Johnson & Johnson Vision

STATISTICAL ANALYSIS PLAN

Protocol CR-6241

Evaluation of senofilcon A With New UV-blocker on a Neophyte Population

Acuvue Oasys with Transitions (senofilcon A with new UV-blocker)

Version: 1.0

Date: 13 May 2019

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Compliance: The study described in this document was performed according to the principles of Good Clinical Practice (GCP).

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TABLE OF CONTENTS

AUTHORIZED SIGNATURES 2

TABLE OF CONTENTS 3

AMENDMENT HISTORY 5

ABBREVIATIONS 5

1. INTRODUCTION 6

2. STUDY OBJECTIVES 6

3. STUDY DESIGN 6
3.1. Overview 6
3.2. Test Articles 6
3.3. Targeted Study Population and Sample Size 6
3.4. Test Article Allocation and Masking 7
3.5. Time and Event Schedule 7

4. STUDY ENDPOINTS 8
4.1. Primary Endpoint 8
4.2. Secondary Endpoint 8
4.3. Other Endpoints 8

5. STATISTICAL HYPOTHESES FOR STUDY OBJECTIVES 9
5.1. Primary Hypotheses 9
5.2. Secondary Hypotheses 9
5.3. Other Hypotheses 9

6. ANALYSIS SETS 9
6.1. All Enrolled 9
6.2. Intent-to-Treat (ITT) 9
6.3. Safety Population 9
6.4. Per-Protocol (PP) 9

7. DEFINITIONS AND DERIVED VARIABLES 9
7.1. Age 9
7.2. Visit Windows 9
7.3. Iris Category 10

8. GENERAL STATISTICAL CONSIDERATIONS 10
8.1. Statistical Software 10
8.2. Summary Statistics 10
8.3. Reporting Numerical Values 10
8.4. Sample Size Justification 11
8.5. Statistical Significance Level 11
8.6. Handling of Missing Data and Drop-outs 11

9. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW..... 11

10. SUBJECT INFORMATION..... 11
10.1. Disposition Information..... 11
10.2. Protocol Deviations..... 12
10.3. Demographics and Baseline Characteristics..... 12
10.4. Treatment Compliance and Extent of Exposure..... 12
10.5. Prior and Concomitant Medications..... 12
10.6. Medical History..... 12

11. STATISTICAL ANALYSIS..... 12
11.1. Primary Analysis..... 12
11.2. Other Analysis..... 13

12. SAFETY EVALUATION..... 13
12.1. Adverse Events..... 13
12.2. Physical Examination Findings..... 13
12.3. Contact Lens Fitting..... 14
12.4. Subject Reported Ocular Symptoms..... 14
12.5. Contact Lens Correct Visual Acuity..... 14
12.6. Contact Lens Deposits..... 14
12.7. Average Daily Wear Time (in Hours)..... 15
12.8. Reasons for Lens Replacement..... 15
12.9. Reasons for Discontinuations..... 15

13. REFERENCES..... 16

14. SAS CODE:..... 16

AMENDMENT HISTORY

Version Number	Revision Date (DD/MM/YYYY)	Reasons for Revision
1.0	13 May 2019	Original Draft

ABBREVIATIONS

AE	adverse event
CI	confidence interval
CRF	case report form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
eCRF	electronic case report form
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
IVRS	interactive voice response system
LOCF	last observation carried forward
PI	principal investigator
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation

1. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for protocol CR-6241 Version 2.0.

This document will serve as the final guidance for all the statistical analysis for this study and will supersede the Statistical Method section in the protocol if there are any discrepancies. Any deviation from the analysis plan will be documented as such in the clinical study report.

2. STUDY OBJECTIVES

The objective of this study is to determine the proportion of subjects that are successfully fit with the investigational contact lens on a population that has never worn contact lenses outside of a doctor's office.

3. STUDY DESIGN

3.1. Overview

This is a 5-visit, multi-site, single-arm dispensing trial. Approximately 135 subjects will be screened and enrolled to ensure that 100 subjects complete.

The study begins with an initial Visit 1 (Day 0). If a subject is found to meet all eligibility criteria, they will be enrolled into the study. Subjects will wear the Test contact lens in a bilateral fashion as daily wear, reusable format for approximately 4-weeks. After the 4-week follow-up visit (visit 4), subjects will wear their habitual spectacles for a period of 1-week.

