REFRACTIVE ERROR SHIFT WITH CONTINUOUS USE (RESCU) LENSES

DISSERTATION

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By

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* * * * *

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ABSTRACT

Low Dk hydrogel contact lenses have been associated with minimal but measurable progression of myopia although evidence to the contrary exists. This so called “myopic creep” has been shown to decrease or reverse when hydrogel lens wearers switch to 30 night and day silicone hydrogel lens wear. To assess the mechanisms contributing to changes in refractive error associated with the refitting of extended wear hydrogel contact lens users with 30-night continuous use silicone hydrogel contact lenses a prospective clinical trial was completed.

Fifteen adapted extended wear low-Dk contact lens patients and five non-contact lens wearers were enrolled and followed for 3-months after fitting with 30-night continuous wear lenses. Patients were examined at 1-day, 1-week, 1-month, 2-months and 3-months. Refractive error evaluation included subjective and automated refractions and wavefront derived measurements. Ocular biometric measurements included topography, pachymetry, axial length, anterior chamber depth and phakometry.

A hyperopic shift of 0.40 diopters was observed in previous myopic low-Dk extended wear hydrogel contact lens users after 3-months of continuous wear of a silicone hydrogel contact lens. Hyperopic shifts are predicted in those subjects with the greatest baseline myopic refractive error. The occurrence of hyperopic shifts are
associated with corneas that experience larger amounts of anterior curvature flattening and are associated with large changes towards more positive values in ocular $4^{th}$ order spherical aberration Zernike term. Corneal thinning (Orbscan I pachymetry) was also associated with the hyperopic shift.
Dedicated to my family and friends. Thanks for the support and inspiration.
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CHAPTER 1
INTRODUCTION

There are approximately 75 million people worldwide that wear contact lenses for refractive error correction, and about half of these wearers are in the United States. Within the United States, about 7 million people (20% of U.S. contact lens wearers) are estimated to wear contact lenses in a continuous wear modality, defined as continuous use of a contact lens for a period greater than 24 hours. Continuous use lenses are attractive to patients because they provide a level of the freedom from spectacle lenses and from the ritual of insertion, removal and cleaning associated with traditional daily wear contact lenses. Patient demand for use of contact lenses overnight was demonstrated in a global survey by CIBA Vision Inc (Duluth, GA), which showed about 77 percent of contact lens wearers in the United States and 50 to 65 percent worldwide expressing a need for more contact lens continuous wear options (Barr, J. T., 1998). Despite this level of interest many practitioners were hesitant to recommend this fitting modality because of reported potential sight-threatening complications that occurred in the mid-1980s with extended wear of low oxygen permeability (Dk) contact lenses.

The response of manufacturers was the development of contact lenses that were up to 600 percent more oxygen permeable, the silicone hydrogel hybrids, which first became available in the United States in 2000. The Bausch & Lomb Inc. (Rochester, NY)
PureVision (Balafilcon A) was the first silicone hydrogel contact lens marketed in the United States and it was initially approved for a maximum of 7-nights continuous wear. The following year, the Ciba Vision Focus Night & Day (Lotrafilcon A) contact lens was approved by the Food and Drug Administration (FDA) for 30-nights continuous wear. The PureVision contact lens was approved for 30-night continuous use in 2001.

After less than two years of availability, silicone hydrogel contact lenses represented about 40 percent of all continuous wear contact lens fitting in the United States (Morgan, P. B., Efron N. et al., 2003). The adoption of silicone hydrogel contact lenses was most prevalent in patients previously using extended wear low-Dk hydrogel contact lenses. In other countries silicone hydrogel usage is estimated to range from 75 to 95 percent in patients practicing continuous wear, representing a total of over half a million patients worldwide (Barr, J. T., 2003; Morgan, P. B., Efron N. et al., 2003). Many eyecare practitioners readily prescribed these hyper-Dk contact lenses due to their perception of high complication rates in patients using low-Dk hydrogel contact lenses in extended wear or even long-term daily wear.

1985). This progressive myopia has also been referred to as myopic creep or adult onset myopia. A few studies and several anecdotal reports have shown that this so called myopic creep may be reversed for some patients when hydrogel lens wearers are refitted to 30-night continuous silicone hydrogel lens wear (Dumbleton, K. A., Chalmers R. L. et al., 1999; Filip, M., Stefaniu I. et al., 2000; McNally, J. J., Chalmers R. et al., 2002). It is suggested that "myopic creep" from low Dk/t hydrogel lenses may be associated with hypoxic tissue changes and that silicone hydrogel lenses may reverse this process by eliminating hypoxia at the cornea. Alternatively, silicone hydrogel lenses may be associated with structural changes of the anterior cornea due to their higher modulus of elasticity compared to low-Dk hydrogel contact lenses causing the reduction of myopia.

This study is a prospective clinical trial to characterize the mechanisms contributing to changes in refractive error associated with the refitting of extended wear hydrogel contact lens users with 30-night continuous use silicone hydrogel contact lenses over a period of 3-months. A secondary purpose of this study is to develop a model for refractive error shift due to contact lens wear.
CHAPTER 2
EXTENDED WEAR: A HISTORICAL REVIEW

2.1 The Low-Dk Era

Continuous wear contact lenses have been available treatment options for refractive error in a variety of forms including hydrogel and rigid lenses for over 20 years, but the hydrogel (soft) contact lens has been the predominant lens of choice. After the invention of the soft contact lens, poly-hydroxyethyl methacrylate (p-HEMA) by Wichterle and Lim in 1960, many practitioners recognized the inconvenience of lens removal, cleaning and disinfection regimens, and began to explore the use of high water content hydrogel contact lenses for extended wear within a decade (de Carle, J., 1972; Rakow, P. L., 1987; Wichterle, O. and Lim D., 1960). In the United States, initial interest in extended wear lenses was primarily motivated by the therapeutic use of these lenses for aphakia or as bandage contact lenses, however it was the cosmetic use of these lenses that provoked the greatest interest (Brennan, N. A. and Coles M. L., 1997). In the United States, extended wear hydrogel lenses were approved for therapeutic use by the FDA in 1979. Extended wear lenses for cosmetic use, specifically the Cooper Permalens (Cooper Vision, Irvine, CA) and the Hydrocurve (Barnes-Hind, Wesley-Jenssen, Des Plaines, IL) were FDA approved in 1981. Initial FDA cosmetic approval of low-Dk extended wear
contact lenses allowed a maximum of 2-weeks of continuous wear, but this interval was later increased to 30-nights continuous use (Epstein, A. B., Perry H. D. et al., 2003).

Extended wear contact lens fitting was readily accepted and experienced significant growth after its approval in the United States, despite the concerns of eye care practitioners over a growing list of complications. Much emphasis was placed upon the oxygen transmissibility (Dk/L) of contact lenses during overnight wear by these investigators, and this factor was cited as the alleged cause of many serious complications (Harvitt, D. M. and Bonanno J. A., 1999; Holden, B. A. and Mertz G. W., 1984; Holden, B. A., Mertz G. W. et al., 1983). The complications were reported to present in varying degrees of severity in the form of conjunctivitis, corneal edema, corneal staining, infiltrative keratitis and ulcerative keratitis.

Although the importance of maintaining an adequate oxygen level at the anterior cornea to minimize ocular complications was recommended in scientific literature, extended wear fitting of low Dk contact lenses continued to be a popular fitting modality until 1989, when the results of two epidemiological studies of contact lens usage and complications were published (Poggio, E. C., Glynn R. J. et al., 1989; Schein, O. D., Glynn R. J. et al., 1989). These studies, completed in the United States, reported the annualized incidence rate of contact lens induced corneal ulcers per 10,000 eyes was about 4 or 5 for daily wear, and between 18 and 20 for extended wear of low-Dk hydrogel contact lenses (MacRae, S., Herman C. et al., 1991; Poggio, E. C., Glynn R. J. et al., 1989; Schein, O. D., Glynn R. J. et al., 1989; Schein, O. D. and Poggio E. C., 1990). These studies prompted a deluge of negative media from the lay press for extended wear resulting in the FDA decision to rescind 30-night extended wear approval for hydrogel
contact lenses. In an announcement from the Public Health Service Department of Health & Human Services, practitioners were notified that extended wear of hydrogel lenses was recommended for a maximum of 7-nights of continuous of wear (Villforth, J., 1989).

The results from the studies from the late 1980’s were validated by subsequent epidemiological research in the Netherlands in 1999, which similarly demonstrated an annualized incidence rate of 20 per 10,000 eyes for corneal ulcers in low-Dk extended wear (Cheng, K. H., Leung S. L. et al., 1999). Other investigations into the incidence of corneal ulcers and the type of low-Dk contact lens used, showed no difference in the frequency of corneal ulcers between extended wear of conventional or disposable hydrogel contact lenses (Nilsson, S. E. and Montan P. G., 1994; Poggio, E. C. and Abelson M., 1993; Poggio, E. C. and Abelson M. B., 1993). Defining daily wear conventional hydrogel lenses as the referent with a relative risk of 1.0, the relative risks associated with low-Dk extended wear are known to increase by a factor of between 2 and 6 compared to daily wear (Brennan, N. A., Coles M. L. et al., 2002; Cheng, K. H., Leung S. L. et al., 1999; MacRae, S., Herman C. et al., 1991; Nilsson, S. E. and Montan P. G., 1994; Nilsson, S. E. and Montan P. G., 1994; Poggio, E. C., Glynn R. J. et al., 1989; Solomon, O. D., Dubow B. W. et al., 1998). The relative risk of ulcerative keratitis was also shown to increase with the number of consecutive nights of wear by approximately a relative risk of 1.0 for each additional night of wear after the first three nights (Poggio, E. C. and Abelson M., 1993; Poggio, E. C. and Abelson M. B., 1993).

Most of these studies referenced an absolute incidence, and although the absolute risk was very low the perception of practitioners and the public was shaded primarily by the relative risk assessment, which was described without referencing the incidence of
other life events with similar morbidity (Myers, R. I. and Weiss E., 1995). Re-examining the issue of relative risk of ulcerative keratitis, it has been known that for daily wearers a 60 times greater risk exists over that of non-wearers and that the risk increased additionally by about 2 to 6 times with extended wear (Brennan, N. A. and Coles M. L., 1997). Eyecare practitioners and the public readily accepted a significantly high relative risk for daily wear contact lenses, but due to media sensationalism and fear of litigation an additional 2 to 6 fold increase was deemed as an unacceptable level of risk for extended wear. A benefit of this lack of confidence in low-Dk extended wear was that manufacturers enthusiastically sponsored research in new hyper-Dk materials.

2.2 Oxygen: Satisfying the Cornea’s Needs

Oxygen is essential for glucose metabolism via aerobic pathways (Kreb’s cycle), in order to create the required energy to maintain clarity and normal cellular function. This system is dependent on an oxygen supply via the atmosphere in the open-eye state, or the palpebral conjunctival and limbal blood vessels in the closed-eye state. The aqueous humor is known to primarily supply the endothelium and the posterior stroma with oxygen, but does not adequately support the anterior cornea (Barr, R. E., Hennessey M. et al., 1977).

Normally the non-contact lens wearing cornea is estimated to swell about 3.2 to 4% overnight and then to de-swell throughout the day in the open eye state (Holden, B. A. and Mertz G. W., 1984; La Hood, D., Sweeney D. F. et al., 1988; Mertz, G. W., 1980). In the closed eye state the oxygen level available is equivalent to an atmospheric concentration of 8.1% (open eye concentration = 20.9% or 155 mmHg) and is normally
the amount provided by the tarsal blood vessels in the closed eye state (Fatt, I. and Bieber M. T., 1968; Holden, B. A. and Sweeney D. F., 1985). The critical oxygen requirement, defined as the minimum amount of oxygen that the cornea requires to function indefinitely without compromise of its normal thickness, was determined to be about 75 mmHg (Holden, B. A. and Mertz G. W., 1984). A reduction in the required oxygen levels results in the cornea using an anaerobic metabolic pathway, which is known to cause corneal swelling due to an influx of water from the anterior chamber. The influx is caused by the accumulation of the anaerobic metabolite lactate which results in corneal acidosis and a decrease of endothelial pump mechanisms normally responsible for keeping the cornea in a state of relative deturgesence (Klyce, S. D., 1981; Langham, M., 1952). Corneal hypoxia is associated with several complications including loss of transparency, decreased epithelial cell mitosis, endothelial bleb response, endothelial pleomorphism and polymegathism, reduced epithelial cell junction integrity, increased risk of infection and inflammation and an increased risk of vascularization (Brennan, N. A. and Coles M. L., 1997; Bruce, A. S. and Brennan N. A., 1990; Bruce, A. S. and Brennan N. A., 1993).

When a contact lens is worn, oxygen is available to the cornea by two mechanisms: tear circulation and via diffusion through the lens material. In an open eye environment, the eyelids interact minimally with hydrogel contact lenses. Blinking the eyelids is typically observed to cause hydrogel lens movement of less than 0.2 mm in a vertical direction, and the oxygenation effect behind the lens created by this movement is negligible (Polse, K. A., 1981; Polse, K. A., McNamara N. A. et al., 1997). When the eye is closed the tears are not circulated behind the lens surface, and diffusion through the lens is the acknowledged route that is followed by oxygen. Therefore oxygen tension at
the anterior cornea in hydrogel lens wear is dependent on overall lens material transmissibility (Dk/L), which is directly proportional to the permeability (Dk) of the lens material and inversely proportional to the thickness of a lens. The permeability of a material is defined as the product of the diffusion (D) and solubility (k) coefficients. In conventional hydrogel contact lenses, it has been demonstrated that oxygen dissolves in and is transported through the aqueous phase, resulting in the transmissibility of hydrogel lenses is primarily a characteristic of water content (Benjamin, W. J., 1993; Tighe, B., 2000).

The minimum required oxygen transmissibility of a hydrogel contact lens to prevent levels of overnight corneal swelling in excess of the normal 4% was determined to be $24 \times 10^{-9}$ (cm$^2$/s)$\cdot$((mlO$_2$/ml-mmHg)) for daily wear and $87 \times 10^{-9}$ (cm$^2$/s)$\cdot$((mlO$_2$/ml-mmHg)) for extended wear (Holden, B. A. and Mertz G. W., 1984). More recent investigations, have suggested that a transmissibility of about 125 (cm$^2$/s)$\cdot$((mlO$_2$/ml-mmHg)) is required to prevent hypoxia in the stroma (Harvitt, D. M. and Bonanno J. A., 1999). In the 1980’s, the maximum transmissibility of hydrogel contact lenses was estimated to be around $30 \times 10^{-9}$ (cm$^2$/s)$\cdot$((mlO$_2$/ml-mmHg)) (Morgan, P. B. and Efron N., 1998). Even though a cornea using extended wear hydrogel contact lenses was shown to be capable of eliminating edema levels of about 8% in the open eye state, it was obvious that no hydrogel contact lens in existence would satisfy the homeostatic metabolic oxygen requirements of the cornea in an overnight wearing schedule (Holden, B. A., Mertz G. W. et al., 1983).
2.3 Beyond the Hydrogel

Hydrogel contact lenses were adequate for daily wear, but in an extended wear modality they resulted in the cornea being in a state of chronic low-grade edema. The results of this chronic stress are known to cause structural and functional changes in the corneal tissues. Since hydrogel contact lenses transmit gases primarily through the aqueous phase, manufacturers traditionally attempted to improve transmissibility by increasing the water content of the lens (Alvord, L., Court J. et al., 1998; Lopez-Alemany, A., Compan V. et al., 2002). But this approach was self-limiting because the permeability of oxygen in water is only about $80 \times 10^{-11}$ \text{cm$^2$/s}$-$(\text{mLO}_2/\text{ml-mmHg})$ (Benjamin, W. J., 1993). Furthermore, high water content lenses tended to have thicker profiles, negating the effect of increasing the water content and actually resulting in lower overall transmissibility profiles. Attempts to manufacture thin high water contact lenses were of limited success due to lens stability, durability, dehydration and comfort. These limitations made hydrogel contact lenses less than ideally suited for extended wear.

Silicone elastomer lenses were the next generation of contact lens materials introduced for extended wear by Dow Corning. These lenses were composed of polymers with a backbone of silicone-oxygen bonds (siloxane), providing a very high oxygen permeability level on the order of $300 \times 10^{-11}$ \text{cm$^2$/s}$-$(\text{mLO}_2/\text{ml-mmHg})$ (Alvord, L., Court J. et al., 1998). The silicone elastomer lenses have been described as reservoirs, providing oxygen in the closed eye state to a greater extent than available just from the tarsal blood vessels. This was based on observations that overnight edema was lower with silicone elastomer lens use versus no lens use (Sweeney, D. F., Keay L. et al., 2000). Unlike hydrogel contact lenses silicone elastomer lenses actually had very low water
content, and were in general highly hydrophobic without the use of surface treatments to improve wettability and reduce deposits. Surface deterioration was a common finding with silicone elastomer lenses as the surface treatment changed over time. The resulting poor surface wettability contributed to the high levels of lipid deposition, excessive drying, poor comfort, and lens adhesion which occasionally gave rise to corneal ulcer formation (Bloomfield, S. E., 1979; Mannarino, A. P., Belin M. W. et al., 1985; Nelson, L. B., Cutler S. I. et al., 1985). The silicone elastomer lenses are now seldom used for extended wear, except in pediatric aphakia.

By the mid 1980’s attention shifted to the use of rigid gas permeable contact lenses for overnight wearing schedules. Rigid gas permeable lenses benefited from having higher transmissibility due to the presence of siloxane and fluorine in the polymer, and also from a more effective tear pump action of the eyelids. The earliest reports of cosmetic overnight use of rigid gas permeable lenses seemed to promise an excellent alternative to hydrogel contact lenses (Levy, B., 1985). Long-term studies in Australia, reported following patients for 10 years in rigid gas permeable lens extended wear, and demonstrated excellent physiological response and vision (Sweeney, D. F., Keay L. et al., 2000). Minor complications with rigid gas permeable lens extended wear were reported to include eyelid ptosis, corneal staining, edema, papillary conjunctivitis and lens adherence (Fonn, D. and Holden B. A., 1986; Fonn, D. and Holden B. A., 1988; Ichijima, H., Imayasu M. et al., 2000; Levy, B., 1991; Swarbrick, H. A. and Holden B. A., 1987). However more serious complications, such as ulcers, abrasions and infiltrates were not eliminated even though the lenses provided superior oxygen transmissibility compared to their hydrogel counterparts. In fact, an analysis of rigid gas permeable lens adverse
reaction reports from premarket extended wear studies showed an equivalent risk for ulcers from hydrogel contact lenses, but higher overall risk rates for other serious adverse events compared to daily wear (MacRae, S., Herman C. et al., 1991). These surprising findings were suggested to be an artifact of rigid lens overnight wear being a relatively new fitting modality for most practitioners that were involved in the sampled studies and that with more practitioner experience the incidence of adverse events would be lower with rigid gas permeable lenses. Even with the initial promise of high-Dk rigid lenses, only moderate success was being reported and indeed another study of rigid gas permeable lens extended wear cited the most common reason for dropouts as lens discomfort (Machara, J. R. and Kastl P. R., 1994). Since most patients were hesitant to use rigid lenses even for daily wear due to initial discomfort issues, rigid gas permeable lenses had a very small extended wear market impact.

2.4 The High-Dk Soft Lens: Twenty-Years in the Making

With the lack of practitioner enthusiasm for conventional hydrogel lens options and the poor patient acceptance of rigid gas permeable lenses for extended wear, the need of a contact lens with the oxygen permeability properties of a rigid lens and the comfort of a soft lens was easily recognized. Silicone was known to have excellent oxygen permeability properties, but the ability to incorporate it into an optically clear, wettable and comfortable lens design took over twenty years of research (Tighe, B., 2000).

