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The influence of in-eye cleaning/re-wetting drops on the performance of 30 day continuous wear silicone hydrogel contact lenses

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Abstract
30 patients were enrolled in a double blind study designed to determine the efficacy and subjective preferences in reducing deposit accumulation, both lipid and protein, between an in-eye cleaning/re-wetting drop and a control re-wetting drop while wearing silicone hydrogel contact lenses on a 30 day continuous wear schedule. The patients had previously worn these contact lenses on a continuous wear schedule for a minimum of two weeks prior to enrollment in this study, and were asked to determine their preferences based on comfort, vision, and contact lens cleanliness. 27 patients completed the study of two thirty day continuous wear periods. With regard to comfort, 55.56% preferred the control drops, 29.63% preferred the in-eye cleaning/re-wetting drops, and 14.81% had no preference. With regard to vision 33.33% preferred the control drops, 25.93% preferred the in-eye cleaning/re-wetting drops, and 40.74% had no preference. With regard to lens cleanliness 48.15% preferred the control drops, 25.93% preferred the in-eye cleaning/re-wetting drops, and the remaining 25.93% had no preference. Biomicroscopy results of contact lens wetting, deposits, and numbers of mucin balls were equivalent for the two drops. In-eye cleaning/re-wetting drops appear to be compatible with silicone hydrogel contact lenses worn on a continuous wear basis and are similar in performance to re-wetting drops.

Degree Type
Thesis

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THE INFLUENCE OF IN-EYE CLEANING/RE-WETTING DROPS ON THE
PERFORMANCE OF 30 DAY CONTINUOUS WEAR SILICONE HYDROGEL
CONTACT LENSES

By

ANDREW ARMSTRONG

RITA WALLACE

A thesis submitted to the faculty of the

College of Optometry

Pacific University

Forest Grove, Oregon

for the degree of

Doctor of Optometry

May 2004

Advisors:

PETER BERGENSKE, OD, FAAO

JENNIFER SMYTHE, OD, MS, FMO

PATRICK CAROLINE, COT, FAAO
Biographies

Andrew Armstrong graduated from the University of Alberta in 1997 with a B.S. and Physics and Mathematics. Andrew found an interest in contact lenses during his studies at Pacific University College of Optometry which inspired his motivation in this study. He plans to practice primary care optometry in the Pacific Northwest.

Rita Wallace graduated from Pacific University in 2001 where she received a B.S. in Visual Science. She will graduate from Pacific University College of Optometry May 2004 and plans to practice in Beaverton, OR with a specialty in contact lenses.
Abstract

30 patients were enrolled in a double blind study designed to determine the efficacy and subjective preferences in reducing deposit accumulation, both lipid and protein, between an in-eye cleaning/re-wetting drop and a control re-wetting drop while wearing silicone hydrogel contact lenses on a 30 day continuous wear schedule. The patients had previously worn these contact lenses on a continuous wear schedule for a minimum of two weeks prior to enrollment in this study, and were asked to determine their preferences based on comfort, vision, and contact lens cleanliness. 27 patients completed the study of two thirty day continuous wear periods. With regard to comfort, 55.56% preferred the control drops, 29.63% preferred the in-eye cleaning/re-wetting drops, and 14.81% had no preference. With regard to vision 33.33% preferred the control drops, 25.93% preferred the in-eye cleaning/re-wetting drops, and 40.74% had no preference. With regard to lens cleanliness 48.15% preferred the control drops, 25.93% preferred the in-eye cleaning/re-wetting drops, and the remaining 25.93% had no preference.

Biomicroscopy results of contact lens wetting, deposits, and numbers of mucin balls were equivalent for the two drops. In-eye cleaning/re-wetting drops appear to be compatible with silicone hydrogel contact lenses worn on a continuous wear basis and are similar in performance to re-wetting drops.

Key Words:

In-eye cleaning/re-wetting drops, silicone hydrogel contact lenses, comfort, vision, cleanliness
Acknowledgments

We would like to extend our thanks Dr. Peter Bergenske, Dr. Jennifer Smythe, and Patrick Caroline for their help and guidance. We would also like to express our gratitude to Alcon Laboratories for providing the funding for this study.
**Introduction**

Practitioners have long been concerned over the increased rate of ocular complications associated with hydrogel contact lenses worn on an extended or continuous wear basis. While problems such as corneal edema and neovascularization resulting from hypoxia have decreased with the advent of silicone hydrogel contact lenses, other findings, such as surface deposits, are still a concern.

Surface deposits may lead to decreased wettability of the contact lenses, decreased comfort, decreased visual acuity, and may potentially result in triggering an inflammatory response such as papillary conjunctivitis. These findings could limit wear time, necessitate replacement of contact lenses more frequently, and perhaps lead to drop out from contact lens wear altogether.

In-eye cleaning/re-wetting drops have been shown to be beneficial in HEMA-based contact lenses leading to fewer surface deposits, increased wettability, and increased patient comfort. These products utilize surfactants to reduce protein binding which increases both comfort and wettability. The purpose of this study was to determine if the use of an in-eye cleaning/re-wetting drop with continuous wear of silicone hydrogel contact lenses influences subjective performance and surface characteristics. The aims of the study were:

1. To determine if the use an in-eye cleaning/re-wetting drop offered better subjective comfort and visual performance in comparison to a simple re-wetting drop with continuous wear of the lenses;
(2)  To determine if there was a difference in the amount and type of surface deposits on the lenses when using an in-eye cleaning/re-wetting drop versus a re-wetting drop; and,

(3)  To determine if there was a difference in surface wettability with the use of an in-eye cleaning/re-wetting drop versus a re-wetting drop with continuous wear of the lenses.
Methods

The study was a randomized double-blind cross-over design in which subjects wore silicone hydrogel contact lenses on a continuous wear basis during two phases. Subjects used in-eye cleaning/re-wetting drops and re-wetting drops for one month each. The subjects were asked to wear the lenses, on a continuous basis for up to one month and instill each masked-label drop three times a day.

The subjects were evaluated at the following intervals:

- Dispensing visit
- Two weeks
- One month
  - Second dispensing visit
  - Two weeks
- One month

Subjects were initially randomly dispensed either in-eye cleaning/re-wetting drops or re-wetting drops. Prior to dispense each subject completed a "wash-out" period of either spectacle lens wear or daily disposable soft contact lens wear for three days. Subjects were advised to not use any lens care or lens drops during wash-out periods. At the end of one month (28 days +/- 3 days), the subjects once again underwent a three day "wash-out" period to ensure that experiences from Phase I did not influence Phase II. Each, were then dispensed a new pair of lenses and crossed-over to the second lens drop for the second month long phase.
For each phase, subjects returned on the 28th day (+/- 3 days) at which time the lenses were removed and collected by the investigators. The lenses were sent to the CCLR in Waterloo, Ontario where they will be assessed for surface deposition. The individuals assessing lens surface deposition were also masked to the lens drops utilized with each lens.

