SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I.   GENERAL INFORMATION

       Device Generic Names: paflufocon B and paflufocon D rigid gas permeable contact lenses

       Device Trade Names: Paragon CRT™ (paflufocon B) and CRT™ 100 (paflufocon D),
                               Paragon Quadra RG™ (paflufocon B) and Quadra RG™ 100
                               (paflufocon D) Rigid Gas Permeable Contact Lenses for Corneal
                               Refractive Therapy

       Applicant's Name and Address: Paragon Vision Sciences
                                         947 East Impala
                                         Mesa, AZ 85204-6619

       Date of Panel Recommendation: January 18, 2002

       Premarket Approval Application (PMA) Supplement Number: P870024/S43

       Date of Notice of Approval to Applicant:

II.   INDICATIONS FOR USE

       The Paragon CRT™ (paflufocon B) and Paragon CRT™ 100 (paflufocon D) rigid gas
       permeable Contact Lenses for Corneal Refractive Therapy are indicated for use in the reduction
       of myopic refractive error in non-diseased eyes. The lenses are indicated for overnight wear in
       a Contact Lens Corneal Refractive Therapy fitting program for the temporary reduction of
       myopia up to 6.00 diopters in eyes with astigmatism up to 1.75 diopters. The lenses may be
       disinfected using only a chemical disinfection system.

       The Paragon Quadra RG™ (paflufocon B) and Paragon Quadra RG™ 100 (paflufocon D)
       Rigid Gas Permeable Contact Lenses for Corneal Refractive Therapy are indicated for the
       reduction of myopic refractive error in non-diseased eyes. The lenses are indicated for
       overnight wear in a Contact Lens Corneal Refractive Therapy fitting program for the temporary
       reduction of myopia up to 3.00 diopters in eyes with astigmatism up to 1.50 diopters. The
       lenses may be disinfected using only a chemical disinfection system.

       Note: To maintain the Contact Lens Corneal Refractive Therapy effect of myopia reduction
              overnight lens wear must be continued on a prescribed schedule. Failure to do so can
              affect daily activities (e.g., night driving), visual fluctuations and changes in intended
              correction.

III.   CONTRAINDICATIONS

PARAGON CRT™ and PARAGON Quadra contact lenses for Corneal Refractive Therapy should not be used when any of the following conditions exist:

- Acute and subacute inflammations or infection of the anterior segment of the eye.

- Any eye disease, injury, or abnormality that affects the cornea, conjunctiva or eyelids.

- Severe insufficiency of tears (dry eyes).

- Corneal hypoesthesia (reduced corneal sensitivity).

- Any systemic disease that may affect the eye or be exacerbated by wearing contact lenses.

- Allergic reactions of ocular surfaces or adnexa which may be induced or exaggerated by wearing contact lenses or use of contact lens solutions.

- Allergy to any ingredient, such as mercury or thimerosal, in a solution which is to be used to care for contact lenses.

- Any active corneal infection (bacterial, fungal or viral).

- If eyes become red or irritated.

IV.   WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the device labeling (Attached).

V.   DEVICE DESCRIPTION

Paragon CRT™ and Paragon CRT™ 100 (Sigmoid Proximity Control Design)

Paragon CRT™ design contact lenses are manufactured from Paragon HDS® (paflufocon B) and Paragon CRT™ 100 design contact lenses are manufactured from Paragon HDS® 100 (paflufocon D). The lenses are designed to have congruent anterior and posterior surfaces each consisting of three zones:
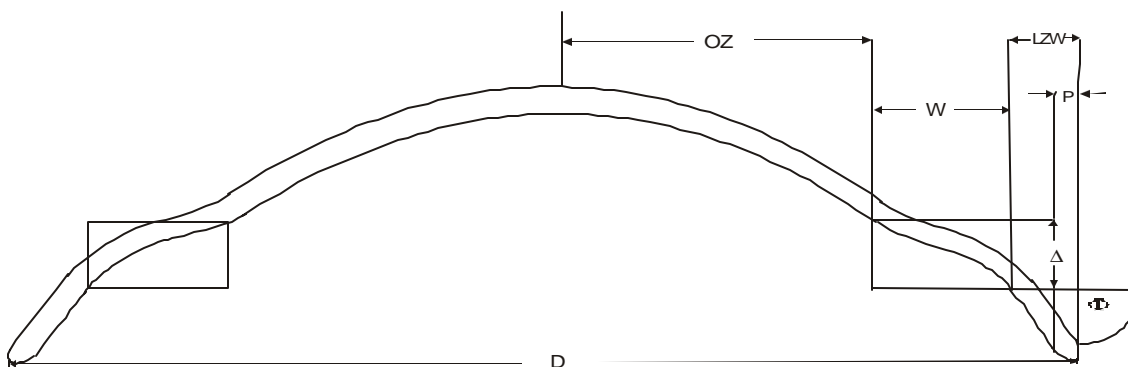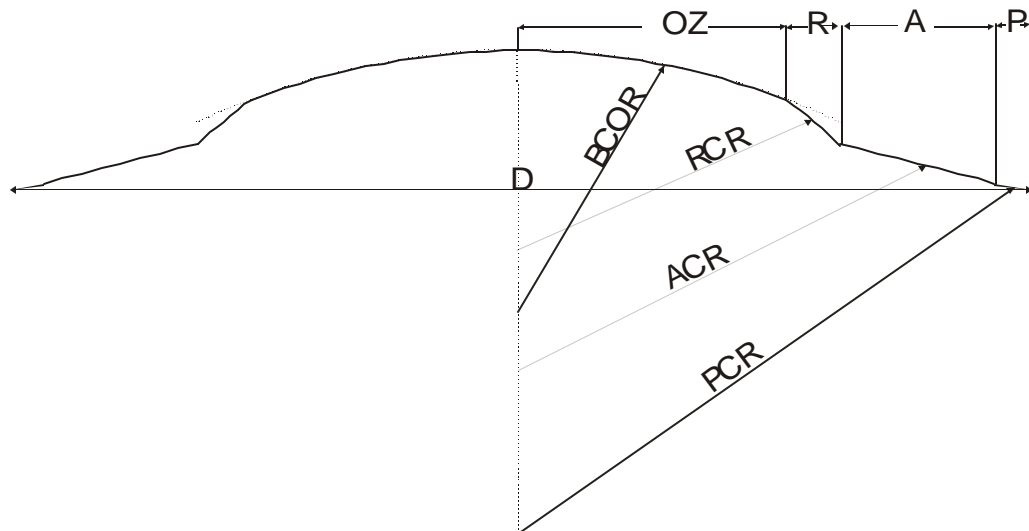
1.   The central spherical zone (OZ).

2.   A mathematically designed sigmoid corneal proximity" Return Zone" (W).

3.   A non-curving "Landing Zone" (LZW).

The lens design also includes a convex elliptical edge terminus smoothly joining the anterior and posterior surfaces.

Paragon CRT™ and Paragon CRT™ 100 designs for contact lens corneal refractive therapy are to be worn overnight with removal during all or part of each following day. Both materials are thermoset fluorosilicone acrylate polymer with a water content of less than 1%. The lens designs for corneal refractive therapy are available as lathe cut firm contact lenses with blue and green tints. The blue tinted lens contains D&C Green No. 6. The green lens contains D&C Green No. 6 and Perox Yellow No. 9.

Paragon Quadra RG™ and Paragon Quadra RG™ 100 (Reverse geometry Proximity Control Design)

Paragon Quadra RG™ and Paragon Quadra RG™ 100 four zone reverse geometry design is manufactured in Paragon HDS® and Paragon HDS® 100 (paflufocon B and D) rigid gas permeable contact lens materials. The designs have posterior surfaces consisting of four zones:

1.   The central spherical or aspheric zone (OZ).

2.   An annular "Reverse Zone(s)" (R) surrounding the central zone with a curvature steeper (shorter radius) than the central zone .

3.   An "alignment zone(s)" (A) generally paralleling the underlying corneal surface.

4.   A peripheral curve(s) (P) with a radius selected to create "edge lift" to promote tear flow under the lens and avoid impingement of the peripheral curve on the cornea.

The lens design also includes a "rounded" edge terminus extending from the anterior to the posterior surfaces to promote comfort.

The Paragon Quadra RG™ and Paragon Quadra RG™ 100 designs for corneal refractive therapy are to be worn overnight with removal during all or part of each following day. Both materials are thermoset fluorosilicone acrylate copolymer with a water content of less than 1%. Paragon Quadra RG™ and Paragon Quadra RG™ 100 are available with a handling aid for locating the lens. The tinted lens materials, paflufocon B and D, contain D&C Green No. 6, Perox Yellow No. 9, D&C Violet No. 2, and/or D&C Red No. 17 as color additives.

VI.   ALTERNATIVE PRACTICES OR PROCEDURES

The alternative practices and procedures to correcting myopia by wearing these lenses include wearing daily wear RGP lenses in a reverse geometry design, daily and extended wear RGP or soft (hydrophilic) contact lenses, spectacles, and refractive surgeries such as LASIK.

