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ANHANG 3

FINAL STUDY REPORT (AMENDED)

Phase III double blind, randomised, multi-centre study to determine the safety and efficacy of a 1% (w/v) Sodium Hyaluronate solution from two separate sources during intraocular cataract extraction and lens implantation surgery

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Investigators Declaration

The signatories below have signed to certify that they have read this document and are in agreement with the conclusions of this report.

Professor D L Easty..... Date 28th Nov 95

Dr C Illingworth..... Date 28/11/95

Mr P Condon..... Date 28/Nov 95

Dr T Kennelly..... Date 4/12/95

Mr P Rosen..... Date 12-12-95

Miss B Sallustio..... Date 1-12-95

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Statement on Draft and Procedure for Finalisation

The final amended draft of this report was prepared on 20 November 1995. The Report was distributed to all the Investigators involved in the Study for their comment and signature. In addition, it was distributed to the Quality Assurance Auditor, Mr B White, Medical Statistician, Dr R Prescott, the Medical Advisor, Mr G Mackintosh and the Research Advisor, Dr E Hansson.

The report was finalised when all the interested parties had made comment and the document had been signed by all the Clinical Investigators.

DECLARATION

We, the undersigned, hereby declare that this study was performed in accordance with the principles of Good Clinical Practice. The study was conducted according to the procedures herein described and this report represents a true and accurate record of the results obtained.

..... Date 20/11/95

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SUMMARY

One hundred and thirty-nine patients (47 male and 92 female) of mean age 74.8 years (S.D. 8.6 years) with a known history of cataract (unilateral or bilateral) were recruited into a multi-centre randomised controlled study to assess the safety and efficacy of Sodium Hyaluronate 1% (w/v) from two separate sources when used during intraocular cataract extraction and lens implantation surgery. Four patient data sets from Centre OX were excluded from analysis because of major protocol violations. Patients who were willing and able to give informed consent were screened using the study entry criteria prior to surgery and allocated the next available study number. Patients either received treatment with 1% (w/v) Sodium Hyaluronate from a bacterially fermented source (*Streptococcus equi*) or 1% (w/v) Sodium Hyaluronate from a rooster comb source, according to a predetermined randomisation list. Baseline assessments were made of intraocular pressure (I.O.P.), flare in the anterior chamber, cells in the anterior chamber and any side-effects or unwanted symptoms were recorded. A 20ml blood sample (bloods were not taken from patients at Oxford (Centre OX)) was taken at baseline to measure lymphocyte transformation. On the day of surgery, the duration of the operative procedure was noted, the surgeon recorded his evaluation of the operative procedure success and his subjective assessment of the viscoelastic's performance. The patients were assessed on a further 3 occasions post-operatively in line with the routine hospital procedure. On each occasion IOP, flare and cells in the anterior chamber were recorded. A 20ml blood sample was taken at each visit. In addition, the Investigator recorded any unwanted symptoms / side effects elicited voluntarily by the patient and his own assessment of the patient's progress.

One hundred and thirty-eight operations were conducted on 135 patients who were followed up for 2 months. Three patients who had bilateral cataracts were willing and able to give informed consent, and underwent the second operation as part of the study. The second operation was conducted a minimum of 14 days after the first operation. On breaking the randomisation code at all centres, it was revealed that 68 patients received the bacterially fermented product and 70 patients received the rooster comb product. Of the three bilateral patients, one was conducted using bacterially fermented product, the other two used rooster comb product. The characteristics of both groups differed slightly, but none of the differences in either treatment limb were greater than that expected by chance.

All operations were judged to be successful in each of the treatment groups, with the exception of one patient who received the rooster comb product and developed peroperative (during surgery) complications. The performance of the bacterial source Sodium Hyaluronate was rated as either good or very good in 87% operative procedures. The rooster comb source product was rated either good or very good in 94% operative procedures. This difference was not statistically significant ($p = 0.21$). Patients in Bristol (Centre B) showed a pattern of very small mean reduction in IOP in both treatment groups, with no suggestion of differences between treatments. Some differences were seen in IOP between treatment groups in Ireland (Centre EB), where patients were seen the day after surgery, but these differences were not statistically significant. In Centre OX there was a mean increase in IOP of 5.6mmHg at the first post-operative visit. The increase was greater in patients who received the rooster comb product but the difference between treatments was not significant.

Subjective assessment of iritis by cellular response, was greater at Centre EB than in the other two centres. Overall, moderate to severe responses were recorded in 25 (19%) of patients at the first post-operative visit, falling to 3 (2%) of patients at the next visit. At the final visit cellular response was recorded as none in all but 11 (8%) of patients who had mild cellular response. The responses recorded were similar in both treatment groups throughout follow-up.

Overall 86% of patients showed some degree of flare at the first post-operative visit. With the exception of 7 patients, who had faint flare at Visit 5, all reported flare had resolved by Visit 5. There was no indication of a treatment difference. Of those seven patients, three received the bacterially fermented product and four received the rooster comb product.

Overall 85% of patients were rated as having a good or very good recovery throughout the study. The patient recovery steadily improved over the study period with 90% of patients being classified as either "good" or "very good" at Visit 5. There was no significant difference in patient recovery between treatment groups throughout the study. The patients' visual acuity (VA) recorded at the final visit was 6/12 or greater in 74.8% of patients. Patients whose VA was less than 6/12 were noted as having ongoing intraocular pathology which were not related to the current study. No difference in the final visual acuity was observed between treatment groups.

The results of the blood samples taken from these patients for lymphocyte transformation testing are the subject of a separate report.

Throughout the study 17 adverse events were recorded. Twelve of these adverse events were peroperative complications. Two cases of infective endophthalmitis, one in each treatment group, were reported, one case showed *staphylococcus* on enhanced culture from a vitreous tap, negative laboratory findings were recorded in the second case. The remaining three adverse events, two of which were reported as death, were unrelated to the study.

No difference was detected in any of the clinical measurements between treatments in this study.

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INTRODUCTION

Sodium Hyaluronate, a large polysaccharide molecule is present in nearly all connective tissue matrices of vertebrate organisms[1]. In the human body it is an important structural element of the skin, subcutaneous and interstitial connective tissues, synovial tissue and fluid, umbilical cord, and the vitreous. In the eye, Sodium Hyaluronate is found not only in the vitreous but also, in a much lower concentration, in the aqueous humour and in the connective tissues of the angle[2].

Balazs in 1958 first suggested using Sodium Hyaluronate as a vitreous replacement[3]. Since its early uses, Sodium Hyaluronate has been used routinely to facilitate anterior segment surgical procedures. The benefits of viscoelastics in surgical procedures such as cataract extraction are well documented[4].

