

**SUMMARY MINUTES**

**OF THE**

**OPHTHALMIC DEVICES PANEL MEETING**

**OPEN SESSION**

**October 3, 2003**

**Gaithersburg Marriott  
Gaithersburg, MD**

## **OPHTHALMIC DEVICES PANEL ROSTER**

**October 3, 2003**

Jayne S. Weiss, MD

Chair

### **Voting Members**

Arthur Bradley, PhD

Anne L. Coleman, MD, PhD

Michael R. Grimmatt, MD

Allen C. Ho, MD

Alice Y. Matoba, MD.

Timothy T. McMahon, OD

### **Deputized Voting Members**

Karen Bandeen-Roche, PhD

Marian Macsai-Kaplan, MD

William D. Mathers, MD

Oliver D. Schein, MD

Joel Sugar, MD

### **Consultants**

James P. McCulley, MD

R. Michael Crompton, JD, MPH, RAC

Industry Representative

Glenda V. Such, MEd

Consumer Representative

## **FDA PARTICIPANTS**

Sara M. Thornton

Panel Executive Secretary

A. Ralph Rosenthal, MD

Director, Division of Ophthalmic and ENT Devices

Malvina B. Eydelman, MD

Medical Officer,  
Division of Ophthalmic and ENT Devices

Gerry W. Gray, PhD

Statistician, Office of Surveillance and Biometrics

Donna R. Lochner

Chief, Intraocular & Corneal Implants Branch

Roselie A. Bright, ScD

Statistician, Office of Surveillance and Biometrics

## CALL TO ORDER

**Panel Executive Secretary Sara Thornton** called the meeting to order at 8:34 AM and welcomed everyone to the 106<sup>th</sup> meeting of the panel. After introducing the new panel member, **Dr. Oliver Schein** and acting industry representative, **R. Michael Crompton**, she requested that the remaining panel members introduce themselves. Following the reading of the conflict of interest statement, **Executive Secretary Thornton** stated that **Dr. Schein** was granted a full waiver to participate, while **Dr. James McCulley** was granted a limited waiver restricting him from voting. Other matters were considered concerning **Doctors: Bradley, Schein, Coleman, Grimmett, Ho and Weiss** and all of these panelists could participate fully in the meeting. **Ms Thornton** read the appointments to temporary voting status for **Doctors: Bandeen-Roche, Mathers, Sugar, Macsai-Kaplan and Schein**.

**Dr. Ralph Rosenthal** presented a plaque to **Dr. Alice Matoba** in recognition of the completion of her term as a voting member of the panel.

## OPEN PUBLIC HEARING

**Dr. Steven Schallhorn** stressed the need for surgical options besides laser in situ keratomileusis (LASIK), especially in patients with higher orders of myopia who are not good candidates for refractive surgery. He stated that patients with high refractive errors may not be good candidates because current technology induces a number of aberrations on the cornea which can result in visual symptoms. To make his point, he presented data on the quality of vision after refractive surgery.

## OPEN COMMITTEE SESSION

### Division Update

In his division update, **Dr. Rosenthal** announced the hiring of new employees: **LT CMD Lori Austin Hansberry, RN; Joseph Blustein, MD; Clay Buttemere, MD;** and **LTJG Brad Cunningham**, will be working in the Ophthalmic Devices Branch. **Ethan Cohen, PhD** will be shared with the Office of Science and Technology, while **Srinivas Nandkumar, PhD** and **Antonio Pereira, MD** will be working in the Ear, Nose and Throat Devices Branch.

### Branch Update

**Donna Lochner** stated that PMA P010059 was in its final stages of review with a decision expected in the near future on the Morcher GmbH endocapsular tension ring for use in capsular bag stabilization in patients with pseudo-exfoliation syndrome or situations involving compromised zonules. Also in final stages of review is PMA P03002, for C & C Vision CrystaLens, Accommodating Intraocular Lens. In the panel review in May 2003, the panel granted approvable with the conditions that the patient satisfaction data be stratified by pupil size and some labeling revisions be made. Another stipulation is that the lens should provide accommodative amplitude of about 1 diopter (D).

