EVALUATION OF EFFICACY AND SAFETY OF ZARACCOM F260 INTRAOCULAR LENSES IN CATARACT TREATMENT:

A National, Multicenter, Prospective Clinical Device Study Including Historical Control Group

FINAL ANALYSIS REPORT

Protocol Date	**:**	03 July 2006
Final Report Date	**:**	23 Oct 2009
Interim Analysis 1 Report Date	**:**	23 Aug 2007
Number of Centers	**:**	3
Clinical Device	**:**	Zaraccom F260 hydrophobic, foldable, acrylic, posterior chamber intraocular lens
Coordinating Investigator	**:**	Assoc Prof Kadir Eltutar, MD Ministry of Health, Istanbul Education and Research Hospital Ophthalmology Clinics Istanbul Tel: 0212 5884400(6070)
Sponsor Representative	**:**	Pınar Kaymak Anadolu Tıp Teknolojileri A.Ş. Organize San. Bol. 2. Kisim 5. Cadde No.10 58060 Sivas Tel: 0346 218 14 18
Study Dates	**:**	March 2007 – March 2009

The present study has its origins in Declaration of Helsinki and has been conducted in compliance with the EN ISO 14155, Good Clinical Practice, and ethical considerations designated by the relevant Legal Regulations concerning Clinical Trials in Turkey.

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SYNOPSIS

Study title	Evaluation of efficacy and safety of Zaraccom intraocular lenses in cataract treatment: A national, multicenter, prospective clinical device study including historical control group.
Final Report Date	23 Oct 2009
1st Interim analysis report date	23 Aug 2007
Indication	Cataract
Clinical device	Zaraccom F260 hydrophobic, foldable, acrylic, posterior chamber intraocular lens
Study design	A national, multicenter, prospective clinical device study including historical control group
Objectives	Primary objective: • To evaluate the efficacy of Zaraccom lenses in cataract treatment in comparison to the data from the historical control group presented in [ISO 11979-7:2001(E) Annex D] standards on the clinical evaluation of intraocular lenses. Secondary objective: • To evaluate the safety of Zaraccom lenses in cataract treatment in comparison to the data from the historical control group presented in [ISO 11979-7:2001(E) Annex D] standards on the clinical evaluation of intraocular lenses.
Number of centers	3
Planned sample size	390 patients
Analyzed sample size	363 patients
Patient selection criteria	Inclusion criteria: Patients fulfilling all the below criteria were included in the study: • Age ≥18 years, • Female or male, • Diagnosed with cataract, • Planned surgery, • Patients who were informed about the study and whose written informed consent for participation were obtained from themselves or their legal representatives. Exclusion criteria:

	Patients fulfilling at least one of the below criteria were not included in the study: • Patients with a chronic disease that could constitute a handicap for the surgery, • Patients who were allergic to the medication that would possibly be administered during, before or after the operation.
Control group	Data for post-operative visual acuity and adverse event rates presented for 300 historical patients in ISO 11979-7:2001(E) Annex D will be used as the control data in the final analysis.
Study procedures	Patients who could possibly be included in the study were determined by the physicians in the corresponding centers and were informed about the study. The following procedures were implemented on the patients in the first evaluation after their informed consents were obtained. Data were recorded on the pre-operative report form as specified in ISO 11979-7:2001(E). • Assessment of patients' eligibility for the study. • Ophthalmologic history and examination, • Operation history, • Concomitant disease Clinical status of the patients who were placed intraocular lenses into posterior chamber during the cataract surgery were reported by post-operative status report form in the post-operative 1^{st}-2^{nd}, 7^{th}-14^{th}, 30^{th}-60^{th}, 120^{th}-180^{th} and 330^{th}-420^{th} days: • Ophthalmologic examination, • Medication used since the previous visit, • Developed pathologies and complications • Evaluation of the adverse events
Evaluation criteria	<u>Primary Evaluation Criteria:</u> • Ratio of the patients having post-operative Best Corrected Visual Acuity (BCVA) of 0.5 (6/12; 20/40) or more, as had been specified in ISO 11979-7:2001(C). • The time passed for the post-operative BCVA to be 0.5 (6/12; 20/40). <u>Secondary Evaluation Criterion:</u> • Number, severity, relation with the study device and outcome of the complications, pathologies and adverse events that develop within the study period and comparison of these data with the data presented in ISO 11979-7:2001(E) Annex D.
Statistical Analysis	<u>Sample size:</u>

	In accordance with the suggestions in ISO 11979-7:2001(E), 390 patients were planned to be recruited. Statistical analysis plan: The statistical analysis of the study was performed by SPSS v.15.0 program in accordance with ISO 11979-7:2001 (E) . Descriptive statistics were given as frequency and cross tables for categorical variables; as mean, median, standard deviation, minimum and maximum for numerical variables. Mantel Haenszel Chi Square test was used to determine linear association between the increasing ordinal categories of variables. McNemar test was used for the analysis of paired qualitative groups. Pearson Chi square and Fisher's tests were applied to investigate the significance between groups. Level of statistical significance was set at $p<0.05$.
Date of study initiation and planned termination	The study was planned to start in March 2007 and terminate in March, 2009.
Results	Totally, 363 patients (females 49.03%, males 50.97%) were analyzed and the mean age was 67.11±10.19. *Efficacy Results*: Post-operative evaluations demonstrated that there was statistically significant difference between the age groups with respect to visual acuity (VA) and no statistically significant difference was present in the rates of VA according to genders. Compared to pre-operative values, visual acuity was significantly improved at post-operative 1^{st}-2^{nd} days, 7^{th}-14^{th} days, 30^{th}-60^{th} days, 120^{th}-180^{th} days and 330^{th}-420^{th} days ($p<0.001$ for each). In the comparison of VA rates between the patients with and without pre-operative ocular pathology, statistically significant difference was observed between groups on the post-operative 1^{st}-2^{nd} days ($p<0.001$), 7^{th}-14^{th} days ($p<0.001$) and 30^{th}-60^{th} days ($p=0.002$). Total numbers of patients who had insufficient visual acuity were 95 on post-operative 1^{st}-2^{nd} days, 35 on post-operative 7^{th}-14^{th} days, 15 on post-operative 30^{th}-60^{th} days, 19 on post-operative 120^{th}-180^{th} days and 9 on post-operative 330^{th}-420^{th} days. There was an improvement in visual acuity with time. *Safety Results:* Number, severity, relation with the study device and outcome of the complications, pathologies and adverse events that develop within the study period would be compared with the data presented in ISO 11979-7:2001(E). However the adverse events given in the historical data were not observed in the present study. Adverse events were observed in only 1.38% of the evaluated patients during the study (n=5). Only one adverse event was found to be related to the intraocular lenses. The observed adverse events were posterior capsular opacification (n=4) and zonular weakness (n=1). There was no serious adverse event during the study.

Conclusions	Visual acuity rates were significantly improved after surgery. On post-operative period, a fast and significant improvement was observed in the visual acuity of the patients. Totally 5 patients had adverse events during the study (1.38%) and only one of them was related to the intraocular lenses. The results of the present study show that Zaraccom Foldable F260 Hydrophobic, Acrylic Intraocular Lens is obviously effective and safe in improving visual acuity after cataract surgery which is a safe and easy procedure.