VII.   MARKETING HISTORY

On December 31, 1987, the applicant received approval of a PMA for the paflufocon A contact lens material for daily wear lenses. In November 1988 a PMA supplement was approved for the paflufocon B material (a modification of the paflufocon A material) for daily wear and in 1989 another supplement approval for extended wear. The applicant, again, modified the material and received approval for a PMA supplement for daily and extended wear of the paflufocon D material in November 1993. In each if these submissions the devices were demonstrated to be safe and effective for the intended uses for both daily wear and for extended wear from 1-7 days.

For the same lens materials, paflufocon B and paflufocon D, the applicant submitted premarket notification applications (K000224 and K010109) for the Paragon HDS-OK™ reverse geometry design for daily wear corneal refractive therapy (orthokeratology). The HDS-OK™ manufactured in paflufocon B was cleared for daily wear on April 17, 2000 while the lens manufactured in paflufocon D was cleared for marketing on February 28, 2001. The peripheral curve geometries for the HDS-OK™ orthokeratology lens design are the same as those for Quadra RG™ lens design.

Paragon has recently launched a market trial of its lens in Toronto, Canada using only trained and certified fitters, but too few patients have been fit to draw any conclusions other than to state that there have been no reports to date of any complications. Furthermore, no literature reports of complications in Europe or Australia are known to Paragon.

VIII.   POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects on health associated with overnight wear contact lenses include eye problems such as corneal ulcers, epithelial microcysts, infiltrates and endothelial polymegathism. The risk of corneal ulcer has been shown to be greater among users of overnight wear contact lenses than among users of daily wear contact lenses. The risk among overnight wear users

increases with wear time. In addition, smoking increases the risk of corneal ulcers for contact lens users, especially when lenses are worn overnight or while sleeping. Strict compliance with the proper lens care regimen and wearing schedule is essential in minimizing risk.

IX.   SUMMARY OF PRECLINICAL STUDIES

The application includes by reference the preclinical tests and results in the approved original PMA (P870024), all related supplements and substantially equivalent premarket notification applications 510(k)'s K000224 and K010109.

X.   SUMMARY OF CLINICAL STUDIES - Paragon Quadra RG™ and Quadra RG™ 100

The Paragon Quadra RG™ lens designs was studied in a 3 month daily wear clinical study as the HDS-OK™ lens made with the paflufocon B lens material. That clinical study also served as the basis for clinical performance data to determine the substantial equivalency of the HDS-OK™ lens made with paflufocon D. The Summary of Safety and Effectiveness for the daily wear clinical study is attached.

XI.   SUMMARY OF CLINICAL STUDIES - Paragon CRT™ and Paragon CRT™ 100

Objectives

The objective of the clinical study was to assess the safety and effectiveness of the Paflufocon B and D corneal refractive therapy lenses contact lens devices worn overnight to treat myopia and myopia with astigmatism.

A. Study Design

This was a controlled prospective, material randomized double masked study involving eleven clinical centers. Subjects were screened for eligibility criteria and participation interest only. The first eye was treated on June 16, 2000. The last eye treatment of the 18 and over cohort occurred on February 7, 2001 when enrollment was suspended pending approval to expand enrollment to subjects that are 12 years of age or older.

A three month interim report was submitted to FDA for the purpose of demonstrating sufficient safety and effectiveness to allow the inclusion criteria to be amended from age 18 to age 12. Approval to lower the inclusion criteria to age 12 was granted on March 26, 2001 and the maximum enrollment was increased from 200 to 225 subjects.

A total of 218 subjects received baseline evaluation and 205 were dispensed lenses and treated in the study through August 23, 2001. The database was frozen for the purpose of this report on April 8, 2002. At that time, one hundred twenty two subjects, (240 eyes) completed a minimum of nine months of treatment. One subject remains active awaiting the nine month visit.

Eligibility Criteria

a) **Inclusion Criteria**

1. Male or female subjects, of any race, and at least 18 years old (amended to 12 years) at the time of the pre-treatment examination.
2. The prospective eye(s) must have naturally occurring refractive myopia from -0.5 to -6.0 diopters sphere (spectacle plane), with up to –1.75 diopters of refractive astigmatism (spectacle plane), as determined by manifest refraction (phoropter or trial frame with a 12.5 mm vertex distance). Patients must have best spectacle corrected visual acuity of at least 0.04 logMAR in each eye.
3. The prospective eye(s) must demonstrate refractive stability, confirmed by clinical records. Neither the spherical nor the cylindrical portion of the manifest refraction may have changed more than 0.5 D during the 12-month period immediately preceding the baseline examination. The astigmatic axis may not vary by more than 15 degrees.
4. If the subject wore rigid contact lenses in the prospective eye(s), lens use must cease at least four (4) weeks prior to the pre-treatment examination. The subject must have two central keratometry readings taken that are at least one week apart. The two readings shall not differ by more than 0.50 diopter in either meridian. The mires should be regular.
5. Subjects must be willing and capable to return for all scheduled follow-up visits for a period of at least 12 months.

b) Exclusion Criteria

1. Female subjects who were pregnant, breast-feeding or intended to become pregnant over the course of the study.
2. Subjects with a history of any of the following medical conditions: collagen vascular disease, autoimmune disease, immunodeficiency diseases, ocular herpes zoster or simplex, endocrine disorders (including, but not limited to active thyroid disorders and diabetes), lupus, and rheumatoid arthritis.
    NOTE: The presence of diabetes (either type 1 or 2), regardless of disease duration, severity or control, specifically excluded subjects from eligibility.

3. Subjects with a history of intraocular or corneal surgery (including cataract extraction), active ophthalmic disease or abnormality (including, but not limited to, blepharitis, recurrent corneal erosion, dry eye syndrome, neovascularization > 1mm from limbus), clinically significant lens opacity, clinical evidence of trauma (including scarring), or with evidence of glaucoma or propensity for narrow angle glaucoma as determined by gonioscopic examination in either eye.
    NOTE: This included any subject with open angle glaucoma, regardless of medication regimen or control. Additionally, any subject with an IOP greater than 21 mm Hg at baseline was specifically excluded from eligibility.

4. Subjects with evidence of keratoconus, corneal irregularity, or abnormal videokeratography in either eye.
5. Subjects with pupil size greater than 5.5 mm in photopic illumination as measured with infrared pupilometry, pupil detection component of computer assisted video keratography, or slit lamp reticle.
6. Subjects who are participating in any other clinical trial (FDA or other).

1. Safety Endpoints

The primary endpoints used to evaluate the safety of the treatment are:

a) The proportion of eyes with a loss of two or more lines of BSCVA.
b) The proportion of eyes with a post-treatment BSCVA of worse than 20/40.
c) The proportion of eyes with adverse events.
d) The proportion of eyes with slit lamp findings greater than level 2 at any follow-up visit.
e) The proportion of eyes with symptoms, problems and complaints at each follow-up visit.

2. Effectiveness Endpoints

The effectiveness endpoints from the FDA Guidance Document, "Guidance for Premarket Submissions of Orthokeratology Rigid Gas Permeable Contact lenses", are used to profile the overall effectiveness of the treatment of myopia and myopia with astigmatism with the proximity control lenses in Paflufocon B and D.

The primary effectiveness endpoints are:

a) The proportion of eyes that achieve an UCVA of 20/20 or better and 20/40 or better.
b) The proportion of eyes that have a reduction in manifest refraction spherical equivalent (MRSE) at nine months of treatment.
c) The proportion of eyes that achieve predictability (attempted versus achieved) of the manifest refraction spherical equivalent of within ± 0.50 D and ± 1.00 D.
d) The proportion of eyes that achieve stability of manifest refraction spherical equivalent as defined by a change of no more than 0.50 D and no more than 1.00 D manifest refraction spherical equivalent between the subjective refraction measures of two consecutive visits.
e) The proportion of eyes that have a reduction of corneal curvature and absolute corneal astigmatism at nine months of treatment.

3. Patient Assessments

The clinical trial was protocol controlled. The protocol detailed the procedures and methods for the initial examination, dispensing and all scheduled and non-scheduled follow up visits.

The protocol stipulated uniform testing procedures for logMAR acuity measures. Bailey Lovie Charts were employed with a total correct letter count and test distance recorded on the case report form. The resultant logMAR acuity was calculated. The boundary for a line of vision was set at 0.04 logMAR below the threshold. For example, the 20/20 boundary was set at 0.04, equivalent to $20/20^{-2}$. The boundary for the category of eyes targeted for emmetropia was set from –0.25 to +0.50 D. Exact dioptric values and results were used to determine the boundaries for accuracy, stability and change in the MRSE

The investigators were responsible for the final lens parameters. All lenses used in treatment have a proximity control zone (return zone) that joins the optic zone that is flatter in radius than the cornea to the peripheral landing zone. The proximity control zone returns the lens to the cornea to achieve centration and precise clearance to allow the corneal apex to retreat during treatment. The following methods were followed to determine the lens design:

A diagnostic lens is selected having a radius of curvature corresponding to the intended keratometric correction. The return zone depth was determined using diagnostic lenses having 50 micron steps of return zone depth. This was followed by fluorescein pattern observations of landing zone angle in 2 degree increments to determine the landing zone that was tangent to the cornea midway between the midpoint of the landing zone and the edge. The investigator determined the final lens prescription based on the apparent fluorescein pattern as indicated in the diagnostic lens set fitting guide.

