

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	lotrafilcon A hydrophilic contact lens
Device Trade Name:	Focus [®] Night & Day [™] (lotrafilcon A) soft contact lens
Applicant's Name and Address:	CIBA Vision Corporation 11460 Johns Creek Parkway Duluth, GA USA 30097
Date(s) of Panel Recommendation:	July 20, 2001
Premarket Approval (PMA) Application Number:	PMA P010019
Date of Good Manufacturing Practice Inspection:	July 12 and September 27, 2001
Date of Notice of Approval to Applicant:	October 11, 2001

II. INDICATIONS FOR USE

Focus[®] NIGHT & DAY[™] (lotrafilcon A) soft contact lenses are indicated for the optical correction of refractive ametropia (myopia and hyperopia) in phakic or aphakic persons with non-diseased eyes and with up to approximately 1.50 diopters of astigmatism.

Focus[®] NIGHT & DAY[™] TORIC (lotrafilcon A) soft contact lenses are indicated for the optical correction of refractive ametropia (myopia and hyperopia) in phakic or aphakic persons with non-diseased eyes with 6.00 diopters (D) or less of astigmatism.

Focus[®] NIGHT & DAY[™] PROGRESSIVES (lotrafilcon A) soft contact lenses are indicated for the optical correction of refractive ametropia (myopia and hyperopia) and/or presbyopia in phakic or aphakic persons with non-diseased eyes who may require a reading addition of +3.00 diopters (D) or less and who may have up to approximately 1.50 diopters of astigmatism.

The lenses may be prescribed for extended wear for up to 30 nights of continuous wear, with removal for disposal, or cleaning and disinfection prior to reinsertion, as recommended by the eye care professional.

(The Focus[®] Night & Day[™] (FN&D) (lotrafilcon A) lens was cleared for Daily Wear under K970746 on May 9, 1997.)

III. CONTRAINDICATIONS

- Inflammation or infection of the anterior chamber of the eye
- Active disease, injury or abnormality affecting the cornea, conjunctiva or eyelids
- Microbial infection of the eye
- Insufficiency of lacrimal secretion (dry eye) that interferes with contact lens wear
- Corneal hypoesthesia (reduced corneal sensitivity)
- Use of any medication that is contraindicated or interferes with contact lens wear, including eye medications
- Any systemic disease which may be exacerbated by or interferes with contact lens wear
- Allergic reactions of ocular surfaces or adnexa that may be caused by or exaggerated by wearing contact lenses
- Allergy to any ingredient in a solution which must be used to care for the contact lenses
- Subject history of recurring eye or eyelid infections, adverse effects associated with contact lens wear, intolerance or abnormal ocular response to contact lens wear
- If eyes become red or irritated

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in Focus[®] Night & Day[™] soft contact lens labeling (Attached).

V. DEVICE DESCRIPTION

FN&D soft contact lenses are available in a spherical, toric or progressive multifocal lens design. The lens material is approximately 24% water and 76% lotrafilcon A, a fluorosilicone containing hydrogel polymer which is surface treated.

The lens may be prescribed in spherical powers ranging from +20.00D to -20.00D, toric lens powers to correct up to 6.00D of astigmatism, and multifocal power to provide up to +3.00D of reading add power.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The alternative practices and procedures to correcting vision by wearing FN&D soft contact lenses include wearing other daily and extended wear soft contact lenses, rigid gas permeable daily and extended wear contact lenses, spectacles, and corrective surgeries such as radial keratotomy, photorefractive keratectomy and LASIK.

VII. MARKETING HISTORY

United States

To date, FN&D soft contact lenses have not been marketed in the U.S.

International

FN&D soft contact lenses bear the CE mark and were introduced to the world market in early 1999 for use up to 30 nights extended wear. The FN&D lens has over 250,000 wearers and is marketed in over 40 countries. The soft contact lens has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects on health associated with extended wear contact lenses include eye problems such as corneal ulcers, epithelial microcysts, infiltrates and endothelial polymegathism. The risk of corneal ulcer has been shown to be greater among users of extended wear contact lenses than among users of daily wear contact lenses. The risk among extended wear users increases with the number of consecutive days that the lenses are worn between removals, beginning with the first overnight use. In addition, *smoking increases the risk of corneal ulcers for contact lens users, especially when lenses are worn overnight or while sleeping.* Strict compliance with the proper lens care regimen and wearing schedule is essential in minimizing risk.

IX. SUMMARY OF PRECLINICAL STUDIES

The objective of the preclinical studies was to provide reasonable assurance of the safety of the FN&D soft contact lens prior to clinical testing.

FN&D soft contact lenses have undergone a comprehensive battery of biocompatibility, physiochemical, lens care compatibility and sterility/stability testing to include:

Biocompatibility Studies

Toxicology Tests

Cytotoxicity Tests (USP L929 Agar Overlay, Direct Contact and MEM Elution Assays, and ISO Cell Growth Inhibition Assay)	Pass
USP Systemic Injection Test	Systemically non-toxic
Primary Ocular Irritation Test	Non-irritating to ocular tissue
Guinea Pig Maximization Test	No evidence of causing delayed dermal contact sensitization
28 Day DW Ocular Irritation Test	Non-irritating to ocular tissue after 28 days of daily wear
One Month EW Ocular Irritation Test	No evidence of ocular irritation after 30-day continuous wear
Reverse Mutation Assay	Non-mutagenic
Chromosomal Aberration	Negative for inducing chromosomal aberrations
Unscheduled DNA Synthesis	No evidence of causing unscheduled DNA synthesis
Leachables Testing	Low % and similar to predicate lenses

Physical and Chemical Characterization Tests

- % Water Content: 24
- Oxygen Permeability (Dk): 140
(cm²/sec)(ml O₂/ml•mmHG) x 10⁻¹¹
- % Light Transmittance: ≥99

- Mechanical Properties:
 - Young's modulus of elasticity (Mpa): 1.2
 - Stress at break (Mpa): 0.8
 - % Maximum Elongation: 150
 - Toughness at break (mJ/cm³): 764
- Refractive Index: 1.43