1 SIGNATURE PAGE

Name Kadir Eltutar		Signature:
Title		
Responsibility in the Study	Coordinating Investigator	Date: …/……/…….
Name Pınar Kaymak		Signature:
Title		
Responsibility in the Study	Sponsor Representative	Date: …/……/…….
Name Sevilay Akköse		Signature:
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Responsibility in the Study	CRO Medical Writer	Date: …/……/…….
Name Bengi Uğuz		Signature:
Title		
Responsibility in the Study	CRO Statistician	Date: …/……/…….
Name Ayşe Uslu		Signature:
Title		
Responsibility in the Study	CRO Study Coordinator	Date: …/……/…….

2 INTRODUCTION

2.1 Background

Cataract is defined as any opacity on crystalline lens which is responsible for focusing the light and obtaining clear and sharp images. This opacity can develop by aging of crystalline lens, disruption of replacing new lens fibres with existing ones, disruption of the arrangement of lens fibres providing the optical clarity, accumulation of yellow and brown pigments with aging and reducing light transmission (1). Advanced age, current cigarette smoking, diabetes mellitus and female sex are the most common risk factors in the development of cataract. Success of the studies investigating the treatment of cataract is essential as the patients with age-related cataract are estimated to be 40 million people by the year 2020 (2).

Cataract surgery is the most common ophthalmic procedure which includes the removal of the opacified lens to improve the visual acuity, and also is the only method applied in the treatment of cataract worldwide (3). The criteria for cataract surgery are extreme loss of visual function and inability for self-care (4). Post operative complications such as ocular inflammation, hemorrhage, post-operative infection, retinal breaks and detachment, corneal edema and posterior capsule opacity should be considered while deciding on the surgery.

Substantial developments have been achieved in cataract surgery, in respect of the techniques used in the surgery as well as the properties of the intraocular lenses. Presently, facoemulsification, performed by the placement of intraocular lens (IOL) in the posterior chamber of the eye, is the most commonly preferred method (5). Objective of the efforts spent on the development of the lens structures is to provide maximum biocompatibility (6). For this reason, some optical criteria such as good solubility, lack of spherical aberrations and minimized intraocular reflection effect and mechanical criteria like smooth surface, low weight, minimized anterior-posterior diameter and use of non-biodegradable materials that are inert to external factors such as UV, should be considered while designing IOLs (7). All the biocompatibility tests that the designed IOL material should be passed through are mentioned in the Intraocular Lens Guidance Document (8).

The mostly encountered post-operative complication in cataract surgery is the posterior capsule opacification with an incidence of 10-20%, which is followed by glaucoma, uveitis, dislocation and hyphema (9). Concerning these complications, various studies have been performed to examine the association between the IOL structure and the

encountered problems. These studies have demonstrated the importance of selecting the correct IOL biomaterial in order to obtain the optimum clinical outcome (10,11)

Currently, the materials primarily used in the structure of IOLS are silicone and acrylic/methacrylate polymers; while the lenses in acrylic group can be classified as polymethacrylate (PMMA) and foldable (9). IOLs made of hydrophobic acrylic materials have particularly been shown to display better capsular biocompatibility compared to other types (10). In terms of lens design, one-piece lenses with modified haptic design have led to better outcomes (12). Capsular rupture, vitreous loss, lens decentration and luxation, wrong calculation of IOL dioptre and damage of IOL during implantation are some observed complications during lens implantation. Concerning these complications, various studies have been performed to examine the association between the IOL structure and the encountered problems. These studies have demonstrated the importance of selecting the correct IOL biomaterial in order to obtain the optimum clinical outcome (10,11).

The aim of the present study is to evaluate the efficacy and safety of Zaraccom Foldable F260 Hydrophobic, Acrylic Intraocular Lenses designed to be used in cataract surgery.

2.2 Zaraccom Foldable F260 Hydrophobic, Acrylic Intraocular Lens

2.2.1 Mechanical Properties

F260 Hydrophobic, Acrylic Intraocular lens is a one-piece (mono-block) lens having a sharp edge design which is thought to prevent posterior capsule opacification. The measurements of the parameters providing intracapsular stability are: optical diameter 6.00 mm, total length 12.50 mm, and haptic angle 0^0. Optical design of the lens is biconvex, no positioning hole is present, and its thin structure enables folding. Refractive index of the F260 intraocular lens is 1.51, A constant is 118.4 and anterior chamber depth is 5.2. Hydrophobic acrylic (acrylate-methacrylate copolymer) material was used in its structure and the lens was designed and produced properly to absorb UV rays and resist YAG laser.

2.2.2 Raw Material

In the production of Zarracom Foldable Hydrophobic Acrylic Lenses, a homogenous composite formed by the addition of monomers having high purity and quality which enable polymerization, give the foldability property and are highly able to absorb UV

rays was added to the structure of high purity and quality oligomeric methacrylate material.

2.2.3 Indications

Zaraccom Lenses IOL's indicated in case of congenital, traumatic and spontaneous cataracts.

2.2.4 Contra-indications

To date there are no absolute contraindications to Intraocular Lenses' implantation.

Relative contra-indications include some forms of:

- Chronic active uveitis
- Retinal diseases in which the implant may interfere with retinal surgery

2.2.5 Complications

Cataract surgery, with or without lens implantation might be associated with:

- Ocular inflammation
- Hemorrhage
- Intraocular pressure elevation
- Post operative infection
- Retinal breaks and detachment
- Cystoid macular edema
- Corneal edema
- Posterior capsule opacity

Complications related with intraocular lens implantation:

- Capsular rupture
- Vitreous loss
- Lens decentration and luxation
- Wrong calculation of IOL dioptre
- Damage of IOL during implantation

3 OBJECTIVES

3.1 Primary Objective

The primary objective of the present study is to evaluate the efficacy of Zaraccom lenses in cataract treatment in comparison to the data from the historical control group presented in [ISO 11979-7:2001(E) Annex D] standards on the clinical evaluation of intraocular lenses.

3.2 Secondary Objective

The secondary objective is to evaluate the safety of Zaraccom lenses in cataract treatment in comparison to the data from the historical control group presented in [ISO 11979-7:2001(E) Annex D] standards on the clinical evaluation of intraocular lenses.

4 STUDY PLAN

4.1 Study Design

This study was designed as a national, multicenter, prospective clinical device study including historical control group.

4.2 Patient Selection

4.2.1 Inclusion Criteria

Patients fulfilling all the below criteria were included in the study:

- Age ≥18 years,
- Female or male,
- Diagnosed with cataract,
- Planned surgery,
- Patients who were informed about the study and whose written informed consent for participation were obtained from themselves or their legal representatives.

4.2.2 Exclusion Criteria

Patients fulfilling at least one of the below criteria were not included in the study:

- Patients with a chronic disease that could constitute a handicap for the surgery
- Patients who are allergic to the medication that would possibly be administered during, before or after the operation.

4.3 Control Group

Data for post-operative visual acuity and adverse event rates presented for 300 historical patients in ISO 11979-7:2001(E) Annex D was used as the control data in the final analysis.

4.4 Planned and Analyzed Sample Size

According to ISO 11979-7:2001(E) Annex C, 390 patients were planned to be included in the study. Totally, 363 patients were analyzed in the study.

4.5 Study Center

The study was conducted in İstanbul Education and Research Hospital in coordination of Associate Prof. Kadir Eltutar, in Atatürk Education and Research Hospital in coordination of Associate Prof. İzzet Can and in Cumhuriyet University School of Medicine, Department of Ophthalmology, in coordination of Associate Prof. Ilker Toker. The investigators and the number of patients in these centers are given in Table 1. The responsible investigator or the staff charged by the investigator has been responsible from the implementation of the study procedures.

