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Title: Optive Brand For Day And Night Dry Eye Management

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OCULAR TECHNOLOGY GROUP - *International*

STUDY NAME: OPTIVE BRAND FOR DAY AND NIGHT DRY EYE MANAGEMENT

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1 Introduction

The current Statistical analysis plan concerns the study descriptive statistics for all the study variables and the comparative statistics for the primary and secondary endpoints.

2 Study Description

2.1 Endpoints

The primary end points are:

i. OSDI total score.
ii. Measured lissamine green bulbar conjunctival staining (mm^2).

The secondary end points are symptomatology upon waking (VAS scale).

[redacted]

2.2 Hypotheses

The primary hypotheses that to be tested are that:

i. One-month treatment of moderate to severe dry eye sufferers with an eyedrop / gel combination will reduce overall dry eye symptomatology. The null hypothesis and alternative hypotheses are:

H_0: $\mu OSDI_{FU} \leq \mu OSDI_{BL}$

H_1: $\mu OSDI_{FU} > \mu OSDI_{BL}$

where $\mu OSDI_{FU}$ denotes the mean OSDI score at the follow-up visit and $\mu OSDI_{BL}$ at the baseline visit.

ii. One-month treatment of moderate to severe dry eye sufferers with an eyedrop / gel combination will decrease conjunctival staining. The null hypothesis and alternative hypotheses are:

H_0: $\mu CS_{FU} \geq \mu CS_{BL}$

H_1: $\mu CS_{FU} < \mu CD_{BL}$

where μCS_{FU} denotes the mean measured conjunctival staining at the follow-up visit and μCS_{BL} at the baseline visit.

The secondary hypothesis that to be tested is that:

i. One-month treatment of moderate to severe dry eye sufferers with an eyedrop / gel combination will reduce symptomatology upon waking. The null hypothesis and alternative hypotheses are:

H_0: $\mu CW_{FU} \geq \mu CW_{BL}$

H_1: $\mu CW_{FU} < \mu CW_{BL}$

where μCW_{FU} denotes the mean comfort reported upon waking on a 100-pt VAS scale at the follow-up visit and μCW_{BL} at the baseline visit, where the higher the score the worse is the symptom.

[redacted]

iii. The improvement in symptomatology will be apparent after the first week of treatment and will improve over the one-month period.

2.3 *Study population*

The initial study population is to include up to 40 screened participants to have 35 participants enrolled into the investigational phase and to achieve a cohort of 30 participants completing the study.

The inclusion criteria include the following:
i. Age at least 18 years;
ii. OSDI score of ≥ 23;
iii. Ocular comfort at waking <65 on 100-point scale;
iv. Conjunctival staining Grade ≥ 2 (scale 0 to 4) in at least one eye;
v. Use of eyedrops for the relief of dry eye symptoms for at least one month.

2.4 *Study Products*

The treatment regimen is:
i. Optive® Fusion a CE marked eyedrop, manufactured by Allergan Pharmaceuticals Ireland, containing 0.1% sodium hyaluronate, 0.5% carmellose sodium and 0.9% glycerol for daytime use. The eyedrop will be used as needed up to four times a day but at least twice a day;
ii. Optive® Gel Drop a CE marked gel manufactured by Allergan Pharmaceuticals Ireland, containing 0.5% carboxymethylcellulose sodium and 0.9% glycerol for night time use. The eyedrop will be used once in the evening; the gel drop being instilled any time during the last hour prior to sleep.

The treatment regimen is to be used for one month (30 ± 3 days).

2.5 *Study Design*

The study is conducted as an open label, bilateral, prospective, interventional single arm clinical study, however, the investigator carrying out the tear film kinetics and tissue staining analyses post-hoc are masked for these activities.

The participants attend a total of three scheduled visits over a five-week period.
i. Enrolment visit;
ii. Baseline / Dispensing visit (7 ± 1 days from enrolment);
ii. One-month follow-up visit (30 ± 3 days from dispensing).

