ocular Hypertension.

**Protocol No.** : CLR\_16\_33 V1 Amendment 3 20Sep2018

**Plan Version No.** : 1

**Plan Version Date** : 22APR2021

# STATISTICAL ANALYSIS PLAN

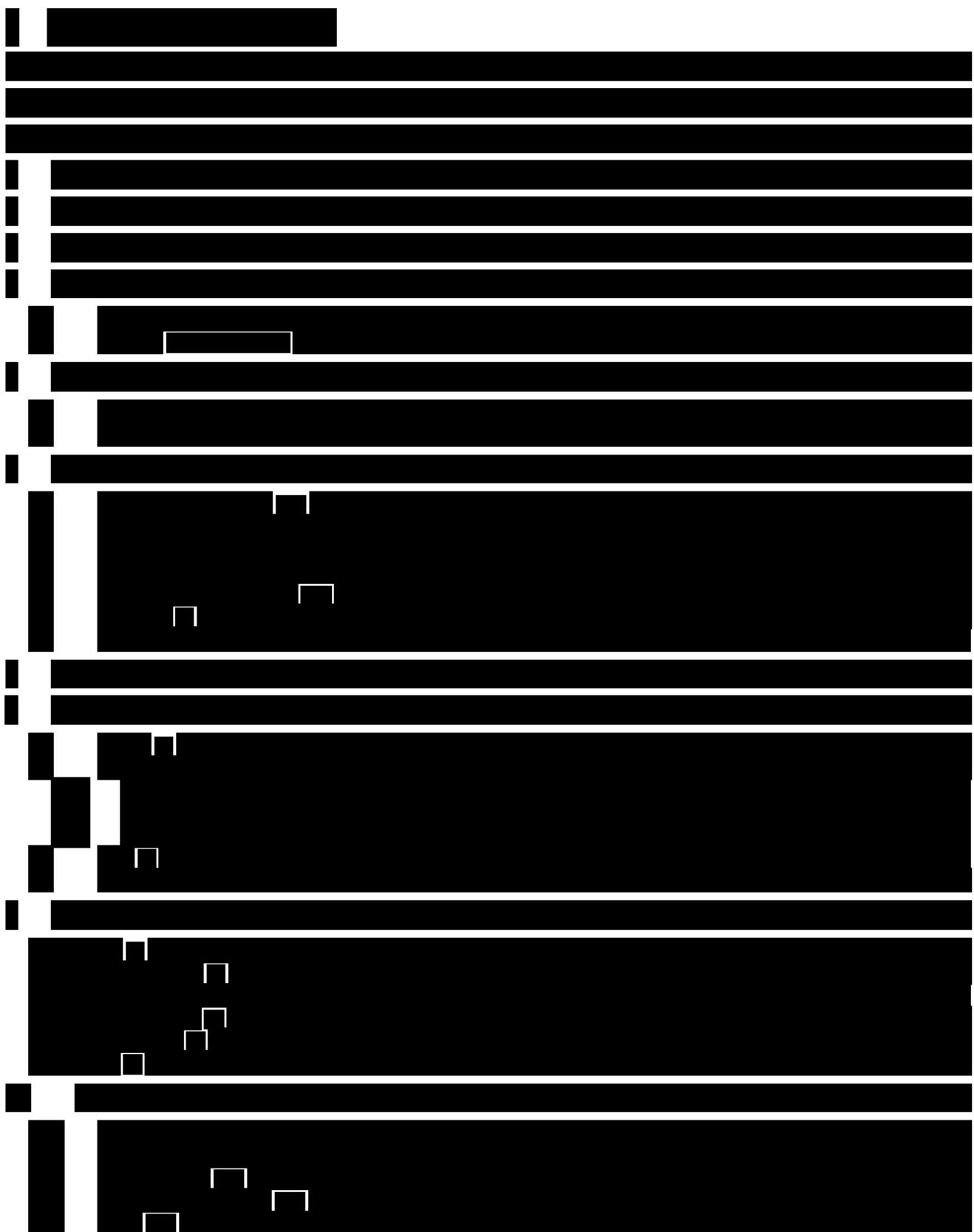


# STATISTICAL ANALYSIS PLAN

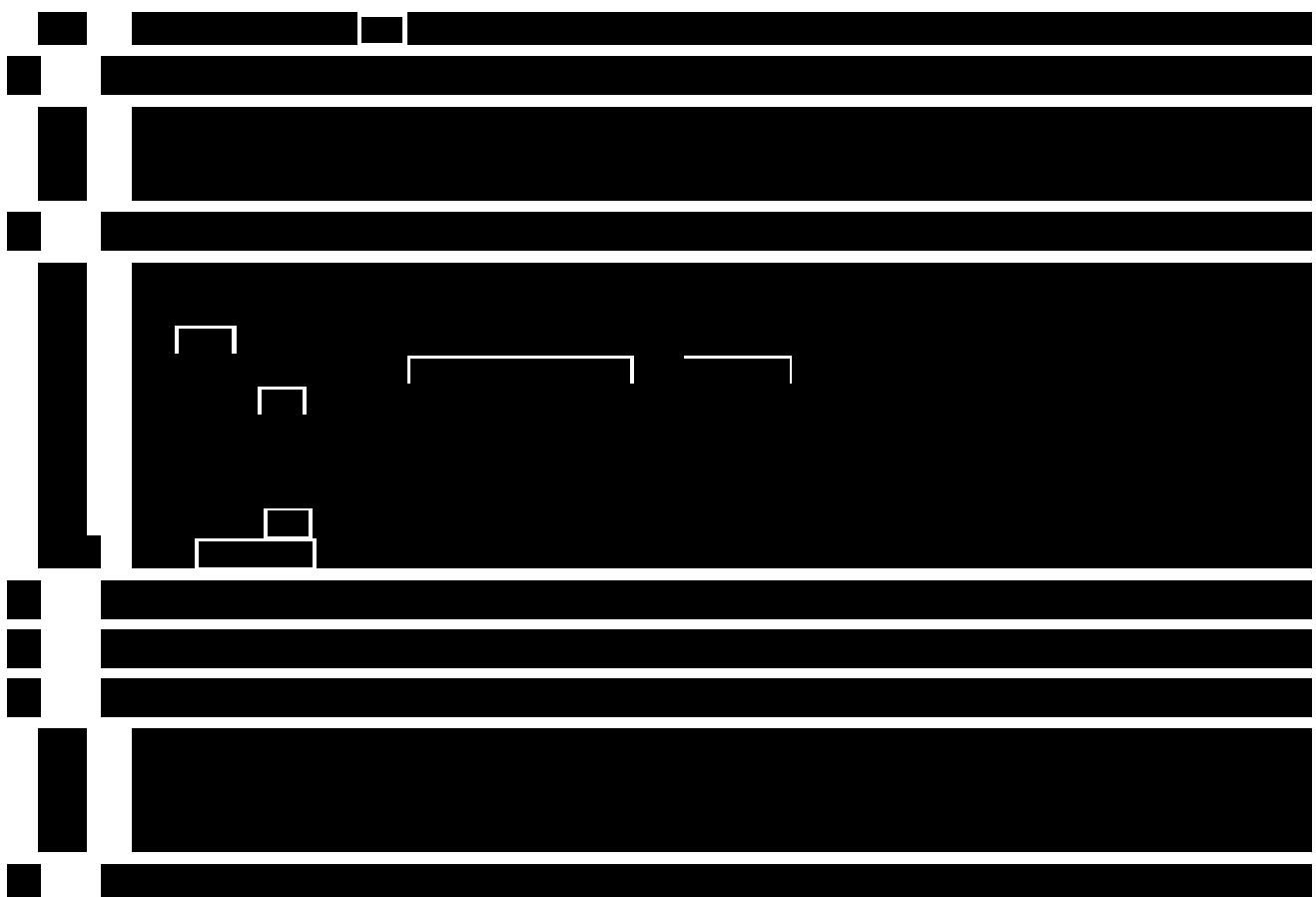


## STATISTICAL ANALYSIS PLAN DETAILS

TRIAL FULL TITLE	A Randomized, Multi-Center, Investigator-Masked, Parallel Group, Equivalence Study of Once Daily Brimonidine Tartrate Ophthalmic Suspension Compared with Three Times Daily Alphagan® P in Subjects with Open Angle Glaucoma or Ocular Hypertension.	
PROTOCOL NUMBER	CLR 16 33	
CT IDENTIFIER	NCT03450629	
SAP VERSION	2.0	
SAP VERSION DATE	22APR2021	