Table 1. Study Centers

Center No	Center	Coordinator Investigator	Investigators	Patient Number
1	İstanbul Education and Research Hospital	Assoc. Prof. Kadir Eltutar	Betül İlkay Sezgin-Tamer Eryiğit	125
2	Atatürk Education and Research Hospital	Assoc. Prof. İzzet Can	Assoc. Prof. Tamer Takmaz	126
3	Cumhuriyet University School of Medicine	Assoc. Prof. Mustafa İlker Toker	Cengiz Caner, MD	112

4.6 Study Procedures

Patients who could possibly be included in the study were determined by the physicians in the center and informed about the study. The following procedures were implemented on the patients in the first evaluation after their informed consents were obtained. Data were recorded on the pre-operative report form as specified in ISO 11979-7:2001(E).

- Assessment of patients' eligibility for the study.
- Ophthalmologic history and examination,

- Operation history,
- Concomitant diseases.

Clinical status of the patients who were placed intraocular lens into posterior chamber during the cataract surgery were reported by post-operative status report form in the post-operative 1^{st}-2^{nd}, 7^{th}-14^{th}, 30^{th}-60^{th}, 120^{th}-180^{th} and 330^{th}-420^{th} days:

- Ophthalmologic examination,
- Medication used since the previous visit,
- Developed pathologies and complications,
- Evaluation of the adverse events.

4.7 Evaluation Criteria

4.7.1 Primary Evaluation Criteria

- Ratio of the patients having post-operative Best Corrected Visual Acuity (BCVA) of 0.5 (6/12; 20/40) or more, as had been specified in ISO 11979-7:2001(E) Annex C.
- The time passed for the post-operative BCVA to be 0.5 (6/12; 20/40).

4.7.2 Secondary Evaluation Criterion

- Number, severity, relation with the study device and outcome of the complications, pathologies and adverse events that develop within the study duration and comparison of these data with the data presented in ISO 11979-7:2001(E) Annex D.

5 STATISTICAL METHODS

5.1 Sample Size Calculation

In accordance with the suggestions in ISO 11979-7:2001, 390 patients were planned to be recruited.

5.2 Data Entry

Regular site monitoring ensured the quality of the conductance of the trial. Data entry, verification, and validation were carried out using standard computer software. Moreover, every modification in the database could be traced using an audit trail. A data checking plan was established to define all automatic validation checks, as well as

supplemental manual checks, to ensure data quality. All discrepancies were researched until resolved.

5.3 Statistical Analysis

The statistical analysis of the study was performed by SPSS v.15.0 program in accordance with ISO 11979-7:2001 (E). Descriptive statistics were given as frequency and cross tables for categorical variables; as mean, median, standard deviation, minimum and maximum for numerical variables. Mantel Haenszel Chi Square test was used to determine linear association between the increasing ordinal categories of variables. McNemar test was used for the analysis of paired qualitative groups. Pearson Chi square and Fisher's tests were applied to investigate the significance between groups. Level of statistical significance was set at $p<0.05$.

6 STUDY ADMINISTRATIVE STRUCTURE AND RESPONSIBILITIES

6.1 Responsibilities of the Investigator

6.1.1 Protocol Compliance

It is the investigators' responsibility to conduct the study in compliance with the protocol. The investigators can utilize other healthcare staff for implementation of the study procedures.

6.1.2 Informed Consent

It is the investigators' responsibility to obtain patients' informed consents.

6.1.3 Case Report Forms

Patient data were completely and accurately recorded on the case report forms (CRF) by the responsible investigators or the co-investigators in charge, using a black pencil.

It is the investigators' responsibility to provide an accurate and complete data collection.

In order to confirm the accuracy and completion of the data, the pages of CRFs have been signed by the investigator who did the recordings.

All corrections on the CRFs have been performed so that the erroneous original data would be decipherable. The investigator, who performed the correction, noted the date and paraphed the correct data. If the reason of the correction was not clear, it has been noted alongside.

6.1.4 Adverse Event Reporting

The investigators followed-up the included patients in respect of the development of adverse events, evaluated the adverse events in terms of intensity, severity and relation with the study device, and recorded these evaluations on CRF.

In case of deaths related to the use of the study device and serious adverse events, the responsible investigator was obliged to inform the Ministry of Health and the Local Ethics Committee within 24 hours.

6.1.5 Monitorization

It is the investigators' responsibility to make the study documentation and source documents (hospital records, examination records, etc) available for the review of the monitor and to provide the monitor the necessary physical conditions and adequate time. Omega CRO was responsible for the monitorization of the study.

6.1.6 Study Device

The investigators or the co-investigators charged by the responsible investigators should appropriately record and keep the study device.

6.1.7 Filing

It is the investigators' responsibility to appropriately keep the study records. All documents should be kept in a secure zone and safety regulations should be obeyed.

6.2 Responsibilities of the Sponsor

The present study was conducted in the sponsorship of the Anadolu Tıp Teknolojileri A.Ş. It is the sponsor's responsibility to design the protocol, CRF, patient informed consent forms and other documentation, to print these in adequate numbers and distribute to the center; to supply the study center with the devices that are to be used within the context of the study; to charge the monitor for the monitorization of the centers before, during and after the study; to collect the data at the end of the study and to perform statistical analysis; to prepare interim and final study reports and to transmit to Ethics Committees.

The sponsor can delegate some or all of its responsibilities to a Contract Research Organization. This situation does not eliminate any of the sponsor's responsibilities.

In the present study monitorization, statistical evaluation and preparation of study report were performed by Omega CRO.

6.3 Monitorization of the Study

The monitor charged by the sponsor has frequently contacted the investigators before, periodically during and after the study. These contacts were by visiting or phoning the centers in the time intervals set by the sponsor. During these visits, the monitor reviewed the case report forms for confirmation of complete recording and compliance to the protocol. In these visits, the monitor also evaluated the issues such as adverse event reporting, appropriateness of patient information and informed consent acquisition procedures, the conditions where study devices were kept and presence of enough number of the device, investigator's file and other problems of the visited center.

6.4 Publication of the Study Results

Coordinating investigator, together with the other investigators, ensures that no data is published before all data are collected and analysis is completed.

The sponsor reserves all rights to review the obtained data prior to the presentation and publication of them. The reason for this is not to prevent or limit the publication or presentation, instead; it gives the sponsor the possibility to protect the acquired data and comment on the yet not represented information.

Before submission of an abstract or a manuscript of the study, the sponsor should provide the investigators with 14 days and 28 days, respectively, to comment on the abstract or the manuscript. All parties should consider the comments that have rational scientific origins.

7 ETHICAL ISSUES

The study has been conducted in compliance with EN ISO 14155, final version (2004) of the Declaration of Helsinki, Good Clinical Practice and the ethical regulations set by the Legal Regulations for the Clinical Studies in Turkey.

7.1 Ethical Investigation

All study documentation was presented to the local ethics committee of the center prior to the study initiation. The study procedures were initiated after the approval of the coordinating center was obtained. The study documentation was not presented to Central Ethics Committee of Ministry of Health, since there is no regulation of Ministry of Health concerning medical device studies.

7.2 Patient Information and Written Consent

All recruited patients were informed about the study and included after acquisition of their written informed consents for participation.

During a routine clinical application of patients, complete and satisfactory oral and written information regarding the structure, objectives, possible risks and benefits of the study were given by the investigator or the staff. The patients were also notified that they could stop participation at any time. If the patients were willing to participate, the Informed Consent Forms were signed. Signed informed consent forms were obtained before any study procedure had been performed. The original copies of the informed consent forms were kept by the investigators whereas the other copy was given to the patients.

