UniversityHospital Heidelberg

# Report to HOYA:

# IOL optic material purity study (Vivinex project)

# (Confidential)

The study was performed at The David J Apple International Laboratory for Ocular Pathology, University of Heidelberg, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany and at the Institute of Applied Mathematics, Im Neuenheimer Feld 293, 69120 Heidelberg, Germany

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In cooperation with: Steinbeis Technology Transfer Center (IVCRC)

## 1. Research Objective

This research was carried out at the request of the IOL manufacturer. The objective was to independently determine the optical purity of the IOL material from Vivinex iSert XY1 (HOYA) in comparison to CT LUCIA 601P (Zeiss), AcrySof SN60WF (Alcon), Tecnis ZCB00 (AMO), Avansee PN6A (Kowa) and Aktis NS-60YG (Nidek) regarding glistening formation[1]. Glistenings are counted as MV/mm² and the severity of glistenings is graded according to the Miyata Scale[2].

## 2. Introduction

The Vivinex iSert XY1 is manufactured by HOYA Surgical Optics GmbH, De-Saint-Exupéry-Str. 8, 60549 Frankfurt am Main.
The CT LUCIA® 601P IOL is manufactured by Carl ZEISS Meditech AG, Göschwitzer Straße 51-52, 07745 Jena.
The AcrySof® SN60WF is manufactured by Alcon Pharma GmbH, Blankreutestraße 1, 79108 Freiburg.
The Tecnis® ZCB00 is manufactured by AMO Germany GmbH, Rudolf-Plank-Str. 31, 76275 Ettlingen.
The Avansee™Preset PN6A is manufactured by Kowa Company, Ltd., 4-14, 3-Chome, Nihonbashihoncho, Chuo-ku, Tokyo 103-8433, Japan.
The Aktis SP NS-60YG is manufactured by NIDEK Co. Ltd., 34-14 Maehama, Hiroishi-cho, Gamagori, Aichi 443-0038, Japan.
Five IOLs with a labelled power of +20.0 D of each mentioned model were subjected to accelerated in vitro glistening formation procedure[1].

## 3. Methodology

**Equipment:** EMZ-8TR Trinocular Zoom Stereo Microscope (Meiji Techno, Japan)
Camera INFINITY1-2CB (Lumen*era*® corporation, Canada)
Image analysis software DT-M. DT-Max iSolution (IMT i-Solution Inc., UK)

### 3.1. Accelerated in vitro glistening formation procedure

The lenses are immersed in water at 45°C for 24h (**Fig. 1A,B**). Afterwards the temperature is reduced to 37°C using a water bath (**Fig. 1C**). The lenses are incubated at 37°C for 2.5h. The lens samples are subsequently analysed and measured.

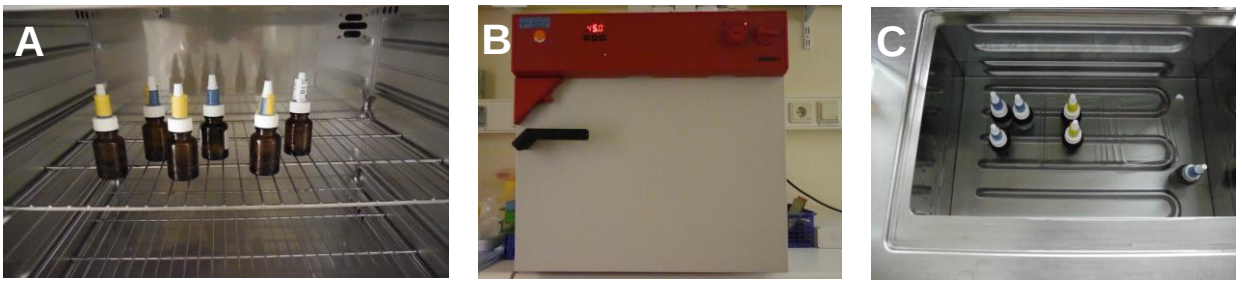



**Figure 1: A,B: The IOL samples are placed in an oven at 45°C±1°C. C: They are moved to a 37°C±1°C water bath where they are incubated for another 2.5 hours.**

After this time the samples are analysed under the microscope (**Fig. 2**). Using the digital camera two images are taken of each IOL:

- a fourteen-fold magnification of the total IOL is used to calculate the glistening density
- a ninetyfold magnification image which we use to evaluate the number of glistenings.