The earliest documentation on making a silicone moiety compatible with a hydrophilic monomer in a soft contact lens is found in a patent awarded to Tanaka in 1979 (Tanaka, K., Takahashi K. et al., 1979). In this patent, Tanaka et al. (1979)
described a copolymerization of TRIS, a monomer with a silicone-carbon backbone frequently used in rigid contact lenses with a hydrophilic monomer. Their attempt to create this copolymer specifically involved the modification of the TRIS monomer by the addition of a hydroxyl group (Tanaka, K., Takahashi K. et al., 1979). However, the benefit of increased oxygen permeability imparted by silicone content in Tanaka’s lens material was negated by other material properties including poor wettability, increased lipid deposition, and poor lens movement. Subsequently, a variety of hydrophilic groups were investigated, but until the mid 1990’s a silicone hydrogel copolymer for contact lenses was not commercially manufactured.

Currently, there are two siloxane-hydrogel copolymer based lenses commercially available in the global contact lens market with approval for up to 30 nights of continuous wear. The exact nature of the copolymer materials is proprietary, but several researchers have proposed models of the substrates based on public United States patent literature. These lenses are the Bausch & Lomb PureVision (Balafilcon A) and the Ciba Vision Focus Night & Day (Lotrafilcon A). The Balafilcon A contact lens likely is composed of the TRIS derivative tris-(trimethylsiloxy) silylpropylvinyl carbamate (TVPC), which has a hydrophobic silicone moiety for oxygen permeability and a hydrophilic carbamate moiety for improved compatibility with the hydrophilic monomer n-vinylpyrrolidone (Kunzler, J. F., 1999; Lopez-Alemany, A., Compan V. et al., 2002). Lotrafilcon A is thought to be based on a fluoroether macromer co-polymerized with TRIS monomer and the hydrophilic monomer N, N-dimethyl acrylamide (Lopez-Alemany, A., Compan V. et al., 2002; Tighe, B., 2000).
The presence of siloxane moieties in both of these lens materials caused their surfaces to be relatively hydrophobic, and the application of gas plasma surface treatments were required to improve surface wettability (Nicolson, P. C., 2003). The PureVision lens is treated with a plasma oxidation technique converting the exposed surface organic-silicone in the TRIS derivative to inorganic silicate on the surface of the Balafilcon A material (Tighe, B., 2000). In the final lens material the surface of the lens has been observed under Electron Force Microscopy to have a checkerboard pattern. It has been proposed that the island-like pattern is formed because the Balafilcon A is plasma treated in the dry state and then hydrated in saline, resulting in the thin silicate film being broken into smaller sections (Lopez-Alemany, A., Compan V. et al., 2002; Nicolson, P. C., 2003). The 10 to 25 nm silicate islands are hydrophilic and are close enough together so that saline or similar liquids can bridge over the hydrophobic Balafilcon A regions, rendering the surface wettable. The Focus Night & Day material surface is modified by a slightly different gas plasma technique. A plasma polymerization of a mixture of trimethylsilane, oxygen and methane is deposited as a layer on to the surface of the exposed Lotrafilcon A material (Weikart, C. M., Matsuzawa Y. et al., 2001). This 25 nm hydrophilic layer is “grown” onto the Lotrafilcon A substrate and is observed to form a continuous, but gently undulating surface instead of the segmented surface seen on the PureVision surface (Tighe, B., 2000). Plasma surface treatments were the catalyst that allowed the hyper Dk silicone hydrogel contact lens materials to be used clinically, without many of the complications associated with the previous silicone based lens materials.
CHAPTER 3
EFFECTS OF CONTACT LENSES ON THE CORNEA

Contact lenses are medical devices in direct contact with ocular tissues. All low or hyper Dk soft or rigid contact lenses are known to cause changes in the structure and function of these tissues in daily or extended wear. The cornea is commonly described as being composed of five layers (anterior to posterior): the epithelium, Bowman’s layer, stroma, Descemet’s membrane and the endothelium. The effects of contact lenses on the morphology of the epithelium, stroma and endothelium are the most often cited, while Bowman’s layer and Descemet’s membrane are typically described as acellular zones and are fairly stable with or without contact lens usage. Changes in the endothelium typically cause morphological changes in the epithelium and stroma secondary to hypoxia. The corneal architecture is known to change with contact lens usage, and the effects of these changes are often manifested in changes in thickness, curvature, and refractive error.

3.1 Corneal Thickness Changes: Epithelium and Stroma

Previous studies have demonstrated that contact lenses can alter corneal thickness. Most of these studies observed an initial short-term thickening of the cornea, most likely the result of epithelial or stromal edema (Cox, I., Zantos S. G. et al., 1990; Harris, M. G., Sarver M. D. et al., 1981; Mandell, R. B., Polse K. A. et al., 1970; Sanchis-Gimeno, J. A.,
Lleo A. et al., 2003; Snyder, A. C. and Schoessler J. P., 1983). With longer periods of contact lens wear, on the order of several years, an overall thinning of the cornea is observed (Holden, B. A., Sweeney D. F. et al., 1985; Liesegang, T. J., 2002; Myrowitz, E. H., Melia M. et al., 2002).

The epithelial layer has been studied extensively in daily and extended wear of contact lenses, particularly cell proliferation, cell migration and mitosis, surface cell sizes, cell exfoliation and the thickness of the epithelial layer. The normal epithelium has been described as self-renewing and continuously moving (Ladage, P. M., Yamamoto K. et al., 2002; Wilson, G., 2000). The progenitor cells of the cornea are the stem cells from the basal cell layer of the limbal epithelium (Kruse, F., 1994; Zieske, J. D., 1994). These cells divide and become Transient Amplifying (TA) cells and are seen to migrate centripetally toward the center of the cornea along the basal surface between 1.7 to 32 μm per day (Auran, J. D., Koester C. J. et al., 1995; Ladage, P. M., Yamamoto K. et al., 2002; Wilson, G., 2000). Evidence has been presented to suggest that stem cells can be modulated to differentiate more rapidly after a surface injury (Cotsarelis, G., Cheng S. Z. et al., 1989). As the TA cells leave the basal corneal surface in a vertical direction, and are described as terminally differentiated forming the wing cells and superficial squamous cells. Eventually, the superficial squamous cells are exfoliated (sloughed) off of the cornea, in a process of apoptosis (cell suicide) (Ren, D. H. and Wilson G., 1996; Yamamoto, K., Ladage P. M. et al., 2001). These processes were combined into a simplified model for epithelial turnover called the X, Y, Z Hypothesis, where X indicated basal cell migration, Y indicated vertical movement and Z indicated the rate of cell sloughing (Thoft, R. A. and Friend J., 1983).
Past estimates of the turnover rate of the normal corneal epithelium found that about 7 days were required for the cycle in a mouse eye model, and only about 4 days in a rat eye model (Hanna, C. and O'Brien J. E., 1960). More recent research has suggested that the cycle time may be substantially longer. Fluorescent labeling of basal cells, allowed their migration to be monitored, and some labeled cells remained in the basal layer for up to 2 weeks before beginning the vertical migration (Beebe, D. C. and Masters B. R., 1996).

Recent research in epithelial renewal, has demonstrated that there is regional variation in the proliferation and exfoliation. Specifically, a perilimbal band of cells has been identified as the most active region of cell proliferation, with a reduction moving more centrally into the cornea (Ebato, B., Friend J. et al., 1988; Ladage, P. M., Jester J. V. et al., 2003; Ladage, P. M., Yamamoto K. et al., 2002; Ren, D. H., Petroll M. et al., 1999). Exfoliation of the surface cells showed an opposite pattern to the proliferation. The majority of the dead cells are usually found in the central cornea compared to the peripheral cornea (Ladage, P. M., Jester J. V. et al., 2003; Yamamoto, K., Ladage P. M. et al., 2002). Eyelid shearing force is one suggested mechanism contributing to the increased central corneal cell sloughing, but other factors are likely associated (Ladage, P. M., Yamamoto K. et al., 2002; Li, L., Ren D. H. et al., 2002).

The normal homeostatic epithelial turnover (proliferation, migration and exfoliation) is affected by any type of contact lens wear (Ladage, P. M., Yamamoto K. et al., 2001; Yamamoto, K., Ladage P. M. et al., 2002; Yamamoto, K., Ladage P. M. et al., 2001). Proliferation changes in the basal epithelium were reported with the use of low-Dk hydrogel contact lenses on rabbit corneas (Hamano, H. and Hori M., 1983). Epithelial
mitosis was reduced by 94% in central and peripheral epithelium after 2 days of low-Dk extended wear contact lens use. Another study demonstrated an 81.2% reduction with low-Dk rigid gas permeable lenses and a 36.6% reduction with hyper-Dk rigid gas permeable lenses in central epithelial proliferation during extended wear (Ren, D. H., Petroll M. et al., 1999).

In a similar study using soft contact lenses for overnight wear for 2 nights, a similar suppression of epithelial basal cell proliferation was observed. Traditional hydrogel contact lenses caused a reduction of about 40.8%, while hyper-Dk silicone hydrogel lenses were observed to cause a reduction of about 33.8% (Ladage, P. M., Ren D. H. et al., 2003). In the same study prolonged eyelid closure, by suturing, also caused a significant decrease in proliferation by about 47% in the central cornea. Surprisingly, regardless of the type of contact lens or degree of oxygen permeability, suppression of epithelial proliferation is observed in the first 48 hours of extended wear. Mechanical effects are most likely associated with why a hyper-Dk silicone hydrogel, which provides on average an atmosphere equivalent oxygen tension behind the lens, still caused a reduction of the basal epithelial cell proliferation. In a study of the movement of basal cells toward the ocular surface in an extended wear contact lens environment, an inhibitory effect on the vertical movement was measured (Ladage, P. M., Jester J. V. et al., 2003). The delay in vertical migration was most evident in the central cornea.

In keeping a constant number of cells in the epithelium, and hence a constant thickness, the corneal epithelial cell exfoliation rate has been proposed as a driving force for epithelial cell proliferation. Ladage et al. (2003) suggested that as fewer epithelial cells are exfoliated, a coupled reduction of the epithelial cell proliferation would be
necessary. Several studies have supported the finding that contact lens wear suppressed the normal surface apoptotic process, resulting in less exfoliated epithelial cells (Li, L., Ren D. H. et al., 2002; O'Leary, D. J., Madgewick R. et al., 1998; Yamamoto, K., Ladage P. M. et al., 2001). Importantly, all contact lenses suppressed the exfoliation rate by a similar amount. The availability of oxygen under the lens surface was not observed as the predominate factor in determining epithelial exfoliation rate (Yamamoto, K., Ladage P. M. et al., 2002). A secondary result of the longer residence time on the cornea, epithelial cells are also observed to have larger cell sizes (Lemp, M. A. and Gold J. B., 1986; Mathers, W. D., Sachdev M. S. et al., 1992; Tsubota, K., Hata S. et al., 1996).

Ladage et al. (2003) reported another surprising finding in a study of epithelial cell proliferation when using silicone hydrogel contact lenses. After the initial suppression of the epithelial cell proliferation of about a week, a significant hyperactivity of basal cell proliferation was seen in the peripheral epithelium of the central and superior cornea. They reported a similar adaptive reaction in a cornea with the eyelid sutured closed. It was suggested that this response was a result of a delay in epithelial cells entering a proliferative cycle or possibly a physiological adaptation to the new environment. No comparison was available using low-Dk hydrogel contact lenses for the same amount of time (1 week) as the silicone hydrogel contact lens. In the same study, Ladage et al. (2003) also measured suppression of epithelial cell proliferation in the control non-contact lens wearing fellow eye. This indicated a sympathetic response was occurring in the fellow eye, controlled by some centralized mechanism. Similar sympathetic responses of the contralateral cornea to scrape injury or to contact lens use have been reported in previous studies (Estil, S., Haaskjold E. et al., 2001; Fonn, D., du
Toit R. et al., 1999). Further studies are needed to investigate the effect of these unexpected findings of epithelial cell turnover.

Contact lens wear is known to suppress central basal epithelial cell proliferation, delay mitotic activity of epithelial cells, delay in the centripetal basal cell movement, delay vertical migration of post-mitotic cells, reduce epithelial cell apoptosis and exfoliation, and increase surface cell size. Based on the partially inverse association with lens transmissibility and epithelial cell proliferation, but not with exfoliation, central corneal epithelial thinning is predicted with long-term low-Dk contact lens extended wear (Ladage, P. M., Ren D. H. et al., 2003).

Studies of corneal or epithelial pachymetry in long-term contact lens wearers have presented evidence that supports this model, but there are several studies that found conflicting results. A recent study using confocal microscopy to measure central epithelial thickness, found no difference between long term (> 10 years) daily wear contact lens wearing corneas and control corneas, but peripherally a thinning of about 10% was measured (Patel, S. V., McLaren J. W. et al., 2002). Ultra-high frequency ultrasound measurements of corneas in contact lens wearers also showed more epithelial thinning in the periphery than in the central region (Reinstein, D. Z., Silverman R. H. et al., 1994). These studies were done on soft contact lens wearers but did not control for contact lens design. At the time the studies were done, it is likely that the subject’s were using low to mid-Dk hydrogel contact lenses. Another study that described subjects using extended wear contact lenses for over 10 years agreed with the Ladage et al. (2003) model and found a decrease of central epithelial thickness of about 6% with contact pachymetry compared to control corneas (Holden, B. A., Sweeney D. F. et al., 1985). At
that time the study hypothesized that a reduction of epithelial metabolism, secondary to hypoxia, caused a change in the mitotic activity of the basal cells. Holden et al. (1985) also reported when the hypoxic environment was removed, normal epithelial metabolism resumed and after a period of about 33 days, the epithelial thickness was observed to return to normal. This finding is in agreement with the epithelial basal cell hyperactivity that was observed with silicone hydrogel contact lenses.

Another, interesting investigation of hydrogel extended wear in cat corneas demonstrated a reduction in the density of hemidesmosomes in the basal epithelia, which are structures that are responsible for epithelial adhesion to the underlying stroma (Madigan, M. C. and Holden B. A., 1992; Madigan, M. C., Holden B. A. et al., 1987). The study noted that edema alone was not responsible for a separation of the epithelial basal cells from the Basement Membrane, but it is possible that with a minor reduction in epithelial adhesion, molding of the epithelium would be more likely. The regional epithelial thickness measurements could then be influenced by molding effects of contact lenses (Carney, L. G., 1975).

Holden et al. (1985) observed that the corneal stroma thinned with contact lens extended wear at a rate of approximately 2 µm per year, using a contact pachymetry instrument. The measured stromal thickness early in the time course of lens cessation did not accurately represent the stromal thinning because of concurrent stromal edema. They documented that the stromal edema resolved over a period of about 1 week after lens wear cessation and by about 1 month the stromal thinning was apparent.

Chronic stromal edema in extended wear leading to biochemical changes in the ground substance composition has been proposed as a possible explanation for long-term
thinning (Holden, B. A., Mertz G. W. et al., 1983; Liu, Z. and Pflugfelder S. C., 2000). The collagen fibrils and extracellular matrix of stromal tissues are maintained by keratocytes, fibroblastic cells forming a syncytium throughout the stromal thickness. It has been suggested that chronic edema may amplify keratocyte apoptosis, a controlled form of cell death without the release of degradative enzymes (Liu, Z. and Pflugfelder S. C., 2000). An apoptotic response of stromal keratocytes is observed during wound healing in scrape injuries. Interleukin (IL)-1α and IL-1β are released from epithelial cells after a wound is inflicted, and when injected directly into the mouse corneal stroma they were observed to cause localized keratocyte apoptosis (Wilson, S. E., He Y. G. et al., 1996). It is possible that contact lenses may cause chronic microtrauma and a release of IL-1α and IL-1β from epithelial cells (Liu, Z. and Pflugfelder S. C., 2000). With the loss of keratocytes, there would be a down-regulation in collagen replacement and new collagen production resulting in a loss of stromal substance over time. A reduction of keratocyte density was observed in the anterior and posterior stroma of extended wear patients in one study, and another study using electron microscopy showed significant morphological changes after chronic edema from extended wear (Efron, N., Perez-Gomez I. et al., 2002; Jalbert, I. and Stapleton F., 1999; Kanai, A. and Kaufman H., 1973). Patel et al. (2002) observed no change in keratocyte density in long term contact lens wear, indicating more research is necessary to confirm this hypothesis.

3.2 Corneal Curvature Changes

Transient corneal curvature changes with the use of contact lenses have been reported in previous studies (Carney, L. G., 1975; Harris, M. G., Sarver M. D. et al.,
1975; Hovding, G., 1983; Liu, Z. and Pflugfelder S. C., 2000; Miller, D., 1968; Rengstorff, R. H., 1971; Sanaty, M. and Temel A., 1996). The majority of studies examined the effects of rigid gas permeable contact lenses on horizontal and vertical keratometric values. Some demonstrated an increase in corneal curvature and others showed a decrease or no change in curvature. Several investigations showed that initially a steepening of the cornea occurred particularly in the vertical meridian (Kok, J. H., Hilbrink H. J. et al., 1992; Liu, Z. and Pflugfelder S. C., 2000; Sanaty, M. and Temel A., 1996). In long term rigid lens wear, it has been reported that an overall flattening of the cornea occurred in daily wear or extended wear schedules (Briceno-Garbi, E. A., 1984; Iskeleli, G., Oral A. Y. et al., 1996; Polse, K. A., Sarver M. D. et al., 1987; Rengstorff, R. H., 1979). Sphericalization of the cornea has also been reported in long term rigid lens wear (Kame, R. T. and Kennedy J. R., 1996).

Soft hydrogel contact lens effects on corneal curvature have been less well documented. Harris et al. (1975) were among the first to measure a clinically significant increase in corneal toricity of about 0.23 ± 0.18 diopters in the vertical meridian after 1 month of hydrogel lens wear. Another study of hydrogel extended wear observed an increase of about 0.25 diopters of with-the-rule toricity, caused by a steepening of the vertical meridian and flattening of the horizontal meridian over a period of about 5 years (Rengstorff, R. H. and Nilsson K. T., 1985). Liu and Pflugfelder (2000) also reported that contact lens wearing subjects were on average about 1 diopter steeper compared to a non-contact lens wearing control group over a period of at least 5 years. A study of daily wear of hydrogel lenses also found a central steepening of corneal curvature occurred after 3 months (Hill, J. F., 1976).
There are very few studies looking at changes in the posterior corneal curvature with contact lens usage. Most studies have focused on the anterior cornea, but one study examined adapted contact lens wearers using a low-Dk hydrogel in a closed eye environment and observed corneal swelling. The unique finding in this particular study was that the corneal swelling measured, was best represented by a model where the posterior surface of the cornea deformed (Erickson, P., Comstock T. L. et al., 1999).

Keratometric changes with silicone hydrogel contact lenses have also been documented. A flattening of about 0.35 diopters was measured in both principle meridians in subjects refitted from low-Dk hydrogel contact lenses into hyper-Dk silicone hydrogel lenses (Dumbleton, K. A., Chalmers R. L. et al., 1999; Filip, M., Stefaniu I. et al., 2000). The flattening of the cornea occurring with these lenses may be due to the higher modulus of elasticity of these lenses compared to Etafilcon A hydrogel lenses that subjects had been using previously.

3.3 Refractive Error Changes

Contact lenses, particularly hydrogel lenses, have been associated with an increase in myopic refractive error in several studies (Barnett, W. A. and Rengstorff R. H., 1977; Dumbleton, K. A., Chalmers R. L. et al., 1999; Harris, M. G., Sarver M. D. et al., 1975; Hill, J. F., 1976). Most of the studies demonstrated an increase in myopia between 0.30 to 0.50 diopters, and demonstrated a steepening of the central corneal curvature. In early reports of myopic shifts with hydrogel contact lens use, Harris et al. (1975) reported a myopic progression of 0.35 diopters over a 9 month period. In another study using hydrogel contact lenses in daily wear, an average increase of 0.50 diopters
was observed in only 3 months (Barnett, W. A. and Rengstorff R. H., 1977). Myopic progression with hydrogel contact lens use was initially associated with the use of thick daily wear hydrogels and the resultant hypoxic corneal environment. Evidence has also been presented to suggest that myopia increased with extended wear to a greater extent than with daily wear. Low water content hydrogels contact lenses were purported to produce a greater amount of myopia progression than medium or high water content lenses on an extended wear schedule (McGlone, V. and Farkas B., 1992). In a prospective study design, adapted daily wear patients refitted with low-Dk hydrogels for extended wear experienced a significant increase in myopia on the order of 0.35 diopters (Dumbleton, K. A., Chalmers R. L. et al., 1999). In a retrospective study, significant myopia progression of at least -1.00 diopters over 5 years was observed in about 20% of young myopic adults wearing hydrogel contact lenses, and up to 36% of patients experienced a refractive shift of at least -0.75 diopters (Bullimore, M. A., Jones L. A. et al., 2002). Another investigation documented a faster rate of myopia progression in myopes over -3.00 diopters than lower myopes, and a progression of -0.50 diopters in 37% of the sample studied (O'Neal, M. R. and Connon T. R., 1987).