Solution Compatibility Testing

- Cycling Studies: Pass
 - AOSEPT Regimen
 - Quick Care System
 - Focus Lens Drops
 - Optifree
 - Renu
- Preservative Uptake and Release: Pass
 - Sorbic Acid
 - Polyquad
 - PHMB

Analysis of Worn Lenses

- **Dk Performance of Lotrafilcon A Following Thirty Night Extended Wear**
Prior studies have measured the oxygen permeability (Dk) at 140 barrers and oxygen transmissibility (Dk/t) of 175 barrers at 34° C for a lens of 80 micron thickness. Results from the study demonstrated that oxygen transmission properties were not affected after 30 nights of extended wear.
- **Protein Biocompatibility Studies on (lotrafilcon A) Clinical & Rabbit Lenses**

In the analysis of protein deposition of worn lenses from clinical trials FN&D and control lenses were worn for daily and extended wear periods for 6, 14, and 30 days. In addition, test (lotrafilcon A) lenses worn on rabbit eyes for 30 night extended wear were also analyzed.

Control lenses were worn on a daily-wear modality for an average of 14 days accumulated far more protein than FN&D lenses worn for 30 days (276.9 ± 154.8 vs 0.07 ± 0.2 $\mu\text{g}/\text{lens}$, respectively $p=0.000$). The control lenses, worn in a 6 night extended wear (6N EW) modality attracted far more protein than the (lotrafilcon A) lenses worn for 30 nights (30N EW) continuously in humans (818.3 ± 88.9 vs 5.2 ± 4.2 $\mu\text{g}/\text{lens}$ respectively $p=0.00$).

FN&D rabbit lenses worn for 30 nights continuously in rabbits accumulated 36.4 ± 33.8 μg protein/lens

- **Microbial Evaluation of (lotrafilcon A) lenses – Monthly Extended Wear**

This study involved microbiological evaluations of FN&D lenses worn for monthly periods of extended wear and control lenses worn for weekly periods of extended wear. **The total number of lenses sampled for each lens type ranged between 16 and 44. Statistical analysis was not performed.** None of the test lenses grew fungus during the entire study. The common type of aerobic organisms for both lens types was coagulase negative staphylococcus group and the most frequently isolated anaerobe was *Propionibacterium acnes*. The percent of FN&D lenses that supported growth were 38% at 2 months, 42% at 4 months, 40 percent at 5 months and 22.7% at 7 months. The percent of control lenses that supported growth were 34% at 2 months, 39% at 4 months and 38% at 7 months. Total colony forming units per lens (CFU/lens) ranged from 0 – 2100 CFU/lens for control lenses and 0 - 720 CFU/lens for FN&D lenses.

Oxygen Transmissibility (Dk/t) over requested designs and power ranges

Dk/t across the central optic zone:	Relative to 87 Dk/t*
For spherical, toric and progressive multifocal design	Meets or exceeds
Powers +10D to –15D	
Above +10D to +20D and -15 D to –20D	Slightly below

* Investigative Ophthalmology and Visual Science, October 1984, Vol. 25, pp 1161-1167

Shelf-life Stability Testing

- An expiration date of 60 months has been established for sterilized lenses packaged in foil sealed blister packs.

Conclusion of the Preclinical Studies

The results of the preclinical studies support the safety of the FN&D soft contact lens for its intended use.

X. Summary of Clinical Studies

A. FN&D Monthly Extended Wear: Safety and Efficacy Study

1. Objective

The objective of this clinical trial was to determine whether the FN&D lens, when worn for up to one month extended wear and replaced on a monthly basis, performed as well as the control lens, when worn for up to one week extended wear and replaced on a weekly basis.

2. Study Design

This clinical trial was a prospective, randomized, control led, open label clinical trial lasting one year. A total of 1395 subjects (697 FN&D Test and 698 control) were enrolled in the clinical trial at 59 investigative sites throughout the United States. An equal number of subjects were randomized to the test and control groups at each site. Subjects wore either the test or the control lens (a 55% water Group IV ionic lens,) bilaterally for the duration of the trial.

FN&D lenses were worn on a monthly extended wear schedule. Monthly extended wear meant that at the end of any one month of extended wear, the subject removed the lens for one night prior to beginning a new cycle of lens wear. Control lenses were worn on a weekly extended wear schedule. Weekly extended wear meant that at the end of any six (6) nights of extended wear, the subject had to remove the lens for one night prior to beginning a new cycle of lens wear. For subjects assigned to FN&D, scheduled lens replacement was monthly. For subjects assigned to control lenses, scheduled lens replacement was weekly.

All subjects used the AOSep® system for both test or control lenses when cleaning and disinfecting was required. Alternatively, the QuickCARE® disinfection system could be used for short-term lens removal from the eyes. CIBA Vision® Lens Drops or Allergan Lens Plus® Rewetting Drops were provided.

Baseline characteristics and demographics were summarized using descriptive statistics such as means, proportions, and standard deviations. The primary safety endpoint analysis was based on the proportion of subjects in each group who developed corneal infiltrates \geq Grade 3 or infiltrates with overlying fluorescein staining. To guard against potential bias due to discontinuation rate differences, a standard lifetable model was used to consider all data from all subjects. For the primary safety endpoint, a non-inferiority statistical design was employed. The equivalence margin was set at 5%.

Additional safety endpoints were:

- Percent of discontinuations and reasons
- Frequency / Severity of Adverse events
- Percent of temporary interruption of lens wear and reasons
- Frequency / severity of subjective symptoms and problems
- Frequency / severity of biomicroscopy signs
- Percent of eyes for which final spherical equivalent refractive error differs from initial spherical refractive error by greater than one diopter
- Percent of eyes for which final keratometry readings differ from initial keratometry readings by greater than one diopter in either meridian
- Percent of eyes for which final best corrected visual acuity differs from initial best corrected visual acuity by two lines or greater

The following efficacy endpoints were analyzed:

- Percentage of subjects able to successfully maintain extended wearing schedule
- Percentage of eyes maintaining Snellen contact lens visual acuity within 2 lines of dispensing.