4. Demographic Data

A total of 218 subjects received baseline evaluation and 205 were dispensed lenses and treated in the study through August 23, 2001. The database was frozen for the purpose of this report on September 25, 2001. At that time, ninety-five subjects, (188 eyes) completed a minimum of nine months of treatment. Clinical investigators and sites were selected in an effort to provide sufficient diversity in geographic access, climate and elevation, urban and rural living, and racial mix for a resultant study population that represents the intended population to be treated.

As of the cut-off date for the amended clinical report, the data for 121 subjects (240 eyes) were analyzed following 9 months of treatment. The mean age of these subjects was 34.98 years (ranging from 12 to 56 years). There were 73 female and 48 male subjects. The completed subjects included adolescents and adults. There were 12 adolescent subjects (24 eyes) that completed 9 months of treatment. There were 188 Caucasians, 1 African American, 13 Asian/Pacific Islanders, and 3 Hispanics.

Table 1 (attached) presents demographic information for all patients analyzed for safety. The ratio of women to men enrolled was consistent with the contact lens wearing population. The pre-treatment refractive characteristics of the study population are represented in Table 2 (attached).

5. Accountability

Two hundred eighteen subjects underwent baseline evaluation in the study. Of these, 205 subjects (408 eyes) had lenses dispensed and wore them for at least one night of treatment. The safety analysis was conducted on all 408 treated eyes of the 205 subjects. Of the 205 subjects, 121 subjects (240 eyes) completed nine months of treatment and 1 subject remained active awaiting the 9-month visit.

The efficacy analysis was conducted on 110 subjects (220 eyes) of the 121 that completed nine months of treatment. Twenty eyes of 11 subjects were not included due to intermittent or interrupted wear during the last month of treatment preceding the nine-month visit. The lowest safety accountability at a single visit was 93% (238/256 eyes) with an average accountability of 96.8%. The lowest efficacy accountability at a single visit was 92.5% (222/240 eyes) with an average accountability of 96%.

Of the 205 subjects, 83 were discontinued prior to the nine month visit and 1 subject (2 eyes) was not due for their nine month visit. Of these 83 subjects, 44 discontinued for reason of unacceptable vision and 8 discontinued for reason of comfort. The remainder

was loss of interest, lost to follow up and missed visits, other and one subject that was reported to discontinue due to a protocol violation was because of pregnancy and the desire to discontinue at the 6 month follow up visit. Table 3 (attached) reports the tabulation of subjects that were discontinued prior to the nine-month visit and the reason for discontinuation.

B. Effectiveness Data Analysis and Results

Analysis of effectiveness outcomes was performed on the cohort of eyes that completed a minimum of 9 months of post dispensing follow up, and had consistent wear prior to the nine-month visit. In this trial, 220 eyes fit this criterion. The treatment is temporary and regression occurs within 72 hours. A period of intermittent or interrupted lens wear creates difficulty evaluating treatment effectiveness. Several subjects experienced the loss or damage to one of their lenses or elected to vary from the established wearing schedule for the investigation. As a result, the respective eyes were disqualified from the efficacy analysis.

1. **Analysis of manifest refraction spherical equivalent (MRSE)**

   Table 4 (attached) presents the uncorrected visual acuity (UCVA) of all eyes available for efficacy analysis following 9 months of treatment. The UCVA results are stratified by pretreatment MRSE. The analysis of all eyes targeted for emmetropia is valuable for profiling the number of eyes that achieved 20/40 or better. In this trial, 90.2% of eyes (185/205) achieved 20/40 or better at nine months of treatment.

   The analysis of UCVA of 20/20 or better as a measure of effectiveness is most meaningful for eyes with the ability to achieve a best spectacle corrected visual acuity (BSCVA) of at least 20/20 pre-treatment. These eyes have the capacity to achieve an uncorrected visual acuity of 20/20 post-treatment, unlike those eyes that cannot be corrected to 20/20 pre-treatment. Of the 205 of the 220 completed eyes targeted for emmetropia, 159 demonstrated 20/20 BSCVA at the baseline evaluation.

   Of the 159 eyes targeted for emmetropia with pretreatment BSCVA of 20/20 or better, 59.1% obtained 20/20 or better uncorrected visual acuity and 91.8% obtained 20/40 or better visual acuity at 9 months.

   The analysis was conducted for the adolescent subset to profile the efficacy of the treatment for that group. The UCVA of the adolescent 22 eyes was 20/20 or better for 10 eyes (45.5%) and 20/40 or better for 20 eyes (90.91%).

2. **Analysis of manifest refraction spherical equivalent (MRSE)**

   The analysis of the reduction in manifest refraction spherical equivalent at the nine-month visit provides an endpoint to assist in profiling the effectiveness of the treatment. Tables 5 and 6 (attached) report the change in diopters of the manifest refraction spherical equivalent (MRSE) from the baseline to the nine-month post dispensing follow-up visits stratified by pretreatment MRSE for nine-month efficacy qualified eyes.

   At the nine-month visit for all eyes, 98.7% of eyes (217/220) demonstrated a reduction in the MRSE of pretreatment myopia. The trend is present for a corresponding increase in

the refractive error reduction with greater pretreatment MRSE. Twenty-four eyes, 10.9% (24/220) demonstrated a reduction in MRSE of greater than 4.00 D.

At 6 months post-treatment, 54.92% of subjects were within ±0.50 D of intended MRSE; 91.9% were within ±1.0 D and 96.89% were within ±2.0 D for all eyes treated. When analyzed by dioptric categories, 84.9% of eyes that attained post-treatment MRSE within ±0.50D had pretreatment refractive errors of 4.0D or less; 82.95% were within ±1.0D; and 83.42% were within ±2.0D. The greatest accuracy of this treatment modality is for those refractive errors that are 4.0D MRSE and less. Table 7 (attached) shows that these results were consistent for the 9-month analysis.

No adolescent eyes demonstrated an increase in MRSE from baseline to the 9-month visit. Two eyes of the same subject with a pretreatment MRSE of -1.00 D demonstrated no change from baseline. The subject reported wearing the lenses only 4 nights per week since the 6-month visit.

3. Analysis of Predictability (attempted vs. achieved)

Table 7 (attached) provides the accuracy of treatment of the 9 month efficacy qualified eyes at the one, two, three, six and nine month follow up visits.

For the 9 month efficacy qualified eyes, more than 50% demonstrate post treatment MRSE within $\leq$ 0.50 D of the attempted target for post treatment follow up from the 3 through 9 month visits. More than 85% demonstrate accuracy within $\leq$1.00 D through the same post treatment interval.

4. Analysis of Stability (Attached Tables 8 and 9)

The analysis of the stability of the MRSE is presented as the number of eyes that manifest less than or equal to 0.50, 0.75, 1.00 and >1.00 diopter of difference in MRSE measured in two consecutive visits measured at the three month to six month and six month to nine month visits. Stability of outcome is evaluated for qualified eyes with subjective refraction at all three visits. This cohort is comprised of 202 eyes.

The attached Table 8 shows that from three to six months, 75.7% of eyes (179/202) demonstrated less than or equal to 0.50 D of difference in the MRSE while 95.1% of eyes (192/202) demonstrated less than or equal to 1.00 D of difference in the MRSE. The mean of the differences for all eyes was a decrease (toward target) in MRSE of – 0.078 D. This indicates a rate of continued reduction in the MRSE between the 3 and 6 month visits that would approach 0.25 D per year.

The attached Table 9 shows for the adolescent subset from six to nine months 81.8% of eyes (18/22) demonstrated ≤0.50 D of difference in the MRSE while 90.9 % of eyes (20/22) demonstrated ≤1.00 D of difference in the MRSE.

The mean of the difference for all eyes was an increase in MRSE of 0.028 D. This indicates a rate of regression in the MRSE between the 6-month and 9-month visits that would approach 0.12 D per year if sustained.

5. **Change in Corneal Curvature and Refractive Cylinder**

The reduction in refractive error and improvement in unaided visual acuity is the result in part of a change in the corneal radius as measured by keratometry. The keratometer measures the corneal curvature in the two principal meridians at a chord diameter slightly less than 3 millimeters. The keratometer does not provide data of the local curvature inside or outside of the location of its measurement. While video-keratographers were used in this trial, their methods of measurement and calculation of corneal eccentricity varied widely. The accuracy and repeatability of the simulated keratometer readings are not established and varied across instruments.

For the purpose of this trial, the change in the absolute corneal cylinder and the change in curvature in the flat meridian at nine months of treatment are analyzed as endpoints to profile the effectiveness of the treatment.

Nine eyes, 4.1% (9/220) manifested more than one diopter of increase in corneal cylinder from baseline to the nine month visit. Four of these were equal to or less than 1.25 D and three were greater than 1.50 D. Only one eye, 0.5% (1/220) demonstrated an increase of greater than 2.00 D. The increase in absolute corneal cylinder of that eye was measured to be 2.25 D.