## Sponsor Presentation

**Pre-market approval application P030016: STAAR Implantable Contact Lens (ICL™)**  
**Dr. Helene Lamielle, Chief Scientific Officer**, introduced the concept of the implantable lens and the agenda for the company's presentation. She noted that the device was implanted into patients between 21 and 45 years old, who had preoperative myopias of -3.0 to -20.0 D.

Noting that the procedure is similar to standard cataract surgery, **Dr. Steven Slade, Clinical Investigator, Consultant to STAAR Surgical**, described the surgical implantation of the lens into the posterior chamber of the eye. He reviewed the study design, eligibility criteria, effectiveness parameters and safety parameters. Safety parameters included a preservation of best corrected visual acuity, slit lamp findings, intraocular pressure, contrast sensitivity with and without glare, and reports of complications in adverse events. Under the heading of accountability, he pointed out that 369 or 77.2% of the original number remained in the study after three years. The majority of the study was Caucasian (84.7%) with an average mean myopia of -10.1D before surgery. He went on to review various levels of preoperative myopia to show that most patients had rapid improvement in their visual acuity with good stability through out the study period. At the end of the study 95% of the entire cohort achieved at least 20/40 visual acuity and 99% were very, extremely, or moderately satisfied with the surgical outcome.

**Dr. John A. Vukich, Clinical Investigator, Consultant to STAAR Surgical** reviewed safety outcomes discussing best spectacle corrected visual acuity, complications and adverse events, lens opacities, inflammation, patient symptoms and contrast sensitivity. Visual acuity not only improved rapidly in the post-operative period, but was maintained throughout the three year study for both corrected and uncorrected vision. The most marked improvement in visual acuity was experienced by the patients with the worst myopia (greater than -15D). Perioperative and postoperative complications (<1.0%) were reviewed. No appreciable change in patient symptoms was noted during the study.

**Dr. Henry F. Edelhauser, Consultant to STAAR Surgical**, detailed the methodology for the specular microscopy readings of approximately 1300 images with a mean number of 93 cells counted in each image. Stressed corneas show changes that can be quantitated by percent hexagonality, pleomorphism, and coefficient of variation (CV). Furthermore, endothelial morphology has been shown to be the most sensitive measure of corneal endothelial stability. The STAAR ICL lens produces no change in hexagonal cells or coefficient of variation during the clinical trial, and a cumulative mean cell loss of 8.4% to 9.7% occurred at the end of the study. He concluded by stating that the STAAR lens did not appear to stress the cornea, and that the corneal endothelium appeared to stabilize between the third and fourth postoperative years.

**Dr. Vukich, Clinical investigator, consultant to STAAR Surgical**, concentrated his attention on the results from the group of patients who had myopias of greater the 15D. During this study, their mean postoperative spherical equivalent was reduced from -17.3D to -2.2 D for an average correction of 88% of pre-existing myopia. This group had the greatest risks of complications (retinal detachments, nuclear opacities and sub-capsular opacities), but also enjoyed the greatest benefits. He stated that STAAR is committed to long-term surveillance of the study population with regard to endothelial cell analysis; believes that a

comprehensive training program is an essential part of achieving successful outcomes and plans to require formal training and certification for all surgeons who use the device; believes that labeling can be developed to adequately communicate the risks as well as the benefits of the ICL.

### **Panel Questions for the Sponsor**

The panel had many questions for the sponsors. Did the age of the cornea affect endothelial cell robustness? Did studying cells in the center of the field measure what was occurring in the cornea when the damage may be peripheral? Other questions directed to **Dr. Edelhauser** concerned distribution of cells in the cornea and the loss rate of cells at which time the cornea cannot maintain itself. Other issues included: size and rotational changes in the lens, percentage of patients wearing contact lenses before surgery, performance of gonioscopy, lens-iris touch and pupil size.

### **FDA Presentation**

**Donna Lochner** presented the history of the approval process for this lens. Starting with the first panel meeting in October 23, 1998, she chronicled the development of the various parameters and tests that were established during this five year period. Finally, she thanked all the FDA participants in the review process.

**Dr. Malvina Eydelman** noted that this pre-market application was precedent setting. She then went on to summarize data the panel needed for the panel discussion. The points of concern were: lens opacification, the effect of surgical experience, vault measurements, the sizing of the intraocular contact lens from external measurements, safety and efficacy in high myopic patients, acute intraocular pressure rises in the early postoperative period and labeling issues. In addition she requested panel input on issues that would be common to all phakic IOLs, such as possible requirements for exclusion of subjects with low endothelial cell density as a function of age. With each of these points, she posed the FDA questions to the panel.

