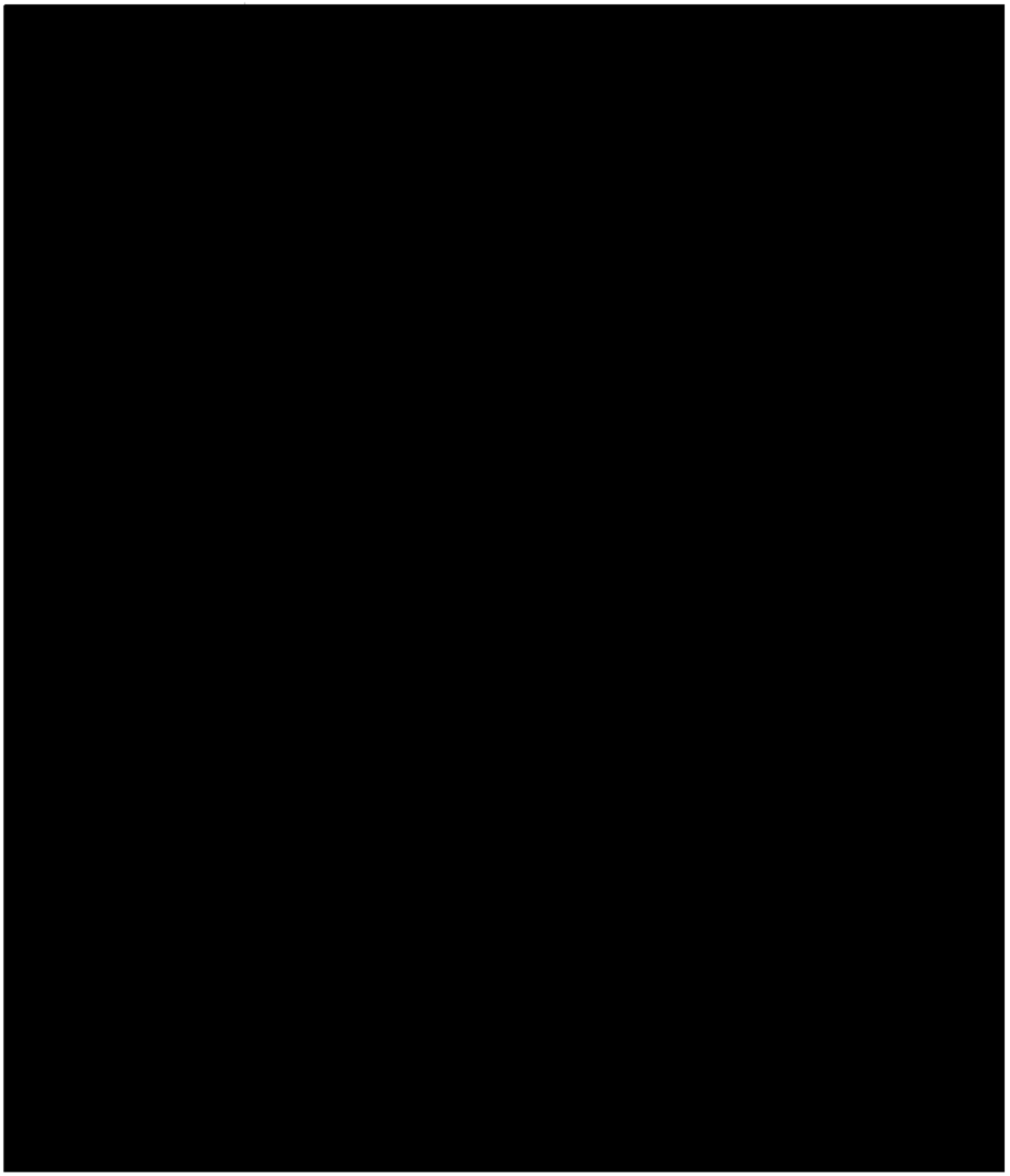
PROTOCOL # PS-1701 0314 5529-SACT

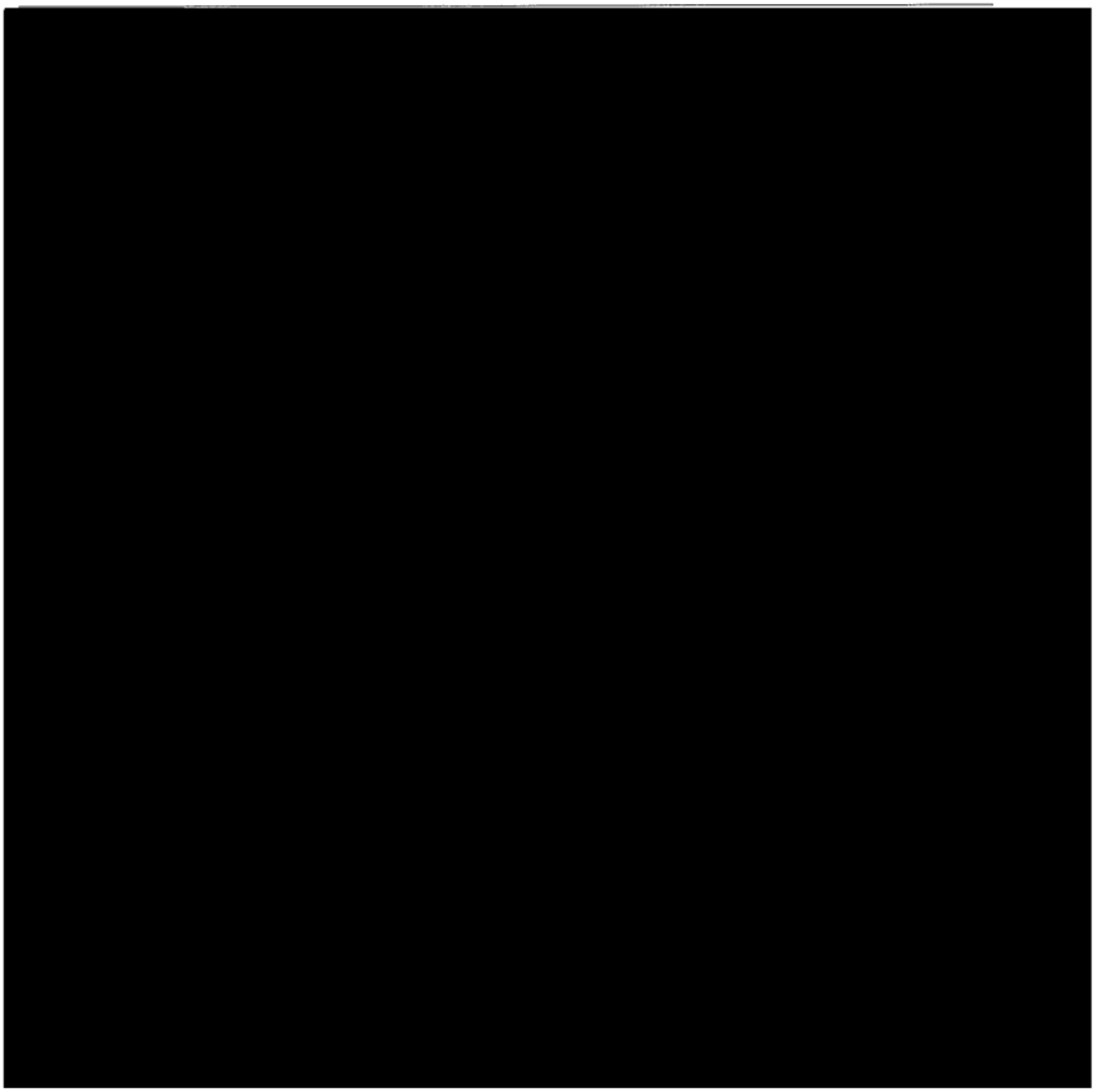
A Multi-Center, Evaluator Blinded, Randomized Clinical Study to Evaluate the Efficacy and Tolerance of Two Acne Treatment Regimens on Subjects with Mild to Moderate Acne Vulgaris

STATISTICAL ANALYSIS PLAN (SAP)

Based on Protocol Final Version 1.0, 06Mar2017

Date: 19Oct2017, Version 1.0





CONTENTS

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1. INTRODUCTION

1.1. Study Objectives

The objective of this study is to evaluate and compare the efficacy and tolerance of two different acne treatment regimens (a cleanser used with a currently marketed red and blue light acne light therapy mask alone vs. the cleanser used with the same mask in conjunction with a light therapy topical gel-cream) in subjects with mild to moderate acne over a 12-week period.

1.2. Study Design

This is a multi-center, 2-cell, full-face, randomized, evaluator-blind clinical usage study. Up to 136 subjects will be enrolled to finish with at least 90 subjects (targeting 45 subjects per cell). The target population is 12- to 40-year-old males and females of any skin type who have mild to moderate acne vulgaris on the face. Up to 50% of the enrolled subjects may be male.

Subjects will be randomly assigned to use one of the two acne treatment regimens at home for 12 weeks. Each subject will be instructed to wash his/her face twice daily (morning and evening) with the AM & PM Cleanser. In the evening after washing, subjects assigned to Regimen 1 will use the PM Mask Treatment for 10 minutes, while subjects assigned to Regimen 2 will apply the PM Gel-Cream full-face and let it dry prior to using the PM Mask Treatment for 10 minutes (mask treatment should begin within 15 minutes after PM Gel-Cream application).

Regimen 1:

AM:
• AM & PM Cleanser [redacted]
PM:
• AM & PM Cleanser
• PM Mask Treatment
• Replacement Mask Activators

Regimen 2:

AM:
• AM & PM Cleanser [redacted]
PM:
• AM & PM Cleanser [redacted]

- PM Gel-Cream [redacted]
- PM Mask Treatment [redacted]
- Replacement Mask Activators [redacted]

Subjects will be assessed at Baseline (Week 0), within 20 minutes after the first product usage, Week 1, Week 2, Week 4, Week 8, and Week 12, according to the Schedule of Events in Table 1 below.

Table 1. Schedule of Events

Time Points/Procedures	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Screening/ Baseline (Week 0)	Post-1st Product Usage[a]	Week 1 (± 1 day)	Week 2 (± 3 day)	Week 4 (± 3 day)	Week 8 (± 3 day)	Week 12 (± 3 day)
Informed consent (and assent, as applicable) with HIPAA disclosure & photograph release	X						
Collect demographics (including Fitzpatrick Skin Type & skin sensitivity), general medical history, & concomitant medications	X						
Interview for compliance			X	X	X	X	X
15-minute acclimation	X		X	X	X	X	X
Acne lesion counts	X[b]			X	X	X	X
Investigator Global Acne (IGA) assessment	X[b]		X	X	X	X	X
Review of eligibility	X						
Subject qualification by medically qualified staff	X						

Enrollment & randomization	X						
Additional investigator efficacy assessments	X		X	X	X	X	X
[redacted]							
(Pre-weighed, as applicable) IP dispensed with subject instructions and daily diary[c]	X Starter Kit				X Replacement Kit	X Replacement Kit	
Supervised first use of IP per evening instructions	X						
Daily diary reviewed			X	X	X	X	X
IP weighed/checked for use compliance (as applicable)			X	X	X	X	X
IP and daily diary collected					X Used Activator	X Used Activator	X
Collect/record adverse events (AEs) and changes in health/medications	X AEs only	X AEs only	X	X	X	X	X
Subject disposition							X[d]

[a]Post-1st Product Usage time point should occur within 20 minutes after the initial product usage.