Subject Eligibility Criteria

Inclusion Criteria

Prior to consideration for this clinical investigation, each prospective subject must have met the following conditions:

1. The subject must have no known ocular or systemic allergies which might interfere with contact lens wear.
2. The subject must have no known systemic disease, or need for medication, which might interfere with contact lens wear, i.e. antihistamines.
3. The subject must have normal eyes (no ocular medications or ocular infection of any type).
4. The subject must have a visual acuity best correctable to 20/20 with spectacles for each eye.
5. The subject must be spherically correctable to a distance visual acuity of 20/30 or better for each eye.
6. The subject must read and sign the Statement of Informed Consent and be provided with a copy of the form.
7. The subject must appear and be willing to adhere to the instructions set forth in this clinical protocol.

8. The subject, based on their knowledge, must NOT be pregnant or lactating at the time of enrollment.

9. The subject, based on their knowledge, must NOT have an infectious disease (e.g., hepatitis, tuberculosis) or an immunosuppressive disease (e.g., HIV).

10. The subject, based on their knowledge, must NOT be diabetic.

11. The subject must have a contact lens prescription between +6.00 D Sph and –10.00 D Sph.

12. The subject must be corrected to 20/30 or better in each eye with the study contact lenses and satisfied with the vision and comfort of each lens.

13. The subject must be an adapted wearer of silicone hydrogel contact lenses (minimum of two weeks of previous successful continuous wear prior to study enrollment).

In an effort to standardize the sample population of subjects for this investigation, it was essential that subjects be carefully screened for any atypical condition. Therefore, in addition to satisfying the above criteria, subjects must have had a complete ocular examination in the last 12 months to ensure that none of the contraindications described below applied before being considered eligible to participate in this study.
**Exclusion Criteria**

No subject was entered into this study who was known to have or currently exhibit any of the following conditions:

1. Ocular or systemic allergies which might interfere with contact lens wear.
2. Systemic disease or use of medication which might interfere with contact lens wear.
3. Clinically significant (grade 3 or 4) corneal edema, corneal vascularization, corneal staining, bulbar hyperemia, tarsal hyperemia or any other abnormality of the cornea which might cause unsafe contact lens wear.
4. Any active ocular infection or ocular surface disease.
5. Any corneal distortion resulting from previous hard contact lens wear.
6. Pregnancy or lactation.

**Informed Consent**

If the subject was deemed eligible, the investigators or monitor explained in detail the nature of the study and the subject's requirements for participation in the two-month study. Interested subjects were asked to read the Statement of Informed Consent Form and the principal investigators and/or the study monitor answered any and all questions. All participants were required to sign both copies of the Statement of Informed Consent Form and were provided a copy of the consent form.
Ocular Examination

Candidates for this study were screened from the outpatient clinic at Pacific University College of Optometry in Forest Grove, Oregon. All candidates for the study were required to have undergone a complete, dilated ocular examination within the past 12 months. Subject eligibility was established at the Enrollment Visit Examination and a total of 30 subjects were selected. The subjects were required to meet all of the previously described inclusion criteria to be considered eligible for this study.

A modified ocular examination was performed at the Enrollment Visit. The examination included the following:

- detailed patient history
- slit lamp examination, including NaFl evaluation
- habitual silicone hydrogel contact lens fit evaluation with the slit-lamp
  habitual contact lens spherical over-refraction

Lens Dispensing

Eligible subjects were dispensed a new pair of lenses in the most appropriate lens parameters based on the lens-fit evaluation and over-refraction.

Study Lens Parameters

 Silicon Hydrogel Contact Lenses:    Base Curves:  8.4 and 8.6 mm
                                    Powers:  +6.00 D to –10.00 D.
                                    Diameter:  13.8 mm
Detailed oral and written instructions were given to each subject describing the study requirements.

Subjects were instructed to:

- wear the same pair of lenses throughout the course of each study phase
- return for regularly scheduled follow-up visits
- immediately report any abnormalities, e.g., ocular complications, lost or uncomfortable lenses to the investigators or monitors
- instill the lens drops three times a day in both eyes
- refrain from instilling a lens drop within one hour before scheduled study visits

Adverse Reactions and Discontinuations

Subjects were instructed that if they experienced ocular irritation or disturbance of vision, they should contact the investigator or monitor on-call for the study. Three subjects did not complete all phases. Two subjects dropped out in the first two week session as they were not comfortable with the silicone hydrogel contact lenses. The third contracted an upper respiratory infection between the first and second month phases, and was discontinued due to this unrelated illness.

If for any reason a lens needed to be removed, subjects were instructed to rinsed it for a minimum of 10 seconds with saline and then reinsert.
Two-Week Follow-Up Visit

For both Period 1 and Period 2, at the two-week and one-month follow-up visits the subjects completed subjective questionnaires assessing comfort and lens-awareness symptoms with the initial lens drops.

An investigator masked to the type of lens drops the subject was using performed an examination that included the following:

- distance visual acuity
- near visual acuity
- slit-lamp examination including surface deposit assessment and grading of posterior debris (number of mucin balls)
- spherical over-refraction in phoropter if indicated by entrance visual acuity

Phase II, Lens Drop Crossover

At the completion of the one-month visit each subject completed a three-day "wash-out" period as previously described and was dispensed a new pair of Focus Night and Day lenses. The subjects were once again given detailed oral and written instructions on the wearing of the contact lenses,

Subjects were instructed to:

- wear the same pair of lenses throughout the course of the month
- return for regularly scheduled follow-up visit one month later
• immediately report any abnormalities, e.g., ocular complications, lost or damaged lenses, to the investigators or monitor.

• instill the lens drops three times a day in both eyes

Along with standard one-month assessments, at the final visit subjects were then asked to complete an additional overall lens drop preference survey.

Subject participation in the study concluded after completion of the two-month visit.
**Results**

**Data Analysis**

**Statistical Method**

This study followed a 2x2 cross over design in which subjects were randomly assigned to in-eye cleaning/re-wetting drops (indicated in these analyses as “G”) or re-wetting drops (“W”). Due to the cross over design it was important to consider possible time and carry-over effects. A carry-over effect was not considered to be too great a concern due to the nature of the treatments, but was tested for nevertheless.

Time deserves careful consideration, as it is possible that ratings of comfort will be affected by adaptation to the lens wear.