# STATISTICAL ANALYSIS PLAN



# STATISTICAL ANALYSIS PLAN



## 2 ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
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
GAT	Goldmann Applanation Tonometry
GCP	Good clinical practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of technical requirements for pharmaceuticals for human use
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-To-Treat
LOCF	Last Observation Carried Forward
logMAR	logarithm of the Minimum Angle of Resolution
MAO	Monamine Oxidase Inhibitor
MedDRA	Medical Dictionary of Regulatory Affairs
MMRM	Mixed Model of Repeated Measures
NCT	Non-contact tonometer
OPD	(in-)Office physician dispensing
OU	Both eyes
POC	Proof-of-concept
PP	Per Protocol
PT	Preferred Term
QD	(Quaque Die) once daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SPARC	Sun Pharma Advanced Research Company, Ltd.
SUSAR	Suspected Unexpected Serious Adverse Reaction
TOST	Two one-sided tests
TEAE	Treatment-Emergent Adverse Event
TID	Three Times Daily

# STATISTICAL ANALYSIS PLAN



[REDACTED]

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

## 4 INTRODUCTION

### 4.1 Preface

Sun Pharma Advanced Research Company Ltd. (SPARC; Sponsor) has developed a once daily (QD) long-acting ophthalmic product consisting of 0.35% brimonidine tartrate suspension

[REDACTED]

# STATISTICAL ANALYSIS PLAN



## 4.2 Purpose of the analyses

To evaluate the efficacy of once daily (QD) dosing of brimonidine tartrate ophthalmic suspension 0.35% compared with Alphagan® P 0.1% dosed 3 times a day (TID) in subjects with open-angle glaucoma or ocular hypertension.

## 5 STUDY OBJECTIVES AND ENDPOINTS

### 5.1 Study Objectives

This study is designed to obtain estimates on the mean IOP at each of the 3 time points (8:00 AM, 10:00 AM, 4:00 PM) on [REDACTED] week 12 in order to compare brimonidine tartrate 0.35% ophthalmic suspension, dosed QD at 8:00 AM and Alphagan® (brimonidine tartrate ophthalmic solution 0.1%), dosed TID at approximately 8:00 AM, 2:00 PM, and 8:00 PM.

#### Primary Objectives:

The primary objective is to evaluate the efficacy of QD dosing with SPARC's brimonidine tartrate ophthalmic suspension 0.35% compared with Alphagan® (brimonidine tartrate ophthalmic solution 0.1%) dosed TID in subjects with open-angle glaucoma, or ocular hypertension.

[REDACTED]

[REDACTED]

### 5.2 Endpoints

#### Primary Efficacy Endpoint:

Primary efficacy endpoint will be the time-matched mean IOP (study eye) measures at each of the 3 time points (8:00 AM, 10:00 AM, 4:00 PM) on [REDACTED] week 12. These sample values will be used to compute the point estimates for the primary estimand defined by the difference across treatment groups in IOP at each of the 9 time points (3 times within each of 3 days).

[REDACTED]

[REDACTED]

[REDACTED]

#### Safety Endpoints:

- AEs

[REDACTED]

[REDACTED]

[REDACTED]

# STATISTICAL ANALYSIS PLAN



## 6 STUDY METHODS

### 6.1 General Study Design and Plan

- This is a multicenter, investigator/ evaluator -masked, randomized, parallel group, equivalence study.  
[REDACTED]
- The investigator or designated evaluator, masked to treatment assignment, will perform all ophthalmic examinations. Unmasked study coordinator may perform all study procedures other than ophthalmic/clinical examination, or treatment of the subjects.
- Study Duration:
  - Visit 1: (Day-42 to Day -1): Screening
  - Visit 2: (Day 0) Baseline/Randomization
  - Visit 3: (Week 2 ± 2 Days) Efficacy/Safety Evaluation
  - Visit 4: (Week 6 ± 2 Days) Efficacy/Safety Evaluation
  - Visit 5: (Week 12 ± 2 Days) Efficacy/Safety Evaluation and study exit