3 Analysis

3.1 *Database*

The final analysis for the CSR concerns the closed-out database when all participants have been exited from the study.

3.2 *Data Sets*

Three data sets will be produced as defined below:

i. Safety Analysis Data Set
Safety analyses will be conducted using this data set. The Safety Analysis Data Set will include all the participants enrolled into the study.

ii. Full Analysis Data Set

The Full Analysis Data Set will include of all participants who have been exposed to any product evaluated in this study.

iii. Per protocol Data Set
The Per Protocol Data Set will include all the participants who have completed the study as per the protocol, this set will include only participants who have completed the study without any major deviation judged to affect the validity of the data.

Listings and descriptive statistics will be produced for the latter two data sets and comparative statistics will only be produced for the Per Protocol Data Set.

3.3 *Normality Testing*

All primary and secondary endpoints, being continuous endpoints, will be checked for normality graphically and by statistical tests prior to the comparative statistics being carried out. The Q-Q Probability plot will be used to examine the values against a normality distributed data. Statistical (Normality) testing will be carried out by Kolmogorov Smirnov, and Shapiro Wilk tests. The derived histograms and the values of kurtosis and skewness will be taken into consideration when verifying normality and deciding upon the statistical model to use

If the normality assumption does not hold, the data will be transformed; the transformation method chosen will depend upon the skewness and the kurtosis values. The following transformations are the key transformation methods that will be considered for the recorded variables the transformations will be carried in the following order until normality or near normality is achieved: square root, logarithm and inverse. If the data after applying transformations differs statistically from normal, then a non-parametric model will be used.

3.4 *Descriptive Statistics*

3.4.1 General

For all the key parameters recorded, summary tables including descriptive and/or distribution statistics will be given for both the per protocol analysis and the full analysis data sets.

All enrol participants, defined as subjects who signed the consent form will constitute the safety data set. All subjects who meet the eligibility criteria, adhere to the protocol, and successfully complete the full study assessment will be available for the per-protocol analysis. Participants with missing data will be included in the analysis unless there is some non-response-related reason to exclude them, such as a protocol violation/invalid data.

For continuous variables, the following descriptive statistics will be reported: mean, median, standard deviation, minimum, maximum and sample size. For ordinal variables, the following statistics will be reported: median, mode, minimum, maximum, quartiles, sample size and distribution tables will be produced.

3.4.2 Output

The descriptive statistics will be reported both for the full analysis population and the per protocol population.

3.5 *Comparative Statistics*

3.5.1 General

The study design does not include a control group the efficacy of the regimen will be measured by comparing the data recorded at the dispensing visit, prior product dispensing visit (Baseline) to the data recorded at the 30-Day follow-up visit (Response).

In this study two sets of analyses will be carried out for each primary and secondary variables. The first set will follow a linear model approach to account for all the data characteristics (e. g. multiple data for the same response variable for a given timepoint). The second set will be based on simplistic testing such as the t-test or if not applicable an equivalent non-parametric test.

3.5.2 Primary Endpoints

LINEAR MODEL ANALYSIS

The primary variables OSDI total score and measured lissamine green bulbar conjunctival staining are parametric variables.

The primary variables being continuous variables ideally parametric testing will be carried out. Therefore, if the variables are normality distributed or close to normally distributed before or after transformation allowing parametric analysis parametric statistics will be carried out using the following model:

OSDI Total Score: A linear mixed model will be used. The model will include time (Baseline / Dispensing visit, One-month follow-up visit) as repeated measures fixed factor. The subject ID will be a random factor. The covariance structure that best models the residuals errors from the same subject across the time periods will be selected according to the AICC criterion. Possible structures will include Compound Symmetry (CS), Heterogeneous Compound Symmetry (CSH), Ante-Dependent (ANTE (1)), Autoregressive (AR1), Unstructured (UN). In case that the Hessian Matrix is not positive definite, random effect will be removed from the model. The comparisons of OSDI scores between baseline and one month follow up will be carried out using a 95% confidence interval from the least square mean differences in percentage from the mixed linear model.