[b]Part of eligibility review.
[c]Additional IP and diary units may be dispensed as needed/previous units collected.
[d]Subject disposition will be recorded at final study visit or at the time of subject discontinuation from the study. If a subject discontinues prior to this visit, every effort will be made to complete these procedures (if the subject agrees).

2. INTERIM ANALYSES

No interim analysis is planned. Final analyses will be performed at the official database release.

3. ANALYSIS SETS

3.1. Full Analysis Set

On the basis of the intent-to-treat (ITT) principle, the Full Analysis Set will include all randomized subjects who use the study products and have baseline and at least one post-baseline efficacy or tolerance data point.

3.2. Per-Protocol Analysis Set

The Per-Protocol Analysis Set will include all subjects completing the study without major protocol deviations. The subjects with major protocol deviations will be determined before unblinding.

A secondary analysis based on the per-protocol analysis set will be performed on the primary efficacy endpoint.

3.3. Safety Analysis Set

The Safety Analysis Set will include all randomized subjects who use study products.

4. ENDPOINTS AND COVARIATES

For each efficacy endpoint, summary statistics will be provided by treatment group at each time point. For continuous variables, descriptive summaries will include number of subjects, mean, standard deviation, median, minimum and maximum values. Distributions of categorical variables will be summarized by presenting the number and percent of subjects in each response category.

4.1. Efficacy Endpoints

4.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change from baseline in global face total lesion count at Week 12. The total lesion count is the sum of inflammatory lesions (papules and pustules), open comedones, and closed comedones.

4.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

a) The percent change from baseline in face total lesion count:
   - Mean across all post-baseline visits (Week 2, Week 4, Week 8, and Week 12)
   - Mean of Week 2 and Week 4
   - Mean of Week 4 and Week 8
   - Mean of Week 8 and Week 12
   - Week 2, Week 4, and Week 8 analyzed separately

b) Acne lesion counts at Week 2, Week 4, Week 8, and Week 12. Each of the following lesions will be analyzed for the total face:
   - Open comedones
   - Closed comedones
   - Inflammatory acne lesions (papules and pustules are counted together)
   - Non-inflammatory acne lesions (sum of open comedones and closed comedones)
   - Total lesion counts (sum of inflammatory and non-inflammatory acne lesions counts)

c) IGA assessment using Modified Cook's Scale at Week 1, Week 2, Week 4, Week 8, and Week 12. Half points may be used:

0	Clear	Residual hyperpigmentation and erythema may be present.

1	Almost Clear	A few scattered comedones and a few (less than five) small papules.
2	Mild	Easily recognizable; less than half the face is involved. Many comedones and many papules and pustules.
3	Moderate	More than half of the face is involved. Numerous comedones, papules, and pustules.
4	Severe	Entire face is involved. Covered with comedones, numerous papules and pustules, and few nodules and cysts.
5	Very Severe	Highly inflammatory acne covering the face; with nodules and cysts present.

d) Additional investigator efficacy assessments of the following parameters at Week 1, Week 2, Week 4, Week 8, and Week 12:

Parameter	Scale (Half-points may be used)									
	0 = None	1-3 = Mild			4-6 = Moderate			7-9 = Severe		
Overall Redness of Inflammatory Lesions	0 = no redness associated with the inflammatory lesions	1	2	3	4	5	6	7	8	9 = overall, inflammatory lesions exhibit severe degree of redness
Overall Size of Inflammatory Lesions	0 = no longer visible	1	2	3	4	5	6	7	8	9 = overall size is very large