During eye surgery to replace a lens made opaque by cataract the eyeball must be penetrated to remove the lens and replace it with an artificial one. Sodium Hyaluronate is introduced into the anterior chamber through a small cannula, before lens extraction to protect the corneal endothelium and to maintain a deep anterior chamber. The maintenance of a deep anterior chamber during surgery allows efficient manipulation during surgery and produces less trauma to the corneal endothelium and other surrounding tissues[5]. In order to implant an intraocular lens an additional amount of Sodium Hyaluronate may be introduced before insertion of the lens and may be used to coat the artificial lens and surgical instruments.

The intraocular lens is then introduced into the anterior chamber. Once the intraocular lens has been implanted the Sodium Hyaluronate is removed by irrigation with a sterile solution of isotonic saline to avoid elevated intraocular pressure in the post-operative period[6].

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5. Balazs, E A., Miller, D.& Stegmann, R. Viscosurgery and the use of Hyaluronate in intraocular lens implantation 1979. Paper presented at the International Congress and First Film Festival on Intraocular Implantation, Cannes France.

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The amount of Sodium Hyaluronate administered during surgery should be sufficient to maintain the integrity and depth of the anterior chamber, to enable safe insertion of the lens, without leaving any excess material in the eye.

It is the viscoelastic property of Sodium Hyaluronate that makes it an ideal support material in ophthalmic surgery. Its use as a 1% (w/v) solution (in phosphate buffered saline) during surgery not only maintains a deep anterior chamber affording valuable space during operative procedures but also reduces post-operative problems i.e. reported post-operative corneal endothelial cell loss after extracapsular cataract extraction using Ringer's lactate averaged 14% and using Sodium Hyaluronate averaged 6% ($p < 0.01$)[7].

Over the last decade experience with Sodium Hyaluronate has been limited to the use of a preparation called Healonid↓, a product manufactured from rooster combs by Pharmacia. Two recent double blind studies comparing commercially available Sodium Hyaluronate 1% (w/v) and a bacterially fermented (*Streptococcus equi*) Sodium Hyaluronate solution 1% (w/v) have shown no statistically significant difference between the two products when used in cataract surgery[8,9]. These studies measured IOP, Corneal Thickness, and Endothelial Cells Counts pre- and post-surgery.

The aim of the current study was to compare the performance in patients of the bacterial source Sodium Hyaluronate manufactured by Fermentech Medical Ltd and the existing rooster comb source Sodium Hyaluronate. The study looked specifically at the inflammatory response generated by both products following cataract extraction and lens implantation surgery.

REFERENCES

7.Stegmann, R., & Miller, D. Extracapsular cataract extraction with hyaluronate sodium. Ann. Ophthamol 1982 ; 14: 813 - 815.

8.CT9101. G Mackintosh. . A randomised, comparative study to determine the safety and efficacy of OPHTHALIN* versus Healonid® (both 1% w/v Sodium Hyaluronate solutions) during intraocular surgery. In Press.

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↓ Registered Trademark Pharmacia AB, Sweden

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PATIENTS AND METHODS

Study Design

The Study was a prospective double blind multi-centre study to assess the safety and efficacy of a bacterially fermented source of Sodium Hyaluronate 1% (w/v) compared to a standard reference product.

Study Population

The study population consisted of adults with proven cataracts (unilateral or bilateral) requiring surgery to replace the affected lens. All patients had previously presented to or had been referred to, the study centre and had a well documented history of cataract.

Measurements

a. Efficacy

The primary measure of efficacy in this study was the investigators' assessment of success, of the operative procedure. Success in this study was purely the physical success of maintaining a deep anterior chamber enabling the artificial lens to be implanted.

In those patients for whom a bilateral operation was planned over the designated time scale, the measurement of efficacy was the investigators' assessment of success of both the operative procedures.

b. Safety

The measures of safety and tolerance in this study were:-

a] A rise in intraocular pressure.
b] Iritis, as determined by the number of cells per defined field.
c] Iritis as determined by flare in the anterior chamber.
d] Adverse events.
e] Immunological blood results reported in a separate document

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INCLUSION CRITERIA

a. Patients aged over 18yrs (Adult males, post menopausal females, or females with a recognised reliable form of contraception) with proven cataract (bilateral or unilateral) who would normally have been considered eligible for surgery to replace the affected lens.

b. Patients with bilateral cataract, where it was planned to operate on both eyes within a 6 month period.

EXCLUSION CRITERIA

a. Patients whose Intraocular Pressure was ≥ 22 mm Hg.

b. Patients with glaucoma, a personal history of glaucoma or an anatomic anomaly causing glaucoma.

c. Patients receiving any topical applied drugs which influencde Intraocular Pressure i.e. timolol, acetazolamide.

d. Patients with previous significant anterior segment inflammation or trauma (surgical or otherwise). **This did not exclude previous cataract surgery patients who had an uneventful operation and recovery period.**

e. Patients who during their previous cataract operation and recovery period, demonstrated significant signs of inflammation due to the Sodium Hyaluronate used during surgery.

f. Patients with known corneal endothelial cell count of ≤ 1000 cells / mm^2.

g. Patients who received anticoagulant 4 days prior to surgery.

h. Patients who received an experimental drug within the previous six weeks.

i. Patients with known hypersensitivity to Sodium Hyaluronate or any other viscoelastic substances.

j. Positive pregnancy test, unreliable contraception, lactating mothers.

k. Patients incapable of giving written informed consent or complying with the protocol.

l. Patients unwilling to have blood samples taken

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Procedures

Informed Consent

The Investigator explained and discussed the study with every patient. Every patient was made aware of the hazards which were known or may have been reasonably predicted with particular reference to the study. The patient was informed of the alternative treatments available and reassured that there was no obligation to participate. The patient could at any time withdraw from the study without giving a reason if they did not want to, in the knowledge that their treatment would not be affected in any way.

Informed consent was obtained from all patients in accordance with the Declaration of Helsinki. An example of the Patient Information Leaflet and Informed Consent Forms are shown in the sample Case Record Forms (Appendix 2).

Blinding & Randomisation

The surgeon was aware of which source of Sodium Hyaluronate the patient received. The outer packages were all identical except for the Randomised Code Numbers. It was impossible to blind the syringes to be used during surgery, therefore it was ensured that the Investigator making the assessment of patient recovery was unaware of the source and did not handle the syringe.

Only the Production Department of Fermentech were aware of the details of randomisation code. Attached to each individual patient's Case Record Form (CRF) was a sealed envelope for use in emergency containing details of which product the patient had received. This sealed code-break envelope was opened only in case of emergency and the Clinical and Regulatory Departments of Fermentech were informed immediately.

