EVALUATION OF EFFICACY AND SAFETY OF ZARACCOM UF60125 INTRAOCULAR LENSES IN CATARACT TREATMENT:

A National, Single-center, Prospective Clinical Device Study Including Historical Control Group

INTERIM ANALYSIS REPORT-1

Protocol Date	**:**	01 Jan 2008
Interim Analysis Report Date	**:**	20 Oct 2008
Interim Analysis Report Version	**:**	v1
Number of Centers	**:**	1
Clinical Device	**:**	Zaraccom UF60125 hydrophobic, acrylic, biconvex optic, foldable, monobloc posterior chamber intraocular lens
Coordinating Investigator	**:**	Assistant Prof. Ilker Toker, MD Cumhuriyet University School of Medicine, Department of Ophthalmology, 58140 Sivas Tel: 0346 219 13 00/2225
Sponsor Representative	**:**	Pınar Kaymak Anadolu Tıp Teknolojileri 1. Organize San. Bol. 2. Kisim 5. Cadde No.10 58060 Sivas Tel: 0346 218 14 18
Study Dates	**:**	April 2008 – October 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 UF60125 intraocular lenses in cataract treatment: A national, single center, prospective clinical device study including historical control group.
Interim analysis report date	20 Oct 2008
Interim analysis report version	v1
Indication	Microincision Cataract Surgery
Clinical device	Zaraccom UF60125 hydrophobic, acrylic, biconvex optic, foldable, monobloc posterior chamber intraocular lens
Study design	A national, single center, prospective clinical device study including historical control group
Objectives	Primary objective: • To evaluate the efficacy of Zaraccom UF60125 lenses in microincision cataract surgery in comparison to the data from the historical control group presented in [ISO 11979-7:2006(E) Annex B] standards on the clinical evaluation of intraocular lenses. Secondary objective: • To evaluate the safety of Zaraccom UF60125 lenses in microincision cataract surgery in comparison to the data from the historical control group presented in [ISO 11979-7:2006(E) Annex B] standards on the clinical evaluation of intraocular lenses.
Number of centers	1
Planned sample size	100 patients
Analyzed sample size	49
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 100 historical patients in ISO 11979-7:2006(E) Annex B and ISO/TR 22979:2006(E) 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 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 11979-7:2006. • 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	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 11979-7:2006(A). • The time passed for the post-operative BCVA to be 0.5 (6/12; 20/40). Secondary Evaluation Criterion: • 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 11979-7:2006(E) Annex B.

Statistical Analysis	Sample size: In accordance with the suggestions in ISO 11979-7:2006 and ISO/TR 22979:2006(E) 100 patients were planned to be recruited. Statistical analysis plan: All study data were summarized using descriptive statistics (e.g. mean, median, standard deviation, ratio). Age group analyses and the comparison of the data from pre-operative and post-operative examinations were performed by the appropriate parametric or non-parametric tests according to the type and distribution of the data. Level of statistical significance was set at $p<0.05$.
Date of study initiation and planned termination	The study was planned to start in April 2008 and terminate in October, 2009.
Results	Totally, 49 patients (females 42.9, males 57.1%) were analyzed and the mean age was 68.7±11.7. Efficacy Results: Visual acuity (VA) did not display any significant difference between the age groups at pre-operative and 1^{st}-2^{nd} day post operative time point ($p=0.071$; $p=0.109$, respectively). Compared to pre-operative values, visual acuity was significantly improved at post-operative 1^{st}-2^{nd} day ($p=0.001$) Complete improvement in all age groups was observed at the post operative 7^{th}-14^{th} days. Safety Results: No adverse event was observed.
Conclusions	Preoperatively, VA rates of 60.9% of the patients were <0.5. On post-operative 1^{st}-2^{nd} days, no statistically significant difference was found in VA rates with regards to the age groups. Visual acuity rates were significantly improved on day 14 after surgery and VA rates of the patients assessed were above 0.5. On post-operative 1^{st}-2^{nd} days, a fast and significant improvement was observed when compared with pre-operative VA rates and 68.3% of patients had post-operative VA rates higher than 0.5. No adverse event was observed till the time of the interim analysis. The interim results of the present study show that Zaraccom Foldable UF60125 Hydrophobic, Acrylic Intraocular Lens is obviously effective and safe in improving visual acuity after microincision cataract surgery which is a safe and easy procedure.

1 SIGNATURE PAGE

Name İlker Toker		Signature:
Title		
Responsibility in the Study	Coordinating Investigator	Date: …/……/…….
Name Pınar Kaymak		Signature:
Title		
Responsibility in the Study	Sponsor Representative	Date: …/……/…….
Name Banu Bayyurt		Signature:
Title		
Responsibility in the Study	CRO Medical Writer	Date: …/……/…….
Name Hilal Aşık		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.