Subjects were eligible for study participation if they were at least 18 years old, signed informed consent, and complied with inclusion and exclusion criteria specified in the protocol. These criteria permitted inclusion of subjects who needed correction in both eyes that was correctable to a distance visual acuity (VA) of 20/40 or better in each eye with spherical hydrogel contact lenses and excluded subjects with conditions that would interfere with efficacy and safety assessments or expose the subject to an unacceptable risk. Pregnant or lactating women were included in the study, as these individuals comprise a significant portion of the contact lens wearing population.

3. Subject Assessments

At each study visit, subjects were given enough lenses to last until the next study visit, allowing for scheduled and unscheduled lens replacements. All other visits for any reason were recorded as Unscheduled Visits. Whenever possible, subjects were evaluated toward the end of the lens replacement cycle. Subjects were allowed to use their FN&D lenses for up to 35 days before replacement to assure that this was possible. Follow-up visits were scheduled for 24 hours, 1 week, and 1, 3, 6, 9, and 12 months after starting extended wear.

Adverse events were defined as any undesirable clinical occurrence in a subject whether it was considered to be device related or not. Adverse Device Effects were those adverse events considered to be device-related. Adverse Device Effects were further classified as Serious Adverse Device Effects, Significant Adverse Device Effects, or Non-significant Adverse Device Effects according to their severity.

Discontinuations could be due to a variety of reasons such as best interest of the subject, voluntary withdrawal by the subject, protocol deviations, lack of follow-up (lost-to-follow-up = 2 consecutive visits missed), relocation, neophytes who had not initiated extended wear within 45 days of enrollment, and if subjects switched from extended to daily wear indefinitely. Completion was defined as wearing the test or control lenses for 12 months after initiation of extended wear and the subject had the required evaluations performed.

4. Demographic Data

The test and control groups were comparable with regard to age, lens power, and type of habitual correction at the start of the study. In each group the age ranged from 18 to 70 years with a Test group mean of 34.5 years and a control group mean of 34.8 years. Lens power ranged from +6.00 D to -6.00 D for the Test group (Test mean = -3.05 D) and +4.50 to -6.50 for the control group (control mean = -2.98 D). There were 78 (11.9%) lens wear neophytes in the dispensed Test group and 93 (13.7%) lens wear neophytes in the dispensed control

group. Previously successful DW subjects accounted for 47.4% of the Test group and 47.1% of the control group. Previously successful EW subjects accounted for 39.7% of the Test group and 38.5% of the control group. A small number of RGP wearers and previously unsuccessful soft lens wearers were enrolled in each group.

Gender distribution was the same in each group, 70% female and 30% male. The study population showed no differences in distribution of ethnicity. Smokers comprised 15.7% of the FN&D group and 14.0% of the control group.

5. Data Analysis and Results

Primary Safety Endpoint Events

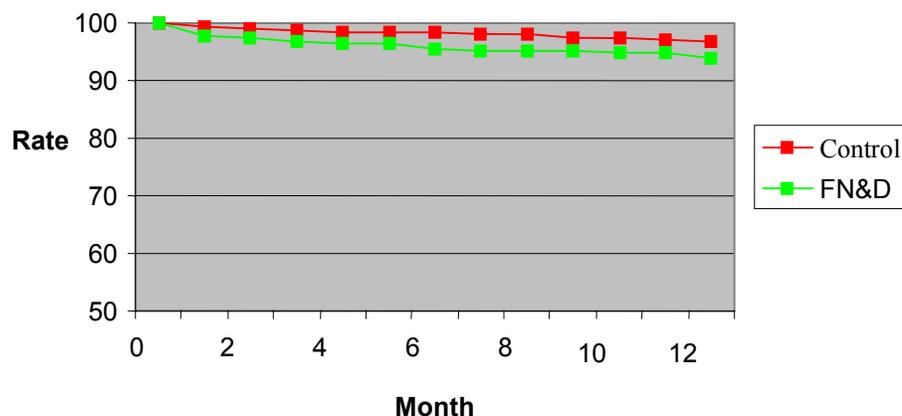
A total of 33 (5.0%) of the FN&D subjects and 21 (3.1%) of the control subjects experienced one or more of the endpoint infiltrates during the trial. These incidence rates are not statistically different. ($p = 0.073$, chi-square)

One peripheral ulcer (CLPU) in the control group that occurred at 6 months was not included in these endpoint rates. The subject had been seen by another ophthalmological practice during the holiday season. The diagnosis of CLPU was re-confirmed by ophthalmologist and later by the investigator due to the subsequent persistent scar, but data concerning infiltrates was not available.

Annualized Rate - Statistical Test of Non-inferiority

In order to estimate an annualized rate for these endpoint infiltrates, life-table (survival) analysis was used to compensate for potential exposure time differences caused by differing dropout rates for each group. Based on this survival analysis, shown in Graph 1, the estimated annualized rate for subjects experiencing one or more of these infiltrates was 6.1% per person-year for FN&D (95% CI = 4.1% to 8.2%), and 3.3% per person-year for the control group (95% CI = 1.9% to 4.7%).

Graph 1: Survival Analysis for Endpoint Infiltrates



Using these lifetable rates and testing the null hypothesis of inferiority yielded a p-value of 0.047, sufficient to reject the null hypothesis of inferiority.

The control group rate in this analysis was slightly underestimated. The analysis included all of the FN&D endpoints; however, in addition to excluding the CLPU mentioned previously, it excluded another control group endpoint infiltrate event reported as a CLPU at the 12-month visit. The statistician calculated the lifetable rate at 365 days. Because the actual date of this subject's scheduled 12-month visit was at 378 days since dispensing, the infiltrate event was not included in the 365-day analysis. To have included this event in a lifetable analysis would have caused a significant overestimation of the control group rate since so few subjects were actually in the study past 365 days. For comparison purposes, including this final endpoint in the analysis increased the control group estimate to 5.7%, with a much larger 95% confidence interval (0.8% to 10.7%).