However, there have been several studies that have documented minimal to no change in the degree of myopia associated with long-term hydrogel lens wear (Andreo, L. K., 1990; Horner, D. G., Soni P. S. et al., 1999). The existence of myopic progression with hydrogel contact lenses was debated by Andreo et al. (1990), who demonstrated in a retrospective study that the progression cited in most literature could be attributed to a normal physiologic rate of progression. In a prospective randomized 3-year study of adolescents, hydrogel contact lens wearers were observed to have no difference in
spherical equivalent myopia progression compared to spectacle lens wearers (Horner, D. G., Soni P. S. et al., 1999). A criticism of this study was that contact lens wearing subjects wore different lens designs and were refitted into another lens design half way through the course of the study. Further studies are needed to definitively confirm myopic progression with hydrogel contact lenses.

Some studies have shown that this myopic creep may be reversed for some patients when low-Dk hydrogel lens wearers are refitted to 30-night continuous wear silicone hydrogel lenses (Dumbleton, K. A., Chalmers R. L. et al., 1999; Filip, M., Stefaniu I. et al., 2000; McNally, J. J., Chalmers R. et al., 2002). It was suggested that "myopic creep" from low Dk/t hydrogel lenses is associated with hypoxic tissue changes and that the hyper-Dk silicone hydrogel lenses reverse this process by eliminating hypoxia at the cornea (Sweeney, D. F., 2003). An alternative hypothesis was that silicone hydrogel lenses caused a reduction of myopia by a flattening of curvature of the anterior cornea.

3.3.1 Elements Contributing to Corneal Refractive Change

In those circumstances where patients do experience a change in refractive error, such as an increase or decrease in myopia, the most frequently attributed variable of corneal change was the anterior surface curvature (Carney, L. G., Mainstone J. C. et al., 1997; Dumbleton, K. A., Chalmers R. L. et al., 1999; Rengstorff, R. H., 1969). However, refractive error shifts may be explained by other variables including changes in the posterior corneal curvature, corneal thickness, anterior chamber depth and index of refraction. The total corneal power is determined by a combination of the above variables.
An increase in one variable could lead to a refractive power change, but the refractive shift from a single variable could also be masked by a change in the relative combination of several components. In mathematical modeling, steepening the anterior corneal radius of curvature by 0.10 mm caused an increase in refractive corneal power by 0.62 diopters, and a steepening of the posterior curvature by 0.10 mm caused a decrease in corneal power by about 0.09 diopters (Rengstorff, R. H. and Arner R. S., 1971). An increase in the index of refraction of the cornea by 0.05, a condition that would be possible with a reduction of swelling in a previously edematous cornea, would result in a decrease in total corneal power by about 0.72 diopters (Rengstorff, R. H. and Arner R. S., 1971). A decrease in the total corneal power is explained because the shift in the index of refraction has a greater impact at the posterior corneal surface due to its shorter radius of curvature compared to the anterior corneal surface. The same study also showed that a decrease in corneal thickness by about 0.05 mm would cause a decrease in corneal power by about 0.01 diopters. Additionally, an anterior chamber depth increase of about 0.1 mm was shown to cause an increase in corneal power by about 0.21 diopters. Based on these calculations, Rengstorff and Arner (1971) demonstrated that anterior corneal curvature and index of refraction would have the greatest impact on the total refractive power of the cornea, and that a thickness change from corneal edema for example would not account for much total corneal power change without the contribution of other variables. Another observation based on theoretical calculations with schematic eye models showed that an axial length decrease of 0.10 mm is predicted to cause an increase of approximately 0.30 diopters of myopia.
3.4 Aberration Changes

With the introduction of refractive surgery and the development of several clinical instruments for the measurement of ocular aberrations, the field has undergone significant growth. Aberrations are known to reduce image quality of any optical system due to irregularities in media and lenses or simply by the orientation of the optical elements in the system (Thibos, L. N. and Hong X., 1999). These aberrations may be described by a series of polynomial functions (Zernike polynomials) used to describe the shape of a deformed wavefront from an ideal flat wavefront. The human eye is an ocular system that demonstrates such aberrations including coma and spherical aberration Zernike modes (Liang, J., Grimm B. et al., 1994).

Several reports have described the association of aberrations and refractive error. These studies in general reported that myopia was accompanied with greater levels of higher order aberrations, defined as those aberrations beyond defocus and astigmatism on the Zernike pyramid (Carkeet, A., Dong Luo H. et al., 2002; He, J. C., Sun P. et al., 2002; Paquin, M. P., Hamam H. et al., 2002). Aberration measurement suggested that the coma Zernike term was found more frequently and in greater amounts in eyes with higher myopic errors (Paquin, M. P., Hamam H. et al., 2002). He et al. (2002) described larger amounts of higher order aberrations in myopes than in emmetropes on average. A recent cross-sectional investigation has suggested that the variation of aberrations between subjects has minimal correlation with the type or degree of refractive error (Cheng, X., Bradley A. et al., 2003). This study did determine that eyes with astigmatism also tended to have greater levels of higher order aberrations.
Some studies have measured aberrations in eyes while the contact lenses are worn or the difference in optical systems with or without lenses (Dorronsoro, C., Barbero S. et al., 2003; Hong, X., Himebaugh N. et al., 2001; Lu, F., Mao X. et al., 2003; Patel, S., Fakhry M. et al., 2002). However, the change in wavefront aberrations of a neophyte human ocular system due contact lenses (rigid, hydrogel, or silicone hydrogel) have not been described in published controlled studies. Furthermore, there were no published studies found documenting the change in ocular aberrations, as a result of refitting the cornea with a different type of contact lens, such as from a hydrogel to a silicone hydrogel in normal corneas.
CHAPTER 4
OCULAR BIOMETRY

Ocular biometry refers to the measurement of the dimensions of the component structures of an ophthalmic system such as the human eye. The refractive contribution of a change in a component feature of the cornea, axial length and crystalline lens has been of significant interest in the research of myopic progression. A highly repeatable measurement of these component structures is desirable in studies of refractive error change, to ensure that suspected changes over time are not a result of measurement variability. Several instruments were used in this study to measure different components of the ocular system, and the use of these devices has been described in detail for research and clinical use.

4.1 Pachymetry Measurement

Central corneal thickness measurement by two non-invasive optical techniques, based on slit scanning topography and partial coherence interferometry, have received significant attention with the growing interest in continuous wear contact lenses. The standard of care has been ultrasound pachymetry, but it is an invasive technique requiring applanation of a probe to the corneal surface. The ultrasound pachymetry measurement procedure itself has been suggested to influence the mean corneal thickness and
variability observed due to possible compression of the corneal tissues being measured (Chakrabarti, H. S., Craig J. P. et al., 2001; Gordon, A., Boggess E. A. et al., 1990; Lattimore, M. R., Jr., Kaupp S. et al., 1999). Still, others have suggested that corneal indentation does not have an effect on pachymetry measurement (Solomon, O. D., 1999). Ultrasound is further limited by the fact that it can only measure a single region, limited by the diameter of the applanation probe, and that in repeated measurements the same location may not be measured (Fakhry, M. A., Artola A. et al., 2002; Gordon, A., Boggess E. A. et al., 1990). Traditional optical pachymetry, using an instrument such as the Payor-Holden Optical Pachymeter, was not used in this study because of the poor repeatability of measurements obtained with this technique (Marsich, M. W. and Bullimore M. A., 2000). That study reported that the optical pachymetry method has 95% limits of agreement of – 61 µm to + 32 µm, which was poorer than limits reported for other techniques.

The Bausch & Lomb Orbscan I Anterior Segment Analyzer (Orbscan I) is designed for scanning, mapping, and displaying the geometry of the anterior segment of the eye. Slit images are projected onto the eye with equidistant angles from the optical axis through entrance pupil and the Bausch & Lomb Orbscan I optical head. A video camera coaxial with the optical axis records the images of the slits as they passed over the corneal surface. The images are processed by using an edge detection algorithm to determine the location of all of the edges the slit beam strikes during the exam. Through triangulation, the elevation for the anterior and posterior corneal surfaces is determined. Corneal thickness is then calculated by subtraction of the anterior and posterior corneal surfaces and is displayed graphically in a colored map with regional averages displayed.
In a study comparing ultrasound and Orbscan I based central corneal pachymetry, it was demonstrated that the Orbscan had the best day-to-day repeatability with 95% limits of agreement of – 10 to + 17 µm versus ultrasound based pachymetry repeatability of – 22 to + 24 µm (Marsich, M. W. and Bullimore M. A., 2000). In another investigation of central corneal thickness the Orbscan demonstrated 95% limits of agreement of ± 19 µm (Cho, P. and Cheung S. W., 2002). Other studies have reported the repeatability of the Orbscan for central pachymetry to be approximately ± 6 µm, ± 8.42 µm and ± 9.08 µm (Boscia, F., La Tegola M. G. et al., 2002; Lattimore, M. R., Jr., Kaupp S. et al., 1999; Yaylali, V., Kaufman S. C. et al., 1997). The Orbscan technique of corneal pachymetry is repeatable and efficient.

Optical coherence tomography (OCT) is a non-invasive optical imaging technique that measures light waves reflected off of tissue interfaces for high resolution cross-sectional imaging (Hirano, K., Ito Y. et al., 2001; Izatt, J. A., Hee M. R. et al., 1994). This technique is a form of low coherence interferometry (Michelson type), using a reference path length to generate interference patterns, which are directly related to the amount of infra-red light reflected back from a tissue interface where there is a change in the index of refraction.

The reflected beam contains information generated at a single point, similar to an A-scan on ultrasound biometry with peaks representing a shift in tissue planes. A 2-dimensional image (B-scan) is generated when 100 adjacent scans are measured and displayed graphically with false color-images (Fujimoto, J. G., Brezinski M. E. et al., 1995; Hrynchak, P. and Simpson T., 2000). As the scan length is varied, the lateral resolution of the OCT is influenced such that the longer the scan length the lower the
spatial resolution. However, even with very small scan lengths, lateral resolution is
diffraction limited to about 25 µm (Chauhan, D. S. and Marshall J., 1999). The limit of
axial resolution has been documented to range between 10 – 20 µm depending on the
wavelength of the light source used (Fujimoto, J. G., Brezinski M. E. et al., 1995).

The application of OCT imaging to the corneal thickness was first applied by Izatt
et al. (1994). The strongest reflections were from the anterior surface of the cornea, and
subsequent tissue boundaries between the epithelium and stroma, the stroma and
endothelium, and the posterior surface of the cornea (Hirano, K., Ito Y. et al., 2001). The
advantage of the OCT technique is that the corneal epithelial thickness may also be
measured (Feng, Y., Varikooty J. et al., 2001). The epithelial thickness was determined
by the separation of the first and second peaks on the average A-scan. As the B-scan
length is increased or non-apical regions of the cornea are measured, the intensity of the
reflected beam drops off rapidly resulting in false impressions of corneal curvature and
an overestimation of corneal thickness because the incident beam is no longer
perpendicular to the corneal surface (Hirano, K., Ito Y. et al., 2001; Muscat, S., McKay N.
et al., 2002). Without significant modifications in focusing or patient fixation, current
commercial OCT systems are limited to the measurement of the central cornea.

In studies of corneal pachymetry measurements using the OCT, Muscat et al.
(2002) reported inter-operator repeatability with 95% limits of agreement of −3 to +4
µm, and that a 1.75 µm difference in thickness would be detected with 90% power by
different operators. Intersession repeatability was also demonstrated to have 95% limits
of agreement of −16 to +7 µm, and that a single observer could detect a difference of
5.45 µm at different visits with 90% power (Muscat, S., McKay N. et al., 2002). The
reproducibility of OCT corneal thickness was estimated to be ± 5.8 µm (Wirbelauer, C., Scholz C. et al., 2002). Another study demonstrated a repeatability of ± 2.8 µm for total central corneal thickness and ± 2.7 µm for central epithelial thickness (Fonn, D., Wang J. et al., 2000; Wang, J., Fonn D. et al., 2002). The OCT has been shown to provide excellent precision for the measurement of corneal and epithelial thickness. However, commercially available OCT devices designed for retinal evaluation can only be used to measure the central corneal or epithelial thickness without significant modifications of the system. The ideal corneal OCT system would maintain perpendicularity of the entrance beam and the corneal surface.

4.2 Phakometry Measurement

In any longitudinal investigation involving the description of refractive error and its contributory components, the effect of a potential change in the crystalline lens power must be calculated. The technique of phakometry, first described in 1924, involved the simultaneous viewing of each of the Purkinje images (I, III and IV) reflected from the anterior cornea, anterior and posterior crystalline lens, and the measurement of the relative height of each of these images (Tscherning, M., 1924). An alternative technique used the variable separation of two small light sources, instead of a single reflected image (Mutti, D. O., Zadnik K. et al., 1992; Smith, G. and Garner L. F., 1996; Van Veen, H. G. and Goss D. A., 1988). The radii of curvature of the crystalline lens are calculated from the relative height measurements of each of the Purkinje images. A video based system described by Mutti et al. (1992) allowed for the Purkinje images to be recorded more easily in their separate focal planes compared to using flash photography. These images
were then digitized and the separation of the targets was measured to estimate height for each Purkinje image. Based on the measured improvement in repeatability resulting from taking multiple measures, Purkinje image I was digitized 6 times, Purkinje image IV was digitized 4 times and Purkinje image III was digitized 2 times for each eye (Mutti, D. O., Zadnik K. et al., 1992). Capturing a greater number of images did not improve the repeatability significantly. The repeatability of the video phakometry system was estimated to be $\pm 0.52$ diopters for the anterior lens power, $\pm 0.73$ diopters for posterior lens power and $\pm 0.88$ diopters for the total lens power (Mutti, D. O., Zadnik K. et al., 1992). By eliminating crystalline lens power changes during the course of a refractive error shift study, it can be concluded with reasonable certainty that other components such as corneal curvature or thickness were responsible for total ocular power changes.

4.3 Axial Length and Anterior Chamber Depth Measurement

Axial length and anterior chamber depth are variables that are important in the assessment of refractive error. Both of these variables are used in calculations of ocular power. The ultrasound A-scan technique has been the conventional method of measuring these variables, but requires the use of topical anesthetics and applanation of the cornea with a probe. The Zeiss IOLMaster is a non-invasive optical technique of measuring the axial length and anterior chamber depth. It utilizes partial coherence interferometry, using a 780 nm laser diode in a Michelson interferometer configuration (Haigis, W. and Lege B. A. M., 2000; Santodomingo-Rubido, J., Mallen E. A. et al., 2002). The resolution of the device has been suggested to be about 0.01 mm for both anterior chamber depth and axial length measurement. However, the instrument is unable to generate a measurement of the
crystalline lens thickness at this time. Previous studies have suggested that ultrasound contact techniques may underestimate axial length or anterior chamber depth measurements due to the indentation of the anterior cornea (Lam, A. K., Chan R. et al., 2001).

Inter-observer repeatability studies using the IOLMaster device for axial length measurement was estimated to have a standard deviation of ± 21.5 µm, and for anterior chamber depth a standard deviation of ± 29.8 µm (Vogel, A., Dick H. B. et al., 2000). Inter-observer repeatability was estimated to have a standard deviation of ± 25.6 µm, and for anterior chamber depth a standard deviation of ± 33.4 µm (Vogel, A., Dick H. B. et al., 2000).

The variability of the ultrasound A-scan technique is estimated to have 95% limits of agreement of ± 0.29 mm for anterior chamber depth, ± 0.20 mm for crystalline lens thickness and of ± 0.37 mm for vitreous chamber depth (Zadnik, K., Mutti D. O. et al., 1992). Ultrasound is still a necessary technique, if the variables of interest include the crystalline lens thickness.

4.4 Corneal Curvature Measurement

Videokeratography is a technique to measure the anterior corneal curvature using the image of a small placido cone reflected off the anterior cornea. Change in the corneal curvature of the anterior cornea is known to significantly contribute to refractive error change (Carney, L. G., Mainstone J. C. et al., 1997; Rengstorff, R. H., 1965). Repeatability of corneal topography has been reported as ± 0.50 diopters centrally, ± 0.65
diopters paracentrally and ± 0.80 to ± 1.00 diopters midperipherally (Zadnik, K., Friedman N. E. et al., 1995). This same study determined that automated corneal topography had better repeatability than manual keratometry. Manual keratometry repeatability was ± 0.49 diopters and ± 0.65 diopters for the horizontal and vertical meridians respectively.

4.5 Refraction Measurement

Refractive error measurements are considered as very important for most studies of visual function. Refractive error measurement may include a psychophysical response in the form of visual acuity testing concurrently with subjective determination of the subject’s prescription. Alternatively, refractive error may be measured objectively without input from the subject. In many studies of refractive error, analyses of results have been calculated using the conventional clinical specification of spherocylindrical powers (Sphere, cylinder and axis) (Raasch, T. W., Schechtman K. B. et al., 2001). Analyses using this refractive error format are known to present problems because the in Polar coordinate notation, the components are not independent. An alternative analysis technique using a Fourier transformation of refractive error and vector space has been proposed (Thibos, L. N. and Horner D., 2001; Thibos, L. N., Wheeler W. et al., 1997). The clinical refraction notation is converted from Polar coordinates into Cartesian coordinates using a spherical equivalent (SE) component, and J₀ and J₄₅ Jackson Cross-Cylinders with orientations of 0° and 45°, and is specified in x, y and z space. The dioptric strength of a particular refraction is then specified by the length of the vector
extending from the origin to the point defined in the Fourier domain (Raasch, T. W., Schechtman K. B. et al., 2001).

Repeatability of the manifest subjective refraction data in 40 normal subjects was determined by Raasch et al. (2001). The 95% limits of agreement for the refractive components were ± 0.51 diopters, ± 0.23 diopters and ± 0.16 diopters for the SE, \( J_0 \) and \( J_{45} \) components respectively. These values were determined using a standardized refraction protocol, similar to the technique used in this study. An earlier study calculated the 95% limits of agreement for subjective refraction of – 0.90 to + 0.65 diopters, – 0.37 to + 0.39 diopters and – 0.31 to + 0.31 diopters for the SE, \( J_0 \) and \( J_{45} \) components respectively (Bullimore, M. A., Fusaro R. E. et al., 1998). Another study that used standard clinical notation for refractive error calculated repeatability for five normal subjects using the manifest subjective and objective refraction (Autorefractor) (Rosenfield, M. and Chiu N. N., 1995). This study determined 95% limits of agreement of ± 0.27 diopters for sphere, ± 0.16 diopters for cylinder and ± 17.1 degrees for axis with the subjective measurement technique, and ± 0.31 diopters for sphere, ± 0.37 diopters for cylinder and ± 31.1 degrees for axis with the objective measurement technique. The relatively poor agreement for cylinder power and axis in this study is likely due to the non-orthogonal nature of the analysis. Another investigation of automated refraction using vector notation, revealed 95% limits of agreement of – 0.36 to + 0.40 diopters, – 0.21 to + 0.21 diopters and – 0.18 to + 0.17 diopters for the SE, \( J_0 \) and \( J_{45} \) components respectively (Bullimore, M. A., Fusaro R. E. et al., 1998). These studies have suggested that a minimum threshold for a statistically significant shift in refractive
error is between ± 0.30 diopters to ± 0.75 diopters for manifest subjective refractions (Rosenfield, M. and Chiu N. N., 1995; Zadnik, K., Mutti D. O. et al., 1992).