The emergency code-break labels were examined at the end of the study to ensure they were intact and had not been tampered with.

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Operation Procedure

Patients recruited to the study had their cataract removed by either extra capsular extraction or phacoemulsification technique, as outlined below, dependent on the individual surgeon's preference.

Procedure for Extra Capsular Extraction

A favoured lid speculum was placed in the eye. A superior rectus stay suture was inserted to help immobilise the eye[10]. The cornea was kept moist and clear by regular application of sterile isotonic saline. The eye was then ready for surgery.

An opening was made into the anterior chamber of the affected eye, into which Sodium Hyaluronate was injected. An anterior capsulotomy or capsulorhexis was performed. The initial incision was then extended after which the lens nucleus was evacuated. The lens cortex was irrigated / aspirated with a sterile balanced salt solution/Hartmans after which a further injection of Sodium Hyaluronate was administered. The intraocular implant was coated with hyaluronate and then implanted into the eye. All excess Sodium Hyaluronate was removed as before by irrigation / aspiration with a sterile solution of balanced salt solution/Hartmans. The stay sutures were removed, followed by the lid speculum. The operation was complete and the appropriate dressings were applied.

Procedure for Phacoemulsification.

A 6mm limbal conjunctival incision (this was a corneal pocket incision in Centre OX) was made followed by a half thickness frown shaped scleral incision, 4.5 to 5mm in cord length. The scleral incision was undermined using a crescent knife and a 2.5mm keratome used to enter the eye making a valvular type wound. After filling the anterior chamber with viscoelastic, a capsulorhexis was performed using forceps (utilising a needle in Centre OX). Hydrodissection was then performed.

Phacoemulsification was performed by a divide and conquer technique. The residual cortex was removed with automated irrigation aspiration. Sodium Hyaluronate was then used to fill the anterior chamber and capsular bag before implantation of the intraocular lens into the capsular bag. Following implantation the Sodium Hyaluronate was removed. At the end of the procedure a subconjunctival injection of Gentamicin alone, or a combination of Gentamicin and Betnesol was made into the conjunctival flap adjacent to the wound. The infusion fluid was BSS mixed with Adrenaline produced by Alcon or locally in the pharmacy department.

REFERENCES

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DRUGS AND DOSAGE

All patients received treatment with 1% w/v Sodium Hyaluronate administered by the same method. The amount of Sodium Hyaluronate varied, depending on the specific clinical requirements for each individual patient. The amount of Sodium Hyaluronate administered in each case was recorded.

Medication Form, Route of Administration And Dose Regime :

0.5 ml of 1% w/v Sodium Hyaluronate in Phosphate Buffered Saline supplied in a sterile syringe. The Sodium Hyaluronate was applied locally to the eye using the sterile cannula supplied. The dose regime was one application during surgery. The time of administration was noted on the appropriate page of the Case Record Form.

Duration of Therapy : < 1 Day (i.e. duration of surgical procedure)

Reference Drug	Sodium Hyaluronate (1% w/v in PBS)
Dose Regimen	Single application 1% w/v Sodium Hyaluronate

CLINICAL TRIAL SUPPLIES

All medication for the study was supplied by Fermentech Medical Limited. All medication was packed in labelled boxes containing 1 sterile disposable syringe: Sodium Hyaluronate 1%.

Formulation - Fermentech Source	Rooster Comb Source
Each ml contains	Each ml contains
Sodium Hyaluronate 10 mg Sodium chloride 8.5 mg Disodium hydrogen phosphate dihydrate 0.28 mg Sodium dihydrogen phosphate dihydrate 0.045 mg Water for injection qs	Sodium Hyaluronate 10 mg Sodium chloride 8.5 mg Disodium hydrogen phosphate dihydrate 0.28 mg Sodium dihydrogen phosphate hydrate 0.04 mg Water for injection qs
Batch Number: 512112, Expiry 14/10/95	Batch Number: UE50727, Expiry 5/5/97

Storage Sodium Hyaluronate was stored at 2 - 8 degrees C, was protected from light and freezing. These conditions were strictly adhered to.

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Labelling, Emergency Code-Break

The outer package and syringe contained the patient number. The label on the outer packaging had a tear off portion bearing the patient's number which was affixed to the appropriate Medication Page of the Case Record Form.

In addition, the label also carried the Company Name, Address "Keep out of the reach of children" and "Clinical Trial Material - Study Number CT9405B, CT9405OX or CT9405EB".

A sealed envelope indicating which product the patient received was attached to each individual patient's case record form. This was only opened in an emergency to reveal the patient's medication. Fermentech Medical Ltd was informed of all code breaks. On completion of the study, all unopened emergency code break envelopes were returned to Fermentech Medical Ltd.

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Visit Schedules / Assessments And Recordings

Visit 1 [Pre-operative assessment] - Patients who were considered eligible for recruitment into the study were examined and questioned about their relevant medical history prior to admission. If they were eligible for the study they were given the patient information leaflet (Appendix 2) and the opportunity to ask questions. The patient was asked to give his/her informed consent. Baseline assessments of intraocular pressure, iritis as both cellular response and flare in the anterior chamber were recorded at this visit. The investigator assessed the baseline values using the Langham Pneumo-Applanation Tonometer and a Slit Lamp Microscope adjusted to the standardised predetermined settings [see Assessments].

The details of the physical examination and the medical history were transcribed into the Case Record Forms along with all other relevant information including demographics, concomitant medication, and baseline clinical details. A 20ml blood sample was taken according to the standard procedure outlined under the Assessments Section - Blood Sampling Procedure, **blood samples were not taken from patients in Centre OX.**

Visit 2 [Operative procedure] - The patients underwent surgery to remove the lens affected by cataract and replace the lens with a prosthesis. During the operative procedure the surgeon used Sodium Hyaluronate as per routine clinical practice. After the surgery had been completed the surgeon made an assessment of the efficacy of the Sodium Hyaluronate and noted any relevant points concerning the operative procedure, success etc.

Patients were asked if they had suffered any Adverse Events or had any comments.

A 20ml blood sample was taken 2 hours after surgery according to standard procedure, **blood samples were not taken from patients in Centre OX.**

Day Case Surgery - If the investigator was satisfied with the patient's progress, the patient was discharged in accordance with routine hospital procedure. The patient was given a follow-up appointment to be seen by the investigator 1 or 7 days after their operation depending on routine practice.