Subjects were asked to rate comfort on a 100 point scale at each visit. They were asked to rate the comfort upon awakening, during the day, and in the evening before retiring. Higher scores indicate better comfort. We considered ratings of comfort obtained for three time-of-day categories: Upon awakening (AM), throughout the day (DAY) and in the late evening (EVE).

Analysis of comfort data was performed using NCSS Statistical Software (329 North 1000 East, Kaysville, Utah, 84037). The data were entered into three variables. The first variable contains the sequence number. For these analyses sequence “1” was used for subjects having the "G" drops in the first phase (order is GW) and the "W" in the second. “2” was used to indicate those using the "W" drops in the first phase (order WG). The second variable contains the response in the first phase, and the third variable contains
the response in the second phase. Thus, each row of data represented the complete response for a single subject.

Cross over design analysis is designed to test primarily for equivalence. If equivalence is rejected, we can test further for relative superiority or inferiority.

We have chosen for analysis the responses at the end of each phase as it was felt these would best reflect the efficacy of the tested articles.

AM Comfort

Cross-Over Analysis Summary Section: AM Comfort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimated Effect</th>
<th>Standard Error</th>
<th>T Value (DF=24)</th>
<th>Prob</th>
<th>Confidence Limit</th>
<th>Confidence Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>-2.43</td>
<td>4.09</td>
<td>-0.59</td>
<td>0.5587</td>
<td>-10.88</td>
<td>6.02</td>
</tr>
<tr>
<td>Period</td>
<td>12.02</td>
<td>4.09</td>
<td>2.93</td>
<td>0.0072</td>
<td>3.57</td>
<td>20.47</td>
</tr>
<tr>
<td>Carryover</td>
<td>4.44</td>
<td>18.48</td>
<td>0.24</td>
<td>0.8123</td>
<td>-33.70</td>
<td>42.58</td>
</tr>
</tbody>
</table>

Interpretation of the Above Report

The two treatment means in this 2x2 cross-over study are not significantly different at the 0.0500 significance level (the actual significance level was 0.5587). The average response to treatment G was 54.88 and the average response to treatment W was 52.45.
A preliminary test rejected the assumption of equal period effects at the 0.0500 significance level (the actual significance level was 0.0072). A preliminary test failed to reject the assumption of equal carryover effects at the 0.0500 significance level (the actual significance level was 0.8123).

**Cross-Over Analysis Detail Section: AM Comfort**

<table>
<thead>
<tr>
<th>Seq.</th>
<th>Period</th>
<th>Treatment</th>
<th>Count</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>G</td>
<td>17</td>
<td>47.76</td>
<td>27.42</td>
<td>6.65</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>G</td>
<td>9</td>
<td>62.00</td>
<td>19.07</td>
<td>6.36</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>W</td>
<td>17</td>
<td>57.35</td>
<td>27.20</td>
<td>6.60</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>W</td>
<td>9</td>
<td>47.56</td>
<td>16.12</td>
<td>5.37</td>
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<tr>
<td>1</td>
<td>Difference (W-G)/2</td>
<td>17</td>
<td>4.79</td>
<td>8.82</td>
<td>2.14</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Difference (W-G)/2</td>
<td>9</td>
<td>7.22</td>
<td>11.85</td>
<td>3.95</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Total G+W</td>
<td>17</td>
<td>105.12</td>
<td>51.69</td>
<td>12.54</td>
<td></td>
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<tr>
<td>2</td>
<td>Total G+W</td>
<td>9</td>
<td>109.56</td>
<td>26.16</td>
<td>8.72</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>26</td>
<td>54.88</td>
<td>5.14</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>W</td>
<td>26</td>
<td>52.45</td>
<td>4.96</td>
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<td>34</td>
<td>52.56</td>
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<td>2</td>
<td>18</td>
<td>54.78</td>
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<td>1</td>
<td>26</td>
<td>47.66</td>
<td>5.00</td>
<td></td>
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<td></td>
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<tr>
<td>2</td>
<td>26</td>
<td>59.68</td>
<td>5.11</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
**Interpretation of the Above Report**

This report shows the means and standard deviations of various subgroups of the data. The least squares mean of treatment G is 54.88 and of treatment W is 52.45. Note that least squares means are created by taking the simple average of their component means, not by taking the average of the raw data. No adjustment is made for the unequal sample sizes.

**Equivalence Based on the Confidence Interval of the Difference: AM Comfort**

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Lower Limit</th>
<th>Lower 90.0% Confidence Limit</th>
<th>Upper 90.0% Confidence Limit</th>
<th>Upper Limit</th>
<th>Equivalent at the 5.0% Sign. Level?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortest C.I.</td>
<td>-10.98</td>
<td>-9.43</td>
<td>4.58</td>
<td>10.98</td>
<td>Yes</td>
</tr>
<tr>
<td>Westlake C.I.</td>
<td>-10.98</td>
<td>-8.05</td>
<td>8.05</td>
<td>10.98</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Note: Westlake's k2 = -1.37 and k1 = 2.56.

**Interpretation of the Above Report**

Average bioequivalence of the two treatments has been found at the 0.0500 significance level using the shortest confidence interval of the difference approach since both confidence limits, -9.43 and 4.58, are between the acceptance limits of -10.98 and 10.98.

Average bioequivalence of the two treatments has been found at the 0.0500 significance level using Westlake's confidence interval of the difference approach since both confidence limits, -8.05 and 8.05, are between the acceptance limits of -10.98 and 10.98.
Equivalence Based on the Confidence Interval of the Ratio: AM Comfort

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Lower Limit</th>
<th>90.0% Confidence Limit</th>
<th>Upper Limit</th>
<th>90.0% Confidence Limit</th>
<th>Equivalent at the 5.0% Sign. Level?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortest C.I.</td>
<td>80.00</td>
<td>82.81</td>
<td>108.34</td>
<td>120.00</td>
<td>Yes</td>
</tr>
<tr>
<td>Westlake C.I.</td>
<td>80.00</td>
<td>85.34</td>
<td>114.66</td>
<td>120.00</td>
<td>Yes</td>
</tr>
<tr>
<td>Fieller's C.I.</td>
<td>80.00</td>
<td>83.03</td>
<td>109.74</td>
<td>120.00</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Interpretation of the Above Report

Average bioequivalence of the two treatments has been found at the 0.0500 significance level using the shortest confidence interval of the ratio approach since both confidence limits, 82.81 and 108.34, are between the acceptance limits of 80.00 and 120.00.

Average bioequivalence of the two treatments has been found at the 0.0500 significance level using Westlake's confidence interval of the ratio approach since both confidence limits, 85.34 and 114.66, are between the acceptance limits of 80.00 and 120.00.