Refractive error was measured objectively with the Zywave wavefront sensor and repeatability was calculated for a series of normal patients in Fourier space (Bullimore, M. A., Dobos M. J. et al., 2003). This study reported 95% limits of agreement of – 0.23 to + 0.27 diopters, – 0.16 to + 0.16 diopters and – 0.10 to + 0.14 diopters for the SE, J0 and J45 components respectively for the PPR3.5 derived wavefront refraction. Bullimore et al. (2003) compared the Zywave refraction findings to cycloplegic autorefraction results and documented a better repeatability with the Zywave. These findings suggested that a wavefront derived refraction may provide more repeatable measures than previously accepted procedures for the longitudinal study of refractive error.
5.1 Overview

This is a prospective clinical trial to characterize the mechanisms contributing to changes in refractive error associated with the refitting of extended wear hydrogel contact lens users with 30-night continuous use silicone hydrogel contact lenses. Two cohorts of subjects were enrolled in the Refractive Error Shift with Continuous Use (RESCU) Lenses Study as part of the 3-year Ciba Focus Night & Day Launch Trial, consisting of a group of previous Acuvue (Etafilcon A) (Vistakon, Jacksonville, FL) extended wear lens users and another group composed of non-contact lens wearers. All subjects were fitted with Ciba Focus Night & Day (Lotrafilcon A) Silicone Hydrogel contact lenses in this study. Each subject was followed for a period of 3 months, consisting of a baseline visit and follow-up visits scheduled at intervals of 1 day, 1 week, 1 month, 2 months and 3 months. Examinations included visual acuity measurements, manifest refraction, autorefraction, slit lamp biomicroscopy, contact lens fitting evaluation, corneal topography, corneal pachymetry, ocular phakometry, axial length, anterior chamber depth measurement, ocular aberration analysis, tonometry and a dilated fundus examination at the baseline visit. Subjects recruited for this study were also recruited for participation in a 3-year evaluation of the Ciba Focus Night & Day contact lens for 30-night continuous
wear. The examination requirements of this study were different than the Ciba trial, but included all the elements of the Ciba clinical trial in order to facilitate subject participation in the studies concurrently. After conclusion of this study all subjects continued their participation in the Ciba clinical trial, barring any adverse events that would disqualify them from participation in either study. Methodology of the Ciba Focus Night & Day Launch Trial is not described in detail unless the resulting data were used significantly in this study. Significant amounts of data were gathered during the course of the concurrent studies with regard to the contact lens fitting procedure, lens fitting assessments and ocular signs and symptoms in order to ensure subject safety. For each visit, only data related to the purpose of the RESCU Lenses study is presented and analyzed in this report. This study protocol and all recruitment tools were approved by The Ohio State University’s Institutional Review Board in accordance with the tenets of the Declaration of Helsinki.

5.2 Subject Recruitment

Subjects were recruited via telephone by using The Ohio State University College of Optometry patient database. When contacted by telephone, subjects were presented with a script requesting their participation in the Refractive Error Shift with Continuous Use (RESCU) Lenses Study as part of the 3-year Ciba Focus Night & Day Launch Trial. Over 400 potential subjects were contacted by telephone, and provided with details about the study. Alternative recruitment techniques included the use of print advertisements in The Ohio State University campus newspaper, the Lantern, and of flyers posted in various medical centers across the university. Two groups of subjects were recruited for
this study, including a group of previous low-Dk Etafilcon A extended wear contact lens users (n=15) and a group of non-contact lens wearers (n=5). All subjects were advised that they would be fitted for 30-night continuous wear.

3.2.1 Eligibility Criteria

Twenty patients (40 eyes) were screened according to the inclusion and exclusion criteria prior to receiving Informed Consent and being enrolled into the study.

5.2.1.1 Inclusion Criteria

Each subject was required to meet the following inclusion criteria to be eligible for this study:

- Absolute spherical myopia (not spherical equivalent) of -1.00 to -10.00 D, and no more than -1.00 D of refractive astigmatism as expressed in spectacle minus cylinder form (by manifest subjective refraction) in both eyes.
- Best corrected Snellen visual acuity of at least 20/20 in both eyes.
- Willing to use the full distance vision prescription in both eyes, and no interest in wearing contact lenses using the monovision fitting technique.
- At least 18 years of age.
- Signed Informed Consent.
- Willing to return for a minimum of 3 months of follow-up visits.
- Willing to wear Ciba Focus Night & Day contact lenses for up to 30-nights continuously barring any adverse event or complication.
• Low-Dk lens extended wear to 30-night continuous wear cohort:
  o Adapted extended wear use of Etafilcon A hydrogel lenses for at least 3 or more nights continuously for at least the past 6 months.
  o No history of adverse events with extended wear of Etafilcon A hydrogel lenses.

• Contact lens neophyte to 30-night continuous wear cohort:
  o Has not worn contact lenses within 6 months.
  o Capable of handling soft contact lenses (application, removal and cleaning regimens).

5.2.1.2 Exclusion Criteria

Subjects were excluded from participation in this study if any of the following criteria were met:

• Ocular surface disease (Severe acne rosacea, Sjogren’s or other severe dry eye disease).

• Any ocular disease including keratoconus or other corneal degenerations or dystrophies.

• Any signs of active ocular inflammatory conditions including striae, microcysts, edema, or peripheral corneal vascularization greater than grade 1.

• Any eyelid disease/disorder.

• Glaucoma or ocular hypertension.

• Aphakia or ambylopia
• Current rigid contact lens wearer.
• Previous corneal refractive surgery.
• Collagen vascular disease.
• Diabetes.
• Patient reported pregnancy or breast feeding prior to study initiation or report of the patient becoming pregnant during the course of the study will be withdrawn.
• Cigarette or cigar smoking.
• Use of any medication affecting wound healing.

5.3 Examination Procedure

Eligibility of each subject was confirmed and Informed Consent was obtained prior to enrollment. Subjects underwent visual acuity measurements, manifest refraction, auto-refraction, slit lamp biomicroscopy, contact lens fitting evaluation, corneal topography, corneal pachymetry, ocular phakometry, axial length, anterior chamber depth measurement, ocular aberration analysis, tonometry and a dilated fundus examination. A summary of the experimental design is presented in Appendix A. The baseline and monthly visits were estimated to take about 2.5 to 3 hours each.

5.3.1 Visual Acuity

Visual acuity was measured with Snellen projected visual acuity charts, using standard clinical techniques. Distance visual acuity was recorded monocularly and binocularly. Snellen charts were used for habitual acuity, best corrected subjective manifest acuity, best corrected subjective contact lens acuity and spherical over-
refraction contact lens acuity. Snellen acuity was collected primarily to ensure subject eligibility, to aid in contact lens fitting and satisfy the requirements of the Ciba Focus Night & Day Launch trial.

All remaining acuity measurements were collected using Bailey-Lovie visual acuity charts (two high-contrast and two low-contrast) at a distance of 4 meters. The chart must have a standard luminance calibrated to be between 75 and 110 cd / m² at the beginning of each examination. Visual acuity was measured using high and low contrast targets in the following order: best corrected manifest visual acuity in each eye and then both eyes, and best corrected contact lens corrected acuity in each eye and then both eyes. Patients were required to read each letter from left to right and were encouraged to guess if they did not recognize a letter. The patient continued reading down the chart until a total of 3 letters were missed in any order on a given line, at which time visual acuity measurement was stopped. The number of letters read correctly was recorded and logMAR visual acuity and Snellen equivalent visual acuity were calculated for each patient using the conversion chart in Appendix B. If the patient failed to correctly identify all five letters in the top row, the charts were moved to a test distance of 1.0 m, and the measurements were retaken. A summary of the sequence of visual acuity measurements, test conditions, targets, and scoring is included in Appendix B.

5.3.2 Subjective Refraction Technique

Subjective manifest refraction was performed by an independent examiner without previous knowledge of the subject’s refractive prescription. An independent examiner was used in order to minimize the influence of investigator bias in the
refraction process. A standardized protocol was followed using an American Optical phoropter (American Optical, Buffalo, NY). The manifest refraction measurement began with the phoropter set to a zero equivalent power. The examiner presented a 20/100 Snellen letter target at the end of the exam lane, and performed retinoscopy to approximate the subject’s refractive error in the right eye. After retinoscopy, the target size was reduced to a range of letters from 20/40 to 20/20. The subject was asked to read the lowest line visible from left to right. If the 20/20 line was visible after retinoscopy, plus lenses were added in progressively increasing powers until the 20/20 was completely unreadable. Then minus power was added (plus power reduced) in 0.25 D steps until any single letter was recognizable on the 20/20 line. At this point minus power was added in 0.25 D steps up to a maximum of 0.75 D of minus power until the subject reported no additional improvement. The Jackson Cross-Cylinder was used to determine the correct cylinder power and axis required to correct for astigmatism up to a maximum of 1.00 D. Similar to the sphere refraction component, only 0.25 DC changes and a maximum of 5 degree axis shifts were presented to subjects for comparisons. After cylinder power was determined, the sphere power was re-checked as described above. The final manifest refraction was recorded, and the procedure was repeated for the fellow eye. The examiner recorded each subject’s refractive error in the standard minus cylinder notation using a Polar coordinate system (Sph x Cyl x Axis). No balancing technique was used for the manifest refraction to achieve the minimum negative power consistently for best visual acuity (Sweeney, D. F., Keay L. et al., 2000).
5.3.3 Corneal Topography (Anterior Corneal Curvature Measurement)

Corneal topography was performed on each subject at the baseline, 1 month, 2 month and 3 month visits using the Keratron Corneal Topographer (Alliance Medical, Jacksonville, FL) a small cone system providing maximal corneal coverage of the placido reflection. Each eye was measured twice and the placido images were saved to the hard-drive for subsequent analysis of anterior corneal curvature data. After corneal topography, subjects were fitted with the Night & Day silicone hydrogel contact lenses and underwent a slit lamp biomicroscope examination.

5.3.4. Slit Lamp Biomicroscope Examination

The following slit lamp biomicroscopy procedure was performed on the right eye first and then on the left eye:

- The slit lamp was set at ¾ maximum illumination. Using 10× magnification and a diffuse, wide-open illumination beam, the eyelids and lashes were scanned for signs of inflammation.
- The palpebral and bulbar conjunctivae were scanned in all quadrants.
- Eversion of the upper eyelid was performed to scan the superior tarsal conjunctiva at 7-10× magnification.
- The limbus was observed at higher magnification by using an approximately 3 mm wide parallelepiped (16×).
- Approximately a 3 mm wide parallelepiped at 16× or greater magnification was used to scan the entire cornea for signs of microcysts, edema, previous scars, and vascularization or ghost vessels.
• The anterior chamber, iris, and crystalline lens were evaluated
• About a 2 mm wide parallelepiped beam was placed at the limbus to observe the cornea by using sclerotic scatter for signs of edema or opacification.
• Sodium fluorescein was instilled into the lower fornix, a 16× magnification setting, a wide-open slit beam, a cobalt filter over the light source, and a yellow (Tiffen or equivalent) filter over the slit-lamp objectives were used to observe for corneal staining.

Slit lamp biomicroscopy was performed at each visit.

5.3.5 Automated (Manifest) Refraction

The Humphrey Autorefactor/Keratometer (HARK) 599 was used in this study for an objective measurement of subjects’ refractive error in both eyes. The auto-refraction was measured in the manifest condition, prior to the instillation of any mydriatic eye drops. Each eye was measured once and a hard copy of the results was printed out. Auto-refraction was performed at the baseline and monthly visits.

5.3.6 Axial Length Measurement

The axial length of each eye was measured using the Zeiss IOLMaster, a partially coherent interferometer. Each eye was measured 5 separate times and an average axial length was calculated. Only acquisitions when the signal to noise ratio was greater than a value of 5, were used in the calculated average. Axial length was measured at the baseline and monthly visits.
5.3.7 Anterior Chamber Depth Measurement

The anterior chamber depth of each eye was measured using the Zeiss IOLMaster, a partially coherent interferometer. Each eye was measured 5 separate times and an average anterior chamber depth was calculated and recorded. Only acquisitions where the signal to noise ratio was greater than a value of 5 were used in the calculated average. Anterior chamber depth was measured at the baseline and monthly visits.

5.3.8 Crystalline Lens Thickness Measurement using Ultrasonic Biometry

A partial coherence interferometer is unable to measure the position of the anterior and posterior surface of the lens capsule, and therefore the IOLMaster could not be used to determine the crystalline lens thickness. Rather the traditional ultrasonic A-Scan technique was employed. The Humphrey Ultrasonic Biometer 820, operating at a frequency of 10MHz in the A-Scan mode, was used to measure the lens thickness of each eye. All eyes were dilated with 1 drop of 1% Tropicamide, at least 20 minutes prior to measurement. Each eye was anesthetized with 1 drop of 0.5% Proparacaine, and the probe of the ultrasound was applanated normal to the central cornea, until the instrument automatically signaled a successful acquisition. A total of 5 separate measurements were collected on each eye, and an average lens thickness was calculated and recorded. Ultrasound biometry A-Scan measurements were performed at the baseline and monthly visits.
5.3.9 Corneal Pachymetry

Corneal pachymetry was measured using two different non-contact optical techniques. The first method used the Bausch & Lomb Orbscan I Anterior Segment Analyzer. This is an instrument designed for scanning, mapping, and displaying the geometry of the anterior segment of the eye with visible light. Corneal thickness is calculated by subtraction of the posterior elevation from the anterior elevation surface maps. The Orbscan I Anterior Segment Analyzer was calibrated prior to beginning of the study and periodically during the course of the study. Calibration consisted of the measurement of a series of test spheres, and verification that the pachymetry values reported were less than 5 µm on repeated measures. Two acquisitions per eye were recorded at each visit.

The second technique to measure corneal thickness used the Humphrey Optical Coherence Tomographer (OCT) II. The OCT II is an infra-red type Michelson interferometer that is designed for evaluation of the retinal surface. The results displayed by the instrument are a series of false color image sections, representing the amount of infra-red light from a super luminescent diode source reflected by tissues that the incident light passes through. Each image is composed of a series of 100 A-scans displayed on a logarithmic scale, with peaks representing a change in tissue boundaries such as moving from the epithelium to the stroma.

The OCT image acquisition technique was adapted to measure the cornea. The scan length of the instrument was set to a 1.0 mm diameter circular scan. The subject was positioned on the chin rest with their eyes closed. The instrument was focused until the front surface of the eyelid became visible as a false color image. The subject was then
instructed to open their eyes and the false color image was observed to shift. The instrument was refocused until another false color image, representing the cornea came into view again. A second camera/monitor was used to ensure that the center of the cornea was being measured. An image was captured when the false color image showed a highly reflective surface (indicated by the colors red and yellow). A total of 3 images per eye were acquired with the OCT II. Pachymetry measurements were performed at the baseline and monthly visits.

5.3.10 Crystalline Lens Phakometry

The radii of curvature of the crystalline lens were measured using a video capture system of the Purkinje images I, III, and IV as described in previous research (Mutti, D. O., Zadnik K. et al., 1992). All eyes were dilated with 1 drop of 1% Tropicamide, at least 20 minutes prior to measurement. The subject was positioned in the slit lamp camera system, presented with a fixation target and had the fellow eye occluded with an eye-patch. The Purkinje images were centered in the pupil, and the video recorder was engaged. The slit lamp was focused in the proper focal plane to capture Purkinje I, Purkinje IV and finally Purkinje III respectively. The procedure was repeated for the fellow eye. The video images were later digitized into still images using the freeze frame function and a computer video capture card. Purkinje image I was digitized 6 times, Purkinje image IV was digitized 4 times and Purkinje image III was digitized 2 times for each eye as recommended by Mutti et al (1992). The heights of the digitized images were analyzed to determine the anterior and posterior crystalline lens and corneal curvatures using a calibration equation determined using a standard test surface. Crystalline lens
power was calculated from these values with ray tracing. Phakometry was measured at
the baseline and monthly visits.

5.3.11 Ocular Aberrometry

The aberration wavefront was measured for each eye using the Bausch & Lomb
Zywave WaveFront Aberrometer, a Hartmann-Shack type instrument. All eyes were
dilated with 1 drop of 1% Tropicamide, at least 20 minutes prior to wavefront
measurement. A minimum pupil diameter of 6.0 mm was required before any
measurements were acquired (Figure 3). Each patient had two wavefront images captured
at the baseline and monthly visits.

The wavefront shape is mathematically represented by a series of Zernike
polynomials up to the 5th order and displayed as a color map. The wavefront data was
used to determine the presumed phoropter refraction (PPR) at a pupil diameter of 3.5 mm.
This accomplished by an algorithm analyzing the shape of the wavefront and using a least
squares fit the wavefront of with a toric surface to optimize the retinal image. This
refraction value was used as a second objective refraction technique, and simulated the
manifest condition by only using data isolated from the central 3.5 mm. The sphere,
cylinder and axis components were recorded from the (PPR3.5) refraction estimate in
standard polar coordinate clinical notation. Ocular spherical aberration was also recorded
from the 4th order Zernike term over a 6.0 mm pupil diameter. A minimum 6.0 mm pupil
diameter is required by the Zywave in order to sample enough centroids in the Hartmann-
Shack image to describe the higher-order wavefront. The raw Hartmann-Shack images
were saved as *.ZYW files. These files were exported onto CD-R media for later analysis.
Electronic data from the clinical Zywave, the *.ZYW image files, were converted to *.REF files using an investigational version of the Zywave software made available through Bausch & Lomb. The *.REF files were generated by manually restricting the analysis region to the central 3.5 mm and 6.0 mm in the investigational Zywave software program. The *.REF files were data mined for the PPR3.5 refraction values and 6.0 mm spherical aberration Zernike coefficients using the “*.REF to Access” Conversion Tool, a Visual Basic software program. The data mined from the *.REF file were automatically entered in to a Microsoft Access 2000 database, which could then be queried for the required values.

5.3.12 Refractive Error in Fourier Space

Refractive error measurements obtained with the subjective manifest technique, auto-refraction and wavefront (PPR3.5) derived refractions were converted from standard polar coordinate clinical notation to a Fourier series. The polar coordinate component for each measurement was converted to a combination of: a spherical equivalent (SE) component, and J₀ and J₄₅ Jackson Cross-Cylinders with orientations of 0° and 45°, according to a previously described Fourier transformation (Thibos, L. N. and Horner D., 2001; Thibos, L. N., Wheeler W. et al., 1997). The power of these three Fourier components may be interpreted as (x, y, z) coordinates in a vector representation of the power profile, such that each component of the subject’s prescription can be observed in isolation allowing for more accurate statistical analyses.
5.4 Special Analysis Techniques of Raw Biometry Data

Electronic data from the OCT II, Orbscan I and Keratron were analyzed using data mining software algorithms to harvest and output the data in a format more appropriate for this study. The final output from these software algorithms consisted of text files of raw data that were imported into spreadsheets using Microsoft Excel XP or directly into a statistical analysis software package.

5.4.1 Corneal Curvature Data (Regional Analysis)

Corneal curvature data were analyzed using the Keratron source data. The Keratron was selected over the Orbscan I Anterior Segment Analyzer because it provided the greatest proportion of corneal coverage, due to the nature of its placido cone. The data from the Keratron were analyzed by using the Keratron Utility program. Curvature data were analyzed in three regions across the corneal surface (Figure 1). The regions defined by zones centered in the horizontal direction on the $0^\circ$ to $180^\circ$ axis of a unit circle and in the vertical direction centered on the $90^\circ$ and $270^\circ$ axis of a unit circle. The spread of the zones were limited to $15^\circ$ on either side of the specified axes. The zones were further sub-divided into central (2.75 mm radius), mid-peripheral (2.75 - 3.25 mm radius) and peripheral (3.25 - 4.5 mm radius) measured out from the center along the specified axes. The average curvature was calculated in the horizontal and vertical meridians in the central, mid-peripheral and peripheral regions.

5.4.2 Pachymetry Data: Orbscan I analysis

Corneal pachymetry data was analyzed using the Orbscan I Anterior Segment Analyzer source data. Pachymetry from the Orbscan I is calculated from a subtraction of
the posterior elevation from the anterior elevation data. The Orbscan Recorder module was used in addition to a macro written specifically to analyze the pachymetry data in three regions across the corneal surface (Figure 2). The regions defined by three zones centered on the axis of the measurement. The regions were divided into central (0.5 mm radius), mid-peripheral (0.50 – 1.75 mm radius) and peripheral (1.75 - 4.5 mm radius). The average pachymetry was calculated in the central, mid-peripheral and peripheral regions.