To better understand the effects of the implantable lens on the endothelial cell of the cornea, **Dr. Gerry Gray** analyzed specular microscopic data in subsets of patients in this study. He presented two key issues. The first one is: at what point in time can we say that any effect of the actual surgical procedure, whether it would be just due to surgical trauma and/or some amount of remodeling, would the cell loss be negligible? The second one is: Could we use the data to determine what might happen after 5,10, 20 years later? , It appears that the rate of endothelial cell loss between 3 and 4 years is no different than the annual rate before that, bearing in mind that there are only the 57 subjects at 4 years.

Dr. Gray posed two main questions to the panel. The first one asked if there was sufficient data to support the conclusion that the losses in the first three years are reflective of surgical trauma with some prolonged remodeling period that culminates in a stabilization after 3 years and if not, what minimum eyes in follow up would they they recommending to make that assessment. The second questions related to the anterior chamber depth (ACD) as a statistically significant predictor of endothelial cell loss. He asked whether the device is safe at various depths: 2.8 mm to 3.0 mm and greater than 3.0 mm.

## Panel Questions for FDA

**Dr. Weiss** was concerned and **Dr. Gray** confirmed that for the larger cohort groups, which would have more statistical strength, the study did not show a leveling off of cell loss in the cornea at three years. Dr. Bradley asked if an analysis had been done to find out how much of the variance was explained by the linear model Dr. Gray used. The number was not available at that time; Dr. Bradley asked that the number be made available then or after the meeting. **Dr. McCulley** questioned whether there was any statistical analysis assessing the variability in size and shape of the corneal cells. **Dr. Macsai** emphasized that a history of who in the study wore lenses and who didn't preoperatively would help in the analysis of endothelial cell data. She also thought that endothelial cell data analysis of the eyes that had secondary intervention would be important. **Dr. McCulley** stressed that the time for corneal endothelial cell remodeling after injury and the degree to which it is injury dependent or age dependent is critical in knowing how to interpret the cell density, shape and size changes.

## Additional Comments from the Sponsor

**Dr. Vukich** stated that eight of nine sites contributed endothelial cell data. The patients on whom endothelial cell data were collected included those with secondary interventions. The data on those with secondary interventions showed no difference in endothelial cell density

Although the sponsor did not measure pupil size directly, their contrast sensitivity testing at low light levels (when the pupil is larger), did not result in a demonstrable difference postoperatively.

## COMMITTEE DELIBERATIONS

### Primary Panel Reviewers

**Dr. Macsai** expressed concern that the vast majority of the study patients were Caucasian and that 65 eyes with preexisting conditions with exclusion criteria were still included in the study. She felt that data from those 65 patients would provide information that would help patients who might be treated in an off label manner. She recommended that limbal pathology be included in the exclusion criteria. She had concerns about the need for this lens in patients with -3 D myopia until she would see data that this is superior to refractive surgery already available. She is mainly concerned about the effect of the device on the endothelium particularly since young patients would have the implant for possibly up to 40 years which, according to Dr. Gray's chart, their endothelial cells would drop to a dangerous limit.

Dr. Macsai discussed the panel questions as follows:

1a. The greatest dilemma concerning this device is determining the minimal number of cells for a viable cornea and the long term effect of the device on the corneal endothelium.

1b. Citing the short anterior chamber depth correlation with endothelial cell loss, she recommended this device be placed in eyes with anterior chamber depths greater than 3.0 mm.

2. Lens opacification is proportional to surgeon inexperience, and therefore she suggested follow-up of the patients with lens opacification and the need for surgeon training prior to lens implantation. Also, If a patient has replacement surgery of the device, this group should be followed separately for endothelial cell loss.

3. She mentioned that the use of the horizontal white-to-white measurement in obtaining the anterior chamber depth measurement to determine the sizing of the lens , may not be accurate, and the sponsor might consider the use of a more accurate system for obtaining those critical measurements.

4. She does not recommend approval for the device in the younger study population with myopia between -15D to -20D. She felt that, in the absence of a developed guidance for the younger population, that approval at this time would arbitrarily set a standard for future studies. She concurred with revising the indications statement to read “reduction of” and not “correction of” myopia for this range.