One adolescent eye, 4.2% (1/24) manifested more than one diopter of increase in corneal cylinder from baseline to the nine month visit. The increase in absolute corneal cylinder in this eye was 1.25 D.

6. **Change in MRSE as a function of the change in the Flat Meridian**

Most importantly is the analysis of the change in MRSE as a function of the change in the flat meridian from pretreatment levels. Table 10 (attached) reports the change in the flat meridian at 9 months of treatment for all efficacy qualified eyes targeted for emmetropia, stratified by the pretreatment MRSE.

Analysis of Keratometry Change in the Flat Meridian at 9 months post-treatment shows that all eyes experienced some degree of change in the flat k meridian. Overall, there is a flattening of the flat k meridian with this treatment modality.

7. **Analysis of Refractive and Keratometric Stability**

An analysis of the mean of the differences of the post treatment measures as compared with the baseline and serial measures provides value in studying the change over time as well as the stability of the treatment.

The mean of the differences of the MRSE and mean keratometry from baseline to one month, one to two months, two to three months, three to six months and six to nine months for the efficacy qualified eyes targeted for emmetropia were provided.

The analysis indicates that the major portion of the treatment occurs in the first month with continued reduction of the MRSE thereafter. The rate of change in the mean of the differences supports stability before 3 months post treatment.

This analysis also indicates that the major portion of the treatment occurs in the first month with continued minor reduction of the mean keratometry thereafter.

The mean of the differences for the adolescent subset targeted for emmetropia that completed nine months of treatment reflects the lower baseline MRSE mean for the adolescent subset. The combined mean of the differences from 3 to 6 to 9 months is useful to project the annual rate of change to approximately 0.12 D.

8. Analysis of Wearing Time

The subjects were instructed to apply their lenses within 30 minutes of going to sleep and to remove them within 30 minutes of awakening. The wearing time generally corresponds to the expected distribution of sleep time per night. The average wear time during this study was 6.1 to 8 hours per night. There does not appear to be a relationship between length of wear and unaided visual acuity.

9. Analysis of Post lens removal UCVA Regression

An analysis of the rate of regression of MRSE and UCVA over time was conducted to provide information regarding the change over time following lens removal. Per the protocol, subjects were evaluated at 8, 24, 48, and 72 hours after removal of the lenses following either the six or nine month scheduled visit.

The original premise was that regression post lens removal was related to the magnitude of treatment applied such that the larger the correction achieved, the greater the regression rate. This was analyzed by conducting regression analyses in dioptric treatment ranges stratified by achieved correction of: 0.12 to 1.50D; 1.62 to 3.00D; 3.12 to 4.50D; and > 4.50D. Each of the corneas within these stratifications would likely have experienced similar reshaping and would likely respond with similar rates of return to pretreatment conditions.

The established nine month refraction as well as the refraction at each of the evaluation time points post lens removal were plotted against the actual time at which the regression measurement was made. The trend varied from eyes having low achieved treatment to eyes with higher achieved treatment. These results are consistent with the original premise that greater amounts of corrections regress at greater rates. Data are reported in Table 14 (attached).

C. Safety Data Analysis and Results

1. Change in BSCVA from Baseline

Table 11 (attached) provides the change in lines of BSCVA at the 9-month post-treatment interval for all completed eyes in the study. The majority of eyes, 69.17% had no change in BSCVA from baseline. Thirty-three (33) eyes had a gain of 1 line, no eyes had a gain of

2 lines, and 4 eyes had a gain of >2 lines in BSCVA as compared to baseline. Concurrently, 28 eyes (11.67%) had a loss of 1 line, 2 eyes (0.83%) lost 2 lines; and 5 eyes (2.08%) had BSCVA losses of >2 lines as compared to baseline.

An important note is that there were no losses of >2 lines in refractive errors up to –3.0D as compared to refractive errors above –3.0D. Also, the losses of >2 lines were low even for those refractive errors above –3.0D.

For the 24 adolescent subjects, the change in lines of BSCVA at the 9-month post-treatment interval 18 eyes (75.0%) had no change in BSCVA from baseline, 5 eyes (20.83%) gained 1 line, and 1 eye (4.17%) gained 2 lines. There were no eyes with loss of BSCVA.

There were no losses worse than 20/40 at the nine-month visit. At prior visits eyes measured worse than 20/40 BSCVA were re-tested when possible with a contact lens in place. Three eyes found to have worse than 20/40 BSCVA did not have a contact lens applied because of the grade of staining. In the remaining cases the acuity improved to within one line of vision indicating that the loss was due to wavefront aberration in the anterior corneal plane.

There were no measures of permanent or persistent loss of 2 or more lines of vision. All eyes with BSCVA losses of 2 or more lines were re-examined at a subsequent visit and found to be within one line of the baseline measure.

2. Adverse Reactions

There were no persistent losses or reductions of sight or deaths attributable to treatment during the course of this trial. There were 4 events reported on Adverse Event Forms. Each of the events were, by definition, study related complications and not adverse events.

One subject scratched the eye with a lens plunger and/or lens, one subject had a red and slightly irritated eye presumed to be bacterial conjunctivitis, one subject had tearing and discomfort, and one subject had diffuse subepithelial infiltrative keratitis. In each case the condition resolved.

3. Slit Lamp Findings

Slit lamp findings greater than grade 2 were reported as grade 3 for edema (18 incidents); staining (9 incidents); and injection (1 incident). All findings greater than grade 2 resolved without further complications. There were no positive slit lamp findings greater than grade 2 for any adolescent subjects at any time during the study.

4. Symptoms, Problems and Complaints

Subjects were asked to report symptoms and complaints as part of the dispensing visit and each follow up visit. These complaints are tabulated as follows for 2,197 eye exams:

Discomfort	770	Itching/Burning	99
Blurred Vision	408	Photophobia	59

Variable Vision	358	Halos	109
Dryness/Scratching	264	Lens needs Cleaning	17
		Other	113

The symptom of discomfort is prevalent at dispensing and improves through the treatment. Blur and variable vision were reported at every visit. The report of symptoms, problems and complaints does not differentiate whether the blur is with or without the lenses.

5. Intraocular Pressure

Table 12 (attached) reports the change in intraocular pressure from baseline to each follow up visit for all the 408 eyes enrolled. Of the 240 completed eyes at nine months, 92.3% (203 eyes) showed no change or a variation between +/- 5mmHG.

6. Device Failures and Replacements

The modality is designed as a single lens treatment. Investigators were permitted one retreatment lens per eye and were allowed to reorder lenses in the event of loss or damage. If additional retreatment lenses were required, the investigators were instructed to request authorization from the study monitor. There were 82 lenses reordered for 240 eyes. Of these, 10 were reordered to replace lost or damaged lenses. There were 2 reordered due to deposits and 70 were used for purpose of re-treatment. Table 13 reports the number of lens reorders for the completed eyes after the original dispensing.

7. Persistent Corneal Change

The protocol stipulated that all discontinued eyes must be followed at one month intervals until the keratometry measures were equal to or less than 0.50 diopter of difference from the baseline value in each meridian. At the same follow up visits the manifest refraction and best spectacle corrected visual acuity was reported and inspected for return to the baseline measure. Persistent corneal change can be profiled by analysis of the return to baseline keratometry, refraction and best spectacle corrected visual acuity. An analysis was performed on all eyes having 3 or more weeks of treatment. The length of treatment and time to return to baseline was tabulated as a function of the pre treatment manifest refraction spherical equivalent.

Of the 83 discontinued subjects (166 eyes), 44 eyes of 22 subjects discontinued with two weeks or less treatment and were found to be at baseline upon dispensing or upon the first follow up visit. Four subjects, (8 eyes) discontinued without returning for a final visit and were lost to follow up. Fourteen subjects (28 eyes) miss serial post discontinuation visits or reported for scheduled post treatment visits having discontinued wear between visits without notification to the investigator and were found to be at baseline at the discontinuation visit. These subjects were excluded from the analysis since the time to baseline is unknown and would have to be estimated.

D. Additional Data Analysis and Results

1. Analysis of lens material

Statistical testing for evaluating the clinical effects of the material used to manufacture the lenses was performed after the database was locked for the initial PMA submission. Analysis by material was conducted on the subset that had completed nine months of treatment at that time. The efficacy points analyzed were:

- Uncorrected visual acuity of 20/40 or better and 20/20 or better for eyes targeted for emmetropia with pretreatment best corrected acuity of 20/20 or better
- Accuracy of the attempted vs. achieved of $\pm$ 0.50 D and $\pm$1.00 D of the 9 month MRSE
- Stability of $\pm$ 0.50 D and $\pm$1.00 D between the three and six month and six and 9 month measured MRSE.

There was not a statistically significant difference between materials for the three efficacy outcomes analyzed.

Analysis by material was also conducted for the safety variables of Slit Lamp Findings by visit and the incidence of symptoms, problems and complaints by visit.
Of the six slit lamp variables reported at eight intervals (48 statistical tests in all), the finding of edema at unscheduled visits was the only p-value that approached the predetermined level of statistical significance between the two materials.