Average bioequivalence of the two treatments has been found at the 0.0500 significance level using Fieller's confidence interval of the ratio approach since both confidence limits, 83.03 and 109.74, are between the acceptance limits of 80.00 and 120.00.
Equivalence Based on Schuirmann's Two One-Sided Hypothesis Tests: AM Comfort

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Lower</th>
<th>Upper</th>
<th>5.0%</th>
<th>Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schuirmann's 2 1-Sided Tests</td>
<td>2.09</td>
<td>-3.27</td>
<td>1.71</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Interpretation of the Above Report

Average bioequivalence of the two treatments was found at the 0.0500 significance level using Schuirmann's two one-sided t-tests procedure. The probability level of the t-test of whether the treatment mean is not too much lower than the reference mean is 0.0238. The probability level of the t-test of whether the treatment mean is not too much higher than the reference mean is 0.0016. Since both of these values are less than 0.0500, the null hypothesis of average bioequivalence was rejected in favor of the alternative hypothesis of average bioequivalence.

Equivalence Based on Two One-Sided Wilcoxon-Mann-Whitney Tests: AM Comfort

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Lower</th>
<th>Lower</th>
<th>Upper</th>
<th>Upper</th>
<th>Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 1-Sided MW Tests</td>
<td>265.00</td>
<td>0.0295</td>
<td>177.00</td>
<td>0.0025</td>
<td>No</td>
</tr>
</tbody>
</table>

Interpretation of the Above Report

Average bioequivalence of the two treatments was not established at the 0.0500 significance level using the nonparametric version of Schuirmann's two one-sided tests procedure which is
based on the Wilcoxon-Mann-Whitney test. The probability level of the test of whether the treatment mean is not too much lower than the reference mean is 0.0295. The probability level of the test of whether the treatment mean is not too much higher than the reference mean is 0.0025. Since at least one of these values is greater than 0.0500, the null hypothesis of average bioequivalence was not rejected.

**Equivalence Based on Anderson and Hauck’s Hypothesis Test: AM Comfort**

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Pr(-TL)</th>
<th>Pr(TU)</th>
<th>Level</th>
<th>Sign. Level?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson and Hauck's Test</td>
<td>0.0238</td>
<td>0.0016</td>
<td>0.0222</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Interpretation of the Above Report**

Average bioequivalence of the two treatments was found at the 0.0500 significance level using Anderson and Hauck's test procedure. The actual probability level of the test was 0.0222.
Interpretation of the Sequence-by-Period Means

The sequence-by-period means plot shows the mean responses on the vertical axis and the periods on the horizontal axis. The lines connect like treatments. If there is no period, carryover, or interaction effects, two horizontal lines would be displayed. The distance between these lines represents the magnitude of the treatment effect. The tendency for both lines to slope up represents period and carryover effects. The fact that the lines do not cross represents absence of period-by-treatment interaction, a type of carryover effect.
Interpretation of the Profile Plot

The profile plot displays the raw data for each subject. The response variable is shown along the vertical axis. The two sequences are shown along the horizontal axis. The data for each subject is depicted by two points connected by a line. The subject's response to the reference formulation is shown first followed by their response to the treatment formulation. Hence, for sequence 2, the results for the first period are shown on the right and for the second period on the left.
Plot of Sums and Differences: AM Comfort

Interpretation of the Sums and Differences Plot

The sums and differences plot shows the sum of each subject's two responses on the horizontal axis and the difference between each subject's two responses on the vertical axis. Dot plots of the sums and differences have been added above and to the right of the scatter plot, respectively.

Each point represents the sum and difference of a single subject. Different plotting symbols are used to denote the subject's sequence. A horizontal line has been added at zero to provide an easy reference from which to determine if a difference is positive (favors treatment G) or negative (favors treatment W). The degree to which the plotting symbols tend to separate along the horizontal axis represents the size of the carryover effect. The degree to which the plotting symbols tend to separate along the vertical axis represents the size of the treatment effect.
Period Plot: AM Comfort

Interpretation of the Period Plot
The Period Plot displays a subject's period 1 response on the horizontal axis and their period 2 response on the vertical axis. The plotting symbol is the sequence number.

Probability Plots: AM Comfort
Interpretation of the Probability Plots

These plots show the differences (P1-P2) on the vertical axis and values on the horizontal axis that would be expected if the differences were normally distributed. The first plot shows the differences for sequence 1 and the second plot shows the differences for sequence 2. The assumption of normality holds, as the points fall close to a straight line.

DAY Comfort

Cross-Over Analysis Summary Section: DAY Comfort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimated Effect</th>
<th>Standard Error</th>
<th>T Value (DF=24)</th>
<th>Prob Level</th>
<th>Confidence Lower 95.0%</th>
<th>Confidence Upper 95.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>0.99</td>
<td>2.49</td>
<td>0.40</td>
<td>0.6944</td>
<td>-4.15</td>
<td>6.13</td>
</tr>
<tr>
<td>Period</td>
<td>7.66</td>
<td>2.49</td>
<td>3.07</td>
<td>0.0052</td>
<td>2.52</td>
<td>12.80</td>
</tr>
<tr>
<td>Carryover</td>
<td>-9.39</td>
<td>12.85</td>
<td>-0.73</td>
<td>0.4719</td>
<td>-35.91</td>
<td>17.13</td>
</tr>
</tbody>
</table>

Interpretation of the Above Report

The two treatment means in a 2x2 cross-over study are not significantly different at the 0.0500 significance level (the actual significance level was 0.6944). The design had 17 subjects in sequence 1 (GW) and 9 subjects in sequence 2 (WG). The average response to treatment G was 71.19 and the average response to treatment W was 72.18.

A preliminary test rejected the assumption of equal period effects at the 0.0500 significance level (the actual significance level was 0.0052). A preliminary test failed to reject the assumption of
equal carryover effects at the 0.0500 significance level (the actual significance level was 0.4719).