5.4.3 Pachymetry Data: OCT II analysis

Total central corneal and epithelial pachymetry data was analyzed from the OCT II source data. Pachymetry was analyzed with a 1.0mm diameter circular scan centered over the entrance pupil. The OCT II raw files were exported and analyzed with a software program designed to average the B-scan measurements and generate an estimate of the total corneal thickness and corneal epithelial thickness (Mahmoud, unpublished). The three highest successive peaks on the average A-scan graph were detected (Figure 4). These are referred to as the major peaks. Smaller (minor) peaks were present, but did not represent a change in tissue layers and were ignored for this analysis. The first major peak represented the air-epithelium (tears) interface, the second major peak corresponded to the interface between the epithelium and stroma, and the final major peak represented the endothelium-aqueous interface. The first major peak was designated the zero x-intercept on the average A-scan plot and the axial distance to the subsequent peaks was determined by subtraction of a constant. The corneal epithelial thickness was defined as the axial distance between the first and second major peaks and the total corneal
thickness as the distance between the first and last major peak on the average A-Scan image. An average of three measurements was reported for each eye measured.

5.5 Statistical Analysis

Data collected in the RESCU Lenses study were analyzed using Microsoft Excel XP and SAS version 8.0. For the cohort of neophytes fitted to continuous wear, only means and standard deviations are reported. The Etafilcon A to continuous wear cohort was analyzed using parametric statistics when normality testing was passed otherwise the corresponding non-parametric test was used.

Measurements taken at each visit were compared with repeated measures analysis of variance (ANOVA). The ANOVA was used to test for effects of visit, eye, or the interaction of visit and eye on each of the outcome variables. In the analysis of refractive error, the additional factor of instrument was included along with interactions of visit and eye with instrument. In the absence of a significant effect of eye or any interaction involving eye, subsequent analyses were performed using the average of the responses in all eyes (Searlu, S. R., Casella G. et al., 1992).

When the analysis indicated a significant effect of visit, pair-wise comparisons were performed. To control the overall error rate when making these comparisons, it was necessary to employ some multiple comparison adjustment. Adjustment methods included Tukey’s method when all possible comparisons were desired, Dunnett’s method when only comparisons with baseline were desired, or Bonferonni’s method when only a small subset of all possible comparisons were desired (e.g. comparing adjacent visits).
Analysis of variance is a parametric procedure. As such, in the analysis certain assumptions are made about the data being analyzed. If these assumptions are not satisfied, the results of the procedure are suspect. In such cases, Friedman’s test, a non-parametric analysis procedure, was used to compare the visits. Post-hoc comparisons were performed using methods described by Friedman.

Mixed model analysis was used to model changes in refractive error from baseline to 3 months as a function of 1) baseline measurements of the other components and 2) change from baseline to 3 months in each of the components. Mixed modeling statistical procedures were chosen because data from both eyes was pooled for analysis. A \( \beta \) statistic, the slope of the line of best fit, was reported for each calculation. Initial models were constructed using each component alone to determine its individual effect on change in refractive error (univariate modeling). Additional modeling was performed to find the best set of components to describe the change in refractive error. For all mixed model analyses, the measurement of refractive error obtained via wavefront PPR3.5 refraction was used.

5.5.1 Sample Size Calculation

Based on an expected refractive error shift of at least 0.25 diopters after refitting hydrogel extended wear subjects into silicone hydrogel contact lenses for continuous wear, we predicted a required sample size of 13 eyes to achieve a power of 90\% at significance level of 0.05. A standard deviation for refractive error measurement of 0.25 diopters was assumed based on available literature (Dumbleton, K. A., Chalmers R. L. et al., 1999). In order to satisfy the sample size calculation for refractive error shift in the
low-Dk hydrogel refitted cohort, a sample of 15 subjects (30 eyes) were enrolled for that cohort. If the eye measured had an effect, or there was an interaction between eyes or visit, the sample of 15 subjects would have still satisfied the sample size calculation. In the absence of any interactions or effects associated with eye measured, the low-Dk refitted cohort effectively had double the size of the required sample, because the each eye could be treated as if they were data points.
The age and gender distributions for both cohorts are illustrated in Table 1 and Table 2. The subjects refitted from Acuvue hydrogel contact lenses reported using Acuvue contact lenses for a minimum of 3 nights per week. No subject in the contact lens neophyte group reported wearing contact lenses within 1 year of this study. All subjects were refitted with a full distance prescription in both eyes.
There were 7 females (47%) in the Acuvue cohort, and 1 female (25%) in the neophyte cohort. The mean age (± SD) of the Acuvue cohort was 31.9 (± 7.4) years. The mean age (± SD) of the neophyte cohort was 32.7 (± 8.5) years.

6.1 Refractive Error Analysis

Refractive errors measured with the subjective manifest technique, auto-refractor and wavefront aberrometer (PPR3.5) were converted to Fourier space and represented with 3 power vectors. The average amount of nearsightedness in the Acuvue cohort was about 2 diopters more myopic than the in the neophyte cohort at the baseline visit. There was very little difference between the cohorts in the astigmatism variables.

The mean spherical equivalent (SE) components from each instrument at each visit in the neophyte cohort are presented in Table 3. The autorefractor derived refraction showed a trend to measure a more myopic SE compared to the other techniques by about 0.30 to 0.40 diopters. The wavefront PPR3.5 refraction was typically only about 0.10 diopters different than the manifest subjective refraction for SE. This relationship was observed to exist at every visit.

In the neophyte cohort the J₀ and J₄₅ astigmatism components both demonstrated small differences among the instruments at the baseline visit (Table 4 and Table 5). However, the variability of both the J₀ and J₄₅ measurements was large and in fact much larger than the differences observed between methods. It was not possible to discern a statistically significant difference among the instruments in their ability to measure the astigmatic components of refractive error at the baseline visit or any other visit.
The neophyte group showed a mean hyperopic shift of less than +0.25 diopters in the SE component from baseline to the 3 month visit for the wavefront PPR3.5 derived refraction. However, examination of the individual subject wavefront PPR3.5 refraction change from baseline to the 3 month visit showed 4 eyes increased in myopia by an average of 0.17 diopters, 3 eyes shifted towards hyperopia by about 0.20 and 1 eye did not change. Overall, there was no consistent change in the SE component in the neophyte group fitted with silicone hydrogel contact lenses. Any changes observed were in general not clinically significant.

The Acuvue cohort (n=15) demonstrated a statistically significant difference between the measured mean spherical equivalent (SE) among the instruments (ANOVA, p < 0.0001) (Table 6). The autorefractor derived SE measurement was significantly more myopic than either the wavefront PPR3.5 or manifest subjective refraction measurements by about 0.5 diopters on average at the baseline visit. There was no significant difference between the wavefront PPR3.5 refraction and the subjective manifest refraction. The difference among each refraction technique’s measurement of SE was consistent over course of the study. There was also no statistically significant interaction observed with visit and method of refraction (ANOVA, p = 0.2473).

Post-hoc analysis of the effect of visit on the SE component revealed that the baseline visit was significantly more myopic than both the 2- and 3-month visits, and that the 1 month visit was significantly more myopic than the 3 month visit (ANOVA, p < 0.0001). The hyperopic shift was observed to be statistically significant at about 0.27 diopters of change. The total change in the SE refraction component from baseline to the
3 month visit revealed a hyperopic shift of about 0.40 diopters in the wavefront PPR3.5 refraction.

The differences in the measured J₀ astigmatism component using the factor of refraction technique were not statistically significant (ANOVA, p = 0.2842). The three methods of refraction differed by less than 0.07 diopters at all visits (Table 7). Furthermore, the variability in the J₀ astigmatism component was more than double the magnitude of the average difference of refraction measured by each technique.

The J₄₅ astigmatism component demonstrated a statistically significant difference with method of refraction as a factor, such that the manifest subjective refraction showed less myopic astigmatism in the oblique meridians than either the wavefront PPR3.5 or autorefractiion technique (ANOVA, p = 0.0092) However, the measured differences were less than 0.053 diopters at every visit and are not likely clinically significant (Table 8).

Analysis of the effect of visit on the J₀ astigmatism component revealed no significant difference (ANOVA, p = 0.0833). The largest difference observed between visits was about 0.05 diopters, and the variability observed was more than double this value (Table 7). There were no significant differences in the measured J₄₅ astigmatism component based on the visit (ANOVA, p = 0.7187). Differences between visits were observed to be less than about 0.02 diopters in magnitude. There was also no significant interaction between the visit and method of refraction factors for either the J₀ (p = 0.5901) or the J₄₅ (p = 0.7924) astigmatic components (ANOVA).

A final analysis of the SE component of the Acuvue cohort from wavefront aberrometer refractive error measured at a pupil diameter of 6.0 mm (PPR6.0), demonstrated a hyperopic shift of about 0.37 diopters. This shift was almost identical to
the overall hyperopic shift seen with the PPR3.5 data between baseline and 3 months. The mean SE from the PPR6.0 measure was slightly more myopic, by 0.40 diopters, compared to the PPR3.5 measurement (Table 20).

6.2 Phakometry Analysis

Individual ocular component measurements were analyzed for change over time and the mean crystalline lens power calculated from these values were also analyzed for change. Neophyte cohort phakometric data is presented in Table 9. Data from the Acuvue cohort are presented in Table 10.

6.2.1 Axial Length

In the neophyte cohort the range of change observed in the mean axial length between the baseline visit and the 3 month visit was less than 0.06 mm. The variability in this group was more than fourteen times larger than the largest difference in mean axial length at any visit.

The Acuvue cohort demonstrated no statistically significant change in axial length (ANOVA, p = 0.5594) from baseline to 3 months. The largest difference between any of mean axial length visit measurements was 0.06 mm, and variability in this group was about nineteen times larger.
6.2.2 Vitreous Chamber Depth

Mean vitreal chamber depth had a range of 0.21 mm between measurement from baseline and 3 months in the neophyte cohort. The variability observed was three times larger than the mean vitreous chamber depth range.

In the Acuvue cohort, a range of only 0.01 mm was measured for the mean vitreous chamber depth. Variability in the mean vitreal chamber depths was in general was about 1.10 mm. There was no statistically significant change seen the vitreous chamber depth (ANOVA, p = 0.1664) due to the high variability of the observed mean values at each visit.

6.2.3 Anterior Chamber Depth

Anterior chamber depth measured with the IOL Master showed very little difference between the baseline and 3 month visit. The range of 0.04 mm was observed for the mean anterior chamber depths in the neophyte cohort between baseline and 3 months, and the variability was about six times as large.

For the Acuvue cohort a marginally statistically significant change in the anterior chamber depth was observed between the baseline and 3 month visit with a p-value of 0.044 (ANOVA), however post-hoc pairwise comparisons (Tukey’s) were unable to identify which visits were significantly different. The largest difference among the values was 0.04 mm and the variability was about eight times larger than this range.
6.2.4 Crystalline Lens Thickness

Lens thickness was measured using the contact ultrasound pachymeter. In the neophyte group, the range of mean lens thickness values was 0.24 mm between the baseline and 3 month visit. Standard deviations in this group ranged from 0.20 to 0.32 mm.

The Acuvue cohort showed a statistically significant difference between visits (ANOVA, \( p = 0.0364 \)). Post-hoc analysis (Tukey’s) revealed that at 1 month the crystalline lens was thinner than what was measured at the 3 month visit. No statistically significant difference was seen among the baseline visit and 1 month, or the 1 month and 2 month visit, or the 2 month and 3 month visit. The difference between the largest and smallest mean lens thickness measurement was 0.05 mm, and the variability around these means was about 5 times larger.

6.2.5 Crystalline Lens Index

In the neophyte cohort, there was very little difference in the mean index of refraction measured at each visit. The mean index of the crystalline lens had a range of 0.011 among the visits in this group.

There was no statistically significant difference in the mean index of refraction for the Acuvue cohort (ANOVA, \( p = 0.8084 \)). The range of values observed for the mean index of refraction was 0.001 and the variability in this group was about ten times larger.
6.2.6 Anterior Lens Curvature

The anterior lens curvature range observed in the neophyte group was 0.46 mm of curvature between the baseline visit and the 3 month visit. The variability of curvature measured in this same group was about 2.3 times greater.

In the Acuvue group, there was no statistically significant difference observed between the baseline and 3 month visit (ANOVA, \( P = 0.9781 \)). The difference observed in the largest and smallest mean value was 0.07 mm and variability was around eighteen times greater.

6.2.7 Posterior Lens Curvature

The posterior lens curvature range observed in the neophyte group was 0.61 mm of curvature between the baseline visit and the 3 month visit.

In the Acuvue group, there was no statistically significant difference observed between the baseline and 3 month visit (ANOVA, \( P = 0.9241 \)). The difference observed in the largest and smallest mean value was 0.05 mm and variability was around nineteen times greater.

6.2.8 Calculated Crystalline Lens Power

Mean lens power in the neophyte group had a range of about 0.95 diopters between the baseline and 3 month visit.

In the Acuvue cohort, the calculated mean lens power was observed to have a range of 0.38 diopters. Variability in this group over the visits was about four times larger.
than the range of means. There was no statistically significant difference in the observed mean lens powers (ANOVA, $p = 0.3310$).

### 6.3 Corneal Pachymetry Analysis

Central corneal and epithelial pachymetry results from the Optical Coherence Tomographer II were analyzed and means (SD) are reported in Table 11 and Table 12. The Orbscan I Anterior Segment Analyzer was also used to determine total corneal thickness in a variety of regions and its mean (SD) results are reported in Table 13 and Table 14.

#### 6.3.1 OCT II Pachymetry

The mean central epithelial thickness in the neophyte group had a range of about 11.3 µm between the means measured at the baseline and 3 month visits. In the Acuvue group there was no statistically significant difference in the epithelial thickness measurements across visits (ANOVA, $p = 0.2443$). The range of the mean epithelial thickness in the Acuvue cohort was only about 4 µm and the variability was about 10 µm.

The results of the mean central corneal thickness measurements for the neophyte group show a range of 17 µm and variability about 3 times larger than this range. There was a statistically significant difference calculated for total central corneal thickness in the Acuvue cohort (ANOVA, $p = 0.0114$). Post-hoc analysis revealed that the corneal thickness at the 3 month visit was increased centrally compared to the baseline visit. The difference between the baseline and 3 month visit was about 5.8 µm, and the variability of the corneal thickness measurement at these visits was more than five times larger.
6.3.2 Orbscan I Pachymetry

In the neophyte cohort very little change was observed from visit to visit, but the central cornea was observed to be thinner than the other regions. The regions defined as central (1.0 mm), midperipheral (1.0 – 3.5 mm) and peripheral (3.5 – 9.0 mm) demonstrated ranges in mean pachymetry of 0.010 mm, 0.007 mm and 0.003 mm respectively. In all regions, the variability of the measurement was more than double the range of mean values.

The Acuvue cohort showed a statistically significant difference for the central corneal thickness (1.0 mm region) using the factor of visit (ANOVA, p < 0.0001). Post-hoc pairwise analysis demonstrated that the baseline visit was significantly thicker than the 1, 2 or 3 month visits (Tukey’s). Similarly the midperipheral region had a statistically significant difference between the baseline visit and subsequent visits (ANOVA, p < 0.0001). Post-hoc analysis confirmed that the baseline corneal thickness was greater than in other study visits. Analysis of the peripheral region also showed a statistically thicker cornea at baseline (ANOVA, p < 0.0003) than at the other study visits (Tukey’s ). The central corneal region was observed to be thinned more than the midperipheral or peripheral regions at all visits.

6.4 Corneal Curvature Analysis

Mean regional corneal curvatures from the Keratron Corneal Topographer for the neophyte cohort are presented in Table 15 and Table 16, and for the Acuvue cohort in Table 17 and Table 18.
The horizontal meridian curvature in the neophyte showed minimal change over time in all regions. The central-horizontal region was on average steeper than the midperipheral region by about 2.0 diopters and 6.0 diopters steeper than the peripheral region. A similar pattern was apparent in the vertical meridian of the neophyte group across all visits. The central-vertical cornea was on average steeper than the midperipheral region by about 2.0 diopters and 3.0 diopters steeper than the peripheral region. In general, the vertical meridian tended to be steeper than the horizontal meridian.

In the Acuvue cohort, a statistically significant difference was seen for the central cornea in the horizontal meridian (ANOVA, p = 0.0106) and in the vertical meridian (ANOVA, p < 0.0001). Post-hoc pairwise comparisons (Tukey’s) revealed that in the horizontal meridian the baseline central curvature was steeper than that observed at the 2 month visit. In the vertical meridian, post-hoc testing demonstrated that the baseline central curvature was steeper than the curvature measured at both the 2 and 3 month visits.

In the midperipheral corneal regions, in the Acuvue cohort, there was a statistically significant change in curvature in the horizontal meridian (ANOVA, p = 0.0162) over the course of the study. The baseline horizontal-midperipheral curvature was significantly steeper than at the 2 and 3 month visits (Tukey’s). The midperipheral-vertical curvature did not show a statistically significant change (ANOVA, p = 0.1038).

The Acuvue cohort was observed to have no statistically significant change in peripheral curvature in either the horizontal (ANOVA, p = 0.4618) or in the vertical meridian (ANOVA, p = 0.6803). On average, the vertical meridian was slightly steeper than horizontal meridian at all visits, in all regions.
6.5 Spherical Aberration Analysis

The total 6.0 mm wavefront deviation for the total ocular spherical aberration term measured with the Zywave WaveFront Aberrometer for each is visit is presented in Table 19 for the neophyte group and in Table 20 for the Acuvue cohort. There was not a statistically significant difference in the ocular 4th order spherical aberration Zernike term measured at any visit on the Zywave Aberrometer (ANOVA, p = 0.2970). On average there was a reduction of the ocular 4th order spherical aberration Zernike term by about 0.03 μm between baseline and 3 months. The corneal surface 4th order ocular spherical aberration Zernike term data derived from the Keratron Corneal Topographer are presented in Table 21 for the neophyte and Acuvue cohorts. There was a statistically significant difference measured in the 4th order corneal spherical aberration Zernike term (ANOVA, p = 0.0002) from baseline through the 3 month visit. The 4th order spherical aberration surface Zernike term at the 3 month visit was about 0.22 μm smaller compared to the baseline visit.

6.6 Univariate Model of Refractive Error Change

Refractive error (SE) shift between the baseline and the 3 month visit was modeled using inferential statistics as a function of the importance of the baseline measurement of each variable of interest in isolation from each other. The results of the univariate analysis are presented in Table 22. When each component was considered in isolation, only baseline spherical equivalent refractive error demonstrated a statistically significant relationship to the change in refractive error (β = -0.115, p = 0.0037). No other component reached a significance level of p = 0.05. The univariate analysis for the
single best ocular component that predicted hyperopic shift showed that lower levels of baseline spherical equivalent myopia were associated with lower levels amounts of hyperopic shift. Conversely, large myopic errors at baseline were associated with larger hyperopic changes by the 3 month visit.

Another univariate analysis was conducted on the effect of the degree of change in each variable from baseline to 3 months on the spherical equivalent refractive error shift. This analysis is presented in Table 23. Epithelial thickness showed a statistically significant relationship to the SE component ($\beta = -0.019, p = 0.0242$). Small changes in epithelial thickness were related to large changes in SE refractive error. Central corneal curvature (horizontal meridian) change from baseline to 3 months also showed a statistically significant association to SE refractive error, such that small changes in the curvature were related to large changes in SE refractive error ($\beta = -0.305, p = 0.0147$). The change in spherical aberration by 3 months was significantly related to SE refractive error change ($\beta = 2.623, p < 0.0001$). Large changes in spherical aberrations were related to large changes in SE refractive error. A marginally significant relationship was observed with anterior lens curvature ($\beta = 0.143, p = 0.0579$). This suggested that a large change in anterior lens curvature would be associated with a trend for a large change in SE refractive error.

**6.7 Multivariate Model of Refractive Error Change**

Refractive error (SE) shift between the baseline and the 3 month visit as a function of the best set of ocular components at baseline was modeled using inferential statistics. The results of this multivariate analysis are presented in Table 24. The best set
of variables at baseline to predict refractive error (SE) shift were baseline spherical
equivalent refractive error ($\beta = -0.077$, $p = 0.0043$), peripheral corneal curvature
(horizontal meridian) ($\beta = -0.062$, $p = 0.0111$), and peripheral corneal curvature (vertical
meridian) ($\beta = 0.069$, $p = 0.0013$).

