Appendix F: Literature Review on Accommodative Assessments of the Crystalens Accommodative IOL

Since the approval of the parent IOL, there has been much discussion in the published literature about the true accommodative ability of this lens platform. This is because of the limited data regarding accommodative amplitude that was presented for the parent IOL approval. In addition, there have been significant improvements in the methods for measuring accommodative amplitude since the approval of the parent Crystalens IOL.

The Crystalens was designed to move forward along the axis of the eye in response to contraction of the ciliary muscle (accommodative effort). However, the Applicant acknowledges that the exact mechanism of action has not been fully elucidated. It has been proposed that part of the mechanism of action of the Crystalens is not due to a true overall focal shift, but to increased aberrations or astigmatism (from tilt) related to ciliary muscle contraction¹.

FDA conducted a systematic literature review to assess the issue of accommodation related to the Crystalens Accommodating IOL by searching and evaluating the existing clinical literature. The search strategy was developed by DEPI and DOED clinicians and engineers. Three major databases, EMBASE, MEDLINE and Pubmed were used, the search terms includes the ‘crystalens’ and all its model names/numbers, limiting human studies and studies in English. The time period covered is from 2000 and 2012. Here is the full search term:

crystalens OR (crystalens AND toric) OR (iol OR (intraocular AND lens) AND (at50 OR 'at-50' OR at50ao OR 'at-50ao' OR at52ao OR 'at 52ao' OR at52se OR 'at0-52se' OR at-50se OR at50se OR 'at-45' OR at45 OR 'at-45se' OR at45se OR 'at45-hd100' OR 'at-45-hd100' OR ao1uv OR 'ao-1uv' OR ao2uv OR 'ao-2uv')) AND [humans]/lim AND [english]/lim AND [2000-2012]/py

A total of 131 articles were found from the three major databases, from year 2000 to year 2012. Excluding one article that is a duplicate (published on two different journals); 42 unrelated to this device; 42 non-studies; and 4 non-English, there are 42 unique papers identified.

On February 7, 2013 the Pubmed search was updated and one additional article was captured that was included in our analysis. Of these 43 articles, only ten articles discussed measurement of the amplitude of accommodation with a Crystalens model. Please note that other published articles assessed near acuities, but did not attempt to measure amplitude of accommodation. These were not covered by this review. Three articles discussed exclusively subjective measurements of accommodative amplitude. All three of these studies were done by assessing defocus curves using the Crystalens HD model.² ³ ⁴ These are not discussed here, because the HD model uses a unique optical design that confuses the issue of subjective accommodation assessment.⁵ The seven remaining articles all used methods of objectively assessing accommodation and three of
these also used subjective measures. However, we note that subjective methods are subject to the same limitations as acuity measurements.

The objective measurements were of three basic types.

1. One study used a dynamic retinoscopy methodology that is not well defined in the article. In addition, it reports an unusually high accommodation value for the control monofocal lens (0.91 ± 0.24 D), raising some concern about this methodology.

2. Four studies measured changes in anterior chamber depth (ACD) in response to accommodative stimulus (pharmacologic or near visual stimulus). [It should be noted that stimulation with pilocarpine is thought to elicit an artificial and much stronger ciliary muscle response than is normally attained with visual stimulus.]

3. Three studies measured optical dioptric changes using a dynamic aberrometer or refractometer/autorefractor. Two of the three studies using these optical methods involved less than 5 eyes. (One of these small studies measured both ACD changes and dioptric changes, as well as small haptic angulation changes.)

Only three studies used a control group (monofocal IOL): the one using dynamic retinoscopy, one using a dynamic aberrometer, one using ultrasound biomicroscopy (UBM). For the objective evaluations, the latter two studies by Marchini\textsuperscript{6} and by Zamora-Alejo\textsuperscript{5} appear to be strongest based upon methodology. See table below.
## Table: Accommodation Studies Summary