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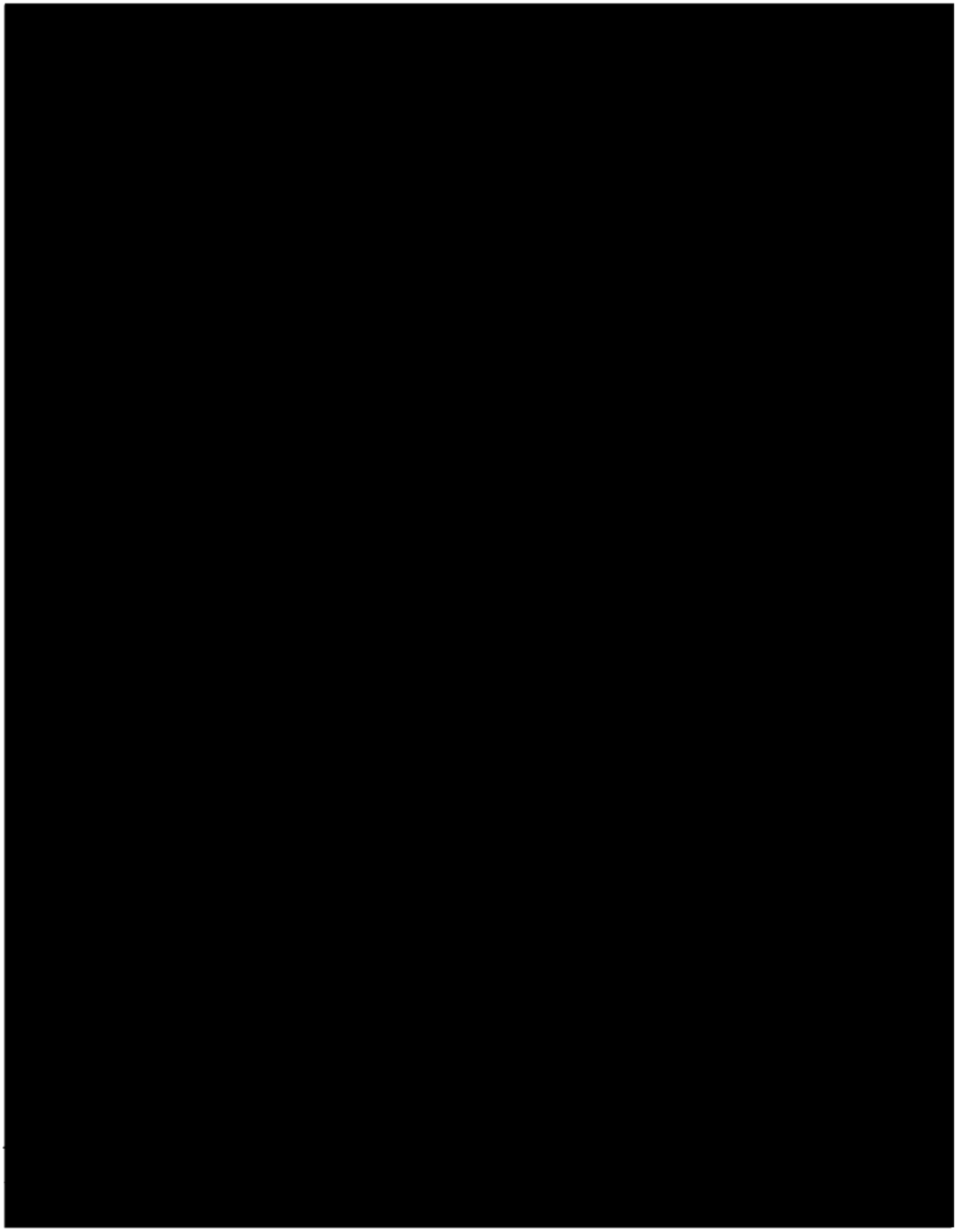

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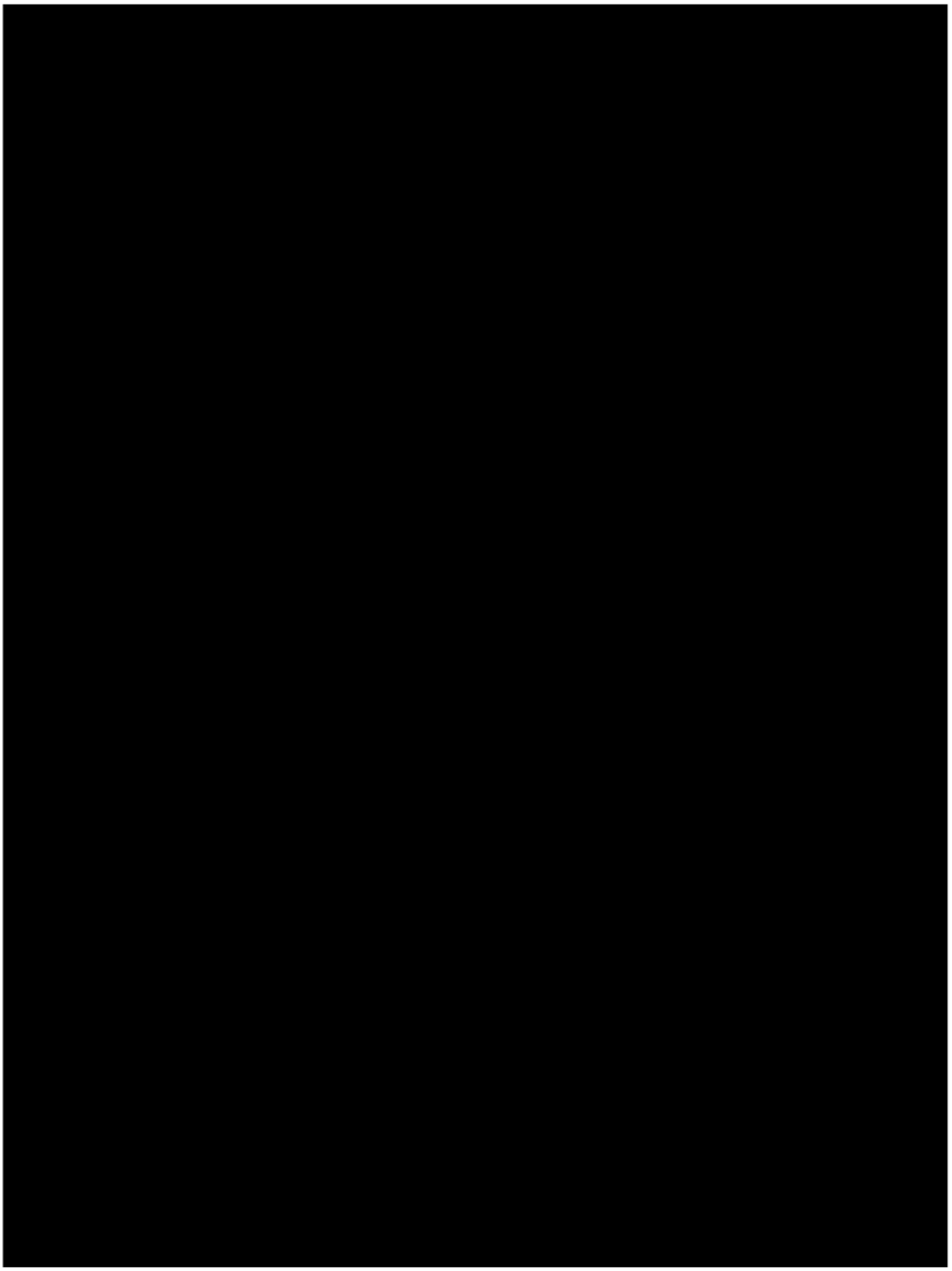