8 PROTOCOL DEVIATIONS

The historical control group presented in [ISO 11979-7:2001(E) Annex D] would be compared to the data obtained in the present study. However, the adverse events given in the historical data were not observed in the study. Therefore the data obtained in the present study were analyzed without historical control group.

9 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND DEATH

9.1 Definitions

9.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence in a patient administered a device or a clinical investigation subject, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medical (investigational or marketed) device, whether or not considered related to the medical device.

9.1.2 Serious Adverse Event

A Serious Adverse Event (SAE) is any untoward medical occurrence that results in at least one of the below:

- Results in death,
- Is life-threatening,

- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/ incapacity,
- Results in a congenital anomaly, neoplasm or birth defect.

Moreover, occurrences that do not result in death, that are not life-threatening or necessitate hospitalization but include a medical significance or require medical and surgical interventions to prevent the occurrence of the above mentioned outcomes are considered serious as well.

9.1.3 Unexpected Adverse Event

A medical occurrence that's nature, severity and incidence has not been formerly discussed in the current investigator's brochure, overall study plan or somewhere else is considered an unexpected adverse event if it is suspected to be reasonably related to the investigated device.

9.2 Adverse Event Reporting

All serious and unexpected adverse events should officially be reported.

In case of death or observation of serious adverse events that are related to study device, the Ministry of Health and local ethics committee should be informed both orally and in writing within 24 hours, by the investigator.

All serious and unexpected adverse events are also reported to ethics committees via the interim reports (minimum 2 per year) and the final study report.

The adverse event form attached to the CRF should also be completed for all adverse events that develop during the follow-up period.

Study name, center and patient data, a clear definition of the adverse event, dates of onset/termination, severity, intensity, causality relationship with the device, outcome and treatment strategies should be reported both during the official reporting and completion of the adverse event form.

9.3 Severity Assessment

Severity indicates the intensity of a medical occurrence, while seriousness refers to a medical occurrence that ends up with the outcomes mentioned in section 9.1.2 and is used to indicate reporting necessity. For this reason, a severe adverse event is not necessarily a serious event. For example, hours of nausea can be severe but clinically not serious. In terms of severity, adverse events are generally classified into 3 groups:

Mild: AE is perceivable but does not affect daily activity and does not necessitate medical treatment.

Moderate: AE decreases daily activity, necessitates medical treatment.

Severe: As limiting as to prevent working or performing daily activity, necessitates medical treatment. All SAEs are also considered severe.

9.4 Assessment of Relation to Study Device

The causality relationship between the AE and the device is assessed in four different levels according to the strength of the relationship: Probable relationship, possible relationship, doubtful relationship, and unrelated. Presence of outside factors, a logical time-line between the implantation of the device and the development of the event, and exclusion of other causes should be considered in the investigation of causality with the used device. According to this assessment, causality relationship is defined as follows.

9.4.4 Probable Relation

An AE's relationship with the study device is considered "probable" under the following conditions:

1- If there is a logical time lapse and sequence between the implantation of the device and the development of AE,

2- If AE cannot be logically explained by the known clinical condition of the patient, environmental and toxic factors or other treatments administered to the patient,

3- If AE follows a known and likely response pattern for the suspected drug,

9.4.5 Possible Relation

This category includes AEs that though are not very likely to be causally related to the study device, this possibility cannot be excluded. The relationship of an AE and study device is considered "possible" under the following conditions:

1- If there is a logical time lapse and sequence between the device implantation and the development of AE,

2- If AE cannot be logically explained by the known clinical condition of the patient, environmental and toxic factors or other treatments administered to the patient,

3- If AE follows a known and likely response pattern for the suspected device.

9.4.6 Doubtful

In general this category includes AEs that follow the below listed conditions:

1- If there is no logical time lapse and sequence between the device implantation and the development of AE,

2- If AE can be logically explained by the known clinical condition of the patient, environmental and toxic factors or other treatments administered to the patient,

3- If AE does not follow a known and likely response pattern for the suspected device.

9.4.7 Unrelated

This category includes AEs that can be clearly and unquestionably linked to outside factors (i.e., disease, environment) and do not meet the criteria listed for “doubtful”, “possible” or “probable” relationship. Table 2 summarizes the assessment of relation to the study device.

Table 2. Assessment of the relation between the adverse event and study device.

AE characteristics	**Relation to device**			
	Probable	Possible	Doubtful	Unrelated
Certainly linked to external factors	-	-	-	+
Has logical time lapse between the device implantation	+	+	-	-
Can onset based on the clinical condition of the patient, environmental and toxic factors or other treatments administered to the patient	-	-	+	+
Follows a known and likely response pattern for the suspected device	+	+	-	-

10 RESULTS

10.1 Demography

The analysis was performed on the data obtained from 363 patients (females 49.03%, males 50.97%). The mean age of the patients was 67.11±10.19 years. Distribution of the patients according to age groups is presented in Table 3.

Table 3. Distribution of the patients according to age decades.

Age Groups (year)	Number	(%)
<=50	22	6.06
51-60	65	17.91
61-70	132	36.36
71-80	123	33.88
81+	21	5.79
Total	363	100.00

10.2 Efficacy Results

10.2.1 Pre-Operative Results

Visual acuity (VA) measured before the operation with respect to the age groups, is presented in Table 4. No significant difference was observed in the VA rates between the age groups (p=0.095, Mantel Haenszel test).

Table 4. Distribution of the patients according to pre-operative VA rates and age groups.

		Pre-Operative VA		
Age (year)		**<0.5**	**≥0.5**	**Total**
<=50	**n**	16	5	21
	%	76.19	23.81	100.00
51-60	**n**	50	10	60
	%	83.33	16.66	100.00
61-70	**n**	107	20	127
	%	84.25	15.75	100.00
71-80	**n**	97	17	114
	%	85.09	14.91	100.00
81+	**n**	20	0	20
	%	100.00	0.00	100.00
Total	**n**	290	52	342
	%	84.80	15.20	100.00

10.2.2 Post-Operative Results

VA rates on the post-operative 1^{st}-2^{nd} days with respect to the age decades are presented in Table 5. Statistically significant difference was observed between the age groups with respect to VA ($p<0.001$, Mantel Haenszel test).

Table 5. Distribution of the patients according to the VA rates on post-operative 1^{st}-2^{nd} days and age groups.

		Post-operative (1^{st}-2^{nd} days) VA		
Age (year)		**<0.5**	**≥0.5**	**Total**
<=50	**n**	3	19	22
	%	13.64	86.36	100.00
51-60	**n**	12	53	65
	%	18.46	81.54	100.00
61-70	**n**	43	88	131
	%	32.82	67.18	100.00
71-80	**n**	42	77	119
	%	35.29	64.71	100.00
81+	**n**	12	9	21
	%	57.14	42.86	100.00
Total	**n**	112	246	358
	%	31.20	68.80	100.00

VA rates on the post-operative 7^{th}-14^{th} days with respect to the age decades are presented in Table 6. On the post-operative 7^{th}-14^{th} days, VA rates of all age groups improved. There was a statistically significant difference between the age groups with respect to VA (p=0.001, Mantel Haenszel test)

Table 6. Distribution of the patients according to the VA rates on post-operative 7^{th}-14^{th} days and age groups.

		Post-operative (7^{th}-14^{th} days) VA		
Age (year)		**<0.5**	**≥0.5**	**Total**
<=50	**n**	0	19	19
	%	0.0	10.00	100.00
51-60	**n**	3	52	55
	%	5.45	94.55	100.00
61-70	**n**	8	107	115
	%	6.96	93.04	100.00
71-80	**n**	15	89	104
	%	14.42	85.58	100.00
81+	**n**	5	15	20
	%	25.00	75.00	100.00
Total	**n**	31	282	313
	%	9.90	90.10	100.00

VA rates on the post-operative 30th-60th days with respect to the age decades are presented in Table 7. VA rates of the group aged over 50 years improved completely. Statistically significant difference was observed between the age groups (p=0.041, Mantel Haenszel test).