If a subject is dispensed the study lens at the initial visit, 4 follow-up visits will be conducted. The follow-up visit occurs approximately 1-, 2-, 4- and 5-weeks after the initial visit. Unscheduled follow-up visits may occur during this study. Subjects will be advised to wear the study lens at least 5 days per week and 6 hours per day. Lens replacement is scheduled at the 2-week follow-up visit.

3.2. Test Articles

Table 1: Test Article Label

Test Article	Label
ACUVUE OASYS with Transitions (senofilcon A based contact lens with new UV-blocker)	Test

3.3. Targeted Study Population and Sample Size

Approximately 135 subjects will be enrolled to ensure that at least 100 subjects will complete the study. Enrolled subjects will be healthy adult males and females of any race or ethnicity that have never worn a contact lens outside of the doctor's office. Subjects will be between 18 and 39 years of age (inclusive). All subjects are required to have an updated pair of spectacles within the prior six months and at least for two weeks. Habitual wearers of Transitions spectacle lenses will comprise 15-20% of the sample.

Table 2: Planned Enrollment Strategy by Lens type and Site

	Total
Enrolled	135
Randomized	126
Completed	100
Number of enrolled per site	19-20

3.4. Test Article Allocation and Masking

This is a single arm study; therefore, all eligible subjects will be assigned the Test lens in a bilateral fashion.

All subjects will be described the Test lens prior to fitting. As such, the lens will be unmasked (open-label). Subjects will be aware of the identity of the investigational product. Investigators and clinical site personnel involved in the data collection will not be masked as to the identity of the investigational product.

3.5. Time and Event Schedule

Table 3: Time and Events Schedule

Visit Information	Visit 1 Screening, Baseline, Fit SCL	Visit 2 SCL FU-1	Visit 3 SCL FU-2	Visit 4 SCL FU-3, Spectacle	Visit 5 Spectacle FU-1 Final Eval
Time Point	Day 1	Day 7 ± 1 After V1	Day 7 ± 1 After V2	Day 14 ± 2 After V3	Day 7 ± 1 After V4
Estimated Visit Duration	2.5 hours	1.5 hours	1.5 hours	1.5 hours	1.5 hours
Statement of Informed Consent	x				
Demographics	x				
Medical History/Concomitant Medications	x	x	x	x	x
Habitual Contact Lens Information	x				
Inclusion/Exclusion Criteria	x				
Entrance Visual Acuity	x	x	x	x	x
Subjective Sphero-Cylindrical Refraction	x				
Slit Lamp Biomicroscopy	x	x	x	x	x
Lens Insertion & Settling	x		x		
Visual Acuity and Over Refraction	x		x		
Lens Power Modification (if applicable)	x		x		

Visit Information	Visit 1 Screening, Baseline, Fit SCL	Visit 2 SCL FU-1	Visit 3 SCL FU-2	Visit 4 SCL FU-3, Spectacle	Visit 5 Spectacle FU-1 Final Eval
Time Point	Day 1	Day 7 ± 1 After V1	Day 7 ± 1 After V2	Day 14 ± 2 After V3	Day 7 ± 1 After V4
Estimated Visit Duration	2.5 hours	1.5 hours	1.5 hours	1.5 hours	1.5 hours
Subject Reported Ocular Symptoms	x	x	x	x	x
Lens Fit Assessment	x	x	x	x	x
Insertion / Removal	x				
Exit Snellen Distance Visual Acuity	x	x	x	x	x
Dispense Patient Instruction Guide	x				
Dispense Test Article	x		x		
Lens wear Compliance			x		
Follow-up Questionnaire					x
Surface Deposits		x	x	x	
Study Completion					x

4. STUDY ENDPOINTS

4.1. Primary Endpoint

Proportion of subjects that can be successfully fit in the Test lens:
Successful fit is determined by the eye care practitioner (ECP/investigator) at the 4-Week follow-up evaluation and is based on the following individual questionnaire item, "Based on your professional judgement of acceptable physiology, comfort, vision, and handling after four weeks of lens wear, do you consider your subject successfully fit with the study lenses?" (Response set: Yes/No).

4.2. Secondary Endpoint

Not applicable.