A multivariate analysis was conducted on the effect of the baseline spherical
equivalent as well as the amount of change in the best set of variables from baseline to
the 3 month visit on the spherical equivalent refractive error shift. The results are
described in Table 25. The components that showed a significant association were
baseline refractive error (SE) ($\beta = -0.065$, $p = 0.0259$), midperipheral corneal curvature
(horizontal meridian) ($\beta = -0.195$, $p = 0.0227$), and spherical aberration ($\beta = 1.786$, $p =
0.0012$).
CHAPTER 7
DISCUSSION

A total of twenty subjects were enrolled in to the RESCU Lenses Study and fitted with the Focus Night & Day silicone hydrogel contact lens. They were assigned to two different cohorts. The first cohort consisted of previous Etafilcon A hydrogel contact lens wearers (n = 15) and the second cohort consisted of contact lens neophytes (n = 5). One subject from the neophyte group could not tolerate the lens comfort and was exited from the study in less than 1 month, leaving a total 19 subjects in the study. In statistical analyses, it was observed that no significant interaction between eyes, or significant effect of eye was present. Based on these observations, it was determined that all subsequent analyses would be based on a pooled data set of both eyes for each cohort. Unequal sample sizes were chosen for the cohorts, to more rigorously evaluate the suspected refractive error shift in the Acuvue cohort.

Refractive error was quantified by three techniques including manifest subjective refraction, autorefraction and wavefront derived refraction (PPR3.5). The analysis of the vector components revealed that the autorefractor consistently measured more myopic spherical equivalent values in both cohorts. There was no statistical or clinical difference in the instruments for measurement of the astigmatism vectors (J_0 and J_{45}) in the neophyte cohort. The Acuvue cohort showed a statistically significant but non-clinical difference
for the J45 term, because the variability was so high. Our sample of patients in both cohorts were required to have less than – 1.00 diopters of astigmatism as an enrollment criteria. It is likely that much of the variability in measurement of the astigmatism vectors was due to the fact that our sample had a very low level of astigmatism, hence our subjects were more tolerant to errors in cylinder axis shift (Rosenfield, M. and Chiu N. N., 1995). Furthermore, it is possible that any statistical difference in the oblique astigmatism vector (Raasch, T. W., Schechtman K. B. et al., 2001) component is due to the bias of a clinician based refraction. A clinician performing a subjective refraction may bias the principle meridians towards the horizontal and vertical axes, causing a manifest subjective refraction to be different from objectively obtained measurements for astigmatism components.

In general, the autorefractor reported spherical equivalent values that were clinically similar to the other measurement techniques, but the agreement between the other methods was superior. The autorefractor reported values slightly more myopic than the other methods, possibly due to an accommodative response during the testing procedure. The manifest subjective refraction was clinically indistinguishable to the objectively measured wavefront derived (PPR3.5) refraction. The wavefront refraction was used for the analysis of change in refractive error because it provided an objective measurement free from the bias of the patient and investigator. An obvious criticism of our study is that we did not control the pupil size during the manifest measurement. However, the manifest and wavefront (PPR3.5) spherical equivalent refractions were essentially identical in our Acuvue cohort. The algorithm to calculate the Phoropter Predicted Refraction (PPR) 3.5 uses an assumed average pupil diameter of 3.5 mm,
which is the typical human pupil diameter in a mesopic (low) lighting condition. Data from Bausch & Lomb Inc. (Rochester, NY) has demonstrated that the Zywave wavefront PPR3.5 spherical equivalent refraction is highly correlated ($r^2 = 0.98$) to the manifest subjective sphere refraction in a study including several clinical sites (Cox, unpublished). However, it is important to remember that the 3.5 mm pupil diameter is an average, and not an individual subject’s pupil diameter. It is reasonable to expect that if a given subject’s pupil diameter is substantially different than 3.5 mm, that the PPR3.5 refraction would also be different than measured by the manifest refraction. It should not be assumed that the PPR3.5 refraction will be the same as the manifest refraction for a 6 mm (photopic condition) pupil. This is in fact what is observed, when the wavefront data was analyzed for SE refractive error over a 6.0 mm pupil diameter (PPR6.0). The refraction measured at 6.0 mm was more myopic than at 3.5 mm as expected.

This study successfully demonstrated a statistically significant change, in the objectively measured average SE refractive error (derived from the wavefront PPR3.5), of +0.40 diopters in previous myopic extended wear contact lens wearers (Acuvue cohort) over the 3 month course of the study. In fact, only 3 eyes in the Acuvue cohort demonstrated no refractive error shift or a myopic shift of less than 0.10 diopters. The PPR6.0 refraction data demonstrated a greater amount of myopia, but also demonstrated an almost identical amount of hyperopic shift in the SE component between the baseline and 3 month visits.

At the 1 month visit, the refractive error shift was only about +0.10 diopters and the difference from baseline was not clinically or statistically significant in the Acuvue cohort. But by the second month of using the silicone hydrogel contact lenses, subjects
showed a hyperopic shift of 0.27 diopters. There was a statistical difference in the mean SE refractive error measured between baseline and 2 month visit in the Acuvue cohort. The amount of SE refractive error shift approached the minimum threshold of the amount of refractive change required for statistical significance advocated by Rosenfield et al. (1995), although it is below the amount recommended by Zadnik et al. (1992). The previous recommendations for minimum thresholds for significant change were based upon less repeatable measurement techniques than was used in this study for refractive error measurement. It is proposed that the SE refractive error changes of + 0.27 diopters by 2 months or + 0.40 diopters by 3 months, are statistically significant (ANOVA, p < 0.05) in our sample of pooled eyes and that the recommendation of Zadnik et al. (1992) is not applicable in this instance due to improved repeatability in the refractive error measurement technique (Bullimore, M. A., Dobos M. J. et al., 2003).

The hyperopic shift observed in our Acuvue cohort is in agreement with results that have been observed in previous studies by Dumbleton et al. (1999) and Filip et al. (2000). The previous studies reported a myopic shift in patients that were prospectively fitted after low-Dk extended wear for a period of 9 months. Of these low-Dk wear patients, a smaller sample of 13 patients was selected to be refitted into Ciba Focus Night & Day silicone hydrogel contact lenses. The authors did not provide selection criteria for how these patients were chosen for the cohort refitted with the Focus Night & Day silicone hydrogel contact lenses other than claiming the subjects were eligible to continue in their study and that each subject had demonstrated a minimum shift of – 0.25 diopters in the previous study phase. The potential for selection bias exists in the previous studies and the results must be assessed with this knowledge. These authors also used
autorefractive data from a Nikon AutoRef Keratometer (NRK-8000) for refractive error comparison, a technique which has been shown to be less repeatable than a Zywave wavefront derived PPR3.5 refraction (Bullimore, M. A., Dobos M. J. et al., 2003).

McNally et al. (2002) reported on a much larger sample of subjects wearing Focus Night & Day silicone hydrogel contact lenses from a pre-market launch study, but the data were collected from about 15 different clinical centers with 1 or more clinicians obtaining subjective refractive error measurements. The patients enrolled into this pre-market launch study were a mixture of previous contact lens daily wear or extended wear low-Dk hydrogel lens users, and the analysis was done on pooled data from both eyes. Some of the eyes in this study (4.9 %) demonstrated a hyperopic shift of at least 0.625 diopters, but the baseline characteristics of these patients were not presented. The refractive data from the McNally et al. (2002) also showed a cohort of eyes that increased in myopia (1.5 %) while wearing Focus Night & Day silicone hydrogel lenses. Dumbleton et al. (1999) also found that about 8% of previous low-Dk daily wear subjects refitted to silicone hydrogel contact lenses for 30 night continuous wear had an increase in myopia of – 0.50 diopters over 9 months. These studies were not controlled for clinician bias or previous contact lens wear and cannot effectively isolate these factors, but the results do demonstrate trends suggesting patients wearing silicone hydrogel contact lenses are more likely to experience a hyperopic shift than a myopic shift.

The neophyte cohort in the RESCU Lenses Study, showed no overall significant change in the mean spherical equivalent refractive error. The SE component in this cohort demonstrated no net change in refractive error, but an equivalent number of eyes showed a small increase in myopia compared to others that showed a small decrease in myopia or
no change at all. This suggests that previous low-Dk extended wear in the Acuvue cohort, was likely an important factor in those individuals that did demonstrate a hyperopic shift when refitted with silicone hydrogel contact lenses. Extended wear of low-Dk hydrogel contact lenses has previously been shown to put the cornea in a state of chronic hypoxia resulting in chronic low-grade corneal edema which is known to cause functional and structural changes in the cornea (Brennan, N. A. and Coles M. L., 1997; Holden, B. A., Sweeney D. F. et al., 1985).

The RESCU Lenses Study Neophyte cohort was small and could not statistically demonstrate a mean refractive error difference between the baseline and 3 month visit, but it did control for previous contact lens wear. The McNally et al. (2002) study did not control for previous contact lens wear. There was also no consistent orthokeratologic effect in the Neophyte cohort. Additionally, in a stratified analysis of change in baseline myopia, Dumbleton et al. (1999) observed a greater change in myopes between – 3.00 and – 6.00 diopters than in lower myopes. The Neophyte cohort was on average less myopic than the Acuvue cohort and this may account for the differences observed in degree of refractive error shift between these groups in the RESCU Lenses Study.

Ocular biometry was performed in this study in an attempt to describe the factors that contributed towards the hyperopic shift in the Acuvue cohort. On evaluation of the change in the mean value measured for each ocular component contributing to refractive error in the Acuvue cohort, only the crystalline lens thickness, corneal thickness and anterior corneal curvature demonstrated significant change from baseline through the 3 month visit. In normal adult patients, such as in our sample, changes in the crystalline lens phakometry parameters are not expected in a 3 month period. Most often changes in
phakometry are expected in a young developing population, where there is a likelihood of ocular change due to growth. However, it is very important that such variables be considered in any longitudinal of refractive error, even in adult populations, since each component itself could contribute to the change in a patient’s refractive power. Mean crystalline lens thickness in the Acuvue cohort was observed to have significantly thinned from the 1 month visit to the 3 month visit. Although the analysis predicted a statistically significant mean difference for crystalline lens thickness of 0.04 mm, the high variability (± 0.29 mm) suggested that clinically there was no difference in lens thickness from month to month. The other lenticular variables of anterior lens curvature, posterior lens curvature, crystalline lens index of refraction, and other ocular variables of axial length, anterior chamber depth and vitreous chamber depth also demonstrated no significant difference between the baseline visit and the 3 month visit. Based on these observations it was determined that there was likely no change in crystalline lens power over the 3 months in this investigation. This was confirmed by the fact that there was no statistically significant difference observed in the calculated crystalline lens power at any visit.

Secondly, it was determined that there was no statistically significant change in the overall size of the axial length or in the relative axial position of the crystalline lens within this system.

Therefore the refractive error hyperopic shift observed in the Acuvue cohort is most likely a result of a change in the corneal structure or orientation due to refitting with a silicone hydrogel contact lens. In the Acuvue cohort a statistically significant thinning of the cornea from the center out to a diameter of approximately 9.0 mm was observed from baseline through the 3 month visit using Orbscan I Anterior Segment Analyzer data.
A greater amount of thinning was observed in the central cornea than in the peripheral cornea in the Acuvue cohort. This finding is reasonable since the central cornea tends to swell the most under hypoxic conditions and thus is likely to show the greatest thinning when normal oxygen tension is restored (Cox, I., Zantos S. G. et al., 1990; Sanchis-Gimeno, J. A., Lleo A. et al., 2003). The periphery may be resistant to swelling forces due to lamellar orientation and intraocular pressure, and thus experiences proportionally less swelling than the central cornea. Also the peripheral corneal tissues may acquire oxygen via the limbal vascular supply, limiting the peripheral corneal effects in contact lens induced hypoxia. It is important to note that the pachymetry function of the Orbscan I device is considered to be a repeatable measurement in non-diseased optically clear corneas, and that posterior corneal surface tracking problems reported in post-refractive surgery patients were not applicable in this study because there was no appreciable increase in corneal haze (Lattimore, M. R., Jr., Kaupp S. et al., 1999; Marsich, M. W. and Bullimore M. A., 2000; Roberts, C. J., Mahmoud A. et al., 2003).

The overall corneal thinning observed in the Acuvue cohort by the Orbscan I Anterior Segment Analyzer, is likely due to the elimination of the hypoxic environment created by the low-Dk hydrogel contact lenses when hyper-Dk silicone hydrogel contact lenses were fitted. The return of normal oxygen tension at the cornea is followed by gradual resumption of normal corneal metabolism and relative state of deturgescence. As the cornea de-swells an increase in the index of refraction is expected. This change in index of refraction would be associated with a reduction of corneal power (Rengstorff, R. H. and Arner R. S., 1971). The finding of corneal thinning due to de-swelling and the speculated increase in corneal index of refraction is in agreement with the reduction of
myopic refractive power after re-fitting with silicone hydrogel contact lenses in the Acuvue cohort.

In this study, total corneal thickness was observed to decrease using the Orbscan I Anterior Segment Analyzer, but the opposite effect was observed with the Optical Coherence Tomographer II. With the OCT II the mean total corneal thickness appeared to increase by about 5 µm between baseline and 3 months, but a very high variability of the measurement was about 23 µm was observed. The mean epithelial thickness in the Acuvue cohort showed little to no change and the variability of the epithelial measurements had similarly high variability to that measured for total corneal thickness. It is thought that the high variability of measurements in this study are associated with the inexperience of the operator of the OCT II device for corneal measurements, and that the device was not designed for use on the cornea and prone to errors due to focusing or alignment. A scan length of 1.0 mm was used in this study and it is possible that the entrance beam was not exactly perpendicular to the corneal surface. This would result in a longer optical pathway and an overestimation of the corneal thickness, explaining the paradoxical thickening of the cornea observed in this study in comparison to that measured by the Orbscan I, a clinically accepted technique for corneal pachymetry. Additionally, if the reasonable assumption is made that the corneas in the Acuvue cohort were edematous to some extent due to low-Dk hydrogel contact lens extended wear, then it would be logical to also expect a slightly lower corneal index of refraction. Optical coherence tomography assumes a normal average index of refraction in its determination of the amount reflectance from the infra-red test beam, and any deviation would result in
an inappropriate calculation of thickness. A criticism of this study is that it did not
directly measure the corneal index of refraction.

The mean anterior corneal curvature of the Acuvue cohort that was fitted with
silicone hydrogel lenses, showed significant central flattening (vertical and horizontal),
significant midperipheral flattening in the horizontal meridian, and no significant change
in the peripheral regions due to the higher variance of the measurement in the peripheral
cornea. The mean curvature change was significantly flatter by the second month in the
regions mentioned above, corresponding to when a statistically significant refractive error
shift was observed. The overall anterior corneal shape change observed in the Acuvue
cohort was that the cornea assumed a less prolate shape compared to baseline corneal
curvature values.

The anterior corneal curvature flattening measured on eyes using the silicone
hydrogel contact lenses is similar to the orthokeratologic effect observed with rigid gas
permeable lenses (Swarbrick, H. A., Wong G. et al., 1998). It was suggested that central
corneal flattening was accompanied with central epithelial thinning and midperipheral
corneal thickening accounting for the refractive error change observed in orthokeratology.
Mechanical effects from the rigid contact lens were reasoned to be the cause of epithelial
and/or stromal molding. The Focus Night & Day silicone hydrogel contact lenses have a
considerably higher modulus of elasticity than hydrogel contact lenses, and it is possible
that these lenses have a similar mechanical interaction to rigid gas permeable contact
lenses when underneath the eyelid in overnight wear. In addition, in an hypoxic
environment the epithelial adhesion is known to be reduced, and thus the epithelial layer
is likely to be more malleable or deformable by a contact lens with a high modulus of
elasticity (Madigan, M. C. and Holden B. A., 1992; Madigan, M. C., Holden B. A. et al., 1987). With the elimination of the relative anoxic environment at the cornea, it is possible that the shifted epithelial layers would have improved adhesion resulting in a change in the shape of the anterior cornea.

Alternatively, with the elimination of the hypoxic low-Dk hydrogel environment to which Acuvue cohort was subject prior to refitting with silicone hydrogel lenses, it is possible that a previously steepened cornea experienced a flattening returning to its pre-contact lens use curvature independent of lens wear (Hill, J. F., 1976; Liu, Z. and Pflugfelder S. C., 2000). However, Dumbleton et al. (1999) observed no change in corneal curvature when low-Dk hydrogel extended wear patients were placed in a non-contact lens wearing condition. This finding supports the hypothesis that silicone hydrogel contact lenses contribute to the molding of the anterior cornea when refitting from low-Dk hydrogel contact lenses. The central flattening observed in this study is in agreement with previous reports of flattening with silicone hydrogel contact lens use (Dumbleton, K. A., Chalmers R. L. et al., 1999; Filip, M., Stefaniu I. et al., 2000).

However, previous studies only compared central curvature flattening as measured using the Nikon AutoRef Keratometer (NRK-8000).

Mixed modeling analysis of pooled data suggested predictive variables for those patients who experienced a hyperopic shift when refitted from low-Dk hydrogel contact lenses into silicone hydrogel lenses. In the Acuvue cohort, the baseline refractive spherical equivalent error (degree of myopia) was the only variable, when considered in isolation that adequately predicted a hyperopic shift. The analysis suggested that patient’s with higher degrees of myopic spherical equivalent errors at baseline, were more likely to
demonstrate a hyperopic shift, after fitting with silicone hydrogel contact lenses. These patients were also more likely to have greater degrees of hyperopic shift compared to patients with a lower baseline degree of myopia. Based on this finding, it is possible that our neophyte group did not show a significant hyperopic shift because it had a lower degree of baseline myopic spherical equivalent compared to the Acuvue cohort.

It is reasonable to consider that subjects with higher levels of baseline myopia in low-Dk extended wear would have been subject to greater levels hypoxia and corneal edema and due to the reduced oxygen transmissibility of the hydrogel lenses these patients would need relative to lower myopes. Higher myopes use hydrogel lenses that are on average thicker than lower myopes, and in hydrogel contact lenses this is known to translate into lower corneal oxygen tension. These subjects would experience the greatest degree of refractive error shift (myopic) and would consequently require a greater hyperopic shift to return to pre-low-Dk extended wear conditions (Dumbleton, K. A., Chalmers R. L. et al., 1999).

When each variable was analyzed for the effect of the degree of change that occurred in that variable over 3 months, we found that epithelial thinning measured with the OCT II was predictive of large amounts of refractive error hyperopic shift. Although this variable was statistically significant, when the scatter plot of epithelial thickness by the OCT II versus the change is SE is examined, it is difficult to assume any relationship. A substantial number of observations were plotted on the zero difference line, and more than half of the observations fell within ± 5 µm of difference (Figure 1). It is unlikely that the corneal epithelial thickness change is a good predictor for degree of hyperopic shift in patients refitted with silicone hydrogel contact lenses.
A similar picture is observed for anterior lens curvature, which approached significance, where the scatter plot reveals that the p-value suggests a stronger relationship than actually present. The p-value suggested that longer changes in radii of anterior lens curvature were marginally related to larger hyperopic shifts, but there is significant spread in the data points.

Central anterior corneal curvature change in the horizontal meridian was predictive of hyperopic shifts, such that a small amount of corneal curvature flattening leads to a large degree of reduction in myopic spherical equivalent. This predictive model is supported by previous literature from Rengstorff et al. (1969), showing that anterior corneal flattening led to a reduction of corneal power. Considering this finding in addition to the observation that higher myopes demonstrated greater hyperopic shifts, it can be suggested that the thicker lens profile of a higher minus contact lens design and resultant higher modulus of elasticity could affect the degree of anterior curvature flattening observed.