Incidence Rates of Adverse Device Effects

Table 1 shows the number and percentage of eyes that experienced one or more Adverse Device Effects for each lens group. The table is arranged from most severe to least severe type of event. If an eye had more than one event, it was counted only once in this analysis and was counted in the most severe event experienced. This type of analysis allows the calculation of the incidence rate for number of eyes with at least one Adverse Device Effect. This same type of analysis is carried through to Other Eyes Requiring Treatment (Table 2).

Based on this analysis, the incidence rate for eyes with one or more Adverse Device Effect was 9.4% for FN&D and 8.3% for the control group. There was no statistical difference between these rates ($p = 0.30$, Chi-square).

A total of twelve (12) FN&D eyes and six (6) control group eyes experienced more than one Adverse Device Effect.

Other Subjects Requiring Treatment

A number of subjects required some form of management or treatment for signs or symptoms that were not considered as Adverse Device Effects. Examples of the measures taken were temporary removal of lenses, temporary reductions in wear schedule, use of allergy medications, lid scrubs, or compresses. Continuing from the analysis in Table 1, Table 2 shows the percentage of eyes for which these treated signs or symptoms were the most severe finding for that eye. Therefore, eyes that were previously counted as an Adverse Device Effect in Table 1 are not counted again in this analysis.

The percentage of eyes that received one or more treatments was greater for FN&D (10.2%) as compared to the control group (5.6%).

The primary reason for this difference was due to a greater frequency of treatment for contact lens symptoms or for contact lens-associated papillary conjunctivitis (CLPC). This was attributed to less-than-optimal lens fits due to the limited parameters of lens geometry available in the trial (one base curve only for FN&D).

Table 1: Eyes with at least one Adverse Device Effect categorized by most severe event

Eyes Dispensed:	FN&D		control		
FN&D = 1316 control = 1362	n	%	n	%	p
Serious Adverse Device Effect					
Loss of best corrected acuity > 2 lines	0	0.00%	0	0.00%	-
Microbial or Infectious Keratitis	0	0.00%	0	0.00%	-
Central ulcer	0	0.00%	1	0.07%	1.0*
Optical axis (4mm) scar with ac rxn	1	0.08%	0	0.00%	0.49*
Moderate or mild uveitis	1	0.08%	0	0.00%	0.49*
CLPU & ant. chamber rxn	1	0.08%	0	0.00%	0.49*
Infiltrative Keratitis & ant. chamber rxn	0	0.00%	2	0.15%	0.50*
Other: Optic neuritis	0	0.00%	1	0.07%	1.0*
Eyes with Serious Adverse Device Effect	3	0.23%	4	0.29%	1.0*
Significant Adverse Device Effect					
CLPU, non-infectious peripheral ulcer	11	0.84%	5	0.37%	0.13*
Severe Infiltrative Keratitis (≥Gr3 infiltrate)	7	0.53%	5	0.37%	0.57*
Moderate Infiltrative Keratitis (<Gr3 infiltrate)	34	2.58%	21	1.54%	0.06**
Conjunctivitis	47	3.57%	53	3.89%	0.66**
Temporary Refractive change > 1.00 D	2	0.15%	0	0.00%	0.24*
Severe (gr 4) staining, edema, microcysts, injection	1	0.08%	0	0.00%	0.49*
Moderate to severe peripheral neovascularization	0	0.00%	0	0.00%	-
Other	3	0.23%	5	0.37%	0.73*
Eyes with Significant Adverse Device Effect	105	7.98%	89	6.53%	0.15**
Non-significant Adverse Device Effect					
Asymptomatic Infiltrates	9	0.68%	5	0.37%	0.29*
Superior Epithelial Arcuate Lesion (SEAL)	2	0.15%	0	0.00%	0.24*
Hordeolum / Chalazion	4	0.30%	15	1.10%	0.04*
Eyes with Non-Significant Adverse Device Effects	15	1.14%	20	1.47%	0.57*
TOTAL EYES with at least one Adverse Device Effect 123 9.4% 113 8.3% 0.30**					

*Fisher's Exact Test

**Chi-square Test

Table 2: Other Eyes Requiring Treatment

Eyes Dispensed:	FN&D		control		
FN&D = 1316 control = 1362	N	%	n	%	p
Other Eyes Requiring Treatment					
CLPC (Contact lens-associated papillary conjunctivitis)	51	3.88%	11	0.81%	<0.001**
Other physiology, biomicroscopy ≤ grade 3	51	3.88%	45	3.30%	0.43**

Seasonal allergies	12	0.91%	8	0.59%	0.37
Contact lens symptoms	19	1.44%	7	0.51%	0.02*
Other symptoms	1	0.08*	5	0.37%	0.22*
Total Eyes	134	10.2%	76	5.6%	<0.001**

*Fisher's Exact Test

**Chi-square Test

Discontinuations

Of the 697 subjects randomized to FN&D lenses, 658 were dispensed lenses. Of the 698 subjects randomized to the control lenses, 681 were dispensed lenses. The difference in the two groups was due to the inability to fit a number of FN&D subjects with a single base curve.

Overall, 175 (26.6%) of FN&D subjects and 102 (15.0%) control subjects discontinued from the trial. The percent of subjects discontinued is based on the number of subjects dispensed. FN&D had a higher discontinuation rate for reasons of unacceptable acuity, discomfort, inadequate lens fit, and a positive biomicroscopic finding on slit lamp examination .