Table 7. Distribution of the patients according to the VA rates on post-operative 30th-60th days and age groups.

Post-operative (30th-60th days) VA				
Age (year)		**<0.5**	**≥0.5**	**Total**
<=50	**n**	0	20	20
	%	0.00	100.00	100.00
51-60	**n**	2	41	43
	%	4.65	95.35	100.00
61-70	**n**	6	103	109
	%	5.50	94.50	100.00
71-80	**n**	4	81	85
	%	4.71	95.29	100.00
81+	**n**	4	13	17
	%	23.53	76.47	100.00
Total	**n**	16	258	274
	%	5.84	94.16	100.00

VA rates on the post-operative 120th-180th days with respect to the age decades are presented in Table 8. VA rates of the group aged over 50 years improved completely. Statistically significant difference was observed between the age groups (p=0.042, Mantel Haenszel test).

Table 8. Distribution of the patients according to the VA rates on post-operative 120th-180th days and age groups.

Post-operative (120th-180th days) VA				
Age (year)		**<0.5**	**≥0.5**	**Total**
<=50	**n**	0	19	19
	%	0.00	100.00	100.00
51-60	**n**	1	58	59
	%	1.69	98.31	100.00
61-70	**n**	9	106	115
	%	7.83	92.17	100.00
71-80	**n**	8	94	102
	%	7.84	92.16	100.00
81+	**n**	2	14	16
	%	12.50	87.50	100.00
Total	**n**	20	291	311
	%	6.43	93.57	100.00

VA rates on the post-operative 330th-420th days with respect to the age decades are presented in Table 9. No statistically significant difference was observed between the age groups (p=0.593, Mantel Haenszel test).

Table 9. Distribution of the patients according to the VA rates on post-operative 330th-420th days and age groups.

Post-operative (330th-420th days) VA				
Age (year)		**<0.5**	**≥0.5**	**Total**
<=50	**n**	1	13	14
	%	7.14	92.86	100.00
51-60	**n**	0	38	38
	%	0.00	100.00	100.00
61-70	**n**	3	92	95
	%	3.16	96.84	100.00
71-80	**n**	2	66	68
	%	2.94	97.06	100.00
81+	**n**	1	9	10
	%	10.00	90.00	100.00
Total	**n**	7	218	225
	%	3.11	96.89	100.00

Numbers of patients having VA ≥0.5 are given according to gender in Table 10. No statistically significant difference was observed in the rates of VA according to genders (post-operative 1st-2nd days p=0.954, 7th-14th days p=0.335, 30th-60th days p=0.262, 120th-180th days p=0.303 and 330th-420th days p=1.000).

Table 10. Sufficient VA rates in gender groups (VA≥0.5)

	Post-operative VA≥0.5				
	1st-2nd days	**7th-14th days**	**30th-60th days**	**120th-180th days**	**330th-420th days**
	n/Total	n/Total	n/Total	n/Total	n/Total
Female	120/175	144/157	124/134	151/159	111/115
Male	126/183	138/156	134/140	140/152	107/110
Total	246/358	282/313	258/274	291/311	218/225

10.2.3 Pre- and Post-operative Comparisons

A comparison of pre-operative and post-operative 1st-2nd day's VA rates is presented in Table 11. Compared to pre-operative values, a significant improvement was observed at post-operative 1st-2nd days (p<0.001, McNemar).

Table 11. Comparison of pre-operative and post-operative 1st-2nd day's VA rates.

			Post-operative 1st-2nd days VA		
			<0.5	**≥0.5**	**Total**
Pre-operative VA	**<0.5**	**n**	93	196	289
		%	32.18	67.82	100.00
	≥0.5	**n**	11	41	52
		%	21.15	78.85	100.00
	Total	**n**	104	237	341
		%	30.50	69.50	100.00

VA rates on the post-operative 7th-14th, 30th-60th, 120th-180th and 330th-420th days are presented with comparison to pre-operative rates in Tables 12, 13, 14 and 15. A significant improvement was observed at all post-operative reporting periods when compared to pre-operative values (p<0.001, McNemar).

Table 12. Comparison of pre-operative and post-operative 7th-14th day's VA rates.

			Post-operative 7th-14th days VA		
			<0.5	**≥0.5**	**Total**
Pre-operative VA	**<0.5**	**n**	26	230	256
		%	10.16	89.84	100.00
	≥0.5	**n**	2	40	42
		%	4.76	95.24	100.00
	Total	**n**	28	270	298
		%	9.40	90.60	100.00

Table 13. Comparison of pre-operative and post-operative 30th-60th day's VA rates.

			Post-operative 30th-60th days VA		
			<0.5	**≥0.5**	**Total**
Pre-operative VA	**<0.5**	**n**	15	209	224
		%	6.70	93.30	100.00
	≥0.5	**n**	0	37	37
		%	0.00	100.00	100.00
	Total	**n**	15	246	261
		%	5.75	94.25	100.00

Table 14. Comparison of pre-operative and post-operative 120th-180th day's VA rates.

			Post-operative 120th-180th days VA		
			<0.5	**≥0.5**	**Total**
Pre-operative VA	**<0.5**	**n**	15	243	258
		%	5.81	94.19	100.00
	≥0.5	**n**	2	38	40
		%	5.00	95.00	100.00
	Total	**n**	17	281	298
		%	5.70	94.30	100.00

Table 15. Comparison of pre-operative and post-operative 330th-420th day's VA rates.

			Post-operative 330th-420th days VA		
			<0.5	**≥0.5**	**Total**
Pre-operative VA	**<0.5**	**n**	7	179	186
		%	3.76	96.24	100.00
	≥0.5	**n**	0	32	32
		%	0.00	100.00	100.00
	Total	**n**	7	211	218
		%	3.21	96.79	100.00

10.2.4 Post-Operative Best-Case VA

The rates of patients having post-operative best-case VA were found to be decreased with the increase in age for all post-operative follow-up visits except the post-operative 330th-420th days (Table 16). The rates of patients having post-operative best-case VA did not differ according to gender (Table 17). The rate of patients having visual acuity≥0.5 had an increasing trend in the subsequent follow-up visits for both males and females.

Table 16. Best-case VA according to age

Age (year)	1st-2nd days		7th-14th days		30th-60th days		120th-180th days		330th-420th days	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
<=50	19/22	86.4	19/19	100.0	20/20	100.0	19/19	100.0	13/14	92.9
51-60	53/65	81.5	52/55	94.5	41/43	95.3	58/59	98.3	38/38	100.0
61-70	88/131	67.2	107/115	93.0	103/109	94.5	106/115	92.2	92/95	96.8
71-80	77/119	64.7	89/104	85.6	81/85	95.3	94/102	92.2	66/68	97.1
81+	9/21	42.9	15/20	75.0	13/17	76.5	14/16	87.5	9/10	90.0
Total	246/358	68.7	282/313	90.1	258/274	94.2	291/311	93.6	218/225	96.9

Table 17. Best-case VA according to gender

	1st-2nd days		7th-14th days		30th-60th days		120th-180th days		330th-420th days	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Female	120/175	68.6	144/157	91.7	124/134	92.5	151/159	95.0	111/115	96.5
Male	126/183	68.9	138/156	88.5	134/140	95.7	140/152	92.1	107/110	97.3
Total	246/358	68.7	282/313	90.1	258/274	94.2	291/311	93.6	218/225	96.9

10.2.5 Pre-operative Ocular Pathology and

10.2.6 Visual Acuity

The details of pre-operative ocular pathology are given in the Table 18. The most common pathology observed was pseudoexfoliation with the rate of 7.71% (n=28). Other pathologies observed were glaucoma (1.65%), previous glaucoma surgery (0.28%), poor pupil dilation (3.86%), previous uveitis (0.28%), diabetic retinopathy (1.11%), macular degeneration (0.83%) and amblyopia (0.28%).