This evaluation of the number of glistenings is performed with i-Solution image processing software.

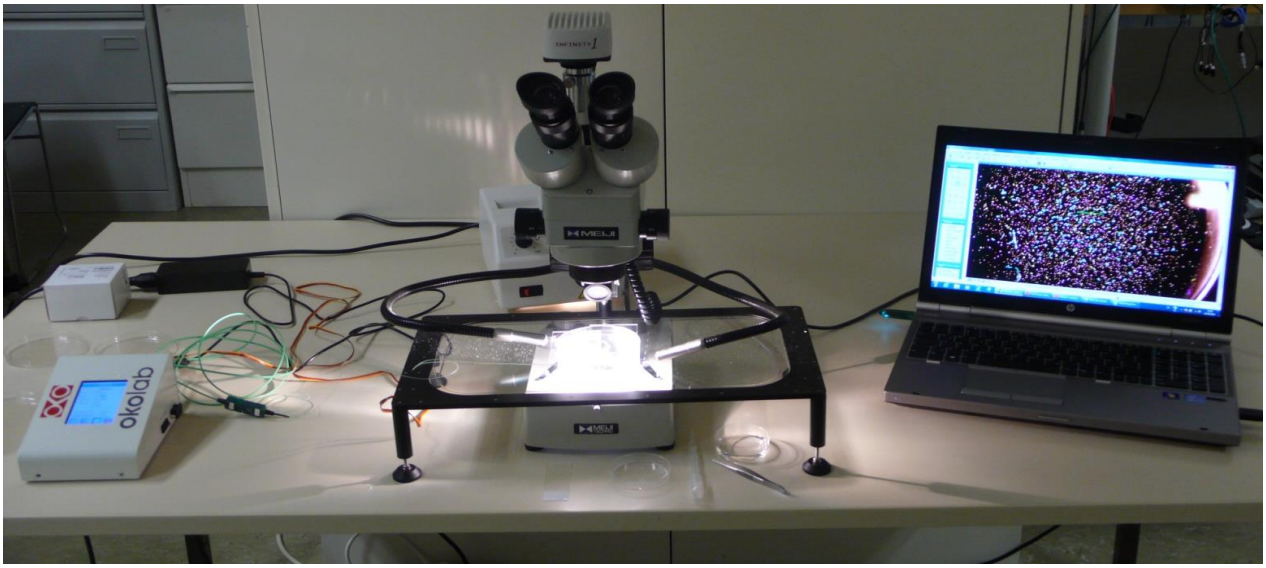



**Figure 2: The IOL samples are analysed under the microscope and images are taken with a digital camera.**

### 3.2. Image Processing

The images taken with the digital camera are analysed with the i-Solution software after the following treatments:

- The “noise” (irregular optical fluctuations that accompany the image of the glistenings but are not part of it and tend to obscure it) is removed by a smoothing procedure using the nonlinear median filter[3]
- Contrast and brightness are optimized

- A 'thresholding' procedure (**Fig. 3**) in which we define the threshold value which separates the image information in a binary image that means in a fore- and background[4]. Then, the objects (glistenings) are counted in the foreground, their mean area is evaluated and statistical outliers are removed.

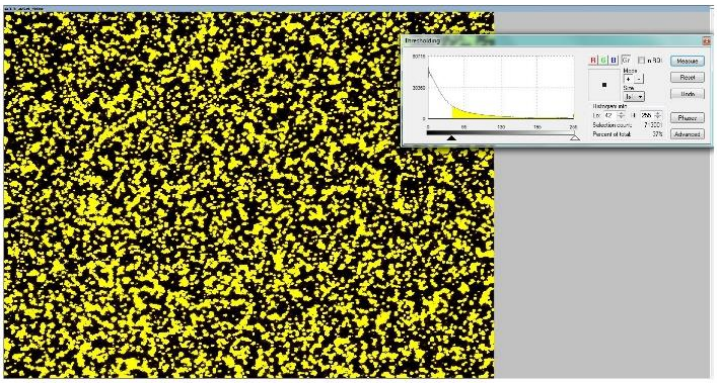


**Figure 3: Tresholding for an IOL transforms the image in a binary one: yellow is the foreground and black the background.**

Finally the glistenings are counted using the 'objects editing' procedure (**Fig. 4**) that is included in this i-Solution software package.
This evaluation is only suitable if the number of glistenings is moderate. If the number of glistenings is too high an alternative method for evaluation is used to separate them from their background. With the procedure 'objects editing' we count the glistenings in the area of focus and determine their size. The smaller objects in the background can be added to this amount. The larger objects consist of conglomerations of glistenings. Based on the histogram of each image we consider specific groups. For each group we develop a formula for the number of glistenings using the mean size of the object, their number and the real size of glistenings.