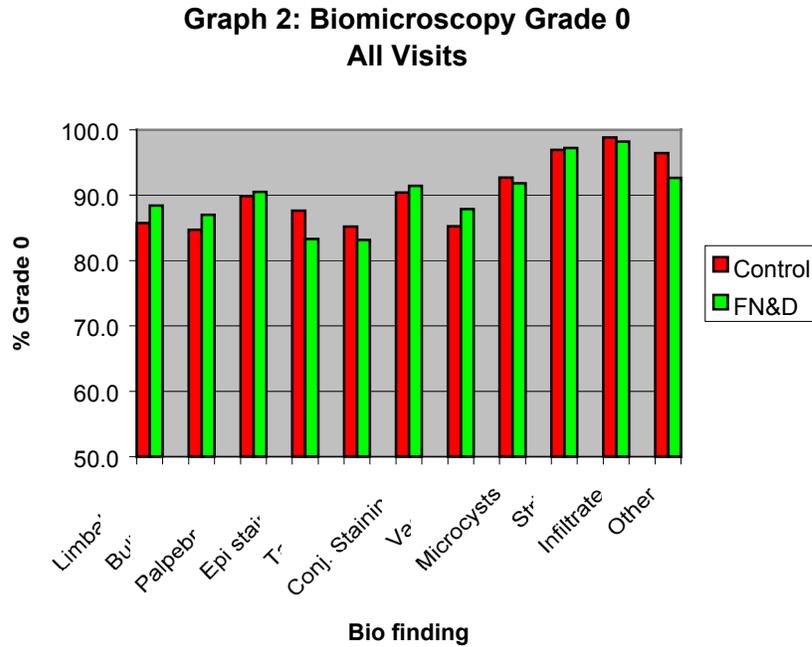
The unacceptable acuity with some FN&D lenses was examined early in the trial and found to be caused by poor optics in some of the lenses. Investigation showed that a small percentage of the lenses were stuck to the inside base of the foil pack and, upon removal from the foil pack, the optics of the lens was distorted. Appropriate corrective action was taken in the manufacture of the product to correct the problem.

For FN&D, the discomfort and lens fit discontinuations may be related. The FN&D lens was available in only one design (8.6/13.8) during this trial. In contrast, the control lens was available in multiple geometries (8.4 and 8.8 mm base curve for minus powers, 9.1 mm base curve for plus powers). Results show that in the minus powers both the control lens geometries were used extensively; 32% were dispensed with the 8.4mm base curve and the remaining were dispensed with the 8.8 mm base curve. Approximately 99% of all observations of lens fit in the dispensed FN&D group achieved an acceptable fit rating by the investigators. However, a flat fit with FN&D may also result in small amounts of edge lift, which may be better, judged by subjective reports of lens awareness or discomfort than by biomicroscopy observation. Of the 58 FN&D subjects discontinued for discomfort, 33 (57%) discontinued within the first week of being dispensed and a further 12 (21%) discontinued within the first month, indicating that the discomfort was present very early in the trial and likely due to a sub-optimal fit.

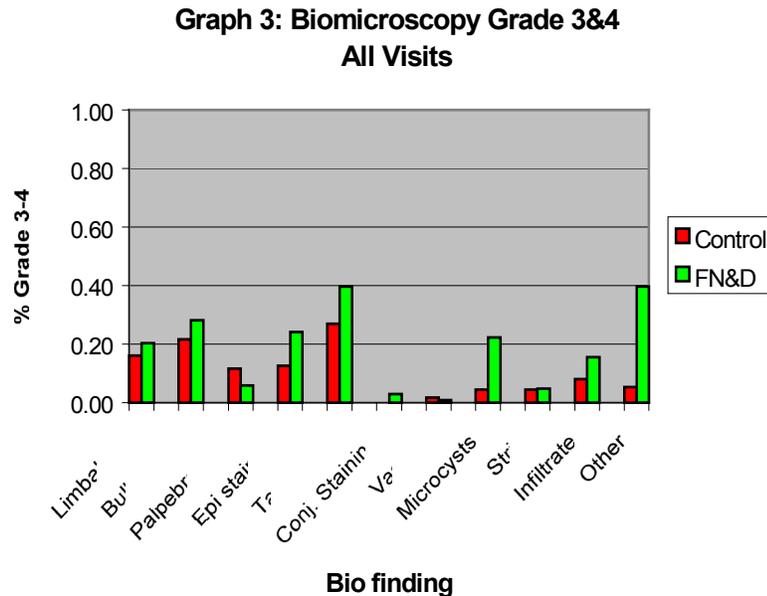
Sixteen (16) FN&D and 3 control subjects were discontinued for Positive Biomicroscopy. Of these, 5 FN&D and 1 control subjects were due to infiltrative endpoint adverse events. One (1) additional control subject was discontinued for Other- ulcer. Four (4) of the FN&D subjects were discontinued for contact lens-associated papillary conjunctivitis. These are all discussed in the following section.

Biomicroscopy

Overall, for all visits and all eyes, 90.1% of the FN&D and 90.3% of the control group biomicroscopy findings were rated as grade 0. Graph 2 shows the percent of Grade 0 slit lamp findings, by category, throughout the trial for all subjects and all visits.



Overall, for all visits and all subjects, 0.2% of the FN&D and 0.1% of the control group biomicroscopy findings were rated as grade 3 or greater. Graph 3 shows the percent of Grade 3 and 4 biomicroscopy findings by category throughout the trial for all subjects and all visits.



Symptoms / Problems / Complaints

Overall, the type and frequency of symptoms were similar for FN&D and control group lenses and are considered typical of contact lens wear.

The most frequently reported symptom in both groups was dryness. The overall incidence rate for completed and discontinued control subjects was 24.2% and 21.9%, respectively. The overall incidence rate for completed and discontinued FN&D subjects was 19.8% and 13.4%, respectively. For all subjects and all visits, FN&D was statistically superior to the control lens in terms of showing fewer reports of dryness ($p < 0.001$, SAS proc mixed).

Some of the largest differences between the two groups was found in the discontinued subjects. Amongst the discontinued subjects, the control subjects had more complaints of dryness and FN&D subjects had more complaints of discomfort, burning/stinging and tearing. As previously discussed, this discomfort is likely related to sub-optimal lens fit due to the single lens geometry available for FN&D in this trial.

Keratometric / Refractive Changes

A total of 36 (3.1%) control group eyes and 45 (4.7%) FN&D eyes had keratometry measurements change by more than 1.00 diopter. The maximum change was 4.25 D with the control lens and 3.00 D with FN&D. Seventy one percent (71%) of the changes in keratometry over 1.00 diopter associated with FN&D resulted in corneal flattening, while

61% of the changes over 1.00 diopter associated with the control lens resulted in corneal steepening. Many of the explanations given by the investigator for these changes involved investigator and instrument error and recovery from or creation of corneal edema.