Phacoemulsification is the most common extracapsular lens extraction method which enables microincision cataract surgery that can be performed by a small incision of only 2.2 mm. Small incision results in less alteration of the shape of the cornea and enables controlled surgery. Small incision cataract surgery is another method which is sutureless manual cataract surgery. Although this method can be rapidly performed, effects of the surgery are not definite as phacoemulsification method (5).

Microincision cataract surgery (MICS or alternatively phakonit and biaxial phacoemulsification) is a novel method performed with a smaller incision which minimize surgical trauma, decrease surgically induced astigmatism and eliminate optical disturbances in the corneal optics caused by the incision and the wound-healing process (6). In MICS, naked phacoemulsification needle is used to decrease the incision size (7). Smaller incision sizes decrease the surgical aggressiveness and have similar biocompability when compared with the traditional cataract surgery (8). MICS also provides better visual quality by improving the optical quality of the cornea (9).

The most advanced technique performed by microincision surgery is with foldable intraocular lens implants. The first intraocular lenses have been implanted with incisions of 6 mm and needed suturing. Today, self sealing foldable silicone or acrylic/methacrylate intraocular lenses are developed (3).

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).

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 (12). All the biocompatibility tests that the designed IOL material should be passed through are mentioned in the Intraocular Lens Guidance Document (13). 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 (14).

The aim of the present study is to evaluate the efficacy and safety of Zaraccom Foldable UF60125 Hydrophobic, Acrylic Intraocular Lenses designed to be used in microincision cataract surgery.

2.2 Zaraccom Foldable UF60125 Hydrophobic, Acrylic Intraocular Lens

2.2.1 Mechanical Properties

UF60125 Hydrophobic, Acrylic Intraocular lens is a single piece (monobloc), foldable lens which is designed as an optic device to be implanted behind the iris, in the capsular bag from an incision of 2,2/2,4 mm with cartridge micro injection system for microincision cataract surgery. The intraocular lenses consist of acrylic with chemically bonded UV-absorber which has biconvex optic with supporting haptics as posterior chamber lenses. Refractive index of the UF60125 intraocular lens is 1.51. These lenses are sterilized with ethylene oxide and compatible to be used in YAG laser applications. The measurements of the parameters providing intracapsular stability are: optical diameter 6.00 mm, total length 12.50 mm. A constant is 118.4. The power of these lenses is +0 through and +40 dioptre.

2.2.2 Raw Material

In the production of Zarracom Foldable Hydrophobic Acrylic Lenses, a homogenous composite is formed by the addition of high purity and quality monomers which provide the foldability property to the material. Also due to their high ability to absorb UV rays, lenses with the structure of high purity and quality of oligomeric methacrylate material are obtained.

3 OBJECTIVES

3.1 Primary Objective

The primary objective of the present study is to evaluate the efficacy of Zaraccom UF60125 lenses in microincision cataract surgery in comparison to the data from the historical control group presented in [ISO 11979-7:2006(E) Annex B] standards on the clinical evaluation of intraocular lenses.

3.2 Secondary Objective

The secondary objective is to evaluate the safety of Zaraccom UF60125 lenses in microincision cataract surgery in comparison to the data from the historical control group presented in [ISO 11979-7:2006(E) Annex B] standards on the clinical evaluation of intraocular lenses.

4 STUDY PLAN

4.1 Study Design

This study was designed as a national, single center, 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 100 historical patients in ISO 11979-7:2006(E) Annex B and ISO/TR 22979:2006(E) will be used as the control data in the final analysis.

4.4 Planned and Analyzed Sample Size

By the time interim analysis was performed, 49 patients were included in the study.

4.5 Study Center

The study was conducted in Cumhuriyet University School of Medicine, Department of Ophthalmology, in coordination of Assistant Prof. Ilker Toker. The responsible investigator or the staff charged by the investigator has been responsible from the implementation of the study procedures.

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 11979-7:2006(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 1st-2nd, 7th-14th, 30th-60th, 120th-180th and 330th-420th 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 11979-7:2006(A).
- 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 11979-7:2006(E) Annex B.

5 STATISTICAL METHODS

5.1 Sample Size Calculation

In accordance with the suggestions in ISO 11979-7:2006 and ISO/TR 22979:2006(E) 100 patients were planned to be recruited.

5.2 Data Entry

5.3 Statistical Analysis

All study data obtained till the time of the analyses were summarized using descriptive statistics (e.g. mean, median, standard deviation, and ratio). Age group analyses and the comparison of the data from pre-operative and post-operative examinations were performed by the appropriate parametric or non-parametric tests according to the type and distribution of the data. 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 has been 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 have 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 is 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.

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 has been conducted in the sponsorship of the Anatolia Medicine Technologies Co. 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 pass some or all of its responsibilities to a Contract Research Organization. This situation does not eliminate any of the sponsor's responsibilities.