While the difference lacked statistical significance, the proportion was greater for paflufocon B than for D. It is expected that the use of the moderate Dk material could result in edema in persons having higher corneal oxygen requirements, even though both paflufocon B and D are approved for 7 days of extended wear in conventional designs.

Analysis by material of the reported symptoms, problems and complaints was conducted on nine variables reported at eight intervals (72 statistical tests in all). The complaint of halos at the two month visit was the only p-value that resulted in statistical significance. For the reports of halos, the proportion was greater at both intervals for paflufocon B than for D. It is possible that the halos reported in greater proportion with the moderate Dk material may be related to hypoxia and corneal edema.

Overall both materials performed well as evaluated in this study and are equivalent in performance.

2. Comparative Analysis of lens designs

As reported in the device description section of this summary, the CRT lens design used in the overnight study had specific features that represented some difference from generic 4 curve Quadra RG design. In order to address effectiveness concerns of the Quadra RG design used overnight, a further analysis of existing data was provided.

The data from the daily wear submission cleared for marketing by FDA cleared for the open eye treatment of up to 3.00 D of myopia with up to 1.50 D of astigmatism included four generic reverse geometry designs. The prior generic data from the 3 month open eye trial was re-analyzed to demonstrate the efficacy of the generic design in comparison to the proximity control design used in the overnight clinical trial.

This efficacy comparison used subsets of the data from each of the two clinical trials derived from all eyes with up to –3.00 D of pretreatment MRSE for all subjects 12 years of age and older that reported at the three month visits. There were 78 eyes in the generic design open eye study subset and 72 eyes in the specific design overnight study subset with up to –3.00 D of pretreatment MRSE.

The efficacy endpoints of uncorrectred visual acuity, reduction in pretreatment MRSE, accuray of attempted vs. achieved reducrion in MRSE, stability and keratometry change in the flat meridian were compared. There were not statistically significan differences found for the parameters evaluated, with the exception of a statistically significant difference in the change in keratometry in the flat meridian (p=0.1). The analysis showed that a greater proportion of eyes experienced an increased flattening of the flat keratometry meridian in the eyes with higher myopia treated in the overnight study as compared to the open eye study.

Selected outcomes of the measures analyzed are reported below:

- Uncorrected visual acuity
  The proportion of eyes that achieve an UCVA of 20/20 or better and 20/40 or better. Both clinical trials utilized the same logMAR charts under the same conditions. In each case the protocol stipulated reporting the letter count and test distance for all measures. The logMAR and corresponding Snellen values were calculated from the letter count and test distances reported. UCVA for eyes targeted for emmetropia with a pretreatment BSCVA of 20/20 or better was selected from the two databases. From the open eye dataset, 56 eyes met the comparison criteria. 52.7% achieved post treatment UCVA of 20/20 and 94.6% achieved 20/40. From the overnight dataset, 61 eyes met the comparison criteria. 57.4% achieved post treatment UCVA of 20/20 and 88.5% achieved 20/40.

- Change in MRSE
  From the 78 eyes analyzed from the open eye dataset 70.6% were within +/- .50D and 98.5% within +/- 1.00D. From the 72 eyes in the overnight dataset, 73.6% % were within +/- .50D and 97.2% within +/- 1.00D.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

The results of the preclinical studies and clinical studies provide reasonable assurance of the safety and effectiveness of the devices for the subject population, refractive conditions and specified wearing modality. Although the potential exists for minor differences in physiological response by gender for the target population, minimal number of clinically significant findings does not indicate that gender differences are of clinical importance for these devices.

XII. PANEL RECOMMENDATION

At an advisory meeting held on January 18, 2002, the Ophthalmic Devices Panel recommended that Paragon Vision Sciences' PMA for the Paragon CRT™, CRT™100, Quadra RB, and Quadra RG100 rigid gas permeable contact lenses for overnight

orthokeratology be approved subject to submission to, and approval by, the Center for Devices and Radiological Health (CDRH) of the following:

CRT Lenses

1. Revise indications to include "in ages 18 years and older"

2. Revise labeling to include

   a. Information noting that the study population was mostly Caucasian women.
   b. A statement that the discontinuation rate of use was 34.6% with the reasonsfor discontinuation included.
   c. Statement that no data is known on those excluded from the study.
   d. Include data on patients who are post treatment uncorrected visual acuity (UCVA) targeted for emmetropia, stratified by mean refractive spherical equivalent (MRSE).
   e. Include statement that orthokeratology does not affect the magnitude of pretreatment astigmatism.
   f. Include data on the post lens removal decrease in treatment affect with time stratified by refractive error.
   g. List transient changes in post treatment best corrected visual acuity (BSCVA).
   h. Emphasize that lenses need to be worn each night overnight. Failure to do so can affect activities of daily living, e.g., night driving, visual fluctuations, changes in intended correction. Some wearers may need corrective lenses during the day.
   i. State that 10-15% of the study patients did not achieve 20/40 UCVA with the trend worsening for higher myopic patients.
   j. Caution Statement that corneal edema is more prevalent with the use of the lens in high altitudes.
   k. Inclusion of refraction data on the time from removal of the lens to recovery to baseline visual acuity and MRSE, stratified by preoperative MRSE.
   l. Side effect data to include discomfort rates, punctate epithelial keratopathy, and other clinical findings.
   m. Alternative therapies delineated in the patient information booklet, e.g., spectacles, contact lenses, refractive surgery alternatives.
   n. Statement on satisfaction rates.
   o. Transmissibility data showing the Dk/L values of the two contact lens materials to be placed in the physicians' information.
   p. Physician and patient informational materials should be clarified for the target audience.

3. Physician certification or training should be required prior to the use of the lens

Quadra Lenses

In addition to numbers 1, 2, and 3 above, the sponsor should submit further analysis of existing data to address effectiveness concerns.

XIII.   CDRH DECISION

CDRH concurred with the Ophthalmic Devices Panel's recommendation of January 18, 2002, and issued a letter to Paragon Vision Sciences on February 27, 2002, advising that its PMA

was approvable subject to their submission of an amendment adequately addressing the conditions listed above as recommended by the Panel. In amendments received by FDA on April 23, May 7 and June 3, 2002, Paragon Vision Sciences adequately addressed conditions 2 and 3 of the Panel's conditions for the CRT™ and CRT™ 100 lenses and all the conditions for the Quadra RG™ and Quadra RG™ 100 lenses.

In regards to condition 1 (above) of the Panel's recommendation, there are several considerations for not concurring with the recommendation and thereby not limiting the age of treatment in the indication for use. Although there were limited data reported, those data reported on adolescents did comprise 11% of the completed dataset. FDA notes that adolescent subjects in this clinical study had fewer positive slit lamp findings (none greater than grade 2) and no reports of adverse reactions.

Adolescent patients wearing rigid contact lenses, both gas permeable (RGP) and polymethylmethacrylate (PMMA) has been an accepted practice since their initial availability. Adolescent subjects have worn both daily wear and extended wear RGP lenses up to 7 days and beyond and have been included in clinical studies of these lenses.

Although there are no reports in the orthokeratology literature specific to adolescent subjects, the primary effectiveness concern in this age group is their expected progression of myopic refractive error as they grow. However, the contact lens base curve can be adjusted to correct for any refractive error progression over time. In addition, the long safety term effects of rigid gas permeable lens use for reshaping the cornea has not been established for any specific age population.
CDRH does not believe that the approval of these devices for overnight corneal refractive therapy without an age restriction would pose any additional compromise of safety or effectiveness for adolescent patients when used in accordance with the approved labeling.

FDA issued an approval order on   .

XIV.   APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

Table 1				
Demographic Information of All Enrolled and Treated Subjects N=205, (408 Eyes Treated)				
Category	**Classification**	**n**	**% Eyes**
Gender	**Male**	**80**	**39.0**
	Female	**125**	**61.0**
Eyes	**Right**	**205**	**50.2**
	Left	**203**	**49.8**
Race	**Caucasian**	**188**	**91.7**
	African American	**1**	**0.5**
	Asian / Pacific Islander	**13**	**6.3**
	American Indian / Aleut	**0**	**0.0**
	Eskimo	**3**	**1.5**
	Hispanic	**0**	**0.0**
	Latino		
Current CL History	**None**	**37**	**18.1**
	Hydrogel	**154**	**75.1**
	Rigid	**14**	**6.8**
Age (in Years)	**Average**	**33.66**	
	Standard Deviation	**± 12.4**	
	Minimum	**12**	
	Maximum	**58**	