Table 18. Pre-operative ocular pathology*

		No	Yes	Total
Pseudoexfoliation	N	335	28	363
	%	92.29	7.71	100.00
Glaucoma	N	357	6	363
	%	98.35	1.65	100.00
Previous glaucoma surgery	N	362	1	363
	%	99.72	0.28	100.00
Poor pupil dilation	N	349	14	363
	%	96.14	3.86	100.00
Previous uveitis	N	362	1	363
	%	99.72	0.28	100.00
Diabetic retinopathy	N	356	4	360
	%	98.89	1.11	100.00
Macular degeneration	N	359	3	362
	%	99.17	0.83	100.00
Amblyopia	N	361	1	362
	%	99.72	0.28	100.00
Other	N	362	1	363
	%	99.72	0.28	100.00

*More than one ocular pathology can be present in one patient

In the comparison of VA rates between the patients with and without pre-operative ocular pathology, it was observed that 73.10% of the patients without preoperative ocular pathology had sufficient visual acuity on the post-operative 1st-2nd days (Table 19). However 35.71% of the patients with preoperative ocular pathology had VA≥0.5. There was a statistically significant difference between groups that had and did not have pre-operative ocular pathology with respect to visual acuity (p<0.001, Pearson Chi square test).

Table 19. VA according to presence of pre-operative ocular pathology on post-operative 1st-2nd days

			Post-operative 1st-2nd days VA		
			<0.5	**≥0.5**	**Total**
Pre-operative ocular pathology	Not present	N	85	231	316
		%	26.90	73.10	100.00
	Present	N	27	15	42
		%	64.29	35.71	100.00
	Total	N	112	246	358
		%	31.28	68.72	100.00

Visual acuity rates on the post-operative 7th-14th days and 30th-60th days with respect to the presence or absence of pre-operative ocular pathology are presented in Table 20 and Table 21. Statistically significant difference was observed between groups that had and did not have pre-operative ocular pathology with respect to visual acuity (p<0.001 for post-operative 7th-14th days VA and p=0.002 for post-operative 30th-60th days VA).

Table 20. VA according to presence of pre-operative ocular pathology on post-operative 7th-14th days

			Post-operative (7th-14th days) VA		
			<0.5	**≥0.5**	**Total**
Pre-operative ocular pathology	Not present	N	20	254	274
		%	7.30	92.70	100.00
	Present	N	11	28	39
		%	28.21	71.79	100.00
	Total	N	31	282	313
		%	9.90	90.10	100.00

Test	p
Fisher's exact	<0.001

Table 21. VA according to presence of pre-operative ocular pathology on post-operative 30th-60th days

			Post-operative (30th-60th days) VA		
			<0.5	**≥0.5**	**Total**
Pre-operative ocular pathology	Not present	N	9	228	237
		%	3.80	96.20	100.00
	Present	N	7	30	37
		%	18.92	81.08	100.00
	Total	N	16	258	274
		%	5.84	94.16	100.00

Test	p
Fisher's exact	0.002

There was no statistically significant difference in VA rates on the post-operative 120th-180th days and 330th-420th days with respect to the presence or absence of pre-operative ocular pathology (p=0.260 and p=0.236, respectively).

Table 22. VA according to presence of pre-operative ocular pathology on post-operative 120th-180th days

			Post-operative (120th-180th days) VA		
			<0.5	**≥0.5**	**Total**
Pre-operative ocular pathology	Not present	N	16	260	276
		%	5.80	94.20	100.00
	Present	N	4	31	35
		%	11.43	88.57	100.00
	Total	N	20	291	311
		%	6.43	93.57	100.00

Test	p
Fisher's exact	0.260

Table 23. VA according to presence of pre-operative ocular pathology on post-operative 330th-420th days

			Post-operative (330th-420th days) VA		
			<0.5	**≥0.5**	**Total**
Pre-operative ocular pathology	Not present	N	5	190	195
		%	2.56	97.44	100.00
	Present	N	2	28	30
		%	6.67	93.33	100.00
	Total	N	7	218	225
		%	3.11	96.89	100.00

Test	p
Fisher's exact	0.236

Statistically significant increase was observed between the rates of VA of patients with and without pre-operative ocular pathology during all post-operative follow-up visits (Table 24).

Table 24. The rates of sufficient or insufficient VA in the patients with or without pre-operative ocular pathology

Pre-operative ocular pathology		<0.5		>=0.5	
		N	%	N	%
Not present	VA of operated eye after 1-2 days	50	31.25	110	68.75
	VA of operated eye after 7-14 days	9	5.63	151	94.37
	VA of operated eye after 30-60 days	6	3.75	154	96.25
	VA of operated eye after 120-180 days	5	3.12	155	96.88
	VA of operated eye after 330-420 days	5	3.12	155	96.88
Present	VA of operated eye after 1-2 days	16	69.57	7	30.43
	VA of operated eye after 7-14 days	6	26.09	17	73.91
	VA of operated eye after 30-60 days	4	17.39	19	82.61
	VA of operated eye after 120-180 days	1	4.35	22	95.65
	VA of operated eye after 330-420 days	1	4.35	22	95.65

Cochran's Q Test	p
Not present	<0.001
Present	<0.001

10.2.7 VA According to Centers

The patient numbers in each center are given in Table 25.

Table 25. Number of patients in the centers

Center No	N	%
1	125	34.44
2	126	34.71
3	112	30.85
Total	363	100.00

Rates of VA were significantly different between study centers on post-operative 1st-2nd days and 7th-14th days (p<0.001, Pearson Chi Square test) (Tables 26 and 27).

Table 26. VA according to the centers on post-operative 1st-2nd days

			Post-operative 1st-2nd days VA		
			<0.5	**≥0.5**	**Total**
Center No	1	N	13	112	125
		%	10.40	89.60	100.00
	2	N	59	66	125
		%	47.20	52.80	100.00
	3	N	40	68	108
		%	37.04	62.96	100.00
	Total	N	112	246	358
		%	31.28	68.72	100.00

Table 27. VA according to the centers on post-operative 7th-14th days

			Post-operative (7th-14th days) VA		
			<0.5	**≥0.5**	**Total**
Center No	1	N	2	116	118
		%	1.69	98.31	100.00
	2	N	14	108	122
		%	11.48	88.52	100.00
	3	N	15	58	73
		%	20.55	79.45	100.00
	Total	N	31	282	313
		%	9.90	90.10	100.00

In the VA evaluations of post-operative 30th-60th, 120th-180th and 330th-420th days, no statistically significant difference was observed between centers (Tables 28, 29, 30).