5. She stated that, in general, the safety and effectiveness data support approval of the device from -3.0D to -15.0D. Because of her concerns about long term endothelial cell loss, she recommended that a warning be put in the labeling that endothelial cell counts be obtained pre and post operatively for a long time. If there is a decrease in the long term count, the device should be explanted to protect the patient from bullous keratopathy in the future.

6. Due to the occurrence of an acute rise in intraocular pressure after implantation of this device, **Dr. Macsai** recommended reexamination of the patients at 4 to 6 hours and again at 24 hours after surgery.

7. She asked that the Agency mandate pupil measurements in the future to give patients a better idea of whether there is a likelihood of glare and haloes postoperatively. Also, **Dr. Macsai** wanted to include a summary of the patient’s quality of vision questionnaire in the labeling.

**Dr. Sugar** found the accountability, efficacy up to the -15D range, and stability in the study to be good. He was concerned about the patients who required enlargement of their laser iridotomies post-operatively because of elevated intraocular pressures. The sponsor should develop a better means of assessing them, both their spacing and size, so that the patients won’t have the high pressure elevations noted in the sponsor’s presentation. While the number of retinal detachments and cataracts were appropriate for the population; however he had concerns that the removal and/or lens exchange may cause more progression of the anterior subcapsular cataract. More data should be collected in these cases. Anterior chamber depth of less than 3.0mm should be a contraindication for the surgery.

In the labeling of the device, the reason should be given for including the statement, “Surgeons should never touch the center of the optic with instruments when it’s in the eye”. Also, specific data should be given to substantiate the patients’ quality of vision assessment.

On the questions for panel discussion, he added:

- 1a. Additional endothelial cell loss data should be captured at four and five years after surgery.
- 1b. Anterior chamber depths of less than 3.0 mm should contraindicate implantation of this lens.

**Dr. Grimm** wanted the following information to be placed into the public record. The vault is not stable and changes with time, body position and during measurement. The crystalline lens is also changing in time, and touching of the two lenses may lead to cataractogenesis, pigment dispersions, inflammation and/or the disruption of the normal aqueous humor dynamics. It is unlikely that the device will remain stable in the eye for the life-time of use. There is valid scientific evidence indicating a lack of correlation between white-to-white measurements and sulcus dimensions and material facts to that effect should be included in physician labeling. The sponsor demonstrated no pigment dispersion in the study group, a finding that is not consistent with other comparable study groups. The lack of gonioscopy data and ultrasound data to determine angle anatomy alteration following implantation represent a major study design flaw. Another design error is the absence of pupil size measurements. Relevant analysis should have included the rate of visual aberrations with increasing optic pupil mismatch. Stratification of the patient's symptoms by lens optic diameter was not done and should be required for later review by the Agency. Because endothelial cell loss remains a risk, particularly for patients in their twenties, who may be at risk for running out of endothelial corneal cells during their life times, he recommended obtaining up to 5 years of data on the cohort, pre-approval to help determine if the loss stabilizes over time.

Labeling should include learning curve issues, the increased rate of vision loss with time for high myopes as compared to lower myopes, and patient and physician labeling should highlight the issue of possible increased intraocular pressures postoperatively. With regard to learning curve issues, he recommended course training or case supervision by an experienced surgeon for early cases. He would exclude patients with anterior chamber depths less than 3 mm from this study.

## **PANEL DISCUSSION**

The discussion has been placed in numerical order for clarity; however, the actual discussion did not occur in sequential order.

**1a. Is there sufficient data to support the sponsor's conclusion that losses in the first three years are reflective of surgical trauma with prolonged remodeling, culminating in stabilization of cell loss after three years? If not what are the minimal number of eyes and minimal length of follow-up that you can recommend for assessment?**

There was panel consensus that there are no data demonstrating stabilization of cell loss between 3 and 4 years. They discussed having a pre-market or post-market study to follow the initial cohort of 206 who had pre-operative specular microscopy for a total of 5 years. The cohort would have annual specular microscopy examinations to determine the amount of endothelial cell loss.