Analysis of the 4th order Zernike ocular spherical aberration term from the Zywave Aberrometer revealed that larger amounts of ocular spherical aberration changes over 3 months would predict a larger hyperopic shifts in subjects refitted in silicone hydrogel lenses. There was less mean negative ocular spherical aberration observed in the 4th order Zernike term comparing baseline to the 3 month visit. This means there was an average increase in positive 4th order ocular spherical aberration, an observation that is commonly seen in other refractive procedures that reduce myopia (Applegate, R. A. and Howland H. C., 1997; Thibos, L. N. and Hong X., 1999). This finding is reasonable considering that spherical aberration is associated with corneal curvature changes relative
to the pupil size present during a given measurement (Paquin, M. P., Hamam H. et al., 2002). A flattening of the cornea and a decrease in the degree of 4\textsuperscript{th} order ocular negative spherical aberration were associated with a decreased degree of spherical myopia in the Acuvue cohort patients. A shift towards a more positive 4\textsuperscript{th} order ocular spherical aberration Zernike term is a common finding observed in cases where the anterior corneal curvature is flattened such as in refractive surgery or orthokeratology, where rigid gas permeable lenses are purposely used for this purpose.

Multivariate analysis of the combined baseline ocular characteristics that best predicted a hyperopic shift in the Acuvue cohort included the baseline degree of myopia, and anterior-peripheral corneal curvature. This finding may be rationalized by the fact that patients with higher degrees of myopia tend to have peripheral corneas that flatten to a lesser degree than lower myopes (Carney, L. G., Mainstone J. C. et al., 1997).

A multivariate analysis of the effect of the degree of change in an ocular component suggested that the baseline refractive error, anterior-horizontal corneal curvature change, and change in ocular spherical aberration Zernike term were associated with the greatest likelihood of a hyperopic shift.

The cornea changed with silicone hydrogel contact lens wear after refitting from low Dk/L hydrogel contact lens extended wear. The anterior cornea was observed to flatten and the total corneal thickness was reduced as measured by the Orbscan I, and there was a shift towards a more positive value for the 4\textsuperscript{th} order spherical aberration Zernike term. Each of these factors was observed to contribute to the degree of hyperopic shift in the Acuvue cohort.
Based on the observations made during this study a model for refractive error change with contact lens usage is proposed. In the cohort of low-Dk/L extended wear contact lens users refitted to a hyper-Dk/L silicone hydrogel contact lens, a noticeable hyperopic shift was observed, concurrently with a change in the shape of the cornea. Shape changes included a flattening of the anterior central corneal curvature and an overall thinning of the cornea, particularly in the central cornea. The corneal curvature flattening was also observed to contribute to less positive 4th order ocular spherical aberration as measured by the Zywave Aberrometer. The changes in the shape of the cornea are thought to be the primary contributing factors to the hyperopic shift. Combinations of mechanical and physiological responses that occur with refitting to hyper-Dk/L continuous wear are reasoned to account for the corneal shape change observed in this study.

If rigid gas permeable contact lenses are on one end of a spectrum of the modulus of elasticity of lens materials and hydrogel contact lenses are on the other end, silicone hydrogel contact lenses would be located between these two extremes. The lens base curve (back surface central curvature) is in general flatter than the front surface radius of the cornea. Silicone hydrogel lenses are less flexible than hydrogel lenses, and are more likely to transfer greater force to the apical cornea from the eyelid during a closed eye condition. Assuming that the corneal epithelium layer has physical properties analogous to the modulus of elasticity of a contact lens material, it would be reasonable to suggest that a silicone hydrogel contact lens would have a higher modulus compared to the epithelium. It is proposed that the silicone hydrogel lenses may be associated with a type of orthokeratologic effect on the cornea due to their relatively higher modulus compared
to hydrogel lenses, resulting in apical curvature flattening. Anterior surface corneal flattening has previously been associated with hyperopic shifts in myopic patients (Swarbrick, H. A., Wong G. et al., 1998).

This study demonstrated an overall thinning of the cornea, but was not able to demonstrate any differential swelling or de-swelling responses in different layers of the cornea because of the limit of resolution of current clinical instruments for the measurement of the human eye. Some of the observed thinning was likely associated with the elimination of corneal hypoxia and resultant de-swelling with the use of silicone hydrogel lenses. However, the silicone hydrogel contact lenses may be associated with a mechanical effect on the epithelial thickness such that this corneal layer is molded by the back surface of the contact lens. A thinner central epithelial layer has been previously observed with orthokeratology (Swarbrick, H. A., Wong G. et al., 1998). It is possible that because the epithelial layer which was previously more malleable due to low Dk/L extended wear, it was susceptible to be flattened and thinned with the presence of a lens with a high modulus of elasticity. Susceptibility of the epithelial layer to stress due to contact lens wear, which would support this hypothesis has been previously documented (Madigan, M. C. and Holden B. A., 1992).
CHAPTER 8
CONCLUSIONS

This study was designed to prospectively determine if a refractive error shift occurred when patients were refitted from low Dk/L hydrogel contact lenses into hyper Dk/L silicone hydrogel contact lenses, and to determine the mechanisms contributing to the shift in refractive power. This clinical study has demonstrated:

1. Wavefront based refractions had better agreement to subjective manifest refractions compared to the traditional method of measuring refractive error in similar studies, an autorefractor.

2. A hyperopic shift of 0.40 diopters on average in previous low-Dk extended wear contact lens patients after 3 months of silicone hydrogel contact lens wear.

3. Hyperopic shifts were more likely in patients with higher myopic errors.

4. Hyperopic shifts were associated with corneas that experienced larger amounts of anterior curvature flattening.

5. Hyperopic shifts were associated with corneas that demonstrated overall thinning within the 3 months of the study.

6. Hyperopic shifts were associated in those subjects with large changes towards more positive values in ocular 4th order spherical aberration Zernike terms.
APPENDIX A

EXAMINATION SCHEDULE
<table>
<thead>
<tr>
<th>Baseline</th>
<th>1-Day</th>
<th>1-Week</th>
<th>1,2 &amp; 3- Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patient History</td>
<td>• Patient History F/U</td>
<td>• Patient History F/U</td>
<td>• Patient History F/U</td>
</tr>
<tr>
<td>• Habitual VA (Snellen)</td>
<td>• Habitual VA (Snellen)</td>
<td>• Habitual VA (Snellen)</td>
<td>• Habitual VA (Snellen/Bailey-Lovie)</td>
</tr>
<tr>
<td>• Manifest Refraction</td>
<td>• CL fit assessment</td>
<td>• CL fit assessment</td>
<td>• CL-SOR</td>
</tr>
<tr>
<td>• Best Corrected Manifest VA (Snellen/Bailey-Lovie)</td>
<td>• Slit Lamp Exam</td>
<td>• Best Corrected CL VA (Snellen)</td>
<td>• Best Corrected CL VA (Snellen/Bailey-Lovie)</td>
</tr>
<tr>
<td>• Topography (Keratron)</td>
<td></td>
<td>• Slit Lamp Exam</td>
<td>• Slit Lamp Exam</td>
</tr>
<tr>
<td>• Slit Lamp Exam</td>
<td></td>
<td></td>
<td>• OCT</td>
</tr>
<tr>
<td>• CL fit/dispense</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CL-SOR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Best Corrected CL VA (Snellen/Bailey-Lovie)</td>
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<td></td>
</tr>
<tr>
<td>• Auto-refraction (Manifest)</td>
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<td></td>
</tr>
<tr>
<td>• Dilate (1% Tropicamide)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• IOL Master (A-scan/Axial Length)</td>
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<tr>
<td>• Ultrasound A-scan</td>
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<tr>
<td>• Orbscan Pachymetry</td>
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<tr>
<td>• Lens Phakometry</td>
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<tr>
<td>• OCT</td>
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<td></td>
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</tr>
<tr>
<td>• Zywave Aberration analysis</td>
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<td></td>
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<tr>
<td>• Dilated fundus exam</td>
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</tbody>
</table>
APPENDIX B

VISUAL ACUITY ASSESSMENT
Visual Acuity Assessment

Introduction
High contrast Bailey-Lovie distance acuities are measured by the examiner during the course of the RESCU Lenses Study. The procedure for measuring visual acuity was originally developed for the Early Treatment of Diabetic Retinopathy Study (ETDRS) using Bailey-Lovie high contrast visual acuity charts. The chart is located at 4 meters, and the white background of the chart has a luminance as specified below.

Visual acuity is measured in two ways in the following order:
1. Bailey-Lovie high and low contrast visual acuity with habitual correction, for each eye separately and both eyes together.
2. Bailey-Lovie high and low contrast visual acuity with refraction over contact lenses for each eye separately.

Mandatory Sequence of Visual Acuity Testing

<table>
<thead>
<tr>
<th>Correction</th>
<th>Contrast Level</th>
<th>Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habitual</td>
<td>High</td>
<td>OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OU</td>
</tr>
<tr>
<td>Habitual</td>
<td>Low</td>
<td>OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OU</td>
</tr>
<tr>
<td>Best Corrected (Over-refraction)</td>
<td>High</td>
<td>OD</td>
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<tr>
<td></td>
<td></td>
<td>OS</td>
</tr>
<tr>
<td>Best Corrected (Over-refraction)</td>
<td>Low</td>
<td>OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS</td>
</tr>
</tbody>
</table>

Calibration of Chart Lighting
The light meter is removed from the pouch. The M button is pressed, and the LCD display illuminates. The only other buttons needed are the horizontal FUNCTION
arrows on the right. These move the square cursor along the settings at the top of the screen. The Cursor must be set to the EV icon.

To calibrate, the investigator should be positioned as close as possible to the letter charts without blocking the illumination falling on them. The M button should be pressed, and the two numbers on the bottom left should be inspected.

<table>
<thead>
<tr>
<th>t</th>
<th>f</th>
<th>EV</th>
<th>cal</th>
<th>ISO</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>EV</td>
<td>94 t' 125</td>
<td>s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.4 2 2.8 4 5.6 8 11 16 22 32 45 64 90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This EV scale is arbitrary (i.e. not in candela/m²), but it has been calibrated such that the target range is **96 to 102 EV**; too low and more light is needed, too high and less light is needed. This range applies to the whole useful area of the chart (the bottom corners are unimportant). Calibration using the high contrast charts and testing in the four shown below is recommended.

**THE LETTERS ARE HERE**

**Areas for visual acuity chart lighting calibration**

**Important:** The numbers 100 and 125 should always appear on the right side of the display when in EV mode. If not, then the settings have been disturbed, most likely from interference with the vertical arrows on the right. These should never be pressed, and
doing so will render your readings worthless. In this event, take the battery out of the meter, and wait 15 seconds and re-insert the battery. Then, the horizontal arrows should be set to move the square cursor to the EV setting. The light meter turns itself off after use.

**Visual Acuity**

For each of the testing conditions listed above in Table 1, the following protocol is completed. Start with visual acuity measurement in the right eye, followed by the left eye, then both eyes together.

1. Visual acuity is measured with the patients’ eyes located 4 meters from the visual acuity chart. The patient may stand or sit for the testing. The Clinician or Technician should ensure that the patient’s head does not move forward or backward during the test so that the patient’s eyes remain at the set test distance.

2. The testing begins in the right eye with the left eye occluded carefully, and when needed, after refraction and placement of the proper lenses in the trial frame.

3. Instruct the patient to read each letter on the chart starting at the top left hand corner with the first line, line by line, letter by letter, from left to right.

4. Advise the patient to read slowly and to keep his or head as still as possible. The pace should not be faster than about one letter per second, so as to achieve the best identification of each letter. Demonstrate the desired pace by reciting, “A, B, C”. If the patient at any point reads too quickly, s/he should be asked to stop, go back to the beginning of the line, and read more slowly.
5. S/he is not to go to the next letter until s/he has given a definite response. If the patient reads a number, s/he should be reminded that the chart contains no numbers and the Clinician should request a letter in lieu of a number.

6. When the patient says s/he cannot read a letter, s/he should be encouraged and required to guess. A maximum effort should be made to identify each letter. If a patient identifies a letter as one of two letters, s/he should be asked to choose one letter and if necessary, to guess. You can suggest that the patient fixate eccentrically or turn or shake his or her head in any manner if this improves visual acuity. If the patient employs these maneuvers, care must be taken to ensure that the fellow eye remains covered and that the patient is not leaning forward.

7. The Clinician or Technician uses the RESCU Lenses Study Visual Acuity Form to record the patient’s answers. Score each letter as right or wrong. Letters read correctly are marked with a “slash” through them. Letters read incorrectly are circled. If all the letters are read correctly, draw a horizontal line through all the letters on that line, or slash through each of the 5 letters on that row. Record a perfect read line by putting a check mark or the number “5” in the right hand column. Testing continues to the next line with smaller letters. The patient continues reading down the chart to the last letter of each line, until the patient has missed 3 letters on a given line. The incorrect letters can occur at the beginning, middle or end of this line and do not have to
be consecutive. Visual acuity testing for an eye stops when the patient has read the last letter of the line with 3 incorrect letters.

8. The Clinician tallies the total number of letters read correctly for each visual acuity measurement of each eye on the Visual Acuity Form and records this total number in the visual acuity section of the RESCU Lenses Study Examination Form.

**Conversion of Bailey-Lovie Visual Acuity at 4 meters to Snellen Equivalent Visual Acuity at 6 meters**

The following chart was used to convert the number of letters correct to Snellen equivalents at 6m.

<table>
<thead>
<tr>
<th># Letters Correctly Identified</th>
<th>Bailey-Lovie @ 4 m</th>
<th>Snellen Equivalent @ 6 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bailey-Lovie @ 4 m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>20/30</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>20/30</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>20/25 +1</td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>20/20 +1</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>20/15</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bailey-Lovie @ 6 m</th>
<th>Snellen Equivalent @ 6 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>20/40</td>
</tr>
<tr>
<td>45</td>
<td>20/30</td>
</tr>
<tr>
<td>50</td>
<td>20/25</td>
</tr>
<tr>
<td>55</td>
<td>20/20 -1</td>
</tr>
<tr>
<td>60</td>
<td>20/15 -1</td>
</tr>
</tbody>
</table>
APPENDIX C

TABLES

98
<table>
<thead>
<tr>
<th>Gender</th>
<th>Acuvue Cohort</th>
<th>Neophyte Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 1: Gender distribution:** Acuvue cohort and Neophyte cohort.

<table>
<thead>
<tr>
<th>Age</th>
<th>Acuvue Cohort</th>
<th>Neophyte Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 29</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>30 – 39</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>40 – 49</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>31.9 (7.4)</td>
<td>32.7 (8.5)</td>
</tr>
</tbody>
</table>

**Table 2: Age distribution:** Acuvue cohort and Neophyte cohort.
<table>
<thead>
<tr>
<th>Measurement Technique</th>
<th>Baseline</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autorefractor</td>
<td>-2.82 (1.48)</td>
<td>-2.81 (1.52)</td>
<td>-2.82 (1.45)</td>
<td>-2.75 (1.39)</td>
</tr>
<tr>
<td>Subjective Manifest</td>
<td>-2.67 (1.41)</td>
<td>-2.53 (1.41)</td>
<td>-2.58 (1.29)</td>
<td>-2.47 (1.18)</td>
</tr>
<tr>
<td>Wavefront (PPR3.5)</td>
<td>-2.51 (1.45)</td>
<td>-2.43 (1.41)</td>
<td>-2.45 (1.32)</td>
<td>-2.24 (1.58)</td>
</tr>
</tbody>
</table>

**Table 3: Refractive Error (Neophyte Cohort):** Mean (SD) spherical equivalent (SE) with different instruments at each visit.
<table>
<thead>
<tr>
<th>Measurement Technique</th>
<th>Baseline (SD)</th>
<th>1 month (SD)</th>
<th>2 months (SD)</th>
<th>3 months (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autorefractor</td>
<td>0.016 (0.17)</td>
<td>-0.001 (0.15)</td>
<td>0.019 (0.16)</td>
<td>0.023 (0.14)</td>
</tr>
<tr>
<td>Subjective Manifest</td>
<td>0.053 (0.18)</td>
<td>0.091 (0.14)</td>
<td>0.090 (0.19)</td>
<td>0.029 (0.16)</td>
</tr>
<tr>
<td>Wavefront (PPR3.5)</td>
<td>-0.025 (0.20)</td>
<td>-0.013 (0.19)</td>
<td>-0.028 (0.18)</td>
<td>0.018 (0.15)</td>
</tr>
</tbody>
</table>

Table 4: Refractive Error (Neophyte Cohort): Mean (SD) astigmatism J₀ component with different instruments at each visit.
<table>
<thead>
<tr>
<th>Measurement Technique</th>
<th>Baseline</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autorefractor</td>
<td>-0.031</td>
<td>-0.079</td>
<td>-0.059</td>
<td>-0.062</td>
</tr>
<tr>
<td></td>
<td>(0.05)</td>
<td>(0.08)</td>
<td>(0.06)</td>
<td>(0.09)</td>
</tr>
<tr>
<td>Subjective Manifest</td>
<td>0.019</td>
<td>-0.039</td>
<td>-0.009</td>
<td>-0.004</td>
</tr>
<tr>
<td></td>
<td>(0.03)</td>
<td>(0.06)</td>
<td>(0.05)</td>
<td>(0.03)</td>
</tr>
<tr>
<td>Wavefront (PPR3.5)</td>
<td>0.011</td>
<td>-0.034</td>
<td>-0.051</td>
<td>-0.048</td>
</tr>
<tr>
<td></td>
<td>(0.08)</td>
<td>(0.09)</td>
<td>(0.14)</td>
<td>(0.08)</td>
</tr>
</tbody>
</table>

**Table 5: Refractive Error (Neophyte Cohort):** Mean (SD) astigmatism J45 component with different instruments at each visit.
Table 6: Refractive Error (Acuvue Cohort): Mean (SD) spherical equivalent (SE) with different instruments at each visit.
<table>
<thead>
<tr>
<th>Measurement Technique</th>
<th>Baseline</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autorefractor</td>
<td>0.053 (0.14)</td>
<td>0.111 (0.15)</td>
<td>0.096 (0.15)</td>
<td>0.078 (0.17)</td>
</tr>
<tr>
<td>Subjective Manifest</td>
<td>0.075 (0.11)</td>
<td>0.096 (0.11)</td>
<td>0.096 (0.12)</td>
<td>0.098 (0.10)</td>
</tr>
<tr>
<td>Wavefront (PPR3.5)</td>
<td>0.024 (0.19)</td>
<td>0.080 (0.18)</td>
<td>0.026 (0.19)</td>
<td>0.043 (0.18)</td>
</tr>
</tbody>
</table>

**Table 7: Refractive Error (Acuvue Cohort):** Mean (SD) astigmatism $J_0$ component with different instruments at each visit.
<table>
<thead>
<tr>
<th>Measurement Technique</th>
<th>Visit</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 month</td>
<td>2 months</td>
<td>3 months</td>
</tr>
<tr>
<td>Autorefractor</td>
<td>0.051 (0.06)</td>
<td>0.062 (0.06)</td>
<td>0.047 (0.08)</td>
<td>0.054 (0.09)</td>
</tr>
<tr>
<td>Subjective Manifest</td>
<td>0.006 (0.06)</td>
<td>0.027 (0.08)</td>
<td>0.015 (0.06)</td>
<td>0.025 (0.10)</td>
</tr>
<tr>
<td>Wavefront (PPR3.5)</td>
<td>0.059 (0.10)</td>
<td>0.044 (0.08)</td>
<td>0.046 (0.08)</td>
<td>0.069 (0.09)</td>
</tr>
</tbody>
</table>