On average there was a trend for the control eyes to become more myopic (mean of -0.15 D for completed subjects) over the one year trial. This was not the case for FN&D, which had a small shift towards hyperopia (mean of +0.05 D for completed subjects).

A total of 11 control and three (3) FN&D eyes had a refractive error change greater than one diopter. Ten of the 11 (91%) control eyes increased in myopia. Reasons attributed to the changes in the control eyes included corneal edema, progressive myopia, myopic creep, and normal myopic progression. All 3 FN&D eyes had a decrease in myopia. Reasons included a reduction in corneal edema (2 eyes) and an over-minused refraction at baseline (1 eye).

Visual Acuity

Best-corrected spectacle visual acuity by eye was compared at the initial and final visits for all subjects. The results are similar for FN&D and control lenses. Two subjects, 1 FN&D (unspecified) and 1 control (edema), had a temporary reduction of vision of two Snellen lines or more of acuity at the final visit compared to the initial visit. At subsequent post-study visits, VA had returned to normal.

Contact lens visual acuity by eye was compared at the initial and final visits for all subjects. The final visit for discontinued subjects was considered as the last visit at which any data was collected. Visual acuities, which were not reported at the final visit, are due to subjects discontinuing without contact lenses being worn at this visit.

Of those eyes with a final contact lens visual acuity reported, 98.1% (1074/1095) of the FN&D eyes and 97.9% (1226/1252) of the control eyes maintained Snellen acuity within two lines of the initial visit lenses as measured with contact lenses at the final visit. Of these, an improvement of more than one Snellen line of acuity with lenses worn at the final visit was reported for 3.0% (33/1095) of the FN&D and 1.0% (12/1252) of the control eyes.

Practitioner-reported reasons for the reduction in acuity with the control lens included changes in refractive status, deposits, and optical defects. Practitioner reported reasons for the reduction in acuity with FN&D included lens deposits, change in refractive status, and defective lenses.

Of those eyes with a final visual acuity reported, 83.0% (909/1095) of the FN&D eyes and 83.6% (1046/1252) of the control eyes had Snellen acuity of 20/20 or better as measured with contact lenses at the final visit.

Wear Time

The percentage of subjects reporting extended wear use of their lenses pooled across all monthly reporting intervals is summarized in Table 3.

Table 3: Nights in a Row Slept in Lenses

Consecutive Nights	Completed Subjects		Discontinued Subjects	
	FN&D %	control %	FN&D %	control %
0 – 2	1.5%	0.2%	5.9%	2.3%
3 – 4	1.0%	2.7%	3.7%	4.0%
5 – 7	2.0%	92.4%	7.8%	85.1%
8 – 14	6.9%	N/A	16.9%	N/A
15 – 21	14.0%	N/A	17.7%	N/A
22 – 31	67.2%	N/A	28.9%	N/A
Not Reported	7.3%	4.7%	19.0%	8.6%

The proportion of subjects wearing their lenses in any extended wear modality with FN&D is similar to that achieved with the control lens. A total of 88.1% of FN&D subjects reported wearing periods of greater than 7 days of continuous wear. Of these, the majority of completed FN&D subjects achieved wearing times between 22 and 31 consecutive nights. Discontinued subjects showed generally shorter wearing periods for both groups. This is not unexpected as some of these subjects were experiencing problems or symptoms and adjusted their wearing time accordingly.

Lens Replacements

Unplanned lens replacements occurred at comparable frequencies for both the test and control lenses for all reasons, except comfort. With regard to comfort, FN&D had a 2.5% replacement versus control's 0.4% rate.

B. FN&D One Week Extended Wear Safety and Efficacy Study (a separate study)

1. Objective

The objective of this clinical trial was to determine whether the FN&D lens, when worn for up to one week extended wear and replaced on a monthly basis, performed as well as or better than the control lens, when worn for up to one week extended wear and replaced on a weekly basis. Data from this study was included by reference into this PMA from a separate PMA submission, P000030.

2. Study Design

This clinical trial was a prospective, randomized, control led, open label clinical trial lasting one year. A total of 450 subjects (305 test and 145 control) were enrolled at 20 investigational sites throughout the United States. Approximately fifteen test and eight control subjects were to be enrolled at each site. Subjects were randomized to wear either the test or the control lens bilaterally for one year.

The primary safety endpoint analysis was based on the proportion of subjects in each group who developed corneal infiltrates with overlying fluorescein staining and/or grade 3.0 corneal infiltrates if no overlying staining was present. To guard against bias, the dropout rates for each group were compared. A Cox Model was used to consider all data from all subjects (including dropouts). The Cox Model involves using life table methods to incorporate the exposure time of the discontinued subjects. The primary efficacy endpoint analysis was based on the proportion of subjects in each group able to successfully maintain the extended wearing schedule. This was calculated using the percent of participants that reported at least 6 consecutive nights of lens wear at the 1, 3, 6, 9, and 12 month visits.

Other primary safety data collected during the study included:

- Adverse events
- Discontinuations
- Biomicroscopy
- Subjective symptoms and problems
- Keratometric and refractive changes
- Best-corrected acuity

The primary efficacy data collected during the study included:

- Wearing time and temporary interruptions of lens wear
- Contact lens visual acuities (Snellen)

Subjects were eligible for study participation if they were at least 18 years old, signed informed consent, and complied with inclusion and exclusion criteria specified in the protocol. Pregnant or lactating women were included in the study as these individuals comprise a significant portion of the contact lens wearing population.

The study population consisted of subjects representative of the general population attending offices for contact lens care. Of the subjects enrolled, 290 test and 145 control subjects were dispensed lenses. The study population ranged in age from 18 to 61 years (Test mean=34 years, control mean = 33 years). Lens power ranged from -1.00 D to -6.50 D (Test mean = -3.23 D, control mean = -3.41 D). Only 26 subjects were neophyte lens wearers. Previous

experience was considered successful for 404/409 (98.8%) of subjects who reported prior lens wear.