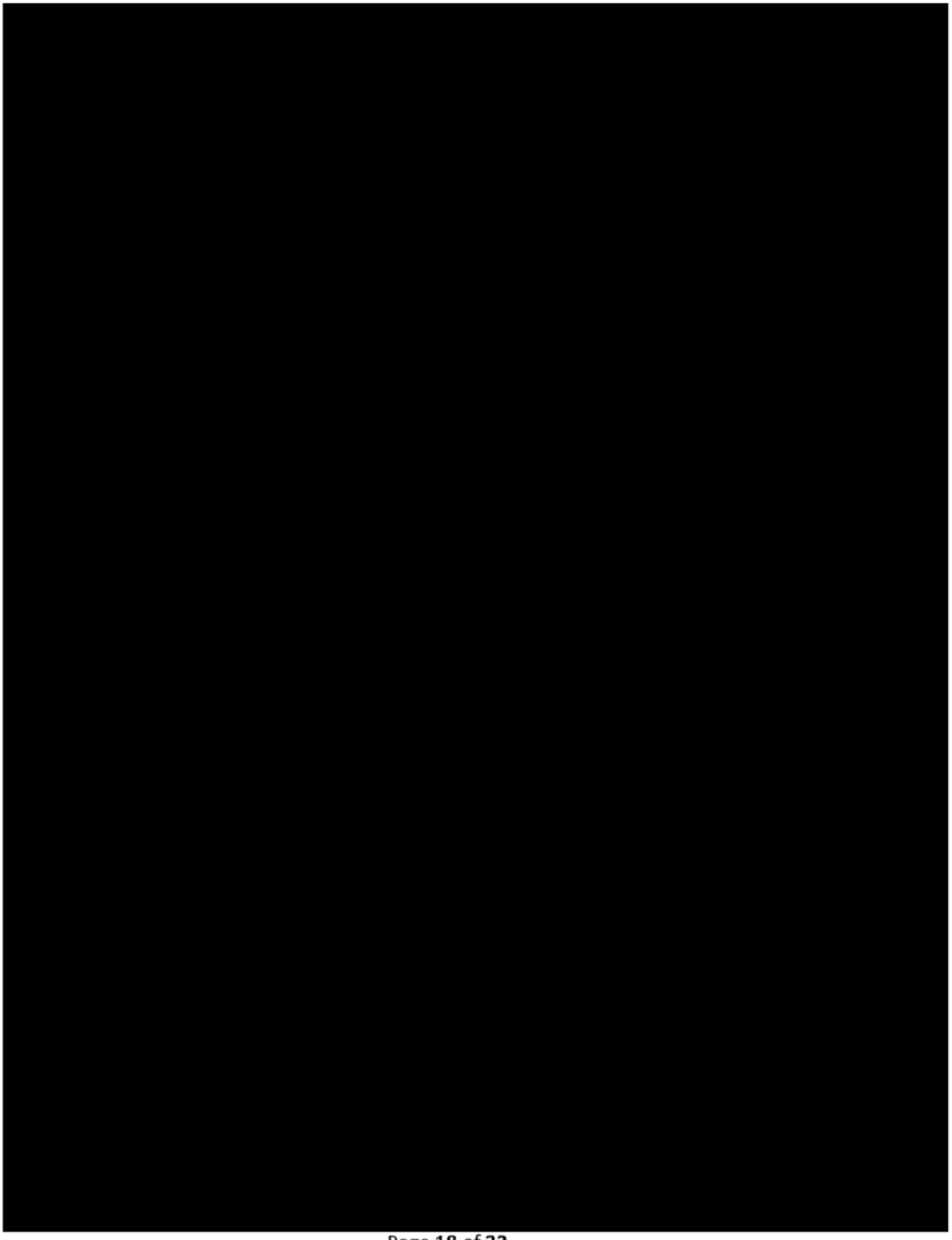

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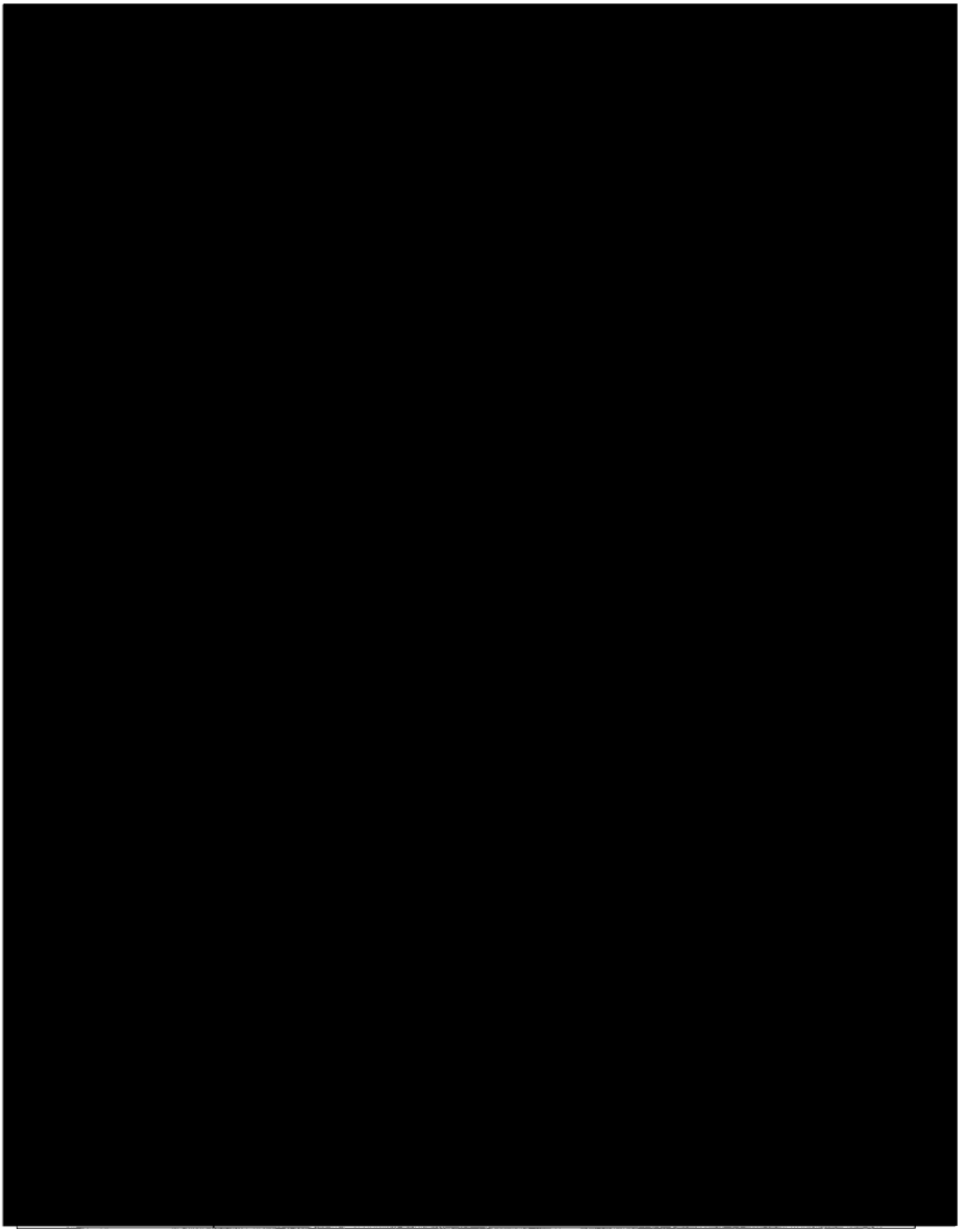

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4.3. Safety Endpoints

Number and percentage of subjects experiencing adverse events.

4.4. Other Endpoints

Not Applicable.

4.5. Covariates

For the primary efficacy variable and secondary efficacy variables, treatment means and between-treatment differences will be assessed by means of an Analysis of Covariance (ANCOVA) model with treatment, gender, and center as factors and the corresponding baseline score as a covariate.

5. HANDLING OF MISSING VALUES

For the analysis of the primary efficacy endpoint, if the global face total lesion count is missing at Week 12 for more than 5% of the subjects, the missing value will be imputed by using the last observation carried forward (LOCF) method.

6. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

6.1. Statistical Decision Rules

For the primary efficacy endpoint, the following comparisons will be performed:

1. Mask alone treatment Week 12 vs. baseline
2. Mask with topical gel-cream treatment Week 12 vs. baseline
3. Mask with topical gel-cream treatment vs. mask alone treatment for non-inferiority
4. Mask with topical gel-cream treatment vs. mask alone treatment for superiority