Table 28. VA according to the centers on post-operative 30th-60th days

			Post-operative (30th-60th days) VA		
			<0.5	**≥0.5**	**Total**
Center No	1	N	3	82	85
		%	3.53	96.47	100.00
	2	N	9	116	125
		%	7.20	92.80	100.00
	3	N	4	60	64
		%	6.25	93.75	100.00
	Total	N	16	258	274
		%	5.84	94.16	100.00

Test	p
Fisher's exact	0.539

Table 29. VA according to the centers on post-operative 120th-180th days

			Post-operative (120th-180th days) VA		
			<0.5	**≥0.5**	**Total**
Center No	1	N	11	102	113
		%	9.73	90.27	100.00
	2	N	4	118	122
		%	3.28	96.72	100.00
	3	N	5	71	76
		%	6.58	93.42	100.00
	Total	N	20	291	311
		%	6.43	93.57	100.00

Test	p
Pearson Chi square	0.131

Table 30. VA according to the centers on post-operative 330th-420th days

			Post-operative (330th-420th days) VA		
			<0.5	**≥0.5**	**Total**
Center No	1	N	1	75	76
		%	1.32	98.68	100.00
	2	N	6	97	103
		%	5.83	94.17	100.00
	3	N	0	46	46
		%	0.00	100.00	100.00
	Total	N	7	218	225
		%	3.11	96.89	100.00

Test	p
Fisher's exact	0.145

10.2.8 Reason for Insufficient Visual Acuity (VA<0.5)

Reasons for insufficient VA (<0.5) on post-operative period are given in Table 31 for all follow-up visits. The detailed reasons for insufficient VA are given in Tables 32, 33, 34, 35 and 36 for all post-operative reporting periods. Total numbers of patients who had visual acuity <0.5 were 95 on post-operative 1st-2nd days, 35 on post-operative 7th-14th days, 15 on post-operative 30th-60th days, 19 on post-operative 120th-180th days and 9 on post-operative 330th-420th days.

Table 31. Reason for insufficient VA (<0.5) on post-operative period when all follow-up visits were evaluated together*.

	N (=122)	%
Unrelated to operation		
Amblyopia	3	2.46
Diabetic retinopathy	3	2.46
Glaucoma	4	3.28
Hypertensive retinopathy	1	0.82
Macular degeneration	24	19.67
Retinal atrophy	1	0.82
Related to operation		
Posterior Capsular Opacification	34	27.87
Iritis	1	0.82
Corneal edema	100	81.97
Residue at anterior capsule of the lens	1	0.82
Pigment on surface of lens	1	0.82
Pupillary fibrinoid	2	1.64
Refraction	13	10.66

*More than one reason can be present in one patient

Table 32. Reason for insufficient VA on post-operative 1st-2nd days*

	N (=95)	%
Unrelated to operation		
Amblyopia	1	1.05
Diabetic retinopathy	1	1.05
Macular degeneration	5	5.26
Related to operation		
Posterior Capsular Opacification	4	4.21
Iritis	1	1.05
Corneal edema	85	89.47
Pupillary fibrinoid	2	2.11
Refraction	5	5.26

*More than one reason can be present in one patient

Table 33. Reason for insufficient VA on post-operative 7th-14th days*

	N (=35)	%
Unrelated to operation		
Amblyopia	1	2.86
Diabetic retinopathy	2	5.71
Glaucoma	2	5.71
Hypertensive retinopathy	5	14.29
Macular degeneration	1	2.86
Related to operation		
Posterior Capsular Opacification	10	28.57
Corneal edema	10	28.57
Refraction	6	17.14
Residue at anterior capsule of the lens	1	2.86
Pigment on surface of lens	1	2.86

*More than one reason can be present in one patient

Table 34. Reason for insufficient VA on post-operative 30th-60th days*

	N (=15)	%
Unrelated to operation		
Glaucoma	2	13.33
Macular degeneration	3	20.00
Related to operation		
Posterior Capsular Opacification	7	46.67
Corneal edema	3	20.00
Refraction	1	6.67

*More than one reason can be present in one patient

Table 35. Reason for insufficient VA on post-operative 120th-180th days*

	N (=19)	%
Unrelated to operation		
Macular degeneration	9	47.37
Related to operation		
Posterior Capsular Opacification	8	42.11
Corneal edema	1	5.26
Refraction	1	5.26

*More than one reason can be present in one patient

Table 36. Reason for insufficient VA on post-operative 330th-420th days*

	N (=9)	%
Unrelated to operation		
Amblyopia	1	11.11
Hypertensive retinopathy	1	11.11
Macular degeneration	2	22.22
Related to operation		
Posterior Capsular Opacification	5	55.56
Total number of patients having VA<0.5	**9**	

*More than one reason can be present in one patient

10.2.9 Post-operative Pathologies

When post-operative pathology and complaints were followed up, pupillary fibrinoid was observed in 5 patients and treatment required increased intraocular pressure was observed in 4 patients on post-operative 1st-2nd days (Table 37); inflammatory findings at the intraocular lens were observed in 5 patients on the post-operative 7th-14th days (Table 38) and in 6 patients on the post-operative 30th-60th days (Table 39); 6 patients had treatment required increased intraocular pressure and 6 patients had inflammatory findings at the intraocular lens on the post-operative 120th-180th days (Table 40) and inflammatory findings at the intraocular lens were observed in 5 patients on post-operative 330th-420th days (Table 41). When all data obtained in the follow-ups were evaluated together, the most common pathology was inflammatory findings at the intraocular lens (4.68%) (Table 42).

Table 37. Pathology on post-operative 1st-2nd days

Post-operative pathology	Present		Not present		Total	
	N	%	N	%	N	%
Wound leakage	1	0.28	362	99.72	363	100.00
Simple anterior hemorrhage	2	0.55	361	99.45	363	100.00
Treatment required increased IOP	4	1.10	357	98.90	361	100.00
Pupillary fibrinoid	5	1.38	356	98.62	361	100.00
Cortical residue	3	0.83	357	99.17	360	100.00

Table 38. Pathology on post-operative 7th-14th days

	Present		Not present		Total	
	N	%	N	%	N	%
Treatment required increased IOP	2	0.64	311	99.36	313	100.00
Inflammatory findings at the intraocular lens	5	1.60	308	98.40	313	100.00
Pupillary fibrinoid	2	0.64	311	99.36	313	100.00
Cortical residue	2	0.64	311	99.36	313	100.00

Table 39. Pathology on post-operative 30th-60th days

	Present		Not present		Total	
	N	%	N	N	%	N
Treatment required increased IOP	1	0.37	271	99.63	272	100.00
Inflammatory findings at the intraocular lens	6	2.21	266	97.79	272	100.00
Cortical residue	1	0.37	271	99.63	272	100.00

Table 40. Pathology on post-operative 120th-180th days

	Present		Not present		Total	
	N	%	N	N	%	N
Inflammatory findings at the intraocular lens	6	1.92	306	98.08	312	100.00
Treatment required increased IOP	6	1.92	306	98.08	312	100.00

Table 41. Pathology on post-operative 330th-420th days

	Present		Not present		Total	
	N	%	N	N	%	N
Inflammatory findings at the intraocular lens	5	2.20	222	97.80	227	100.00

Table 42. Post-operative pathologies in all post-operative follow-ups*

	N (=363)	%
Presence of post-operative pathology	36	9.92
Inflammatory findings at the intraocular lens	17	4.68
Pupillary fibrinoid	6	1.65
Treatment required increased intraocular pressure	5	1.38
Cortical residue	4	1.10
Simple anterior hemorrhage	2	0.55
Wound leakage	1	0.28
Vitreous to wound	1	0.28

*More than one pathology can be present in one patient

10.3Safety Results

10.3.1 Adverse Events

Adverse events were observed in 1.38% of the evaluated patients during the study (n=5). The details of the adverse events are given in Table 43. The observed adverse events were posterior capsular opacification (n=4) and zonular weakness (n=1). Only one adverse event was found to be related to the intraocular lenses. When adverse events were evaluated according to age, 3 of adverse events were observed in the age group of 61-70 years. One adverse event was observed in both age groups of <=50 and 51-60 years.