The panel took up the concern over safety which focused on the rate of endothelial cell loss. Two methods of approval were discussed

1. The device is approvable now with post-market surveillance to include four and five year endothelial cell counts.
2. The device is approvable at four years, providing the data is acceptable, and the post-market surveillance will occur at five years.

The panel was in agreement that patients should be checked for a minimal endothelial corneal cell count before undergoing surgery. The panel was divided on whether to ex-plant the lens if the cell count continued to drop and whether labeling should reflect that the patients be followed with periodic cell counts.

**1b. Do the outcomes of the endothelial cell density analysis provide reasonable assurance of safety for this device for eyes with 1) ACD (anterior chamber depth) of 2.8 to 3.0 mm and 2) ACD greater than 3.0 mm?**

The majority of the panel thought that this surgery should be limited to eyes with ACD greater than 3 mm.

**2a. Do you believe the three year follow-up is sufficient to establish a lens opacification profile associated with this device?**

The consensus of the panel was, yes. Labeling should be added that states that there is a lack of data on the impact of removing and/or replacing the lens on the endothelium and on cataract progression.

**2b. Do you believe surgical experience to be an important factor in ASC development secondary to surgical trauma: If yes, do you believe future users of this lens should be required to undergo special training?**

While the panel realized that the FDA cannot mandate a particular training program, the panel agreed that training should be mandated.

**2c. Do you agree with the recommendation for replacement of the device only in cases of poor vault that exhibit early ASC with UCVA worse than 20/50?**

The panel did not know the answer.

**3. Do you find the method currently recommended by the sponsor for determining the overall diameter of the ICL appropriate?**

**Dr. Sugar** proposed no change in the white to white measurement, while **Dr. Macsai** wanted the sponsors to use the ORB Scanner. Since the question was meant to reflect whether the current measurement technique was adequate, **Dr. Weiss** stated it was what was available.

**4a. Does the safety and efficacy data for the eyes with preoperative myopia greater than -15D to -20D support approval of this refractive range.**

There was a consensus that this device was efficacious in this range of myopia, however most members were uncertain about the safety.

**4b. If approval is recommended for the patients in 4a, should the term “correction of”, as it relates to refractive range be changed?**

The consensus of the panel was to use the words, “reduction of.”

**5. Do the safety and effectiveness outcomes support approval of the ICL for eyes with the following preoperative MRSE: 1) -3.0D to -7.0D 2) -7.0D to -1.0D 3) -10.0D to -15.0D?**

If there is no issue with the endothelial cell count data, the majority of the panel found the device safe and efficacious for the range: -3.0D to -15.0D.

**6. Do you believe specific recommendations regarding postoperative follow-up are needed in the labeling due to acute intraocular rises in the early postoperative period?**

**Dr. Coleman** recommended iridotomies two to three weeks before surgery with confirmation of the patency of the iridotomies prior to implant along with having the patients off of steroids. Postoperatively she recommended thorough washing of viscoelastic from the anterior chamber and postoperative pressure checks at 4-6 hours, 24 hours and 48 hours. The panel members disagreed with the specific timing, but generally agreed with the overall method of care.

**7. Do you have any additional labeling recommendations?**

The panel had numerous suggestions concerning changes and additions to the current labeling, which is summarized in the section below labeled “VOTE”.

**Dr. Rosenthal** wanted to hear a discussion on the concerns of the panel about myopic eyes in the -15D to -20D range. Since there were a small number of study patients in this range, all of the complications may not have been expressed in this group. This patient group showed the greatest benefit and also the greatest risk, however, they expressed the greatest satisfaction with their post-operative results. A majority of the panel also thought that the 15D to -20D range should also be included.

## **OPEN PUBLIC HEARING**

No one came forward to speak at this time.

## **FDA CLOSING COMMENTS**

**Don Calogero** wanted to clarify that the actual rates of endothelial cell loss that this sponsor has from 3 months to 3 years are very different than the levels that ANSI and ISO have which were those discussed and recommended at previous panel meetings

## **SPONSOR CLOSING COMMENTS**

**Dr. Slade** closed by noting this study suggests endothelial loss stabilization. Their measurements of hexagonality and coefficient of variation support absence of endothelial stress. Not only does the lens material have a proven record, but the insertion of this lens is similar to

simplified cataract surgery. Throughout the study there has been no evidence of inflammation, corneal stress or instability. Reasonable safety for this device is suggested by the higher density of cells and probable existence of stem cells in the periphery of the cornea.