To evaluate the efficacy of the mask alone treatment and the mask with topical gel-cream treatment, statistical comparisons for the primary variable will be based on a stepwise procedure starting with comparisons #1 and #2, which evaluate the monadic efficacy of mask alone treatment and the mask with topical gel-cream treatment, respectively. If both comparisons are significant, testing will proceed to comparison #3 to evaluate the non-inferiority of the mask with topical gel-cream treatment to the mask alone treatment; otherwise, comparison #3 will be exploratory. If the mask with topical gel-cream treatment is demonstrated to be non-inferior to the mask alone treatment, then testing will proceed to comparison #4; otherwise, comparison #4 will be exploratory.

6.2. Statistical Hypotheses

For comparisons #1 and #2, the null hypothesis that there is no difference compared to the baseline will be tested against the alternative hypothesis that there is a difference from the baseline.

Specifically, the following hypothesis will be tested:

$$H_0: \mu_d = 0$$

against the two-sided alternative

$$H_1: \mu_d \neq 0$$

where d is the within-treatment change or percent change from baseline, and μ_d is the mean of the treatment group, i.e., the mask alone treatment or the mask with topical gel-cream treatment.

The mask alone treatment and mask with topical gel-cream treatment each will be considered efficacious monadically if the respective mean percent change from baseline is significantly different from zero at the 0.05 significance level, two-sided.