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

No protocol deviation was observed.

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 can not 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 can not 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 can not 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 1 summarizes the assessment of relation to the study device.

Table 1. 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 Sociodemographic Characteristics

The interim analysis was performed on the data obtained from 49 patients (females 42.9, males 57.1%) included so far. The mean age of the patients was 68.7±11.7. Distribution of the patients according to age groups is presented in Table 2.

Table 2. Distribution of the patients according to age decades. Data were presented as n (%).

Age Groups	Number (%)
40-50	4 (8.2)
51-60	5 (10.2)
61-70	12 (24.5)
71-80	24 (49.0)
>80	4 (8.2)
Total	49 (100)

10.2 Efficacy Results

10.2.1 Pre-Operative Results

Visual acuity measured before the operation with respect to the age groups, is presented in Table 3. No significant difference was observed in the VA rates between the age groups (p=0.071, Chi-square test).

Table 3. Distribution of the patients according to pre-operative visual acuity rates and age groups.

		Pre-Operative Visual Acuity		
		<0.5	**>0.5**	**Total**
40-50	**n**	3	1	4
	%	75	25	100
51-60	**n**	3	1	4
	%	75	25	100
61-70	**n**	3	8	11
	%	27.3	72.7	100
71-80	**n**	15	8	23
	%	65.2	34.8	100
>80	**n**	4	0	4
	%	100	0	100
Total	**n**	28	18	46
	%	60.9	39.1	100

10.2.2 Post-Operative Results

Visual acuity rates on the post-operative 1st-2nd days with respect to the age decades are presented in Table 4. No statistically significant difference was observed between the age groups with respect to visual acuity (p=0.109, Chi-square test).

Table 4. Distribution of the patients according to the visual acuity rates on post-operative 1st-2nd days and age groups.

		Post-operative (1st-2nd days) VA		
		<0.5	**>0.5**	**Total**
40-50	**n**	0	3	3
	%	0	100	100
51-60	**n**	1	3	4
	%	25	75	100
61-70	**n**	1	11	12
	%	8.3	91.7	100
71-80	**n**	10	11	21
	%	47.6	52.4	100
>80	**n**	2	2	4
	%	58.3	41.7	100
Total	**n**	14	30	44
	%	31.8	68.2	100

Visual acuity rates on the post-operative 7^{th}-14^{th} days with respect to the age decades are presented in Table 5. On the post-operative 7^{th}-14^{th} days, visual acuity rates of all age groups improved completely.

Table 5. Distribution of the patients according to the visual acuity rates on post-operative 7^{th}-14^{th} days and age groups.

		Post-operative (7^{th}-14^{th} days) VA	
		>0.5	**Total**
51-60	**n**	1	1
	%	100	100
61-70	**n**	5	5
	%	100	100
71-80	**n**	5	5
	%	100	100
Total	**n**	11	11
	%	100	100

10.2.3 Pre- and Post-operative Comparisons

A comparison of pre-operative and post-operative 1^{st}-2^{nd} day's visual acuity rates is presented in Table 6. Compared to pre-operative values, a significant improvement was observed at post-operative 1^{st}-2^{nd} days (p=0.001, McNemar).

Table 6. Comparison of pre-operative and post-operative 1st-2nd day's visual acuity rates.

			Post-operative 1st-2nd days VA		
			<0.5	**>0.5**	**Total**
Pre-operative VA	**<0.5**	**n**	10	18	28
		%	35.7	64.3	100
	>0.5	**n**	3	10	13
		%	23.1	76.9	100
	Total	**n**	13	28	41
		%	31.7	68.3	100

Visual acuity rates on the post-operative 7th-14th days are presented with comparison to pre-operative rates in Table 7.

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

			Post-operative 7th-14th days VA	
			>0.5	**Total**
Pre-operative VA	**<0.5**	**n**	6	6
		%	100	100
	>0.5	**n**	4	4
		%	100	100
	Total	**n**	10	10
		%	100	100

According to the pre-operative AV rates, which were mostly smaller than 0.5 (60.9%), the efficiency of IOL was observed with complete and significant improvement at the end of the last follow up visit (100%; p=0.011, Cochran's Q) (Figure 1).