In-Patient Surgery - The standard post-operative recovery procedures of the hospital were followed with these patients. When the investigator was satisfied with the patient's progress, the patient was discharged in accordance with routine hospital procedure. The patient was given a follow-up appointment to be seen by the investigator 1 or 7 days after their operation depending on routine practice.

Visit 3 Day 1 or 7 - Patients were asked if they had suffered any Adverse Events or had any comments. Patients then had their eye examined. The investigator recorded IOP, Flare in the anterior chamber and Iritis/cellular response. The investigator made his assessment using the Slit Lamp Microscope adjusted to the standardised predetermined settings.

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The Investigator made an assessment of the patient's recovery and noted any details on raised IOP and details of any drugs administered or changes in concomitant medication. The patient was given his/her next follow-up appointment (Visit 4) with the investigator 21 - 28 days after their operation.

Visit 4 Day 21 or 28 - Patients were asked if they had suffered any Adverse Events or had any comments. Patients then had their eye examined. The investigator recorded IOP, Flare in the anterior chamber and Iritis/cellular response. The investigator made his assessment using the Slit Lamp Microscope adjusted to the standardised predetermined settings. A 20ml blood sample was taken according to standard procedure, **blood samples were not taken from patients in Centre OX.**

The Investigator made an assessment of the patient's recovery and noted any relevant points including; any rise in IOP, any inflammation, and details of all drugs administered or changes in concomitant medication. The patient was given a follow-up appointment to be seen by the investigator 4 weeks from the date of this visit i.e. 56 - 63 days after their operation.

Visit 5 Day 56 - 63 - The procedures performed at Visit 4 were followed exactly. In addition, the Investigator made a final overall assessment of the patient's recovery and noted any relevant points. A 20ml blood sample was taken according to standard procedure, **blood samples were not taken from patients in Centre OX.**

Unilateral Cataract Extraction - If the patient required only a unilateral cataract extraction, he/she had completed the study. The Investigator filled out the Study Completion Form in the Case Record Forms.

Bilateral Cataract Extraction - If the patient was scheduled to have bilateral cataract extraction, a date was given for the second operation and the Case Record Forms retained. The procedures and visits schedule for the second phase of the study were identical to that of the first operation. When the bilateral cataract patients completed the second phase of the study, the Investigator completed the Study Completion Form in the Case Record Forms.

Assessments

All patients had baseline and three post-operative measurements recorded of IOP, Flare and Cells in the anterior chamber. A 20ml blood sample (with the exception of patients at Centre OX) was taken at the same intervals as the clinical measurements according to the procedure outlined below. Flare and cells in the anterior chamber were assessed utilising a slit lamp adjusted to a pre-determined standard setting using the international rating scales outlined overleaf.

Blood Sampling Procedure - Using a 20ml syringe, a "whole blood" sample of 20mls was taken. The blood was immediately transferred to the vacuum sealed collection tubes supplied by Fermentech Medical Limited. The top of the tube was not removed. The needle was inserted through the septum in the tube cap and the blood allowed to flow into the tube; it was not necessary to depress the syringe plunger as the blood was drawn into the tube by vacuum. Each tube drew approximately 5mls of blood depending on the vacuum within the tube. A minimum of four tubes were supplied per sample per patient - to be used as required. The tubes were mixed gently and kept at room temperature.

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SLIT LAMP SETTING

Flare in the anterior chamber was determined using the slit lamp microscope adjusted to a standardised predetermined setting **[3mm beam/1mm wide/maximum intensity].** This was assessed by the Investigator using the following categorical rating scale:

NONE / COMPLETE ABSENCE
FAINT / BARELY DETECTABLE +
MODERATE / IRIS & LENS DETAIL CLEAR ++
MARKED / IRIS & LENS DETAILS NOT CLEARLY VISIBLE +++
INTENSE / IRIS & LENS DETAILS NOT CLEARLY VISIBLE INCLUDES FIBRIN PLASTIC AQUEOUS ++++

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Iritis (Cellular response) was measured using the slit lamp microscope adjusted to the standardised predetermined setting **[3mm beam/1mm wide/maximum intensity]**. This was assessed by the Investigator using the scale outlined below to determine the number of cells per field:

NONE /	NO CELLS
MILD /	1-10
MODERATE /	11-20
SEVERE /	21 - 49
EXTREME /	>50

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REFERENCES

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ADVERSE EVENTS

All adverse events (A/E) were recorded on Adverse Events forms and those which were classified as serious were reported to the study sponsor immediately. Adverse events were classified by intensity (mild, moderate or severe) and by causality (probable, possible, unrelated, insufficient evidence).

DATA MANAGEMENT

At the study initiation, the CRA reviewed facilities for suitability and ensured that the Investigators and other relevant staff understood the Protocol. During the study the CRA monitored study progress and data collection. A total of 30 monitoring visits (10 per centre on average) were performed. A source data verification check was performed on a randomly selected sample (54%) of patients recruited.

A computer database for both CRFs and AE forms data was set up for this study using Microsoft Access. Relevant data was exported from this system into D-Base IV format to an SAS system for statistical analysis.

Archives - all data generated and recorded during this study, including a copy of the Final Report, will be stored in the scientific archives of Fermentech Medical Ltd for 15 years after the issue of Final Report.

The Investigator will retain copies of all CRFs at the institution where the study was conducted for 15 years.

STATISTICAL ANALYSIS

Statistical Methods

All results are presented on a by-centre basis. The data consists of the results of 138 cataract operations, performed on 135 patients. In this analysis all results are presented on a by-eye basis. Comparison of the changes in intraocular pressure between the two treatment groups is by means of the independent sample t-test. Comparison of the categorical outcome variables (cellular response, flare, overall performance and patient recovery) are by means of an Exact Trend Test. SAS version 6.04 on an IBM compatible PC was used for all calculations except the Trend Test, which was performed on StatXact. Two tailed tests are used throughout, and for the Trend Test this is obtained by doubling the one-tailed exact probabilities.

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RESULTS ANALYSIS

PATIENTS AND METHODS

Subjects

Sex	43 Male : 92 Female
Mean Age	74.8 years (Range 50 to 90 years)
Mean Duration of History of Cataract	30.2 months (Range 4 to 240 months)

The first patient was recruited into the Study on 2 May 1994 and the last patient completed the study on 3 April 1995.

The demographic data and medical history by centre and treatment group, of all patients recruited to the study including the three bilateral patients is outlined in **Table 1**. None of the differences observed between the two treatment groups are greater than would be expected by chance.

Table 1 Comparison of Treatment Groups at the Time of Randomisation

A) CENTRE B

	OPHTHALIN* (N = 52)			Healonid (N = 52)		
	Number	Mean	S.D.	Number	Mean	S.D.
Age (Years)	52	75.4	9.3	52	75.0	7.5
Duration (months)	52	31.0	41.4	52	30.5	39.2
Intraocular Pressure (mmHg)	52	15.1	3.1	52	14.9	2.9
	Number			Number		
Sex						
Male	17			16		
Female	35			36		
Side						
Left	28			24		
Right	24			28		
Ethnic Group						
Caucasian	51			52		
Asian	1			0		
Bilateral Operations	2			4		

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Table 1

B) CENTRE OX

	OPHTHALIN* (N = 7)			Healonid (N = 7)		
	Number	Mean	S.D.	Number	Mean	S.D.
Age (Years)	7	74.7	12.1	7	77.9	6.2
Duration (months)	7	36.3	29.1	7	28.9	24.8
Intraocular Pressure (mmHg)	7	14.9	3.3	7	14.6	3.3
Sex						
Male	2			4		
Female	5			3		
Side						
Left	5			3		
Right	2			4		
Ethnic Group						
Caucasian	7			7		
Bilateral Operations	0			0		

C) CENTRE EB

	OPHTHALIN* (N = 10)			Healonid (N = 10)		
	Number	Mean	S.D.	Number	Mean	S.D.
Age (Years)	10	72.3	9.3	10	74.2	11.2
Duration (months)	10	20.6	14.1	10	26.7	25.3
Intraocular Pressure (mmHg)	10	16.2	3.0	10	16.0	2.9
	Number			Number		
Sex						
Male	3			3		
Female	7			7		
Side						
Left	5			3		
Right	5			7		
Ethnic Group						
Caucasian	10			10		
Bilateral Operations	0			0		

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Intervals Between Visits

The three centres differed in their planned visit schedules, according to the routine practice for post-cataract surgery follow-up, in the individual hospitals. The observed distribution of time interval between visits is summarised by treatment group and centre in **Tables 2 & 3**. Variation was seen in the adherence to planned visit schedules. In all centres the intervals and adherence to planned visit schedules were similar for both treatment groups.

Table 2

Intervals in Days Between Visits and Date of Operation by Centre

	Number	Mean	S.D.
Visit 3			
Centre B	101	7.3	1.6
Centre OX	14	11.6	3.8
Centre EB	20	1.0	0.0
Visit 4			
Centre B	101	21.9	3.8
Centre OX	14	35.5	16.2
Centre EB	19	28.9	3.7
Visit 5			
Centre B	101	63.5	3.3
Centre OX	14	68.7	19.6
Centre EB	19	56.3	9.3

Table 3

Timing of Postoperative Visits (Days) by Treatment Group and Centre

	Bacterial Source H.A.			Rooster Comb H.A.		
	Number	Mean	S.D.	Number	Mean	S.D.
Centre B						
Visit 3	50	7.4	2.0	51	7.2	1.2
Visit 4	50	22.2	4.8	51	21.6	2.4
Visit 5	52	63.1	2.4	50	63.9	4.1
Centre OX						
Visit 3	7	12.4	4.0	7	10.9	3.7
Visit 4	7	35.7	15.5	7	35.3	18.1
Visit 5	7	71.1	25.7	7	66.3	12.4
Centre EB						
Visit 3	10	1.0	0.0	10	1.0	0.0
Visit 4	9	27.2	0.7	10	30.1	18.1
Visit 5	10	54.5	8.9	9	58.6	9.4

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CLINICAL MEASUREMENTS

Primary Efficacy Variable

The success of the operative procedure was the primary outcome variable for the study. The operation was judged as successful in all instances, with the exception of one patient who received the rooster comb source Sodium Hyaluronate. This patient experienced peroperative complications not related to the study medication.

Secondary Efficacy Variable

Change in Intraocular Pressure

The intraocular pressures are summarised in **Table 4**. In Centre B there was a pattern of a very small mean reduction in intraocular pressure in both treatment groups, with no suggestion of differences between the treatments. The results from the other 2 centres are less consistent, which may reflect the small numbers of patients on which they are based. In Centre OX, there was a mean increase of 5.6mmHg at the first post-operative visit, with this being non-significantly larger in the Rooster Comb Source Sodium Hyaluronate group. The main contribution to this mean increase came from Patient 533 whose intraocular pressure rose from 10mmHg to 40mmHg and Patient 540 with a rise from 18mmHg to 33mmHg. Both were in the Rooster Comb Source Sodium Hyaluronate group. At subsequent visits, mean intraocular pressures were raised only slightly from baseline, with no outstanding high levels, and no suggestion of a difference between the treatment groups. In the Centre EB, post-operative IOPs differed little from baseline, with the exception of 2 patients in the Bacterial Source Sodium Hyaluronate group, whose pressures rose from 21mmHg to 38mmHg on the first post-operative day (Patient 94), and from 12mmHg to 30mmHg (Patient 103). This centre conducted exclusively all surgery using phacoemulsification technique where a smaller incision is made and suture, and therefore no leakage is expected. Amalgamation of data from all 3 centres is slightly problematical because of the different time intervals, but it is interesting to note that these results show almost identical mean changes from baseline in the two treatment groups.

Table 4

a) B

Intraocular Pressures (mmHg) by Visit, Treatment and Centre

	Bacterial Source H.A.			Rooster Comb Source H.A.				95% C. I. for difference	
	N	Mean	S.D.	N	Mean	S.D.	P	Bacterial Source H.A. - Rooster Comb Source H. A.	
								Lower Limit	Upper Limit
Baseline	52	15.1	3.1	52	14.9	2.9			
Visit 3 (Day 7)	50	13.8	4.1	51	14.1	3.4			
Difference from baseline		-1.1	5.4		-0.9	3.9	0.82	-2.1	1.6
Visit 4 (Day 21)	49	14.6	3.8	51	14.7	3.8			
Difference from baseline		-0.6	4.8		-0.4	4.6	0.80	-2.1	1.6
Visit 5 (Day 63)	51	13.5	2.4	50	13.5	2.9			
Difference from baseline		-1.5	4.0		-1.4	3.5	0.99	-1.5	1.5
Max Postoperative value	51	16.4	3.9	51	16.2	3.7			
Difference from baseline		1.4	4.9		1.2	4.4	0.81	-1.6	2.0

Table 4

b) CENTRE OX

Intraocular Pressures (mmHg) by Visit, Treatment and Centre

	Bacterial Source H.A.			Rooster Comb Source H. A				95% C. I. for difference	
	N	Mean	S.D.	N	Mean	S.D.	P	Bacterial Source H.A. - Rooster Comb Source H. A.	
								Lower Limit	Upper Limit
Baseline	7	14.9	3.3	7	14.6	3.3			
Visit 3 (Day 7)	7	18.0	5.8	7	22.7	10.2			
Difference from baseline		3.1	5.9		8.1	11.2	0.32	-15.4	5.4
Visit 4 (Day 21)	7	17.1	4.0	7	14.4	4.0			
Difference from baseline		2.3	5.2		-0.1	4.9	0.38	-3.4	8.3
Visit 5 (Day 63)	7	16.6	3.6	7	16.9	1.9			
Difference from baseline		1.7	5.3		2.3	3.4	0.81	-5.8	4.6
Max Postoperative value	7	19.9	4.9	7	24.1	8.9			
Difference from Baseline		5.0	4.9		9.6	10.4	0.31	-14.0	4.9

Table 4

c) CENTRE EB

Intraocular Pressures (mmHg) by Visit, Treatment and Centre

	Bacterial Source H.A.			Rooster Comb Source H. A.				95% C. I. for difference	
	N	Mean	S.D.	N	Mean	S.D.	P	Bacterial Source H.A. - Rooster Comb Source H. A.	
								Lower Limit	Upper Limit
Baseline	10	16.2	3.0	10	16.0	2.9			
Visit 3 (Day 1)	10	19.7	9.0	10	14.6	6.7			
Difference from baseline		3.7	8.8		-1.4	6.6	0.17	-2.4	12.2
Visit 4 (Day 28)	9	16.0	3.4	10	16.3	2.3			
Difference from baseline		-0.1	3.1		0.3	4.4	0.82	-4.1	3.3
Visit 5 (Day 60)	10	14.8	2.9	9	16.1	3.9			
Difference from baseline		-1.4	2.7		0.3	3.9	0.27	-4.9	1.5
Max Postoperative value	10	21.3	7.8	10	19.2	3.3			
Difference from Baseline		5.1	7.3		3.2	3.8	0.48	-3.6	7.4

Table 4

d) ALL SUBJECTS

Intraocular Pressures (mmHg) by Visit, Treatment and Centre

	Bacterial Source H.A.			Rooster Comb Source H. A.				95% C. I. for difference	
	N	Mean	S.D.	N	Mean	S.D.	P	Bacterial Source H.A. - Rooster Comb Source H. A.	
								Lower Limit	Upper Limit
Baseline	69	15.2	3.1	69	15.1	2.9			
Visit 3	67	15.1	5.7	68	15.1	5.6			
Difference from baseline		0.0	6.3		0.0	6.0	0.96	-2.0	2.2
Visit 4	65	15.0	3.8	68	14.9	3.7			
Difference from baseline		-0.2	4.7		-0.2	4.5	0.99	-1.6	1.6
Visit 5	68	14.0	2.7	66	14.2	3.2			
Difference from baseline		-1.1	4.0		-0.8	3.7	0.64	-1.6	1.0
Max Postoperative value	68	17.5	5.0	68	17.5	5.0			
Difference from Baseline		2.3	5.5		2.3	5.7	0.98	-1.9	1.9

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Cellular Response

No patients showed a pre-operative cellular response. The post-operative cellular responses were assessed as greater in the Centre EB than the other two centres, throughout follow-up **(Table 5).** Centre OX assessed the responses more favourably than Centre B at the first post-operative visit, but was similar thereafter. Overall, the responses were assessed as moderate or severe in 25 (19%) of patients at the first post-operative visit, falling to 3 (2%) at the next visit. At the final visit only mild cellular responses were seen in 11 (8%) patients. Responses were similar in both treatment groups throughout follow-up.

Table 5

Cellular Response by Visit, Treatment Group and Centre

Response	Centre B		Centre OX		Centre EB		All Subjects	
Visit 3	Bacterial Source H.A.	Rooster Source H.A.	Bacterial Source H.A.	Rooster Source H.A.	Bacterial Source H.A.	Rooster Source H.A.	Bacterial Source H.A.	Rooster Source H.A.
None	3	5	4	3	1	0	8	8
Mild	42	40	3	3	3	3	48	46
Moderate	4	6	0	1	4	3	8	10
Severe	1	0	0	0	2	4	3	4
Exact Trend Test	p = 0.83		p = 0.69		p = 0.47		p = 0.71	
Visit 4								
None	38	38	4	5	2	4	44	47
Mild	12	12	3	2	6	5	21	19
Moderate	0	0	0	0	1	1	1	1
Severe	0	1	0	0	0	0	0	1
Exact Trend Test	p = 0.74		p = 1.00		p = 0.78		p = 1.00	
Visit 5								
None	51	48	6	7	6	6	63	61
Mild	1	2	1	0	4	3	6	5
Exact Trend Test	p = 0.97		p = 1.00		p = 1.00		p = 1.00	

Anterior Chamber Flare

No patients exhibited anterior chamber flare pre-operatively. Reporting rates for anterior chamber flare varied markedly between centres **(Table 6)**. Whereas none was reported for 9 of 14 patients from Centre OX at the first post-operative visit, there were only 6 of 101 for Centre B where flare was absent at the corresponding time. Intense anterior chamber flare was reported at the first post-operative visit for 1 patient in the Bacterial Source Sodium Hyaluronate. By the time of the second post-operative visit, 71% of patients had no anterior chamber flare reported, at this stage, there were only 2 patients with moderate or marked flare and these were in the Rooster Comb Sodium Hyaluronate group. Only 7 patients (5%) had faint anterior chamber flare at the time of the final visit. Overall, the distribution of amount of anterior chamber flare was almost identical in the two treatment groups at every post-operative visit.

Table 6

Anterior Chamber Flare by Visit, Treatment Group and Centre

Response	Centre B		Centre OX		Centre EB		All Subjects	
Visit 3	Bacterial Source H.A.	Rooster Source H.A.	Bacterial Source H.A.	Rooster Source H.A.	Bacterial Source H.A.	Rooster Source H.A.	Bacterial Source H.A.	Rooster Source H.A.
None	3	3	5	4	3	1	11	8
Faint	40	45	1	1	4	5	45	51
Moderate	6	3	1	2	3	4	10	9
Intense	1	0	0	0	0	0	1	0
Exact Trend Test	p = 0.31		p = 0.78		p = 0.55		p = 1.00	
Visit 4								
None	33	35	7	5	6	9	46	49
Faint	17	14	0	2	3	1	20	17
Moderate	0	1	0	0	0	0	0	1
Marked	0	1	0	0	0	0	0	1
Exact Trend Test	p = 0.91		p = 0.46		p = 0.50		p = 0.95	
Visit 5								
None	51	46	6	7	9	9	66	62
Faint	1	4	1	0	1	0	3	4
Exact Trend Test	p = 0.34		p = 1.00		p = 1.00		p = 0.95	

Investigator Assessment of Overall Performance of Sodium Hyaluronate

This was assessed as'Very Good' for all operations in Centre EB. In contrast, only two of 14 operations at Centre OX has overall Sodium Hyaluronate performance assessed as 'Very Good', with intermediate results in Centre B. Combining the responses of 'Good' and 'Very Good', as was done in the interim report, gives success rates of 87% (59/68) in the Bacterial Source Sodium Hyaluronate group and 94% (65/69) in the Rooster Comb Source Sodium Hyaluronate group. This difference is not statistically significant (Chi - squared with Yates' correction = 1.43; p = 0.23). However, utilising all the subjective grades of outcome in a Trend test does show a statistically significant difference (p = 0.008).

Table 7

Investigators' Overall Assessment Sodium Hyaluronate Performance by Treatment Group and Centre

	Centre B		Centre OX		Centre EB		All Subjects	
Assessment	Bacterial Source H.A.	Rooster Comb Source H.A.	Bacterial Source H.A.	Rooster Comb Source H.A.	Bacterial Source H.A.	Rooster Comb Source H.A.	Bacterial Source H.A.	Rooster Comb Source H.A.
Very Good	10	29	1	1	10	10	21	40
Good	35	19	3	6	0	0	38	25
Average	5	3	3	0	0	0	8	3
Very Poor	1	1	0	0	0	0	1	1
Exact Trend Test	p = 0.008		p = 0.39		Not applicable		p = 0.008	

Investigators' Assessment of Patient Recovery

Patient recovery was assessed most highly in Centre EB with 80% of patients assessed as very good on the first post-operative day **(Table 8).** Centre B assessed just under half of its patients as having a very good recovery at the first post-operative visit, rising to 60% at the final visit. Centre OX did not assess any patients as having a very good recovery at the time of the final visit. The two treatment groups showed very similar results throughout follow-up.

Table 8

Investigators' Assessment of Patient Recovery by Visit, Treatment Group and Centre

Recovery	Centre B		Centre OX		Centre EB		All Subjects	
Visit 3	Bacterial Source H.A.	Rooster Comb Source H.A.	Bacterial Source H.A.	Rooster Comb Source H.A.	Bacterial Source H.A.	Rooster Comb Source H.A.	Bacterial Source H.A.	Rooster Comb Source H.A.
Very Good	20	26	1	1	8	8	29	35
Good	26	16	3	4	2	1	31	21
Average	3	8	3	0	0	1	6	9
Poor	0	1	0	2	0	0	0	3
Very Poor	1	0	0	0	0	0	1	0
Exact Trend Test	p = 0.93		p = 1.00		p = 1.00		p = 1.00	
Visit 4								
Very Good	27	25	0	0	8	9	35	34
Good	19	18	5	4	0	1	24	23
Average	3	7	2	2	1	0	6	9
Very Poor	1	1	0	1	0	0	1	2
Exact Trend Test	p = 0.52		p = 0.66		p = 0.95		p = 0.52	
Visit 5								
Very Good	32	29	0	0	9	9	41	38
Good	17	17	5	4	0	0	22	21
Average	2	4	2	2	1	0	5	6
Very Poor	1	0	0	1	0	0	1	1
Exact Trend Test	p = 0.88		p = 0.71		p = 1.00		p = 0.85	

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Visual Acuity

Broadly similar distributions for visual acuity were seen in all centres. Fifty-four (78.3%) patie in the Bacterial Source Sodium Hyaluronate. treatment group had the desired visual acuity of 6/ or greater compared to 47 (71.2%) patients in the Rooster Comb Source Sodium Hyaluron treatment group. This difference was not statistically significant (Chi-squared with Yate correction = 0.55, p = 0.46).

Table 9

Visual Acuity by Treatment Group - All Subjects

Visual Acuity	Bacterial Source H.A.	Rooster Comb Source H.A
6/6	5	11
6/7.5	1	0
6/8	1	0
6/9	29	24
6/12	18	12
Total	**54 (78.3%)**	**47 (71.2%)**
6/18	6	6
6/24	4	5
6/36	2	2
6/60	0	4
3/60	1	0
1/60	1	0
CF	1	1
HM	0	1
Total	**15 (21.7%)**	**19 (28.8%)**

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Adverse Events

Table 10 summarises by centre and treatment group the adverse events recorded throughout the study. In total seventeen adverse events were recorded. Surgical adverse events were reported for 12 patients. Two cases of infective endophthalmitis were reported, one in each treatment group. The results of enhanced cultures from the patient in the Bacterial Source Sodium Hyaluronate treatment group isolated a *Staphylococcus* species which was not typed. The laboratory results were inconclusive from the patient who received Rooster Comb Source Sodium Hyaluronate. Both patients commenced appropriate intensive antibiotic therapy and were not withdrawn from the study. The two deaths which occurred during the study, one in each treatment group, were unrelated to the test products. Cause of death was recorded as degenerative heart disease in the patient who received Rooster Comb Source Sodium Hyaluronate and carcinoma in the patient who receive Bacterial Source Sodium Hyaluronate.

Table 10 Adverse Events

Patient Number	Centre	Adverse Event	Treatment Group
94	EB	Ruptured Posterior Capsule	Bacterial Source H.A.
206	B	Posterior Capsule Tear	Rooster Comb Source H.A.
381	B	Infective Endophthalmitis	Bacterial Source H.A.
387	B	Vitreous Loss	Rooster Comb Source H.A.
391	B	Retrobulbar Haemorrhage	Rooster Comb Source H.A.
391	B	Vitreous Loss	Rooster Comb Source H.A.
391	B	Renal Colic	Rooster Comb Source H.A.
395	B	Limited Anterior Vitrectomy	Rooster Comb Source H.A.
396	B	Vitreous Loss	Rooster Comb Source H.A.
519	B	Death	Rooster Comb Source H.A.
536	OX	Death	Bacterial Source H.A.
540	OX	Vitreous Loss	Rooster Comb Source H.A.
545	B	Iris Prolapse	Bacterial Source H.A.
547	B	Endophthalmitis	Rooster Comb Source H.A.
547	B	Vitreous Loss	Rooster Comb Source H.A.
549	B	Dislocated Lens	Rooster Comb Source H.A.
559	B	Iris Prolapse	Rooster Comb Source H.A.

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DISCUSSION

Previous studies[8,9] have compared both Sodium Hyaluronate from a rooster comb source and bacterial fermented source. The analysis of these studies showed no statistically significant difference between the two products in respect of IOP, corneal thickness and endothelial cell count. Whilst the results of these small studies indicated similarity with the rooster comb Sodium Hyaluronate, which has been available for over ten years, further clinical experience with the new product was desirable.

Concerns over potential immunological risks from any biological material led to a more detailed post-operative assessment of inflammation than would be normally carried out as routine post-operative cataract surgery follow-up. The current study was designed to specifically show any effect this product may have had on post-operative inflammation in the eye when compared to the standard viscoelastic.

Investigators were instructed in the use of a standardised rating scale to assess iritis and all slit lamp were adjusted to a pre-determined setting in order to minimise variation in this subjective assessment. However, the reported incidence of iritis measured by cellular response and anterior chamber flare in this study showed between centre variation, this variation was consistent for both treatment groups. One explanation for the between centre variation may be the visit schedules followed at each centre. At Centre EB the first post-operative visit was carried out the day after surgery when one would expect more activity in the eye. At the other two centres the first post-operative visit was conducted between Day 7 and Day 14 post-surgery. The decision to allow different visit schedule intervals was taken to mimic the routine clinical follow-up in these units.

A moderate to severe cellular response was recorded for 11 (16.4%) patients in the Bacterial Source Sodium Hyaluronate treatment group and 14 (20.6%) patients in the Rooster Comb Source Sodium Hyaluronate at the first post-operative visit. At the final visit only mild cellular response was seen in 11 patients, 6 (8.7%) in the Bacterial Source Sodium Hyaluronate treatment group and 5 (7.6%) patients in the Rooster Comb Source Sodium Hyaluronate treatment group. The difference between treatment groups was not statistically significant. The treatment similarities were also evident when measuring iritis by anterior chamber flare. Twenty patients in total, 11 in the Bacterial Source Sodium Hyaluronate treatment group and 9 in the Rooster Comb Source Sodium Hyaluronate treatment group, were reported as having moderate/intense anterior chamber flare at the first post-operative visit. By the final visit only faint flare was reported in 3 patients in the Bacterial Source Sodium Hyaluronate treatment group and 4 patients in the Rooster Comb Source Sodium Hyaluronate treatment group. The overall incidence of iritis in the current study exceeds that reported by the earlier authors. Nishi & Nishi[12] 1988 reported a 5% incidence of mild to moderate uveitis in post-cataract surgery patients. This difference may be due to a variety of

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clinical, investigator and patient differences between studies including the type of intraocular lens implant used e.g. PMMA or silicone. However, the reported incidence of iritis in the current study is consistent between treatment groups and would therefore indicate that there is no greater risk of inflammation from the product manufactured by a bacterial fermentation than the standard product.

Only one subjective measurement of performance between the two products reached the conventional level for statistical significance. The Investigators' assessment of the overall performance of Sodium Hyaluronate, when analysed in the original discreet outcome grades showed a statistically significant preference for the Rooster Comb product. This one parameter is purely a subjective preference which may well have been influenced by the alternative presentation and packaging of the product and the surgeons' previous experience and knowledge of the standard viscoelastic used in cataract surgery. If the results are analysed as acceptable or not acceptable, i.e. good or below average performance, there is no significant difference between treatment groups. The greatest proportion i.e. in 92% of cases , the products were rated as good or very good and are therefore considered equally satisfactory for the purpose of use. In view of the multiple tests which have been applied, a single significant finding would not be unduly surprising, even if the treatments were truly identical in their effects.

CONCLUSION

Most of the end-points in this trial are subjective, and it is therefore unsurprising that there are substantial inter-centre differences in the distribution across the terms used to describe outcome. However, the similarity of results for both treatment groups is quite striking, for both the subjective outcomes and for the objective measure of intraocular pressure. In terms of the primary outcome of operative success, all patients treated with Bacterial Source Sodium Hyaluronate were operative successes, as were all but one of the patients treated with Rooster Comb Source Sodium Hyaluronate. The clinical results from this study demonstrate that the concerns over the potential risks from biological material are unfounded. The inflammatory responses from both treatment groups, indicating any immunological potential from the compounds, were similar.

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List of Abbreviations and Glossary

H.A. - Sodium Hyaluronate

H.A. from Rooster Comb Source - Healonid

H.A. from Bacterial Fermentation Source - OPHTHALIN

V/A - Visual Acuity

I.O.P. - Intraocular Pressure

Flare - Anterior Chamber Flare

Cellular Response - Anterior Chamber Cells

HPMC - Hydroxypropylmethylcellulose

S.D. - Standard Deviation

(w/v) - weight/volume

(p - value) - probability

< - less than

> - greater than

mmHg - millimetres of mercury

mm - millimetres

BSS - Balanced Salt Solution

PBS - Phosphate Buffered Saline

CRA - Clinical Research Associate

CRF - Case Record Form

AE - Adverse Event

Centre B - Bristol Eye Hospital

Centre EB - Waterford Regional Hospital

Centre OX - Radcliffe Infirmary, Eye Unit, Oxford

TO WHOM IT MAY CONCERN

Final Study Report (Amended) CT9445FSRXF

Phase III double blind, randomized, multi-centre study to determine the safety and efficacy of 1% (w/v) Sodium Hyaluronate solution from separate sources during intraocular cataract extraction and lens implantation surgery.

The comparator materials were of the same composition the only difference being the source of the sodium hyaluronate.

Bacterial sodium hyaluronate – manufactured by Fermentech Ltd. The company name was subsequently changed to Fermentech Medical Ltd. then Vitrolife UK Ltd and is currently Hyaltech Ltd. The batch of material used in this clinical study was manufactured specifically for the study. The formulation has subsequently been marketed as the products Ophthalin®, Dispasan®, Gelbag® and Z-HYALIN™.

Rooster comb sodium hyaluronate – manufactured at the time of the study by Pharmacia and marketed under the product names Healonid® and Healon®. The marketing of Healon has been transferred through a series of companies and is now the responsibility of Abbot Medical Optics, Inc.

The principal component of the comparator materials is sodium hyaluronate 10mg/ml. Excipients are added to ensure the isotonicity of the viscoelastic solution. Disodium hydrogen phosphate dehydrate and sodium dihydrogen phosphate dehydrate are added to stabilize the pH. Initially the concentrations of the phosphates in the bacterial sodium hyaluronate product were identical to those present in the marketed product Healon. Through manufacturing experience the concentration of the phosphates has been adjusted to ensure stability of the product throughout its shelf life.

E.M. Donaldson, Regulatory Affairs Manager,
For and on behalf of Hyaltech Ltd.

Date

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