To compare the mask with topical gel-cream treatment vs. mask alone treatment for non-inferiority (#3), the following hypothesis will be tested:

$$H_0: \mu_A - \mu_B \geq 15\%$$

against the one-sided alternative

$$H_1: \mu_A - \mu_B < 15\%$$

where μ_A and μ_B are the mean percent change at Week 12 of global face total acne lesion count of the mask with topical gel-cream and the mask alone treatment, respectively. The difference between treatment groups will be computed as mask with topical gel-cream minus the mask alone treatment, and non-inferiority will be concluded if the upper bound of the two-side 95% confidence interval is less than 15 percentage points.

For the superiority (#4) test comparing the mask with topical gel-cream treatment vs. the mask alone treatment, with respect to an efficacy variable, the null hypothesis that there is no difference between the two treatments will be tested against the alternative hypothesis that there is a difference.

Specifically, the following hypothesis will be tested:

$$H_0: \mu_A - \mu_B = 0$$

against the two-sided alternative

$$H_1: \mu_A - \mu_B \neq 0$$

where μ_A and μ_B are the means of the mask alone treatment and the mask with topical gel-cream treatment, respectively. Superiority will be concluded if the upper bound of the two-sided 95% confidence interval of the treatment difference is less than 0.

With the stepwise procedure, the familywise error rate will be controlled at the 0.05 level.

6.3. Statistical Methods

6.3.1. Method for Primary Efficacy Endpoint

The mean percent change from baseline in global face total lesion count at Week 12 within the mask with topical gel-cream treatment cell and the mask alone treatment cell will each be tested using a one-sample t-test.

If both of the above comparisons are significant, the non-inferiority of the mask with topical gel-cream treatment to the mask alone treatment will be evaluated; otherwise, this comparison will be exploratory. Treatment means and between-treatment differences will be assessed by means of an ANCOVA model with treatment, gender, and center as factors and the corresponding baseline score as a covariate. The difference between treatment groups will be computed as the mask with topical gel-cream minus the mask alone treatment, and non-inferiority will be concluded if the upper bound of the two-side 95% confidence interval is less than 15 percentage points.

If the mask with topical gel-cream treatment is demonstrated to be non-inferior to the mask alone treatment, the superiority of the mask with topical gel-cream treatment versus the mask alone treatment will be evaluated. Superiority will be concluded if the upper bound of the two-sided 95% confidence interval of the treatment difference is less than 0.

Impact of center on treatment effect will be assessed in a separate analysis by including the center-by-treatment interaction in the ANCOVA model above. Summary statistics will be presented by treatment and center with no statistical comparison between treatments within a center.

If the global face total lesion count is missing at Week 12 for more than 5% of the subjects, the missing value will be imputed by using the last observation carried forward (LOCF) method. In addition, a sensitivity analysis will be performed using a repeated measure mixed model based on the observed data. The model will include the baseline score as the covariate and terms for treatment, gender, center, visit, baseline-by-visit, and treatment-by-visit interactions. The covariance matrix will be assumed unstructured.

6.3.2. Methods for Secondary and Tertiary Efficacy Endpoints

6.3.2.1. Acne Lesion Counts

Summary statistics of the global face acne lesion counts (open comedones counts, closed comedones counts, inflammatory acne lesion counts, non-inflammatory acne lesion counts, and total lesion counts analyzed separately), change from baseline, and the percent change from baseline (only for inflammatory lesions, non-inflammatory lesions, and total) will be presented by visit and treatment group. The corresponding 95% confidence interval of mean change from baseline and percentage change from baseline will be calculated within treatment group by visit.

Due to the small number (or zero count) of closed comedones and open comedones at baseline, percent change will not be calculated by subject for these two types of lesions. Instead, percent change from baseline in group mean will be presented for each treatment. This will be calculated as post-baseline mean minus baseline mean divided by baseline mean times 100.

The percent (%) of subjects who had improvement in counts and percent (%) of subject who had worsening in counts will also be provided. A reduction of 1 or more lesion from baseline will be considered an improvement. An increase of one or more lesion will be considered a worsening.

Treatment means and between-treatment differences in change from baseline and percent change from baseline will be assessed by means of an ANCOVA model with treatment, gender, and center as factors and the corresponding baseline acne lesion counts as a covariate. The two-sided 95% confidence interval of the between-treatment difference will be constructed.

