CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation
CLINICAL STUDIES

NDA/Serial Number:	022572/000
Drug Name:	Optomycin™ Kit for Ophthalmic Use (0.2 mg mitomycin per vial)
Indication(s):	Treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery by topical application to the exposed site of a filtering bleb during trabeculectomy surgery.
Applicant:	Mobius Therapeutics LLC
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EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In this NDA 22572 (505b (2) submission), the applicant is seeking approval for Optomycin™ Kit which contains 0.2 mg mitomycin per vial for the treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery by topical application to the exposed site of a filtering bleb during trabeculectomy surgery.

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

1.2 Brief Overview of Clinical Studies

The applicant has provided a summary of clinical efficacy (SCE) which presents efficacy data gathered from 22 published papers describing prospective clinical studies with mitomycin as adjuvant therapy during trabeculectomy surgery. The endpoints of these studies were related to intraocular pressure (IOP). The applicant claims, taken together, these studies fulfill the statutory requirement for substantial evidence of the efficacy of mitomycin in glaucoma filtration surgery.

In addition, the applicant has also submitted the efficacy findings from 14 published papers that were retrospective studies and two major review articles (Wilkins 2006 and Abraham 2006) to support the efficacy of mitomycin in filtration surgery. These 14 retrospective studies with mitomycin and two major review articles are not reviewed by this reviewer.

The 22 prospective studies used to establish the efficacy of mitomycin are grouped (categorized as Group-1 and Group-2 by the applicant) as follows:

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

The applicant reports that the prospective, randomized, controlled, and masked nature of each of the 9 studies in this group allows each study to meet the regulatory definition of an adequate and well controlled study (21 CFR 314.126). The applicant further mentions that these studies met the regulatory requirements for adequate and well controlled studies.

● Four studies were placebo-controlled (Carlson 1995, Cohen 1996, Costa 1996, and Robin 1997). The study conducted by Robin and colleagues was also a dose-comparison study.

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●Three studies compared treatment with mitomycin plus surgery to surgery alone (Andreanos 1997, Martini 1997, and Rasheed 1999), and one study used an active treatment control (Wudunn 2002).

●One study employed a dose-comparison control (Sanders 1998).

A total of 480 eyes were treated with mitomycin, with doses ranging from 0.1 to 0.5 mg/mL and exposure times from 2 to 4 minutes (with duration of follow-up after surgery ranged from 12 to 24 months).

Table 1, Table 2, Table 3 and Table 4 provide brief description of the nine Group-1 studies:

Table 1: Summary of Mitomycin versus Placebo Studies (4 Studies)

Study	Design	Population	No. Patients/ No. Eyes	Doses	Duration of Follow-up
Carlson, 1995	Randomized Placebo-controlled Double-masked	Combined phacoemulsification and trabeculectomy in adults	14/14 15/15	Mitomycin 0.5mg/mL/3.5 min Placebo	6 to 30 months
Cohen, 1996	Randomized Placebo-controlled Double-masked	Combined glaucoma/ cataract surgery in Adults	36/36 35/35	0.5mg/mL/ 2.5 min Salt solution	12 months
Costa, 1996	Randomized Placebo-controlled Double-masked	Adults with Advanced glaucoma	14/14 14/14	0.2mg/mL/3 min Saline	Up to 24 months
Robin 1997	Long-term Dose-response Prospective Placebo-controlled Double-masked	Patients undergoing trabeculectomy	75/71 75/78 75/77 75/74	Placebo 0.2mg/mL/2 min Mitomycin0.2mg/ mL/4 min Mitomycin 0.4mg/mL/2 min	12 months

Data source: Table 1 (Page 14) in Module 2.7 Clinical Summary of the NDA submission.

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Table 2: Summary of Mitomycin versus No Treatment (3 Studies)

Study	Design	Population	No. Patients/No. Eyes	Doses	Duration of Follow-up
Andreanos, 1997	Long-term Dose-response Prospective Placebo-controlled Double-masked	Adults with uncontrolled POAG after previous filtering surgery failure	24 patients 22 patients	2nd trab w/Mitomycin 0.4mg/mL 2nd trab without Mitomycin	18 months
Martini, 1997	Prospective Randomized Controlled Evaluator-masked	Adults	24/30 Mitomycin 24/30 Untreated	0.1mg/mL/3 min	12 months
Rasheed, 1999	Prospective Randomized Single-masked POAG/CACG	Adults	25/25 25/25	0.3-0.4mg/mL/ 4min Trab alone	18 months

Data source: Table 1 (Page 14) in Module 2.7 Clinical Summary of the NDA submission.
Note: POAG = Primary open-angle glaucoma; Trab = Trabeculectomy.

Table 3: Summary of Mitomycin versus 5-Fluorouracil Study

Study	Design	Population	Total # of Patients (103)/ No. of Eyes	Doses	Duration of Follow-up
WuDunn 2002	Prospective Double-masked Randomized	Patients with uncontrolled IOP despite maximally tolerated medical therapy or laser	-/57 -/58	5-FU 50mg/mL/5 min Mitomycin 0.2mg/mL/2 min	12 months

Data source: Table 1 (Page 14) in Module 2.7 Clinical Summary of the NDA submission.
Note: 5-FU = 5-Fluorouracil

Table 4: Summary of Mitomycin Dose Comparison Study

Study	Design	Population	No. Patients/ No. Eyes	Doses	Duration of Follow-up
Sanders 1998	Prospective Randomized POAG/previous surgery	Patients who are at higher risk from previous conjunctival incisional surgery	25/25 25/25	0.2mg/mL/2 min 0.4mg/mL/2 min	12 months

Data source: Table 1(Page 14) in Module 2.7 Clinical Summary of the NDA submission.
Note: POAG = Primary open-angle glaucoma

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

The 13 studies in this group were conducted in a prospective manner. The applicant reports that most studies were randomized and controlled, and all appear to have been well designed and well executed. The applicant termed these 13 studies as prospective studies of uncertain designs. The literature describing these studies does not indicate that masking was used to reduce bias. In this reviewer's opinion, the data from these studies

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provide supporting evidence of the efficacy of mitomycin in glaucoma filtration surgery. The 13 studies are summarized in ***Appendix-3.***

1.3 Statistical Issues and Findings

Statistical Issues:

There are no major statistical issues with this submission.