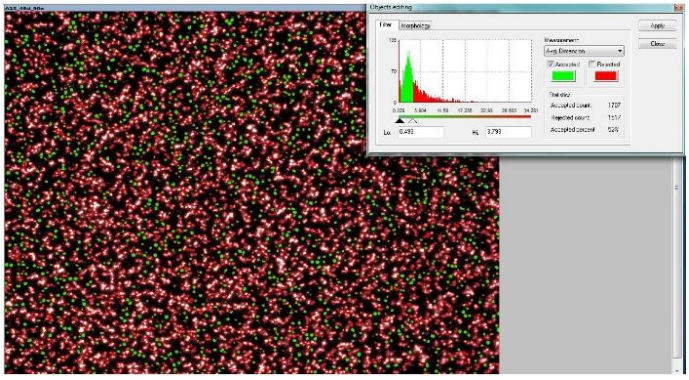


**Figure 4: Object counting for an IOL: glistenings in the area of focus (green) and glistenings of altered size: small ones in the background and conglomerations which have to be counted separately.**

### 3.3. Density Calculations

When we evaluate the number of glistenings using the image analysis is information localized in the IOL center, the region with the highest glistening density (**Fig 5A**). The resulting numbers also do not match with the real dimensions of the IOL. Prior to the calculations we have to calibrate these dimensions and calculate two conversion factors for each magnification. From the images with fourteen-fold magnification we calculate the area of the IOL occupied by the glistenings using the measured radius of this area and the calibration factor (**Fig. 5B**). To calculate the glistening density we take into account the curvature of the IOL, the measured glistening density from the ninetyfold magnification and the calibration factor. With this we get a formula for the glistening density measured in microvacuoles per square millimeter (MVs/mm²). To the density we assign a grade of glistenings severity according to the Miyata scale[2]. The IOLs are divided in four classes: IOLs with glistening of grade 0 (< 25 MVs/mm²), IOLs with glistening of grade 1 (> 25 MVs/mm² and < 100 MVs/mm²), IOLs with glistening of grade 2 (> 100 MVs/mm² and < 200 MVs/mm²) and IOLs with glistening of grade 3 (> 200 MVs/mm²).

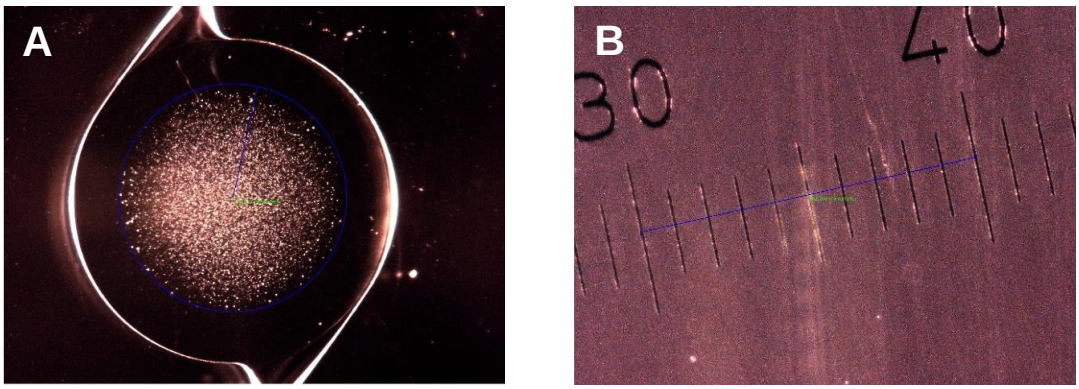



**Figure 5: A: Area of IOL occupied with glistenings after accelerated material deterioration tests and B: microscale used for calibration.**

## 4. Results and Analysis

### 4.1. Optical purity study

Stereomicroscope images (**Fig.6**) of all five IOLs from all manufacturers were taken immediately after incubation and the images underwent analysis with i-Solution software for calculation of total amount of microvacuoles within the lens. Subsequently, values were converted to MV/mm² (**Fig.7**). The severity of the glistenings was graded according to the Miyata Scale[2] (**Fig.8**) and the IOLs were compared with each other.