Pretreatment Refractive Cylinder (DC)	£1.0D	1.25 to 2.00D	2.25 to 3.00D	3.25 to 4.00D	4.25 to 5.00D	5.25 to 6.00D	6.25 to 7.00D	Total
	n	n	n	n	n	n	n	n
	%	%	%	%	%	%	%	%
	Col %	Col %	Col %	Col %	Col %	Col %	Col %	Col %
0.00	7	24	22	7	6	0	0	66
	3.18	10.91	10	3.18	2.73	0	0	30%
	41.18	30	32.35	21.88	37.50	0	0	
0.12 to 0.50	6	33	23	18	5	2	0	87
	2.73	15.00	10.45	8.18	2.27	0.91	0	39.55%
	35.29	41.25	33.82	56.25	31.25	28.57	0	
0.62 to 1.00	2	17	16	4	2	3	0	44
	0.91	7.73	7.27	1.82	0.91	1.36	0	20%
	11.76	21.25	23.53	12.50	12.50	42.86	0	
1.12 to 1.50	2	5	3	1	3	2	0	16
	0.91	2.27	1.36	0.45	1.36	0.91	0	7.27%
	11.76	6.25	4.41	3.13	18.75	28.57	0	
1.62 to 2.00	0	1	4	2	0	0	0	7
	0	0.45	1.82	0.91	0	0	0	3.18%
	0	1.25	5.88	6.25	0	0	0	
Total	17	80	68	32	16	7	0	220
	7.73	36.36	30.91	14.55	7.27	3.18	0	100%

Table 2
Pretreatment Refractive Cylinder
Stratified by Pretreatment Sphere
All Efficacy Qualified Eyes (N=220)
Pretreatment Sphere (DS)

Reason for Discontinuation	Number of Patients
Unacceptable Vision	44
Lack of Interest	12
Lost to follow-up	9
Lack of Comfort	8
Other	6
Missed Visits	3
Protocol Violation	1

Table 3
Reason for Discontinuation
(N=83 Subjects, 166 Eyes)

Table 4 Uncorrected Visual Acuity (UCVA) at the 9 Month Visit Stratified by Pre-treatment Manifest Refraction Spherical Equivalent. All Efficacy Qualified Eyes (N=220)								
Post treatment UCVA)	**Pre Treatment Myopia (MRSE)**							
	£ 1.0D	**1.25 to 2.00D**	**2.25 to 3.00D**	**3.25 to 4.00D**	**4.25 to 5.00D**	**5.25 to 6.00D**	**6.25 to 7.00D**	**Total N %**
20/20 or better	5	40	32	18	7	1	0	103
	2.27%	18.18%	14.55%	8.18%	3.18%	0.45%	0%	46.82%
	62.50%	67.80%	40.51%	42.86%	31.82%	12.50%	0%	
20/32 or better	6	58	67	36	14	5	0	186
	2.73%	26.36%	30.45%	16.36%	6.36%	2.27%	0%	84.55%
	75%	98.31%	84.81%	85.71%	63.64%	62.50%	0%	
20/40 or better	6	58	69	37	17	6	0	193
	2.73%	26.36%	31.36%	16.82%	7.73%	2.73%	0%	87.73%
	75%	98.31%	87.34%	88.10%	77.27%	75.00%	0%	
20/64 or better	8	59	78	39	20	7	2	213
	3.64%	26.82%	35.45%	17.73%	9.09%	3.18%	0.91%	96.82%
	100%	100%	98.73%	92.86%	90.91%	87.50%	100%	
20/80 or better	8	59	78	40	21	8	2	216
	3.64%	26.82%	35.45%	18.18%	9.55%	3.64%	0.91%	98.18%
	100%	100%	98.73%	95.24%	95.45%	100%	100%	
20/200 or better	8	59	79	42	22	8	2	220
	3.64%	26.82%	35.91%	19.09%	10%	3.64%	0.91%	100%
	100%	100%	100%	100%	100%	100%	100%	
Sub-Total	8	59	79	42	22	8	2	220
	3.64%	26.82%	35.91%	19.09%	10.00%	3.64%	0.91%	100%
Not Reported	0	0	0	0	0	0	0	0
Total	8	59	79	42	22	8	2	220

Change at 9 Months (DSE)	Table 5 Refractive Change in Diopters from Baseline to Month 9 Stratified by Pretreatment MRSE All 9 Month Efficacy Qualified Eyes (N = 220)							
	Pretreatment Myopia (MRSE)							
	£ 1.0D	1.12 to 2.00D	2.12 to 3.00D	3.12 to 4.00D	4.12 to 5.00D	5.12 to 6.00D	6.12 to 7.00D	Total
	n	n	n	n	n	n	n	n
	%	%	%	%	%	%	%	%
	Col %	Col %	Col %	Col %	Col %	Col %	Col %	Col %
No Change 0.00	2	0	0	0	0	0	0	2
	0.9%	0%	0%	0%	0%	0%	0%	0.9%
	25.0%	0%	0%	0%	0%	0%	0%	
Decrease								
0.12 to 0.50	2	2	1	0	0	0	0	5
	0.9%	0.9%	0.5%	0%	0%	0%	0%	2.3%
	25.0%	3.4%	1.3%	0%	0%	0%	0%	
0.62 to 1.00	4	12	4	0	0	0	0	20
	1.8%	5.5%	1.8%	0%	0%	0%	0%	9.1%
	50%	20.3%	5.1%	0%	0%	0%	0%	
1.12 to 1.50	0	23	11	1	0	0	0	35
	0%	10.5%	5.0%	0.5%	0%	0%	0%	15.9%
	0%	39.0%	13.9%	2.4%	0%	0%	0%	
1.62 to 2.00	0	20	27	1	0	0	0	48
	0%	9.1%	12.3%	0.5%	0%	0%	0%	21.8%
	0%	33.9%	34.2%	2.4%	0%	0%	0%	
2.12 to 2.50	0	2	19	5	1	0	0	27
	0%	0.9%	8.6%	2.3%	0.5%	0%	0%	12.3%
	0%	3.4%	24.1%	11.9%	4.5%	0%	0%	
2.62 to 3.00	0	0	13	12	2	0	0	27
	0%	0%	5.9%	5.5%	0.9%	0%	0%	12.3%
	0%	0%	16.5%	28.6%	9.1%	0%	0%	
3.12 to 3.50	0	0	2	12	3	0	0	17
	0%	0%	0.9%	5.5%	1.4%	0%	0%	7.7%
	0%	0%	2.5%	28.6%	13.6%	0%	0%	
3.62 to 4.00	0	0	1	8	3	1	1	14
	0%	0%	0.5%	3.6%	1.4%	0.5%	0.5%	6.4%
	0%	0%	1.3%	19.0%	13.6%	12.5%	50%	
>4.00	0	0	0	3	13	7	1	24

	0%	0%	0%	1.4%	5.9%	3.2%	0.5%	10.9%
	0%	0%	0%	7.1%	59.1%	87.5%	50%	
Increase								
0.12 to 0.50	0	0	1	0	0	0	0	1
	0%	0%	0.5%	0%	0%	0%	0%	0.5%
	0%	0%	1.3%	0%	0%	0%	0%	
Total	8	59	79	42	22	8	2	220
	100%	100%	100%	100%	100%	100%	100%	100%

Table 6
Adolescent Refractive Change in Diopters from Baseline to Month 9
Stratified by Pretreatment MRSE
All 9 Month Efficacy Qualified Eyes (N = 24)

Change at 9 Months (DSE)	Pretreatment Myopia (MRSE)							Total
	£ 1.0D	1.12 to 2.00D	2.12 to 3.00D	3.12 to 4.00D	4.12 to 5.00D	5.12 to 6.00D	6.12 to 7.00D	
	n	n	n	n	n	n	n	n
	%	%	%	%	%	%	%	%
	Col %	Col %	Col %	Col %	Col %	Col %	Col %	Col %
No Change 0.00	2	0	0	0	0	0	0	2
	8.3%	0%	0%	0%	0%	0%	0%	8.3%
	100%	0%	0%	0%	0%	0%	0%	
Decrease								
0.12 to 0.50	0	0	0	0	0	0	0	0
	0%	0%	0%	0%	0%	0%	0%	0%
	0%	0%	0%	0%	0%	0%	0%	
0.62 to 1.00	0	4	0	0	0	0	0	4
	0%	16.7%	0%	0%	0%	0%	0%	16.7%
	0%	40%	0%	0%	0%	0%	0%	
1.12 to 1.50	0	4	1	0	0	0	0	5
	0%	16.7%	4.2%	0%	0%	0%	0%	20.8%
	0%	40%	12.5%	0%	0%	0%	0%	
1.62 to 2.00	0	2	2	0	0	0	0	4
	0%	8.3%	8.3%	0%	0%	0%	0%	16.7%
	0%	20%	25.0%	0%	0%	0%	0%	
2.12 to 2.50	0	0	4	0	0	0	0	4
	0%	0%	16.7%	0%	0%	0%	0%	16.7%
	0%	0%	50%	0%	0%	0%	0%	
2.62 to 3.00	0	0	1	2	0	0	0	3
	0%	0%	4.2%	8.3%	0%	0%	0%	12.5%
	0%	0%	12.5%	100%	0%	0%	0%	
3.12 to 3.50	0	0	0	0	0	0	0	0
	0%	0%	0%	0%	0%	0%	0%	0%
	0%	0%	0%	0%	0%	0%	0%	
3.62 to 4.00	0	0	0	0	0	0	0	0
	0%	0%	0%	0%	0%	0%	0%	0%
	0%	0%	0%	0%	0%	0%	0%	
>4.00	0	0	0	0	0	1	1	2
	0%	0%	0%	0%	0%	4.2%	4.2%	8.3%
	0%	0%	0%	0%	0%	100%	100%	
Increase								