Findings:

This reviewer looked into 22 prospective studies 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.

Despite these variations of designs and doses, the results were convincing because all the studies showed the advantage of using mitomycin in glaucoma filtration surgery. In the following, we summarize the findings:

Group 1 Studies:

The findings based on 9 group-1 studies are summarized below:

● Out of the four placebo-controlled studies(Carlson, Cohen, Costa, and Robin), in three studies (Cohen, Costa, and Robin), the difference in mean IOP in the mitomycin-treated groups as compared with placebo-treated groups was statistically significant in favor of the mitomycin groups. In Carlson study, there was a numerical advantage of mitomycin treated group over placebo group with respect to mean change in IOP.

● In the three surgery plus mitomycin versus surgery-alone controlled studies (Andreanos, Martini, and Rasheed), the difference in mean IOP was significantly lower and the success rates significantly higher in the mitomycin-treated groups compared with the placebo-treated (no mitomycin) groups.

● In the double-masked active-controlled study (Wudunn 2002), the success rates of mitomycin-treated group were similar to that of the 5-FU-treated group.

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●In the dose-comparison controlled study (Sanders), both doses of mitomycin (0.2 and 0.4 mg/mL/2min) significantly reduced IOP; there were no statistically significant differences in IOP between the 0.2 and 0.4 mg/mL doses of mitomycin. In addition, in Robin's placebo-controlled dose-response study (Group1: placebo; Group 2: mitomycin 0.2mg/mL/2min; Group 3: mitomycin 0.2mg/mL/4min, and Group 4: mitomycin 0.4mg/mL/2 min), statistically significant treatment-related differences in IOP between mitomycin treated groups and placebo groups were seen. However, there were no statistically significant differences in IOP among Group 2, Group 3 and Group 4.

Based on the totality of evidence from Group-1 studies, there is substantial evidence of the efficacy of mitomycin in glaucoma filtration surgery. The proposed dose of mitomycin 0.2 mg/mL lies within the studied dosage range 0.1 to 0.5 mg/mL. Also the proposed application time 2 minutes lies within studied exposure time range 2 to 4 minutes. Thus, the proposed dosage of mitomycin is acceptable for approval.

The individual study results (Group-1 studies) are summarized in Table 5, Table 6, Table 7, and Table 8.

Table 5: Efficacy Results for Mitomycin versus Placebo (4 Studies)

Study	Doses	Major Efficacy Findings
Carlson, 1995	Mitomycin 0.5mg/ mL/3.5min Placebo	At 12 months, mean (±SD) postoperative IOP was 12.6 (±1.0) mmHg in Mitomycin group and 16.2 (±1.5) mmHg in placebo group (p-value: 0.06 by t-test)
Cohen, 1996	0.5mg/mL/ 2.5 min Salt solution	Change from BL in mean IOP at 12 months post surgery: –7.65 mmHg in Mitomycin group and –2.62 mmHg in placebo group (p-value: 0.001)
Costa,1996	0.2mg/mL/3 min Saline	Mean IOP significantly lower in Mitomycin group at Day 1 (p-value=0.021), 6 month (p-value=0.001) and final visit (p-value=0.001).
Robin 1997	Placebo Mitomycin 0.2mg/mL/2 min Mitomycin 0.2mg/mL/4 min Mitomycin 0.4mg/mL/2 min	Significant treatment-related difference in IOP, with decrease in IOP in all three Mitomycin groups.

Data source: Table 1 (Page 14) in Module 2.7 Clinical Summary of the NDA submission.

Table 6: Efficacy Results for Mitomycin versus No Treatment (3 Studies)

Study	Doses	Major Efficacy Findings
Andreanos, 1997	2nd trab w/Mitomycin 0.4mg/mL 2nd trab w/o Mitomycin	Mean (±SD) postoperative IOP was 12.5 (±3.2) mmHg in Mitomycin group and 19.6 (±6.1) in non-mitomycin group (p-value<0.001). Good IOP control (≤20 mmHg) was 83.3% in Mitomycin group and 63.6% in non-mitomycin group
Martini, 1997	0.1mg/mL/3 min	Mean (±SD) IOP at 1 year: Mitomycin: 11.1 (±3.1) mmHg; control: 16.4 (±6.1) mmHg (p-value=0.0001). .
Rasheed, 1999	0.3-0.4mg/mL/ 4min Trab alone	IOP-VALUE<20 mmHg: Mitomycin 84%; Control 12%

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Data source: Table 1 (Page 14) in Module 2.7 Clinical Summary of the NDA submission.
Note: Trab = Trabeculectomy.

Table 7: Efficacy Results for Mitomycin versus 5-Fluorouracil Study

Study	Doses	Major Efficacy Findings
WuDunn 2002	% FU 50mg/mL/5 min Mitomycin 0.2mg/mL/2 min	Change in IOP(p-value=0.0001) IOP≤21mmHg: Mitomycin: 89%; 5FU: 94% IOP≤18mmHg: Mitomycin: 87%; 5FU: 94% IOP≤15mmHg: Mitomycin: 78%; 5FU: 81% IOP≤12mmHg: Mitomycin: 65%; 5FU: 67%

Data source: Table 1 (Page 14) in Module 2.7 Clinical Summary of the NDA submission.

Table 8: Efficacy Results for Mitomycin Dose Comparison Study

Study	Doses	Major Efficacy Findings
Sanders 1998	Mitomycin 0.2mg/mL/2 min Mitomycin 0.4mg/mL/2 min	IOP decreased from baseline in both treatment groups, but no statistical significant difference between groups at any time point.

Data source: Table 1 (Page 14) in Module 2.7 Clinical Summary of the NDA submission.

Group-2 Studies:

There are 13 group-2 studies. The efficacy tables for the Group-2 studies are provided in ***Appendix-4.*** The efficacy findings are summarized as follows:

● In the single mitomycin dose vs. no treatment study (Hagiwara 2000), there was significant decrease in IOP in the operated eye and no decrease in IOP in the untreated eyes.

● Among the four active controlled studies (Turacli, Mermoud, Kozobolis, and Vijaya), three studies (Turacli, Mermoud and Kozobolis) showed successful IOP reduction in mitomycin treated group over the controlled group. However, there were no significant differences between mitomycin and 5-FU group with respect to success rates for all criteria in one study (Vijaya)

● There were five multiple-dose comparison studies (Hong 1993, Kitazawa 1993, Maquet 2005, Shin 1995, and Shin 1998). The efficacy results for these 5 studies are summarized below:

▪ In Hong study (with 2 dose groups:0.2mg/mL/ 5 min or 0.4mg/mL/5 min), the combined IOP decreased significantly at all time points up to 12 months.

▪ In Maquet study (with four treatment groups: No Mitomycin, 0.1mg/mL/ 2 min, 0.2mg/mL/ 2 min and 0.4mg/mL/ 2 min), no significant differences were observed in final mean IOP among the mitomycin-treated groups (p = 0.196).

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However, when mitomycin was not used, the final IOP was higher than if it had been used.

▪ In Kitazawa study (with two treatment groups: 0.02mg/mL/5 min and 0.2mg/mL/5 min), 11 eyes (100%) in the 0.2mg group and 7 eyes (63.6%) in the 0.02mg group achieved successful control of IOP with or without topical antiglaucoma medication.

▪ In Shin study (with four treatment groups: No Mitomycin, 0.5mg/mL/ 1min 0.5mg/mL/ 3 min and 0.5mg/mL/ 5 min), there was no significant difference at each follow-up time in the final IOP among the four groups (no mitomycin or a subconjunctival application of 1-, 3-, or 5-minute mitomycin 0.5mg/mL) or between the control and the total mitomycin group.

▪ In Shin 1998 (with four treatment groups: Control, 0.5mg/mL/ 1, 3, or 5 min), there was no statistically significant difference (p-value=0.117) in filtration success of primary glaucoma triple procedure between the control and mitomycin groups.

● In the three single-dose studies (Nuijts, Unlu, and Kobayashi), some subgroups were compared within a particular dose. Significant benefits were observed between subgroups in all three studies.

In summary, the Group-2 studies provided supporting evidence of the efficacy of mitomycin in glaucoma filtration surgery.

2.0 INTRODUCTION

The applicant reports that in discussion with the Agency (Division of Anti-Infective and Ophthalmology Products, Pre-IND meeting, December 6, 2006), it was agreed that the existing published literature, and information in referenced NDAs, provides an extensive collection of data for the toxicological evaluation, safety evaluation and efficacy evaluation of mitomycin for the intended ocular indication. The applicant further reports that the Agency agreed that this information was adequate to support the submission of a 505(b)(2) new drug application and, accordingly, the applicant has not conducted nor sponsored any additional nonclinical or clinical studies of mitomycin. In discussion with the Agency (Division of Anti-Infective and Ophthalmology Products, Pre-IND meeting, March 30, 2007), it also was agreed that pertinent chemistry, manufacturing and controls data (e.g., method of fill, sterility and terminal testing) from an authorized manufacturer of Mitomycin-C, applicable to the new unit dose, would be sufficient to augment referenced CMC data from the approved NDA and ANDA-marketed products.

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Data sets and all modules containing clinical study reports were not submitted electronically since this is a 505(b) (2) submission based on the published literature. The full electronic path for the study results according to CDER EDR naming convention is as follows:

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3.0 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Introduction

In this NDA 22572 (505b (2) submission), the applicant is seeking approval for Optomycin™ as a system for delivering antifibrotic agents in glaucoma filtration surgery. The applicant provided 22 prospective studies to establish the efficacy of mitomycin.

Objective:

To evaluate the efficacy of mitomycin in glaucoma filtration surgery.

Primary endpoints:

Primary efficacy assessed by evaluating the efficacy of mitomycin **i**n glaucoma filtration surgery. The efficacy variables (IOP related) were reported in the published peer-reviewed literature.

Statistical Methodology:

The analyses included in these studies are based on descriptive summaries of mean IOP and other related measures with IOP.

Summary of Group 1 Studies: Prospective, Randomized, Controlled, Masked Studies:

1. Mitomycin versus Placebo (4 Studies):

In the following, we summarize mitomycin versus Placebo (4 Studies) studies:

1. Carlson 1997: Mitomycin Augmentation in Combined Phacoemulsification and Trabeculectomy

This randomized double masked, placebo controlled study in 29 adult patients investigated whether intraoperative application of subconjunctival mitomycin during combined phacoemulsification and trabeculectomy was an effective means of improving filtration. Effective filtration was defined as overall lower IOP and reduced antiglaucoma medication use. Twenty-nine patients with a visually significant cataract and glaucoma were randomized in a double masked fashion to receive intraoperative mitomycin (0.5mg/mL/3.5min) or placebo in 1 eye only. Patients were followed for 6 to 30 months after surgery. The efficacy results are summarized in Table 9.

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Table 9: Efficacy Results of Mitomycin Augmentation in Combined Phacoemulsification and Trabeculectomy-12-Month Comparison (Carlson 1997)

12-Month Outcomes	Mitomycin 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[a]
Mean change in IOP in mmHg (±SD)	5.6 (±1.3)	2.6 (±1.3)	.11[a]
No. (%) patients with IOP between 5 mmHg and 15 mmHg	11/13 (85%)	5/12 (42%)	.04[b]
No. (%) patients with IOP controlled without medications	13/13 (100%)	10/15 (67%)	.04[c]
Visual Acuity 20/40 or better	13/14 eyes	14/15 eyes	NS

Note:
a: Student's t test.
b: Repeated measures of Analysis of variance.
c:Fisher's exact

Data source: Table 2 (Page 18) in Module 2.7 Clinical Summary of the NDA submission

It can be seen from Table 9 that at 12 months, mean (±SD) postoperative IOP was12.6 (±1.0) mmHg in mitomycin group and 16.2 (±1.5) mmHg in placebo group (p-value 0.06). On average, the patients treated with mitomycin had postoperative IOP levels 3.0 mmHg lower than did the placebo group (p-value =0.04, ANOVA) throughout the study. The main endpoint (Mean change in IOP) was not statistically significant when compared with placebo. However, the results of this study suggest that intra-operative mitomycin application (during combined placeemulsification and tubeculectomy) improved early filtration.

2. Cohen 1996: Mitomycin in Combined Glaucoma and Cataract Procedures

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 of 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.
The efficacy results are summarized in Table 10.

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Table 10: IOP and Medication Outcomes following Mitomycin in Combined Glaucoma and Cataract Procedures (Cohen 1996)

Mean IOP and Change from Baseline in mmHg	Mitomycin (N = 36)		Placebo (N = 35)		Between Treatment P-value
	Mean (±SD)	(No. of Eyes)	Mean (±SD)	(No. of Eyes)	
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 Baseline	–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 Baseline	–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 Baseline	–7.65	26	–2.62 (±4.42)	26	0.001

Data source: Table 3 (Page 19) in Module 2.7 Clinical Summary of the NDA submission.

It can be seen from Table 10 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-value=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-value=0.002 to 0.004).

3. Costa 1996:

This prospective, randomized, double-masked study examined the efficacy and safety of low dose 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 as IOP ≤15 mmHg without medication. Qualified success was defined as IOP ≤15 mmHg with medication. Failure was defined as IOP >15 mmHg with medication. The efficacy results are summarized in Table 11.

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Table 11: Success Rates and IOP after Low Dose trabeculectomy with Mitomycin (Costa 1996)

Outcomes	Mitomycin (n = 14)	Placebo (n = 14)	P-value (t-test)
No. (%) Patients with Success			
Complete (IOP ≤15 mmHg without meds)	10 (71.4%)	3 (21.4%)	0.022
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
Failure (IOP >15 mmHg with meds)	2 (14.3%)	10 (71.4%)	0.007
Mean (±SD) IOP in mmHg at			
1 Day (n = 28)	5.30 (±3.92)	10.71 (±5.73)	0.021
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
Last follow-up (n = 28) (range: 7–24 months)	12.78 (±3.90)	18.35 (±4.53)	0.002
Mean (±SD) number of antiglaucoma medications at last follow-up	0.35 (±0.84)	1.57 (±1.08)	0.002

Data source: Table 4(Page 20) in Module 2.7 Clinical Summary of the NDA submission.

It can be seen from Table 11 that the mean IOP (±SD) was significantly lower in the mitomycin treated group at the following time points: first postoperative day (p-value=0.021), 6-month interval (p-value=0.001), and at the final visit (p-value=0.002). The percentage of eyes classified as complete successes was significantly higher in the mitomycin group when compared to the placebo group (p-value=0.022), and the incidence of failures was significantly higher in the placebo group when compared to the control group (p-value=0.007). There was a statistically significant difference in frequency of trabeculectomy failure between the groups at 6 months and thereafter (p-value<0.05). The mean time of trabeculectomy survival was 13.1 (±8.8) months for the mitomycin group and 4.0 (±5.1) months for the placebo group (p-value=0.0036). The log rank test revealed a statistically significant difference between the groups (p-value=0.0065).

4. Robin 1997

This prospective, double-masked, placebo-controlled, 1-year study was designed to evaluate the long-term 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 surgery and the physician

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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.

The efficacy results are summarized in Table 12.

Table 12: Estimated Difference Between Mitomycin-Treated Groups: Dose-Response Study of Mitomycin in Glaucoma Filtration Surgery (Robin, 1997)

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

Data source: Table 5 (Page 21) in Module 2.7 Clinical Summary of the NDA submission.

It can be seen from Table 12 that 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. All three mitomycin-treated groups showed a statistically significant difference in IOP compared with placebo.

2. Prospective, Randomized, Controlled, Masked Studies: Mitomycin versus No Treatment (3 Studies)

In the following, we summarize Mitomycin versus no treatment (3 Studies) studies:
1. Andreanos 1997:
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 IOP for a period of 1 to 3 years after the first trabeculectomy were enrolled. All patient were randomized to a second trabeculectomy with 0.4mg/mL/2–3 min mitomycin (Group A: 24 patients) or without (Group B: 22 patients). The efficacy results are summarized in Table 13.

Table 13: IOP Changes and IOP Control—Second Glaucoma Surgery with and without Mitomycin (Andreanos 1997)

Postoperative Outcomes at 18 Months	Trab + Mitomycin (n = 24)	Trab Only (n = 22)	P-value (t-test)
Mean (±SD) IOP in mmHg	12.5 (± 3.2)	19.6 (±6.1)	<0.001
IOP control	83.3%	63.6%	Not significant

Data source: Table 6 (Page 21) in Module 2.7 Clinical Summary of the NDA submission.

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It can be seen from Table 13 that at 18 months the mean (±SD) postoperative IOP was 12.5 (±3.2) mmHg in the mitomycin group and 19.6 (±6.1) mmHg in the control group; this difference was statistically significant: p-value<0.001. IOP control, defined as IOP =20 mmHg, was achieved in 83.3% of the mitomycin and 63.6% of the control group. However, this difference was not statistically significant.

2. Martini 1997:

This prospective, randomized, controlled, evaluator-masked study in adult patients was designed to assess the effectiveness and adverse effects of intraoperative low-dose 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 =18 mmHg without medication; a qualified success was defined as IOP =18 mmHg with topical tension-lowering drugs; a failure was defined as IOP = 18 mmHg at two evaluations despite adjunctive therapy.

The efficacy results are summarized in Table 14.

Table 14: Success Rate and IOP Outcomes after Trabeculectomy with Low-Dose Mitomycin at 1-Year Follow-up (Martini 1997)

Outcomes at 1-Year Follow-up	Mitomycin (n = 30)	No Mitomycin (n = 30)	P-value (t-test)
Total success[b] rate (IOP ≤18 mmHg with or without meds)	96.6%	73.3%	<0.0001
Mean (±SD) IOP in mmHg	11.1 (±3.1)	16.4 (±6.1)	<0.0001
Mean (±SD) IOP in fully successful cases (≤18 mmHg)	10.7 (±3.0)	13.4 (±2.6)	<0.001
Mean (±SD) IOP in patients who required bilateral surgery (n = 12)	11.1 (±2.9)	14.9 (±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.

Data source: Table 7 (Page 25) in Module 2.7 Clinical Summary of the NDA submission.

Reference ID: 2872799

It can be seen from Table 14 that at 12 months, Mean (±SD) IOP in Mitomycin was 11.1 (±3.1) mmHg and Mean (±SD) IOP in control was 16.4 (±6.1) mmHg (p-value=0.0001). It can be concluded that mitomycin was a useful (significantly) adjunct to glaucoma surgery.

3. Rasheed 1999:

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 0.4mg/mL of mitomycin for 4 minutes. All patients were followed for 18 months postoperatively. The efficacy results are summarized in Table 15.

Table 15: IOP Outcomes after Initial Trabeculectomy with Mitomycin in Primary Glaucoma (Rasheed 1999)

Effectiveness Parameters	Mitomycin (n = 25)	Control (n = 25)
Successful IOP control	23 eyes (92%)	17 eyes (68%)
Mean (±SD) postoperative IOP in mmHg[a]	10.2 (±3.9)	16.1 (±5.1)
No (%) Patients (N = 25) with the following:		
IOP-VALUE<12 mmHg	15 (60%)	5 (20%)
IOP-VALUE<15 mmHg	18 (72%)	8 (32%)
IOP-VALUE<20 mmHg without hypotensive meds	21 (84%)	12 (48%)
IOP-VALUE<20 mmHg with 1 to 3 hypotensive meds	2 (8%)	8 (32%)
IOP>20 mmHg with hypotensive medications	2(8%)	8 (32%)
	25 (100%)	25 (100%)

a: The difference between treatment groups was statistically significant: p-value=0.015.
Data source: Table 8 (Page 26) in Module 2.7 Clinical Summary of the NDA submission.

It can be seen from Table 15 that the mitomycin treated group was superior for all measures of success. Successful IOP control (IOP <20 mmHg with or without hypotensive medication) was seen in 23 eyes (92%) of the Mitomycin group and 17 eyes (68%) of the control group at mean time points of 17.8 (±1.1) months and 17.8 (±1.2), respectively.

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3. Prospective, Randomized, Controlled, Masked Studies (mitomycin versus 5-Fluorouracil)

In the following, we summarize mitomycin versus 5-Fluorouracil study:

WuDunn 2002:

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. The assignment schedule was generated in blocks of 50 (25 per group) by a study coordinator who was not involved in the surgical procedure or clinical care. If the second eye of a patient was also enrolled, it was assigned to the opposite group of the first eye. Thus, if both eyes of a patient were enrolled, 1 eye received 5-FU and the fellow eye received mitomycin.

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. Secondary outcome measures included IOP, best-corrected visual acuity, complications, and interventions. One-hundred fifteen eyes of 103 patients were enrolled in the study: 58 eyes received mitomycin and 57 received 5-FU. The efficacy results are summarized in Table 16.

Table 16: Efficacy Results at 6 and 12 Months— 5-FU versus Mitomycin in Primary Trabeculectomy (WuDunn, 2002)

	6 Months		12 Months	
Dose Groups	Mitomycin (n=58)	5-FU (n =57)	Mitomycin (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)

Note: 5-FU = 5-Fluorouracil; IOP = Intraocular pressure; MmHg = millimeters of mercury.
Data source: Table 9(Page 27) in Module 2.7 Clinical Summary of the NDA submission.

There were no statistically significant differences between treatment groups for any measure of success at any time point. The study suggest that intraoperative topical Mitomycin had numerical advantage over intra-operative topical 5-FU in reducing IOP of eyes undergoing primary trabeculectomy.

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4. Prospective, Randomized, Controlled, Masked Studies: mitomycin (Dose Comparison Study):

In the following, we summarize mitomycin dose comparison study:

Sanders, 1998: Comparison of 0.2mg/mL to 0.4mg/mL Mitomycin in Higher Risk Trabeculectomy

This prospective, randomized, masked study compared the effectiveness of 0.2mg/mL and 0.4mg/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.

The efficacy results were summarized in Table 17.

Table 17: IOP Before and After Trabeculectomy with Mitomycin Dose Comparison (0.2mg/mL to 0.4mg/mL) (Sanders 1998)

Mean (±SD) IOP in mmHg	mitomycin Dose Groups		
	0.2mg/mL/2min	0.4mg/mL/2min	P-value (Student *t* test)
Before surgery	28.8 (±13.7)	25.0 ± 8.6	0.25
After surgery:			
1 Day	2.8 (±2.8)	3.6 (±3.7)	0.44
1 Week	4.9 (±2.9)	5.16 (±3.9)	0.31
1 Month	13.6 (±7.6)	14.2 (±8.8)	0.81
3 Months	14.4 (±7)	12.7 (±5.7)	0.37
6 Months	13.3 (±4.7)	14.3 (±8.5)	0.65
1 Year	14.2 (±6.3)	13.7 (±6.2)	0.78

Data source: Table 10(Page 29) in Module 2.7 Clinical Summary of the NDA submission.

Overall, there were no statistically significant differences between treatment groups in mean IOP at any time point up to 12 months.

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4.0 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

1.1 Examination of Subgroups

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Statistical Issues:

There are no major statistical issues with this submission.

Collective Evidence:

This reviewer looked into 22 prospective studies 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.

Despite these variations of designs and doses, the results were convincing because all the studies showed the advantage of using mitomycin in glaucoma filtration surgery. In the following, we summarize the findings:

Group 1 Studies:

The findings based on 9 group-1 studies are summarized below:

● Out of the four placebo-controlled studies (Carlson, Cohen, Costa , and Robin), in three studies (Cohen, Costa, and Robin), the difference in mean IOP in the mitomycin-treated groups as compared with placebo-treated groups was statistically significant in favor of the mitomycin groups for up to 24 months. In Carlson study, there was a numerical advantage of mitomycin treated group over placebo group with respect to mean change in IOP. ● In the three surgery plus mitomycin versus surgery-alone controlled studies (Andreanos: 0.4/mL mitomycin, Martini: 0.1 mg/mL mitomycin, and Rasheed: 0.3-0.4 mg/mL mitomycin), the difference in mean IOP was significantly lower and the success rates significantly higher in the mitomycin-treated groups compared with the placebo-treated (no mitomycin) groups.

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● In the double-masked active-controlled study (Wudunn 2002), the success rates of mitomycin-treated group were similar (0.8 unit difference in mean IOP) to that of the 5-FU-treated group.

●In the dose-comparison controlled study (Sanders), both doses of mitomycin (0.2 and 0.4 mg/m) significantly reduced IOP; there were no statistically significant differences in IOP between the 0.2 and 0.4 mg/mL doses of mitomycin. In addition, in Robin's placebo-controlled dose-response study (Group1: placebo; Group 2: mitomycin 0.2mg/mL/2min; Group 3: mitomycin 0.2mg/mL/4min, and Group 4: mitomycin 0.4mg/mL/2 min) statistically significant treatment-related differences were seen. However, there were no statistically significant differences in IOP among Group 2, Group 3 and Group 4.

Based on the totality of evidence from Group-1 studies, there is evidence of the efficacy of mitomycin in glaucoma filtration surgery. However, both the strength of mitomycin solution applied during the procedure and the application times varied 0.1 to 0.5 mg/mL and exposure times from 2 to 4 minutes (mitomycin dosage range from 0.1 to 0.5 mg/mL and exposure times from 2 to 4 minutes, respectively) between the studies. The proposed dose of mitomycin 0.2 mg/ml lies within the studied dosage range 0.1 to 0.5 mg/mL. Thus, the proposed dosage of mitomycin is acceptable for approval.

Group-2 Studies:

There are 13 group-2 studies. The efficacy tables for the Group-2 studies are provided in ***Appendix-4.*** The efficacy findings are summarized as follows:

● In the single mitomycin dose vs. no treatment study (Hagiwara 2000), there was significant decrease in IOP in the operated eye and no decrease in IOP in the untreated eyes.

● Among the four active controlled studies (Turacli, Mermoud, Kozobolis, and Vijaya), three studies (Turacli, Mermoud and Kozobolis) showed successful IOP reduction in mitomycin treated group over the controlled group. However, there were no significant differences between mitomycin and 5-FU group with respect to success rates for all criteria in one study (Vijaya)

● There were five multiple-dose comparison studies (Hong 1993, Kitazawa 1993, Maquet 2005, Shin 1995, and Shin 1998). The efficacy results for these 5 studies are summarized below:

▪ In Hong study (with 2 dose groups:0.2mg/mL/ 5 min or 0.4mg/mL/5 min), the combined IOP decreased significantly at all time points up to 12 months.

▪ In Maquet study (with four treatment groups: No Mitomycin, 0.1mg/mL/ 2 min, 0.2mg/mL/ 2 min and 0.4mg/mL/ 2 min), no significant differences were observed in final mean IOP among the mitomycin-treated groups (p-value =

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0.196). However, when mitomycin was not used, the final IOP was higher than if it had been used.

▪ In Kitazawa study (with two treatment groups: 0.02mg/mL/5 min and 0.2mg/mL/5 min), 11 eyes (100%) in the 0.2mg group and 7 eyes (63.6%) in the 0.02mg group achieved successful control of IOP with or without topical antiglaucoma medication.

▪ In Shin study (with four treatment groups: No Mitomycin, 0.5mg/mL/ 1min 0.5mg/mL/ 3 min and 0.5mg/mL/ 5 min), there was no significant difference at each follow-up time in the final IOP among the four groups (no mitomycin or a subconjunctival application of 1-, 3-, or 5-minute mitomycin 0.5mg/mL) or between the control and the total mitomycin group.

▪ In Shin 1998 (with four treatment groups: Control, 0.5mg/mL/ 1, 3, or 5 min), there was no statistically significant difference (p-value=0.117) in filtration success of primary glaucoma triple procedure between the control and mitomycin groups.

● In the three single-dose studies (Nuijts, Unlu, and Kobayashi), some subgroups were compared within a particular dose. Significant benefits were observed between subgroups in all three studies.

In summary, the Group-2 studies provided supporting evidence of the efficacy of mitomycin in glaucoma filtration surgery.

5.2 Conclusions and Recommendations

Based on the totality of evidence from Group-1 and Group-2 studies from this 505b (2) submission, there is substantial evidence of the efficacy of mitomycin 0.2 mg in glaucoma filtration surgery.

Mushfiqur Rashid, Ph.D.

Statistical reviewer

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Appendices: Appendix-1, Appendix-2, Appendix-3 and Appendix-4

Appendix-1: References of Group 1 Studies

1. 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):719-724.*

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

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5. Andreanos D, Georgopoulos GT, Vergados J, Papaconstantinou D, Liokis N, Theodossiadis P. *Clinical evaluation of the effect of Mitomycin-C-C in re-operation for primary open-angle glaucoma.*

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

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

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

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Appendix-2: Reference for Group-2 Studies

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2. Hong C, Hyung SM, Song KY, Kim DM, Youn DH. *Effects of topical mitomycin C on glaucomaltration 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.*

3. 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.*

4. 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 May;241(5):359-66. Epub 2003 Apr 16.*

5. 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.*

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

7.Mermoud A, Salmon JF, Murray AD. *Trabeculectomy with mitomycin C for refractory glaucoma in blacks. Am J Ophthalmol. 1993 Jul 15;116(1):72-8.*

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Appendix-3: Description of Group-2 Studies

Table A3.1: Comparison of Intraoperative Mitomycin to No Treatment (Hagiwara 2000)

Investigator	Design	Population	No. Patients/ No. Eyes	Dosage	Duration
Hagiwara 2000	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

Data source: Table 12(Page 32), Module 2.7 (Clinical Summary 2.7.3.2.2)

Table A3.2: Comparison of Intraoperative Mitomycin to Active Control (Turacli 1996 Mermoud 1993, Kozobolis and Vijaya 2000)

Investigator	Design	Population	No. Patients/ No. Eyes	Dosage	Duration
Turacli 1996	Prospective Randomized Mitomycin 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
Mermoud 1993	Prospective Matched control group	Black Patients (adults)	26/30 28/30	0.2mg/mL/ 5 min Trab alone	18 mo
Kozobolis 2002	Prospective Randomized Deep Sclerectomy	Open angle	45/45 DS with Mitomycin 45/45 DS w/o Mitomycin	0.2mg/mL/2.5 min	36 mo
Vijaya 2000	Prospective Non-randomized 5-FU vs. Mitomycin		16/3 16/13 16/16	0.2mg/mL/1min 0.4mg/mL/ 1 min 50mg/mL/ 1 min1	11.1 mo

Note: 5-FU = 5-Fluorouracil; CSA = Cyclosporine A; Trab = Trabeculectomy.
Data source: Table 12(Page 32) ,Module 2.7 (Clinical Summary 2.7.3.2.2)

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Table A3.3: Investigating different doses of intraoperative mitomycin(Hong 1993, Kitazawa 1993, Maquet 2005, Shin 1995, and Shin 1998)

Investigator	Design	Population	No. Patients/ No. Eyes	Dosage	Duration
Hong 1993	Prospective	Adults	19/23	0.2mg/mL/5 min or 0.4mg/mL/5 min	12 mo
Kitazawa 1993	Randomized Dose finding	Open angle	11/22	0.02mg/mL/5 min 0.2mg/mL/5 min	Up to 17 mo
Maquet 2005	Prospective Non-randomized Protocol for primary trab or combined surgery	Adults Primary trab or combined surgery	/ 7 /37 /64 /35 124/143 total	No Mitomycin 0.1mg/mL/2 min 0.2mg/mL/2 min 0.4mg/mL/2 min	12 mo
Shin 19	Prospective Randomized PGTP POAG		21/21 21/21 21/21 15/15	No Mitomycin 0.5mg/mL/1min 0.5mg/mL/3 min 0.5mg/mL/5 min	21 months
Shin 1998	Randomized PGTP/ POAG	PGTP w/o Mitomycin PGTP w/Mitomycin	101/101 96/96	0.5mg/mL/ 1, 3, or 5 min	24 months

Note: PGTP = Primary glaucoma triple procedure; POAG = Primary open-angle glaucoma; Trab = Trabeculectomy.
Data source: Table 12(page 32), Module 2.7, Clinical Summary 2.7.3.2.2

Table A3.4: Comparisons of subgroups within a single dose(Nuijts 1990, Unlu 2000 and Kobayashi 2003)

Investigator	Design	Population	No. Patients/ No. Eyes	Dosage	Duration
Kobayashi 2003	Prospective Viscocanal- ostomy vs. trab + Mitomycin	Open angle	25/	0.04%/3 min	12 mo
Nuijts 1997	Prospective Primary glaucoma	White patients (adults)	23/25	0.2mg/mL/5 min	12 mo
Unlu 2000	Prospective Mitomycin and releasable suture technique compared with Mitomycin and permanent sutures	releasable sutures permanent sutures	18/17 18/20	0.2mg/mL/2 min	8.1 months +/- 1.3 months 8.3 months +/- 1.3 months

Note: Trab = Trabeculectomy.
Data source: Table 12(page 32), Module 2.7, Clinical Summary 2.7.3.2.2

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Appendix-4: Efficacy Tables for Group-2 Studies

Table A4.1: Efficacy Results of Intraoperative Mitomycin to No Treatment (Hagiwara 2000)

Investigator	Dosage	Major Efficacy Findings
Hagiwara 2000	0.4mg/mL/ 5 min No treatment	Treated group: Significant decrease in IOP (p-value=0.0002); no decrease in untreated.

Data source: Table 12(page 32), Module 2.7, Clinical Summary 2.7.3.2.2

Table A4.2 Efficacy Results of Intraoperative Mitomycin to Active Control (Turacli 1996 Mermoud 1993, Kozobolis and Vijaya 2000)

Investigator	Dosage	Major Efficacy Findings
Kozobolis 2002	0.2mg/mL/2.5 min	DS/Mitomycin decreased IOP significantly compared with DS alone (p-value<0.05). Complete success occurred in 95% of the DS/Mitomycin group and 72.5% of the DS alone group.
Mermoud 1993	0.2mg/mL/ 5 min Trab alone	IOP significantly lower in Mitomycin group (p-value=0.001). 83% of Mitomycin and 37% of control achieved IOP-VALUE<21mmHg (p-value=0.00006).
Turacli 1996	0.4mg/mL/4 min CSA 2% Control	Successful IOP reduction: Mitomycin: 90% CSA: 85.7% Control: 71.4%
Vijaya 2000	0.2mg/mL/1min 0.4mg/mL/ 1 min 50mg/mL/ 1 min	No significant differences between Mitomycin and 5-FU group success rates for all criteria.

Note: 5-FU = 5-Fluorouracil; CSA = Cyclosporine A; DS = Deep sclerectomy
Data source: Table 12(page 32 Module 2.7, Clinical Summary 2.7.3.2.2

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Table A4.3: Efficacy Results of different doses of intraoperative mitomycin(Hong 1993, Kitazawa 1993, Maquet 2005, Shin 1995, and Shin 1998

Investigator	Dosage	Major Efficacy Findings
Hong 1993	0.2mg/mL/ 5 min or 0.4mg/mL/ 5 min	IOP decreased significantly at all time points up to 12 months. At 12 -month: success rate was 74.7%
Kitazawa 1993	0.02mg/mL/ 5 min 0.2mg/mL/ 5 min	The significant success rate was 100% in 0.2 eyes group and 63.6% in 0.002 eyes. group
Kozobolis 2002	0.2mg/mL/2.5 min	DS/Mitomycin decreased IOP significantly compared with DS alone (p-value<0.05). Complete success occurred in 95% of the DS/Mitomycin group and 72.5% of the DS alone group.
Shin 1995	No Mitomycin 0.5mg/mL/ 1min 0.5mg/mL/ 3 min 0.5mg/mL/ 5 min	Postoperative IOP was significantly lower with significantly less medications at each follow-up for all groups (p-value<0.05). No significant differences among groups at any time point in IOP, medications or best-corrected visual acuity
Shin 1998	Control, 0.5mg/mL/ 1, 3, or 5 min	No statistically significantly in success rate between the control and Mitomycin groups (p-value=0.117).

Data source: Table 12(page 32), Module 2.7, Clinical Summary 2.7.3.2.2
Note: DS = Deep sclerectomy;

Table A4.4: Efficacy Results for subgroups within a single dose(Nuijts 1990, Unlu 2000 and Kobayashi 2003)

Investigator	Dosage	Major Efficacy Findings
Kobayashi 2003	0.04%/3 min	IOP decreased significantly in both treatment groups at all time points. The mean IOP was higher in the viscocanalostomy group (p-value=0.0001)
Nuijts 199	0.2mg/mL/ 5 min	Mean IOP decreased from 26 to 12.5 mmHg (p-value<0.0001) 1 year post-op.
Unlu 2000	0.2mg/mL/ 2 min	Complete success in 88.8% (Group 1) and 85% (Group 2) of eyes; qualified success in all remaining (11.1% in Group 1 and 15% of Group 2) eyes. In the early post-operative period, better control of IOP was achieved in releasable suture group (Group 1).

Data source: Table 12:((Page 32), Module 2.7, Clinical Summary 2.7.3.2.2

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/s/

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12/06/2010

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I concur.