Cross-Over Analysis Detail Section: DAY Comfort

<table>
<thead>
<tr>
<th>Seq.</th>
<th>Period</th>
<th>Treatment</th>
<th>Count</th>
<th>Least Squares Mean</th>
<th>Standard Deviation</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>G</td>
<td>17</td>
<td>69.71</td>
<td>17.54</td>
<td>4.25</td>
</tr>
<tr>
<td>2</td>
<td>G</td>
<td>9</td>
<td></td>
<td>72.67</td>
<td>17.28</td>
<td>5.76</td>
</tr>
<tr>
<td>2</td>
<td>W</td>
<td>17</td>
<td></td>
<td>78.35</td>
<td>14.82</td>
<td>3.60</td>
</tr>
<tr>
<td>1</td>
<td>W</td>
<td>9</td>
<td></td>
<td>66.00</td>
<td>17.98</td>
<td>5.99</td>
</tr>
<tr>
<td></td>
<td>Difference (W-G)/2</td>
<td>17</td>
<td>4.32</td>
<td>6.15</td>
<td>1.49</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difference (W-G)/2</td>
<td>9</td>
<td>3.33</td>
<td>5.81</td>
<td>1.94</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>G+W</td>
<td>17</td>
<td></td>
<td>148.06</td>
<td>30.05</td>
<td>7.29</td>
</tr>
<tr>
<td>Total</td>
<td>G+W</td>
<td>9</td>
<td></td>
<td>138.47</td>
<td>33.30</td>
<td>11.10</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>26</td>
<td></td>
<td>71.19</td>
<td>3.60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>W</td>
<td>26</td>
<td></td>
<td>72.18</td>
<td>3.29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>34</td>
<td></td>
<td></td>
<td>74.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td></td>
<td></td>
<td>69.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>26</td>
<td></td>
<td></td>
<td>67.85</td>
<td>3.65</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td></td>
<td></td>
<td>75.51</td>
<td>3.23</td>
<td></td>
</tr>
</tbody>
</table>

Interpretation of the Above Report

This report shows the means and standard deviations of various subgroups of the data. The least squares mean of treatment G is 71.19 and of treatment W is 72.18. Note that least squares means are created by taking the simple average of their component means, not by taking the average of
the raw data.

Equivalence Based on the Confidence Interval of the Difference: DAY Comfort

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Lower Equivalent Limit</th>
<th>Confidence Limit</th>
<th>Upper Equivalent Limit</th>
<th>Sign. Level?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortest C.I.</td>
<td>-14.24</td>
<td>-3.27</td>
<td>5.25</td>
<td>Yes</td>
</tr>
<tr>
<td>Westlake C.I.</td>
<td>-14.24</td>
<td>-4.56</td>
<td>4.56</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Note: Westlake's $k_2 = -2.23$ and $k_1 = 1.43$.

Interpretation of the Above Report

Average bioequivalence of the two treatments has been found at the 0.0500 significance level using the shortest confidence interval of the difference approach since both confidence limits, -3.27 and 5.25, are between the acceptance limits of -14.24 and 14.24.

Average bioequivalence of the two treatments has been found at the 0.0500 significance level using Westlake's confidence interval of the difference approach since both confidence limits, -4.56 and 4.56, are between the acceptance limits of -14.24 and 14.24.
Equivalence Based on the Confidence Interval of the Ratio: DAY Comfort

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Equivalence Limit</th>
<th>Confidence Limit</th>
<th>Confidence Limit</th>
<th>Equivalent Limit</th>
<th>Sign. Level?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortest C.I.</td>
<td>80.00</td>
<td>95.41</td>
<td>107.38</td>
<td>120.00</td>
<td>Yes</td>
</tr>
<tr>
<td>Westlake C.I.</td>
<td>80.00</td>
<td>93.59</td>
<td>106.41</td>
<td>120.00</td>
<td>Yes</td>
</tr>
<tr>
<td>Fieller's C.I.</td>
<td>80.00</td>
<td>94.62</td>
<td>108.67</td>
<td>120.00</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Interpretation of the Above Report

Average bioequivalence of the two treatments has been found at the 0.0500 significance level using the shortest confidence interval of the ratio approach since both confidence limits, 95.41 and 107.38, are between the acceptance limits of 80.00 and 120.00.

Average bioequivalence of the two treatments has been found at the 0.0500 significance level using Westlake's confidence interval of the ratio approach since both confidence limits, 93.59 and 106.41, are between the acceptance limits of 80.00 and 120.00.

Average bioequivalence of the two treatments has been found at the 0.0500 significance level using Fieller's confidence interval of the ratio approach since both confidence limits, 94.62 and 108.67, are between the acceptance limits of 80.00 and 120.00.
Equivalence Based on Schuirmann's Two One-Sided Hypothesis Tests: DAY Comfort

<table>
<thead>
<tr>
<th>Test Type</th>
<th>T Value</th>
<th>T Value</th>
<th>T Value</th>
<th>DF</th>
<th>Sign. Level?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schuirmann's 2 1-Sided Tests</td>
<td>6.11</td>
<td>-5.32</td>
<td>1.71</td>
<td>24</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Interpretation of the Above Report

Average bioequivalence of the two treatments was found at the 0.0500 significance level using Schuirmann's two one-sided t-tests procedure. The probability level of the t-test of whether the treatment mean is not too much lower than the reference mean is 0.0000. The probability level of the t-test of whether the treatment mean is not too much higher than the reference mean is 0.0000. Since both of these values are less than 0.0500, the null hypothesis of average bioinequivalence was rejected in favor of the alternative hypothesis of average bioequivalence.

Equivalence Based on Two One-Sided Wilcoxon-Mann-Whitney Tests: DAY Comfort

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Ranks</th>
<th>Level</th>
<th>Ranks</th>
<th>Level</th>
<th>Sign. Level?</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 1-Sided MW Tests</td>
<td>302.00</td>
<td>0.0001</td>
<td>163.00</td>
<td>0.0002</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Interpretation of the Above Report

Average bioequivalence of the two treatments was found at the 0.0500 significance level using the nonparametric version of Schuirmann's two one-sided tests procedure which is based on the
Wilcoxon-Mann-Whitney test. The probability level of the test of whether the treatment mean is not too much lower than the reference mean is 0.0001. The probability level of the test of whether the treatment mean is not too much higher than the reference mean is 0.0002. Since both of these values are less than 0.0500, the null hypothesis of average bioinequivalence was rejected in favor of the alternative hypothesis of average bioequivalence.

Equivalence Based on Anderson and Hauck’s Hypothesis Test: DAY Comfort

<table>
<thead>
<tr>
<th>Equivalent</th>
<th>Pr(-TL)</th>
<th>Pr(TU)</th>
<th>Level</th>
<th>Sign. Level?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson and Hauck's Test</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Interpretation of the Above Report

Average bioequivalence of the two treatments was found at the 0.0500 significance level using Anderson and Hauck’s test procedure. The actual probability level of the test was 0.0000.
Interpretation of the Sequence-by-Period Means

The sequence-by-period means plot shows the mean responses on the vertical axis and the periods on the horizontal axis. The lines connect like treatments. If there is no period, carryover, or interaction effects, two horizontal lines would be displayed. The distance between these lines represents the magnitude of the treatment effect. The fact that both lines slope up represents likely period or carryover effects. The fact that the lines cross suggests period-by-treatment interaction, a type of carryover effect.
Plot of Subject Profiles: DAY Comfort