Lissamine green bulbar conjunctival staining: A linear mixed model will be used. The model will include time (Baseline / Dispensing visit, One-month follow-up visit), region (nasal and temporal) as repeated measures fixed factors as well as with all the possible interactions. The eye will be taken into consideration as repeated measure but not as fixed factor. The subject ID will be a random factor. The covariance structure that best models the residuals errors from the same subject across the time and eye will be selected according to the AICC criterion. Possible structures will include Compound Symmetry (CS), Heterogeneous Compound Symmetry (CSH), Ante-Dependent (ANTE (1)), Autoregressive (AR1), Unstructured (UN). In case that the Hessian Matrix is not positive definite, random effect will be removed from the model. The comparisons of Lissamine green bulbar conjunctival staining between baseline and one month follow up will be carried out using a 95% confidence interval from the least square mean differences in percentage from the mixed linear model.

If the variables cannot be normalized the following model will be applied:

OSDI Total Score: A generalized mixed linear model will be used. Possible models will include Gamma regression model with a Log link function or a Negative Gaussian with Log link function. The model will include time (Baseline / Dispensing visit, One-month follow-up visit) as repeated measures fixed factors. The subject ID will be a random factor. The covariance structure that best models the residuals errors from the same subject across the time and eye will be selected according to the AICC criterion. Possible structures will include Compound Symmetry (CS), Heterogeneous Compound Symmetry (CSH), Ante-Dependent (ANTE (1)), Autoregressive (AR1), Unstructured (UN). In case that the Hessian Matrix is not positive definite, random effect will be removed from the model. The comparisons of OSDI score between baseline and one month follow up will be carried out using a 95% confidence interval from the least square mean differences in percentage from the generalized mixed linear model.

Lissamine green bulbar conjunctival staining: A generalized mixed linear model will be used. Possible models will include Gamma regression model with a Log link function or a Negative Gaussian with Log link function. . A linear mixed model will be used. The model will include time (Baseline / Dispensing visit, One-month follow-up visit), region (nasal and temporal) as repeated measures fixed factors as well as with all the possible interactions. The eye will be taken into consideration as repeated measure but not as fixed factor. The subject ID will be a random factor. The covariance structure that best models the residuals errors from the same subject across the time and eye will be selected according to the AICC criterion. Possible structures will include Compound Symmetry (CS), Heterogeneous Compound Symmetry (CSH), Ante-Dependent (ANTE (1)), Autoregressive (AR1), Unstructured (UN). In case that the Hessian Matrix is not positive definite, random effect will be removed from the model. The comparisons of Lissamine green bulbar conjunctival staining between baseline and one month follow up will be carried out using a 95% confidence interval from the least square mean differences in percentage from the generalized mixed linear model.

SIMPLISTIC SINGLE FACTOR ANALYSIS

The primary variables OSDI total score and measured lissamine green bulbar conjunctival staining are parametric variables.

The primary variables being continuous variables ideally parametric testing will be carried out. Therefore, if the variables are normality distributed or close to normally distributed before or after transformation allowing parametric analysis parametric statistics the following test will be applied:

OSDI Total Score: A paired t-test approach will be followed. The test will compare the OSDI scores recorded at the two visits (Baseline / Dispensing visit, One-month follow-up visit). The comparisons of the OSDI scores between baseline and one month follow up will be carried out taking 95% as the threshold of significance.

Lissamine green bulbar conjunctival staining: A paired t-test approach will be followed. Lissamine green bulbar conjunctiva staining is recorded and quantified separately for the right and left eyes and for the nasal and temporal bulbar regions; therefore, in order to prevent sample size overestimation by accounting for each measurement the analysis will be carried out on the mean staining of the two zones of the two eyes to have a single data point per visit. The test will compare the mean staining recorded at the two visits (Baseline / Dispensing visit, One-month follow-up visit). The comparisons of the mean staining between baseline and one month follow up will be carried out taking 95% as the threshold of significance.