### 6.2 Inclusion-Exclusion Criteria

#### Inclusion Criteria:

Each subject must:

1. Be male or female, of 18 years of age or older
2. Provide signed and dated informed consent in accordance with GCP and local legislation prior to any study procedure.
3. Have open angle glaucoma, (with or without pseudo exfoliation, pigment dispersion component) or ocular hypertension in both eyes and likely to be controlled on monotherapy

  
[REDACTED]

## STATISTICAL ANALYSIS PLAN



7. Females of childbearing potential must not be pregnant or lactating (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin). Women of childbearing potential must agree to the use of a reliable method of contraception (e.g., total abstinence, intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], oral, transdermal, injected or implanted non- or hormonal contraceptive), throughout the study. A sterile sexual partner is not considered an adequate form of birth control. Subjects on hormonal contraceptives must have been on the same hormonal contraceptive for at least one month before the Screening and continue throughout the duration of the study. A female is considered of childbearing potential if she has had her first menses and she is either: not postmenopausal for at least 12 consecutive months prior to enrollment; or not surgically sterilized by bilateral tubal ligation, or bilateral oophorectomy, or hysterectomy. Male subjects with female partners of childbearing potential who are not using birth control as described above must use a barrier method of contraception (e.g., condom) if not surgically sterile (i.e., vasectomy).
9. Be able and willing to follow study instructions and complete all required visits.

# STATISTICAL ANALYSIS PLAN



## **Exclusion Criteria:**

Each subject must not:

1. Have angle closure glaucoma or a history of acute angle closure treated with a peripheral iridotomy
2. Have uncontrolled systemic disease (e.g., diabetes) which might interfere with the study
3. Current or history of severe hepatic or renal impairment. Have severe cardiovascular disease unless his/her disease is controlled, and clearance has been obtained from the treating primary care physician or cardiologist
4. Subjects with depression, cerebral or active coronary insufficiency or orthostatic hypotension.
5. (If female of childbearing potential) Be pregnant, nursing, or planning a pregnancy during study entry and through the duration of the study.
6. Have clinically relevant, abnormally low or high blood pressure or pulse rate
7. [REDACTED]

## STATISTICAL ANALYSIS PLAN



26. Have a condition or be in a situation which, in the investigator's opinion, may put the subject at a significant risk, may confound study results, or may interfere significantly with the subject's participation in the study. This criterion provides an opportunity for the investigator to exclude subject based on clinical judgment, even if other eligibility criteria are satisfied.

## 6.4 Study Termination

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

# STATISTICAL ANALYSIS PLAN



required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). Additionally:

1. If the investigator terminates or suspends the study without prior agreement of the sponsor, the investigator should inform the institution (where the study is conducted) where applicable, and the investigator/institution should promptly inform the sponsor and the EC, and should provide the sponsor and the IEC a detailed written explanation of the termination or suspension.
2. The sponsor may discontinue entire study at any time, for ethical or scientific or business reasons. If the sponsor terminates or suspends a study, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IEC and provide the IEC a detailed written explanation of the termination or suspension.
3. If the IEC terminates or suspends its approval/favourable opinion of a study, the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

## 6.5 Randomization, Masking, and Unmasking

- **Subject Number**

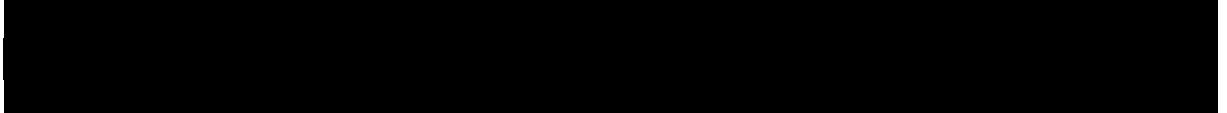
At the screening visit after signing the informed consent form (ICF) each subject will be allotted a subject number. The subject number will uniquely identify each subject in the study. The subject number will appear on all study documents relating to that subject. Subject numbering is described separately in data management plan.