**Subject Profile Plot**

The **profile plot** displays the saw data for each subject. The **response variable** is shown along the vertical axis. The two sequences are shown along the horizontal axis. The data for each subject is depicted by two points connected by a line. The subject's response to the reference formulation is shown first followed by their response to the treatment formulation. Hence, for sequence 2, the results for the first period are shown on the right and for the second period on the left.
Interpretation of the Sums and Differences Plot

The sums and differences plot shows the sum of each subject's two responses on the horizontal axis and the difference between each subject's two responses on the vertical axis. Dot plots of the sums and differences have been added above and to the right of the scatter plot, respectively. Each point represents the sum and difference of a single subject. Different plotting symbols are used to denote the subject's sequence. A horizontal line has been added at zero to provide an easy reference from which to determine if a difference is positive (favors treatment G) or negative (favors treatment W). The degree to which the plotting symbols tend to separate along the horizontal axis represents the size of the carryover effect. The degree to which the plotting symbols tend to separate along the vertical axis represents the size of the treatment effect.
Period Plot: DAY Comfort

Interpretation of the Period Plot

The Period Plot displays a subject’s period 1 response on the horizontal axis and their period 2 response on the vertical axis. The plotting symbol is the sequence number.

Probability Plots: DAY Comfort
Interpretation of the Probability Plots

These plots show the differences (P1-P2) on the vertical axis and values on the horizontal axis that would be expected if the differences were normally distributed. The first plot shows the differences for sequence 1 and the second plot shows the differences for sequence 2. The assumption of normality holds, as the points fall close to a straight line.

EVE Comfort

Cross-Over Analysis Summary Section: EVE Comfort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimated Effect</th>
<th>Standard Error (DF=24)</th>
<th>T Value</th>
<th>Prob</th>
<th>Confidence Limit</th>
<th>Confidence Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>4.83</td>
<td>3.23</td>
<td>1.50</td>
<td>0.1477</td>
<td>-1.83</td>
<td>11.49</td>
</tr>
<tr>
<td>Period</td>
<td>3.94</td>
<td>3.23</td>
<td>1.22</td>
<td>0.2342</td>
<td>-2.72</td>
<td>10.60</td>
</tr>
<tr>
<td>Carryover</td>
<td>-17.03</td>
<td>15.61</td>
<td>-1.09</td>
<td>0.2861</td>
<td>-49.23</td>
<td>15.18</td>
</tr>
</tbody>
</table>
Interpretation of the Above Report

The two treatment means in a 2x2 cross-over study are not significantly different at the 0.0500 significance level (the actual significance level was 0.1477). The treatment order designated sequence 1 (GW) and 9 subjects in sequence 2 (WG). The average response to treatment G was 60.07 and the average response to treatment W was 64.89.

A preliminary test failed to reject the assumption of equal period effects at the 0.0500 significance level (the actual significance level was 0.2342). A preliminary test failed to reject the assumption of equal carryover effects at the 0.0500 significance level (the actual significance level was 0.2861).
Cross-Over Analysis Detail Section: EVE Comfort

<table>
<thead>
<tr>
<th>Seq.</th>
<th>Period</th>
<th>Treatment Count</th>
<th>Least Squares Mean</th>
<th>Standard Deviation</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>G</td>
<td>17</td>
<td>62.35</td>
<td>22.12</td>
<td>5.36</td>
</tr>
<tr>
<td>2</td>
<td>G</td>
<td>9</td>
<td>57.78</td>
<td>24.32</td>
<td>8.11</td>
</tr>
<tr>
<td>2</td>
<td>W</td>
<td>17</td>
<td>71.12</td>
<td>18.31</td>
<td>4.44</td>
</tr>
<tr>
<td>1</td>
<td>W</td>
<td>9</td>
<td>58.67</td>
<td>16.64</td>
<td>5.55</td>
</tr>
<tr>
<td>Difference (W-G)/2</td>
<td>17</td>
<td>4.38</td>
<td>9.01</td>
<td>2.19</td>
<td></td>
</tr>
<tr>
<td>Difference (W-G)/2</td>
<td>9</td>
<td>-0.44</td>
<td>4.63</td>
<td>1.54</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>G+W</td>
<td>17</td>
<td>133.47</td>
<td>36.39</td>
<td>8.82</td>
</tr>
<tr>
<td>Total</td>
<td>G+W</td>
<td>9</td>
<td>116.44</td>
<td>40.64</td>
<td>13.55</td>
</tr>
<tr>
<td>G</td>
<td>26</td>
<td>60.07</td>
<td>4.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W</td>
<td>26</td>
<td>64.89</td>
<td>3.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>66.74</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>58.22</td>
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</tr>
<tr>
<td>1</td>
<td>26</td>
<td>60.51</td>
<td>4.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>64.45</td>
<td>4.23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interpretation of the Above Report

This report shows the means and standard deviations of various subgroups of the data. The least squares mean of treatment G is 60.07 and of treatment W is 64.89. Note that least squares means are created by taking the simple average of their component means, not by taking the average of the raw data. No adjustment is made for the unequal sample sizes.
Equivalence Based on the Confidence Interval of the Difference: EVE Comfort

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Lower 90.0% Limit</th>
<th>Upper 90.0% Limit</th>
<th>Upper Limit</th>
<th>Equivalent at the 5.0% Sign. Level?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortest C.I.</td>
<td>-12.01</td>
<td>-0.69</td>
<td>10.35</td>
<td>12.01</td>
</tr>
<tr>
<td>Westlake C.I.</td>
<td>-12.01</td>
<td>-9.08</td>
<td>9.08</td>
<td>12.01</td>
</tr>
</tbody>
</table>

Note: Westlake's \( k_2 = -4.31 \) and \( k_1 = 1.32 \).

Interpretation of the Above Report

Average bioequivalence of the two treatments has been found at the 0.0500 significance level using the shortest confidence interval of the difference approach since both confidence limits, -0.69 and 10.35, are between the acceptance limits of -12.01 and 12.01.

Average bioequivalence of the two treatments has been found at the 0.0500 significance level using Westlake's confidence interval of the difference approach since both confidence limits, -9.08 and 9.08, are between the acceptance limits of -12.01 and 12.01.
Equivalence Based on the Confidence Interval of the Ratio: EVE Comfort

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Lower Limit</th>
<th>Lower 90.0%</th>
<th>Upper Limit</th>
<th>Upper 90.0%</th>
<th>Equivalent at the 5.0% Sign. Level?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortest C.I.</td>
<td>80.00</td>
<td>98.84</td>
<td>117.23</td>
<td>120.00</td>
<td>Yes</td>
</tr>
<tr>
<td>Westlake C.I.</td>
<td>80.00</td>
<td>84.88</td>
<td>115.12</td>
<td>120.00</td>
<td>Yes</td>
</tr>
<tr>
<td>Fieller's C.I.</td>
<td>80.00</td>
<td>95.80</td>
<td>122.16</td>
<td>120.00</td>
<td>No</td>
</tr>
</tbody>
</table>

Interpretation of the Above Report

Average bioequivalence of the two treatments has been found at the 0.0500 significance level using the shortest confidence interval of the ratio approach since both confidence limits, 98.84 and 117.23, are between the acceptance limits of 80.00 and 120.00.