Table 43. Distribution of adverse events

	N (=363)	%
Adverse Events	5	1.38
Occurrence time of adverse event		
Post-operative 1^{st}-2^{nd} days	1	0.28
Post-operative 7^{th}-14^{th} days	1	0.28
Post-operative 330^{th}-420^{th} days	3	0.83
Severity of adverse events		
Mild	4	1.10
Severe	1	0.28
Causal relationship with the device		
Possible relationship	1	0.28
Unrelated	4	1.10
Definition of adverse event		
Posterior Capsular Opacification	4	1.10
Zonular weakness	1	0.28
Age groups		
<=50	1	0.28
51-60	1	0.28
61-70	3	0.83
Centers		
Center No 1	4	1.10
Center No 2	1	0.28

10.3.2 VA Rates According to the Adverse Events

Visual acuity rates of patients who had or did not have adverse events on post-operative period are given in Tables 44, 45, 46, 47 and 48. Post-operative evaluations demonstrated that patients having adverse events possessed VA≥0.5 on the post-

operative 1st-2nd days, 30th-60th days, 120th-180th days, 330th-420th days. Only one patient having adverse event had VA<0.5 on the post-operative 7th-14th days.

Table 44. VA according to the. adverse event on post-operative 1st-2nd days

			VA<0.5	VA≥0.5	Total
Adverse event	Not present	N	112	245	357
		%	31,37	68,63	100,00
	Present	N	0	1	1
		%	0,00	100,00	100,00
	Total	N	112	246	358
		%	31,29	68,71	100,00

Table 45. VA according to the adverse event on post-operative 7th-14th days

			VA<0.5	VA≥0.5	Total
Adverse event	Not present	N	30	281	311
		%	9.65	90.35	100.00
	Present	N	1	1	2
		%	50.00	50.00	100.00
	Total	N	31	282	313
		%	9.90	90.10	100.00

Table 46. VA according to the adverse event on post-operative 30th-60th days

			VA<0.5	VA≥0.5	Total
Adverse event	Not present	N	16	257	273
		%	5.86	94.14	100.00
	Present	N	0	1	1
		%	0.00	100.00	100.00
	Total	N	16	258	274
		%	5.84	94.16	100.00

Table 47. VA according to the adverse event on post-operative 120th-180th days

			VA<0.5	VA≥0.5	Total
Adverse event	Not present	N	20	289	309
		%	6.47	93.53	100.00
	Present	N	0	2	2
		%	0.00	100.00	100.00
	Total	N	20	291	311
		%	6.43	93.57	100.00

Table 48. VA according to the adverse event on post-operative 330th-420th days

			VA<0.5	VA≥0.5	Total
Adverse event	Not present	N	7	214	221
		%	3.17	96.83	100.00
	Present	N	0	4	4
		%	0.00	100.00	100.00
	Total	N	7	218	225
		%	3.11	96.89	100.00

10.3.3 Adverse Events in the Study Centers

No statistically significant difference was observed between centers with respect to rates of adverse event (p=0.110, Fisher's exact test) (Table 49). Four adverse events were observed in Center 1 and remaining one adverse event was observed in Center 2.

Table 49. Distribution of adverse events in the study centers

			Adverse Event		
			Not present	Present	Total
Center no	1	N	121	4	125
		%	96.80	3.20	100.00
	2	N	125	1	126
		%	99.21	0.79	100.00
	3	N	112	0	112
		%	100.00	0.00	100.00
	Total	N	358	5	363
		%	98.62	1.38	100.00

Test	p
Fisher's exact	0.110

10.3.4 Serious Adverse Events

No serious adverse event was observed.

10.3.5 Deaths

No death was reported.

11 CONCLUSIONS

The final analysis of the study was performed on the data obtained from 363 patients (females 49.03%, males 50.97%). The mean age of the patients was 67.11±10.19 years. Preoperatively, no significant difference was found between the VA rates according to age groups (p=0.095).

According to post-operative evaluations, there was statistically significant difference between the age groups with respect to VA on post-operative 1^{st}-2^{nd} days, 7^{th}-14^{th} days, 30^{th}-60^{th} days and 120^{th}-180^{th} days ($p<0.001$, $p=0.001$, $p=0.041$, $p=0.042$, respectively). No statistically significant difference was observed in the rates of VA according to genders (post-operative 1^{st}-2^{nd} days $p=0.954$, 7^{th}-14^{th} days $p=0.335$, 30^{th}-60^{th} days $p=0.262$, 120^{th}-180^{th} days $p=0.303$ and 330^{th}-420^{th} days $p=1.000$).

In the comparison of pre-operative VA rates with post-operative values, a significant improvement was observed at post-operative 1^{st}-2^{nd} days, 7^{th}-14^{th} days, 30^{th}-60^{th} days, 120^{th}-180^{th} days and 330^{th}-420^{th} days ($p<0.001$ for each). When the rates of visual acuity of patients with and without preoperative ocular pathology were evaluated in all post-operative follow-up visits, statistically significant increase was observed in the VA of both groups. In the comparison of VA rates between the patients with and without pre-operative ocular pathology, statistically significant difference was observed between groups on the post-operative 1^{st}-2^{nd} days ($p<0.001$), 7^{th}-14^{th} days ($p<0.001$) and 30^{th}-60^{th} days ($p=0.002$). However, there was no statistically significant difference in visual acuity rates on the post-operative 120^{th}-180^{th} days and 330^{th}-420^{th} days with respect to the presence or absence of pre-operative ocular pathology ($p=0.260$ and $p=0.236$, respectively).

Total numbers of patients who had insufficient visual acuity were 95 on post-operative 1^{st}-2^{nd} days, 35 on post-operative 7^{th}-14^{th} days, 15 on post-operative 30^{th}-60^{th} days, 19 on post-operative 120^{th}-180^{th} days and 9 on post-operative 330^{th}-420^{th} days. The main reasons for insufficient visual acuity related with operation were corneal edema on post-operative 1^{st}-2^{nd} days (89.47% of the patients); posterior capsular opacification (28.57%) and corneal edema (28.57%) on post-operative 7^{th}-14^{th} days; posterior capsular opacification (46.67%) and corneal edema (20.00%) on post-operative 30^{th}-60^{th} days; posterior capsular opacification (42.11%) on post-operative 120^{th}-180^{th} days and posterior capsular opacification (55.56%) on post-operative 330^{th}-420^{th} days.

Number, severity, relation with the study device and outcome of the complications, pathologies and adverse events that develop within the study period would be

compared with the data presented in ISO 11979-7:2001(E) Annex D. However, the adverse events given in the historical data were not observed in the present study.

Adverse events were observed in only 1.38% of the evaluated patients during the study (n=5). The observed adverse events were posterior capsular opacification (n=4) and zonular weakness (n=1). Only one adverse event was found to be related to the intraocular lenses.

Post-operative evaluations demonstrated that patients having adverse events possessed VA≥0.5 on the post-operative 1^{st}-2^{nd} days, 30^{th}-60^{th} days, 120^{th}-180^{th} days, 330^{th}-420^{th} days. Only one patient having adverse event had VA<0.5 on the post-operative 7^{th}-14^{th} days.

The results of the final analysis performed on 363 patients showed that Zaraccom Foldable F260 Hydrophobic, Acrylic Intraocular Lens is safe and effective in terms of improving visual acuity after cataract surgery in patients with cataract.

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