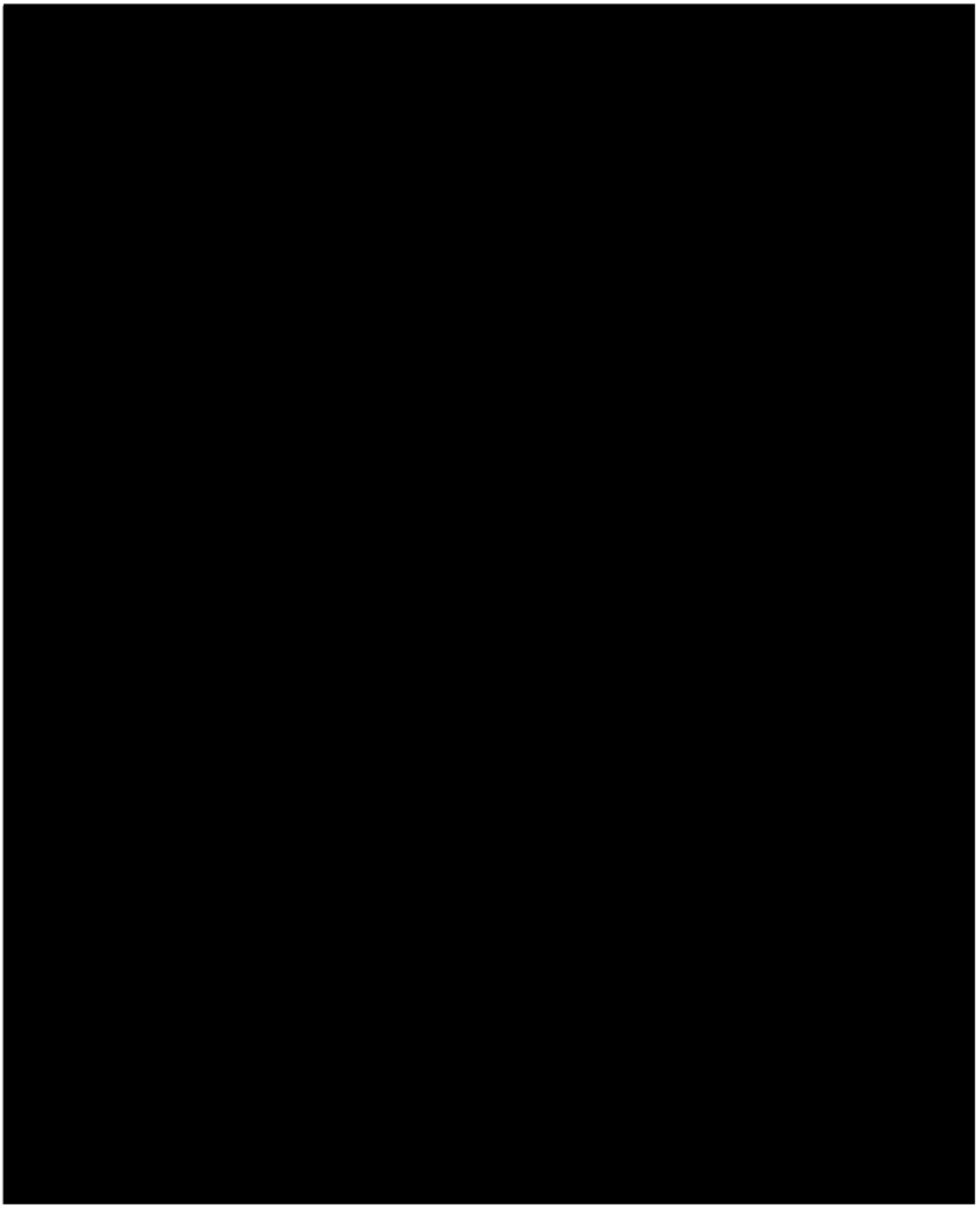
6.3.2.2. Investigator Global Acne Assessment

Investigator Global Acne Assessment and the change from baseline will be presented by visit and treatment group using summary statistics. The corresponding 95% confidence interval of mean change from baseline will be calculated within each treatment group by visit. The percentage of subjects who had improvement in counts from the baseline (score reduced from baseline by half-point or greater) within each treatment group will also be summarized by visit.

Treatment means and between-treatment differences in change from baseline will be assessed by means of an ANCOVA model with treatment, gender, and center as factors and the corresponding baseline score as a covariate. The two-sided 95% confidence interval of the between-treatment difference will be constructed.

6.3.2.3. Investigator Additional Efficacy Assessment

The Investigator Additional Efficacy Assessments will be summarized and analyzed similarly to the Investigator Global Acne Assessment. The percentage of subjects who had improvement in counts from the baseline (score reduced from baseline by half-point or greater) within each treatment group will also be summarized by visit.



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6.4. Statistical Analyses

The Quantitative Sciences Department at the Sponsor will be responsible for statistical analyses.

Summary statistics will be provided by treatment group at each time point. For continuous variables, descriptive summaries will include number of subjects, mean, standard deviation, median, minimum and maximum values. Distributions of categorical variables will be summarized by presenting the number and percent of subjects in each response category.

6.4.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all randomized subjects as well as for the full analysis set, the per-protocol analysis set, and the safety analysis set. A summary will also be provided by center for all randomized subjects.

6.4.2. Efficacy Analyses

All efficacy analyses will be based on the Full Analysis Set which will be the primary analysis. As a secondary analysis, the primary efficacy endpoint will be analyzed based on the Per-Protocol Analysis Set.

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6.4.4. Safety Analyses

The safety analysis will be based on the Safety Analysis Set.

Adverse events will be classified as treatment-emergent or non-treatment-emergent. Treatment-emergent AEs are those AEs not present prior to first study product usage.

The number and percentage of subjects experiencing treatment-emergent adverse events will be summarized by treatment, MedDRA version 20.0 system organ class, and preferred term.

The number and percentage of subjects experiencing treatment-related AEs will be summarized by treatment, MedDRA system organ class, and preferred term. Treatment-related AEs are events evaluated by the investigator as being possible, probable, or very likely related to study product. AEs with an unknown relationship to treatment will be considered to be treatment-related.

The number and percentage of subjects who were discontinued from the study due to adverse events and the number and percentage of subjects experiencing serious adverse events will be summarized by treatment, MedDRA system organ class, and preferred term.

The number of subjects with treatment-emergent adverse events will be summarized by severity (mild, moderate, and severe) for all adverse events and also for treatment-related adverse events. Subjects will be counted only once for each system organ class and preferred term by selecting the most severe event.

Listings of all adverse events will be provided. Treatment-emergent AEs and non-treatment-emergent AEs, if present, will be listed separately.

7. REFERENCES

There are no references.

8. CHANGES FROM THE PROTOCOL