<table>
<thead>
<tr>
<th>Objective Method</th>
<th>Primary Author</th>
<th>N</th>
<th>Time postop</th>
<th>Crystalens Model</th>
<th>Control Pharm Agent For Near stim.</th>
<th>Objective Measurement</th>
<th>Subjective Amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement of Change in ACD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial Coherence interferometry</td>
<td>Koepl et al⁷</td>
<td>30 eyes 18 pts</td>
<td>3 mos</td>
<td>AT-45</td>
<td>-- pilo</td>
<td>backward movement (no acc)</td>
<td>--</td>
</tr>
<tr>
<td>UBM</td>
<td>Marchini et al⁸</td>
<td>20 eyes 14 pts</td>
<td>3 mos*</td>
<td>AT-45</td>
<td>--</td>
<td>0.32 mm</td>
<td>1.08 D</td>
</tr>
<tr>
<td>UBM</td>
<td>Marchini et al⁸</td>
<td>29 eyes 19 pts in AT-45 (≈ in each arm)</td>
<td>12 mos*</td>
<td>AT-45</td>
<td>mono-focal IOL</td>
<td>0.17 mm</td>
<td>1.19 D</td>
</tr>
<tr>
<td>[also see Stachs, below]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aberrometry/ Refractometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartinger Optometer (also 3D ultrasound to measure ACD)</td>
<td>Stachs et al⁹</td>
<td>4 eyes</td>
<td>1 mo.</td>
<td>AT-45</td>
<td>-- pilo</td>
<td>0.44 D (also 0.13 mm ACD change)</td>
<td>--</td>
</tr>
<tr>
<td>Dynamic aberrometer</td>
<td>Tahir et al¹⁰</td>
<td>1 eye</td>
<td>29 mos</td>
<td>AT-52SE</td>
<td>--</td>
<td>No Defocus change</td>
<td>--</td>
</tr>
<tr>
<td>Dynamic autorefractor</td>
<td>Zamora-Alejo et al¹¹</td>
<td>20 eyes 10 pts in HD (≈ in each arm)</td>
<td>~3 – 4 mos</td>
<td>Crystalens HD</td>
<td>mono-focal IOL</td>
<td>Negative acc.</td>
<td>Negative Acc.</td>
</tr>
<tr>
<td>Dynamic Retinoscopy</td>
<td>Macsai et al¹¹</td>
<td>112 eyes 56 pts per arm</td>
<td>AT-45</td>
<td>mono-focal IOL</td>
<td>--</td>
<td>2.42 D</td>
<td>0.91 D</td>
</tr>
</tbody>
</table>

* also assessed at other time points
** monocular defocus method
The studies with measurement of ACD changes found changes between negative movement and about 0.3 mm. The second study by Marchini, was the only one with a control. This was also the only study in our list in which subjects were “randomized” into the treatment arms. Patients were pseudo-randomized into 3 arms: AT-45, a different accommodating IOL, and a monofocal IOL. The investigators measured 29 AT-45-implanted eyes and found 0.17 ±0.27 mm [mean ± SD] forward movement at 12 months and 0.24±0.17 mm movement at 1 month postoperatively. The study found approximately no movement in the monofocal control. No pharmacologic agent was used to stimulate accommodation in this study. It should be noted that there is not a 1 to 1 relationship between IOL forward movement and dioptric magnitude of accommodation. The relationship depends upon axial length, corneal curvature, IOL power, and other factors. Theoretical optical calculations indicate that dioptric change per mm can vary between about 0.8 D/mm to 2.3 D/mm. If a typical value is taken as 1.5 D/mm, then 0.2 mm movement corresponds to 0.3 diopters; 0.3 mm corresponds to 0.45 D.

The 2013 study by Zamora-Alejo et al. was the only aberrometry/refractometry study with any significant number of eyes (~20 eyes studied in each arm). Using a binocular open-field autorefractor, this study found mean accommodation to be slightly negative in both arms.

There were two studies with subjective measurements of accommodative amplitude that used control groups. The Macsai study was the largest study in this list with 112 eyes (56 patients) per arm, using the AT-45 Crystalens model and a monofocal control. Subjects were not randomized between treatments, but testing order was randomized and the tester was blinded. Using subjective defocus testing, the study found a difference in the mean monocular amplitude of accommodation between the two arms of ~1 diopter. The second Marchini study (59 subjects/80 eyes) was a prospective pseudo-randomized controlled study. Using minus lenses to blur (at distance), this study found that the control group had a slightly larger mean amplitude of accommodation than the Crystalens group. All groups showed approximately 1 diopter of amplitude at 1 and 12 months, with no differences between arms statistically significant.
References:


