

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022572Orig1s000**

**MEDICAL REVIEW(S)**

## Deputy Division Director Summary Review for NDA 22-572

<b>Date</b>	February 6, 2012
<b>From</b>	Wiley A. Chambers, M.D.
<b>NDA #</b>	22-572
<b>Applicant</b>	Mobius Therapeutics, LLC
<b>Date of Original Submission</b>	June 21, 2010
<b>Date of Resubmission</b>	August 8, 2011
<b>Type of Application</b>	505(b)(2)
<b>Name</b>	Mitosol (mitomycin for solution)
<b>Dosage forms / Strength</b>	Topical solution, 0.2 mg/mL
<b>Proposed Indication(s)</b>	An antimetabolite indicated for use as an adjunct to ab externo glaucoma surgery.
<b>Recommended Action:</b>	Approval

### 1. Introduction

Mitomycin C (MMC) is an antibiotic derived from *Streptomyces caespitosus* that has antimetabolic properties. Mitomycin has been shown to inhibit fibroblast proliferation by preventing DNA synthesis, thereby potentially reducing the amount of scar tissue formed after trabeculectomy.

### 2. Background

There are no approved drug products for the proposed indication - for use as an adjunct to ab externo glaucoma surgery.

This is a 505(b)(2) application primarily based on literature. Reference literature reports, surveys, and articles cited in this review are representative of the published literature.

The Form 356h submitted by Mobius Therapeutics, LLC, lists Mutamycin (mitomycin for injection), ANDA 62-336 (Bristol Myers Squibb) as the reference listed drug (RLD) product.

An orphan designation for mitomycin for solution for the treatment of treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery was granted on January 8, 2008.

### 3. CMC

The proposed packaging for Mobius product consists of a "kit" which includes a vial of mitomycin for solution (containing a sterile, lyophilized mixture of 0.2 mg mitomycin and 0.4 mg mannitol) and associated components for the reconstitution of mitomycin and for the delivery of drug to the eye. Essential components of the packaging/kit include a prefilled syringe containing (b)(4) sterile water for injection for reconstitution of mitomycin and pre-cut surgical sponges for administration of the resulting solution to the eye. The sponges are held in a plastic tray which also serves as a container for the saturation with the drug solution. Other components are provided for handling and disposal of the cytotoxic agent. Components are packaged in (b)(4) trays with (b)(4) lidding.

**Drug Product Components/Composition**

Ingredients	Compendial Reference	Qty. (mg) / mL	Batch Quantity
Mitomycin	USP/Ph. Eur.	0.2	(b) (4)
Mannitol	USNF/Ph. Eur.	0.4	(b) (4)
Water for Injection	USP/Ph. Eur.	1 mL	(b) (4)

**Specification(s)**

The proposed specification for Mitomycin for Solution, 0.2 mg/Vial is presented in the table below. To facilitate comparison, the CMC reviewer has included the current specifications for Mitomycin for Injection USP and for the Intas and Bedford/BVL Mitomycin for Injection products.

**Mitomycin for Ophthalmic Solution**

Attribute	Analytical Procedure	Proposed Acceptance Criteria
Appearance	In house	Blue-violet cake or powder, free from visible evidence of contamination in amber vial.
Constituted Solution	USP<1>	a) Sample powder should dissolve completely leaving no visible residue. b) Sample solution is not significantly less clear than an equal volume of diluent (water for injection) in a similar vessel and examined similarly. c) Sample solution should be essentially free from particles of foreign matter than could be observed on visual inspection.
Identification	USP	The Rf value of the principal spot obtained from the sample solution should correspond to that of the Mitomycin standard solution similarly prepared.
Reconstitution Time	In house	(b) (4)
pH	USP<791>	(b) (4)
Particulate Matter	USP<789>	(b) (4)
Bacterial Endotoxin	USP<85>	(b) (4)
Sterility	USP<71>	(b) (4)
Water	USP<921>	(b) (4)
Uniformity of dosage unit (By content uniformity)	USP<905>	(b) (4)
Related substances	In house	(b) (4)
Assay	USP<621>	(b) (4)
Residual Solv		(b) (4)

The CMC reviewer recommends approval. The manufacturing facilities are all considered to be in compliance with cGMPs.

#### **4. Nonclinical Pharmacology/Toxicology**

No original studies were performed or submitted. This application was submitted with published literature references. Mitomycin is a known DNA alkylating agent so it may be considered positive for genetic toxicity. No carcinogenicity data were provided, but its use in oncology treatment is referenced. The label for the reference listed drug indicates that systemic mitomycin is carcinogenic.

#### **5. Clinical Pharmacology/Biopharmaceutics**

The pharmacokinetic characteristics of mitomycin have been previously well-described for the intravenous formulation with the same active and inactive ingredients. The applicant has submitted a request for waiver of the requirement for submission of evidence of *in vivo* bioavailability for the proposed mitomycin kit based on the rationale that the bioavailability to the RLD is self-evident because on the local application.

#### **6. Sterility Assurance**

This product is a kit which after revision consists of a (b) (4)

[REDACTED]

Sterility assurance has been found to be acceptable.

#### **7. Clinical/Statistical - Efficacy**

This is a 505(b)(2) application primarily based on literature. The application includes efficacy data gathered from 22 published papers describing prospective clinical studies with mitomycin as adjuvant therapy to glaucoma filtration surgery, primarily trabeculectomy. The Medical Officer's Review contains a more complete description of the 22 literature articles.

There is adequate support from the literature to support efficacy for Mitosol (mitomycin for solution) in the treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery. In the most representative four placebo-controlled studies (Carlson, Cohen, Costa, and Robin), the mean IOP in the mitomycin-treated groups as compared with placebo-treated groups was lower by approximately 3 mmHg.

- In Carlson et al, 1997, the difference in mean IOP at Month 12 was not statistically significant, although mitomycin-treated subjects had numerically lower IOPs (roughly 13 mm Hg versus 16 mmHg).

- In Cohen et al, 1996, mitomycin-treated subjects had lower mean IOPs (roughly 15 mm Hg versus 17 mmHg,  $p = 0.058$ ).
- In Costa et al, 1996, the mean IOP was significantly lower in the mitomycin treated group at the following time points: first postoperative day ( $p=0.021$ ), 6-month interval ( $p=0.001$ ), and at the final visit ( $p=0.002$ ) (without correction for multiplicity).

Mean IOP at Month 6 was roughly 12 mmHg for mitomycin-treated subjects and 17 mmHg for placebo. Mean IOP at last follow-up (ranging from Month 7-24) was roughly 13 mmHg for mitomycin-treated subjects and 18 mmHg for placebo.

- In Robin et al, 1997, all three mitomycin-treated groups showed a statistically significant difference in IOP compared with placebo at Month 12 ( $p \leq 0.001$ ). Mean IOP data for the four groups were not provided. The estimated between group difference in IOP between placebo and Group 2 was 2.0 mmHg. The estimated between group difference in IOP between placebo and Group 3 and Group 4 was 3.0 mmHg.

In the three surgery plus mitomycin versus surgery-alone controlled studies (Andreanos, Martini, and Rasheed), the difference in mean IOP was lower by approximately 5 mmHg.

- In Andreanos et al, 1997, the mean ( $\pm$ SD) postoperative IOP was 12.5 ( $\pm$ 3.2) mmHg in the mitomycin group and 19.6 ( $\pm$ 6.1) mmHg in the control group at Month 18; this between group difference was statistically significant:  $p < 0.001$ .
- In Martini et al, 18997, the difference in mean IOP at Month 12 was statistically significant; mitomycin-treated subjects had lower IOPs (roughly 11 mm Hg versus 16 mmHg).
- In Rasheed et al, 1999, the mean postoperative IOP at Month 18 (average IOP recorded during last six months of follow-up) is lower for mitomycin treated subjects (roughly 10 mmHg) versus non-mitomycin treated subjects (roughly 16 mmHg). It is not clear that this difference is statistically significant.

## 8. Safety

The results for the safety report consisted of 23 controlled trials, 32 observational studies, 9 case series, and 65 case reports. The 23 controlled trials were conducted in 1,588 eyes, 1,085 of which were treated with mitomycin.

All 23 controlled trials included mitomycin applied topically to the exposed site of a filtering bleb, as adjunct therapy during trabeculectomy. Five were conducted in the United States, 10 in Europe (Croatia, Greece, Italy, the Netherlands, and Poland), 6 in Asia (India and Japan), and 2 in Africa (Congo and Ghana). Sixteen trials used randomized controlled designs, 1 used a

randomized controlled trial with case control, 4 used randomized crossover designs, 1 used a sequential crossover design, and 1 used a prospective non-comparative, nonrandomized, unmasked design. Among the controlled trials, doses of mitomycin ranged from 0.04 mg/mL to 0.5 mg/mL, and application times ranged from 0.5–5 minutes. Hypotony, choroidal detachment, shallow anterior chamber, hyphema, corneal endothelial defects, and cataract progression are seen with a lower frequency range of 0-3% and an upper frequency range of approximately 30-50%. All of these are known adverse events seen with the trabeculectomy procedure alone. There is great variation in the adverse event rates reported for these more serious adverse events; these rates are presumably dependant on the skill of the surgeon and the specific surgical population.

In summary there is adequate support from the literature to support the safety for Mitosol (mitomycin for solution) in treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery. The most frequent adverse reactions to Mitosol occur locally and are often related to an extension of the pharmacological activity of the drug. These include hypotony, choroidal detachment, shallow anterior chamber, hyphema, corneal endothelial defects, and cataract progression.

#### **9. Advisory Committee Meeting**

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

#### **10. Pediatrics**

Mitosol (mitomycin for solution) has received Orphan Designation; a pediatric assessment is therefore not required and has not been provided in this application. Safety and effectiveness of Mitosol (mitomycin for injection) in pediatric patients has not been established.

#### **11. Other Relevant Regulatory Issues**

##### **DSI**

The studies were conducted 10-15 years ago and demonstrate consistency in replication. After discussion with the Division of Scientific Investigations (DSI), a DSI audit was considered a good use of resources.

##### **FINANCIAL DISCLOSURE**

This is a 505(b)(2) application primarily based on 15 year old literature.

##### **DMEPA**

The Division of Medication Error Prevention and Analysis (DMEPA) initially reviewed the name Optomycin, (b) (4) the alternative names provided by the applicant ( (u) (4) and (u) (4) ). DMEPA notified Mobius that they considered the proposed name Optomycin unacceptable, and Mobius withdrew the name. Mobius submitted a new proprietary name,

(b) (4) DMEPA found this name unacceptable (b) (4)  
(b) (4) Mobius withdrew the name, (b) (4) and submitted a  
new proprietary name, Mitosol.

In a review dated 12/6/10 there were no concerns identified by DMEPA, and the name was found acceptable. DMEPA conditionally re-approved the name, Mitosol, in a letter dated 12/13/2011.

### **BIostatISTICS**

The Biostatistics reviewer evaluated the 22 prospective studies submitted by the applicant to examine the efficacy of mitomycin. As noted in the Clinical Review, the 22 studies had varying endpoints (Mean change in IOP in mmHg, overall lower IOP, % of patients with IOP between 5 mmHg and 15 mmHg, Successful IOP reduction, etc.) and different time of evaluation (6 months to 30 months), and differences in patient characteristics. Based on the totality of evidence, the reviewer concluded there is substantial evidence of the efficacy of mitomycin 0.2 mg in glaucoma filtration surgery.

### **12. Labeling**

The labeling of the product as submitted by the applicant is considered adequate to ensure safe and reliable reconstitution, transportation, and application of the product for the intended indication. At the Agency's request, a labeling comprehension studies were performed and the labeling was revised based on information learned in these studies.

(b) (4)

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

### **13. Regulatory Action**

NDA 22-572 Mitosol (mitomycin for solution) is recommended to be approved based on the information submitted to date for use as an adjunct to ab externo glaucoma surgery.

Wiley A. Chambers, MD  
Deputy Director  
Division of Transplant and Ophthalmology Products

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

WILEY A CHAMBERS  
02/06/2012

Medical Officer's Review #2

**NDA 22-572**  
**SDN – 34**

**Submission Date:** January 20, 2012  
**Receipt Date:** January 20, 2012

**SDN – 35**

**Submission Date:** January 27, 2012  
**Receipt Date:** January 27, 2012  
**Review Date:** February 2, 2012

**Applicant:**

Mobius Therapeutics, LLC  
4041 Forest Park Avenue  
St. Louis, MO 6310S USA

**Applicant's**  
**Representative:**

Ed Timm, President  
314-615-6930

**Drug:**

Mitosol (mitomycin for solution)

**Pharmacologic**  
**Category:**

antimetabolite

**Submitted:**

The applicant submitted a complete response to the Complete Response letter dated, December 22, 2010.

Draft labeling was submitted by Mobius Therapeutics, LLC on January 20, 2012. With the exception of the prefilled syringe label, the submitted labeling required minor editorial revisions.

Final proposed labeling was submitted by Mobius Therapeutics, LLC on January 27, 2012.

Following is the applicant's proposed labeling for the product.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

**Reviewer's Comments:**

*The carton, the outer tray label, the inner tray label, vial label, prefilled syringe label (submitted January 20, 2012), the instructions for use, and the package insert are acceptable.*

**Recommendations:**

The carton, the outer tray label, the inner tray label, vial label, prefilled syringe label (submitted January 20, 2012), the instructions for use, and the package insert are acceptable.

NDA 22-573 for Mitosol (mitomycin for solution) is recommended for approval with the labeling submitted on January 20, 2012 (prefilled syringe) and January 27, 2012 (carton, outer tray label, inner tray label, vial label, the instructions for use, and the package insert), provided the remaining CMC and Product Quality Microbiology issues from the December 22, 2010, Complete Response Letter have been resolved.

William M. Boyd, MD  
Clinical Team Leader

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

WILLIAM M BOYD  
02/02/2012

WILEY A CHAMBERS  
02/02/2012

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-572
Priority or Standard	Priority
Submit Date(s)	June 21, 2010
Received Date(s)	June 22, 2010
PDUFA Goal Date	December 22, 1010
Division / Office	DAIOP/OAP
Reviewer Name(s)	William Boyd, M.D.
Review Completion Date	December 20, 2010
Established Name	mitomycin for solution
(Proposed) Trade Name	Mitosol
Therapeutic Class	Antibiotic
Applicant	Mobius Therapeutics, LLC
Formulation(s)	lyophilized powder/cake for reconstitution
Proposed Dosing Regimen	topical application to the surgical site of glaucoma filtration surgery
Proposed Indication(s)	Treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery
Intended Population(s)	patients with refractory glaucoma requiring trabeculectomy

Template Version: [March 6, 2009](#)

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>5</b>
1.1	Recommendation on Regulatory Action .....	5
1.2	Risk Benefit Assessment.....	5
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	5
1.4	Recommendations for Postmarket Requirements and Commitments .....	6
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND .....</b>	<b>6</b>
2.1	Product Information .....	6
2.2	Tables of Currently Available Treatments for Proposed Indications .....	6
2.3	Availability of Proposed Active Ingredient in the United States .....	7
2.4	Important Safety Issues With Consideration to Related Drugs.....	7
2.5	Summary of Presubmission Regulatory Activity Related to Submission .....	7
2.6	Other Relevant Background Information .....	8
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES.....</b>	<b>8</b>
3.1	Submission Quality and Integrity .....	8
3.2	Compliance with Good Clinical Practices .....	8
3.3	Financial Disclosures.....	9
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b>	<b>9</b>
4.1	Chemistry Manufacturing and Controls .....	9
4.2	Clinical Microbiology.....	13
4.3	Preclinical Pharmacology/Toxicology .....	14
4.4	Clinical Pharmacology .....	14
4.4.1	Mechanism of Action.....	14
4.4.2	Pharmacodynamics/Pharmacokinetics .....	15
<b>5</b>	<b>SOURCES OF CLINICAL DATA.....</b>	<b>16</b>
5.1	Tables of Studies/Clinical Trials .....	16
5.2	Review Strategy .....	21
5.3	Discussion of Individual Studies/Clinical Trials.....	21
5.3.1	Group 1 Studies: Prospective, Randomized, Controlled, Masked Studies ...	22
5.3.2	Group 2 Studies: Prospective Studies of Uncertain Design .....	22
<b>6</b>	<b>REVIEW OF EFFICACY .....</b>	<b>22</b>
6.1	Indication: Treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery .....	24
6.1.1	Methods - Literature .....	24
6.1.1. A	Group 1 Studies: Prospective, Randomized, Controlled, Masked Studies .....	24
6.1.1. A.1	Mitomycin versus Placebo .....	24
6.1.1. A.2	Mitomycin versus No Drug Treatment .....	33

6.1.1. A.3 Mitomycin versus 5-FU .....	38
6.1.1. A.4 Mitomycin Dose Comparison .....	40
6.1.1. B Group 2 Studies: Prospective Studies of Uncertain Design.....	42
6.1.1. C Other Literature Sources .....	57
6.4 Demographics .....	58
6.5 Subpopulations.....	61
6.6 Analysis of Clinical Information Relevant to Dosing Recommendations.....	61
6.7 Discussion of Persistence of Efficacy and/or Tolerance Effects .....	62
6.8 Additional Efficacy Issues/Analyses .....	62
<b>7 REVIEW OF SAFETY.....</b>	<b>63</b>
7.1 Methods.....	63
7.1.1 Studies/Clinical Trials Used to Evaluate Safety .....	63
7.1.2 Categorization of Adverse Events.....	64
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	64
7.2 Adequacy of Safety Assessments .....	66
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations .....	67
7.2.2 Explorations for Dose Response.....	67
7.2.3 Special Animal and/or In Vitro Testing .....	67
7.2.4 Routine Clinical Testing .....	67
7.2.5 Metabolic, Clearance, and Interaction Workup .....	67
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	67
7.3 Major Safety Results .....	67
7.3.1 Deaths.....	68
7.3.2 Nonfatal Serious Adverse Events .....	68
7.3.3 Dropouts and/or Discontinuations .....	68
7.3.4 Significant Adverse Events .....	68
7.3.5 Submission Specific Primary Safety Concerns .....	68
7.4 Supportive Safety Results .....	69
7.4.1 Common Adverse Events .....	69
7.4.2 Laboratory Findings .....	69
7.4.3 Vital Signs .....	69
7.4.4 Electrocardiograms (ECGs) .....	69
7.4.5 Special Safety Studies/Clinical Trials.....	69
7.4.6 Immunogenicity .....	69
7.5 Other Safety Explorations.....	69
7.5.1 Dose Dependency for Adverse Events .....	69
7.5.2 Time Dependency for Adverse Events.....	70
7.5.3 Drug-Demographic Interactions .....	70
7.5.4 Drug-Disease Interactions.....	70
7.5.5 Drug-Drug Interactions.....	70
7.6 Additional Safety Evaluations .....	70

7.6.1	Human Carcinogenicity .....	70
7.6.2	Human Reproduction and Pregnancy Data.....	70
7.6.3	Pediatrics and Assessment of Effects on Growth .....	71
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	71
7.7	Additional Submissions / Safety Issues .....	71
<b>8</b>	<b>POSTMARKET EXPERIENCE.....</b>	<b>73</b>
<b>9</b>	<b>APPENDICES .....</b>	<b>75</b>
9.1	Literature Review/References .....	75
9.2	Advisory Committee Meeting.....	79
9.3	Labeling Recommendations .....	79

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

NDA 22-572, Mitosol (mitomycin for solution), is not recommended for approval for the treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery.

The labeling of the product as submitted by the applicant is not adequate to ensure safe and reliable reconstitution, transportation, and application of the product for the intended indication.

### 1.2 Risk Benefit Assessment

There is adequate support from the literature to support efficacy for Mitosol (mitomycin for solution) in the treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery. In the four placebo-controlled studies (Carlson, Cohen, Costa, and Robin), the mean IOP in the mitomycin-treated groups as compared with placebo-treated groups was lower. It was statistically significant in favor of the mitomycin groups from 6 to 24 months in the majority of these trials (Cohen, Costa, and Robin).

There is adequate support from the literature to support the safety for Mitosol (mitomycin for solution) in treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery provided the mitomycin can be adequately labeled for reconstitution and administration. The most frequent adverse reactions to Mitosol occur locally and are often related to an extension of the pharmacological activity of the drug and/or markedly reduced intraocular pressure from trabeculectomy. These include hypotony, choroidal detachment, shallow anterior chamber, hyphema, corneal endothelial defects, and cataract progression.

The labeling of the product as submitted by the applicant **is not adequate** to ensure safe and reliable reconstitution, transportation, and application of the product for the intended indication. See Section 7.7 of this review.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no Postmarket risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

## 1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended Postmarket Requirements or Phase 4 Commitments.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Mitomycin C (MMC) is an antibiotic derived from *Streptomyces caespitosus* that has antimetabolic properties. Mitomycin has been shown to inhibit fibroblast proliferation by preventing DNA synthesis, thereby potentially reducing the amount of scar tissue formed after trabeculectomy.

Per Mobius, the development of Mitosol (mitomycin for solution) is meant to address issues with the off-label use of mitomycin in glaucoma filter surgery:

- There is no assurance of sterility, concentration, and/or delivered dosage.
- There is no secure method of sterile product transfer from the circulating nurse to the surgical field, the area in the operating room where sterility is maintained.
- The amount of mitomycin accumulated in the sponge is subject to wide surgeon and/or nurse induced variables.
- Reconstituted solutions have limited shelf life.

Mobius asserts that their Mitosol (mitomycin for solution), which consists of a sterile single-use package/kit in a 0.2 mg mitomycin concentration, offers the following benefits:

- There is reconstitution of the mitomycin solution on the field, thereby minimizing shelf-life issues.
- Mitomycin is precisely measured, addressing consistent concentration.
- The mitomycin solution is prepared in a single dose volume.
- The dosage form is delivered to the surgical site by way of a standardized delivery system.
- The dosage form is available with an integral disposal package

### 2.2 Tables of Currently Available Treatments for Proposed Indications

There are no approved drug products for the proposed indication - treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery.

### **2.3 Availability of Proposed Active Ingredient in the United States**

Mitomycin is currently available in injectable dosage forms (lyophilized) in US market, and the reference listed drug product for this application is Mutamycin of Bristol Myers Squibb – ANDA 062336. No ophthalmic dosage form of mitomycin is available in US market.

### **2.4 Important Safety Issues With Consideration to Related Drugs**

Per the RLD package insert:

Mutamycin is not recommended as single-agent, primary therapy. It has been shown to be useful in the therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed. Mutamycin is not recommended to replace appropriate surgery and/or radiotherapy.

The use of Mutamycin results in a high incidence of bone marrow suppression, particularly thrombocytopenia and leukopenia. Therefore, the following studies should be obtained repeatedly during therapy and for at least eight weeks following therapy: platelet count, white blood cell count, differential, and hemoglobin. The occurrence of a platelet count below 100,000/mm<sup>3</sup> or a WBC below 4,000/mm<sup>3</sup> or a progressive decline in either is an indication to withhold further therapy until blood counts have recovered above these levels.

Patients should be advised of the potential toxicity of this drug, particularly bone marrow suppression. Deaths have been reported due to septicemia as a result of leukopenia due to the drug.

Patients receiving Mutamycin should be observed for evidence of renal toxicity.

Mutamycin has been found to be carcinogenic in rats and mice. At doses approximating the recommended clinical dose in man, it produces a greater than 100% increase in tumor incidence in male Sprague- Dawley rats, and a greater than 50% increase in tumor incidence in female Swiss mice.

### **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

A submission dated September 21, 2006, contained a request for a pre-NDA meeting to discuss the suitability of the current literature to support submission of a 505(b)(2) New

Drug Application. A Pre-Investigational New Drug Application (PIND) file for this drug product was opened on October 5, 2006, identified by PIND number 75,734.

A Pre-IND meeting was held on December 6, 2006.

An orphan designation for mitomycin for solution for the treatment of treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery was granted on January 8, 2008.

A second Pre-IND meeting was held on July 20, 2009.

## **2.6 Other Relevant Background Information**

This is a 505(b)(2) application primarily based on literature. Reference literature reports, surveys, and articles cited in this review are representative of the published literature. There is no evidence that these references refer to trials not conducted in accordance with acceptable clinical ethical standards.

The Form 356h submitted by Mobius Therapeutics, LLC, lists Mutamycin (mitomycin for injection), ANDA 062336 (Bristol Myers Squibb) as the reference listed drug (RLD) product.

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

Reference literature reports, surveys, and articles cited in this review are representative of the published literature. There is no evidence that these references refer to trials not conducted in accordance with acceptable clinical ethical standards.

### **3.2 Compliance with Good Clinical Practices**

Reference literature reports, surveys, and articles cited in this review are representative of the published literature. There is no evidence that these references refer to trials not conducted in accordance with acceptable clinical ethical standards.

### 3.3 Financial Disclosures

This is a 505(b)(2) application primarily based on literature. The literature studies were conducted approximately 15 years ago. In accordance with 21 CFR Part 54, no financial disclosure is appropriate for this application. There are no “covered clinical studies” in this submission.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

The proposed packaging for Mobius product consists of a “kit” which includes a vial of mitomycin for solution (containing a sterile, lyophilized mixture of 0.2 mg mitomycin and 0.4 mg mannitol) and associated components for the reconstitution of mitomycin and for the delivery of drug to the eye. Essential components of the packaging/kit include a prefilled syringe containing (b) (4) sterile water for injection for reconstitution of mitomycin and pre-cut surgical sponges for administration of the resulting solution to the eye. The sponges are held in a plastic tray which also serves as a container for the saturation with the drug solution. Other components are provided for handling and disposal of the cytotoxic agent. Components are packaged in (b) (4) trays with (b) (4) lidding.

The “kit” is opened in the operating room and a sterile inner tray removed. (b) (4)

(b) (4) The contents of the vial are reconstituted with 1 mL sterile water for injection (prefilled syringe). The reconstituted mitomycin solution (0.2 mg/mL) is withdrawn into the syringe and transferred to a small plastic tray containing an assortment of small surgical sponges (b) (4). Excess solution is removed from the tray and the sponges are applied to the eye by the surgeon. The entire Kit and used materials are then disposed of in a chemotherapy waste bag.

**Outer Tray**



**Inner Tray (sterile contents)**



Clinical Review  
 William Boyd, M.D.  
 NDA 22-572  
 Mitosol (mitomycin for solution)

### Drug Product Components/Composition

Ingredients	Compendial Reference	Qty. (mg) / mL	Batch Quantity
Mitomycin	USP/Ph. Eur.	0.2	(b) (4)
Mannitol	USNF/Ph. Eur.	0.4	
Water for Injection	USP/Ph. Eur.	(b) (4) 1 mL	

### Specification(s)

The proposed specification for Mitomycin for Solution, 0.2 mg/Vial is presented in the table below. To facilitate comparison, the CMC reviewer has included the current specifications for Mitomycin for Injection USP and for the Intas and Bedford/BVL Mitomycin for Injection products.

#### Mitomycin for Ophthalmic Solution (MIM3325-1 and MIM3325-S1)

Attribute	Analytical Procedure	Acceptance Criteria	ANDA 64144 Intas Mitomycin for Injection*	ANDA 64117 BenVenue Mitomycin for Injection	Mitomycin for Injection USP
Appearance	In house	Blue-violet cake or powder, free from visible evidence of contamination in amber vial.	Same	Grey cake or powder free from visible signs of contamination	-
Constituted Solution	USP<1>	a) Sample powder should dissolve completely leaving no visible residue. b) Sample solution is not significantly less clear than an equal volume of diluent (water for injection) in a similar vessel and examined similarly. c) Sample solution should be essentially free from particles of foreign matter than could be observed on visual inspection.	Same	Same	Meets requirements for Constituted Solutions under Injections <1>.
Identification	USP	The Rf value of the principal spot obtained from the sample solution should correspond to that of the Mitomycin standard solution similarly prepared.	By TLC	By TLC	By TLC
Reconstitution Time	In house				(b) (4)
pH	USP<791>				

Particulate Matter	USP<789>
Bacterial Endotoxin	USP<85>
Sterility	USP<71>
Water	USP<921>
Uniformity of dosage unit (By content uniformity)	USP<905>
Related substances	In house
Assay	USP<621>
Residual Solvents	

(b) (4)

(b) (4)

## 4.2 Clinical Microbiology

There is no clinical microbiology review for this product. Although an antibiotic by pharmacologic class, it is a potent DNA alkylating agent that inhibits DNA replication

and cell proliferation. For the proposed ophthalmic indication, mitomycin acts as an antiproliferative, suppressing cell proliferation that would take place in wound healing and scarring.

### 4.3 Preclinical Pharmacology/Toxicology

No original studies were performed or submitted. This application is made under 505(b)(2), and published literature references are provided.

Mitomycin is an alkylating agent isolated from *Strep. Caespitosus*. It forms stable crosslinks between DNA strands at guanine residues, inhibiting DNA synthesis and cell proliferation, and promoting apoptosis. This action is independent of the phase of the cell cycle. This activity is used for anti-tumor activity by inhibiting DNA synthesis in rapidly proliferating neoplastic cells. For the proposed ophthalmic indication, mitomycin acts as an antiproliferative, suppressing cell proliferation that would take place in wound healing and scarring. Specifically, DNA replication is inhibited in fibroblasts and vascular endothelial cells, decreasing cellularity and fibrosis of the surgical bleb.

No genetic toxicity studies were provided. Mitomycin is a known DNA alkylating agent so may be considered positive for genetic toxicity.

No carcinogenicity data were provided. Since the proposed clinical use is for a single topical application, no carcinogenicity studies to support this application are necessary. The approved label for the reference listed drug indicates that systemic mitomycin is carcinogenic.

### 4.4 Clinical Pharmacology

#### 4.4.1 Mechanism of Action

Mitomycin is an antibiotic derived from *Streptomyces caespitosus* that has anti-proliferative properties. Available for many decades as a cancer chemotherapeutic agent, mitomycin C is a potent DNA alkylating agent. It forms stable crosslinks between DNA strands at guanine residues, inhibiting DNA synthesis and cell proliferation, and promoting apoptosis. This action is independent of the phase of the cell cycle. This activity is used for anti-tumor activity by inhibiting DNA synthesis in rapidly proliferating neoplastic cells.

#### 4.4.2 Pharmacodynamics/Pharmacokinetics

As described in this 505(b)(2) application, the pharmacokinetic characteristics of mitomycin have been previously well-described for the IV formulation with the same active and inactive ingredients. The applicant has submitted a request for waiver of the requirement for submission of evidence of in vivo bioavailability for the proposed mitomycin kit based on the rationale that the bioavailability to the RLD is self-evident because this 505(b)(2) NDA is based upon the reference listed drug Mutamycin (Mitomycin for Injection USP; Bristol Myers Squibb; NDA 062336).

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

This is a 505(b)(2) application primarily based on literature.

The application includes efficacy data gathered from 22 published papers describing prospective clinical studies with mitomycin as adjuvant therapy to glaucoma filtration surgery, primarily trabeculectomy.

Nine prospective, randomized, controlled, masked studies are identified from the literature by the applicant and listed in Table 5.1 A. below. Thirteen additional studies were identified from the literature by the applicant as conducted prospectively but not necessarily randomized or controlled and are listed in Table 5.1 B. below.

Table 5.1 A - Group 1 Studies: Prospective, Randomized, Controlled, Masked Studies (9 Studies)

Study	Design	Population	No. Patients/ No. Eyes	Doses	Duration of Follow-up
Mitomycin versus Placebo, (4 Studies)					
Carlson, 1995 [5.4.14]	Randomized Placebo-controlled Double-masked	Combined phacoemulsification and trabeculectomy in adults	MMC: 14/14 Placebo: 15/15	MMC 0.5mg/mL/3.5min Placebo	6 to 30 months
Cohen, 1996 [5.4.18]	Randomized Placebo-controlled Double-masked	Combined glaucoma/ cataract surgery in 1 eye Adults	36/36 35/35	0.5mg/mL/ 2.5 min Salt solution	12 mo

Clinical Review  
 William Boyd, M.D.  
 NDA 22-572  
 Mitosol (mitomycin for solution)

Table 5.1 A cont'd - Group 1 Studies: Prospective, Randomized, Controlled, Masked Studies (9 Studies)

Study	Design	Population	No. Patients/ No. Eyes	Doses	Duration of Follow-up
Costa, 1996 [5.4.22]	Randomized Placebo-controlled Double-masked	Adults Advanced glaucoma	14/14 14/14	0.2mg/mL/3 min Saline	Up to 24 mo
Robin, 1997 [5.4.91]	Long-term Dose-response Prospective Placebo-controlled Double-masked		75/71 75/78 75/77 75/74	Placebo 0.2mg/mL/2 min 0.2mg/mL/4 min 0.4mg/mL/2 min	12 mo
Mitomycin C versus No Treatment (3 Studies)					
Andreasos, 1997 [5.4.4]	Randomized Re-operation for POAG Masked evaluator	Adults with uncontrolled POAG after previous filtering surgery failure	24 patients with MMC 22 patients without	2nd trab w/MMC 0.4mg/mL MMC 2nd trab w/o MMC	18 mo
Martini, 1997 [5.4.71]	Prospective Randomized Controlled Evaluator-masked	Low-dosage MMC and trabeculectomy	24/30 MMC 24/30 Untreated	0.1mg/mL/3 min	12 mo
Mitomycin versus 5-Fluorouracil (1 Study)					
WuDunn 2002 [5.4.123]	Prospective Double-masked Randomized		5-FU /57 MMC /58	50mg/mL/5 min 0.2mg/mL/2 min	12 mo
Mitomycin Dose Comparison Study (1 Study)					
Sanders 1998 [5.4.94]	Prospective Randomized Masked POAG/previous surgery		25/25 25/25	0.2mg/mL/2 min 0.4mg/mL/2 min	12 mo

5-FU = 5-Fluorouracil; CACG = Chronic angle closure glaucoma; MMC = Mitomycin; POAG = Primary open-angle glaucoma; Trab = Trabeculectomy.

<sup>a</sup> Two studies employed dose-comparison as part of their design: Robin and Sanders. The results from the placebo-controlled study conducted by Robin and colleagues are summarized in the *Mitomycin C versus Placebo* section of this table.

Source – Table 1, NDA Section 2.7.3.2

Table 5.1 B - Group 2 Studies: Prospective Studies of Uncertain Design (13 Studies)

Investigator	Design	Population	No. Patients/ No. Eyes	Dosage	Duration
Hagiwara 2000 [5.4.42]	Prospective Visual Prognosis in Normal-Tension Glaucoma	Adults Normal tension glaucoma	21/21 21/21	0.4mg/mL/ 5 min No treatment	2-7 y
Hong 1993 [5.4.44]	Prospective	Adults	19/23	0.2mg/mL/ 5 min or 0.4mg/mL/ 5 min	12 mo
Kitazawa 1993 [5.4.56]	Randomized Dose finding	Open angle	11/22	0.02mg/mL/ 5 min 0.2mg/mL/ 5 min	Up to 17 mo
Kobayashi 2003 [5.4.57]	Prospective Viscocanal- ostomy vs. trab + MMC	Open angle	25/	0.04%/3 min	12 mo
Kozobolis 2002 [5.4.59]	Prospective Randomized Deep Sclerectomy	Open angle	45/45 DS w MMC 45/45 DS w/o MMC	0.2mg/mL/ 2.5 min	36 mo
Investigator	Design	Population	No. Patients/ No. Eyes	Dosage	Duration
Maquet 2005 [5.4.69]	Prospective Non- randomized Protocol for primary trab or combined surgery	Adults Primary trab or combined surgery	1/7 /37 /64 /35 <i>124/143 total</i>	No MMC 0.1mg/mL/ 2 min 0.2mg/mL/ 2 min 0.4mg/mL/ 2 min	12 mo
Mermoud 1993 [5.4.75]	Prospective Matched control group	Black Patients (adults)	26/30 28/30	0.2mg/mL/ 5 min Trab alone	18 mo
Nuijts 1997 [5.4.81]	Prospective Primary glaucoma	White patients (adults)	23/25	0.2mg/mL/ 5 min	12 mo
Shin 1995 [5.4.99]	Prospective Randomized PGTP POAG		21/21 21/21 21/21 15/15	No MMC 0.5mg/mL/ 1min 0.5mg/mL/ 3 min 0.5mg/mL/ 5 min	21 mo.

Table 5.1 B - Group 2 Studies: Prospective Studies of Uncertain Design (13 Studies)

Investigator	Design	Population	No. Patients/ No. Eyes	Dosage	Duration
Shin 1998 [5.4.101]	Randomized PGTP POAG		PGTP w/o MMC 101/101 PGTP w/MMC 96/96	0.5mg/mL/ 1, 3, or 5 min	24 mo
Turacli 1996 [5.4.111]	Prospective Randomized MMC compared with CSA		30/30  28/28 28/28	0.4mg/mL/ 4 min CSA 2% Control	19.5 mo 17.3 mo 18.2 mo
Unlu 2000 [5.4.112]	Prospective MMC and releasable suture technique compared with MMC and permanent sutures		18/17 releasable sutures  18/20 permanent sutures	0.2mg/mL/ 2 min	8.1 months +/- 1.3 months  8.3 months +/- 1.3 months
Vijaya 2000 [5.4.116]	Prospective Non- randomized 5-FU vs. MMC		16/3 16/13 16/16	0.2mg/mL/ 1 min 0.4mg/mL/ 1 min 50mg/mL/ 1 min	11.1 mo

5-FU = 5-Fluorouracil; CSA = Cyclosporine A; DS = Deep sclerectomy; MMC = Mitomycin; PGTP = Primary glaucoma triple procedure; POAG = Primary open-angle glaucoma; Trab = Trabeculectomy.

Source – Table 12, NDA Section 2.7.3.2.2

**Reviewer's Comments:** *There are two significant errors in the above Table 5.1.B provided by the applicant.*

1) *The applicant has incorrectly described Shin 1995 as article 5.4.99.*

*Shin DH, Hughes BA, Song MS, Kim C, Yang KJ, Shah MI, Juzych MS, Obertynski T. Primary glaucoma triple procedure with or without adjunctive mitomycin. Prognostic factors for filtration failure. Ophthalmology. 1996 Nov;103(11):1925-33*

*The applicant is actually describing and providing tables/data for article 5.1.104:*

*Shin DH, Simone PA, Song MS, Reed SY, Juzych MS, Kim C, Hughes BA. Adjunctive subconjunctival mitomycin C in glaucoma triple procedure. Ophthalmology. 1995 Oct;102(10):1550-8.*

2) *The applicant has incorrectly described Shin 1998 as article 5.4.101.*

*Shin DH, Kim YY, Ren J, Weatherwax AL, Pearlman RB, Kim C, Glover KB, Muenk SB. Decrease of capsular opacification with adjunctive mitomycin C in combined glaucoma and cataract surgery. Ophthalmology. 1998 Jul;105(7):1222-6.*

*The applicant is actually describing and providing tables/data for article 5.1.103:*

*Shin DH, Ren J, Juzych MS, Hughes BA, Kim C, Song MS, Yang KJ, Glover KB. Primary glaucoma triple procedure in patients with primary open-angle glaucoma: the effect of mitomycin C in patients with and without prognostic factors for filtration failure. Am J Ophthalmol. 1998 Mar;125(3):346-52.*

*This error carries through the entire Section 2.7 of the NDA submission.*

## 5.2 Review Strategy

The June 21, 2010, submission was submitted electronically. Subsequent amendments were also submitted in electronically. All literature reports were reviewed. The literature review, package insert, and subsequent labeling comprehension studies formed the basis for the review of efficacy and safety for the proposed indication.

## 5.3 Discussion of Individual Studies/Clinical Trials

This is a 505(b)(2) application primarily based on literature.

The application includes efficacy data gathered from 22 published papers describing prospective clinical studies with mitomycin as adjuvant therapy to glaucoma filtration surgery, primarily trabeculectomy.

The strategy for the literature search is extensively detailed in Sections 2.7.4.2 and 5.3.6.2 of the NDA. Briefly, MEDLINE (via PubMed) and EMBASE were both searched for citations using relevant search terms (i.e. trabeculectomy, filtering surgery, glaucoma, mitomycin, etc.). Searches were repeated after initially being run with an English language limit. Study selection was accomplished through 2 levels of study screening. At Level I screening, any study with an exclusion criterion (e.g. animal or in vitro studies, meta-analyses, no intra-operative ophthalmic use of mitomycin, etc.) was rejected. During full paper screening (Level II), all of the following inclusion criteria must have been present for studies to have passed Level II screening and be included in the final study set:

- Published in the English language
- clinical trial or observational study investigating the use of mitomycin in adults (18+ years) during trabeculectomy procedure for primary open angle glaucoma with at least 1 safety outcome reported

OR

- Case reports or case series of an adverse drug reaction thought to be potentially related to mitomycin use in adults (18+ years) during trabeculectomy procedure for primary open angle glaucoma.

### 5.3.1 Group 1 Studies: Prospective, Randomized, Controlled, Masked Studies

Nine prospective, randomized, controlled, masked studies are identified from the literature by the applicant and listed in Section 5.1, Table 5.1 A., of this review.

The nine studies are further categorized by the applicant as follows:

- 1) Four studies comparing intraoperative mitomycin C to placebo: Carlson 1995, Cohen 1996, Costa 1996, and Robin 1997
- 2) Three studies comparing intraoperative mitomycin C to no drug treatment (i.e., standard surgery): Andreanos 1997, Martini 1997, and Rasheed 1999
- 3) One study comparing intraoperative mitomycin C to 5-FU: WuDunn 2002
- 4) Two studies investigating different doses of intraoperative mitomycin C: Robin 1997, Sanders 1999.

### 5.3.2 Group 2 Studies: Prospective Studies of Uncertain Design

Thirteen additional studies were identified from the literature by the applicant as conducted prospectively but not necessarily randomized or controlled and are listed in Section 5.1, Table 5.1 B, of this review

## 6 Review of Efficacy

### Efficacy Summary

#### Reviewer's Comments:

*This is a 505(b)(2) application primarily based on literature.*

*There is adequate support from the literature to support efficacy for Mitosol (mitomycin for solution) in the treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery*

*In the four placebo-controlled studies (Carlson, Cohen, Costa, and Robin), the mean IOP in the mitomycin-treated groups as compared with placebo-treated groups was lower by approximately 3 mmHg.*

- *In Carlson et al, 1997, the difference in mean IOP at Month 12 was not statistically significant, although mitomycin-treated subjects had numerically lower IOPs (roughly 13 mm Hg versus 16 mmHg).*

- *In Cohen et al, 1996, mitomycin-treated subjects had lower mean IOPs (roughly 15 mm Hg versus 17 mmHg,  $p = 0.058$ ).*
- *In Costa et al, 1996, the mean IOP was significantly lower in the mitomycin treated group at the following time points: first postoperative day ( $p=0.021$ ), 6-month interval ( $p=0.001$ ), and at the final visit ( $p=0.002$ ). It appears no correction was made for multiple endpoints.*

*Mean IOP at Month 6 was roughly 12 mmHg for mitomycin-treated subjects and 17 mmHg for placebo. Mean IOP at last follow-up (ranging from Month 7-24) was roughly 13 mmHg for mitomycin-treated subjects and 18 mmHg for placebo.*

- *In Robin et al, 1997, all three mitomycin-treated groups showed a statistically significant difference in IOP compared with placebo at Month 12 ( $p \leq 0.001$ ). Mean IOP data for the four groups were not provided. The estimated between group difference in IOP between placebo and Group 2 was 2.0 mmHg. The estimated between group difference in IOP between placebo and Group 3 and Group 4 was 3.0 mmHg.*

*In the three surgery plus mitomycin versus surgery-alone controlled studies (Andreanos, Martini, and Rasheed), the difference in mean IOP was lower by approximately 5 mmHg.*

- *In Andreanos et al, 1997, the mean ( $\pm$ SD) postoperative IOP was 12.5 ( $\pm$ 3.2) mmHg in the mitomycin group and 19.6 ( $\pm$ 6.1) mmHg in the control group at Month 18; this between group difference was statistically significant:  $p < 0.001$ .*
- *In Martini et al, 18997, the difference in mean IOP at Month 12 was statistically significant; mitomycin-treated subjects had lower IOPs (roughly 11 mm Hg versus 16 mmHg).*
- *In Rasheed et al, 1999, the mean postoperative IOP at Month 18 (average IOP recorded during last six months of follow-up) is lower for mitomycin treated subjects (roughly 10 mmHg) versus non-mitomycin treated subjects (roughly 16 mmHg). It is not clear that this difference is statistically significant.*

*In the double-masked active-controlled study (Wudunn 2002), the success rate of the mitomycin-treated group was similar to that of the 5-FU-treated group (**note:** F-5U is not approved for this indication).*

## **6.1 Indication: Treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery**

### 6.1.1 Methods - Literature

#### 6.1.1. A Group 1 Studies: Prospective, Randomized, Controlled, Masked Studies

Per the applicant, there is a sufficient level of detail within the following literature references to determine that they represent adequate and well-controlled trials.

##### *6.1.1. A.1 Mitomycin versus Placebo*

*Carlson DW, Alward WL, Barad JP, Zimmerman MB, Carney BL. A Randomized Study of Mitomycin Augmentation in Combined Phacoemulsification and Trabeculectomy. Ophthalmology 1997 Apr; 104(4):7 19-724.*

This randomized double masked, placebo controlled study in 29 adult patients evaluated whether intraoperative application of subconjunctival mitomycin during combined phacoemulsification and trabeculectomy was an effective means of improving filtration. The authors defined effective filtration as overall lower IOP and reduced IOP-lowering medication use.

Subjects with a visually significant cataract and glaucoma were randomized in a double masked fashion to receive intraoperative mitomycin (0.5mg/mL/3.5 min) or placebo in 1 eye only. Patients were followed for 6 to 30 months after surgery.

Masking was accomplished using dilute gentian violet to match the approach of the mitomycin. All procedures were performed in the superotemporal quadrant using a limbal based flap. Methylcellulose sponges were utilized.

On average over the 12 months, the patients treated with mitomycin had postoperative IOP levels 3.0 mmHg lower than did the placebo group ( $p = 0.04$ , ANOVA) throughout the study. Per the authors, the overall lower IOP was present despite the fact that many placebo treated eyes required medication to help control IOPs, while no mitomycin treated eyes required medication.

**Table 2 MMC Augmentation in Combined Phacoemulsification and Trabeculectomy—  
 12-Month Comparison (Carlson 1997)**

<b>12-Month Outcomes</b>	<b>MMC 0.5mg/mL/3.5 min (n = 14)</b>	<b>Placebo (n = 15)</b>	<b>P-value</b>
IOP in mmHg (mean ±SD)	12.6 (±1.0)	16.2 (±1.5)	.06 <sup>a</sup>
Mean change in IOP in mmHg (±SD)	5.6 (±1.3)	2.6 (±1.3)	.11 <sup>a</sup>
No. (%) patients with IOP between 5 mmHg and 15 mmHg	11/13 (85%)	5/12 (42%)	.04 <sup>b</sup>
No. (%) patients with IOP controlled without medications	13/13 (100%)	10/15 (67%)	.04 <sup>c</sup>
Visual Acuity 20/40 or better	13/14 eyes	14/15 eyes	NS
% patients requiring laser suture lysis	43%	80%	0.06 <sup>b</sup>
Mean number laser suture lysis	0.7	2.0	0.005 <sup>b</sup>

IOP = Intraocular pressure; SD = Standard deviation.

<sup>a</sup> Student's *t* test.

<sup>b</sup> Repeated measures of Analysis of variance.

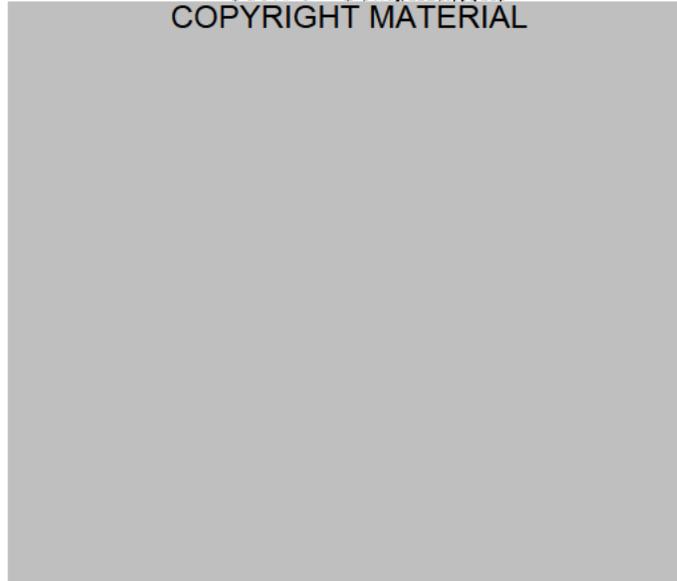
<sup>c</sup> Fisher exact test.

**Reviewer's Comments:** *The difference in mean IOP at Month 12 was not statistically significant, although mitomycin-treated subjects had numerically lower IOPs (roughly 13 mm Hg versus 16 mmHg).*

*The mean change in IOP at Month 12 was not statistically significant, although mitomycin-treated subjects showed numerically higher decreases in IOP from baseline (roughly 6 mmHg versus 3 mmHg).*

*Hypotony was seen in late in one patient in the placebo group. One patient in the mitomycin group developed a coagulase negative staph endophthalmitis 10 months after surgery. See the following table.*

Table 3. Complications  
COPYRIGHT MATERIAL



*Cohen JS, Greff LJ, Novack GD, Wind BE. A placebo-controlled, double-masked evaluation of mitomycin C in combined glaucoma and cataract procedures. Ophthalmology. 1996 Nov; 103(11): 1934-42.*

This prospective, placebo-controlled, double-masked study was performed to determine if adjunctive use of mitomycin would increase the success of combined phacoemulsification, intraocular lens implantation, and trabeculectomy surgery with releasable sutures.

Seventy-two eyes with cataract and glaucoma in 72 consecutive adult patients (1 eye per patient) were randomized to either mitomycin 0.5mg/mL/2.5min or placebo-balanced salt solution. All patients underwent phacoemulsification, posterior chamber intraocular lens implantation, and trabeculectomy surgery with releasable sutures by the same surgeon. The surgeon evaluated the patients 1 day after surgery, at least once a week for 1 month, and then monthly for 3 months after surgery. A masked observer evaluated the patients at 3, 6, and 12 months after surgery.

All procedures were performed in the superotemporal quadrant using a limbal based flap. Cellulose sponges were utilized.

The authors report that the mitomycin group had significantly greater reduction than the placebo group in mean IOP through the first 12 months of follow-up: 7.05 to 7.65 mmHg versus 2.62 to 3.83 mmHg (p=0.001 to 0.028). Through the first 6 months of follow-up,

the mitomycin group required significantly fewer medications: 0.4 to 0.5 versus 1.1 to 1.2 (p=0.002 to 0.004).

There were fewer cases of additional glaucoma surgery in the mitomycin group than in the placebo group: 4 of 36 versus 7 of 35 patients (p=.0301). Postoperative visual acuities were similar in both treatment groups and were markedly improved.

**Table 3 IOP and Medication Outcomes following MMC in Combined Glaucoma and Cataract Procedures (Cohen 1996)**

	MMC (N = 36)		Placebo (N = 35)		Between Treatment P-Value
	Mean (±SD)	(No. of Eyes)	Mean (±SD)	(No. of Eyes)	
Mean IOP and Change from Baseline in mmHg					
Baseline	22.19 (±5.37)	36	20.34 (±5.18)	35	0.144
3 months	14.75 (±4.74)	32	16.83 (±3.73)	30	0.060
Change from BL	-7.47 (±6.41)	32	-2.70 (±4.19)	30	0.001
6 months	14.78 (±3.99)	30	15.55 (±3.82)	28	0.456
Change from BL	-7.05 (±6.02)	30	-3.84 (±4.68)	28	0.028
12 months	14.50 (±4.63)	26	17.15 (±5.21)	26	0.058
Change from BL	-7.65	26	-2.62 (±4.42)	26	0.001
Mean Number of Ocular Hypotensive Medications					
Baseline	2.03 (±1.00)	36	2.46 (±0.85)	35	0.056
3 months	0.38 (±0.61)	32	1.10 (±1.09)	30	0.002
Change from BL	-1.66 (±0.90)	32	-1.27 (±0.78)	30	0.076
6 months	0.50 (±0.82)	30	1.21 (±0.99)	28	0.004
Change from BL	-1.50 (±1.01)	30	-1.18 (±0.86)	28	0.199
12 months	0.58 (±0.86)	26	1.38 (±1.33)	26	0.012
Change from BL	-1.42 (±1.21)	26	-0.96 (± 1.00)	26	0.139

<sup>a</sup> BL = Baseline; IOP = Intraocular pressure; MMC = Mitomycin; SD = Standard deviation.

**Reviewer's Comments:** Mean IOP and IOP change from baseline at **Month 3** were not statistically significant. Mitomycin-treated subjects had numerically lower IOPs (roughly 15 mm Hg versus 17 mmHg). Mitomycin-treated subjects had numerically higher decreases in IOP from baseline (roughly 7 mmHg versus 3 mmHg).

The difference in mean IOP at **Month 6** was not statistically significant, although mitomycin-treated subjects had numerically lower IOPs (roughly 15 mm Hg versus 16 mmHg).

The mean change in IOP at **Month 6** was statistically significant with mitomycin-treated subjects showing higher decreases in IOP from baseline (roughly 7 mmHg versus 4 mmHg, p = 0.028).

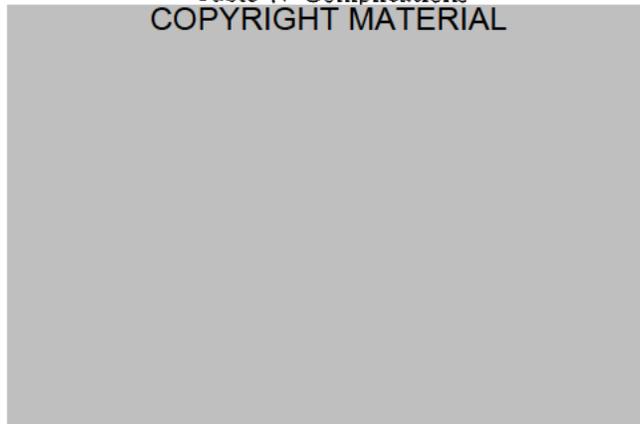
Mean IOP and IOP change from baseline at **Month 12** were statistically significant. Mitomycin-treated subjects had numerically lower IOPs (roughly 15 mm Hg versus 17 mmHg,  $p = 0.058$ ). Mitomycin-treated subjects had numerically higher decreases in IOP from baseline (roughly 8 mmHg versus 3 mmHg,  $p = 0.001$ ).

*It appears no correction was made for multiple endpoints.*

*A filtering bleb leak occurred in 11 of 36 eyes (31%) in the mitomycin group and in 5 of 35 eyes (14%) in the placebo group ( $p = 0.101$ ).*

*There were no significant differences in endothelial cell counts between groups pre and post surgery. See following table.*

Table 7. Complications  
COPYRIGHT MATERIAL



*Costa VP, Comegno PE, Vasconcelos JP, Malta RF, Jose NK. Low-dose mitomycin C trabeculectomy in patients with advanced glaucoma. J Glaucoma. 1996 Jun;5(3): 193-9.*

This prospective, randomized, double-masked study examined the efficacy and safety of intraoperative mitomycin (0.2mg/mL/3min) in primary trabeculectomy. Twenty-eight eyes of 28 patients with advanced primary open-angle glaucoma undergoing trabeculectomy were randomly assigned to either 0.2mg/mL mitomycin or a saline solution for 3 minutes.

The surgeon performing the procedure was masked to the treatment being used. Visual acuity and IOP were measured at 1 day, 1 week, and 1, 3, and 6 months post surgery, and at the last available follow-up. Complete success was defined by the investigators as IOP  $\leq 15$  mmHg without medication. Qualified success was defined as IOP  $\leq 15$  mmHg with medication. Failure was defined as IOP  $> 15$  mmHg with medication.

All procedures were performed in the superotemporal quadrant using a limbal based flap. Methylcellulose sponges were utilized.

The authors report that the mean IOP (SD) was significantly lower in the mitomycin treated group at the following time points: first postoperative day ( $p=0.021$ ), 6-month interval ( $p=0.001$ ), and at the final visit ( $p=0.002$ ). The percentage of eyes classified as complete successes was significantly higher in the mitomycin group when compared to the placebo group ( $p=0.022$ ), and the incidence of failures was significantly higher in the placebo group when compared to the control group ( $p=0.007$ ).

There was a statistically significant difference in frequency of trabeculectomy failure between the groups at 6 months and thereafter ( $p<0.05$ ). The mean time of trabeculectomy survival was 13.1 ( $\pm 8.8$ ) months for the mitomycin group and 4.0 ( $\pm 5.1$ ) months for the placebo group ( $p=0.0036$ ).

**Table 4 Success Rates and IOP after Low Dose trabeculectomy with MMC (Costa 1996)**

Outcomes	MMC (n = 14)	Placebo (n = 14)	P-value <sup>a</sup>
No. (%) Patients with Success			
Complete (IOP $\leq 15$ mmHg without meds)	10 (71.4%)	3 (21.4%)	0.022 <sup>b</sup>
Qualified (IOP $\leq 15$ mmHg with meds)	2 (14.3%)	1 (7.1%)	1.000
Total no. (%) patients	12 (85.7%)	4 (28.5%)	0.007 <sup>b</sup>
Failure (IOP $>15$ mmHg with meds)	2 (14.3%)	10 (71.4%)	0.007 <sup>b</sup>
Mean ( $\pm$ SD) IOP in mmHg at			
1 Day (n = 28)	5.30 ( $\pm 3.92$ )	10.71 ( $\pm 5.73$ )	0.021 <sup>b</sup>
1 Week (n = 28)	6.57 ( $\pm 2.56$ )	9.14 ( $\pm 5.30$ )	0.215
1 Month (n = 28)	12.57 ( $\pm 3.00$ )	14.21 ( $\pm 4.82$ )	0.203
3 Months (n = 28)	13.14 ( $\pm 5.68$ )	15.76 ( $\pm 5.18$ )	0.116
6 Months (n = 28)	12.07 ( $\pm 3.56$ )	17.28 ( $\pm 3.36$ )	0.001 <sup>b</sup>
Last follow-up (n = 28) (range: 7–24 months)	12.78 ( $\pm 3.90$ )	18.35 ( $\pm 4.53$ )	0.002 <sup>b</sup>
Mean ( $\pm$ SD) number of antiglaucoma medications at last follow-up	0.35 ( $\pm 0.84$ )	1.57 ( $\pm 1.08$ )	0.002

Meds = Antiglaucoma medications

<sup>a</sup> Student *t* test.

<sup>b</sup> Statistically significant ( $p<0.05$ ) by Student's *t* test.

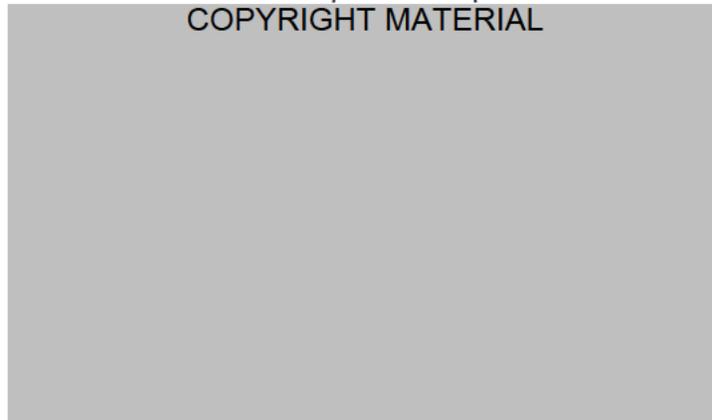
**Reviewer's Comments:** *Agree that the mean IOP was significantly lower in the mitomycin treated group at the following time points: first postoperative day ( $p=0.021$ ), 6-month interval ( $p=0.001$ ), and at the final visit ( $p=0.002$ ). It appears no correction was made for multiple endpoints.*

*Mean IOP at **Month 6** was roughly 12 mmHg for mitomycin-treated subjects and 17 mmHg for placebo. **Mean IOP at last follow-up** (ranging from Month 7-24) was roughly 13 mmHg for mitomycin-treated subjects and 18 mmHg for placebo.*

*Agree that the percentage of eyes classified as complete successes was significantly higher in the mitomycin group when compared to the placebo group ( $p=0.022$ ), and the incidence of failures was significantly higher in the placebo group when compared to the control group ( $p=0.007$ ). It appears no correction was made for multiple endpoints.*

*Early postoperative complications associated with excessive filtration (e.g. shallow AC and choroidal detachment) were more frequent in the mitomycin group. Three of the 14 mitomycin treated subjects and two of the 14 control eyes showed significant visual loss at the last follow-up. Significant visual loss was not defined. The authors state that "lens opacification was the only cause for visual acuity loss in all patients."*

TABLE 4. Postoperative complications  
COPYRIGHT MATERIAL



*Robin AL, Ramakrishnan R, Krishnadas R, Smith SD, Katz JD, Selvaraj S, Skuta GL, Bhatnagar R. A long-term dose-response study of mitomycin in glaucoma filtration surgery. Arch Ophthalmol. 1997 Aug;115(8):969-74.*

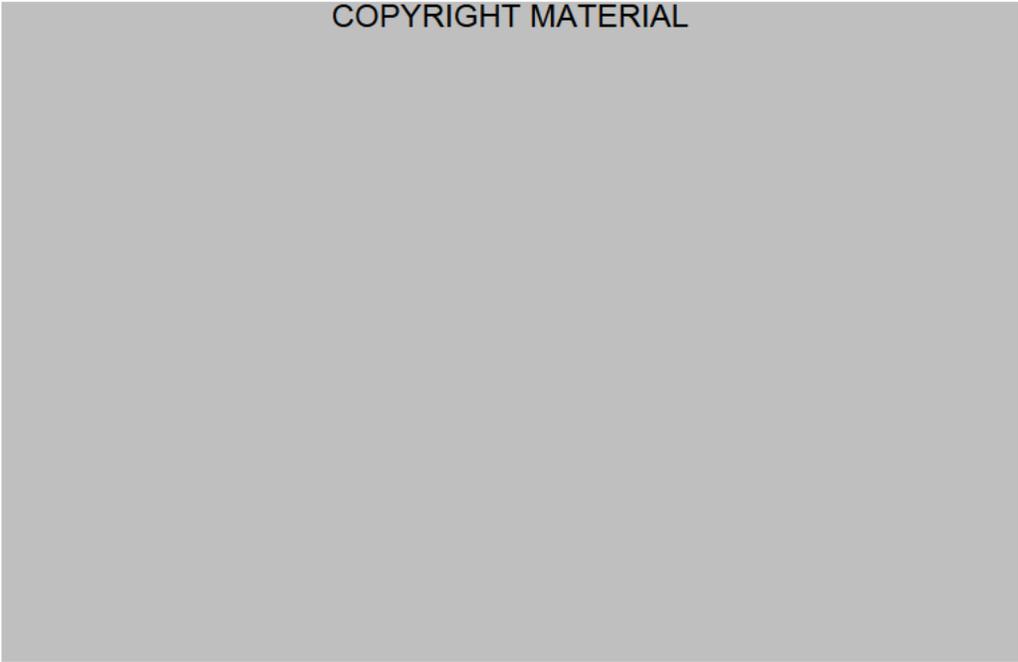
This prospective, double-masked, placebo-controlled, 1 -year study was designed to evaluate the dose-response relationship between mitomycin concentration/duration of exposure and the change in IOP and incidence of complications in patients undergoing trabeculectomy.

Three hundred (300) eyes were randomized into four treatment groups in a prospective, double masked fashion: Group 1: placebo; Group 2: mitomycin 0.2mg/mL/2min; Group 3: mitomycin 0.2mg/mL/4min, and Group 4: mitomycin 0.4mg/mL/2 min. The physician performing the surgeries and the physician performing the measurements were masked to the treatment groups.

The treatment groups were balanced at baseline for age, sex, history, use of glaucoma medications and visual acuity. A single surgeon performed all of the trabeculectomies using a fornix based flap and cellulose sponges.

Significant treatment-related decreases in IOP were observed, with a decrease in IOP in all three mitomycin-treated groups compared with placebo for all times beyond 1 month. The estimated difference in IOP between each mitomycin treated group and placebo, based on the random-effects model and adjusting for differences in age, preoperative IOP, and length of follow-up, is presented. Unadjusted data is not presented. All three mitomycin-treated groups showed a statistically significant difference in IOP compared with placebo.

COPYRIGHT MATERIAL



**Reviewer's Comments:** *Per the authors, all three mitomycin-treated groups showed a statistically significant difference in IOP compared with placebo at **Month 12** ( $p \leq 0.001$ ). Mean IOP data for the four groups were not provided. Unadjusted data is not presented. Per the authors, the estimated between group difference in IOP between placebo and Group 2 was 2.0 mmHg. The estimated between group difference in IOP between placebo and Group 3 and Group 4 was 3.0 mmHg.*

The observed differences in IOP among the three mitomycin-treated groups were not statistically significant ( $p=0.25$ ).

**Table 5 Estimated Difference Between MMC-Treated Groups: Dose-Response Study of MMC in Glaucoma Filtration Surgery (Robin, 1997)**

Group (No Patients/No. Eyes)	Estimated Difference from Placebo (mmHg)	95% CI	P-value
2 (75/78) <sup>a</sup>	2.0	0.8, 3.3	0.001
3 (75/77) <sup>b</sup>	3.0	1.8, 4.3	<0.001
4 (75/74) <sup>c</sup>	2.9	1.6, 4.2	<0.001

CI = Confidence interval.

<sup>a</sup> Group 2 = 0.2mg/mL/2min.

<sup>b</sup> Group 3 = 0.2mg/mL/4min.

<sup>c</sup> Group 4 = 0.4mg/mL/2min.

**Reviewer’s Comments:** *Agree that there was no statistically significant difference between mitomycin-treated groups (varying concentration and duration of exposure) at Month 12.*

Of the 221 subjects with at least 1-year follow-up, more placebo-treated eyes had a final IOP greater than 18mmHg or required medication for IOP control than in any of the mitomycin-treated groups. This difference is not statistically significant.

**Table 6 Success Criteria at 1-Year— Dose-Response Study of MMC in Glaucoma Filtration Surgery (Robin, 1997)**

	Group 1 (n = 55)	Group 2 (n = 63)	Group (n = 54)	Group 4 (n = 49)
Percent of Subjects Meeting Criteria for Success at 1 year				
IOP ≤18 mmHg	78.2	90.5	90.7	91.8
IOP decrease ≥25%	87.3	85.7	92.6	91.8
Free from all medication	85.5	98.4	96.3	93.7
Met all 3 criteria	72.7	79.4	83.3	85.7

Group 1 = placebo; Group 2 = MMC 0.2mg/mL/2 minutes; Group 3 = MMC 0.2mg/mL/4 min, Group 4 = MMC 0.4mg/mL/2 min; MMC = Mitomycin C.

**Reviewer’s Comments:** *Agree that there is not a statistically significant difference in the “Success Criteria” between placebo and mitomycin-treated eyes.*

*A clinically obvious progressive lens opacity (Snellen BCVA decrease of 3 lines) occurred in 54 eyes (18%). The authors do not separate this number by treatment group; they do report after adjusting for age, presence of cataracts at baseline,*

*baseline IOP, and AC depth, subjects in Group 3 appear most at risk for significant cataract at one year.*

*Complications prior to discharge were considered minor or self limited and included choroidal detachment in 13 subjects and macular folds in 19 subjects. The authors report no difference in rate of these complications between groups, but the absolute numbers by group are not provided.*

#### 6.1.1. A.2 Mitomycin versus No Drug Treatment

*Andreanos D, Georgopoulos GT, Vergados J, Papaconstantinou D, Liokis N, Theodossiadis P Clinical evaluation of the effect of mitomycin-C in re-operation for primary open-angle glaucoma. Eur J Ophthalmol. 1997 Jan-Mar;7(1):49-54.*

This study evaluated the effect of mitomycin in a second glaucoma operation after failure of the first operation. Forty-six (46) adult patients with high intraocular pressure for a period of 1 to 3 years after the first trabeculectomy were enrolled. All patients were randomized to a second trabeculectomy with 0.4mg/mL/2-3 min mitomycin (Group A: 24 patients) or without (Group B: 22 patients).

None of the original trabeculectomies were performed with anti-metabolites.

All procedures were performed using a limbal based conjunctival flap. Cellulose sponges were utilized.

At 18 months, the mean ( $\pm$ SD) postoperative IOP was 12.5 ( $\pm$ 3.2) mmHg in the mitomycin group and 19.6 ( $\pm$ 6.1) mmHg in the control group; this difference was statistically significant:  $p < 0.001$ . IOP control, defined as  $IOP \leq 20$  mmHg, was seen in 83% of the mitomycin and 64% of the control group. This difference was not statistically significant.

**Table 7 IOP Changes and IOP Control—Second Glaucoma Surgery with and without MMC (Andreanos 1997)**

Postoperative Outcomes at 18 Months	Number (%) Patients		
	Trab + MMC (n = 24)	Trab Only (n = 22)	P-value
Mean ( $\pm$ SD) IOP in mmHg	12.5 ( $\pm$ 3.2)	19.6 ( $\pm$ 6.1)	<0.001) <sup>a</sup>
IOP control <sup>b</sup>	83.3%	63.6%	N.S.

IOP = Intraocular pressure; N.S. = Not significant; Trab = Trabeculectomy.

<sup>d</sup> Student's t-test.

<sup>e</sup> IOP control was defined as  $IOP \leq 20$  mmHg without medication.

**Reviewer's Comments:** *The authors state there was correlation between the use of mitomycin and "clinical success," but they do not define their criteria.*

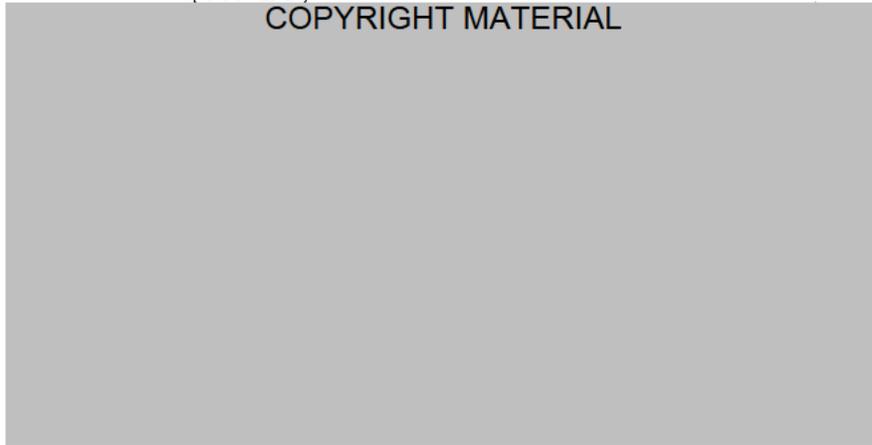
*Agree that the mean ( $\pm$ SD) postoperative IOP was 12.5 ( $\pm$ 3.2) mmHg in the mitomycin group and 19.6 ( $\pm$ 6.1) mmHg in the control group at **Month 18**; this between group difference was statistically significant:  $p < 0.001$ .*

*Agree that IOP control, defined as  $IOP \leq 20$  mmHg, was seen in 83% of the mitomycin and 64% of the control group at **Month 18**. This difference was not statistically significant.*

*Prolonged hypotony was observed in 21% of Group A (Trab + MMC) and 5% of Group B (Trab Only). Visual acuity decreased by two or more Snellen lines in 29% of Group A and 23% of Group B; cataract progression was seen in 25% of Group A and 18% of Group B.*

**TABLE I - COMPLICATIONS OF TRABECULECTOMY  
(TR-EC)**

COPYRIGHT MATERIAL



*Martini E, Laffi GL, Sprovieri C, Scorolli L. Low-Dosage Mitomycin C as an Adjunct to Trabeculectomy. A prospective controlled study. Eur J Ophthalmol 1997 Jan-Mar;7(1):40-8.*

This prospective, randomized, controlled, evaluator-masked study in adult patients was designed to assess the effectiveness and adverse effects of intraoperative mitomycin in filtering glaucoma surgery. Sixty eyes of 48 patients undergoing surgery for uncontrolled glaucoma were randomly assigned to trabeculectomy with or without intraoperative mitomycin (0.1mg/mL/3min). When a previously operated patient's fellow eye had to be operated on, that eye was assigned to the group opposite the first eye, even if this was in contrast with the randomization scheme. Patients were evaluated at 2 to 4 hours, 1, 3, 5, and 7 days, weekly for a month, and 3, 6, and 12 months after surgery by personnel masked to treatment.

A full success was defined as IOP  $\leq$  18 mmHg without medication; a qualified success was defined as IOP  $\leq$  18 mmHg with topical IOP-lowering drugs; a failure was defined as IOP  $\geq$  18 mmHg at two evaluations despite adjunctive therapy.

All procedures were performed using a limbal based conjunctival flap (location unspecified). Cellulose sponges were utilized.

At the 1 year follow up, the total success rate (full + qualified) was 97% in the mitomycin group and 73% in the control group; the mean ( $\pm$ SD) IOP was 11.1 ( $\pm$ 3.1) mmHg and 16.4 ( $\pm$ 6.1) mmHg respectively. This difference was statistically significant in favor of the mitomycin group ( $p < 0.0001$ ).

**Table 8 Success Rate and IOP Outcomes after Trabeculectomy with Low-Dose MMC at 1-Year Follow-up (Martini 1997)**

Outcomes at 1-Year Follow-up	MMC (n = 30)	No MMC (n = 30)	P-value <sup>a</sup>
Total success <sup>b</sup> rate (IOP $\leq$ 18 mmHg with or without meds)	96.6%	73.3%	<0.0001
Mean ( $\pm$ SD) IOP in mmHg	11.1 ( $\pm$ 3.1)	16.4 ( $\pm$ 6.1)	<0.0001
Mean ( $\pm$ SD) IOP in fully successful <sup>b</sup> cases ( $\leq$ 18 mmHg)	10.7 ( $\pm$ 3.0)	13.4 ( $\pm$ 2.6)	<0.001
Mean ( $\pm$ SD) IOP in patients who required bilateral surgery (n = 12) <sup>c</sup>	11.1 ( $\pm$ 2.9)	14.9 ( $\pm$ 3.3)	<0.0001
No. (%) patients who needed further antihypertensive medication during the follow-up to keep IOP below 20mmHg	2 (6.6%)	6 (20%)	–

– = Not calculated. MMC = Mitomycin.

<sup>a</sup> P-value calculated using two-tailed Student's *t* test for unpaired samples.

<sup>b</sup> Full success = IOP  $\leq$ 18 mmHg without medication; qualified success = IOP  $\leq$ 18 mmHg with topical tension-lowering drugs; failure = IOP  $\geq$ 18 mmHg at two evaluations despite adjunctive therapy.

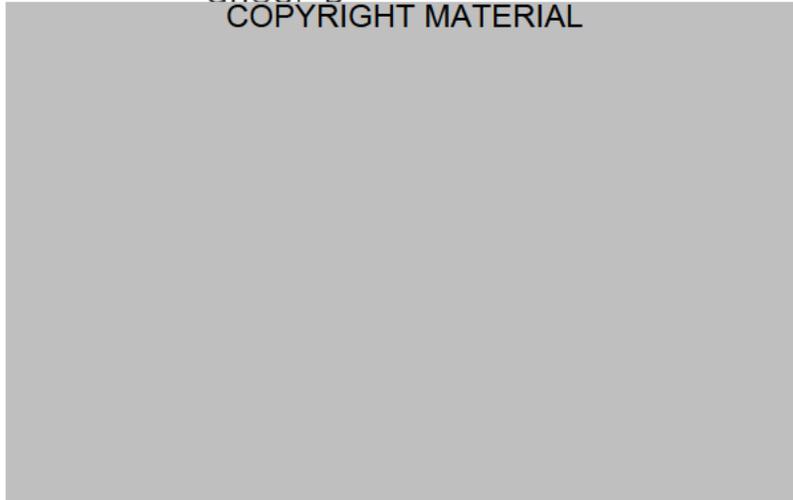
<sup>c</sup> Twelve patients who had bilateral surgery received MMC in 1 eye and no treatment in the other eye.

**Reviewer's Comments:** *The difference in mean IOP at Month 12 was statistically significant; mitomycin-treated subjects had lower IOPs (roughly 11 mm Hg versus 16 mmHg).*

*When the "full success" group (as IOP  $\leq$  18 mmHg without medication) and "qualified success" group (IOP  $\leq$  18 mmHg with topical IOP-lowering drugs) are combined into a "total success" group, the difference between treatment groups is statistically significant at  $p < 0.0001$ . It is not clear that this total success group was predefined.*

*Low/flat anterior chamber was observed in 17% of Group A (Trab + MMC) and 27% of Group B (Trab Only). Two of these cases in Group B required surgical reformation of the anterior chamber and rapidly developed cataracts.*

TABLE VI - COMPLICATIONS IN GROUP A AND  
GROUP B  
COPYRIGHT MATERIAL



*Rasheed el-S. Initial Trabeculectomy with Intraoperative Mitomycin-C Application in Primary Glaucomas. Ophthalmic Surg Lasers 1999 May;30(5):360-6.*

This prospective, randomized, single-masked study compared the overall efficacy of intraoperative application of mitomycin in eyes undergoing trabeculectomy versus trabeculectomy without mitomycin. Twenty-five patients (20 with primary open angle glaucoma and 5 with chronic angle closure glaucoma) underwent trabeculectomy in 1 eye (control group) and trabeculectomy with mitomycin in the other eye (treatment group). Patients in the treatment group received a single application of 0.3 to 0.4 mg/mL of mitomycin for 4 minutes. All patients were followed for 18 months postoperatively.

All procedures performed were fornix-based trabeculectomies (i.e. fornix-based flaps) which utilized unspecified surgical sponges.

Successful IOP control (defined as IOP < 20 mmHg with or without IOP-lowering meds) was seen in 23 eyes (92%) of the mitomycin group and 17 eyes (68%) of the control group at 18 months.

**Table 9 IOP Outcomes after Initial Trabeculectomy with MMC in Primary Glaucoma (Rasheed 1999)**

Effectiveness Parameters	MMC (n = 25) <sup>a</sup>	Control (n = 25) <sup>a</sup>
Successful IOP control	23 eyes (92%)	17 eyes (68%)
Mean (±SD) postoperative IOP in mmHg <sup>b</sup>	10.2 (±3.9)	16.1 (±5.1)
No (%) Patients (N = 25) with the following:		
IOP<12 mmHg	15 (60%)	5 (20%)
IOP<15 mmHg	18 (72%)	8 (32%)
IOP<20 mmHg without hypotensive meds	21 (84%)	12 (48%)
IOP<20 mmHg with 1 to 3 hypotensive meds	2 (8%)	8 (32%)
IOP>20 mmHg with hypotensive medications	2(8%)	8 (32%)
Total	25 (100%)	25 (100%)
No. (%) Patients Requiring Postoperative Surgical Procedures		
Argon laser suture lysis <sup>c</sup>	13 (52%)	21 (84%)
Additional filter <sup>d</sup>	1 (4)	7(28)

IOP = Intraocular pressure; Meds = Antiglaucoma or antihypotensive medications; MMC = Mitomycin.

<sup>a</sup> Trabeculectomy with MMC was performed in 1 eye and trabeculectomy without MMC was performed in the fellow eye. Sequence or order of surgery was randomized by a computer generated table of random numbers.

<sup>b</sup> Mean (±SD) postoperative IOP was defined as the average IOP measurement recorded during the last 6 months of the follow-up period.

<sup>c</sup> The difference between treatment groups was statistically significant: p=0.015.

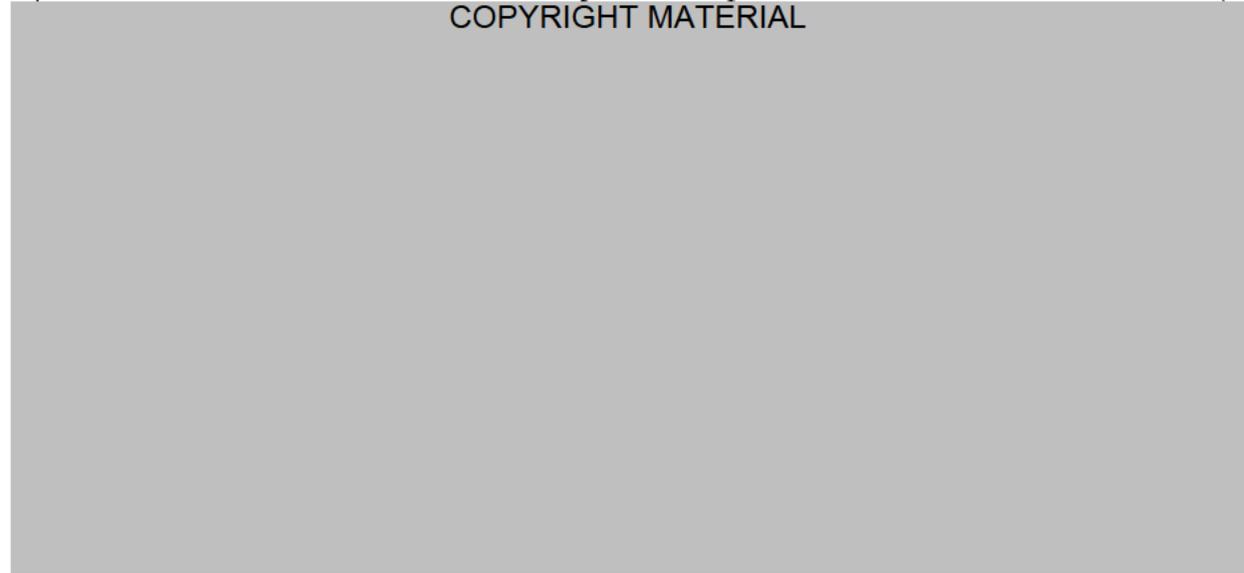
<sup>d</sup> The difference between treatment groups was statistically significant: p=0.020.

**Reviewer's Comments:** *It is not clear that the differences seen between groups in "successful IOP control" are statistically significant.*

*The mean postoperative IOP at **Month 18** (average IOP recorded during last six months of follow-up) is lower for mitomycin treated subjects (roughly 10 mmHg) versus non-mitomycin treated subjects (roughly 16 mmHg). It is not clear that this difference is statistically significant.*

*Additional filtration surgery was needed in one eye of the mitomycin group and 7 eyes of the control group. All five subjects (3 mitomycin, 2 control) with flat anterior chambers required reformation.*

Table 3. Postoperative Complications  
COPYRIGHT MATERIAL



#### 6.1.1. A.3 Mitomycin versus 5-FU

*WuDunn D, Cantor L, Palanca-Capistrano A, Hoop J, Alvi N, Finley C, Lakhani V, Burnstein A, Knotts S. A Prospective Randomized Trial Comparing Intraoperative 5-Fluorouracil Vs Mitomycin-C in Primary Trabeculectomy. Am J Ophthalmology October 2002 V134(4):521- 528.*

This prospective, randomized, double-masked study compared administration of intraoperative 5-fluorouracil (5-FU) and mitomycin (0.2mg/mL/2min) in primary trabeculectomy. One hundred fifteen eyes of 103 patients with uncontrolled IOP despite maximally tolerated medical therapy or laser were randomized to one of the two treatment groups and underwent primary trabeculectomy with either 5-FU 50g/mL/5 min or mitomycin. Patients and surgeon were masked to treatment.

Primary outcome measures included the number of eyes achieving target pressures of 21 mmHg, 18 mmHg, 15 mmHg, and 12 mmHg at 6 and 12 months.

Masking was accomplished using dilute gentian violet to match the approach of the mitomycin. All procedures were performed using a limbal based flap. Methylcellulose sponges were utilized.

One-hundred fifteen eyes of 103 patients were enrolled in the study: 58 eyes received mitomycin and 57 received 5-FU. There were no statistically significant differences between treatment groups for any measure of success at any time point.

**Table 10 Success Criteria at 6 and 12 Months—  
 5-FU versus MMC in Primary Trabeculectomy (WuDunn, 2002)**

Dose Group <sup>a</sup>	6 Months		12 Months	
	MMC (n = 58)	5-FU (n = 57)	MMC (n = 58)	5-FU (n = 57)
Success Criteria				
IOP ≤21 mmHg	95%	95%	89%	94%
IOP ≤18 mmHg	95%	95%	87%	94%
IOP ≤15 mmHg	88%	85%	78%	81%
IOP ≤12 mmHg	77%	86%	65%	67%
Mean (±SD) postoperative IOP in mmHg	9.4 (±4.6)	10.1 (±6.4)	9.9 (±5.0)	10.9 (±6.4)
Mean Medication use (±SD)	0.1 (±0.5)	0.1 (±0.6)	0.1 (±0.5)	0.2 (±0.6)

5-FU = 5-Fluorouracil; IOP = Intraocular pressure; MMC = Mitomycin; MmHg = millimeters of mercury.

<sup>a</sup> 115 eyes of 103 subjects were enrolled in the study: 58 eyes received mitomycin C and 57 eyes received 5-FU.

**TABLE 2.** Best-corrected logMAR Visual Acuity, Intraocular Pressure, and Number of Glaucoma Medications Pre- and Postoperatively

COPYRIGHT MATERIAL

**Reviewer's Comments:** *Agree that there were no statistically significant differences between treatment groups for any measure of success at any time point reported by the authors.*

*There is no placebo control.*

However, the decrease in IOP from preoperative visit to the **Month 12** postoperative was statistically significant for both the 5-FU and MMC groups ( $P < 0.0001$  for each group, paired  $t$  test):

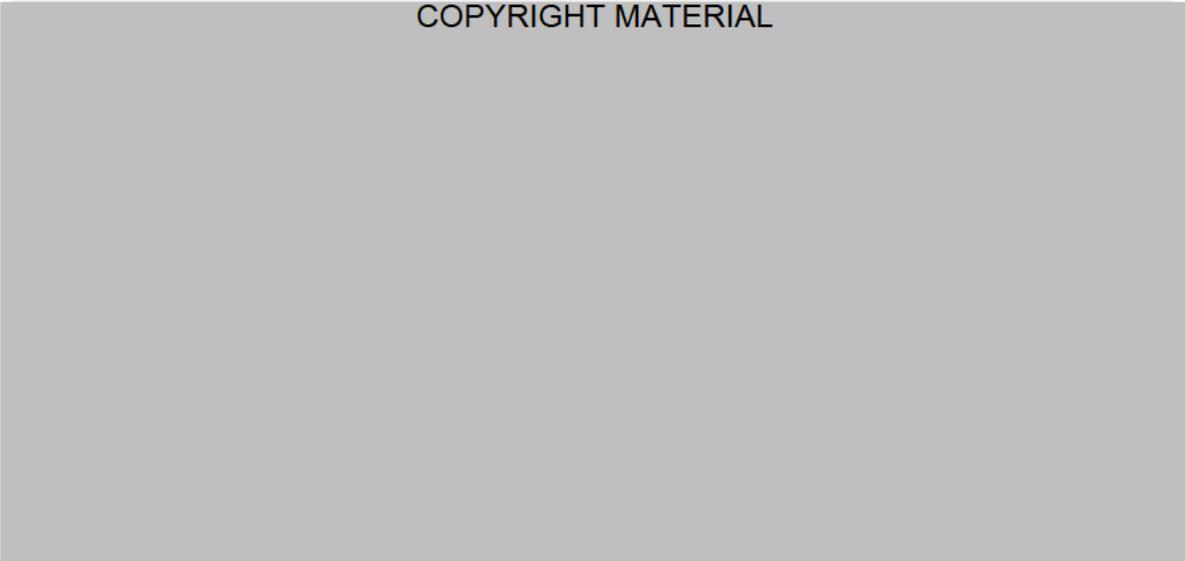
- 1) Postoperative IOPs at **Month 12** (22 mmHg for mitomycin, 24 mmHg for 5-FU)
- 2) Preoperative IOPs (10 mmHg for mitomycin, 11 mm Hg for 5-FU).

The IOP criterion for failure was  $IOP > 21$  mmHg. The three failures in the 5-FU group are attributed by the authors to bleb failures that required revision or further glaucoma surgery. There were two bleb failures in the mitomycin group; in one case the sclera was punctured during placement of a bridge suture causing a vitreous hemorrhage.

Permanent vision loss occurred in four eyes in the mitomycin group: two cases of endophthalmitis associated with bleb leak, one case of delayed suprachoroidal hemorrhage, and one case of severe hypotony maculopathy taking acuity from 20/30 to CF.

**TABLE 3.** Bleb Failures and Complications by 12 Months Post Trabeculectomy

COPYRIGHT MATERIAL



#### 6.1.1. A.4 Mitomycin Dose Comparison

Two articles provided by the applicant describe studies that included dose comparison of mitomycin as part of their design: Robin, et al, and Sanders, et al. Robin et al 1997 is described in Section 6.1.1. A.1 (Mitomycin versus Placebo) of this review.

*Sanders SP, Cantor LB, Dobler AA, Hoop JS. Mitomycin C in higher risk trabeculectomy: a prospective comparison of 0.2- to 0.4-mg/lcc doses. J Glaucoma. 1999 Jun;8(3):193-8.*

This prospective, randomized, masked study compared the effectiveness of 0.2mg/mL and 0.4 mg/mL of mitomycin during filtering surgery in eyes that were at higher risk from previous conjunctival incisional surgery. The eyes of 50 consecutive patients with primary open-angle, pseudoexfoliation, or pigmentary glaucoma who had previously undergone either limbal cataract surgery or trabeculectomy were enrolled. Patients were randomized to receive either 0.2mg/mL/2min or 0.4mg/mL/2min of mitomycin during surgery.

All procedures were performed in the superotemporal quadrant using a limbal based flap. Cellulose sponges were utilized.

The authors report that there were no statistically significant differences between treatment groups in mean IOP at any time point up to 12 months ( $p \geq 0.25$ ).

**Table 11 IOP Before and After Trabeculectomy with MMC—  
 Dose Comparison (0.2mg/mL to 0.4mg/mL) (Sanders 1998)**

Mean ( $\pm$ SD) IOP in mmHg	Mitomycin C Dose Groups		
	0.2mg/ml/2min	0.4mg/ml/2min	P-value <sup>a</sup>
Before surgery	28.8 ( $\pm$ 13.7)	25.0 $\pm$ 8.6	0.25
After surgery			
1 Day	2.8 ( $\pm$ 2.8)	3.6 ( $\pm$ 3.7)	0.44
1 Week	4.9 ( $\pm$ 2.9)	5.16 ( $\pm$ 3.9)	0.31
1 Month	13.6 ( $\pm$ 7.6)	14.2 ( $\pm$ 8.8)	0.81
3 Months	14.4 ( $\pm$ 7)	12.7 ( $\pm$ 5.7)	0.37
6 Months	13.3 ( $\pm$ 4.7)	14.3 ( $\pm$ 8.5)	0.65
1 Year	14.2 ( $\pm$ 6.3)	13.7 ( $\pm$ 6.2)	0.78

IOP = Intraocular pressure; MMC = Mitomycin; mmHg = Millimeters of mercury.

<sup>a</sup> Student *t* test.

**Reviewer's Comments:** *There is no placebo control.*

*Agree that there were no statistically significant differences between mitomycin treatment groups in mean IOP at any time point up to 12 months.*

*The decrease in IOP from preoperative visit to the **Month 12** postoperative is not described as statistically significant for both groups, but based on the drop (29 to 14 mmHg 0.2mg/mL and 25 to 14 mmHg), it would be expected to be significant.*

*Chronic hypotony (IOP  $\leq$  6 mmHg present at post-op month 3) was seen in two subjects in the 0.2 mg/mL group and three subjects in the 0.4 mg/mL group. One subject in the 0.2 mg/mL group developed a suprachoroidal hemorrhage with eventual loss of light perception. Cataract progression was seen in four of the five phakic 0.2 mg/mL group subjects and three of the four 0.4 mg/mL group subjects.*

#### 6.1.1. B Group 2 Studies: Prospective Studies of Uncertain Design

Per the applicant, there is an insufficient level of detail within the following literature references to determine if they represent adequate and well-controlled trials.

**Reviewer's Comments:** *Five of the following 13 prospective trials, classified by the applicant as Group 2 of Uncertain Design, appear to be adequate and well-controlled trials. These include: Kitazawa et al 1993, Kozobolis et al 2002, Shin et al 1995 [5.4.104], Shin et al 1998 [5.4.103], and Turacil et al 1996.*

*Hagiwara Y, Yamamoto T, Kitazawa Y. The effect of mitomycin C trabeculectomy on the progression of visual field defect in normal-tension glaucoma. Graefes Arch Clin Exp Ophthalmol. 2000 Mar;238(3):232-6.*

The visual prognosis and complications in normal-tension glaucoma following unilateral trabeculectomy with adjunctive mitomycin were investigated prospectively. Trabeculectomy with adjunctive mitomycin was carried out in 1 eye for each of 21 patients with normal tension glaucoma (i.e., the eye with clinically more advanced glaucoma was operated on). IOP, visual prognosis, and complications were compared between the operated eyes and the non-operated fellow eyes. The follow-up period ranged from 2 to 7 years.

**Table 13 Outcomes—Effect of MMC Trabeculectomy on Visual Field Defect in Normal Tension Glaucoma (Hagiwara 2000)**

	Operated Eyes (n = 21)		Non-operated Eyes (n = 21)		P-value
	Pre op	Post Op	Pre op	Post Op	
Mean (±SD) IOP in mmHg	14.8 (±1.8)	9.6 (±3.9)	No change		0.002 <sup>a</sup>
MD (±SD) in dB	−12.69 (±6.41)	−14.70 (±5.49) <sup>b</sup>	−7.85 (±5.65)	−11.15 (±5.62) <sup>b</sup>	0.0239 <sup>c</sup>
					0.002 <sup>d</sup>
MD Slope (±SD) in dB/year	−0.37 (±0.60)		−0.71 (±0.89)		0.5243 <sup>e</sup>

dB = Decibel; IOP = Intraocular pressure; mmHg = Millimeters of mercury; MD = Mean deviation; SD = Standard deviation.

- <sup>a</sup> Wilcoxon signed-rank test.
- <sup>b</sup> At the last clinic visit.
- <sup>c</sup> Operated eyes, Wilcoxon signed-rank test.
- <sup>d</sup> Non-operated eyes, Wilcoxon signed-rank test.
- <sup>e</sup> Mann-Whitney U-test.

The mean (±SD) IOP dropped significantly from 14.8 (k1.8) mmHg to 9.6 (k3.9) mmHg in the operated eyes (p=0.0002, Wilcoxon signed-rank test), but did not drop in the non-operated eyes.

**Reviewer’s Comments:** *Although prospective in design, the control arm consisted of the study subjects’ non-operated fellow eye. Thus the trial is non-randomized and uncontrolled for the addition of mitomycin.*

*Without an adequate control, the clinical relevance of the post-operative drop in IOP over 2-7 years in mitomycin-treated eyes from 15 mmHg to 10 mmHg is unclear.*

*The table above provided by the applicant removes the pre-op and post-op IOPs for the non-operated eyes. The mean pre-op IOP was 14.7 ± 1.9 mmHg; the mean post-op IOP was 14.2 ± 1.8 mmHg.*

*The eye with more clinically advanced normal-tension glaucoma underwent trabeculectomy with mitomycin. “More clinically advanced” is not defined by the authors.*

*Hong C, Hyung SM, Song KY, Kim DM, Youn DH. Effects of topical mitomycin C on glaucoma filtration surgery. Korean J Ophthalmol. 1993 Jun; 7(1):1-10.*

This study evaluated the efficacy and safety of using topical mitomycin as an adjunct to glaucoma filtration surgery. Trabeculectomy was performed in 23 eyes of 19 patients with poor surgical prognosis. After the preparation of a scleral flap, 0.2 mg/mL or 0.4 mg/mL mitomycin was applied to the exposed tissue for 5 minutes. The mean follow-up period was approximately 8 months.

At 12 months postoperatively, 74% of patients achieved an IOP of less than or equal to 20 mmHg without IOP-lowering medication.

**Table 14 IOP Outcomes with MMC in Trabeculectomy (Hong, 1993)**

Mean ( $\pm$ SD) preoperative IOP in mmHg	33.8 ( $\pm$ 7.1)
Mean ( $\pm$ SD) postoperative IOP in mmHg at:	
1 Month	10.3 ( $\pm$ 4.4)
3 Months	12.5 ( $\pm$ 6.9)
6 Months	12.4 ( $\pm$ 6.6)
12 Months	12.3 (6.7)
No. (%) eyes with IOP $\leq$ 20 mmHg at 12 months without antiglaucoma medication	17 (74%)

IOP = Intraocular pressure, MMC = mitomycin, mmHg = Millimeters of mercury.

<sup>a</sup> Trabeculectomy was performed in 23 eyes of 19 patients with poor surgical prognosis.

**Reviewer's Comments:** *Although apparently prospective, this trial did not utilize a control group.*

*The entry criteria were relatively broad and included subjects with primary open angle glaucoma, uncontrolled angle-closure glaucoma with laser iridotomy, exfoliative glaucoma with laser iridotomy, and congenital glaucoma with Peter's Anomaly.*

*Kitazawa Y, Suemori-Matsushita H, Yamamoto T, Kawase K. Low-dose and high-dose mitomycin trabeculectomy as an initial surgery in primary open-angle glaucoma. Ophthalmology. 1993 Nov; 100(11):1624-8.*

The purpose of the study was to determine the optimum regimen of intraoperative administration of mitomycin as an adjunct to trabeculectomy. Of 11 patients with primary open-angle glaucoma, 22 eyes that had not undergone any surgical intervention were included. In each patient, 1 eye was randomly allocated to a group that would receive liquid mitomycin in a concentration of 0.2mg reconstituted in 0.5 mL of distilled water and the fellow eye to a group that would receive liquid mitomycin in a concentration of 0.02mg reconstituted in 0.5mL of distilled water. Mitomycin was applied for 5 minutes only once during trabeculectomy. The follow-up period was 6 to 17 months.

11 eyes (100%) in the 0.2 mg group and 7 eyes (63.6%) in the 0.02 mg group achieved successful control of IOP with or without topical IOP-lowering medication.

**Table 15 IOP Control with Low- and High Dose MMC in Trabeculectomy (Kitazawa, 1993)**

	MMC Dose Groups	
	0.2mg/mL	0.02mg/mL
No. (%) eyes with successful IOP control <sup>a</sup> with or without topical medication	11 (100%)	7 (63.6%)

IOP = Intraocular pressure; MMC = mitomycin.

<sup>a</sup> Successful IOP control was defined as  $\leq 20$  mmHg for eyes with a preoperative IOP  $> 24$  mmHg and at least 20% reduction when preoperative IOP was 24 mmHg or lower. IOP control was considered a failure if the IOP measurement did not meet either of the aforementioned criterion of if surgical intervention was considered, regardless of IOP measurement.

**Reviewer's Comments:** *In this prospective trial, subjects were randomized to either a low-dose (0.02 mg/mL) or high dose (0.2 mg/mL) of mitomycin in one eye and the alternate concentration in the other eye. There was no trabeculectomy-only group enrolled.*

*Pre-operative IOP for the 0.2 mg dose was  $23.8 \pm 2.7$  mmHg; for the 0.02 mg dose, the pre-op IOP was  $22.5 \pm 2.6$ . Postoperative IOP for the 0.2 mg dose was  $9.9 \pm 3.7$  mmHg; for the 0.02 mg dose, the post-op IOP was  $11.6 \pm 2.7$ . Mean follow-up was 11 months and 9 months, respectively.*

***This appears to be an adequate and well-controlled trial although it is categorized by the applicant as having uncertain design. Without a trabeculectomy-only/placebo group, the clinical relevance of the comparative post-operative drop in IOP in mitomycin-treated subjects is unclear.***

*Kobayashi It Kobayashi K, Okinami S. A comparison of the intraocular pressure-lowering effect and safety of viscocanalostomy and trabeculectomy with mitomycin C in bilateral open angle glaucoma. Graefes Arch Clin Exp Ophthalmol. 2003 May;241(5):359-66. Epub 2003 Apr 16.*

Twenty-five patients with bilateral primary open-angle glaucoma were enrolled in this prospective clinical study. The eyes of each patient were randomly assigned to receive viscocanalostomy in 1 eye and trabeculectomy with 0.04% mitomycin for 3 minutes in the other eye. Patients were followed up for 12 months. At each visit, best-corrected visual acuity, intraocular pressure, and the appearance of the surgical wound, anterior chamber, and indirect ophthalmoscopy were recorded.

At 12 months, 16 viscocanalostomy-treated eyes (64%) and 22 trabeculectomy-treated eyes (88%) achieved an IOP of less than or equal to 20 mmHg without medication; there was a significant difference between the two groups ( $p=0.0240$ ).

**Table 16 IOP Control in Visco canalostomy and trabeculectomy with MMC in Bilateral Open Angle Glaucoma (Kobayashi, 2003)**

	Visco canalostomy-treated eyes	Trabeculectomy with MMC treated eyes	P-value
Mean ( $\pm$ SD) baseline IOP in mmHg	25.0 ( $\pm$ 2.2)	24.8 ( $\pm$ 2.6)	–
Mean ( $\pm$ SD) postoperative baseline IOP in mmHg <sup>a</sup> at:			
3 months	15.3 ( $\pm$ 1.7)	11.7 ( $\pm$ 4.4)	<0.0001 <sup>a</sup>
6 months	17.1 ( $\pm$ 1.5)	11.8 ( $\pm$ 4.6)	<0.0001 <sup>a</sup>
12 months	17.1 ( $\pm$ 1.5)	12.6 ( $\pm$ 4.3)	<0.0001 <sup>a</sup>
No. (%) eyes at 12 months with IOP $\leq$ 20 mmHg without medication	16 (64%)	22 (88%)	0.0240 <sup>b</sup>

IOP = Intraocular pressure; MMC = mitomycin; mmHg = Millimeters of mercury.

<sup>a</sup> Mean IOP in visco canalostomy-treated eyes was significantly higher than that in trabeculectomy treated eyes at every visit;  $p < 0.001$ , Student's *t* test.

<sup>b</sup> Student's *t* test.

**Reviewer's Comments:** *Although prospective, the author's control group was an alternate procedure (visco canalostomy) not utilizing mitomycin. There was no trabeculectomy-only group enrolled.*

*Without a trabeculectomy-only/placebo group, the clinical relevance of the comparative post-operative drop in IOP in mitomycin-treated subjects is unclear.*

*Kozobolis VP, Christodoulakis EV, Tzanakis N, Zacharopoulos I, Pallikaris IG. Primary deep sclerectomy versus primary deep sclerectomy with the use of mitomycin C in primary open-angle glaucoma. J Glaucoma. 2002 Aug;11(4):287-93.*

This prospective study compared the effectiveness and the safety of primary deep sclerectomy (DS) with and without the use of mitomycin in eyes with open angle glaucoma.

A total of 90 eyes of 90 patients with primary open-angle glaucoma or pseudoexfoliative glaucoma underwent deep sclerectomy (DS). Patients were enrolled consecutively and assigned randomly to undergo DS without the use of mitomycin (DS group) and DS with mitomycin (DSMMC group) in a concentration of 0.2mg/mL for 2.5 minutes, before the superficial scleral flap formation.

The qualified success rate (IOP  $\leq$  21 with or without medication) in the DSMMC group was statistically significant when compared with that in the DS group ( $p = 0.003$ ) at the end of the 36-month follow-up period

**Table 17 IOP, Medication, and Success Rate after Deep Sclerectomy and Deep Sclerectomy with MMC (Kozobolis, 2002)**

	<b>DS</b>	<b>DSMMC</b>	<b>P-value</b>
No. of eyes	45	45	–
IOP in mmHg <sup>a</sup>			
Preoperative	25.84 (±3.66)	27.64 (±4.53)	NS
Postoperative <sup>b</sup>	18.71 (±2.90)	15.96 (±1.71)	0.001 <sup>c</sup>
Difference (%)	7.13 (27.59%)	11.68 (42.25%)	0.05 <sup>c</sup>
Medications			
Preoperative	3.18 (±0.81)	3.02 (±0.62)	NS
Postoperative <sup>d</sup>	0.96 (±0.96)	0.64 (±0.73)	NS
Success Rates			
Complete success <sup>e</sup>	14/40 eyes (42.5%)	20/40 eyes (50%)	NS
Qualified success <sup>f</sup>	29/40 eyes (72.5%)	38/40 eyes (95%)	0.003 <sup>g</sup>

DS = Deep sclerectomy without mitomycin; DSMMC = Deep sclerectomy with mitomycin C; IOP = Intraocular pressure; mmHg = Millimeters of mercury; NS = Not significant; SD = Standard deviation.

<sup>a</sup> Mean (±SD).

<sup>b</sup> At 36-month follow-up.

<sup>c</sup> Chi-squared test.

<sup>d</sup> At the 36-month follow up.

<sup>e</sup> Complete success = Final IOP ≤21 mmHg without antiglaucoma medication.

<sup>f</sup> Qualified success; IOP ≤21 mmHg without or without medications.

<sup>g</sup> Kaplan-Meier analysis.

**Reviewer’s Comments:** *The authors describe an alternate technique for trabeculectomy, i.e. deep sclerectomy, which is presumably non-penetrating. A single surgeon performed all procedures; although subjects were randomly assigned to treatment arm, the post-operative evaluations were presumably performed by unmasked evaluators.*

***This appears to be an adequate and well-controlled trial although it is categorized by the applicant as having uncertain design. Without a trabeculectomy-only/placebo group, the clinical relevance of the comparative post-operative drop in IOP in mitomycin-treated subjects is unclear.***

*At Month 36, there is a statistically significant between-group difference in postoperative mean IOP (roughly 16 mmHg for sclerectomy plus mitomycin alone versus 19 mmHg for sclerectomy alone).*

*Maquet JA, Dios E, Aragon J, Bailez C, Ussa F, Laguna N. Protocol for mitomycin C use in glaucoma surgery. Acta Ophthalmol Scand. 2005 Apr;83(2):196-200.*

This study investigated the use of mitomycin in trabeculectomy or combined surgery (phacoemulsification and trabeculectomy). A total of 143 eyes (60 trabeculectomies and 83 combined surgeries) of 124 patients were divided into four groups: Group 1 (without mitomycin/7eyes); Group 2 (with 0.1 mg/mL mitomycin/37 eyes); Group 3 (with 0.2 mg/mL mitomycin/64 eyes), and Group 4 (with 0.4 mg/mL mitomycin/35 eyes). In every case in Groups 2, 3, and 4, mitomycin was applied for 2 minutes.

The results were analyzed after 12 months of follow-up. Successful IOP control was defined as <21 mmHg and < 6 mmHg if advanced glaucoma were present, always without additional medical treatment.

No significant differences were observed in final mean IOP among the mitomycin-treated groups (p = 0.196).

**Table 18 IOP and Success Rates at 12 Months in MMC Use in Glaucoma Surgery (Maquet, 2005)**

	143 Eyes		P-value
	Preoperative	Postoperative <sup>a</sup>	
IOP in mmHg <sup>b</sup>	24.60 (±0.66)	13.47 (±0.51)	<0.0001 <sup>c</sup>
Success <sup>d</sup>			
No. (%) 143 eyes with IOP <21 mmHg	–	128/143 (89.51%)	–
No (%) failures in eyes with advanced glaucoma <sup>e</sup>		15/143 (10.48%)	–
Overall IOP control for the study		113/143 (79.02%)	–

IOP = Intraocular pressure; MMC = Mitomycin; mmHg = Millimeters of mercury; NS = Not significant; SD = Standard deviation.

<sup>a</sup> At the 12-month follow-up.

<sup>b</sup> Mean (±SD).

<sup>c</sup> Student's *t* test.

<sup>d</sup> Successful IOP control was defined as IOP <21 mmHg and <16 mmHg in advanced

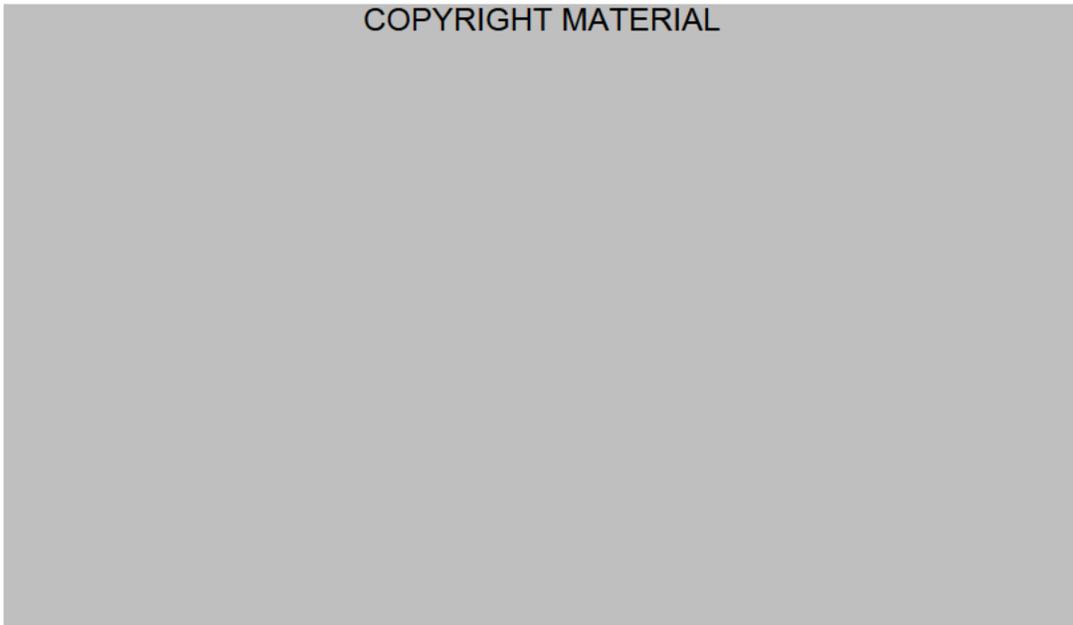


Fig. 1. Mean intraocular pressure (mmHg) at all time intervals. Vertical bars represent 95% CIs.

**Reviewer's Comments:** *This was not a randomized study. There is no description of how the groups were selected; Group 1 only included 7 subjects.*

*When mitomycin was not used (Group 1, 7 eyes), final IOP was higher, but the differences were not statistically significantly different versus baseline. The authors did not provide a between group comparison (no mitomycin versus mitomycin) because they state they enrolled too few subjects in Group 1.*

*Mermoud A, Salmon JF, Murray AD. Trabeculectomy with mitomycin C for refractory glaucoma in blacks. Am J Ophthalmol. 1993 Jul15;116(1): 72-8.*

One intraoperative application of adjunctive mitomycin at the filtration site in patients undergoing trabeculectomy was investigated prospectively in Black patients with refractory glaucoma. A 0.2mg/mL solution of mitomycin was applied between Tenon's capsule and the sclera for 5 minutes before trabeculectomy in 30 eyes of 26 Black patients. The results were compared to those found in a matched group of 30 eyes of 28 patients who underwent trabeculectomy without mitomycin. Surgery was a complete success when the IOP was  $\leq 21$  mmHg without glaucoma medication and a qualified success when the IOP was  $\leq 21$  mmHg with glaucoma medication.

The measurements of mean ( $\pm$ SD) postoperative IOP reduction were significantly lower in the mitomycin group than in the control group ( $p=0.001$ ): 23.0 ( $\pm$ 12.6) mmHg in the

mitomycin group and 10.3 ( $\pm$ 13.2) in the control group. Twenty-five of the 30 eyes (83%) in the mitomycin group had an IOP of less than 21 mmHg without IOP-lowering medication compared to 11 of 30 eyes (37%) in the control group ( $p=0.00006$ ). The difference between the mitomycin group and the control group for glaucoma medication use was significant ( $p=0.003$ ).

**Table 19 Postoperative IOP, Success, and Medication Outcomes—Trabeculectomy with MMC for Refractory Glaucoma in Blacks (Mermoud, 1993)**

	Trab with MMC	Matched Control	P-value
Preoperative value in mmHg <sup>a</sup>	34.9 ( $\pm$ 9.43)	34.2 ( $\pm$ 8.6)	0.733 <sup>b</sup>
Reduction of IOP in mmHg <sup>a</sup>	23.0 ( $\pm$ 12.6)	10.3 ( $\pm$ 13.2)	0.001 <sup>b</sup>
Success rate			
Complete success (n = 30 eyes) <sup>c</sup>	25 (83%)	11 (37%)	0.00006 <sup>b</sup>
Qualified success (n = 30 eyes) <sup>d</sup>	3 (10%)	1 (3%)	–
Failure			
Qualified failure <sup>e</sup>	–	9 (30%)	–
Complete failure <sup>f</sup>	2 (7%)	9 (30%)	–
Postoperative medications per patient for IOP control <sup>g</sup>	0.2 ( $\pm$ 0.14)	0.77 ( $\pm$ 0.16)	0.003 <sup>b</sup>

IOP = Intraocular pressure; MMC = Mitomycin; mmHg = Millimeters of mercury; NS = Not significant; SD = Standard deviation; SE = Standard error of the mean.

<sup>a</sup> Mean ( $\pm$ SD).

<sup>b</sup> Chi-squared test.

<sup>c</sup> Complete success = IOP  $\leq$ 21 mmHg without glaucoma medication

<sup>d</sup> Qualified success = IOP  $\leq$ 21 mmHg with glaucoma medication.

<sup>e</sup> Qualified failure = IOP  $\geq$ 21 mmHg with or without glaucoma medication.

<sup>f</sup> Complete failure = Eye that required further glaucoma drainage operation, developed phthisis bulbi, or lost light perception.

<sup>g</sup> Mean ( $\pm$ SEM).

**Reviewer’s Comments:** *This prospective trial utilized historical matched controls for surgical subjects; subjects were matched by age, gender, type of glaucoma, and pre-operative intraocular pressure. Historical control subjects had previously undergone trabeculectomy without an anti-metabolite in the 1-2 years previous to the study.*

*Agree that the measurements of mean postoperative IOP reduction were significantly lower in the mitomycin group than in the control group ( $p=0.001$ ): roughly 23 mmHg in the mitomycin group and 10 mmHg in the control group.*

*Nuijts RM, Vernimmen RC, Webers CA. Mitomycin C primary trabeculectomy in primary glaucoma of white patients. J Glaucoma. 1997 Oct;6(5):293-7. Review.*

This prospective study evaluated the clinical outcome of 25 eyes in 23 patients who underwent primary trabeculectomy with adjunctive mitomycin for primary glaucoma. Clinical outcome measures included postoperative IOP, change in logarithm of the minimum angle of resolution (LogMAR) visual acuity, and incidence of complications, all measured up to 1 year postoperatively.

The mean ( $\pm$ SD) IOP decreased from 26.0 ( $\pm$ 4.4) mmHg preoperatively to 12.5 ( $\pm$ 3.9) mmHg ( $p < 0.0001$ ) at the 12-month follow-up. The mean LogMAR visual acuity changed from 0.23 ( $\pm$ 0.19) preoperatively to 0.23 ( $\pm$ 0.20) at the 12-month follow-up ( $p = 1.0$ ).

**Table 20 IOP and Visual Acuity Outcomes at 12 Months—MMC in Primary Trabeculectomy (Nuijts, 1997)**

	25 Eyes in 23 Patients		P-value <sup>b</sup>
	Preoperative	Postoperative <sup>a</sup>	
IOP in mmHg <sup>c</sup>	26.0 ( $\pm$ 4.4)	12.5 ( $\pm$ 3.9)	<0.0001
Visual acuity change	0.23 ( $\pm$ 0.19)	0.23 ( $\pm$ 0.20)	1.0 <sup>d</sup>

IOP = Intraocular pressure; MMC = Mitomycin; mmHg = Millimeters of mercury; SD = Standard deviation.

<sup>h</sup> At the 12-month follow up.

<sup>i</sup> Paired *t* test.

<sup>j</sup> Mean ( $\pm$ SD).

<sup>k</sup> LogMAR

**Reviewer’s Comments:** *Although prospective by design, there is no control group. There were no trabeculectomy-only subjects enrolled.*

*Without a trabeculectomy-only/placebo group, the clinical relevance of the comparative post-operative drop in IOP in mitomycin-treated subjects is unclear.*

*Shin DH, Simone PA, Song MS, Reed SY, Juzych MS, Kim C, Hughes BA. Adjunctive subconjunctival mitomycin C in glaucoma triple procedure. Ophthalmology. 1995 Oct;102(10):1550-8.<sup>1</sup>*

This study evaluated the potential benefit of adjunctive subconjunctival mitomycin in patients with primary open-angle glaucoma undergoing primary trabeculectomy combined with phacoemulsification and intraocular lens implantation. Seventy-eight eyes of 78 patients with primary open-angle glaucoma with visually symptomatic

---

<sup>1</sup> See Section 5.1 of this review for discussion of applicant’s transposition of articles by this author.

cataracts and no previous incisional surgery were randomized to receive either no mitomycin or a subconjunctival application of 1-, 3-, or 5-minute mitomycin (0.5mg/mL).

The mean postoperative IOPs were significantly lower with significantly less medications than the preoperative values at each follow-up time (1, 3, 6, 9, 12, 15 months, and last follow-up) for all groups ( $p < 0.05$  for each). However, there was no significant difference at each follow-up time in the final IOP, medications, or best-corrected visual acuity among the four groups or between the control and the total mitomycin group.

**Table 21 IOP Outcomes at Postoperative Time points (Shin, 1995)**

	Control <sup>a</sup>	MMC 1 Min	MMC 3 Min	MMC 5 Min	P-value <sup>b</sup>	Total MMC	P-value <sup>c</sup>
Preoperative IOP in mmHg <sup>a</sup>	20.6 (±7.5)	20.2 (±7.5)	21.7 (±8.2)	20.6 (±5.4)	0.90	20.9 (±7.2)	0.90
No. of eyes	21	21	21	15		57	
Postoperative IOP <sup>a</sup> in mmHg at:							
1 month	14.5 (±4.2)	14.1 (±7.2)	10.8 (±6.1)	15.2 (±9.5)	0.16	13.1 (±7.6)	0.42
No. of eyes	21	21	21	15		57	
3 months	14.7 (±4.3)	13.6 (±4.2)	13.4 (±5.8)	14.8 (±5.9)	0.75	13.8 (±5.2)	0.50
No. of eyes	21	21	21	15		57	
6 months	15.3 (±4.2)	16.3 (±6.7)	13.6 (±7.4)	15.8 (±4.1)	0.53	15.2 (±6.4)	0.93
No. of eyes	21	20	19	14		53	
9 months	15.3 (±5.0)	14.3 (±5.0)	13.3 (±5.0)	14.4 (±4.0)	0.64	14.0 (±4.7)	0.29
No. of eyes	19	19	18	14		51	
12 months	15.9 (±4.9)	13.9 (±3.9)	14.1 (±6.4)	13.9 (±3.4)	0.58	14.0 (±5.0)	0.16
No. of eyes	21	13	21	12		46	
15 months	14.6 (±4.6)	12.8 (±5.2)	13.2 (±5.6)	14.6 (±3.6)	0.79	13.6 (±4.9)	0.48
No. of eyes	15	6	15	9		30	
Last follow-up	13.6 (±4.4)	13.8 (±4.7)	13.0 (±4.5)	14.3 (±3.4)	0.82	13.6 (±4.3)	0.95
No. of eyes	21	21	21	15		57	
P-value <sup>d</sup>	0.0005	0.0001	0.0001	0.0002	–	0.0001	–

IOP = Intraocular pressure; Min = Minute(s); MMC = Mitomycin; mmHg = Millimeters of mercury; SD = Standard deviation.

<sup>a</sup> Mean (±SD).

<sup>b</sup> Factorial analysis of variance.

<sup>c</sup> Unpaired Student's *t* test.

<sup>d</sup> Repeat measures of variance.

**Reviewer's Comments:** *Agree that there was no significant difference at each follow-up time in the final IOP, medications, or best-corrected visual acuity among the four groups or between the control and the total mitomycin group.*

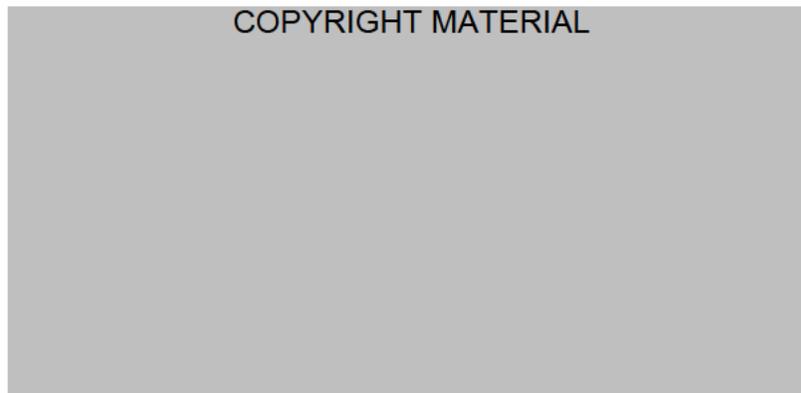
***This appears to be an adequate and well-controlled trial although it is categorized by the applicant as having uncertain design***

*Shin DH, Ren J, Juzych MS, Hughes BA, Kim C, Song MS, Yang KJ, Glover KB. Primary glaucoma triple procedure in patients with primary open-angle glaucoma: the effect of mitomycin C in patients with and without prognostic factors for filtration failure. Am J Ophthalmol. 1998 Mar;125(3):346-52. <sup>2</sup>*

This study investigated the effect of adjunctive mitomycin on primary glaucoma triple procedure in patients with primary open-angle glaucoma with and without one or more of the prognostic factors for filtration failure of primary glaucoma triple procedure. Those factors include being of African-American race, having a preoperative IOP of 20 mmHg or more on maximum tolerated medications, and being on two or more medications preoperatively.

Study patients comprised 197 consecutive patients with primary open-angle glaucoma who were randomly assigned to receive either no adjunctive mitomycin (101 eyes of 101 patients) or adjunctive subconjunctival mitomycin 0.5 mg/mL (96 eyes of 96 patients) during the primary glaucoma triple procedure.

In patients with two or three prognostic factors, a 3-minute application of mitomycin was the most effective in improving the success rate of the primary glaucoma triple procedure ( $p=0.004$ ).



**FIGURE 1. Probability of surgical success in the control group (open circle,  $n = 101$ ) vs the mitomycin C (MMC) group (solid circle,  $n = 96$ ) ( $P = .117$ , Kaplan-Meier survival analysis with Mantel-Cox log rank test).**

---

<sup>2</sup> See Section 5.1 of this review for discussion of applicant's transposition of articles by this author.

**Table 22 Outcomes—MMC in Patients with and without Prognostic Factors (Shin, 1998)**

PGTP in Patients with POAG	P-value
Success of PGTP procedure	0.117 <sup>a</sup>
Filtration outcome	
Subgroups with 3 prognostic factors <sup>b</sup>	<0.05 <sup>a</sup>
Effectiveness of 3-minute MMC in patients with 2 to 3 prognostic factors <sup>b</sup>	0.004 <sup>c</sup>
Subgroups without prognostic factors	>0.05 <sup>a</sup>

IOP = Intraocular pressure; MMC = Mitomycin; mmHg = Millimeters of mercury; SD = Standard deviation.

IOP = Intraocular pressure; MMC = Mitomycin; POAG = Primary open-angle glaucoma; PGTP = Primary glaucoma triple procedure.

<sup>a</sup> Mantel-Cox log rank test.

<sup>b</sup> Prognostic factors were 1) being of African-American race, 2) having a preoperative IOP of 20 mmHg or more on maximum tolerated medications, and 3) being on two or medications preoperatively.

<sup>c</sup> Kaplan Meier survival analysis with log rank comparison.

**Reviewer’s Comments:** *The criteria for success applied to this study analysis was: achievement of target intraocular pressure control with not more than one medication and without requiring any further glaucoma-related surgical procedure, including 5-FU needling revision, and development of a clinically discernible conjunctival filtration bleb. Target IOP was not defined.*

***This appears to be an adequate and well-controlled trial although it is categorized by the applicant as having uncertain design.***

*There was no significant ( $p = 0.117$ ) difference in filtration success rate between the control and mitomycin C groups as shown in the Kaplan-Meier survival plots.*

*The mean postoperative IOPs for mitomycin treated and untreated subjects are not provided in the article.*

*Turacil E, Gunduz K, Aktan G, Tamer C. A Comparative Clinical Trial of Mitomycin C and Cyclosporin A in Trabeculectomy. Eur J Ophthalmol 1996 Oct-Dec; 6(4):398-401.*

This prospective, randomized clinical trial assessed the effects and success rate of mitomycin and cyclosporine A (CSA) used as anti-metabolites in trabeculectomy on the postoperative IOP. Eighty-six consecutive patients were randomly assigned to 3 treatment groups: mitomycin: 30; CSA: 28; and control: 28. The group treated with mitomycin received 0.4mg/mL/4 minutes; the CSA group received a 2% solution for 4 minutes, and the control group received trabeculectomy alone. A successful

postoperative reduction in IOP was defined as a reduction of more than 25% from baseline or reduction of IOP to less than 20 mmHg.

IOP was controlled in 90% of the mitomycin-treated eyes, 86% of the CSA-treated eyes, and 72% of the control eyes. There was a significant decrease in IOP ( $p < 0.01$ ) and in the number of medications needed to control IOP ( $p < 0.01$ ) in the mitomycin C and CSA groups.

**Table 23 Success Outcomes in Trabeculectomy with MMC or Cyclosporine A (Turacli, 1996)**

	MMC (n = 30)	CSA (n = 28)	Control (n = 28)
Successful IOP reduction <sup>a</sup>	27 (90%)	24 (85.7%)	20 (71.4%)
Preoperative IOP in mmHg <sup>b</sup>	32.4 (±4.9)	30.9 (±4.2)	31.3 (±4.5) <sup>c</sup>
Postoperative IOP in mmHg <sup>b</sup>	14.3 (±2.8)	15.5 (±3.1)	18.6 (±3.9)
Preoperative medications	2.9 (±0.8)	2.5 (±0.5)	2.6 (±0.7)
Postoperative medications	0.3 (±0.4)	0.2 (±0.2)	1.2 (±0.3)

ANOVA = Analysis of variance; CSA = Cyclosporine A; IOP = Intraocular pressure; MMC = Mitomycin; mmHg = Millimeters of mercury; SD = Standard deviation.

<sup>a</sup> Successful IOP reduction was defined as a reduction of more than 25% from Baseline or reduction of IOP to less than 20 mmHg.

<sup>b</sup> Mean (±SD).

<sup>c</sup> Difference in IOP between MMC and CSA groups and the control group was statistically significant ( $p < 0.01$ , one-way ANOVA).

<sup>d</sup> Difference in postoperative medication use between MMC and CSA groups and the control group was statistically significant ( $p < 0.01$ , one-way ANOVA).

**Reviewer's Comments:** *Without a trabeculectomy-only/placebo group, the clinical relevance of the comparative post-operative drop in IOP in mitomycin-treated subjects is unclear.*

***This appears to be an adequate and well-controlled trial although it is categorized by the applicant as having uncertain design.***

*The differences between the mitomycin and CSA groups (with respect to both reduction in IOP and reduction of number of meds used to control IOP) were not statistically significant.*

*Unlu K, Aksunger A, Soker J; Ertem M. Mitomycin C primary trabeculectomy with releasable sutures in primary glaucoma. Jpn J Ophthalmol. 2000 Sep-Oct; 44(5). 524-9.*

This prospective study evaluated the effects of mitomycin and a releasable suture technique on outcomes of primary trabeculectomy in primary glaucoma patients.

Patients who underwent primary trabeculectomy with a mitomycin concentration of 0.2mg/mL for 2 minutes were evaluated. Group 1, releasable sutures; Group 2, permanent sutures.

The postoperative reduction in IOP was highly significant ( $p < 0.0001$ ) at all time intervals in both groups.

**Table 24 Outcomes in MMC and Releasable Sutures in Primary Trabeculectomy in Primary Glaucoma (Unlu, 1996)**

	MMC 0.2mg/mL/2min		P-value
	Releasable Sutures	Permanent Sutures	
Postoperative IOP reduction			
At all time intervals	22.58	24.39	<0.0001
Measurements before the 2 <sup>nd</sup> week	21.19	23.74	<0.01
Complete success rate at last visit.	88%	85.0%	-

Intraocular pressure; MMC 0.2mg/mL/2min = Mitomycin concentration of 0.2mg/mL for 2 minutes; mmHg = Millimeters of mercury; SD = Standard deviation.

**Reviewer's Comments:** *This article describes a comparison of two different surgical techniques (releasable versus permanent sutures) in addition to the use of mitomycin in all subjects (i.e. no placebo control).*

*Without a trabeculectomy-only/placebo group, the clinical relevance of the comparative post-operative drop in IOP in mitomycin-treated subjects is unclear.*

*Vijaya L, Mukhesh BN, Shantha B, Ramalingam S, Sathi Devi A V. Comparison of low-dose intraoperative mitomycin-C vs 5-Fluorouracil in primary glaucoma surgery: a pilot study. Ophthalmic Surg Lasers. 2000 Jan-Feb;31(1):24-30.*

This nonrandomized study compared the efficacy and safety of intraoperative application of mitomycin with that of 5-fluorouracil (5-FU) in primary trabeculectomy. The study group comprised 32 eyes of 16 consecutive patients who underwent trabeculectomy for uncontrolled glaucoma of various causes. The first eye received mitomycin (either 0.2 mg/mL or 0.4 mg/mL), and the fellow eye received 5-FU (50 mg/mL), each for 1 minute intraoperatively.

There was no statistically significant difference between mitomycin group and 5-FU group success rates for all three criteria: 1) IOP less than 21 mm Hg; 100% in both groups; 2) IOP less than 21 mmHg with more than 30% drop in IOP; mitomycin C group, 94% and 5-FU group, 75%; and 3) less than 16 mmHg with more than 30% drop in IOP; MMC group 88%, 5-FU group 69%.

**Table 25 Outcomes in Comparison of Low-Dose MMC versus 5-FU in Primary Glaucoma Surgery (Vijaya, 2000)**

	Primary Trabeculectomy in 32 Patients <sup>a</sup>		P-value <sup>b</sup>
	MMC (n = 16)	5-FU (n = 16)	
Preoperative IOP in mmHg <sup>c</sup>	31.4 (±12.7)	27.8 (±8.8)	0.36
Postoperative IOP in mmHg <sup>c</sup>			
3 months	9.50 (±4.1)	10.1 (±3.3)	0.67
6 months	8.8 (±3.1)	11.0 (±3.1)	0.12
Last follow-up	11.1 (±4.0)	12.5 (±3.7)	0.44
Success criteria (No. [%] eyes)			
IOP <21 mmHg	16 (100%)	16 (100%)	1.00
IOP <21 mmHg and >30% drop in IOP	15 (93.8%)	12 (75.0%)	0.33
IOP <16 mmHg and >30% drop in IOP	14 (87.5%)	11 (68.8%)	0.39
Bleb characteristics at last follow-up (No. [%] eyes)			
Non-ischemic	4 (25%)	16 (100%)	<0.01 <sup>d</sup>
Ischemic at last follow-up	12 (75%)	0	<0.01 <sup>d</sup>

IOP = Intraocular pressure; mmHg = Millimeters of mercury; SD = Standard deviation.

<sup>a</sup> Thirty-two eyes of 16 consecutive patients underwent trabeculectomy for uncontrolled glaucoma of various causes. The first eye received mitomycin (either 0.2mg/mL; 3 eyes or 0.4mg/mL; 13 eyes), and the fellow eye received 5-FU (50 mg/mL).

<sup>b</sup> Student's *t* test.

<sup>c</sup> Mean (±SD).

<sup>d</sup> Fischer exact test

**Reviewer's Comments:** *This was a non-randomized study; procedures to minimize bias were not utilized to equalize treatment groups at baseline.*

*Postoperative reductions in IOP were significant at all time intervals evaluated (3 months, 6 months, last follow-up) at p < 0.0001.*

*Without a trabeculectomy-only/placebo group, the clinical relevance of the comparative post-operative drop in IOP in mitomycin-treated subjects is unclear.*

#### 6.1.1. C Other Literature Sources

Fourteen retrospective studies of mitomycin in glaucoma filtering surgery in adult patients were identified by the applicant in Section 2.7.3.6.1 of the NDA. The 14 studies

were reviewed; there was no significant new information provided in these additional literature references.

## 6.4 Demographics

Regarding the 9 prospective, randomized, controlled, masked studies:

The four studies comparing mitomycin to placebo, the three comparing mitomycin with no treatment, and the one study comparing mitomycin to 5-FU were conducted mostly in older adults. Although patients as young as 20 and as old as 90 years of age were enrolled in these studies, the mean ages for these patients were in the fifth decade (Robin, 1997, Rasheed 1999), sixth decade (Costa 1996, Andreanos 1997, Martini 1997, WuDunn 2002), and seventh decade of life (Carlson 1995 and Cohen 1996). In the 9 studies summarized in the following table, approximately 44% of the patients were female and approximately 56% were male.

None of the 9 studies summarized in Table 26 was designed to be conducted in a specific racial or ethnic group. Racial or ethnic data were provided for four studies conducted in the USA (Carlson 1995, Cohen 1996, Sanders 1998, WuDunn 2002) and one study conducted in Brazil (Costa 1996); the majority of patients in these studies were White. Racial or ethnic data were not provided for ex-USA studies, i.e., those conducted in Egypt (Rasheed 1999), Greece (Andreasos 1997), Italy (Martini 1997), and India (Robin 1997).

The majority of all patients in these nine studies took preoperative IOP-lowering medications.

Regarding the 13 prospective studies of uncertain design:

1. Age: of 679 eyes of 649 patients, absolute age ranged from age of 7 years to 83 years.
2. Gender: approximately 56% of the patients were female and approximately 44% were male

Clinical Review  
 William Boyd, M.D.  
 NDA 22-572  
 Mitosol (mitomycin for solution)

Table 26 Demographics and Baseline Characteristics —Prospective, Randomized, Controlled, Masked Studies (9 Studies)

Investigator/Design/ Treatment Groups	Baseline Conditions <sup>a</sup>	No. of Patients/ Eyes	Mean Age <sup>b</sup> (±SD) Range <sup>c</sup>	Sex	Race or Ethnicity	Country Study Conducted
<b>Mitomycin versus Placebo (4 Studies)</b>						
<ul style="list-style-type: none"> <li>– Carlson, 1997</li> <li>– Randomized, double-masked, placebo-controlled study of MMC in combined phacoemulsification and trabeculectomy in 29 adult patients               <ul style="list-style-type: none"> <li>◦ MMC (0.5mg/mL/3.5min)</li> <li>◦ Placebo</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>– IOP in mmHg (±SD)               <ul style="list-style-type: none"> <li>◦ MMC: 18.4 (±2.7)</li> <li>◦ Placebo: 19.1 (±4.0) mmHg</li> </ul> </li> <li>– Medications               <ul style="list-style-type: none"> <li>◦ MMC: 2.7 (±0.9)</li> <li>◦ Placebo: 2.5 (±0.9)</li> </ul> </li> <li>– Prior surgery: NP</li> <li>– VA: All patients had visually significant decreased VA</li> </ul>	<ul style="list-style-type: none"> <li>MMC: 14/14</li> <li>Placebo: 15/15</li> </ul>	<ul style="list-style-type: none"> <li>72.2 years</li> <li>73.0 years</li> </ul>	<ul style="list-style-type: none"> <li>M: 7 (50%)</li> <li>F: 7 (50%)</li> <li>M: 7 (47%)</li> <li>F: 8 (53%)</li> </ul>	<ul style="list-style-type: none"> <li>W: 14 (100%)</li> <li>W: 13 (87%)</li> <li>B: 1 (7%)</li> <li>H: 1 (7%)</li> </ul>	USA
<ul style="list-style-type: none"> <li>– Cohen, 1996</li> <li>– Randomized, placebo-controlled, double-masked study</li> <li>– Combined glaucoma and cataract procedures in adults               <ul style="list-style-type: none"> <li>◦ MMC: 0.5mg/mL/2.5min</li> <li>◦ Placebo</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>– IOP in mmHg (±SD)               <ul style="list-style-type: none"> <li>◦ MMC: 22.19 (±5.37)</li> <li>◦ Placebo 20.34 (±5.18)</li> </ul> </li> <li>– Medications               <ul style="list-style-type: none"> <li>◦ MMC: 2.03 (±1.00)</li> <li>◦ Placebo: 2.46 (±0.85)</li> </ul> </li> <li>– Reasons for surgery               <ul style="list-style-type: none"> <li>◦ Visual problems (in the presence of significant cataract)</li> <li>◦ Inability to visualize optic nerve</li> <li>◦ Uncontrolled IOP</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>MMC: 36/36</li> <li>Placebo: 35/35</li> </ul>	<ul style="list-style-type: none"> <li>76.0 ± 7.0 years (60–90)</li> <li>75.89 ± 6.6 years (62–86)</li> </ul>	<ul style="list-style-type: none"> <li>M: 13</li> <li>W: 23</li> <li>M: 10</li> <li>F: 25</li> </ul>	<ul style="list-style-type: none"> <li>W: 29</li> <li>B: 7</li> <li>W: 29</li> <li>B: 6</li> </ul>	USA

Investigator/Design/ Treatment Groups	Baseline Conditions <sup>a</sup>	No. of Patients/ Eyes	Mean Age <sup>b</sup> (±SD) Range <sup>c</sup>	Sex	Race or Ethnicity	Country Study Conducted
<ul style="list-style-type: none"> <li>– Costa, 1996</li> <li>– Randomized, placebo-controlled, double-masked study</li> <li>– Trabeculectomy in patients adult patients with advanced glaucoma               <ul style="list-style-type: none"> <li>◦ MMC: 0.2mg/mL/3min</li> <li>◦ Saline solution/3min</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>– Mean IOP in mmHg (±SD)               <ul style="list-style-type: none"> <li>◦ MMC: 26.35 (±6.68)</li> <li>◦ Saline: 24.92 (±12.82)</li> </ul> </li> <li>– Mean medication use (±SD)               <ul style="list-style-type: none"> <li>◦ MMC: 2.71 (±0.61)</li> <li>◦ Saline: 2.64 (±0.84)</li> </ul> </li> <li>– Diagnosis               <ul style="list-style-type: none"> <li>◦ MMC POAG (12); CACG (2)</li> <li>◦ Saline POAG (12); CACG (2)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>MMC: 14/14</li> <li>Saline: 14/14</li> </ul>	<ul style="list-style-type: none"> <li>69.10 (±9.72 ) years</li> <li>64.92 (±12.82) years</li> </ul>	<ul style="list-style-type: none"> <li>M: 11</li> <li>F: 3</li> <li>M: 11</li> <li>F: 3</li> </ul>	<ul style="list-style-type: none"> <li>W: 10</li> <li>B: 4</li> <li>W: 9</li> <li>B: 5</li> </ul>	Brazil
<ul style="list-style-type: none"> <li>– Robin, 1997</li> <li>– Long-term, prospective dose-response examining relationship between concentration and duration of MMC in trabeculectomy and decrease in IOP in 300 adults</li> <li>– 4 treatment groups               <ul style="list-style-type: none"> <li>◦ 1) Placebo</li> <li>◦ 2) MMC 0.2mg/mL/2min</li> <li>◦ 3) MMC 0.2mg/mL/4min</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>– Mean IOP in mmHg               <ul style="list-style-type: none"> <li>◦ 1) 29.1</li> <li>◦ 2) 28.1</li> <li>◦ 3) 30.6</li> <li>◦ 4) 30.9</li> </ul> </li> <li>– Prior medications (%):               <ul style="list-style-type: none"> <li>◦ 1) 70.4%</li> <li>◦ 2) 69.2%</li> <li>◦ 3) 62.3%</li> <li>◦ 4) 67.6%</li> </ul> </li> <li>– Prior intraocular surgery: none for any study patient</li> </ul>	<ul style="list-style-type: none"> <li>1) 75/71</li> <li>2) 75/78</li> <li>3) 75/77</li> <li>4) 75/74</li> </ul>	<ul style="list-style-type: none"> <li>1) 51.5 years</li> <li>2) 51.9 years</li> <li>3) 50.2 years</li> <li>4) 53.3 years</li> </ul>	<ul style="list-style-type: none"> <li>1) M: 32.4%</li> <li>2) M: 33.3%</li> <li>3) M: 32.5%</li> <li>4) M: 36.5%</li> </ul>	NP	Southern India

Clinical Review  
 William Boyd, M.D.  
 NDA 22-572  
 Mitosol (mitomycin for solution)

Table 26 Demographics and Baseline Characteristics —Prospective, Randomized, Controlled, Masked Studies (9 Studies)

Investigator/Design/ Treatment Groups	Baseline Conditions <sup>a</sup>	No. of Patients/ Eyes	Mean Age <sup>b</sup> (±SD) Range <sup>c</sup>	Sex	Race or Ethnicity	Country Study Conducted
◦ 4) MMC 0.4mg/mL/2 min						
<b>Mitomycin versus No Adjunctive Treatment (3 Studies)</b>						
– Andreanos, 1997 – Randomized study with masked evaluator – Second antiglaucoma surgery after failure of first surgery in 46 adult patients with high IOP ◦ MMC 0.4mg/mL/2-3min ◦ Trab only (i.e., no MMC)	– Mean IOP in mmHg (±SD): for all study patients 32.4 (±5.2) – Medication use: All patients used topical or systemic medication – Prior surgery: All patients had a filtering operation without antimetabolites 1–3 years earlier, with a mean interval of 21 months after the first surgery – VA: NP	MMC: 24/24  Trab only: 22/22	64.2 years (44–72)  (The treatment groups were balanced as to age and sex.)	Total population: M: 26 F: 20	NP	Greece
– Martini, 1997 – Prospective, randomized, controlled, evaluator- masked study of low-dosage MMC in adults – Trabeculectomy ◦ MMC 0.1mg/mL/3min ◦ Trab only (no MMC)	– Mean IOP in mmHg (±SD) ◦ MMC: 28.8 (±7.4) ◦ Trab only: 28.4 (±9.2) – Medications ◦ MMC: 2.2 (±0.3) ◦ No MMC: 2.3 (±0.5) – Previous ALTP ◦ MMC: 5 (16.6%) ◦ No MMC: 8 (26.6%)	MMC: 24/30  No MMC: 24/30	61.3 (±14.1) years  69.7 (±11.6) years (p=0.013)	M: 21 F: 9  M: 21 F: 9	NP	Italy

Investigator/Design/ Treatment Groups	Baseline Conditions <sup>a</sup>	No. of Patients/ Eyes	Mean Age <sup>b</sup> (±SD) Range <sup>c</sup>	Sex	Race or Ethnicity	Country Study Conducted
– Rasheed, 1999 – Prospective, randomized, single-masked study of trabeculectomy with MMC in 1 eye and standard trabeculectomy in other eye in 25 adult patients ◦ MMC eye 0.3-0.4mg/mL/4min ◦ No MMC eye	– Mean IOP in mmHg (±SD) ◦ MMC: 28.00 (±3.19) ◦ No MMC: 28.10 (±3.14) – Mean medication use (±SD) ◦ MMC: 3.7 (±0.6) ◦ No MMC: 3.7 ((±0.3) – Diagnosis (25 patients) ◦ POAG (21; 84%) ◦ Primary closed angle (4; 16%)	MMC: 25/25 No MMC: 25/25	25 patients: (50.3 (±14.1) years (20–75)	25 patients: M: 13 (52%) F: 12 (48%)	NP	Egypt
<b>Mitomycin versus 5-FU (1 Study)</b>						
– WuDunn, 2002 – Comparison of safety and efficacy of intraoperative 5-FU with MMC in 115 eyes undergoing primary trabeculectomy ◦ 5-FU 50mg/mL/5 min: 57 eyes ◦ MMC 0.2mg/mL/2min: 57 eyes	– Mean IOP in mmHg (±SD) ◦ 5-FU: 24.3 (±8.1) ◦ MMC: 21.9 (±6.6) – Mean medication use (±SD) ◦ 5-FU: 2.7 (±1.2) ◦ MMC: 2.4 (±1.2) – Mean best corrected LogMAR vision (±SD) ◦ 5-FU: 0.19 (±0.35) ◦ MMC: 0.26 (±0.51)	5-FU: 57/57  MMC: 58/58	65.5 (±12.8) years (29–83)  65.4 (±12.1) years (32–82)	M: 28 F: 29  M: 36 F: 22	W: 42 B: 15  W: 42 B: 14 H: 1 A: 1	USA

**Table 26 Demographics and Baseline Characteristics —Prospective, Randomized, Controlled, Masked Studies (9 Studies)**

Investigator/Design/ Treatment Groups	Baseline Conditions <sup>a</sup>	No. of Patients/ Eyes	Mean Age <sup>b</sup> (±SD) Range <sup>c</sup>	Sex	Race or Ethnicity	Country Study Conducted
<b>Mitomycin Dose Comparison Study (1 Study)<sup>d</sup></b>						
– Sanders, 1998 – Randomized, masked, prospective study comparing outcome of trabeculectomy with 1 of 2 doses of MMC – 50 consecutive eyes in adult patients ◦ MMC 0.2mg/mL/2min ◦ MMC 0.4mg/mL/2min	– Mean IOP mmHg (±SD) ◦ 0.2mg/mL: 28.8 (±13.7) ◦ 0.4mg/mL: 25.0 (±8.6) – Medications ◦ 0.2mg/mL: 2.6 ◦ 0.2mg/mL: 3.0 – Previous ALT ◦ 0.2mg/mL: 10 ◦ 0.4mg/mL: 17 – Diagnosis ◦ 0.2mg/mL: POAG (22); ACG (3) ◦ 0.4mg/mL: POAG (22); ACG (3)	0.2mg/mL: 25/25  0.4mg/mL: 25/25	74.2 44 (±14.2) years (44–48)  73.1 (±8.59) years (55–84)	M: 14 F: 11  M: 15 F: 10	W: 21 B: 4  W: 2 B: 2	USA

5-FU = 5-Fluorouracil; A = Asian; ALT or ALTP = Argon laser trabeculectomy; B = Black; CACG = Chronic angle closure glaucoma; F = Female; H = Hispanic, M = Male; MMC = Mitomycin C; NP = Data not provided in publication; POAG = Primary open-angle glaucoma; Trab = Trabeculectomy; W = White.

<sup>a</sup> Baseline conditions include the following, provided when available in the publication: mean preoperative IOP in mmHg (±SD); medication use, expressed as either mean number (±SD) of preoperative medications or percentage of patients taking medications; prior medical history, including surgery; and current diagnoses.

<sup>b</sup> Age given in years, unless otherwise specified.

<sup>c</sup> Range given when available.

<sup>d</sup> Two studies employed dose-comparison as part of their design: Robin and Sanders. The results from the placebo-controlled study conducted by Robin and colleagues are summarized in the *Mitomycin versus Placebo* section of this table.

Source – Table 26, NDA Section 2.7.3.3.1

## 6.5 Subpopulations

None of the demographic factors described in the preceding table appeared to correlate with any specific efficacy outcome.

## 6.6 Analysis of Clinical Information Relevant to Dosing Recommendations

Mitomycin is applied topically at the incision site during filtering surgery to delay wound healing by preventing scarring external to the scleral flap at the level of the conjunctiva–Tenon’s capsule–episcleral interface.

The 22 prospective studies described utilized various doses and durations of mitomycin exposure; there is no evidence that a dose greater than 0.2 mg/mL for greater than 2-3 minutes provides any greater efficacy. Irrigation of the application site was performed in all cases, typically with balanced salt solution, after administration of the mitomycin.

Higher doses of mitomycin or longer exposures were generally not significantly more effective, and in some cases appeared to increase the incidence of adverse events.

## **6.7 Discussion of Persistence of Efficacy and/or Tolerance Effects**

The proposed clinical use is for a single topical application.

## **6.8 Additional Efficacy Issues/Analyses**

None.

## 7 Review of Safety

### **Safety Summary**

This is a 505(b)(2) application primarily based on literature.

There is adequate support from the literature to support the safety for Mitosol (mitomycin for solution) in treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery provided the mitomycin can be adequately labeled for reconstitution and administration.

The most frequent adverse reactions to Mitosol occur locally and are often related to an extension of the pharmacological activity of the drug and/or markedly reduced intraocular pressure from trabeculectomy. These include hypotony, choroidal detachment, shallow anterior chamber, hyphema, corneal endothelial defects, and cataract progression.

The FDA's Adverse Event Reporting System (AERS) adverse event (AE) reports [pertaining to mitomycin ophthalmic preparations between November 1, 1997 and March 31, 2009, in which an indication for use MedDRA preferred term (PT) referable to the eye or extraocular structures was associated with mitomycin exposure] are consistent with the literature findings. See Section 8 of this review.

### **7.1 Methods**

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This is a 505(b)(2) application primarily based on literature.

The June 21, 2010, submission was submitted electronically. Subsequent amendments were also submitted in electronically. All literature reports were reviewed.

The results were tabulated separately by study design to facilitate review for the literature safety report: 23 controlled trials, 32 observational studies, 9 case series, and 65 case reports.

The 9 trials from the literature identified in Section 6.1.1. A as being adequate and well controlled have safety information included in their synopses in Section 6.1 of this review.

See Section 5.3 of this review for a detailed description of the applicant’s literature search methodology.

### 7.1.2 Categorization of Adverse Events

See Section 7.1.3.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The 23 controlled trials were conducted in 1,588 eyes, 1,085 of which were treated with mitomycin. See Appendices, Section 9.1 of this review for a reference listing of the 23 trials.

All 23 controlled trials included at least 1 arm where mitomycin was topically applied to the exposed site of a filtering bleb, as adjunct therapy during trabeculectomy. Five were conducted in the United States, 10 in Europe (Croatia, Greece, Italy, the Netherlands, and Poland), 6 in Asia (India and Japan), and 2 in Africa (Congo and Ghana). Sixteen trials used randomized controlled designs, 1 used a randomized controlled trial with case control, 4 used randomized crossover designs, 1 used a sequential crossover design, and 1 used a prospective non-comparative, nonrandomized, unmasked design. Among the controlled trials, doses of mitomycin ranged from 0.04 mg/mL to 0.5 mg/mL, and application times ranged from 0.5–5 minutes. **Note:** If multiple arms of the same study reported frequencies, only the greatest frequency was included

**Summary Table: Overview of Adverse Events Reported in Controlled Clinical Trials**

Adverse Event	Frequency Range	Locations
<b>Hypotony</b> Hypotony	1.5%-52%	US, US, US, US; Asia (India), EU (Greece), Asia (Japan), Asia (Japan), Asia (Japan), Africa (Congo-Kinshasa), EU (Italy), EU (Italy), Africa (Ghana), EU (Poland)
<b>Hypotony Maculopathy</b> Hypotony maculopathy	0%-18%	US; EU (Greece), Asia (Japan), Asia (Japan), EU (Italy), EU (Poland), EU (Poland), Asia (Japan)
<b>Choroidal Events</b> Choroidal detachment	0%-36%	US, US, US; EU (Greece), Asia (Japan), EU (Italy), EU (Netherlands), Asia (Japan), Asia (Japan), EU (Italy), EU (Italy), EU (Poland), EU (Poland), Asia (Japan)
Choroidal effusion	10%	EU (Italy)

Clinical Review  
 William Boyd, M.D.  
 NDA 22-572  
 Mitosol (mitomycin for solution)

<b>Adverse Event</b>	<b>Frequency Range</b>	<b>Locations</b>
Suprachoroidal hemorrhage	2.5%	US
<b>Retinal Detachment</b>		
Secondary retinal detachments	3%	EU (Poland)
<b>Other Related Events</b>		
Shallow anterior chamber	0%-46%	Asia (India), EU (Greece), Asia (Japan), EU (Netherlands), Asia (Japan), Asia (Japan), Asia (Japan), EU (Croatia), EU (Italy), Africa (Congo-Kinshasa), EU (Italy), Africa (Ghana), EU (Poland), Asia (Japan)
Hypotony-related complications requiring surgery	23.3%	US
<b>Endophthalmitis</b>		
Endophthalmitis	0%-3%	US, US; EU (Italy), EU (Italy), Africa (Ghana), EU (Poland)
<b>Bleb Events</b>		
Bleb/wound leak	0%-27%	US, US, US; Asia (Japan), EU (Netherlands), Asia (Japan), EU (Croatia), EU (Italy), EU (Italy), Africa (Ghana), EU (Poland), EU (Poland), Asia (Japan)
Encapsulated bleb	0%-28.6%	EU (Greece), EU (Italy), Africa (Ghana), EU (Poland), EU (Poland)
Blebitis/bleb infection	0%-1.5%	US; EU (Italy)
Cystic bleb/bleb fibrosis	3.3%-13%	EU (Croatia), EU (Italy)
Failed bleb	8%-10%	Asia (Japan), Asia (Japan)
Thin, avascular bleb	12%	EU (Poland)
<b>Vascular Events</b>		
Hyphema	0%-46%	US, US; Asia (India), EU (Greece), Asia (Japan), EU (Italy), EU (Netherlands), Asia (Japan), Asia (Japan), EU (Croatia), EU (Italy), EU (Italy), EU (Poland)
Anterior chamber inflammation/fibrin reaction	0%-11%	Asia (India), Asia (Japan), EU (Italy), EU (Italy)
Anterior chamber hemorrhage	27%	EU (Italy), EU (Poland)
Hemiretinal vein occlusion	3.3%	US
Vitreous loss	0%	Asia (Japan)
<b>Lenticular Events</b>		
Cataract progression/development	6%-40.3%	Asia (India), EU (Greece), Asia (Japan), Asia (Japan), EU (Italy), EU (Italy), EU (Italy), Africa (Ghana), EU (Poland), EU (Poland), Asia (Japan)
Capsule opacification	50%	EU (Croatia)
Asymmetric cataract evolution in fellow eye	7.1%	EU (Italy)
Rupture of posterior lens capsule	0%	Asia (Japan)

Adverse Event	Frequency Range	Locations
<b>Corneal Events</b>		
Corneal endothelial defect	0%-57%	US, US; Asia (Japan), Asia (Japan), EU (Italy), EU (Italy), EU (Poland), EU (Poland), Asia (Japan)
Posterior synechiae	0%-38%	Asia (Japan), Asia (Japan), EU (Croatia)
Peripheral anterior synechiae	20%	Asia (Japan), Asia (Japan)
Superficial punctate keratitis	5%	Africa (Congo-Kinshasa)
Haemorrhagic Descemet's detachment	0%	Asia (India)
<b>Other Events</b>		
Macular edema	2%-2.6%	US; EU (Italy)
Scleral thinning or ulceration	0%-3.3%	EU (Italy), EU (Poland)
Intraocular lens capture	19%	EU (Croatia)
Iritis	19%	EU (Croatia)
Corneal vascularization	27%	EU (Poland)
Visual acuity decrease	29.2%	EU (Greece)
Cystic conjunctival degeneration	16.6%	EU (Greece)
Aqueous misdirection	0%	Africa (Ghana)
Corneo-lenticular touch	0%	EU (Poland)
Intense sterile uveitis	0%	EU (Poland)
Iris incarceration	0%	EU (Italy)
Shunt rotation	0%	EU (Italy)

Source – Summary Table, NDA Section 2.7.4.2.2

The adverse events reported are consistent with those described in the 22 prospective clinical trials described in Section 6.1.1.A in this review with the exception of corneal endothelial defects.

Hypotony, choroidal detachment, shallow anterior chamber, hyphema, corneal endothelial defects, and cataract progression are seen with a lower frequency range of 0-3% and an upper frequency range of approximately 30-50%. All of these are known adverse events seen with the trabeculectomy procedure alone.

There is great variation in the adverse event rates reported for these more serious adverse events; these rates are presumably dependant on the skill of the surgeon and the specific surgical population.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The 23 controlled trials were conducted in 1,588 eyes, 1,085 of which were treated with mitomycin. Among the controlled trials, doses of mitomycin ranged from 0.04 mg/mL to 0.5 mg/mL, and application times ranged from 0.5–5 minutes.

### 7.2.2 Explorations for Dose Response

Among the 23 controlled trials, doses of mitomycin ranged from 0.04 mg/mL to 0.5 mg/mL, and application times ranged from 0.5–5 minutes.

### 7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed.

### 7.2.4 Routine Clinical Testing

There were no clinical laboratory tests described in the literature supporting this application. The proposed clinical use is for a single topical application.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

There was no metabolic, clearance, or interaction workup described in the literature supporting this application. The proposed clinical use is for a single topical application.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no approved drug products for the proposed indication - treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery.

The proposed clinical use is for a single topical application.

The approved label for the reference listed drug indicates that systemic mitomycin is carcinogenic.

Mitomycin administered parenterally has been shown to be teratogenic in mice and rats when given at doses equivalent to the usual human intravenous dose.

## 7.3 Major Safety Results

### 7.3.1 Deaths

Only one death is reported in the applicant's literature safety report

Per Nuyts et al, 1994<sup>3</sup>,

A 78-year-old white woman with POAG underwent trabeculectomy with MMC (0.5 mg/mL for 5 minutes) in upper nasal quadrant of the right eye. Patient history included failed trabeculectomy with postoperative 5-fluorouracil 19 months earlier. Patient had previously been on 2 antiglaucoma medications (timolol maleate and pilocarpine), had frequent splinter hemorrhages near the margin of the optic nerve head, and had amblyopia in the left eye.

Preoperatively, IOP was 25 mmHg. 6 days later, the patient died of a cerebral hemorrhage. That day, visual acuity was 20/80 and IOP was 12 mmHg. Histopathology of the functioning MMC bleb revealed normal epithelium and many fibroblasts in the conjunctival stroma and Tenon's layer; examination of nonpigmented epithelium revealed variation in thickness, an irregular basal surface, and numerous infoldings, as well as myelin figures, increased melanolipofuscin granules, vacuolated cytoplasm, and disrupted mitochondria.

### 7.3.2 Nonfatal Serious Adverse Events

See Section 7.1.3 for pooled data.

### 7.3.3 Dropouts and/or Discontinuations

The dropout rate is not particularly applicable in these literature reports and is not captured in the applicant's literature safety report. The proposed clinical use is for a single topical application.

### 7.3.4 Significant Adverse Events

See Section 7.1.3 for pooled data.

### 7.3.5 Submission Specific Primary Safety Concerns

See Section 7.1.3 for pooled data.

---

3 Nuyts RM, Greve EL, Geijssen HC, Langerhorst CT. Treatment of hypotonous maculopathy after trabeculectomy with mitomycin C. *Am J Ophthalmol.* 1994;118(3):322- 331.

## **7.4 Supportive Safety Results**

### **7.4.1 Common Adverse Events**

See Section 7.1.3 for pooled data.

### **7.4.2 Laboratory Findings**

There were no clinical laboratory tests described in the literature supporting this application. The proposed clinical use is for a single topical application.

### **7.4.3 Vital Signs**

There were no vital signs data recorded in the literature supporting this application. The proposed clinical use is for a single topical application.

### **7.4.4 Electrocardiograms (ECGs)**

There was no ECG data recorded in the literature supporting this application. The proposed clinical use is for a single topical application.

### **7.4.5 Special Safety Studies/Clinical Trials**

There were no special safety studies or clinical trials conducted for this application.

### **7.4.6 Immunogenicity**

Not applicable. Drug product is not expected to be immunogenic.

## **7.5 Other Safety Explorations**

### **7.5.1 Dose Dependency for Adverse Events**

Among the controlled trials, doses of mitomycin ranged from 0.04 mg/mL to 0.5 mg/mL, and application times ranged from 0.5–5 minutes. Higher doses of mitomycin or longer exposures were generally not significantly more effective, and in some cases appeared to increase the incidence of adverse events.

### 7.5.2 Time Dependency for Adverse Events

The proposed clinical use is for a single topical application. Select literature references follow subjects for up to 24 months after surgery.

### 7.5.3 Drug-Demographic Interactions

None of the demographic factors described in Section 6.4 of this review appeared to correlate with any specific efficacy outcome.

### 7.5.4 Drug-Disease Interactions

No drug-disease evaluations were described in the literature supporting this application. The proposed clinical use is for a single topical application.

### 7.5.5 Drug-Drug Interactions

No drug-drug evaluations were described in the literature supporting this application. The proposed clinical use is for a single topical application.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

No carcinogenicity data were provided. Since the proposed clinical use is for a single topical application, no carcinogenicity studies to support this application are necessary. The approved label for the reference listed drug indicates that systemic mitomycin is carcinogenic.

### 7.6.2 Human Reproduction and Pregnancy Data

Animal reproduction studies have not been conducted with Mitosol. Mitomycin administered parenterally has been shown to be teratogenic in mice and rats when given at doses equivalent to the usual human intravenous dose. Mitomycin produces a greater than 100 percent increase in tumor incidence in male Sprague-Dawley rats, and a greater than 50 percent increase in tumor incidence in female Swiss mice.

Mitosol is contraindicated in women who are or may become pregnant during therapy. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

The Pediatric Research Equity Act of 2003 (PREA), and 21 CFR 314.55 (a) require that sponsors submitting a new application or supplement under section 505 of the Federal Food Drug and Cosmetic Act that involves a new ingredient, new indication, new dosage form, new dosing regimen or new route of administration, submit an assessment of the safety and efficacy of the drug or biological product for the claimed indication in all relevant pediatric subpopulations.

Mobius' Mitosol (mitomycin for solution) has received Orphan Designation; a pediatric assessment is therefore not required and has not been provided in this application. This application was not presented at the Pediatric Review Committee (PeRC).

Safety and effectiveness of Mitosol (mitomycin for injection) in pediatric patients has not been established.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Mitomycin is a non-narcotic and does not have abuse potential. It is an antibiotic shown to have anti-tumor activity; it is a potent carcinogen.

## 7.7 Additional Submissions / Safety Issues

The 120-day Safety Update, submitted on December 3, 2010, provided no new safety information regarding Mitosol (mitomycin for solution) since the original submission of June 21, 2010.

At the Agency's request, a labeling comprehension study was performed on September 21, 2010, using the Mobius-proposed labeling and packaging. The study was performed at [REDACTED] (b) (4) in a "mock operating room" setting.

From the Summary Research Report completed by [REDACTED] (b) (4) on behalf of the applicant:

Respondents were told that this is a new product for delivering mitomycin for ophthalmic use and this research was being conducted to see how the kit would be handled in a typical Operating Room situation. Respondents were told that they were being asked to use the Instructions for Use to perform the required tasks, and after they used the kit, they would be asked about their experience.

Key Findings: 1) The instructions for use (IFU) communicate that there are sterile and non-sterile components included in the kit. However, the construction

of the packaging, i.e. a (b) (4) tray with a sealed (b) (4) lid, led many respondents to question if the overall kit was sterile or non-sterile, since they were used to only sterile kits being packaged this way.

2) Observer's Assessments confirm that 5 of 6 pairs of respondents correctly handled the sterile and non-sterile components of the kit. Only one pair overturned the kit onto the sterile table *before* reading the instructions. This was *not* a function of the IFU, rather, it reflected the need for better labeling on the outer kit.

3) Overall, the IFU could do a better job at naming and visually identifying the components of the kit clearly and consistently. For example:

(b) (4)

4) (b) (4)

5) Observers Assessments noted that a few tasks were not always performed correctly:

- Two of six respondents did not correctly (b) (4)
- Three of six did not correctly (b) (4)
- Two of six respondents did not correctly (b) (4)
- One of six respondents did not correctly (b) (4)
- One of six respondents did not correctly (b) (4)

The Agency requested a second labeling comprehension study be performed by the appropriate operating room personnel after revision to the proposed packaging and labeling of the mitomycin kit is made. As of the date of this review, the report from that second labeling comprehension study is pending.

## 8 Postmarket Experience

This product is not approved or marketed in any country.

See Section 2.4. Mitomycin is currently available in injectable dosage forms (lyophilized) in US market, and the reference listed drug product for this application is Mutamycin of Bristol Myers Squibb – ANDA 062336.

No ophthalmic dosage form of mitomycin is available in US market.

The application contains an FDA Adverse Event Reporting System Summarization Report prepared for Mobius Therapeutics, LLC by [REDACTED] (b) (4). The FDA's Adverse Event Reporting System (AERS) was referenced for all adverse event (AE) reports pertaining to mitomycin ophthalmic preparations between November 1, 1997 and March 31, 2009 in which an indication for use MedDRA preferred term (PT) referable to the eye or extraocular structures was associated with mitomycin exposure.

A total of 33 AE reports were retrieved and are presented in this summarization report.

Note that these adverse events are for all off-label mitomycin ophthalmic indications and are not limited to glaucoma surgery.

TABLE 5  
ADVERSE EVENT MedDRA PREFERRED TERM  
DESCENDING FREQUENCY COUNT  
USA + Non-USA Reports  
Report Qualifiers: All Drug Roles (Suspect, Concomitant, Interacting)  
FDA AERS Database; November 1, 1997 – March 31, 2007

MedDRA Preferred Term	Trabeculectomy (N=10)	Glaucoma/ Intraocular Pressure Surgery (N=13)	Other Ophthalmic Operations/ Symptoms (N=8)	All Mitomycin Ophthalmic Indications (N=31)
Endophthalmitis	70% (N=7)	23.1% (N=3)	0% (N=0)	32.3% (N=10)
Choroidal Detachment	0% (N=0)	30.8% (N=4)	0% (N=0)	12.9% (N=4)
Visual Acuity Reduced	10% (N=1)	15.4% (N=2)	12.5% (N=1)	12.9% (N=4)
Corneal Degeneration	10% (N=1)	15.4% (N=2)	0% (N=0)	9.7% (N=3)
Corneal Oedema	10% (N=1)	0% (N=0)	12.5% (N=1)	6.5% (N=2)
Scleral Disorder Nos	0% (N=0)	0% (N=0)	25% (N=2)	6.5% (N=2)
UVEITIS	0% (N=0)	15.4% (N=2)	0% (N=0)	6.5% (N=2)
Conjunctival Oedema	0% (N=0)	0% (N=0)	12.5% (N=1)	3.2% (N=1)
CONJUNCTIVITIS	0% (N=0)	0% (N=0)	12.5% (N=1)	3.2% (N=1)
CORNEAL DISORDER	0% (N=0)	7.7% (N=1)	0% (N=0)	3.2% (N=1)
Corneal Disorder Nos	0% (N=0)	0% (N=0)	12.5% (N=1)	3.2% (N=1)
Corneal Epithelium Defect	0% (N=0)	0% (N=0)	12.5% (N=1)	3.2% (N=1)
Corneal Graft	0% (N=0)	0% (N=0)	12.5% (N=1)	3.2% (N=1)
Corneal Opacity	0% (N=0)	0% (N=0)	12.5% (N=1)	3.2% (N=1)
DACRYOSTENOSIS ACQUIRED	0% (N=0)	0% (N=0)	12.5% (N=1)	3.2% (N=1)
EYE INFECTION	0% (N=0)	7.7% (N=1)	0% (N=0)	3.2% (N=1)
Eye Pain	0% (N=0)	0% (N=0)	12.5% (N=1)	3.2% (N=1)
Eyelid Oedema	0% (N=0)	0% (N=0)	12.5% (N=1)	3.2% (N=1)
HAEMOPHILUS INFECTION	0% (N=0)	7.7% (N=1)	0% (N=0)	3.2% (N=1)
Intraocular Pressure Decreased	0% (N=0)	7.7% (N=1)	0% (N=0)	3.2% (N=1)
KERATOPATHY	0% (N=0)	7.7% (N=1)	0% (N=0)	3.2% (N=1)
Lacrimation Increased	0% (N=0)	0% (N=0)	12.5% (N=1)	3.2% (N=1)
Maculopathy	0% (N=0)	0% (N=0)	12.5% (N=1)	3.2% (N=1)
Necrosis Nos	0% (N=0)	0% (N=0)	12.5% (N=1)	3.2% (N=1)
OFF LABEL USE	0% (N=0)	0% (N=0)	12.5% (N=1)	3.2% (N=1)
POST PROCEDURAL COMPLICATION	0% (N=0)	7.7% (N=1)	0% (N=0)	3.2% (N=1)
Postoperative Complications Nos	0% (N=0)	0% (N=0)	12.5% (N=1)	3.2% (N=1)
PUPILLARY DISORDER	0% (N=0)	7.7% (N=1)	0% (N=0)	3.2% (N=1)
Retinal Haemorrhage	10% (N=1)	0% (N=0)	0% (N=0)	3.2% (N=1)
RETINOPATHY	0% (N=0)	7.7% (N=1)	0% (N=0)	3.2% (N=1)
SCLEROMALACIA	0% (N=0)	0% (N=0)	12.5% (N=1)	3.2% (N=1)
STAPHYLOCOCCAL INFECTION	0% (N=0)	7.7% (N=1)	0% (N=0)	3.2% (N=1)
STAPHYLOMA	0% (N=0)	7.7% (N=1)	0% (N=0)	3.2% (N=1)
THERAPY NON-RESPONDER	0% (N=0)	7.7% (N=1)	0% (N=0)	3.2% (N=1)
TOXIC ANTERIOR SEGMENT SYNDROME	10% (N=1)	0% (N=0)	0% (N=0)	3.2% (N=1)

Source – Table 5, NDA Section 5.3.6.1

## 9 Appendices

### 9.1 Literature Review/References

The June 21, 2010, submission was submitted electronically. Subsequent amendments were also submitted in electronically. All literature reports were reviewed. The literature review, package insert, and subsequent labeling comprehension studies formed the basis for the review of efficacy and safety for the proposed indication.

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Mobius Therapeutics, LLC in this application for this indication.

#### **Group 1 Studies: Prospective, Randomized, Controlled, Masked Studies (9 Studies)**

Carlson DW, Alward WL, Barad JP, Zimmerman MB, Carney BL. A Randomized Study of Mitomycin Augmentation in Combined Phacoemulsification and Trabeculectomy. *Ophthalmology* 1997 Apr; 104(4):7 19-724.

Cohen JS, Greff LJ, Novack GD, Wind BE. A placebo-controlled, double-masked evaluation of mitomycin C in combined glaucoma and cataract procedures. *Ophthalmology*. 1996 Nov; 103(11): 1934-42.

Costa VP, Comegno PE, Vasconcelos JP, Malta RF, Jose NK. Low-dose mitomycin C trabeculectomy in patients with advanced glaucoma. *J Glaucoma*. 1996 Jun;5(3): 193-9.

Robin AL, Ramakrishnan R, Krishnadas R, Smith SD, Katz JD, Selvaraj S, Skuta GL, Bhatnagar R. A long-term dose-response study of mitomycin in glaucoma filtration surgery. *Arch Ophthalmol*. 1997 Aug;115(8):969-74.

Andreanos D, Georgopoulos GT, Vergados J, Papaconstantinou D, Liokis N, Theodossiadis P Clinical evaluation of the effect of mitomycin-C in re-operation for primary open-angle glaucoma. *Eur J Ophthalmol*. 1997 Jan-Mar;7(1):49-54.

Martini E, Laffi GL, Sprovieri C, Scorolli L. Low-Dosage Mitomycin C as an Adjunct to Trabeculectomy. A prospective controlled study. *Eur J Ophthalmol* 1997 Jan-Mar;7(1):40-8.

Rasheed el-S. Initial Trabeculectomy with Intraoperative Mitomycin-C Application in Primary Glaucomas. *Ophthalmic Surg Lasers* 1999 May;30(5):360-6.

WuDunn D, Cantor L, Palanca-Capistrano A, Hoop J, Alvi N, Finley C, Lakhani V, Burnstein A, Knotts S. A Prospective Randomized Trial Comparing Intraoperative 5-Fluorouracil Vs Mitomycin-C in Primary Trabeculectomy. *Am J Ophthalmology* October 2002 V134(4):521- 528.

Sanders SP, Cantor LB, Dobler AA, Hoop JS. Mitomycin C in higher risk trabeculectomy: a prospective comparison of 0.2- to 0.4-mg/lcc doses. *J Glaucoma*. 1999 Jun;8(3):193-8.

### **Group 2 Studies: Prospective Studies of Uncertain Design (13 Studies)**

Hagiwara Y, Yamamoto T, Kitazawa Y. The effect of mitomycin C trabeculectomy on the progression of visual field defect in normal-tension glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 2000 Mar;238(3):232-6.

Hong C, Hyung SM, Song KY, Kim DM, Youn DH. Effects of topical mitomycin C on glaucoma filtration surgery. *Korean J Ophthalmol*. 1993 Jun; 7(1):1-10.

Kitazawa Y, Suemori-Matsushita H, Yamamoto T, Kawase K. Low-dose and high-dose mitomycin trabeculectomy as an initial surgery in primary open-angle glaucoma. *Ophthalmology*. 1993 Nov;100(11):1624-8.

Kobayashi I, Kobayashi K, Okinami S. A comparison of the intraocular pressure-lowering effect and safety of viscocanalostomy and trabeculectomy with mitomycin C in bilateral openangle glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 2003 May;241(5):359-66. Epub 2003 Apr 16.

Kozobolis VP, Christodoulakis EV, Tzanakis N, Zacharopoulos I, Pallikaris IG. Primary deep sclerectomy versus primary deep sclerectomy with the use of mitomycin C in primary open-angle glaucoma. *J Glaucoma*. 2002 Aug;11(4):287-93.

Maquet JA, Dios E, Aragon J, Bailez C, Ussa F, Laguna N. Protocol for mitomycin C use in glaucoma surgery. *Acta Ophthalmol Scand*. 2005 Apr;83(2):196-200.

Mermoud A, Salmon JF, Murray AD. Trabeculectomy with mitomycin C for refractory glaucoma in blacks. *Am J Ophthalmol*. 1993 Jul;116(1): 72-8.

Nuijts RM, Vernimmen RC, Webers CA. Mitomycin C primary trabeculectomy in primary glaucoma of white patients. *J Glaucoma*. 1997 Oct;6(5):293-7. Review.

Shin DH, Hughes BA, Song MS, Kim C, Yang U, Shah MI, Juzych MS, Obertynski T. Primary glaucoma triple procedure with or without adjunctive mitomycin. Prognostic factors for filtration failure. *Ophthalmology*. 1996 Nov; 103(11): 1925-33.