**Dr. Weiss** thanked the sponsor, primary reviewers, and the members from the FDA who participated in this review and discussion.

## VOTE

**Executive Secretary Thornton** read the voting rules and options. **Dr. Sugar** moved to recommend the device as approvable with conditions. **Doctors Mather** and **Macsai** seconded the motion.

The panel then discussed two major conditions.

1. Post-market collection of endothelial cell data to be performed annually up to and including five years after surgery on the existing cohort. The panel passed the condition with a six-to-five vote.
2. A post market study should be made on a new cohort of patients for up to three years to determine the incidence of cataracts, retinal detachments elevated intraocular pressure and glaucoma. This motion passed with a ten-to-one vote.

Due to the question of long term safety of this device, **Dr. Rosenthal** discussed recalling the device after PMA approval. **Ms Lochner** explained the FDA would have the options of asking for mandatory recall of the product or asking the company to recall the product.

**Dr. Macsai** moved that at the 4 and 5 year checkup of the cohort patients being followed postmarket that the sponsor should also perform gonioscopy and examination of the lens. The panel passed the motion unanimously.

A brief listing of concerns to be included in the studies noted in the previous motions was read by **Dr. Weiss** to include:

1. Preoperative endothelial cell count must be normal for age to qualify for surgery.
2. Serial endothelial cell count in the postoperative period.
3. No surgery on eyes with anterior chamber depth less than 3.0 mm.
4. Information on specular microscopy and cataracts from the post-market study of new patients..
5. Check intraocular pressure within 24 hours postoperatively.

Labeling changes were then listed:

1. Statement: The rate of endothelial cell loss has not yet been documented.
2. Statement: Long term development of glaucoma, synechiae and pigment dispersion is not known.
3. Inclusion of various wording changes.
4. Exclusion criteria: Limbal pathology.
5. Include: The incidence of glare and halos.

5. Statement: higher inverted lens rates and cataract formation with less experienced surgeons.
6. List: More severe complications by per patient and not per eye.
7. Precaution: regarding pigment dispersion.
8. Include: Information on the 65 eyes that were excluded from the cohort.
9. Statement: Risk for retinal detachment remains unknown.
10. Remove Statement: "Improves" quality of vision.
11. The indications statement should state that when the procedure is performed on patients with <15D myopia that the device "corrects" myopia; for patients with >15D of myopia, the device "reduces" myopia.
12. Statement: Patients with higher myopia have lower efficacy and higher risk.
13. Warning: Long term effect of lens on corneal endothelium is not known for all patients.
14. Explain what "diopter" is and do not use abbreviations.
15. Warning: Effect of pupil size on visual results with this device is unknown.
16. Statement: Postoperative medications should be used promptly to avoid elevated intraocular pressure.
17. "Contact" should not be used in the name of the product.
18. It is not known if removing the lens causes further complications.
19. Information from the sponsor on accuracy in axial length measurements.
20. Mandating surgeon training.
21. Efficacious "for improving," not "correcting" myopia above -15D.
22. Intraocular pressure may increase if viscoelastic is not rinsed out.

**Dr. Macsai** moved to approve the above condition regarding the labeling changes,  
**Dr. Bradley** seconded the motion. The panel passed these items in a ten-to-one vote.

The panel next voted on the main motion with the aforementioned conditions. The vote was 8 to 3 that PMA P030016 was approvable with conditions.

**Dr. Weiss** poled the panel for the reasons for their votes. All of the members felt that the device was reasonably efficacious. The long term safety issues prevented three members from approving the device.

## **ADJOURNMENT**

**Ms. Thornton** stated that the schedule of the next meetings will be on the web. She went on to thank the panel for their perseverance in this review.

**Dr. Weiss** adjourned the meeting at 5:58 PM.

I certify that I attended the meeting of the Ophthalmic Devices Panel on October 3, 2003, and that this summary accurately reflects what transpired.

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Sara M. Thornton  
Panel Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

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Jayne S. Weiss MD  
Panel Chair

Summary Minutes prepared by  
Lynne Blei  
8916 Burdette Road  
Bethesda, MD 20817  
(301) 365-4031  
captainblei@comcast.net