- **Randomization**

Subjects who qualify inclusion and exclusion criteria will be randomly assigned to study treatment using Interactive web response system.

- **Masking**

This is an evaluator-masked study.



## STATISTICAL ANALYSIS PLAN



- **Procedures for Unmasking (if applicable)**

When medically necessary, the investigator may need to determine what treatment has been assigned to a subject. Site will contact the designated personnel in SPARC or CRO in case the treatment code needs to be unmasked. When possible (i.e., in non-emergent situations), CRO and/or the study sponsor should be notified before unmasking investigational product.

Unmasking details will be provided to Sponsor's designated safety physician in case of SUSAR for regulatory reporting purpose only.

The code for all subjects will be broken when all subjects have completed the study, and all data for this period has been entered into the database and locked.

A 10x10 grid of black and white blocks. The first column has a light gray header. The second column has a light gray header and a black footer. The third column has a light gray header and a black footer. The fourth column has a light gray header and a black footer. The fifth column has a light gray header and a black footer. The sixth column has a light gray header and a black footer. The seventh column has a light gray header and a black footer. The eighth column has a light gray header and a black footer. The ninth column has a light gray header and a black footer. The tenth column has a light gray header and a black footer.

## STATISTICAL ANALYSIS PLAN



A 10x10 grid of black and white squares. The first column contains a large black blob with white borders. The remaining columns are mostly white with a few black squares scattered across them.

## 6.7 Study Variables

A high-contrast, black and white image showing a large, dark rectangular shape on the left and a smaller, dark rectangular shape on the right, separated by a white space.

# STATISTICAL ANALYSIS PLAN



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

## STATISTICAL ANALYSIS PLAN



# STATISTICAL ANALYSIS PLAN



[REDACTED]

## STATISTICAL ANALYSIS PLAN



A series of eight horizontal black bars of varying lengths, decreasing in size from top to bottom. The bars are positioned against a white background.

## STATISTICAL ANALYSIS PLAN



A series of black horizontal bars of varying lengths and positions on a white background. The bars are arranged in a staggered, non-overlapping pattern. The lengths of the bars range from approximately 10 pixels to 90 pixels. The positions of the bars are roughly aligned vertically, with some horizontal offsets. The bars are solid black and have no internal structure.

## STATISTICAL ANALYSIS PLAN



[REDACTED]

100% of the time, the *hedgehog* is a hedgehog, and the *cat* is a cat. The *hedgehog* is not a *cat*, and the *cat* is not a *hedgehog*.

© 2019 Pearson Education, Inc.

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

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

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

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

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

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

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

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

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

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

© 2013 Pearson Education, Inc.

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

10. *Journal of the American Statistical Association*, 1990, 85, 1302-1313.

## STATISTICAL ANALYSIS PLAN



1. **What is the primary purpose of the proposed legislation?**

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

1. **What is the primary purpose of the study?** The study aims to evaluate the effectiveness of a new treatment for hypertension in a diverse population.

11. **What is the primary purpose of the *Journal of Clinical Oncology*?**

Digitized by srujanika@gmail.com

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

For more information, contact the Office of the Vice President for Research and Economic Development at 505-272-2300 or [research@unm.edu](mailto:research@unm.edu).

© 2019 Pearson Education, Inc.

11. *What is the best way to increase the number of people who use a particular service?*

## STATISTICAL ANALYSIS PLAN



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

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

[REDACTED] [REDACTED]

1. **What is the primary purpose of the study?** The study aims to evaluate the effectiveness of a new treatment for hypertension in a diverse population. The primary outcome is systolic blood pressure, and the secondary outcome is the incidence of cardiovascular events.

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

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

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

A large, dark rectangular area, possibly a redaction, occupies the top portion of the page. It is bounded by a thin white line on the left and a thick white line on the right. The rest of the page is white.