0.12 to 0.50	0	0	0	0	0	0	0	0
	0%	0%	0%	0%	0%	0%	0%	0%
	0%	0%	0%	0%	0%	0%	0%	
Not Reported	0	0	0	0	0	0	0	0
Total	2	10	8	2	0	1	1	24
	100%	100%	100%	100%	0%	100%	100%	100%

	Table 7							
	Accuracy of Targeted Vs. Achieved Correction at 9 Month Visit							
	Stratified by Pretreatment Myopia							
	All 9 Month Efficacy Qualified Eyes (N=220)							
	Pre Treatment Myopia (MRSE)							
	< 1.0D	**1.12 to 2.00D**	**2.12 to 3.00D**	**3.12 to 4.00D**	**4.12 to 5.00D**	**5.12 to 6.00D**	**6.12 to 7.00D**	**Total**
Int. Vs. Ach (DSE)	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**
	%	**%**	**%**	**%**	**%**	**%**	**%**	**%**
	Col %	**Col %**	**Col %**	**Col %**	**Col %**	**Col %**	**Col %**	**Col %**
±0.50 D	5	41	33	23	14	2	1	119
	2.27	18.64	15.00	10.45	6.36	0.91	0.45	54.09%
	62.50	69.49	41.77	54.76	63.64	25.00	500	
±1.00 D	8	59	71	37	20	6	1	202
	3.64	26.82	32.27	16.82	9.09	2.73	0.45	91.82%
	100	100	89.87	88.10	90.91	75.00	500	
±2.00 D	8	59	79	42	21	8	1	218
	3.64	26.82	35.91	19.09	9.55	3.64	0.45	99.09%
	100	100	100	100	95.45	100	500	
±3.00 D	8	59	79	42	22	8	2	220
	3.64	26.82	35.91	19.09	100	3.64	0.91	100%
	100	100	100	100	100	100	100	
> 4.00 D	8	59	79	42	22	8	2	220
	3.64	26.82	35.91	19.09	100	3.64	0.91	100%
	100	100	100	100	100	100	100	
Sub-Total	8	59	79	42	22	8	2	220
	3.64	26.82	35.91	19.09	100	3.64	0.91	100%
Not Reported	0	0	0	0	0	0	0	0
Total	8	59	79	42	22	8	2	220
	3.64	26.82	35.91	19.09	100	3.64	0.91	100%
Undercorr.> 1	0	0	8	5	2	2	1	18
Undercorr.> 2	0	0	0	0	1	0	1	2
Undercorr.> 3	0	0	0	0	0	0	0	0

Change in MRSE (DSE)	Pre Treatment Myopia (MRSE)							
	£ 1.0D n % Col %	1.12 to 2.00D n % Col %	2.12 to 3.00D n % Col %	3.12 to 4.00D n % Col %	4.12 to 5.00D n % Col %	5.12 to 6.00D n % Col %	6.12 to 7.00D n % Col %	Total n % Col %
< 0.50 D	8	45	49	33	14	3	1	153
	3.96	22.28	24.26	16.34	6.93	1.49	0.50	75.74%
	100	84.91	71.01	78.57	700	37.50	500	
£ 0.75 D	8	50	62	37	16	5	1	179
	3.96	24.75	30.69	18.32	7.92	2.48	0.50	88.61%
	100	94.34	89.86	88.10	800	62.50	500	
£ 1.00 D	8	53	64	41	19	6	1	192
	3.96	26.24	31.68	20.30	9.41	2.97	0.50	95.05%
	100	100	92.75	97.62	95.00	75.00	500	
> 1.00 D	0	0	5	1	1	2	1	10
	0	0	2.48	0.50	0.50	0.99	0.50	4.95%
	0	0	7.25	2.38	5.00	25.00	500	
Total	8	53	69	42	20	8	2	202
	3.96	26.24	34.16	20.79	9.90	3.96	0.99	100%
Mean	0.188	-009	-0.100	-080	-0.294	-0.235	0.625	-078
Stdev	0.189	0.386	0.565	0.578	0.614	1.254	0.707	0.569
Lower C L	030	-0.116	-0.235	-0.260	-0.581	-1.284	-5.728	-0.157
Upper C L	0.345	097	036	0.100	-006	0.814	6.978	001

Table 8
Stability of Manifest Refraction Spherical Equivalent from 3 Month to 6 Month Visit
Stratified by Pretreatment Dioptic Group
All Efficacy Qualified Eyes with 3, 6, and 9 month visits (N=202)

Table 9 Adolescent Stability of Manifest Refraction Spherical Equivalent from 6 Month to 9 Month Visit Stratified by Pretreatment Dioptic Group All Adolescent Eyes with 3, 6, and 9 month visits (N=22)								
Change in MRSE (DSE)	Pre Treatment Myopia (MRSE)							
	£ 1.0D n % Col %	1.12 to 2.00D n % Col %	2.12 to 3.00D n % Col %	3.12 to 4.00D n % Col %	4.12 to 5.00D n % Col %	5.12 to 6.00D n % Col %	6.12 to 7.00D n % Col %	Total n % Col %
< 0.50 D	2	8	4	2	0	1	1	18
	9.09	36.36	18.18	9.09	0	4.55	4.55	81.82%
	100%	80%	66.67%	100%	0	100%	100%	
£ 0.75 D	2	9	5	2	0	1	1	20
	9.09	40.91	22.73	9.09	0	4.55	4.55	90.91%
	100%	90%	83.33%	100%	0	100%	100%	
£ 1.00 D	2	9	5	2	0	1	1	20
	9.09	40.91	22.73	9.09	0	4.55	4.55	90.91%
	100%	90%	83.33%	100%	0	100%	100%	
> 1.00 D	0	1	1	0	0	0	0	2
	0	4.55	4.55	0	0	0	0	9.09%
	0	10	16.67%	0	0	0	0	
Total	2	10	6	2	0	1	1	22
	9.09	45.45	27.27	9.09	0	4.55	4.55	100%
Mean	00	0.113	-021	-0.313	.	0.125	0.125	028
Stdev	00	0.538	0.871	0.265	.	.	.	0.569
Lower C L	.	-0.273	-0.935	-2.695	.	.	.	-0.224
Upper C L	.	0.498	0.893	2.070	.	.	.	0.281

Table 10 Keratometry Change in the Flat Meridian at 9 Months Stratified by Pretreatment Dioptic Group All 9 Month Efficacy Qualified Eyes Targeted for Emmetropia (N=205)								
Keratometry Change in Flat Meridian (D)	**Pre Treatment Myopia (MRSE)**							
	£ 1.0D	**1.12 to 2.00D**	**2.12 to 3.00D**	**3.12 to 4.00D**	**4.12 to 5.00D**	**5.12 to 6.00D**	**6.12 to 7.00D**	**Total**
	n	**n**	**n**	**n**	**n**	**n**	**n**	**N**
	%	**%**	**%**	**%**	**%**	**%**	**%**	**%**
	Col %	**Col %**	**Col %**	**Col %**	**Col %**	**Col %**	**Col %**	**Col %**
Flatter								
4.62 to 5.00	0	0	2	0	0	0	0	2
	0	0	0.99	0	0	0	0	0.99%
	0	0	2.78	0	0	0	0	
4.12 to 4.50	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	
3.62 to 4.00	0	0	0	0	0	3	0	3
	0	0	0	0	0	1.48	0	1.48%
	0	0	0	0	0	50	0	
3.12 to 3.50	0	0	0	1	3	1	0	5
	0	0	0	0.49	1.48	0.49	0	2.46%
	0	0	0	2.63	15.00	16.67	0	
2.62 to 3.00	0	0	2	3	7	1	0	13
	0	0	0.99	1.48	3.45	0.49	0	6.40%
	0	0	2.78	7.89	35.00	16.67	0	
2.12 to 2.50	0	3	8	16	3	0	1	31
	0	1.48	3.94	7.88	1.48	0	0.49	15.27%
	0	5.17	11.11	42.11	15.00	0	100	
1.62 to 2.00	0	3	16	10	3	1	0	33
	0	1.48	7.88	4.93	1.48	0.49	0	16.26%
	0	5.17	22.22	26.32	15.00	16.67	0	
1.12 to 1.50	0	17	20	6	4	0	0	47
	0	8.37	9.85	2.96	1.97	0	0	23.15%
	0	29.31	27.78	15.79	20	0	0	
0.62 to 1.00	1	23	13	1	0	0	0	38
	0.49	11.33	6.40	0.49	0	0	0	18.72%
	12.50	39.66	18.06	2.63	0	0	0	
0.12 to 0.50	5	10	9	1	0	0	0	25
	2.46	4.93	4.43	0.49	0	0	0	12.32%
	62.50	17.24	12.50	2.63	0	0	0	
No Change 00	0	0	0	0	0	0	0	0
Steeper								
0.12 to 0.50	0	2	2	0	0	0	0	4
	0	0.99	0.99	0	0	0	0	1.97%
	0	3.45	2.78	0	0	0	0	
0.62 to 1.00	2	0	0	0	0	0	0	2
	0.99	0	0	0	0	0	0	0.99%
	25.00	0	0	0	0	0	0	
Subtotal	8	58	72	38	20	6	1	203
	3.94%	28.57%	35.47%	18.72%	9.85%	2.96%	0.49%	100%
Not Reported	0	0	2	0	0	0	0	2
Total	8	58	74	38	20	6	1	205