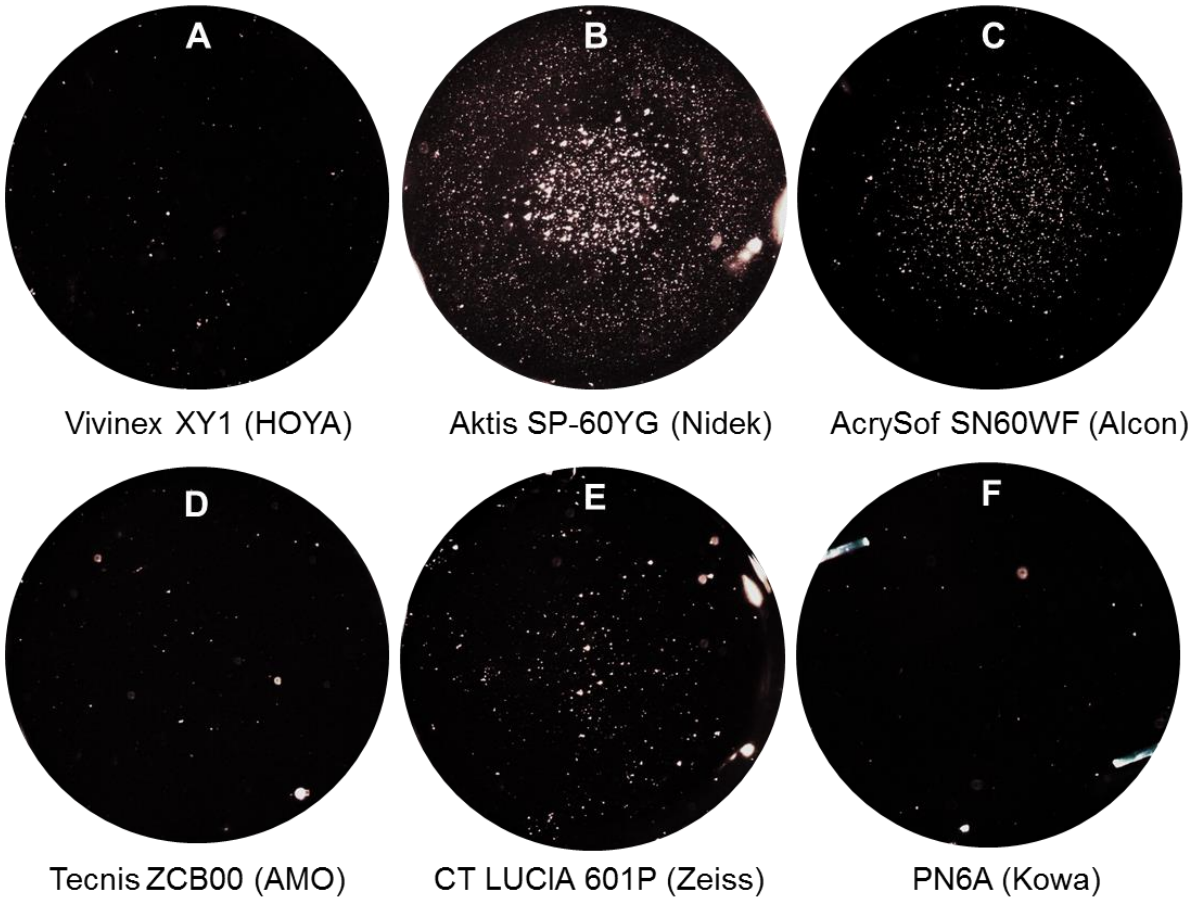



**Figure 6: Microscopic images of representative IOLs after glistening induction.**
**A: Vivinex XY1 (HOYA) – Severity grade 0, B: Aktis SP-60YG (Nidek) – Severity grade 3, C: AcrySof SA60AT (Alcon) – Severity grade 2-3, D: Tecnis ZCB00 (AMO) – Severity grade 0, E: CT LUCIA 601P (Zeiss) – Severity grade 0-1, F: AvanseePreset PN6A (Kowa) – Severity grade 0**