If the variables cannot be normalized the following test will be applied:

OSDI Total Score: the non-parametric equivalent of the paired t-test is Wilcoxon Rank Test. The test will compare the OSDI scores recorded at the two visits (Baseline / Dispensing visit, One-month follow-up visit). The comparisons of the OSDI scores between baseline and one month follow up will be carried out taking 95% as the threshold of significance.

Lissamine green bulbar conjunctival staining: the non-parametric equivalent of the paired t-test, is Wilcoxon Rank Test. The test will compare the mean staining of the two measurement zones of the two eyes to produce a single data point per visit (Baseline / Dispensing visit, One-month follow-up visit). The comparisons of the mean lissamine green staining between baseline and one month follow up will be carried out taking 95% as the threshold of significance.

3.5.3 Secondary Endpoint

LINEAR MODEL ANALYSIS

The secondary variable comfort upon waking is parametric variable.

The secondary variable being a continuous variable ideally parametric testing will be carried out. Therefore, if the variable is normality distributed or close to normally distributed before or after transformation allowing parametric analysis parametric statistics will be carried out using the following model.

A linear mixed model will be used. The model will include time (Baseline / Dispensing visit, One-month follow-up visit) as repeated measures fixed factors. The Eye will be taken into consideration as a repeated factor. The subject ID will be a random factor. The covariance structure that best models the residuals errors from the same subject across the time and eye will be selected according to the AICC criterion. Possible structures will include Compound Symmetry (CS), Heterogeneous Compound Symmetry (CSH), Ante-Dependent (ANTE (1)), Autoregressive (AR1), Unstructured (UN). In case that the Hessian Matrix is not positive definite, random effect will be removed from the model. The comparisons of Lissamine green bulbar conjunctival staining between baseline and one month follow up will be carried out using a 95% confidence interval from the least square mean differences in percentage from the mixed linear model.

If the variable cannot be normalized a generalized mixed linear model will be used. Possible models will include Gamma regression model with a Log link function or a Negative Gaussian with Log link function. . The model will include time (Baseline / Dispensing visit, One-month follow-up visit) as repeated measures fixed factors. The subject ID will be a random factor and Eye will be included as repeated factor. The covariance structure that best models the residuals errors from the same subject across the time and eye will be selected according to the AICC criterion. Possible structures will include Compound Symmetry (CS), Heterogeneous Compound Symmetry (CSH), Ante-Dependent (ANTE (1)), Autoregressive (AR1), Unstructured (UN). In case that the Hessian Matrix is not positive definite, random effect will be removed from the model. The comparisons of the comfort upon waking between baseline and one month follow up will be carried out using a 95% confidence interval from the least square mean differences in percentage from the generalized mixed linear model.

SIMPLISTIC SINGLE FACTOR ANALYSIS

The secondary variable comfort upon waking is parametric variable.