4.3. Other Endpoints

Subjects' response to individual questionnaire items. Subject assessments consist of three surveys assessing the following topics:

1. Subjects' activity history (including how much time subjects spend outdoors, watching TV and using a computer)
2. Subjects' assessment of lens performance compared to their spectacles

5. STATISTICAL HYPOTHESES FOR STUDY OBJECTIVES

5.1. Primary Hypotheses

The primary hypothesis must be met in order to satisfy the primary objective of this study.

1. The proportion of subjects that can be successfully fit with the Test lens will be superior to 50%.

5.2. Secondary Hypotheses

Not applicable.

5.3. Other Hypotheses

Not applicable.

6. ANALYSIS SETS

6.1. All Enrolled

The All Enrolled population will include all participants who sign an informed consent.

6.2. Intent-to-Treat (ITT)

Intent-to-treat will include all the subjects who successfully completed through the 4-Week Follow-up evaluation for which the Eye Care Practitioner completed the bilateral assessment of contact lens fitting; regardless of any protocol deviations.

6.3. Safety Population

This analysis population will include all subjects who are administered the test article. Safety analyses will be based on the safety population.

6.4. Per-Protocol (PP)

Per Protocol Analysis set will be the primary analysis population. It will include all subjects who have successfully completed all visits and did not substantially deviate from the protocol as determined by the trial cohort review committee prior to database hard lock. Justification of excluding subjects with protocol deviations in the per-protocol population set will be documented in a memo to file.

7. DEFINITIONS AND DERIVED VARIABLES

7.1. Age

Age will be calculated using the Date of Birth (DOB) and the date of the consenting the subject and presented as age at last birthday as an integer.
Age = Integer part of [(Date of Baseline visit – Date of Birth) / 365.25]

7.2. Visit Windows

Table 4: Visit Window information

Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)[a]	Target Time Point
1	Baseline	1	1
1	Fitting	1	1
2	1-Week FU	6 to 8	7
3	2-Week FU	13 to 15	14
3	Fitting	13 to 15	14
4	4-Week FU	19 to 22	21
4	Spectacle wear	19 to 22	21
5	5-Week FU	6 to 8	28

[a] The first treatment day is Day 1.

7.3. Iris Category

Iris color will be categorized into either dark or light based on the subjects' hue and lightness of their iris using Johnson & Johnson's Iris Color Scale. If hue is brown or lightness is dark then the subject will be classified as having a dark iris, if hue is light then the subject will be classified as having a light iris. If lightness is medium and hue is green, blue or grey then the subject will be classified as having a light iris; otherwise subjects will be classified as having a dark iris.

8. GENERAL STATISTICAL CONSIDERATIONS

8.1. Statistical Software

All data summaries and statistical analyses will be performed using the SAS software Version 9.4 or higher (SAS Institute, Cary, NC)[1].

8.2. Summary Statistics

Throughout the analysis of data, the results for each subject/eye will be used when available for summarization and statistical analysis. Unscheduled visits will be summarized separately and will be excluded from the statistical analysis.

Summary tables (descriptive statistics and/or frequency tables) will be provided for all baseline variables, efficacy variables and safety variables as appropriate. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum). Frequency count and percentage of subjects or eyes within each category will be provided for categorical data.

8.3. Reporting Numerical Values

Means, medians and confidence/credible intervals will be reported to one decimal place greater than the original data. The standard deviation will be reported to two decimal places greater than the original data. Minimum and maximum will use the same number of decimal places as the original data. P-values greater or equal than 0.0001 will be reported to 4 decimal places; p-values

less than 0.0001 will be reported as "<0.0001". All percentages will be reported to one decimal place.

8.4. Sample Size Justification

This study was designed and powered to test the primary hypothesis. Assuming a true successful rate of 65% (P_T), the sample size was calculated to test whether the true rate is superior to 50% (P_0) with 80% power and 2-sided type I error of 5%. The estimated sample size to test the primary hypothesis (H0 $P_T \leq P_0$, H1: $P_T > P_0$) is 100. The sample size was calculated using PROC POWER for one sample proportion using an exact Test of a Binomial Proportion.

The plan is to enroll approximately 135 subjects with a target completion of 100 subjects. Due to high drop-out rates observed in a previous neophyte study [redacted]. The required sample size for enrollment was increased by 35% to account for this drop-out rate.