Table 11

Change in BSCVA Over Time (All Eyes, N=408)					
	1 Month (n=330) n % (95% CI)	2 Months (n=292) n % (95% CI)	3 Months (n=286) n % (95% CI)	6 Months (n=238) n % (95% CI)	9 Months (n=240) n % (95% CI)
Increase > 2 Lines	2 0.6 (0.1, 2.3)	2 0.7 (0.1, 2.6)	1 0.4 (0, 2.0)	6 2.5 (0.9, 5.5)	4 1.7 (0.5, 4.2)
Increase 2 Lines	2 0.6 (0.1, 2.3)	2 0.7 (0.1, 2.6)	3 1.1 (0.2, 3.2)	4 1.7 (0.5, 4.3)	0 0 (0, 1.3)
Increase 1 Line	34 10.9 (7.7, 14.9)	44 15.9 (11.8, 20.8)	39 14.2 (10.3, 18.9)	31 13.1 (9.1, 18.1)	33 13.9 (9.7, 18.9)
No Change	196 63.0 (57.4, 68.4)	166 60.1 (54.1, 66.0)	184 67.2 (61.2, 72.7)	159 67.4 (61.0, 73.3)	166 69.7 (63.5, 75.5)
Decrease 1 Line	50 16.1 (12.2, 20.6)	43 15.6 (11.5, 20.4)	36 13.1 (9.4, 17.7)	28 11.9 (8.0, 16.7)	28 11.8 (8.0, 16.6)
Decrease 2 lines	10 3.2 (1.6, 5.8)	6 2.2 (0.8, 4.7)	2 0.7 (0.1, 2.6)	1 0.4 (0, 2.3)	2 0.8 (0.1, 3.0)
Decrease > 2 Lines	17 5.5 (3.2, 8.6)	13 4.7 (2.5, 7.9)	9 3.3 (1.5, 6.1)	7 3.0 (1.2, 6.0)	5 2.1 (0.7, 4.8)
Not Reported	19	16	12	2	2
Total	330	292	286	238	240

Table 12 Change in Intraocular Pressure Over Time (All Eyes, N=408)					
	1 Month (n=330) n % (95% CI)	2 Months (n=292) n % (95% CI)	3 Months (n=286) n % (95% CI)	6 Months (n=238) n % (95% CI)	9 Months (n=240) n % (95% CI)
Decrease > 10	1 0.3 (0, 1.9)	0 0 (0, 1.1)	0 0 (0, 1.1)	0 0 (0, 1.3)	0 0 (0, 1.3)
Decrease 6 to 10	10 3.4 (1.6, 6.2)	14 5.2 (2.9, 8.5)	18 6.7 (4.0, 10.4)	13 5.7 (3.0, 9.5)	13 5.5 (3.0, 9.2)
Decrease 1 to 5	136 46.3 (40.5, 52.1)	131 48.3 (42.3, 54.5)	130 48.7 (42.6, 54.9)	111 48.3 (41.6, 54.9)	122 51.7 (45.1, 58.2)
No Change	50 17.0 (12.9, 21.8)	40 14.8 (10.8, 19.6)	38 14.2 (10.3, 19.0)	36 15.7 (11.2, 21.0)	34 14.4 (10.2, 19.5)
Increase 1 to 5	92 31.3 (26.0, 36.9)	80 29.5 (24.2, 35.3)	79 29.6 (24.2, 35.5)	68 29.6 (23.7, 35.9)	63 26.7 (21.2, 32.8)
Increase 6 to 10	5 1.7 (0.6, 3.9)	6 2.2 (0.8, 4.8)	2 0.7 (0.1, 2.7)	2 0.9 (0.1, 3.1)	4 1.7 (0.5, 4.3)
Increase > 10	0 0 (0, 1.0)	0 0 (0, 1.1)	0 0 (0, 1.1)	0 0 (0, 1.3)	0 0 (0, 1.3)
Not Reported	36	21	19	8	4
Total	330	292	286	238	240

Table 13
Description and Number of Lens Reorders Completed Eyes
(N=240)

Reason for Replacement	Number of Lenses Replaced
Poor Centration	31
Under Treatment	19
Lost Lens	7
Excessive Landing Zone Clearance	6
Reverse Zone Bridging	5
Excessive Reverse Zone Junction Clearance	3
Damaged Lens	3
Over Treatment	2
Power Change	2
Landing Zone Bridging	2
Lens Deposits	2
Pathology	0
TOTAL	82

Table 14
Average Hours Post Lens Removal Until Regression To –1.00 Diopter (~20/40)

		Pretreatment Manifest Refractive Spherical Equivalent				
		-1.25 to -2.00 (D)	-2.25 to -3.00 (D)	-3.25 to -4.00 (D)	-4.25 to -5.00 (D)	-5.25 to -6.00 (D)
Refraction at Lens Removal	+0.50	40 to 80+ Hrs	24 to 40 Hrs	18 to 24 Hrs	13 to 15 Hrs	11 to 13 Hrs
	+0.25	30 to 80+ Hrs	21 to 30 Hrs	16 to 21 Hrs	11 to 16 Hrs	10 to 11 Hrs
	Plano	22 to 44 Hrs	16 to 22 Hrs	13 to 18 Hrs	9 to 13 Hrs	7 to 8 Hrs
	-0.25	22 to 29 Hrs	16 to 20 Hrs	11 to 16 Hrs	7 to 11 Hrs	5 to 7 Hrs
	-0.50	18 to 24 Hrs	10 to 18 Hrs	7 to 10 Hrs	6 to 7 Hrs	3 to 5 Hrs
	-0.75	8 to 18 Hrs	5 to 8 Hrs	4 to 5 Hrs	3 to 4 Hrs	2 to 3 Hrs

Table 15 Summary of Key Safety and Effectiveness Variables						
CRITERIA	**9 Months Combined**		**9 Months Adults**		**9 Months Adolescents**	
	n	**%**	**n**	**%**	**n**	**%**
n	**159**		**144**		**15**	
UCVA 20/20 or better * ***	94	59.1	84	58.3	10	66.7
n	**205**		**183**		**22**	
UCVA 20/20 or better* **	103	50.2	93	50.8	10	45.5
UCVA 20/40 or better* **	185	90.2	165	90.2	20	90.9
n	**220**		**196**		**24**	
MRSE Change of 0.12 to 1.00 D	26	11.8	22	11.3	4	16.7
MRSE Change of 1.12 to 2.00 D	83	37.7	74	37.7	9	37.7
MRSE Change of 2.12 to 3.00 D	54	24.6	47	23.9	12	29.2
MRSE Change of 3.12 to 4.00 D	31	14.1	31	15.8	0	0
MRSE Change of 4.12 to 5.00 D	19	8.6	17	8.7	2	8.3
MRSE Change of $\geq$ 5.00 D	5	2.3	5	2.6	0	0
	220		**196**		**24**	
Accuracy MRSE $\pm$ 0.50 D	119	54.1	104	53.1	15	62.5
Accuracy MRSE $\pm$ 1.00 D	202	91.8	178	90.8	24	100
Accuracy MRSE $\pm$ 2.00 D	218	99.1	194	99.0	24	100
n	**202**		**180**		**22**	
Stability; MRSE $\leq$0.50 Change 3 to 6 months	153	75.7	135	75.0	18	81.8
Stability; MRSE $\leq$0.75 Change 3 to 6 months	179	88.6	160	88.9	19	86.4
Stability; MRSE $\leq$1.00 Change 3 to 6 months	192	95.0	171	95.0	21	95.5
Stability; MRSE $\leq$0.50 Change 6 to 9 months	163	80.7	145	80.6	18	81.8
Stability; MRSE $\leq$0.75 Change 6 to 9 months	176	87.1	156	86.7	20	90.9
Stability; MRSE $\leq$1.00 Change 6 to 9 months	183	90.6	163	90.6	20	90.9
n	**240**		**216**		**24**	
Serious Adverse Events	0	0	0	0	0	0
Loss of $\geq$ 2 lines BSCVA	7	2.9	7	3.2	0	0
BSCVA worse than 20/40	0	0	0	0	0	0
Increase of > 1 D Refractive Cyl	2	0.9	2	1.0	0	0
Increase of > 2 D Refractive Cyl	0	0	0	0	0	0
Increase of > 1 D Corneal Cyl	9	4.1	8	4.1	2	9.5

*Excluding eyes intentionally under-corrected
**Includes eyes with a pre-treatment BSCVA worse than 20/20.
***BSCVA 20/20 or better pre-treatment.