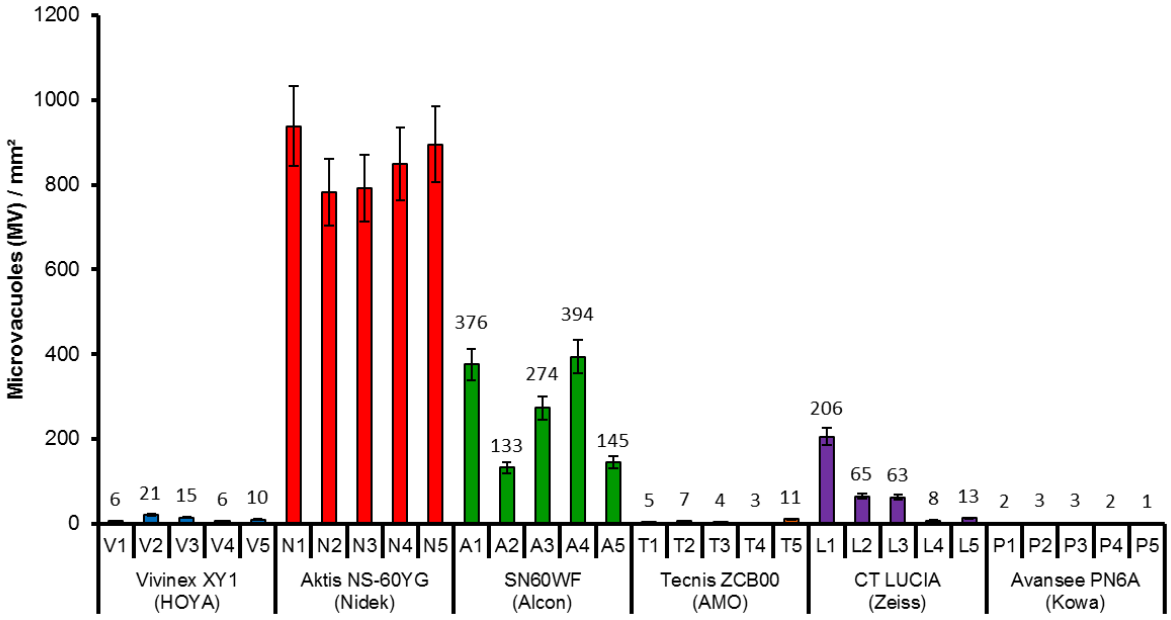



**Figure 7: Glistenings measured in units of microvacuoles / mm² on each single IOL**

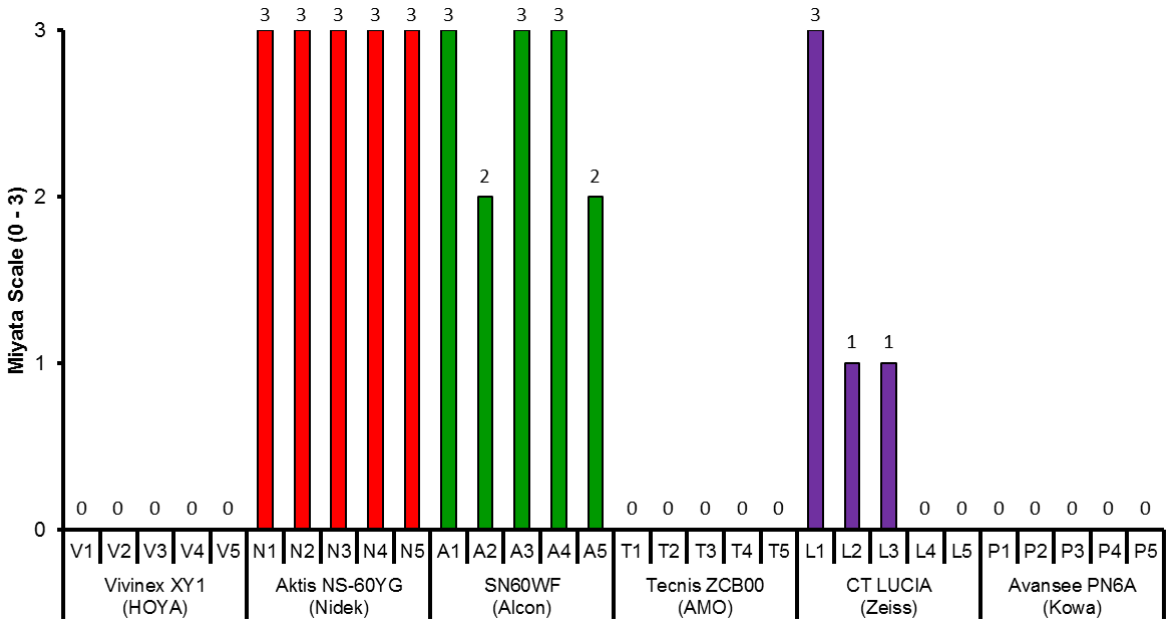
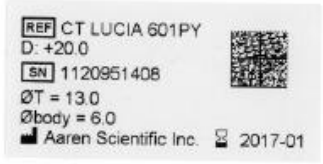
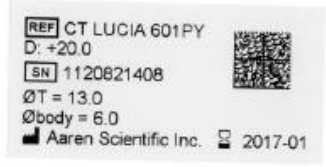
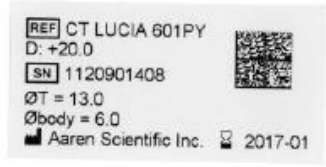
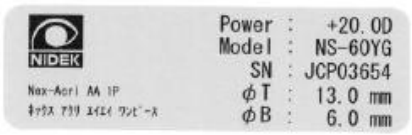
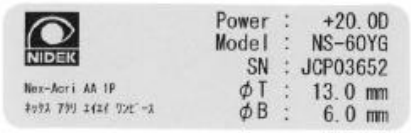
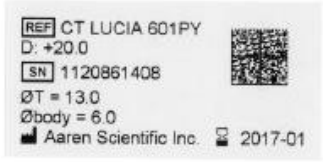
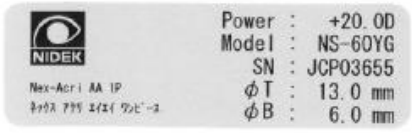
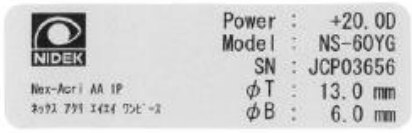
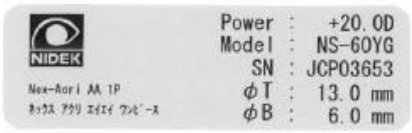