Gender distribution consisted of 66% (191) females in the FN&D group and 76% (111) females in the control group. Although each distribution can be considered representative of the contact lens wearing population, the difference is statistically significant. There was no evidence of any violation in the randomization process that would explain this difference.

3. Subject Assessments

At each study visit, subjects were given enough lenses to last until the next study visit, allowing for scheduled and unscheduled lens replacements. All other visits for any reason were recorded as Unscheduled Visits. Follow-up visits were scheduled for 24 hours, 1 week, and 1, 3, 6, 9, and 12 months after starting extended wear.

Adverse events were defined as any undesirable clinical occurrence in a subject whether it was considered to be device related or not. Adverse events were classified as adverse device effects, undesirable side effects, or other serious adverse events according to criteria specified in the protocol.

Discontinuations could be due to a variety of reasons such as best interest of the subject, voluntary withdrawal by the subject, protocol deviations, lack of follow-up (lost-to-follow-up = 2 consecutive visits missed), relocation, neophytes who had not initiated extended wear within 45 days of enrollment, and if subjects switched from extended to daily wear indefinitely. Completion was defined as wearing the test or control lenses for 12 months after initiation of extended wear and the subject had the required evaluations performed.

4. Demographic Data

The dispensed study population ranged in age from 18 to 61 years (mean = 33-34 years). Gender distribution consisted of 66% (191) females in the FN&D group and 76% (111) females in the control group.

5. Data Analysis and Results

Adverse events were defined in the protocol as Adverse Device Effects (ADE) and Undesirable Side Effects (USE). Table 1 shows the number and percentage of adverse reactions, USEs, and any other treatments for each treatment group.

Table 1: Summary of Adverse Reactions, USEs, and Any Treatment

	Completed				Discontinued			
	FN&D N	EW Lens %	control N	EW Lens %	FN&D N	EW Lens %	control N	EW Lens %
Sample Size								
Subjects	235	100%	130	100%	55	100%	15	100%
Eyes	470	100%	260	100%	110	100%	30	100%
One or More Adverse Reactions								
Subjects	0	0.0%	1	0.8%	0	0.0%	1	6.7%
Eyes	0	0.0%	1	0.4%	0	0.0%	1	3.3%
One or More USEs								
Subjects	32	13.6%	19	14.6%	7	12.7%	5	33.3%
Eyes	49	10.4%	27	10.4%	13	11.8%	7	23.3%
Any Treatment								
Subjects	14	6.0%	8	6.2%	4	9.1%	0	0.0%
Eyes	25	5.3%	10	3.8%	6	5.4%	0	0.0%

No Adverse Device Effects were reported for the FN&D lens. Two (2) cases of Adverse Device Effect were reported for the control lens. Neither subject had permanent loss of vision. A total of 39 FN&D (15.2%) and 24 control (16.6%) episodes of Undesirable Side Effects (USE's) occurred during the trial.

The percentage of completed subjects who received any treatment other than for an ADE or USE (including temporary interruption of lens wear) was similar for FN&D (6.0%) and control (6.2%) lens wearers. For discontinued subjects, any treatment was provided to four (9.1%) discontinued FN&D subjects, but no discontinued control subjects. The types of conditions treated were similar for the two treatment groups.

The percent of subjects discontinued is based on the number of subjects dispensed. Overall, 55 (19.0%) of FN&D subjects and 15 (10.3%) control subjects discontinued from the trial. FN&D had a higher discontinuation rate due to discomfort and fit. The FN&D lens was only available in one design (8.6/13.8) during this trial. The control lens was available in two base curves (8.4 and 8.8 mm). Forty-two percent (42%) were dispensed with the 8.4mm base curve and the remaining lenses were dispensed with the 8.8 mm base curve. Although approximately 97.9% of the dispensed FN&D group achieved an acceptable fit rating by the investigators, an inadequate fit may also be judged by subjective reports of lens awareness or by observation of edge lift. Of the 27 subjects discontinued for discomfort, 23 (85%) discontinued within one week of dispensing. This indicates that the discomfort was present very early in the trial and likely due to a less than optimal fit.

Slit Lamp Findings:

Grade 0 slit lamp findings were reported for 89.8% of the FN&D and 88.3% of the control lens wearers for all subjects and all visits. Completed subjects with Grade ≥ 3 had a rate of $\leq 0.2\%$; whereas, a rate of $\leq 0.1\%$ was recorded for discontinued subjects. A mild trend was shown for FN&D to have a higher percentage of Grade 0 biomicroscopy findings for neovascularization, microcysts, and striae. This was attributed to the oxygen permeability profile of the FN&D material. FN&D also showed less limbal and bulbar redness.

The primary safety endpoint established for this clinical investigation was corneal infiltrates with any overlying staining and/or infiltrates $>$ Grade 2. A total of 12 (4.1%) FN&D and 14 (9.6%) control subjects had infiltrates throughout the clinical trial. Of these, 3.4% (10) and 5.5% (8) control subjects had corneal infiltrates \geq Grade 2. A life table analysis revealed that FN&D had a clinical trend towards being slightly better than control; however, this observation could not be proven statistically significant. For all infiltrates, with or without overlying staining, the life table analysis showed FN&D to perform both clinically and statistically better than control.

Symptoms/Problems/Complaints:

FN&D and control lenses performed similarly with respect to subject reported symptoms, problems and complaints. The most frequently reported symptom was dryness with an incidence rate of 21.3% and 14.6% for completed and discontinued subjects respectively in the FN&D group. The rates for completed and discontinued subjects in the control group were 25.0% and 23.9% respectively. Discontinued subjects in the control group had higher rates of complaint regarding dryness (23.9%) as compared to the FN&D group, 14.6%. FN&D had higher rates of lens awareness and discomfort that were probably related to the limited range of base curves available as compared to control.

Keratometric/Refractive Changes:

Keratometric (K) readings were relatively stable as compared to baseline readings. The mean change was +0.01D.