Average bioequivalence of the two treatments has been found at the 0.0500 significance level using Westlake's confidence interval of the ratio approach since both confidence limits, 84.88 and 115.12, are between the acceptance limits of 80.00 and 120.00.

Average bioequivalence of the two treatments has not been established at the 0.0500 significance level using Fieller's confidence interval of the ratio approach since both confidence limits, 95.80 and 122.16, are not between the acceptance limits of 80.00 and 120.00.
Equivalence Based on Schuirmann's Two One-Sided Hypothesis Tests

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Lower T Value</th>
<th>Upper T Value</th>
<th>Cutoff T Value</th>
<th>DF</th>
<th>Sign. Level?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schuirmann's 2 1-Sided Tests</td>
<td>5.22</td>
<td>-2.23</td>
<td>1.71</td>
<td>24</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Interpretation of the Above Report

Average bioequivalence of the two treatments was found at the 0.0500 significance level using Schuirmann's two one-sided t-tests procedure. The probability level of the t-test of whether the treatment mean is not too much lower than the reference mean is 0.0000. The probability level of the t-test of whether the treatment mean is not too much higher than the reference mean is 0.0178. Since both of these values are less than 0.0500, the null hypothesis of average bioinequivalence was rejected in favor of the alternative hypothesis of average bioequivalence.

Equivalence Based on Two One-Sided Wilcoxon-Mann-Whitney Tests: EVE Comfort

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Lower Sum</th>
<th>Lower Prob</th>
<th>Upper Sum</th>
<th>Upper Prob</th>
<th>Equivalent at the 5.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 1-Sided MW Tests</td>
<td>303.00</td>
<td>0.0000</td>
<td>192.00</td>
<td>0.0230</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Interpretation of the Above Report

Average bioequivalence of the two treatments was found at the 0.0500 significance level using the nonparametric version of Schuirmann's two one-sided tests procedure which is based on the
Wilcoxon-Mann-Whitney test. The probability level of the test of whether the treatment mean is not too much lower than the reference mean is 0.0000. The probability level of the test of whether the treatment mean is not too much higher than the reference mean is 0.0230. Since both of these values are less than 0.0500, the null hypothesis of average bioequivalence was rejected in favor of the alternative hypothesis of average bioequivalence.

Equivalence Based on Anderson and Hauck's Hypothesis Test

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Pr(-TL)</th>
<th>Pr(TU)</th>
<th>Equivalent Prob at the 5.0% Level</th>
<th>Sign. Level?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson and Hauck's Test</td>
<td>0.0000</td>
<td>0.0178</td>
<td>0.0178</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Interpretation of the Above Report

Average bioequivalence of the two treatments was found at the 0.0500 significance level using Anderson and Hauck's test procedure. The actual probability level of the test was 0.0178.
Plot of Sequence-by-Period Means

Interpretation of the Sequence-by-Period Means

The sequence-by-period means plot shows the mean responses on the vertical axis and the periods on the horizontal axis. The lines connect like treatments. If there is no period, carryover, or interaction effects, two horizontal lines would be displayed. The distance between these lines represents the magnitude of the treatment effect. The fact that both lines slope up represents likely period or carryover effects. The fact that the lints cross suggests period-by-treatment interaction, a type of carryover effect.
Plot of Subject Profiles: EVE Comfort

Subject Profile Plot

The profile plot displays the raw data for each subject. The response variable is shown along the vertical axis. The two sequences are shown along the horizontal axis. The data for each subject is depicted by two points connected by a line. The subject’s response to the reference formulation is shown first followed by their response to the treatment formulation. Hence, for sequence 2, the results for the first period are shown on the right and for the second period on the left.
Plot of Sums and Differences: EVE Comfort

Interpretation of the Sums and Differences Plot

The sums and differences plot shows the sum of each subject's two responses on the horizontal axis and the difference between each subject's two responses on the vertical axis. Dot plots of the sums and differences have been added above and to the right of the scatter plot, respectively. Each point represents the sum and difference of a single subject. Different plotting symbols are used to denote the subject's sequence. A horizontal line has been added at zero to provide an easy reference from which to determine if a difference is positive (favors treatment G) or negative (favors treatment W). The degree to which the plotting symbols tend to separate along the horizontal axis represents the size of the carryover effect. The degree to which the plotting symbols tend to separate along the vertical axis represents the size of the treatment effect.
Period Plot: EVE Comfort

Interpretation of the Period Plot

The Period Plot displays a subject's period 1 response on the horizontal axis and their period 2 response on the vertical axis. The plotting symbol is the sequence number.

Probability Plots: EVE Comfort
Interpretation of the Probability Plots

These plots show the differences (P1-P2) on the vertical axis and values on the horizontal axis that would be expected if the differences were normally distributed. The first plot shows the differences for sequence 1 and the second plot shows the differences for sequence 2. The assumption of normality holds, as the points fall close to a straight line.

Subjects

Twenty seven subjects completed both phases of the study. Two subjects were discontinued secondary to lens awareness or discomfort with the study contact lenses and one subject lost a lens from the eye during sleep and was also suffering from an upper respiratory infection. Data was considered only from the subjects completing all phases.

Subject age ranged from 21-52 years and refractive error ranged from +3.00 D to -6.00 D. Ten males and 20 females participated in the study.
Habitual Lens Drops

Prior to study enrollment 7 subjects habitually used lens drops.

Objective Findings
Biomicroscope Examination and Adverse Events

A biomicroscope examination was performed at each visit using a 0-4 scale for each observation. A copy of the examination form is attached. None of the biomicroscopy scores showed a difference between the two types of drops at my point or in either phase.

No adverse responses occurred during the study.

Visual Acuity

No statistical or clinical difference in visual acuity between lens drops was observed at any point.

On-Eye Surface Deposition and Wetting

No clinical or statistical difference could be detected in the grading of front surface wetting, front surface deposits, posterior lens debris or number of mucin balls.

Lenses were collected at the completion of each four week interval and have been sent to the CCLR at the University of Waterloo for laboratory analysis.
Comfort and Awareness: Evidence of Adaptation, Change with time

Comfort and awareness scores were very similar and thus we chose to analyse the comfort scores in the previous section on subjective responses. We noted an apparent effect of adaptation, such that subjects tended to be more comfortable in the second phase, regardless of drop sequence. To illustrate this, an analysis is presented using the Lens Awareness data, combining all subjects in each phase regardless of drops used in that phase.