8.5. Statistical Significance Level

All planned analysis will be conducted with an overall type I error rate of 5%.

8.6. Handling of Missing Data and Drop-outs

Missing or spurious values will not be imputed. The count of missing values will be included in the summary tables and listings.

9. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

There will be no interim analysis conducted for this study.

10. SUBJECT INFORMATION

10.1. Disposition Information

Enrolled subjects will be allocated to one of the three mutually exclusive:

1. Completed: Subjects are considered to have completed the study if they (a) provided informed consent and/or assent; (b) they are eligible; (c) completed all three phases of testing; and (d) have not withdrawn/discontinued from the study.

2. Discontinued: Subjects are considered to have discontinued from the study if (i) test article was administered and (ii) discontinued from the study. Reasons for discontinuation include: (a) Adverse Event (b) unsatisfactory visual response due to test article (c) satisfaction lens fitting due to test article (d) lens discomfort (e) lens handling difficulties (e) withdrew consent during study (f) lost to follow-up (g) subject no longer meets eligibility criteria (h) subject withdrawn by PI to non-compliance to protocol (i) test article no longer available

3. Assigned and Test Article Administered: Total number subjects for which test articles were administered (Completed + Discontinued).

4. Enrolled but Not Dispensed: Subjects are considered to be Enrolled Not Dispensed Subjects if they were (i) enrolled to the study (provided informed consent and/or assent) but failed to satisfy the eligibility criteria (inclusion/exclusion criteria) or (ii) if they are randomized but did not receive a test article.

5. Total enrolled: Completed + Discontinued + Enrolled but Not Dispensed.

10.2. Protocol Deviations

Any protocol deviation that could impact the primary endpoints will result in the subject being excluded from the Per-Protocol analysis population. No analysis on protocol deviations will be performed. All reported protocol deviations will be listed.

10.3. Demographics and Baseline Characteristics

Demographic characteristics will be summarized by Per-Protocol, safety, and all enrolled population using descriptive statistics for continuous variables, and numbers and percentages of subjects for categorical variables. Demographic information will include age, gender, race, iris category and ethnicity.

10.4. Treatment Compliance and Extent of Exposure

Average daily wear time and average daily comfort wear time will be provided in the summary table. Non-compliance will be reported in protocol deviation.

10.5. Prior and Concomitant Medications

Prior and concomitant medications will be documented during screening and updated during the study when applicable. A listing for both prior and concomitant medications will be created for all enrolled subjects.

Disallowed medications for this study include: any ocular medication; estrogens, antihistamines, anticholinergics, beta-blockers and psychotropics.

Concomitant therapies that are disallowed include: Not applicable.

10.6. Medical History

A listing of medical and surgical history will be created for all enrolled subjects.

11. STATISTICAL ANALYSIS

11.1. Primary Analysis

<u>Proportion of subjects with Successful Fit</u>

Successful fit is a binary response where X=1 if a subject can be successfully fit with the Test lens and X=0 otherwise. Successful fit is on a binocular level, therefore, the proportion of subjects that can successfully fit with the Test lens will be compared to the threshold 0.50. A 95% confidence interval using the exact binomial test will be used. Superiority will be concluded in the lower limit of the 95% confidence interval is above 0.50.

11.2. Other Analysis

Subjects responses to individual questionnaire items will be descriptive summarized using proportion and frequency tables

12. SAFETY EVALUATION

12.1. Adverse Events

Summary Table and Listing of all reported ocular and non-ocular AEs and SAEs will be reported.

Adverse events will be presented as Serious Adverse Events, Significant Ocular Adverse Events, Non-significant Ocular Adverse Events and Non-Ocular Adverse Events.

Adverse Events listings will include eye diagnosis, severity of the AE, the number of days the subject spent in the study, the slit lamp findings at discovery of the AE, whether or not it is lens related, the possible cause, and treatments provided to the patient, the outcome, the subjects final Snellen visual acuity, whether or not the subject eye had a scar at the resolution of the AE and the action taken. In addition, the total number of subjects and the total number of eyes with each type of AE (SAEs, ocular AEs and non-ocular AEs) will be tabulated and presented as a footnote in each summary.