Visual Acuity:

Visual acuity showed that the test and control groups performed similarly. A total of 3 (1.0%) control and 10 (1.7%) FN&D eyes had a reduction in acuity of greater than one Snellen line with lenses worn at the final visit. Investigators reported that the reasons for acuity reduction with FN&D included lens deposits and accommodative problems from beginning presbyopia. None of the subjects had a loss of BSCVA. In contrast, 8 (2.6%) control and 18 (3.1%) FN&D eyes had an improvement of more than one Snellen line of acuity with lenses worn at the final visit. Analyses of BSCVA show similar profiles for both test and control lens groups.

Wear Time:

The primary effectiveness endpoint was the percentage of subjects in each group able to successfully maintain the extended wear schedule. For FN&D subjects, 91.8% were able to wear lenses for six (6) consecutive nights. For control subjects, 92.9% were able to wear lenses for 6 consecutive nights. There are no statistically significant differences for wearing time between the two lenses.

The rates for temporary interruption in extended lens wear were similar between the two groups. When subjects had more than one occurrence of interrupted wear; these were counted for each occurrence. There were a total of 27 control instances of prescribed temporary interruptions to contact lens wear during the trial affecting 26 subjects (17.9%). For the FN&D lens, there were 52 FN&D instances affecting 42 (14.5%) of the subjects. These interruptions were temporary, changed to daily wear, or temporary cessation of lens wear altogether.

Other Issues:

Subjects' opinions of the lens were rated on a scale of 1 to 10 with 10 being the most favorable outcome. The percentage of subjective ratings of ≥ 8 was similar for both groups for completed and discontinued subjects, with the smallest percentages for dryness and lens comfort upon awakening. The trend analysis profile also showed similar results between test and control lens groups.

Conclusions drawn from the Clinical Studies

FN&D lenses when worn for up to one month extended wear and replaced on a monthly basis were shown to be non-inferior to the control lens, worn for up to one week extended wear and replaced on a weekly basis in terms of the primary safety endpoint of infiltrates grade 3 or infiltrates with any overlying staining. No statistical differences were found in the incidence rates of adverse events. More FN&D subjects discontinued for lens fit or discomfort compared to control. More subjects reported contact lens papillary conjunctivitis with FN&D compared to control, but the rates were similar to rates published in the literature. Both the discomfort and papillary conjunctivitis may have been related to sub-optimal lens fits resulting from the single base curve used for FN&D in the trial. FN&D lenses were comparable to control for the incidence and severity of biomicroscopy signs, the incidence of subjective symptoms and problems, changes from baseline in refractive error and keratometry, and in maintaining best corrected visual acuity.

The percentage of eyes maintaining final Snellen contact lens visual acuity within two lines of their acuity at dispensing is comparable between the FN&D lens and the control. The FN&D subjects were comparable to the control subjects based on the proportion who were able to successfully maintain extended wear. A total of 88.1% of FN&D subjects reported wearing periods of greater than 7 days of continuous wear. Of these, the majority of

completed FN&D subjects achieved wearing times between 22 and 31 consecutive nights. Generally, fewer days of wear were pursued by subjects and practitioners when symptoms or signs warranted. This may indicate a good understanding and use of the *up to 30 nights* extended wear indication for subjects intolerant of the full indication. Reasons for interruption of extended lens wear, and temporary removals during the day were similar between FN&D and control. Based on subjective questionnaire data, FN&D lenses were found to be statistically superior ($p=0.02$, Student's *t* test) to control lenses in terms of fewer overall complaints of dryness, fewer unscheduled removals because of dryness, and higher subjective satisfaction with *No Dryness Upon Awakening*.

Based upon these findings, the FN&D lens has been shown safe and efficacious for the indication of correction of refractive ametropia and for use up to 30 nights extended wear.

XI CONCLUSIONS DRAWN FROM THE STUDIES

The results of the preclinical and clinical studies provide reasonable assurance of the safety and effectiveness of the FN&D soft contact lens for the subject population, refractive conditions and specified duration of wear. Although the potential exists for minor differences in physiological response by gender for the target population, minimal number of clinically significant findings does not indicate that gender differences are of clinical importance for this device.

XII PANEL RECOMMENDATION

At an advisory meeting held on July 20, 2001, the Ophthalmic Devices Panel, an FDA advisory committee, discussed the data collected from the 30 night clinical study submitted in P010019.

The six night clinical study was the subject of a separate PMA, P000030, which was included by reference into P010019. P000030 was not referred to the Ophthalmic panel for review and recommendation, in accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, because the information in P000030 substantially duplicates information previously reviewed by this panel.

The advisory panel recommended that CIBA Vision's P010019 for the FN&D soft contact lens for extended wear for up to 30 nights of continuous wear be approved subject to, and approval by, the Center for Devices and Radiological Health (CDRH) of the following:

- (1) Addition of clinical outcome data and additional statements related to device risk in the device labeling.
 - ◆ Include data that is specifically concerned with the incidence of giant papillary conjunctivitis (GPC) with the FN&D soft contact lens as compared to the control lens.

- ♦ Include information
 - on the timing of corneal infiltrates in the test and control lens;
 - on subjects who experience an infiltrates subsequently having a six times increase in the rate for a second occurrence and advising that more caution is required with these subjects;
 - on the annualized rates of corneal infiltrates; and,
 - on the fact that the risk of microbial keratitis in the Focus Night and Day lens has not been established and that post market studies are underway to determine the risk.

(2) Post-approval Requirements:

- ♦ A post market study should be undertaken to assess the long term rates of microbial keratitis and associated loss of vision

XIII CDRH DECISION

CDRH concurred with the Ophthalmic Devices Panel's recommendations of July 20, 2001, and issued a letter to CIBA Vision on September 18, 2001, advising that its PMA was approvable subject to an FDA inspection that finds the manufacturing facilities, methods and controls in compliance with the applicable requirements of the Quality System Regulation (21 CFR Part 820).

FDA issued an approval order on October 11, 2001. The applicant's manufacturing facilities were inspected on July 12 and September 27, 2001 and found to be in compliance with the device Good Manufacturing Practice regulations.

XIV APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

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

Postapproval Requirements and Restrictions: See approval order.