Lens Awareness

Lens awareness was rated for awakening, daytime and evening at each interval. At no point was there a difference in awareness scores for the two drops. As with comfort ratings, there were changes noted with time.
Lens Awareness Upon Awakening.

Lens awareness upon awakening, change with time

Lens awareness upon awakening was significantly better in the second phase, regardless of drop type (p<0.01 comparing the 2 week of the second phase to either interval in the first phase. p<0.05 comparing the 4 week visit of the second phase to the 4 week interval in phase one). Note the only baseline data was obtained prior to phase one.

Lens Awareness During the Day

Lens awareness during the day was different (p<0.01) from other intervals and baseline only at the 4 week interval of the first phase.
Lens awareness Daytime, change with time

**Lens Awareness in the Evening**

Evening lens awareness was equal for the two drop types. There was a small but significant (p<0.05) difference in awareness scores for evening for both intervals of the first phase when compared to baseline.
Lens Awareness: Evening, Change with time

Subjective Questionnaires

Subjects responded to the following 10 questions at each of the four intervals:

1. My lenses feel comfortable upon awakening.
2. My lenses feel comfortable all day long.
3. My lenses feel comfortable at the end of the day.
4. My vision is not blurry upon awakening.
5. My eyes do not feel dry during the lens wearing day.
6. These drops keep my lenses clean.
7. These drops are easy to use.
8. I like these drops.
9. My contact lenses feel more comfortable after the use of the drops.
10. The drops keep my lenses clear.

Answers were on a ranked scale of 1 (strongly disagree) to 5 (strongly agree).

The table below shows the p values for difference between the two types of drops when comparing the answers to each of these questions at each interval. There were no significant differences noted.
As changes with time had been noted in the rating scales, the questions were evaluated for a similar trend. Small differences were noted comparing responses at different intervals. No differences were noted with respect to time for questions 4, 5, 7, 9 and 10.

The differences for the other questions are depicted graphically in the next several figures. The “column” indications from left to right indicate phase 1:2 week; phase 1:4 week; phase 2:2 week; and phase 2:4 week.

Question 1: phase 2:2 week answers differ from phase 1:4 week answers (p<0.05)
Question 2: phase 2:2 week answers differ from phase 1:4 week answers (p<0.05)

Question 3: phase 2:2 week answers differ from phase 1:2 week answers (p<0.05)
Question 6: phase 2:2 week answers differ from phase 1:2 week answers (p<0.05)

Question 8: phase 1:4 week answers differ from phase 1:2 week answers (p<0.05)
Subject Preferences

At the end of the study subjects were asked to respond to the following questions:

For each of the following questions, please circle your overall preferences.

(1) With regard to comfort, I prefer:

a. Phase I Drops

b. Phase II Drops

c. I have no preference

The control drop was preferred 2 to 1 over the in-eye cleaning/re-wetting drop. The following chart illustrates the insignificant difference between choice frequencies. "G" indicates the in-eye cleaning/re-wetting drop. "W" indicates the control drop.

Bivariate chi-square analysis of the responses to each question were performed in order to test for significance of differences and for sequence effect. The following plot represents the responses by phase.
Note "Col 1" indicates subjects following "GW sequence, and "Col 2" represents subjects in "WG" sequence. There appears to be an effect such that subjects tended to prefer the drop they finished with. As there were more subjects in the "GW sequence, this gives rise to the appearance that W was strongly preferred, when there does seem to be a substantial sequence effect.

(2) With regard to vision, I prefer:

a. Phase I Drops

b. Phase II Drops

c. I have no preference
This table indicates a majority had no preference with regard to vision.
Forced Choice Question 2: Vision

(Chi-Square = 0.551736, p = 0.7589)

Note "Col 1" indicates indicates subjects following "G W sequence, and "Col 2" represents subjects in "W G sequence. A majority had no preference regardless of sequence. Among those that did, there again appears to be an effect such that subjects tended to prefer the drop they finished with. As there were more subjects in the "G W group, this gives rise to the appearance that W was somewhat preferred, when there does seem to be a sequence effect.
With regard to lens cleanliness, I prefer:

a. Phase I Drops
b. Phase II Drops
c. I have no preference

The following table shows a preference for the control drops:
Note "Col 1" indicates subjects following "GW" sequence, and "Col 2" represents subjects in "WG" sequence. There appears to be an effect such that subjects tended to prefer the drop they finished with. As there were more subjects in the "GW" group, this gives rise to the appearance that "W" was strongly preferred, when there does seem to be a substantial sequence effect.
Discussion

This study evaluated the subjective performance and surface characteristics of in-eye cleaning/re-wetting drops with continuous wear of silicone hydrogel contact lenses. In-eye cleaning/re-wetting drops have been shown to be beneficial in HEMA-based contact lenses leading to fewer surface deposits, increased wettability, and increased patient comfort.

The aims of the study were:

1. To determine if the use of an in-eye cleaning/re-wetting drop offered better subjective comfort and visual performance in comparison to a simple re-wetting drop with continuous wear of the lenses;
2. To determine if there is a difference in the amount and type of surface deposits on the lenses when using an in-eye cleaning/re-wetting drop versus a re-wetting drop;
3. To determine if there is a difference in surface wettability with the use of an in-eye cleaning/re-wetting drop versus a re-wetting drop with continuous wear of the lenses.

We were unable to detect any difference in subjective comfort or lens awareness for the two drops tested. Overall comfort scores were quite good, although two subjects dropped out due to inability to achieve acceptable comfort with the lenses. This appeared to be much more of a lens related issue than anything related to the drops.
A trend towards decreased comfort and increased lens awareness with time was observed, particularly in the first month phase. There appeared to be evidence of adaptation in the second phase, where comfort and awareness were notably better at the four week visit of phase two than they had been at this point in phase one. This is consistent with clinical observation.

The differences described above were elicited via the grading scales. Less substantial differences with time were noted via the questionnaire. The questionnaire also failed to show any difference with regard to the type of drops used.

Observation of slit-lamp findings, and in particular on-eye observation of lens wetting, deposits, numbers of mucin balls were all equivalent for the two drops. In general, wetting and deposition were graded very favorably. No significant changes in slit-lamp findings were observed in either phase.

It is to be noted that all lenses were collected at the conclusion of each phase and have been sent to University of Waterloo where they await analysis for any difference in quantity or nature of deposits.

Conclusions
It appears the use of in-eye cleaning/re-wetting drops is compatible with silicone hydrogel contact lenses worn on a 30 night continuous wear basis, and performance is equivalent to re-wetting drops under these circumstances.
References