**Figure 8: Severity grade according to Miyata Scale for each single IOL**

**IOL Samples used in this study:**

| | | | |
|---|---|---|---|
| P1 | Kowa Model PN6A Power +20.0 D LOT IH7E026 Φ$_T$ 13.0 mm SN IH7E02633 Φ$_B$ 6.0 mm AvanseePreset アバンシィプリセット Acrylic Natural IOL | A1 | MODEL: SN60WF POWER: 20.0 D LENGTH(Ø$_T$): 13.0mm OPTIC(Ø$_B$): 6.0mm SN 21127382 096 EXP DATE 2020-02-29 UV WITH BLUE LIGHT FILTER AcrySof IQ IOL Alcon Laboratories, Inc. |
| P2 | Kowa Model PN6A Power +20.0 D LOT IH7E026 Φ$_T$ 13.0 mm SN IH7E02635 Φ$_B$ 6.0 mm AvanseePreset アバンシィプリセット Acrylic Natural IOL | A2 | MODEL: SN60WF POWER: 20.0 D LENGTH(Ø$_T$): 13.0mm OPTIC(Ø$_B$): 6.0mm SN 21127387 065 EXP DATE 2020-02-29 UV WITH BLUE LIGHT FILTER AcrySof IQ IOL Alcon Laboratories, Inc. |
| P3 | Kowa Model PN6A Power +20.0 D LOT IH7E026 Φ$_T$ 13.0 mm SN IH7E02634 Φ$_B$ 6.0 mm AvanseePreset アバンシィプリセット Acrylic Natural IOL | A3 | MODEL: SN60WF POWER: 20.0 D LENGTH(Ø$_T$): 13.0mm OPTIC(Ø$_B$): 6.0mm SN 21127387 090 EXP DATE 2020-02-29 UV WITH BLUE LIGHT FILTER AcrySof IQ IOL Alcon Laboratories, Inc. |
| P4 | Kowa Model PN6A Power +20.0 D LOT IJVE014 Φ$_T$ 13.0 mm SN IJVE01424 Φ$_B$ 6.0 mm AvanseePreset アバンシィプリセット Acrylic Natural IOL | A4 | MODEL: SN60WF POWER: 20.0 D LENGTH(Ø$_T$): 13.0mm OPTIC(Ø$_B$): 6.0mm SN 21127387 087 EXP DATE 2020-02-29 UV WITH BLUE LIGHT FILTER AcrySof IQ IOL Alcon Laboratories, Inc. |
| P5 | Kowa Model PN6A Power +20.0 D LOT IJVE014 Φ$_T$ 13.0 mm SN IJVE01439 Φ$_B$ 6.0 mm AvanseePreset アバンシィプリセット Acrylic Natural IOL | A5 | MODEL: SN60WF POWER: 20.0 D LENGTH(Ø$_T$): 13.0mm OPTIC(Ø$_B$): 6.0mm SN 21127387 086 EXP DATE 2020-02-29 UV WITH BLUE LIGHT FILTER AcrySof IQ IOL Alcon Laboratories, Inc. |
| V1 | HOYA Aspheric Yellow Model XY1 Ø$_T$ 13.0 mm Power +20.00D Ø$_B$ 6.0 mm SN 1CQ207K1 2018-02 | | |
| V2 | HOYA Aspheric Yellow Model XY1 Ø$_T$ 13.0 mm Power +20.00D Ø$_B$ 6.0 mm SN 1CQ207K2 2018-02 | | |
| V3 | HOYA Aspheric Yellow Model XY1 Ø$_T$ 13.0 mm Power +20.00D Ø$_B$ 6.0 mm SN 1CQ10WA7 2018-01 | | |
| V4 | HOYA Aspheric Yellow Model XY1 Ø$_T$ 13.0 mm Power +20.00D Ø$_B$ 6.0 mm SN 1CQ207J8 2018-02 | | |
| V5 | HOYA Aspheric Yellow Model XY1 Ø$_T$ 13.0 mm Power +20.00D Ø$_B$ 6.0 mm SN 1CQ10WA6 2018-01 | | |