12.2. Physical Examination Findings

Slit lamp findings will be summarized by visit. Any result of the slit-lamp assessment recorded at any scheduled or other unscheduled visits will be tabulated at eye level by visit and grade. If no slit lamp finding is noted in one eye, this will be considered as having a Grade 0 and will be included in the table as well. Possible findings will be reported in the following order: Corneal

- Edema
- Corneal Infiltrates (Yes/No)
- Corneal Neovascularization
- Corneal Neovascularization Location
- Corneal Staining
- Corneal Staining Location s
- Conjunctival Injection
- Tarsal Abnormalities
- Other

12.3. Contact Lens Fitting

Contact lens fitting will be assessed at each lens fitting (dispensing) and each of the 1-, 2- and 4-Week Follow-up evaluations. Frequency by eye of mechanical lens fitting characteristics will be calculated at each fitting and follow-up evaluation. Lens fitting characteristics to be reported are:

- Lens Centration Grade
- Decentered Direction
- Limbal Exposure Grade
- Edge Lift (Present or Absent)
- Primary Gaze Movement Grade
- Upgaze Movement Grade
- Lens Tightness Grade (Push-up Test)
- Acceptable Fitting (yes/no)

12.4. Subject Reported Ocular Symptoms

Ocular symptoms reported at Visits 1 - 4 and any other unscheduled visit will be tabulated by treatment, visit and severity at both eye level and subject level.

Possible symptoms are:

- Burning/Stinging
- Itchiness/Scratchiness
- Dryness
- Lens Awareness
- Grittiness/Foreign Body Sensation
- Redness
- Irritation/Discomfort
- Cloudy/Blurry/Hazy
- Variable Vision
- Other

12.5. Contact Lens Correct Visual Acuity

Contact lens visual acuity will be assessed using Snellen visual acuity Charts at each lens fitting and follow-up evaluation (1-, 2- and 4-Week Follow-up evaluations). CLVA will be assessed both monocularly and binocularly. Summaries for Monocular CLVA and binocular CLVA will be presented using counts and percentages of eyes and subjects, for monocular CLVA and binocular CLVA, respectively. A detailed listing of eyes that have worsened by 2 or more lines at final visit compared to baseline will be presented.

12.6. Contact Lens Deposits

Contact lens deposits will be assessed for each eye at visits 2, 3 and 4 on the front and back surface of the study lens; the amount of deposits will be Graded using the scale:

- None = Grade 0 (No deposition).

- Slight = Grade 1 (Deposition which occupies 1-5% of the lens surface area.)
- Mild = Grade 2 (Deposition which occupies 6-15% of the lens surface area.)
- Moderate = Grade 3 (Deposition which occupies 16-25% of the lens surface area.)
- Severe = Grade 4 (Deposition which occupies =26% of the lens surface area.)

12.7. Average Daily Wear Time (in Hours)

The average daily wear time and the comfortable wear time recorded at Visit 2, 3 and 4 will be summarized at subject level by visit.

12.8. Reasons for Lens Replacement

The number of unplanned replacements, folded lenses and damaged lenses will be tabulated by treatment at eye level and subject level. For damaged lenses, the damage type and its location will be reported.

The reason for lens replacement will be listed.

12.9. Reasons for Discontinuations

The number of discontinued subjects by the analysis time point will be displayed by visit. Reasons for discontinuation include the following:

1. Adverse Event
2. Unsatisfactory lens fitting due to test article
3. Unsatisfactory visual response due to test articles
4. Lens discomfort
5. Withdrew consent during study
6. Lost to follow-up
7. Subject no longer meet eligibility criteria
8. Subject withdrawn by PI due to non-compliance to protocol
9. Test article no longer available
10. Other

13. REFERENCES

1. SAS Institute Inc: SAS® 9.4 Statements: Reference, Third Edition. Cary, NC: SAS Institute Inc; 2014.
2. Chamberlain, P. Clinical Study Report [redacted]. A long-term clinical assessment of daily disposable silicone hydrogel contact lenses on a group of neophytes. February 20, 2008

14. SAS CODE:

Proportion of Subjects with Successful Lens Fit

```
PROC FREQ DATA=ads;
TABLES aval / BINOMIAL (EXACT P=0.50 LEVEL=2) ALPHA=0.05;
ODS OUTPUT BINOMIALCLS= aods;
RUN;
```

Where;
ads=analysis dataset
aval=analysis value
aods=analysis output dataset