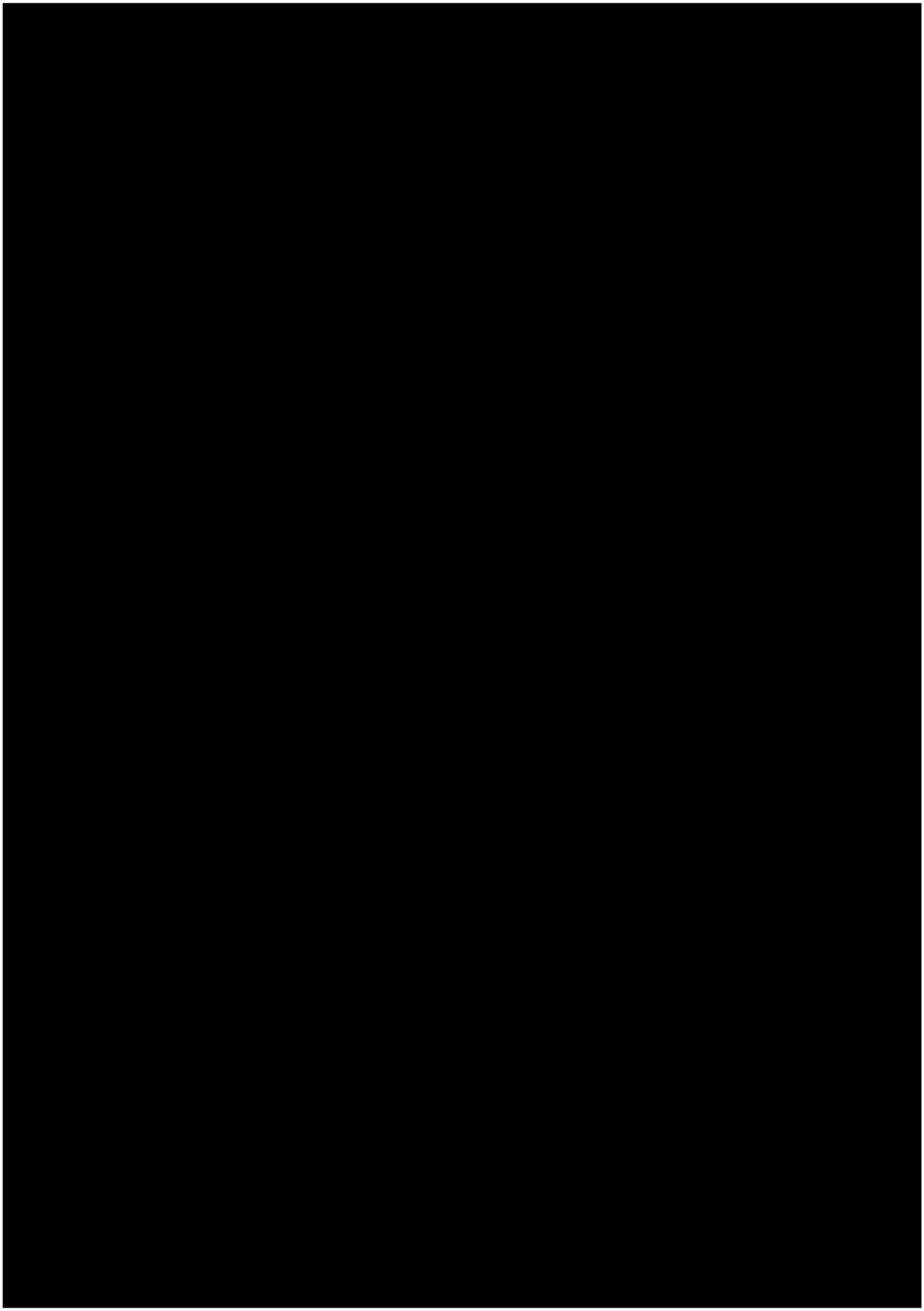
The secondary variable being a continuous variable ideally parametric testing will be carried out. Therefore, if the variable is normality distributed or close to normally distributed before or after transformation allowing parametric analysis parametric statistics the following test will be applied.

A paired t-test approach will be followed. The comfort upon waking is recorded separately for the right and left eyes; therefore, in order to prevent sample size overestimation by accounting for each measurement the analysis will be carried out on the mean VAS score of the two eyes to have a single data point per visit. The test will compare the comfort upon waking scores recorded at the two visits (Baseline / Dispensing visit, One-month follow-up visit). The comparisons of the mean staining between baseline and one month follow up will be carried out taking 95% as the threshold of significance.

If the variables cannot be normalized Wilcoxon Rank Test will be carried out. The test will compare the mean VAS comfort at waking scores of the two eyes to produce a single data point per visit (Baseline / Dispensing visit, One-month follow-up visit). The comparisons of the waking comfort scores between baseline and one month follow up will be carried out taking 95% as the threshold of significance.

3.5.4 Other Aspects of Interest endpoints

[redacted]



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APPROVALS

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