| | |
|---|---|
| **T1**   | **L1**   |
| **T2**   | |
| **T3**   | **L2**   |
| **T4**   | |
| **T5**   | **L3**   |
| **N1**   | |
| **N2**   | **L4**   |
| **N3**   | |
| **N4**   | **L5**   |
| **N5**   | |

## 5. Discussion and Conclusion

Glistenings are fluid-filled microvacuoles that form within the matrix of the IOL when it is exposed to an aqueous environment[1]. They have mostly been reported in hydrophobic acrylic IOLs[1,5-9]. Thomes and Callaghan, using the same method used in our study, compared Alcon AcrySof IOLs from 2012 with Acrysof manufactured in 2003[1]. The laboratory-induced microvacuole density was significantly lower in the 2012 lenses (mean 39.9 MVs/mm$^2$) compared to the 2003 manufacture (mean 315.7 MVs/mm$^2$), (Wilcoxon test of significance, $P < 0.0005$)[1]. In our laboratory we studied a number of hydrophobic lenses using the methodology described here.

The new Vivinex XY1 lenses showed a very low number of glistenings (11.6 ± 5.7 MV/mm²). This refers to severity grade 0 on the Miyata Scale and can therefore be claimed to be "glistening-free". The Aktis SP-60YG material shows the highest amount of glistenings (851.4 ± 59.4 MV/mm²) and refers to severity grade 3+ on the Miyata Scale. The Tecnis ZCB00 (8.0 ± 2.8 MV/mm²) as well as the PN6A (2.2 ± 0.7 MV/mm²) show a comparable low number of glistenings as the Vivinex IOLs and also refer to severity grade 0 "glistening-free". The CT LUCIA 601P material was inconsistent (71.0 ± 71.6 MV/mm²) and refers to severity grade 0-1 on the Miyata Scale. The AcrySof SA60AT material showed a significant number of glistenings (264.4 ± 110.3 MV/mm²) and refers therefore to severity grade 2-3 on the Miyata scale.

It has to be emphasized that our study did not simulate temperature fluctuations in the human eye. Although glistening formation induced *in vitro* by alterations of temperature can produce morphological aspects that in general appear exaggerated in comparison to the clinical situation[10,11], *in vitro* studies are considered appropriate models to predict the clinical outcome[9]. It is uncertain that glistenings produced with such methods arise due to the same mechanism or are of the same kind as those observed in patients[1]. The rate of the temperature fluctuation seems to have a significant effect on the extent of glistening formation. Although *in vitro* analysis might provide an assessment of the tendency of a material to form glistenings, the correlation between *in* vitro test results and *in vivo* observations remains unclear[1,6].

## 5. References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**Signed for The David J Apple International Laboratory for Ocular Pathology**

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