Shin DH, Ren J, Juzych MS, Hughes BA, Kim C, Song MS, Yang KJ, Glover KB. Primary glaucoma triple procedure in patients with primary open-angle glaucoma: the effect of mitomycin C in patients with and without prognostic factors for filtration failure. *Am J Ophthalmol.* 1998 Mar;125(3):346-52.

Turacil E, Gunduz K, Aktan G, Tamer C. A Comparative Clinical Trial of Mitomycin C and Cyclosporin A in Trabeculectomy. *Eur J Ophthalmol*1996 Oct-Dec; 6(4):398-401.

Unlu K, Aksunger A, Soker S, Ertem M. Mitomycin C primary trabeculectomy with releasable sutures in primary glaucoma. *Jpn J Ophthalmol.* 2000 Sep-Oct;44(5):524-9.

Vijaya L, Mukhesh BN, Shantha B, Ramalingam S, Sathi Devi A V. Comparison of low-dose intraoperative mitomycin-C vs 5-Fluorouracil in primary glaucoma surgery: a pilot study. *Ophthalmic Surg Lasers.* 2000 Jan-Feb;31(1):24-30.

#### **Controlled Studies Utilized in Summary Adverse Event Safety Table (23 Studies)**

Agarwal HC, Elankumaran P, Gupta V, Titiyal JS. Comparison of subscleral partial thickness sclerectomy plus trabeculotomy with trabeculectomy for primary open angle glaucoma. *Asian Journal of Ophthalmology.* 2005;7(3):96-100.

Andreanos D, Georgopoulos GT, Vergados J, Papaconstantinou D, Liokis N, Theodossiadis P. Clinical evaluation of the effect of mitomycin-C in re-operation for primary open angle glaucoma. *Eur J Ophthalmol.* 1997;7(1):49-54.

Chihara E, Nishida A, Kodo M, et al. Trabeculotomy ab externo: An alternative treatment in adult patients with primary open-angle glaucoma. *Ophthalmic Surgery.* 1993;24(11):735-739.

De Feo F, Bagnis A, Bricola G, Scotto R, Traverso CE. Efficacy and safety of a steel drainage device implanted under a scleral flap. *Canadian Journal of Ophthalmology-Journal Canadien D Ophtalmologie.* 2009;44(4):457-462.

de Jong L. The Ex-PRESS glaucoma shunt versus trabeculectomy in open-angle glaucoma: a prospective randomized study. *Advances in Therapy.* 2009;26(3):336-345.

Kim YY, Sexton RM, Shin DH, et al. Outcomes of primary phakic trabeculectomies without versus with 0.5- to 1-minute versus 3- to 5-minute mitomycin C. *Am J Ophthalmol.* 1998;126(6):755-762.

Kitazawa Y, Suemori-Matsushita H, Yamamoto T, Kawase K. Low-dose and high-dose mitomycin trabeculectomy as an initial surgery in primary open-angle glaucoma. *Ophthalmology.* 1993;100(11):1624-1628.

Kobayashi H, Kobayashi K. Randomized comparison of the intraocular pressure-lowering effect of phacoviscocanalostomy and phacotrabeulectomy. *Ophthalmology*. 2007;114(5):909-914.

Kobayashi H, Kobayashi K, Okinami S. A comparison of the intraocular pressure-lowering effect and safety of viscocanalostomy and trabeculectomy with mitomycin C in bilateral open-angle glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 2003;241(5):359-366.

Lamping KA, Belkin JK. 5-Fluorouracil and mitomycin C in pseudophakic patients. *Ophthalmology*. 1995;102(1):70-75.

Lemon LC, Shin DH, Kim C, Bendel RE, Hughes BA, Juzych MS. Limbus-based vs fornix-based conjunctival flap in combined glaucoma and cataract surgery with adjunctive mitomycin C. *Am J Ophthalmol*. 1998;125(3):340-345.

Mandic Z, Bencic G, Geber MZ, Bojic L. Fornix vs limbus based flap in phacotrabeulectomy with mitomycin C: Prospective study. *Croatian Medical Journal*. 2004;45(3):275-278.

Mastropasqua L, Carpineto P, Ciancaglini M, Zuppari E, Lobefalo L, Gallenga PE. Delayed post-operative use of 5-fluorouracil as an adjunct in medically uncontrolled open angle glaucoma. *Eye*. 1998;12 ( Pt 4)701-706.

Mwanza JC, Kabasele PM. Trabeculectomy with and without mitomycin-C in a black African population. *Eur J Ophthalmol*. 2001;11(3):261-263.

Reibaldi A, Uva MG. Five-year follow-up of LSL trabeculectomies with low dosage mitomycin-C in primary open-angle glaucoma. *Acta Ophthalmol Scand Suppl*. 2002;23661-62.

Reibaldi A, Uva MG, Longo A. Nine-year follow-up of trabeculectomy with or without low-dosage mitomycin-c in primary open-angle glaucoma. *Br J Ophthalmol*. 2008;92(12):1666-1670.

Russo V, Scott IU, Stella A, et al. Nonpenetrating deep sclerectomy with reticulated hyaluronic acid implant versus punch trabeculectomy: a prospective clinical trial. *Eur J Ophthalmol*. 2008;18(5):751-757.

Shin DH, Hughes BA, Song MS, et al. Primary glaucoma triple procedure with or without adjunctive mitomycin. Prognostic factors for filtration failure. *Ophthalmology*. 1996;103(11):1925-1933.

Shin DH, Kim YY, Sheth N, et al. The role of adjunctive mitomycin C in secondary

glaucoma triple procedure as compared to primary glaucoma triple procedure. *Ophthalmology*. 1998;105(4):740-745.

Singh K, Egbert PR, Byrd S, et al. Trabeculectomy with intraoperative 5-fluorouracil vs mitomycin C. *Am J Ophthalmol*. 1997;123(1):48-53.

Szymanski A, Gierek-Lapinska A, Koziak M, Gierek-Ciaciura S. A fluorophotometric study of corneal endothelium after trabeculectomy using different concentrations of Mitomycin-C. *Int Ophthalmol*. 1997;20(1-3):95-99.

Szymanski A. Scleral free auto-implant plug with mitomycin as limitation of trepanosclerectomy flow in glaucoma filtering surgery. *Int Ophthalmol*. 1997;20(1-3):89-94.

Yamamoto T, Suemori-Matsushita H, Ichien M, Kawase K, Kitazawa Y. Glaucoma filtering surgery and mitomycin C. *Chibret International Journal of Ophthalmology*. 1994;10(3):92-96.

## **9.2 Advisory Committee Meeting**

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

## **9.3 Labeling Recommendations**

A formal labeling review is deferred until additional data is submitted to support the application for Mitosol.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

WILLIAM M BOYD  
12/21/2010

WILEY A CHAMBERS  
12/22/2010

## Cross-Discipline Team Leader Review

<b>Date</b>	December 14, 2010
<b>From</b>	William M. Boyd, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA #</b>	22-572
<b>Applicant</b>	Mobius Therapeutics, LLC
<b>Date of Submission</b>	June 21, 2010
<b>PDUFA Goal Date</b>	December 22, 2010
<b>Type of Application</b>	505(b)(2)
<b>Name</b>	Mitosol (mitomycin for solution)
<b>Dosage forms / Strength</b>	Topical solution
<b>Proposed Indication(s)</b>	Treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery
<b>Recommended:</b>	Not Recommended for Approval

### 1. Introduction

Mitomycin C (MMC) is an antibiotic derived from *Streptomyces caespitosus* that has antimetabolytic properties. Mitomycin has been shown to inhibit fibroblast proliferation by preventing DNA synthesis, thereby potentially reducing the amount of scar tissue formed after trabeculectomy.

Per Mobius, the development of Mitosol (mitomycin for solution) is meant to address issues with the off-label use of mitomycin in glaucoma filter surgery:

- There is no assurance of sterility, concentration, and/or delivered dosage.
- There is no secure method of sterile product transfer from the circulating nurse to the surgical field, the area in the operating room where sterility is maintained.
- The amount of mitomycin accumulated in the sponge is subject to wide surgeon and/or nurse induced variables.
- Reconstituted solutions have limited shelf life.

Mobius asserts that their Mitosol (mitomycin for solution), which consists of a sterile single-use package/kit in a 0.2 mg mitomycin concentration, offers the following benefits:

- There is reconstitution of the mitomycin solution on the field, thereby minimizing shelf-life issues.
- Mitomycin is precisely measured, addressing consistent concentration.
- The mitomycin solution is prepared in a single dose volume.
- The dosage form is delivered to the surgical site by way of a standardized delivery system.
- The dosage form is available with an integral disposal package

## 2. Background

There are no approved drug products for the proposed indication - treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery.

This is a 505(b)(2) application primarily based on literature. Reference literature reports, surveys, and articles cited in this review are representative of the published literature.

The Form 356h submitted by Mobius Therapeutics, LLC, lists Mutamycin (mitomycin for injection), ANDA 062336 (Bristol Myers Squibb) as the reference listed drug (RLD) product.

A submission dated September 21, 2006, contained a request for a pre-NDA meeting to discuss the suitability of the current literature to support submission of a 505(b)(2) New Drug Application. A Pre-Investigational New Drug Application (PIND) file for this drug product was opened on October 5, 2006, identified by PIND number 75,734.

A Pre-IND meeting was held on December 6, 2006.

An orphan designation for mitomycin for solution for the treatment of treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery was granted on January 8, 2008.

A second Pre-IND meeting was held on July 20, 2009.

## 3. CMC

The proposed packaging for Mobius product consists of a "kit" which includes a vial of mitomycin for solution (containing a sterile, lyophilized mixture of 0.2 mg mitomycin and 0.4 mg mannitol) and associated components for the reconstitution of mitomycin and for the delivery of drug to the eye. Essential components of the packaging/kit include a prefilled syringe containing (b) (4) sterile water for injection for reconstitution of mitomycin and pre-cut surgical sponges for administration of the resulting solution to the eye. The sponges are held in a plastic tray which also serves as a container for the saturation with the drug solution. Other components are provided for handling and disposal of the cytotoxic agent. Components are packaged in (b) (4) trays with (b) (4) lidding.

### Drug Product Components/Composition

Ingredients	Compendial Reference	Qty. (mg) / mL	Batch Quantity
Mitomycin	USP/Ph. Eur.	0.2	(b) (4)
Mannitol	USNF/Ph. Eur.	0.4	(b) (4)
Water for Injection	USP/Ph. Eur.	(b) (4) 1 mL	(b) (4)

**Specification(s)**

The proposed specification for Mitomycin for Solution, 0.2 mg/Vial is presented in the table below. To facilitate comparison, the CMC reviewer has included the current specifications for Mitomycin for Injection USP and for the Intas and Bedford/BVL Mitomycin for Injection products.

**Mitomycin for Ophthalmic Solution (MIM3325-1 and MIM3325-S1)**

Attribute	Analytical Procedure	Acceptance Criteria	ANDA 64144 Intas Mitomycin for Injection*	ANDA 64117 BenVenue Mitomycin for Injection	Mitomycin for Injection USP
Appearance	In house	Blue-violet cake or powder, free from visible evidence of contamination in amber vial.	Same	Grey cake or powder free from visible signs of contamination	-
Constituted Solution	USP<1>	a) Sample powder should dissolve completely leaving no visible residue.  b) Sample solution is not significantly less clear than an equal volume of diluent (water for injection) in a similar vessel and examined similarly.  c) Sample solution should be essentially free from particles of foreign matter than could be observed on visual inspection.	Same	Same	Meets requirements for Constituted Solutions under Injections <1>.
Identification	USP	The Rf value of the principal spot obtained from the sample solution should correspond to that of the Mitomycin standard solution similarly prepared.	By TLC	By TLC	By TLC
Reconstitution Time	In house	(b) (4)			
pH	USP<791>				
Particulate Matter	USP<789>				
Bacterial Endotoxin	USP<85>				
Sterility	USP<71>				
Water	USP<921>				
Uniformity of dosage unit (By content uniformity)	USP<905>				

Related substances	In house
Assay	USP<621>
Residual Solvents	

(b) (4)

(b) (4)

The CMC reviewer does not recommend approval and has cited deficiencies:

- 1) The applicant has not demonstrated that the proposed drug product is of comparable identity, strength, quality, purity and potency to the commercially available, approved drug products upon which the clinical studies are based (e.g., the Mitomycin for Injection RLD described in ANDA 64-144 which is cross-referenced in the application).
- 2) There is insufficient information to allow establishment of a suitable drug product specification (e.g., acceptance criteria for impurities and pH).
- 3) There is insufficient information to determine the appropriate expiration dating period.

During a recent preapproval inspection conducted at Synergetics, Inc. (FEI 1000119053), significant deviations from Current Good Manufacturing Practices (cGMP) were observed and disclosed to the firm's management. The Division of Manufacturing and Product Quality has reviewed and concurs with the significance of these deviations. All significant deviations on the form FDA 483 (issued and signed 12/10/2010) and form FDA 463a (signed on 12/10/2010) should be corrected by the firm before this NDA is approved.

Examples of the significant cGMP deviations identified during this preapproval inspection include a Lack of acceptance criteria for the incoming materials and a lack of complete manufacturing and control instructions.

#### **4. Nonclinical Pharmacology/Toxicology**

From the original Pharmacology Toxicology Review finalized 10/28/10:

No original studies were performed or submitted. This application is made under 505(b)(2), and published literature references are provided.

Mitomycin is an alkylating agent isolated from *Strep. Caespitosus*. It forms stable crosslinks between DNA strands at guanine residues, inhibiting DNA synthesis and cell proliferation, and promoting apoptosis. This action is independent of the phase of the cell cycle. This activity is used for anti-tumor activity by inhibiting DNA synthesis in rapidly proliferating neoplastic cells. For the proposed ophthalmic indication, mitomycin acts as an antiproliferative, suppressing cell proliferation that would take place in wound healing and scarring. Specifically, DNA replication is inhibited in fibroblasts and vascular endothelial cells, decreasing cellularity and fibrosis of the surgical bleb.

No genetic toxicity studies were provided. Mitomycin is a known DNA alkylating agent so may be considered positive for genetic toxicity.

No carcinogenicity data were provided. Since the proposed clinical use is for a single topical application, no carcinogenicity studies to support this application are necessary. The approved label for the reference listed drug indicates that systemic mitomycin is carcinogenic.

#### **5. Clinical Pharmacology/Biopharmaceutics**

From the Clinical Pharmacology Review finalized 11/18/2010:

Available for many decades as a cancer chemotherapeutic agent, mitomycin C is a potent DNA alkylating agent. It forms stable crosslinks between DNA strands at guanine residues, inhibiting DNA synthesis and cell proliferation, and promoting apoptosis. This action is independent of the phase of the cell cycle. This activity is used for anti-tumor activity by inhibiting DNA synthesis in rapidly proliferating neoplastic cells.

As described in this 505(b)(2) application, the pharmacokinetic characteristics of mitomycin have been previously well-described for the IV formulation with the same active and inactive ingredients. The applicant has submitted a request for waiver of the requirement for submission of evidence of in vivo bioavailability for the proposed mitomycin kit based on the rationale that

the bioavailability to the RLD is self-evident because this 505(b)(2) NDA is based upon the reference listed drug Mutamycin (Mitomycin for Injection USP; Bristol Myers Squibb; NDA 062336).

## 6. Sterility Assurance

Per the original Product Quality Microbiology review completed on 11/23/10:

This product is a kit which consists of  (b) (4)



Mitomycin is formulated in a facility designed for the production of cytotoxic drugs. Bioburden is sampled  (b) (4)



## 7. Clinical/Statistical - Efficacy

From the Medical Officer Review:

This is a 505(b)(2) application primarily based on literature.

The application includes efficacy data gathered from 22 published papers describing prospective clinical studies with mitomycin as adjuvant therapy to glaucoma filtration surgery, primarily trabeculectomy. The Medical Officer's Review contains a detailed description of the 22 literature articles.

Four studies identified by the applicant as comparing intraoperative mitomycin C to placebo are described here: Carlson 1995, Cohen 1996, Costa 1996, and Robin 1997

### **Prospective, Randomized, Controlled, Masked Studies**

*Carlson DW, Alward WL, Barad JP, Zimmerman MB, Carney BL. A Randomized Study of Mitomycin Augmentation in Combined Phacoemulsification and Trabeculectomy.*

*Ophthalmology* 1997 Apr; 104(4):7 19-724.

This randomized double masked, placebo controlled study in 29 adult patients evaluated whether intraoperative application of subconjunctival mitomycin during combined phacoemulsification and trabeculectomy was an effective means of improving filtration. The authors defined effective filtration as overall lower IOP and reduced IOP-lowering medication use.

The difference in mean IOP at Month 12 was not statistically significant, although mitomycin-treated subjects had numerically lower IOPs (roughly 13 mm Hg versus 16 mmHg).

The mean change in IOP at Month 12 was not statistically significant, although mitomycin-treated subjects showed numerically higher decreases in IOP from baseline (roughly 6 mmHg versus 3 mmHg).

Hypotony was seen in late in one patient in the placebo group. One patient in the mitomycin group developed a coagulase negative staph endophthalmitis 10 months after surgery. See the following table.

**Table 2 MMC Augmentation in Combined Phacoemulsification and Trabeculectomy—12-Month Comparison (Carlson 1997)**

12-Month Outcomes	MMC 0.5mg/mL/3.5 min (n = 14)	Placebo (n = 15)	P-value
IOP in mmHg (mean ±SD)	12.6 (±1.0)	16.2 (±1.5)	.06 <sup>a</sup>
Mean change in IOP in mmHg (±SD)	5.6 (±1.3)	2.6 (±1.3)	.11 <sup>a</sup>
No. (%) patients with IOP between 5 mmHg and 15 mmHg	11/13 (85%)	5/12 (42%)	.04 <sup>b</sup>
No. (%) patients with IOP controlled without medications	13/13 (100%)	10/15 (67%)	.04 <sup>c</sup>
Visual Acuity 20/40 or better	13/14 eyes	14/15 eyes	NS
% patients requiring laser suture lysis	43%	80%	0.06 <sup>b</sup>
Mean number laser suture lysis	0.7	2.0	0.005 <sup>b</sup>

IOP = Intraocular pressure; SD = Standard deviation.

<sup>a</sup> Student's *t* test.

<sup>b</sup> Repeated measures of Analysis of variance.

<sup>c</sup> Fisher exact test.

*Cohen JS, Greff LJ, Novack GD, Wind BE. A placebo-controlled, double-masked evaluation of mitomycin C in combined glaucoma and cataract procedures. Ophthalmology. 1996 Nov; 103(11): 1934-42.*

This prospective, placebo-controlled, double-masked study was performed to determine if adjunctive use of mitomycin would increase the success of combined phacoemulsification, intraocular lens implantation, and trabeculectomy surgery with releasable sutures.

Mean IOP and IOP change from baseline at **Month 3** were not statistically significant. Mitomycin-treated subjects had numerically lower IOPs (roughly 15 mm Hg versus 17 mmHg). Mitomycin-treated subjects had numerically higher decreases in IOP from baseline (roughly 7 mmHg versus 3 mmHg).

The difference in mean IOP at **Month 6** was not statistically significant, although mitomycin-treated subjects had numerically lower IOPs (roughly 15 mm Hg versus 16 mmHg).

The mean change in IOP at **Month 6** was statistically significant with mitomycin-treated subjects showing higher decreases in IOP from baseline (roughly 7 mmHg versus 4 mmHg,  $p = 0.028$ ).

Mean IOP and IOP change from baseline at **Month 12** were statistically significant. Mitomycin-treated subjects had numerically lower IOPs (roughly 15 mm Hg versus 17 mmHg,  $p = 0.058$ ). Mitomycin-treated subjects had numerically higher decreases in IOP from baseline (roughly 8 mmHg versus 3 mmHg,  $p = 0.001$ ).

It appears no correction was made for multiple endpoints.

A filtering bleb leak occurred in 11 of 36 eyes (31%) in the mitomycin group and in 5 of 35 eyes (14%) in the placebo group ( $p = 0.101$ ).

There were no significant differences in endothelial cell counts between groups pre and post surgery.

**Table 3 IOP and Medication Outcomes following MMC in Combined Glaucoma and Cataract Procedures (Cohen 1996)**

	MMC (N = 36)		Placebo (N = 35)		Between Treatment P-Value
	Mean (±SD)	(No. of Eyes)	Mean (±SD)	(No. of Eyes)	
Mean IOP and Change from Baseline in mmHg					
Baseline	22.19 (±5.37)	36	20.34 (±5.18)	35	0.144
3 months	14.75 (±4.74)	32	16.83 (±3.73)	30	0.060
Change from BL	-7.47 (±6.41)	32	-2.70 (±4.19)	30	0.001
6 months	14.78 (±3.99)	30	15.55 (±3.82)	28	0.456
Change from BL	-7.05 (±6.02)	30	-3.84 (±4.68)	28	0.028
12 months	14.50 (±4.63)	26	17.15 (±5.21)	26	0.058
Change from BL	-7.65	26	-2.62 (±4.42)	26	0.001
Mean Number of Ocular Hypotensive Medications					
Baseline	2.03 (±1.00)	36	2.46 (±0.85)	35	0.056
3 months	0.38 (±0.61)	32	1.10 (±1.09)	30	0.002
Change from BL	-1.66 (±0.90)	32	-1.27 (±0.78)	30	0.076
6 months	0.50 (±0.82)	30	1.21 (±0.99)	28	0.004
Change from BL	-1.50 (±1.01)	30	-1.18 (±0.86)	28	0.199
12 months	0.58 (±0.86)	26	1.38 (±1.33)	26	0.012
Change from BL	-1.42 (±1.21)	26	-0.96 (± 1.00)	26	0.139

<sup>a</sup> BL = Baseline; IOP = Intraocular pressure; MMC = Mitomycin; SD = Standard deviation.

*Costa VP, Comegno PE, Vasconcelos JP, Malta RF, Jose NK. Low-dose mitomycin C trabeculectomy in patients with advanced glaucoma. J Glaucoma. 1996 Jun;5(3): 193-9.*

This prospective, randomized, double-masked study examined the efficacy and safety of intraoperative mitomycin (0.2mg/mL/3min) in primary trabeculectomy. Twenty-eight eyes of 28 patients with advanced primary open-angle glaucoma undergoing trabeculectomy were randomly assigned to either 0.2mg/mL mitomycin or a saline solution for 3 minutes.

The mean IOP was significantly lower in the mitomycin treated group at the following time points: first postoperative day (p=0.021), 6-month interval (p=0.001), and at the final visit (p=0.002). It appears no correction was made for multiple endpoints.

Mean IOP at **Month 6** was roughly 12 mmHg for mitomycin-treated subjects and 17 mmHg for placebo. **Mean IOP at last follow-up** (ranging from Month 7-24) was roughly 13 mmHg for mitomycin-treated subjects and 18 mmHg for placebo.

The percentage of eyes classified as complete successes was significantly higher in the mitomycin group when compared to the placebo group (p=0.022), and the incidence of failures

was significantly higher in the placebo group when compared to the control group (p=0.007). It appears no correction was made for multiple endpoints.

Early postoperative complications associated with excessive filtration (e.g. shallow AC and choroidal detachment) were more frequent in the mitomycin group. Three of the 14 mitomycin treated subjects and two of the 14 control eyes showed significant visual loss at the last follow-up. Significant visual loss was not defined. The authors state that “lens opacification was the only cause for visual acuity loss in all patients.”

**Table 4 Success Rates and IOP after Low Dose trabeculectomy with MMC (Costa 1996)**

Outcomes	MMC (n = 14)	Placebo (n = 14)	P-value <sup>a</sup>
No. (%) Patients with Success			
Complete (IOP ≤15 mmHg without meds)	10 (71.4%)	3 (21.4%)	0.022 <sup>b</sup>
Qualified (IOP ≤15 mmHg with meds)	2 (14.3%)	1 (7.1%)	1.000
Total no. (%) patients	12 (85.7%)	4 (28.5%)	0.007 <sup>b</sup>
Failure (IOP >15 mmHg with meds)	2 (14.3%)	10 (71.4%)	0.007 <sup>b</sup>
Mean (±SD) IOP in mmHg at			
1 Day (n = 28)	5.30 (±3.92)	10.71 (±5.73)	0.021 <sup>b</sup>
1 Week (n = 28)	6.57 (±2.56)	9.14 (±5.30)	0.215
1 Month (n = 28)	12.57 (±3.00)	14.21 (±4.82)	0.203
3 Months (n = 28)	13.14 (±5.68)	15.76 (±5.18)	0.116
6 Months (n = 28)	12.07 (±3.56)	17.28 (±3.36)	0.001 <sup>b</sup>
Last follow-up (n = 28) (range: 7–24 months)	12.78 (±3.90)	18.35 (±4.53)	0.002 <sup>b</sup>
Mean (±SD) number of antiglaucoma medications at last follow-up	0.35 (±0.84)	1.57 (±1.08)	0.002

Meds = Antiglaucoma medications

<sup>a</sup> Student *t* test.

<sup>b</sup> Statistically significant (p<0.05) by Student's *t* test.

*Robin AL, Ramakrishnan R, Krishnadas R, Smith SD, Katz JD, Selvaraj S, Skuta GL, Bhatnagar R. A long-term dose-response study of mitomycin in glaucoma filtration surgery. Arch Ophthalmol. 1997 Aug;115(8):969-74.*

This prospective, double-masked, placebo-controlled, 1-year study was designed to evaluate the dose-response relationship between mitomycin concentration/duration of exposure and the change in IOP and incidence of complications in patients undergoing trabeculectomy.

Per the authors, all three mitomycin-treated groups showed a statistically significant difference in IOP compared with placebo at **Month 12** (p ≤ 0.001). Mean IOP data for the four groups were not provided. Unadjusted data is not presented. Per the authors, the estimated between group difference in IOP between placebo and Group 2 was 2.0 mmHg. The estimated between group difference in IOP between placebo and Group 3 and Group 4 was 3.0 mmHg.

COPYRIGHT MATERIAL

There was no statistically significant difference between mitomycin-treated groups (varying concentration and duration of exposure) at **Month 12**.

**Table 5** Estimated Difference Between MMC-Treated Groups:  
Dose-Response Study of MMC in Glaucoma Filtration Surgery  
(Robin, 1997)

Group (No Patients/No. Eyes)	Estimated Difference from Placebo (mmHg)	95% CI	P-value
2 (75/78) <sup>a</sup>	2.0	0.8, 3.3	0.001
3 (75/77) <sup>b</sup>	3.0	1.8, 4.3	<0.001
4 (75/74) <sup>c</sup>	2.9	1.6, 4.2	<0.001

CI = Confidence interval.

<sup>a</sup> Group 2 = 0.2mg/mL/2min.

<sup>b</sup> Group 3 = 0.2mg/mL/4min.

<sup>c</sup> Group 4 = 0.4mg/mL/2min.

### Efficacy Summary Statement

There is adequate support from the literature to support efficacy for Mitosol (mitomycin for solution) in the treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery

In the four placebo-controlled studies (Carlson, Cohen, Costa, and Robin), the mean IOP in the mitomycin-treated groups as compared with placebo-treated groups was lower by approximately 3 mmHg.

- In Carlson et al, 1997, the difference in mean IOP at Month 12 was not statistically significant, although mitomycin-treated subjects had numerically lower IOPs (roughly 13 mm Hg versus 16 mmHg).
- In Cohen et al, 1996, mitomycin-treated subjects had lower mean IOPs (roughly 15 mm Hg versus 17 mmHg,  $p = 0.058$ ).
- In Costa et al, 1996, the mean IOP was significantly lower in the mitomycin treated group at the following time points: first postoperative day ( $p=0.021$ ), 6-month interval ( $p=0.001$ ), and at the final visit ( $p=0.002$ ). It appears no correction was made for multiple endpoints.

Mean IOP at Month 6 was roughly 12 mmHg for mitomycin-treated subjects and 17 mmHg for placebo. Mean IOP at last follow-up (ranging from Month 7-24) was roughly 13 mmHg for mitomycin-treated subjects and 18 mmHg for placebo.

- In Robin et al, 1997, all three mitomycin-treated groups showed a statistically significant difference in IOP compared with placebo at Month 12 ( $p \leq 0.001$ ). Mean IOP data for the four groups were not provided. The estimated between group difference in IOP between placebo and Group 2 was 2.0 mmHg. The estimated between group difference in IOP between placebo and Group 3 and Group 4 was 3.0 mmHg.

In the three surgery plus mitomycin versus surgery-alone controlled studies (Andreanos, Martini, and Rasheed), the difference in mean IOP was lower by approximately 5 mmHg.

- In Andreanos et al, 1997, the mean ( $\pm$ SD) postoperative IOP was 12.5 ( $\pm$ 3.2) mmHg in the mitomycin group and 19.6 ( $\pm$ 6.1) mmHg in the control group at Month 18; this between group difference was statistically significant:  $p < 0.001$ .
- In Martini et al, 18997, the difference in mean IOP at Month 12 was statistically significant; mitomycin-treated subjects had lower IOPs (roughly 11 mm Hg versus 16 mmHg).
- In Rasheed et al, 1999, the mean postoperative IOP at Month 18 (average IOP recorded during last six months of follow-up) is lower for mitomycin treated subjects (roughly 10 mmHg) versus non-mitomycin treated subjects (roughly 16 mmHg). It is not clear that this difference is statistically significant.

In the double-masked active-controlled study (Wudunn 2002), the success rate of the mitomycin-treated group was similar to that of the 5-FU-treated group (**note:** F-5U is not approved for this indication).

## 8. Safety

From the Medical Officer Review:

This is a 505(b)(2) application primarily based on literature.

The results were tabulated separately by study design to facilitate review for the literature safety report: 23 controlled trials, 32 observational studies, 9 case series, and 65 case reports. The 23 controlled trials were conducted in 1,588 eyes, 1,085 of which were treated with mitomycin. See Appendices, Section 9.1 of this review for a reference listing of the 23 trials.

All 23 controlled trials included at least 1 arm where mitomycin was topically applied to the exposed site of a filtering bleb, as adjunct therapy during trabeculectomy. Five were conducted in the United States, 10 in Europe (Croatia, Greece, Italy, the Netherlands, and Poland), 6 in Asia (India and Japan), and 2 in Africa (Congo and Ghana). Sixteen trials used randomized controlled designs, 1 used a randomized controlled trial with case control, 4 used randomized crossover designs, 1 used a sequential crossover design, and 1 used a prospective non-comparative, nonrandomized, unmasked design. Among the controlled trials, doses of mitomycin ranged from 0.04 mg/mL to 0.5 mg/mL, and application times ranged from 0.5–5 minutes.

**Summary Table: Overview of Adverse Events Reported in Controlled Clinical Trials**

Adverse Event	Frequency Range	Locations
<b>Hypotony</b> Hypotony	1.5%-52%	US, US, US, US; Asia (India), EU (Greece), Asia (Japan), Asia (Japan), Asia (Japan), Africa (Congo-Kinshasa), EU (Italy), EU (Italy), Africa (Ghana), EU (Poland)
<b>Hypotony Maculopathy</b> Hypotony maculopathy	0%-18%	US; EU (Greece), Asia (Japan), Asia (Japan), EU (Italy), EU (Poland), EU (Poland), Asia (Japan)
<b>Choroidal Events</b> Choroidal detachment	0%-36%	US, US, US; EU (Greece), Asia (Japan), EU (Italy), EU (Netherlands), Asia (Japan), Asia (Japan), EU (Italy), EU (Italy), EU (Poland), EU (Poland), Asia (Japan)
Choroidal effusion	10%	EU (Italy)

<b>Adverse Event</b>	<b>Frequency Range</b>	<b>Locations</b>
Suprachoroidal hemorrhage	2.5%	US
<b>Retinal Detachment</b>		
Secondary retinal detachments	3%	EU (Poland)
<b>Other Related Events</b>		
Shallow anterior chamber	0%-46%	Asia (India), EU (Greece), Asia (Japan), EU (Netherlands), Asia (Japan), Asia (Japan), Asia (Japan), EU (Croatia), EU (Italy), Africa (Congo-Kinshasa), EU (Italy), Africa (Ghana), EU (Poland), Asia (Japan)
Hypotony-related complications requiring surgery	23.3%	US
<b>Endophthalmitis</b>		
Endophthalmitis	0%-3%	US, US; EU (Italy), EU (Italy), Africa (Ghana), EU (Poland)
<b>Bleb Events</b>		
Bleb/wound leak	0%-27%	US, US, US; Asia (Japan), EU (Netherlands), Asia (Japan), EU (Croatia), EU (Italy), EU (Italy), Africa (Ghana), EU (Poland), EU (Poland), Asia (Japan)
Encapsulated bleb	0%-28.6%	EU (Greece), EU (Italy), Africa (Ghana), EU (Poland), EU (Poland)
Blebitis/bleb infection	0%-1.5%	US; EU (Italy)
Cystic bleb/bleb fibrosis	3.3%-13%	EU (Croatia), EU (Italy)
Failed bleb	8%-10%	Asia (Japan), Asia (Japan)
Thin, avascular bleb	12%	EU (Poland)
<b>Vascular Events</b>		
Hyphema	0%-46%	US, US; Asia (India), EU (Greece), Asia (Japan), EU (Italy), EU (Netherlands), Asia (Japan), Asia (Japan), EU (Croatia), EU (Italy), EU (Italy), EU (Poland)
Anterior chamber inflammation/fibrin reaction	0%-11%	Asia (India), Asia (Japan), EU (Italy), EU (Italy)
Anterior chamber hemorrhage	27%	EU (Italy), EU (Poland)
Hemiretinal vein occlusion	3.3%	US
Vitreous loss	0%	Asia (Japan)
<b>Lenticular Events</b>		
Cataract progression/development	6%-40.3%	Asia (India), EU (Greece), Asia (Japan), Asia (Japan), EU (Italy), EU (Italy), EU (Italy), Africa (Ghana), EU (Poland), EU (Poland), Asia (Japan)
Capsule opacification	50%	EU (Croatia)
Asymmetric cataract evolution in fellow eye	7.1%	EU (Italy)
Rupture of posterior lens capsule	0%	Asia (Japan)

The adverse events reported are consistent with those described in the 22 prospective clinical trials described in Section 6.1.1.A of the Medical Officer's Review with the exception of corneal endothelial defects.

Hypotony, choroidal detachment, shallow anterior chamber, hyphema, corneal endothelial defects, and cataract progression are seen with a lower frequency range of 0-3% and an upper frequency range of approximately 30-50%. All of these are known adverse events seen with the trabeculectomy procedure alone.

There is great variation in the adverse event rates reported for these more serious adverse events; these rates are presumably dependant on the skill of the surgeon and the specific surgical population

#### **POSTMARKETING EXPERIENCE**

This product is not approved or marketed in any country.

### **Safety Summary Statement**

There is adequate support from the literature to support the safety for Mitosol (mitomycin for solution) in treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery provided the mitomycin can be adequately manufactured, stored and labeled for reconstitution and administration.

The most frequent adverse reactions to Mitosol occur locally and are often related to an extension of the pharmacological activity of the drug and/or markedly educed intraocular pressure from trabeculectomy. These include hypotony, choroidal detachment, shallow anterior chamber, hyphema, corneal endothelial defects, and cataract progression.

## **9. Advisory Committee Meeting**

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

## **10. Pediatrics**

The Pediatric Research Equity Act of 2003 (PREA), and 21 CFR 314.55 (a) require that sponsors submitting a new application or supplement under section 505 of the Federal Food Drug and Cosmetic Act that involves a new ingredient, new indication, new dosage form, new dosing regimen or new route of administration, submit an assessment of the safety and efficacy of the drug or biological product for the claimed indication in all relevant pediatric subpopulations.

Mobius' Mitosol (mitomycin for solution) has received Orphan Designation; a pediatric assessment is therefore not required and has not been provided in this application.

Safety and effectiveness of Mitosol (mitomycin for injection) in pediatric patients has not been established.

## 11. Other Relevant Regulatory Issues

### DSI

This is a 505(b)(2) application primarily based on literature. The studies were conducted 10-15 years ago and demonstrate consistency in replication. After discussion with the Division of Scientific Investigations (DSI), a DSI audit was considered a good use of resources.

### FINANCIAL DISCLOSURE

This is a 505(b)(2) application primarily based on literature.

### DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) initially reviewed the name Optomycin, (b) (4) alternative names provided by the applicant ( (u) (4) and (u) (4) ). DMEPA notified Mobius that they considered the proposed name Optomycin unacceptable, and Mobius withdrew the name.

Mobius submitted a new proprietary name, (b) (4) DMEPA found this name unacceptable (b) (4)

Mobius withdrew the name, (b) (4) and submitted a new proprietary name, Mitosol.

In a review dated 12/6/10 there were no concerns identified by DMEPA, and the name was found acceptable. DMEPA conditionally approved the name, Mitosol, in a letter dated 12/9/2010.

### DDMAC

The Division of Drug Marketing, Advertising, and Communications (DDMAC) did not review the submitted labeling this review cycle.

### BIOSTATISTICS

The Biostatistics reviewer evaluated the 22 prospective studies submitted by the applicant to examine the efficacy of mitomycin.

The 22 studies had:

- varying endpoints (Mean change in IOP in mmHg, overall lower IOP, % of patients with IOP between 5 mmHg and 15 mmHg, Successful IOP reduction, etc.) and different time of evaluation (6 months to 30 months), and differences in patient characteristics
- dosing is not unique (0.1 mg/mL to 0.5mg/mL mitomycin)
- different dose groups (two to four drug groups)
- varying follow-up periods.

Based on the totality of evidence from this 505b (2) submission, the reviewer concluded there is substantial evidence of the efficacy of mitomycin 0.2 mg in glaucoma filtration surgery.

### **CDRH**

A consult from the Center for Devices and Radiological Health (CDRH), regarding Mobius Therapeutics, LLC drug product, was completed on November 19, 2010. CDRH had concerns about potential performance issues related to elements of the mitomycin kit components and labeling. Their problem list/information request was transmitted to Mobius. A teleconference was held between the review division, CDRH, and Mobius on 12/8/10.

CDRH recommended additional labeling comprehension work for the mitomycin product.

## **12. Labeling**

NDA 22-572 Mitosol (mitomycin for solution) is not recommended for approval for the treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery.

The labeling of the product as submitted by the applicant **is not adequate** to ensure safe and reliable reconstitution, transportation, and application of the product for the intended indication.

At the Agency's request, a labeling comprehension study was performed on September 21, 2010, using the Mobius-proposed labeling and packaging. The study was performed at [REDACTED] (b) (4) in a "mock operating room" setting.

Section 7.7. of the Medical Officer's Review contains a detailed description of issues related to this failed Labeling Comprehension Study. Respondents did not reliably identify sterile and non-sterile components of the kit; individual tasks involved in the reconstitution and preparation of the mitomycin were not reliably performed. The Agency requested a second labeling comprehension study be performed by the appropriate operating room personnel after revision to the proposed packaging and labeling of the mitomycin kit is made. As of the date of this review, the report from that second labeling comprehension study is pending.

A formal labeling review is deferred until additional data is submitted to support the application for Mitosol.

### **13. Recommendations/Risk Benefit Assessment**

#### **RECOMMENDED REGULATORY ACTION:**

NDA 22-572 Mitosol (mitomycin for solution) is not recommended for approval for the treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery.

#### **Clinical Issues:**

The labeling of the product as submitted by the applicant **is not adequate** to ensure safe and reliable reconstitution, transportation, and application of the product for the intended indication.

Revised labeling should be submitted after adequate directions have been developed.

#### **Chemistry/Manufacturing Issues:**

The applicant has not demonstrated that the proposed drug product is of comparable identity, strength, quality, purity and potency to the commercially available, approved drug products upon which the clinical studies are based (e.g., the Mitomycin for Injection RLD described in ANDA 64-144 which is cross-referenced in the application).

There is insufficient information to allow establishment of a suitable drug product specification (e.g., acceptance criteria for impurities) and determination of an appropriate expiration dating period. The drug product must be sterile and comply with 21 CFR 200.50.

Manufacturing facilities for the drug product are not in compliance with current good manufacturing practice.

#### **RISK BENEFIT ASSESSMENT:**

There is adequate support from the literature to support efficacy for Mitosol (mitomycin for solution) in the treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery, if the drug product is adequately manufactured and stored. In the four placebo-controlled studies (Carlson, Cohen, Costa, and Robin), the mean IOP in the mitomycin-treated groups as compared with placebo-treated groups was lower. It was statistically significant in favor of the mitomycin groups from 6 to 24 months in the majority of these trials (Cohen, Costa, and Robin).

There is adequate support from the literature to support the safety for Mitosol (mitomycin for solution) in treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery provided the mitomycin can be adequately manufactured, stored and labeled for reconstitution and administration. The most frequent adverse reactions to Mitosol occur locally and are often related to an extension of the pharmacological activity of the drug and/or markedly reduced

intraocular pressure from trabeculectomy. These include hypotony, choroidal detachment, shallow anterior chamber, hyphema, corneal endothelial defects, and cataract progression.

As previously discussed, the labeling of the product as submitted by the applicant **is not adequate** to ensure safe and reliable reconstitution, transportation, and application of the product for the intended indication.

**RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:**

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

WILLIAM M BOYD  
12/21/2010

WILEY A CHAMBERS  
12/22/2010

## Division Director Summary Review for NDA 22-572

<b>Date</b>	December 21, 2010
<b>From</b>	Wiley A. Chambers, M.D.
<b>NDA #</b>	22-572
<b>Applicant</b>	Mobius Therapeutics, LLC
<b>Date of Submission</b>	June 21, 2010
<b>Type of Application</b>	505(b)(2)
<b>Name</b>	Mitosol (mitomycin for solution)
<b>Dosage forms / Strength</b>	Topical solution, 0.2 mg/mL
<b>Proposed Indication(s)</b>	Treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery
<b>Action:</b>	Complete Response

### 1. Introduction

Mitomycin C (MMC) is an antibiotic derived from *Streptomyces caespitosus* that has antimetabolic properties. Mitomycin has been shown to inhibit fibroblast proliferation by preventing DNA synthesis, thereby potentially reducing the amount of scar tissue formed after trabeculectomy.

### 2. Background

There are no approved drug products for the proposed indication - treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery.

This is a 505(b)(2) application primarily based on literature. Reference literature reports, surveys, and articles cited in this review are representative of the published literature.

The Form 356h submitted by Mobius Therapeutics, LLC, lists Mutamycin (mitomycin for injection), ANDA 62-336 (Bristol Myers Squibb) as the reference listed drug (RLD) product.

A submission dated September 21, 2006, contained a request for a pre-NDA meeting to discuss the suitability of the current literature to support submission of a 505(b)(2) New Drug Application. A Pre-Investigational New Drug Application (PIND) file for this drug product was opened on October 5, 2006, identified by PIND number 75,734. A Pre-IND meeting was held on December 6, 2006. A second Pre-IND meeting was held on July 20, 2009.

An orphan designation for mitomycin for solution for the treatment of treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery was granted on January 8, 2008.

### 3. CMC

The proposed packaging for Mobius product consists of a "kit" which includes a vial of mitomycin for solution (containing a sterile, lyophilized mixture of 0.2 mg mitomycin and 0.4 mg mannitol) and associated components for the reconstitution of mitomycin and for the delivery of drug to the eye. Essential components of the packaging/kit include a prefilled syringe containing (b) (4) sterile water for injection for reconstitution of mitomycin and pre-cut surgical

sponges for administration of the resulting solution to the eye. The sponges are held in a plastic tray which also serves as a container for the saturation with the drug solution. Other components are provided for handling and disposal of the cytotoxic agent. Components are packaged in (b) (4) trays with (b) (4) lidding.

**Drug Product Components/Composition**

Ingredients	Compendial Reference	Qty. (mg) / mL	Batch Quantity
Mitomycin	USP/Ph. Eur.	0.2	(b) (4)
Mannitol	USNF/Ph. Eur.	(b) (4) <sup>4</sup>	(b) (4)
Water for Injection	USP/Ph. Eur.	1 mL	(b) (4)

**Specification(s)**

The proposed specification for Mitomycin for Solution, 0.2 mg/Vial is presented in the table below. To facilitate comparison, the CMC reviewer has included the current specifications for Mitomycin for Injection USP and for the Intas and Bedford/BVL Mitomycin for Injection products.

**Mitomycin for Ophthalmic Solution (MIM3325-1 and MIM3325-S1)**

Attribute	Analytical Procedure	Proposed Acceptance Criteria	ANDA 64144 Intas Mitomycin for Injection*	ANDA 64117 BenVenue Mitomycin for Injection	Mitomycin for Injection USP
Appearance	In house	Blue-violet cake or powder, free from visible evidence of contamination in amber vial.	Same	Grey cake or powder free from visible signs of contamination	
Constituted Solution	USP<1>	a) Sample powder should dissolve completely leaving no visible residue. b) Sample solution is not significantly less clear than an equal volume of diluent (water for injection) in a similar vessel and examined similarly. c) Sample solution should be essentially free from particles of foreign matter than could be observed on visual inspection.	Same	Same	Meets requirements for Constituted Solutions under Injections <1>.
Identification	USP	The Rf value of the principal spot obtained from the sample solution should correspond to that of the Mitomycin standard solution similarly prepared.	By TLC	By TLC	By TLC
Reconstitution Time	In house	(b) (4)			
pH	USP<791>				
Particulate Matter	USP<789>				
Bacterial Endotoxin	USP<85>				

Sterility	USP<71>
Water	USP<921>
Uniformity of dosage unit (By content uniformity)	USP<905>
Related substances	In house
Assay	USP<621>
Residual Solvents	

(b) (4)

(b) (4)

The CMC reviewer does not recommend approval and has cited deficiencies:

- 1) The applicant has not demonstrated that the proposed drug product is of comparable identity, strength, quality, purity and potency to the commercially available, approved drug products upon which the clinical studies are based (e.g., the Mitomycin for Injection RLD described in ANDA 64-144 which is cross-referenced in the application).
- 2) There is insufficient information to allow establishment of a suitable drug product specification (e.g., acceptance criteria for impurities and pH).
- 3) There is insufficient information to determine the appropriate expiration dating period.

During a recent preapproval inspection conducted at Synergetics, Inc. (FEI 1000119053), significant deviations from Current Good Manufacturing Practices (cGMP) were observed and disclosed to the firm's management. The Division of Manufacturing and Product Quality has reviewed and concurs with the significance of these deviations. All significant deviations on the form FDA 483 (issued and signed 12/10/2010) and form FDA 463a (signed on 12/10/2010) should be corrected by the firm before this NDA is approved. Examples of the significant cGMP

deviations identified during this preapproval inspection include a Lack of acceptance criteria for the incoming materials and a lack of complete manufacturing and control instructions.

#### 4. Nonclinical Pharmacology/Toxicology

No original studies were performed or submitted. This application is made under 505(b)(2), and published literature references are provided. No genetic toxicity studies were provided. Mitomycin is a known DNA alkylating agent so may be considered positive for genetic toxicity. No carcinogenicity data were provided. Since the proposed clinical use is for a single topical application, no carcinogenicity studies to support this application are necessary. The approved label for the reference listed drug indicates that systemic mitomycin is carcinogenic.

#### 5. Clinical Pharmacology/Biopharmaceutics

As described in this 505(b)(2) application, the pharmacokinetic characteristics of mitomycin have been previously well-described for the IV formulation with the same active and inactive ingredients. The applicant has submitted a request for waiver of the requirement for submission of evidence of in vivo bioavailability for the proposed mitomycin kit based on the rationale that the bioavailability to the RLD is self-evident because this 505(b)(2) NDA is based upon the reference listed drug Mutamycin (Mitomycin for Injection USP; Bristol Myers Squibb; NDA 062336).

#### 6. Sterility Assurance

This product is a kit which consists of (b) (4)

[Redacted]

Mitomycin is formulated in a facility designed for the production of cytotoxic drugs. Bioburden is sampled (b) (4)

[Redacted]

The Product Quality Microbiology Reviewer has recommended that the entire kit be sterile. (b) (4)

[Redacted]

(b) (4) This recommendation is consistent with 21 CFR 200.50 which requires ophthalmic products to be sterile.

## 7. Clinical/Statistical - Efficacy

This is a 505(b)(2) application primarily based on literature. The application includes efficacy data gathered from 22 published papers describing prospective clinical studies with mitomycin as adjuvant therapy to glaucoma filtration surgery, primarily trabeculectomy. The Medical Officer's Review contains a detailed description of the 22 literature articles.

There is adequate support from the literature to support efficacy for Mitosol (mitomycin for solution) in the treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery. In the most representative four placebo-controlled studies (Carlson, Cohen, Costa, and Robin), the mean IOP in the mitomycin-treated groups as compared with placebo-treated groups was lower by approximately 3 mmHg.

- In Carlson et al, 1997, the difference in mean IOP at Month 12 was not statistically significant, although mitomycin-treated subjects had numerically lower IOPs (roughly 13 mm Hg versus 16 mmHg).
- In Cohen et al, 1996, mitomycin-treated subjects had lower mean IOPs (roughly 15 mm Hg versus 17 mmHg,  $p = 0.058$ ).
- In Costa et al, 1996, the mean IOP was significantly lower in the mitomycin treated group at the following time points: first postoperative day ( $p=0.021$ ), 6-month interval ( $p=0.001$ ), and at the final visit ( $p=0.002$ ) (without correction for multiplicity).

Mean IOP at Month 6 was roughly 12 mmHg for mitomycin-treated subjects and 17 mmHg for placebo. Mean IOP at last follow-up (ranging from Month 7-24) was roughly 13 mmHg for mitomycin-treated subjects and 18 mmHg for placebo.

- In Robin et al, 1997, all three mitomycin-treated groups showed a statistically significant difference in IOP compared with placebo at Month 12 ( $p \leq 0.001$ ). Mean IOP data for the four groups were not provided. The estimated between group difference in IOP between placebo and Group 2 was 2.0 mmHg. The estimated between group difference in IOP between placebo and Group 3 and Group 4 was 3.0 mmHg.

In the three surgery plus mitomycin versus surgery-alone controlled studies (Andreanos, Martini, and Rasheed), the difference in mean IOP was lower by approximately 5 mmHg.

- In Andreanos et al, 1997, the mean ( $\pm$ SD) postoperative IOP was 12.5 ( $\pm$ 3.2) mmHg in the mitomycin group and 19.6 ( $\pm$ 6.1) mmHg in the control group at Month 18; this between group difference was statistically significant:  $p < 0.001$ .

- In Martini et al, 18997, the difference in mean IOP at Month 12 was statistically significant; mitomycin-treated subjects had lower IOPs (roughly 11 mm Hg versus 16 mmHg).
- In Rasheed et al, 1999, the mean postoperative IOP at Month 18 (average IOP recorded during last six months of follow-up) is lower for mitomycin treated subjects (roughly 10 mmHg) versus non-mitomycin treated subjects (roughly 16 mmHg). It is not clear that this difference is statistically significant.

## 8. Safety

The results were tabulated separately by study design to facilitate review for the literature safety report: 23 controlled trials, 32 observational studies, 9 case series, and 65 case reports. The 23 controlled trials were conducted in 1,588 eyes, 1,085 of which were treated with mitomycin.

All 23 controlled trials included at least 1 arm where mitomycin was topically applied to the exposed site of a filtering bleb, as adjunct therapy during trabeculectomy. Five were conducted in the United States, 10 in Europe (Croatia, Greece, Italy, the Netherlands, and Poland), 6 in Asia (India and Japan), and 2 in Africa (Congo and Ghana). Sixteen trials used randomized controlled designs, 1 used a randomized controlled trial with case control, 4 used randomized crossover designs, 1 used a sequential crossover design, and 1 used a prospective non-comparative, nonrandomized, unmasked design. Among the controlled trials, doses of mitomycin ranged from 0.04 mg/mL to 0.5 mg/mL, and application times ranged from 0.5–5 minutes. Hypotony, choroidal detachment, shallow anterior chamber, hyphema, corneal endothelial defects, and cataract progression are seen with a lower frequency range of 0-3% and an upper frequency range of approximately 30-50%. All of these are known adverse events seen with the trabeculectomy procedure alone. There is great variation in the adverse event rates reported for these more serious adverse events; these rates are presumably dependant on the skill of the surgeon and the specific surgical population.

In Summary, there is adequate support from the literature to support the safety for Mitosol (mitomycin for solution) in treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery provided the mitomycin can be adequately manufactured, stored and labeled for reconstitution and administration. The most frequent adverse reactions to Mitosol occur locally and are often related to an extension of the pharmacological activity of the drug and/or markedly educed intraocular pressure from trabeculectomy. These include hypotony, choroidal detachment, shallow anterior chamber, hyphema, corneal endothelial defects, and cataract progression.

## 9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

## 10. Pediatrics

The Pediatric Research Equity Act of 2003 (PREA), and 21 CFR 314.55 (a) require that sponsors submitting a new application or supplement under section 505 of the Federal Food Drug and Cosmetic Act that involves a new ingredient, new indication, new dosage form, new dosing regimen or new route of administration, submit an assessment of the safety and efficacy of the drug or biological product for the claimed indication in all relevant pediatric subpopulations.

Mobius' Mitosol (mitomycin for solution) has received Orphan Designation; a pediatric assessment is therefore not required and has not been provided in this application. Safety and effectiveness of Mitosol (mitomycin for injection) in pediatric patients has not been established.

## 11. Other Relevant Regulatory Issues

### DSI

This is a 505(b)(2) application primarily based on literature. The studies were conducted 10-15 years ago and demonstrate consistency in replication. After discussion with the Division of Scientific Investigations (DSI), a DSI audit was considered a good use of resources.

### FINANCIAL DISCLOSURE

This is a 505(b)(2) application primarily based on 15 year old literature.

### DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) initially reviewed the name Optomycin, (b) (4) alternative names provided by the applicant ( (u) (4) and (u) (4) ). DMEPA notified Mobius that they considered the proposed name Optomycin unacceptable, and Mobius withdrew the name. Mobius submitted a new proprietary name, (b) (4) DMEPA found this name unacceptable (b) (4) Mobius withdrew the name, (b) (4) and submitted a new proprietary name, Mitosol.

In a review dated 12/6/10 there were no concerns identified by DMEPA, and the name was found acceptable. DMEPA conditionally approved the name, Mitosol, in a letter dated 12/9/2010.

### DDMAC

The Division of Drug Marketing, Advertising, and Communications (DDMAC) did not review the submitted labeling this review cycle.

### BIOSTATISTICS

The Biostatistics reviewer evaluated the 22 prospective studies submitted by the applicant to examine the efficacy of mitomycin. As noted in the Clinical Review, the 22 studies had varying endpoints (Mean change in IOP in mmHg, overall lower IOP, % of patients with IOP between 5

mmHg and 15 mmHg, Successful IOP reduction, etc.) and different time of evaluation (6 months to 30 months), and differences in patient characteristics. Based on the totality of evidence from this 505b (2) submission, the reviewer concluded there is substantial evidence of the efficacy of mitomycin 0.2 mg in glaucoma filtration surgery.

### **CDRH**

A consult from the Center for Devices and Radiological Health (CDRH), regarding Mobius Therapeutics, LLC drug product, was completed on November 19, 2010. CDRH had concerns about potential performance issues related to elements of the mitomycin kit components and labeling. Their problem list/information request was transmitted to Mobius. A teleconference was held between the review division, CDRH, and Mobius on 12/8/10. CDRH recommended additional labeling comprehension work for the mitomycin product.

### **12. Labeling**

The labeling of the product as submitted by the applicant **is not adequate** to ensure safe and reliable reconstitution, transportation, and application of the product for the intended indication.

At the Agency's request, a labeling comprehension study was performed on September 21, 2010, using the Mobius-proposed labeling and packaging. The study was performed at [REDACTED]<sup>(b) (4)</sup> in a "mock operating room" setting. The Medical Officer's Review contains a detailed description of issues related to this failed Labeling Comprehension Study. Respondents did not reliably identify sterile and non-sterile components of the kit; individual tasks involved in the reconstitution and preparation of the mitomycin were not reliably performed. The Agency requested a second labeling comprehension study be performed by the appropriate operating room personnel after revision to the proposed packaging and labeling of the mitomycin kit is made. As of the date of this review, the report from that second labeling comprehension study is pending.

A formal labeling review is deferred until additional data is submitted to support the application for Mitosol.

### **13. Regulatory Action**

NDA 22-572 Mitosol (mitomycin for solution) will not be approved based on the information submitted to date for the treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery. Deficiencies include:

1. There is insufficient information about the drug product to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling. The labeling of the product as submitted is not adequate to ensure safe and reliable reconstitution, transportation, and application of the product for the intended indication.

2. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance and drug product are inadequate to preserve its identity, strength, quality, purity, and stability. Specifically,
  - a. There is not a demonstration that the proposed drug product, Mitosol (mitomycin for solution), 0.2 mg/vial, is of comparable identity, strength, quality, purity and potency to the commercially available, currently approved drug product upon which the clinical studies are based (e.g., cross-referenced mitomycin for injection RLD ANDA 64-144).
  - b. There is insufficient justification of the drug product specification (e.g., acceptance criteria for impurities and pH).
  - c. There is insufficient justification of the expiration dating period.
  - d. The drug product as proposed does not comply with 21 CFR 200.50. The containers of ophthalmic preparations must be sterile at the time of filling and closing, and the container or individual carton must be so sealed that the contents cannot be used without destroying the seal. Eye cups, eye droppers, and other dispensers intended for ophthalmic use should be sterile, and may be regarded as falling below their professed standard of purity or quality if they are not sterile. These articles, which are regulated as drugs, if packaged with the drugs with which they are to be used, should be packaged so as to maintain sterility until the package is opened.
  
3. The methods used in and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug product do not comply with the current good manufacturing practice (cGMP) regulations in parts 210 and 211. Specifically, during a recent preapproval inspection conducted at Synergetics, Inc. (FEI 1000119053), significant deviations from Current Good Manufacturing Practices (cGMP) were observed and disclosed to the firm's management. All facilities and controls will need to comply with the cGMP regulations.

Wiley A. Chambers, MD  
Acting Director  
Division of Anti-Infective and Ophthalmology Products

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

WILEY A CHAMBERS  
12/22/2010