**Table 8: Refractive Error (Acuvue Cohort):** Mean (SD) astigmatism J45 component with different instruments at each visit.
<table>
<thead>
<tr>
<th>Ocular Component</th>
<th>Baseline</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial Length (mm)</td>
<td>25.16 (0.84)</td>
<td>25.11 (0.92)</td>
<td>25.11 (0.85)</td>
<td>25.10 (0.91)</td>
</tr>
<tr>
<td>Vitreous Chamber Depth (mm)</td>
<td>17.59 (0.68)</td>
<td>17.60 (0.76)</td>
<td>17.61 (0.81)</td>
<td>17.80 (1.26)</td>
</tr>
<tr>
<td>Anterior Chamber Depth (mm)</td>
<td>3.62 (0.29)</td>
<td>3.54 (0.25)</td>
<td>3.53 (0.26)</td>
<td>3.58 (0.18)</td>
</tr>
<tr>
<td>Lens Thickness (mm)</td>
<td>3.96 (0.25)</td>
<td>3.96 (0.27)</td>
<td>3.97 (0.20)</td>
<td>3.72 (0.32)</td>
</tr>
<tr>
<td>Lens Index of Refraction</td>
<td>1.464 (0.009)</td>
<td>1.469 (0.003)</td>
<td>1.466 (0.006)</td>
<td>1.475 (0.013)</td>
</tr>
<tr>
<td>Anterior Lens Curvature (mm)</td>
<td>11.55 (1.32)</td>
<td>11.91 (1.29)</td>
<td>11.68 (1.05)</td>
<td>12.01 (1.15)</td>
</tr>
<tr>
<td>Posterior Lens Curvature (mm)</td>
<td>7.86 (0.21)</td>
<td>7.88 (0.46)</td>
<td>7.73 (0.22)</td>
<td>8.34 (0.18)</td>
</tr>
<tr>
<td>Calculated Lens Power (D)</td>
<td>27.35 (1.50)</td>
<td>28.03 (1.25)</td>
<td>27.92 (0.58)</td>
<td>28.30 (2.13)</td>
</tr>
</tbody>
</table>

Table 9: Ocular Components and Phakometry Calculation (Neophyte cohort): Mean (SD)
<table>
<thead>
<tr>
<th>Ocular Component</th>
<th>Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Axial Length (mm)</td>
<td>25.16 (1.18)</td>
</tr>
<tr>
<td>Vitreous Chamber Depth (mm)</td>
<td>17.69 (1.10)</td>
</tr>
<tr>
<td>Anterior Chamber Depth (mm)</td>
<td>3.77 (0.31)</td>
</tr>
<tr>
<td>Lens Thickness (mm)</td>
<td>3.70 (0.27)</td>
</tr>
<tr>
<td>Lens Index of Refraction</td>
<td>1.483 (0.013)</td>
</tr>
<tr>
<td>Anterior Lens Curvature (mm)</td>
<td>12.59 (1.50)</td>
</tr>
<tr>
<td>Posterior Lens Curvature (mm)</td>
<td>8.49 (0.78)</td>
</tr>
<tr>
<td>Calculated Lens Power (D)</td>
<td>29.05 (1.80)</td>
</tr>
</tbody>
</table>

Table 10: Ocular Components and Phakometry Calculation (Acuvue cohort): Mean (SD)
<table>
<thead>
<tr>
<th>Visit</th>
<th>Baseline</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pachymetry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Epithelial Thickness</strong></td>
<td>60.50 (8.70)</td>
<td>59.00 (3.47)</td>
<td>67.33 (11.55)</td>
<td>56.00 (2.83)</td>
</tr>
<tr>
<td><strong>Corneal Thickness</strong></td>
<td>569.00 (43.95)</td>
<td>570.50 (43.00)</td>
<td>566.67 (52.62)</td>
<td>552.00 (70.71)</td>
</tr>
</tbody>
</table>

Table 11: Optical Coherence Tomographer II Pachymetry (Neophyte cohort): Mean (SD) epithelial and corneal thickness (μm).

<table>
<thead>
<tr>
<th>Visit</th>
<th>Baseline</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pachymetry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Epithelial Thickness</strong></td>
<td>58.80 (8.71)</td>
<td>59.33 (10.38)</td>
<td>62.27 (11.39)</td>
<td>59.86 (10.03)</td>
</tr>
<tr>
<td><strong>Corneal Thickness</strong></td>
<td>527.07 (21.89)</td>
<td>531.60 (22.49)</td>
<td>530.93 (23.87)</td>
<td>532.86 (23.23)</td>
</tr>
</tbody>
</table>

Table 12: Optical Coherence Tomographer II Pachymetry (Acuvue cohort): Mean (SD) epithelial and corneal thickness (μm).
### Table 13: Orbscan I Anterior Segment Analyzer Pachymetry (Neophyte cohort): Mean (SD) central, midperipheral and peripheral corneal thickness (mm).

<table>
<thead>
<tr>
<th>Pachymetry</th>
<th>Visit</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 month</td>
<td>2 months</td>
<td>3 months</td>
</tr>
<tr>
<td>Central</td>
<td>0.630 (0.05)</td>
<td>0.621 (0.06)</td>
<td>0.629 (0.06)</td>
<td>0.631 (0.06)</td>
</tr>
<tr>
<td>Midperipheral</td>
<td>0.642 (0.05)</td>
<td>0.635 (0.06)</td>
<td>0.642 (0.06)</td>
<td>0.641 (0.06)</td>
</tr>
<tr>
<td>Peripheral</td>
<td>0.714 (0.05)</td>
<td>0.711 (0.05)</td>
<td>0.713 (0.05)</td>
<td>0.712 (0.05)</td>
</tr>
</tbody>
</table>
### Table 14: Orbscan I Anterior Segment Analyzer Pachymetry (Acuvue cohort): Mean (SD) central, midperipheral and peripheral corneal thickness (mm).

<table>
<thead>
<tr>
<th>Pachymetry</th>
<th>Baseline</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central</strong></td>
<td>0.596 (0.03)</td>
<td>0.587 (0.03)</td>
<td>0.584 (0.03)</td>
<td>0.586 (0.03)</td>
</tr>
<tr>
<td><strong>Midperipheral</strong></td>
<td>0.607 (0.03)</td>
<td>0.600 (0.03)</td>
<td>0.596 (0.03)</td>
<td>0.597 (0.03)</td>
</tr>
<tr>
<td><strong>Peripheral</strong></td>
<td>0.679 (0.03)</td>
<td>0.672 (0.03)</td>
<td>0.670 (0.03)</td>
<td>0.673 (0.03)</td>
</tr>
<tr>
<td>Curvature</td>
<td>Baseline</td>
<td>1 month</td>
<td>2 months</td>
<td>3 months</td>
</tr>
<tr>
<td>--------------</td>
<td>----------</td>
<td>---------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Central</td>
<td>42.17 (1.17)</td>
<td>42.49 (1.57)</td>
<td>42.22 (1.20)</td>
<td>42.20 (1.37)</td>
</tr>
<tr>
<td>Midperipheral</td>
<td>39.95 (1.01)</td>
<td>40.65 (1.22)</td>
<td>40.44 (0.98)</td>
<td>40.38 (0.94)</td>
</tr>
<tr>
<td>Peripheral</td>
<td>36.01 (1.60)</td>
<td>36.37 (1.37)</td>
<td>36.28 (1.44)</td>
<td>35.92 (1.55)</td>
</tr>
</tbody>
</table>

Table 15: Corneal Curvature Neophyte Cohort: Mean (SD) in diopters of curvature in the horizontal meridian (Keratron).
<table>
<thead>
<tr>
<th>Curvature</th>
<th>Baseline</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>43.00</td>
<td>43.36</td>
<td>43.00</td>
<td>42.75</td>
</tr>
<tr>
<td></td>
<td>(1.48)</td>
<td>(1.88)</td>
<td>(1.43)</td>
<td>(1.56)</td>
</tr>
<tr>
<td>Midperipheral</td>
<td>41.39</td>
<td>41.85</td>
<td>41.83</td>
<td>41.14</td>
</tr>
<tr>
<td></td>
<td>(1.16)</td>
<td>(1.30)</td>
<td>(1.54)</td>
<td>(1.08)</td>
</tr>
<tr>
<td>Peripheral</td>
<td>40.47</td>
<td>40.65</td>
<td>41.63</td>
<td>41.07</td>
</tr>
<tr>
<td></td>
<td>(0.82)</td>
<td>(0.65)</td>
<td>(2.15)</td>
<td>(1.88)</td>
</tr>
</tbody>
</table>

**Table 16: Corneal Curvature Neophyte Cohort:** Mean (SD) in diopters of curvature in the vertical meridian (Keratron).
<table>
<thead>
<tr>
<th>Curvature</th>
<th>Baseline</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>44.18</td>
<td>43.96</td>
<td>43.87</td>
<td>43.95</td>
</tr>
<tr>
<td></td>
<td>(1.58)</td>
<td>(1.30)</td>
<td>(1.34)</td>
<td>(1.28)</td>
</tr>
<tr>
<td>Midperipheral</td>
<td>42.04</td>
<td>41.81</td>
<td>41.51</td>
<td>41.55</td>
</tr>
<tr>
<td></td>
<td>(1.83)</td>
<td>(1.25)</td>
<td>(1.42)</td>
<td>(1.32)</td>
</tr>
<tr>
<td>Peripheral</td>
<td>36.21</td>
<td>36.42</td>
<td>36.15</td>
<td>36.14</td>
</tr>
<tr>
<td></td>
<td>(2.62)</td>
<td>(2.38)</td>
<td>(2.22)</td>
<td>(2.00)</td>
</tr>
</tbody>
</table>

**Table 17: Corneal Curvature Acuvue Cohort:** Mean (SD) in diopters of curvature in the horizontal meridian (Keratron).
<table>
<thead>
<tr>
<th>Curvature</th>
<th>Baseline</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central</strong></td>
<td>45.21 (1.39)</td>
<td>44.95 (1.14)</td>
<td>44.76 (1.14)</td>
<td>44.78 (1.12)</td>
</tr>
<tr>
<td><strong>Midperipheral</strong></td>
<td>43.99 (3.51)</td>
<td>42.78 (1.38)</td>
<td>42.80 (1.56)</td>
<td>42.92 (1.48)</td>
</tr>
<tr>
<td><strong>Peripheral</strong></td>
<td>39.36 (3.17)</td>
<td>39.26 (3.22)</td>
<td>39.51 (3.56)</td>
<td>38.98 (3.44)</td>
</tr>
</tbody>
</table>

**Table 18: Corneal Curvature Acuvue Cohort:** Mean (SD) in diopters of curvature in the vertical meridian (Keratron).
### Table 19: Zywave WaveFront Aberrometer Neophyte cohort:

Mean (SD) spherical aberration (µm) and associated SE refractive error component (D) at a 6.0 mm pupil.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Baseline</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular Spherical Aberration</td>
<td>0.190 (0.10)</td>
<td>0.170 (0.12)</td>
<td>0.174 (0.09)</td>
<td>0.151 (0.11)</td>
</tr>
<tr>
<td>Wavefront (PPR 6.0)</td>
<td>-2.90 (1.62)</td>
<td>-2.76 (1.52)</td>
<td>-2.76 (1.47)</td>
<td>-2.82 (1.51)</td>
</tr>
</tbody>
</table>

### Table 20: Zywave WaveFront Aberrometer Acuvue cohort:

Mean (SD) spherical aberration (µm) and associated SE refractive error component at a 6.0 mm pupil.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Baseline</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular Spherical Aberration</td>
<td>0.205 (0.11)</td>
<td>0.170 (0.10)</td>
<td>0.176 (0.11)</td>
<td>0.176 (0.11)</td>
</tr>
<tr>
<td>Wavefront (PPR 6.0)</td>
<td>-4.84 (2.30)</td>
<td>-4.66 (2.10)</td>
<td>-4.55 (2.11)</td>
<td>-4.47 (2.20)</td>
</tr>
</tbody>
</table>
### Table 21: Spherical Aberration

<table>
<thead>
<tr>
<th>Corneal Spherical Aberration</th>
<th>Baseline</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neophyte</td>
<td>- 1.35 (0.11)</td>
<td>- 1.74 (0.58)</td>
<td>- 1.34 (0.28)</td>
<td>- 1.46 (0.17)</td>
</tr>
<tr>
<td>Acuvue</td>
<td>- 1.92 (0.40)</td>
<td>- 1.79 (0.23)</td>
<td>- 1.64 (0.20)</td>
<td>- 1.70 (0.24)</td>
</tr>
</tbody>
</table>

Corneal contribution to ocular spherical aberration (µm) for neophyte and Acuvue cohorts.
<table>
<thead>
<tr>
<th>Ocular Component</th>
<th>β</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SE refractive error component (PPR3.5)</td>
<td>-0.115</td>
<td>0.0037</td>
</tr>
<tr>
<td>Axial length</td>
<td>0.085</td>
<td>0.2818</td>
</tr>
<tr>
<td>Vitreous chamber depth</td>
<td>0.095</td>
<td>0.2567</td>
</tr>
<tr>
<td>Anterior chamber depth</td>
<td>0.140</td>
<td>0.6584</td>
</tr>
<tr>
<td>Lens thickness</td>
<td>-0.166</td>
<td>0.6327</td>
</tr>
<tr>
<td>Lens index</td>
<td>-0.471</td>
<td>0.8434</td>
</tr>
<tr>
<td>Anterior lens curvature</td>
<td>-0.058</td>
<td>0.2717</td>
</tr>
<tr>
<td>Posterior lens curvature</td>
<td>-0.017</td>
<td>0.7845</td>
</tr>
<tr>
<td>Calculated lens power</td>
<td>0.008</td>
<td>0.7160</td>
</tr>
<tr>
<td>OCT II: Epithelial thickness</td>
<td>-0.005</td>
<td>0.6128</td>
</tr>
<tr>
<td>OCT II: Corneal thickness</td>
<td>-0.004</td>
<td>0.3819</td>
</tr>
<tr>
<td>Orbscan: Central corneal thickness</td>
<td>-2.733</td>
<td>0.3679</td>
</tr>
<tr>
<td>Orbscan: Midperipheral corneal thickness</td>
<td>-2.772</td>
<td>0.3629</td>
</tr>
<tr>
<td>Orbscan: Peripheral corneal thickness</td>
<td>-1.610</td>
<td>0.5791</td>
</tr>
<tr>
<td>Keratron Curvature-horizontal: Central</td>
<td>0.080</td>
<td>0.1403</td>
</tr>
<tr>
<td>Keratron Curvature-horizontal: Midperipheral</td>
<td>0.015</td>
<td>0.7570</td>
</tr>
<tr>
<td>Keratron Curvature-horizontal: Peripheral</td>
<td>-0.039</td>
<td>0.2616</td>
</tr>
<tr>
<td>Keratron Curvature-vertical: Central</td>
<td>0.044</td>
<td>0.4872</td>
</tr>
<tr>
<td>Keratron Curvature-vertical: Midperipheral</td>
<td>-0.005</td>
<td>0.8251</td>
</tr>
<tr>
<td>Keratron Curvature-vertical: Peripheral</td>
<td>0.026</td>
<td>0.3009</td>
</tr>
<tr>
<td>Ocular Spherical aberration (6.0 mm)</td>
<td>0.005</td>
<td>0.9953</td>
</tr>
<tr>
<td>Corneal Spherical aberration</td>
<td>-0.134</td>
<td>0.4253</td>
</tr>
</tbody>
</table>

**Table 22: Univariate Model**: Importance of a baseline ocular component for prediction of refractive error shift. In isolation only baseline spherical equivalent was statistically related to a change in refractive error ($\beta = -0.115$, $p = 0.0037$).
<table>
<thead>
<tr>
<th>Ocular Component</th>
<th>$\beta$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial length</td>
<td>-0.032</td>
<td>0.9343</td>
</tr>
<tr>
<td>Vitreous chamber depth</td>
<td>-0.151</td>
<td>0.7257</td>
</tr>
<tr>
<td>Anterior chamber depth</td>
<td>0.219</td>
<td>0.7870</td>
</tr>
<tr>
<td>Lens thickness</td>
<td>0.212</td>
<td>0.8042</td>
</tr>
<tr>
<td>Lens index</td>
<td>4.889</td>
<td>0.2712</td>
</tr>
<tr>
<td>Anterior lens curvature</td>
<td>0.143</td>
<td>0.0579</td>
</tr>
<tr>
<td>Posterior lens curvature</td>
<td>0.1359</td>
<td>0.2518</td>
</tr>
<tr>
<td>Calculated lens power</td>
<td>0.002</td>
<td>0.9748</td>
</tr>
<tr>
<td>OCT II: Epithelial thickness</td>
<td>-0.019</td>
<td>0.0242</td>
</tr>
<tr>
<td>OCT II: Corneal thickness</td>
<td>0.003</td>
<td>0.7610</td>
</tr>
<tr>
<td>Orbscan: Central corneal thickness</td>
<td>2.962</td>
<td>0.7143</td>
</tr>
<tr>
<td>Orbscan: Midperipheral corneal thickness</td>
<td>5.225</td>
<td>0.5200</td>
</tr>
<tr>
<td>Orbscan: Peripheral corneal thickness</td>
<td>12.065</td>
<td>0.1654</td>
</tr>
<tr>
<td>Keratron Curvature-horizontal: Central</td>
<td>-0.305</td>
<td>0.0147</td>
</tr>
<tr>
<td>Keratron Curvature-horizontal: Midperipheral</td>
<td>0.095</td>
<td>0.1010</td>
</tr>
<tr>
<td>Keratron Curvature-horizontal: Peripheral</td>
<td>-0.009</td>
<td>0.9013</td>
</tr>
<tr>
<td>Keratron Curvature-vertical: Central</td>
<td>-0.1156</td>
<td>0.3357</td>
</tr>
<tr>
<td>Keratron Curvature-vertical: Midperipheral</td>
<td>0.023</td>
<td>0.2826</td>
</tr>
<tr>
<td>Keratron Curvature-vertical: Peripheral</td>
<td>-0.005</td>
<td>0.8706</td>
</tr>
<tr>
<td>Ocular Spherical aberration (6.0 mm)</td>
<td>2.623</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Corneal Spherical aberration</td>
<td>-0.181</td>
<td>0.3047</td>
</tr>
</tbody>
</table>

**Table 23: Univariate Model:** Change in ocular component. Change in ocular spherical aberration ($\beta = 2.623$, $p < 0.0001$), epithelial thickness ($\beta = -0.019$, $p = 0.0242$) and horizontal-central curvature ($\beta = -0.305$, $p = 0.0147$), were statistically related to a change in refractive error.
<table>
<thead>
<tr>
<th>Ocular Component</th>
<th>β</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SE refractive error component (PPR3.5)</td>
<td>-0.077</td>
<td>0.0043</td>
</tr>
<tr>
<td>Keratron Curvature-horizontal: Peripheral</td>
<td>-0.062</td>
<td>0.0111</td>
</tr>
<tr>
<td>Keratron Curvature-vertical: Peripheral</td>
<td>0.069</td>
<td>0.0013</td>
</tr>
</tbody>
</table>

**Table 24: Multivariate Model:** Based on the best set of baseline ocular components for prediction of refractive error shift.

<table>
<thead>
<tr>
<th>Ocular Component</th>
<th>β</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline SE refractive error component (PPR3.5)</td>
<td>-0.065</td>
<td>0.0259</td>
</tr>
<tr>
<td>Keratron Curvature-horizontal: Midperipheral</td>
<td>-0.195</td>
<td>0.0227</td>
</tr>
<tr>
<td>Zywave: Spherical aberration (6.0 mm)</td>
<td>1.786</td>
<td>0.0012</td>
</tr>
</tbody>
</table>

**Table 25: Multivariate Model:** Based on the degree of change in baseline (best set of) ocular components that best predicted a refractive error shift.
APPENDIX D

FIGURES
Figure 1: Corneal Curvature Analysis Regions: Zones are centered on the vertical and horizontal meridians with a spread of ± 15 degrees and segmented into central (5.5 mm), midperipheral (5.5 – 6.5 mm) and peripheral (6.5 – 9.0 mm) regions.
Figure 2: Corneal Pachymetry Analysis Regions: Zones are divided into central (1.0 mm), midperipheral (1.0 – 3.0 mm) and peripheral (3.0 – 9.0 mm) regions.
Figure 3: Zywave Analysis Screen: Green circle represents full 6.0 mm pupil and blue circle the PPR 3.5 mm zone.
Figure 4: Optical Coherence Tomography False Color Reflectivity Image and A-scan.
Figure 5: Univariate Analysis: Change in SE refractive error versus change in corneal epithelial thickness.
Figure 6: Univariate Analysis: Change in SE refractive error versus change in anterior lens curvature.
Figure 7: Univariate Analysis: Change in SE refractive error versus change in horizontal-midperipheral corneal curvature.
Figure 8: Univariate Analysis: Change in SE refractive error versus change in spherical aberration root mean square.
REFERENCES