[REDACTED]

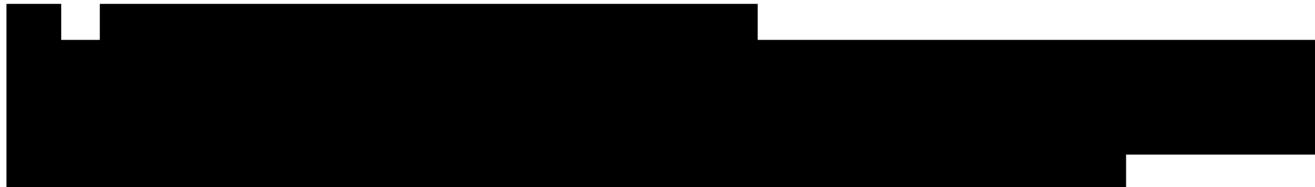
# STATISTICAL ANALYSIS PLAN



## 12.1 Adverse Events

AEs will be coded to System Organ Class (SOC) and Preferred Term (PT) according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA®). All AEs will be listed; however, only treatment-emergent AEs (TEAEs) will be summarized.

The primary safety analysis will summarize ocular (in either eye) and non-ocular TEAEs for all treated subjects using discrete summaries at the subject level by system organ class and preferred term for each treatment group. A TEAE will be defined as occurring after the first dose of study medication. Treatment-related ocular and non-ocular TEAEs will be summarized similarly. Ocular and non-ocular TEAEs will also be summarized by severity. This summary will provide the total number of TEAEs, the number of subjects experiencing at least one ocular or non-ocular TEAE, the number of subjects experiencing SAEs and the number of subjects experiencing TEAEs and SAEs related to IP. The overall summary of TEAEs will also include the maximum severity and maximum relationship to IP for subjects with AEs. The number and percentage of subjects at each level of severity and each level of relationship will be presented.



## STATISTICAL ANALYSIS PLAN



A series of black horizontal bars of varying lengths and positions on a white background, suggesting a redacted document. The bars are irregular in shape, with some having small white gaps or irregular edges. They are positioned in a staggered, non-overlapping manner across the page.

## STATISTICAL ANALYSIS PLAN



1

[REDACTED]

1. **What is the primary purpose of the proposed legislation?**

## ANSWER

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

A 2D bar chart with 10 horizontal bars. The bars are black with white outlines. The first bar is the shortest. The second bar is the longest. The third bar is the second longest. The fourth bar is the third longest. The fifth bar is the fourth longest. The sixth bar is the fifth longest. The seventh bar is the sixth longest. The eighth bar is the seventh longest. The ninth bar is the eighth longest. The tenth bar is the ninth longest.

## STATISTICAL ANALYSIS PLAN



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

Two black rectangular redaction boxes are positioned side-by-side. The box on the left is a smaller, solid black rectangle. The box on the right is a larger, solid black rectangle, approximately twice as wide as the first.

[REDACTED]

A 15x15 grid of black bars on a white background. The bars are arranged in a pattern where the width of each bar in a row increases by one unit from left to right. The first row has 1 bar, the second has 2, the third has 3, and so on up to the 15th row which has 15 bars. The bars are separated by thin white lines.

10 of 10

## STATISTICAL ANALYSIS PLAN



## STATISTICAL ANALYSIS PLAN



A horizontal bar chart showing the distribution of 1000 samples across 10 categories. The x-axis represents the number of samples (0 to 1000) and the y-axis represents the categories. The bars are black with white outlines. Category 10 has the highest count (approx. 350), while categories 1, 2, 3, 4, 5, 6, 7, 8, and 9 have lower counts (approx. 100-150).

[REDACTED]

This figure is a 2D grayscale heatmap or a binary mask. It features a complex, multi-layered structure composed of numerous horizontal and vertical black lines on a white background. The image is highly fragmented, with many black regions of varying sizes and shapes. The overall pattern is abstract and lacks a clear, recognizable subject.

# STATISTICAL ANALYSIS PLAN



[REDACTED]

[REDACTED]

[REDACTED]