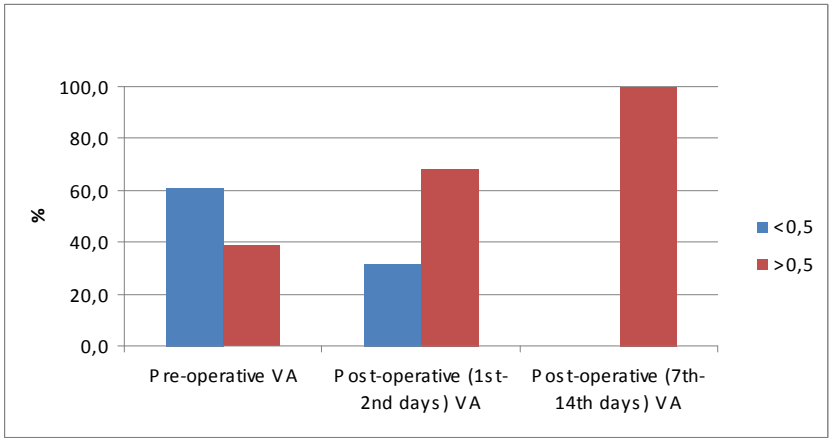

Figure 1. Visual acuity percentage according to follow up visits.

10.3Safety Results

10.3.1 Adverse Events

No adverse event was observed.

10.3.2 Serious Adverse Events

No serious adverse event was observed.

10.3.3 Deaths

No death has been reported.

11 CONCLUSIONS

The results of this interim analysis performed on 49 patients showed that Zaraccom Foldable UF60125 Hydrophobic, Acrylic Intraocular Lens is effective in terms of improving visual acuity after microincision cataract surgery in patients with cataract. Preoperatively, no significant difference was found between the VA rates according to age groups (p=0.071).

on post-operative 1^{st}-2^{nd} days, no statistically significant difference was found in VA rates with regards to the age groups (p=0.109) and 68.2% of patients had post-operative VA rates above 0.5, in this period. On day 14 following the surgery, visual acuity of all patients assessed was above 0.5.

A significant improvement was found (p=0.001) on post-operative 1^{st}-2^{nd} days, comparet with preoperative assessment and it is notable to indicate that 68.3% of patients had post-operative VA rates higher than 0.5.

Microincision cataract surgery is a promising procedure which is generally defined as improving visual acuity with reducing surgical complications. Till the time of the interim analysis no adverse event was observed.

The interim results of this study indicate that Zaraccom Foldable UF60125 as a developed intraocular lens in terms of efficiency and safety. The final results of this study, which will represent comparisons with the data for post-operative visual acuity and adverse event rates presented for 100 historical patients in ISO 11979-7:2006(E) Annex B and ISO/TR 22979:2006(E) as the control data.

12 REFERENCES

1. Allen D, Vasavada A. Cataract and surgery for cataract. BMJ 2006;333: 128-132.
2. Mukesh BN, Le A, Dimitrov PN, Ahmed S, Taylor HR, McCarty CA. Development of Cataract and Associated Risk Factors. Arch Ophthalmol 2006;124:79-85.
3. Woodcock M, Shah S, Smith RJ. Recent advances in customising cataract surgery. BMJ 2004;328:92-6.
4. Brian G, Taylor H. Cataract blindness – challenges for the 21st century. Bulletin of the World Health Organization 2001;79(3):249–256.
5. Allen D, Vasavada A. Cataract and surgery for cataract. BMJ 2006;333:128-132.
6. Alio´JL, Schimchak P, Monte´s-Mico´ R, MPhil, Galal A. Retinal image quality after microincision intraocular lens implantation. J Cataract Refract Surg 2002;31:1557-1560.
7. Thomas R, Navin S, Parikh R. Learning micro incision surgery without the learning curve. Ophthalmology Practice 2008;56:135-137.
8. Alió J, Rodriguez-Prats JL, Galal A. Advances in microincision cataract surgery intraocular lenses. Curr Opin Ophthalmol. 2006;17(1):80-93.
9. Yao K, Tang X, Ye P. Corneal astigmatism, high order aberrations, and optical quality after cataract surgery: microincision versus small incision. J Refract Surg. 2006;22(9): 1079-82.
10. Abela-Formanek C, Amon M, Schauersberger J, Kruger A, Nepp J, Schild G. Results of hydrophilic acrylic, hydrophobic acrylic, and silicone intraocular lenses in uveitic eyes with cataract. J Cataract Refract Surg 2002;28:1141–1152.
11. Abela-Formanek C, Amon M, Schauersberger J, Schild G, Kolodjaschna J, Barisani-Asenbauer T, Kruger A. Uveal and capsular biocompatibility of 2 foldable acrylic intraocular lenses in patients with uveitis or pseudoexfoliation syndrome. J Cataract Refract Surg 2002;28:1160–1172.
12. Holladay JT. Evaluating the intraocular lens optic. Survey of Ophthalmology. 1986;30(6):385-390.

13. Intraocular Lens Guidance Document U.S. Department of Health and Human Services Food and Drug Administration Center for Devices and Radiological Health Intraocular and Corneal Implants Branch Division of Ophthalmic Devices Office of Device Evaluation.

14. Apple DJ, Solomon KD, Tetz MR, et al. Posterior capsule opacification. Surv Ophthalmol 1992;37:73-116.