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 Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	200890
Drug Name:	Pilocarpine hydrochloride
Indication(s):	(1) Reduction of elevated IOP in patients with open angle glaucoma or ocular hypertenstion (2) (b) (4) acute angle-closure glaucoma (3) Prevention of (b) (4) postoperative elevated IOP associated with (b) (4) laser surgery (b) (4) (4) Induction of Miosis
Applicant:	Alcon Inc
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Keywords: 505 (b)2, IOP, Miosis, glaucoma surgery

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

This statistical review evaluates the evidence submitted in NDA 200890 for approval of pilocarpine hydrochloride solution 1%, 2%, and 4%. Since the NDA type is 505(b)(2), this evaluation is based mostly on results of published studies.

1.1 Conclusions and Recommendations

There is substantial evidence from the literature to support the efficacy of pilocarpine 2% or 4% for the two following indications:

1- Reduction of elevated IOP in patients with open angle glaucoma or ocular hypertenstion
2- Induction of Miosis

There is insufficient evidence to support the efficacy of pilocarpine for the two following indications:

1. (b) (4) acute angle-closure glaucoma
2. Prevention of (b) (4) postoperative elevated IOP associated with (b) (4) laser surgery (b) (4)

Note that the clinical review team considered the indication of ***'management of acute angle closure glaucoma'*** *instead of the indication sought by the applicant of* (b) (4) (b) (4) *Since it is unclear to me how the management of acute angle closure glaucoma can be assessed and quantified, I leave it to the clinical review team to comment on this indication.*

1.2 Statistical Issues and Findings

I will discuss the efficacy findings for each of the four indications separately:

1.2.1 Reduction of elevated IOP in patients with open angle glaucoma or ocular hypertension

There is overwhelming evidence to support this indication. The evidence for approval of this indication comes from the applicant's own 4 clinical studies and over 19 published studies. Supportive evidence also comes from the FDA approval of these related drugs or devices: pilocarpine hydrochloride gel, Ocusert Pilo 20 and Ocusert Pilo 40 for the same indication.

Selected results quantifying the effect of pilocarpine in lowering elevated IOP are shown in Table 1 and Table 2. Table 1 presents the results from studies C-90-42, C-91-54 and C-91-47 on subjects who had open angle glaucoma or ocular hypertenstion. Subjects in these three studies had a 3 week run in of Betaxolol 0.25% , had high IOP after this run-in period at baseline, and took pilocarpine 2% three times a day after baseline. Table 2 summarizes the findings of study

C90-105 conducted by applicant (also published in Drance 1998) and two other publications: Vogel et al (1992) and Sharma and Gupta (1997). These three studies are long term studies of the effect of pilocarpine 2 or 4% in lowering baseline IOP in subjects with open angle glaucoma or ocular hypertension. More detailed results are shown in Table 5 to Table 7 in the review.

Table 1: Selected results from studies C-90-42, C-91-54 and C-91-47

	Baseline (8 AM) after betaxolol run in		Day 14 (8 AM) change from baseline		Day 45 (8 AM) change from baseline		Day 90 (8 AM) change from baseline	
Studies	N	Mean ± SD	N	Change* ± SD (CI**)	N	Change* ± SD (CI**)	N	Change* ± SD (CI**)
C-90-42	16	25.5 ± 1.8	16	0.4 ±2.65 (1 -1.8)	16	2.1 ± 2.56 (0.7 - 3.5)	15	1.4 ± 3.16 (0.35 - 3.1)
C-91-54	54	25.4 ± 2.4	50	1.7 ± 2.5 (1 - 2.4)	43	2.5 ± 2.9 (0.6 – 2.4)	41	1.6 ± 2.8 (0.7 - 2.5)
C-91-47	48	26.6 ± 3	46	2.9 ± 3.2 (2 - 3.8)	43	2 ± 3.1 (1.1 - 2.9)	38	0.9 ± 3.6 (0.3 - 2.1)

* Mean change from baseline is calculated by subtracting from the baseline IOP at 8AM the IOP on that day at 8AM

** CI is the 95% confidence interval without adjusting for multiplicity.

Table 2: Summary of results from study C-90-105 and three publications.

Results	Baseline: Sample size IOP (mmHg) CI**	On treatment: Sample Size (N) Mean Change from Baseline (mmHg)* CI**						
Time	Baseline	Month 0***	Month 4	Month 8	Month 12	Month 16	Month 20	Month 24
Vogel et al (1992)	N=45 27.9 (26.4 -29.4)	N=45 7.4 (5.6 - 9.2)	N=41 7.1 (5.3 -8.9)	N=31 6.3 (4.1 -8.5)	N=26 6.6 (4.4 - 8.8)	N=26 7.1 (5.0 -9.2)	N=24 6.2 (4.0 -8.4)	N=20 6 (3.6 -8.4)
Time	Baseline	Month 3	Month 6	Month12	Month 18	Month 24		
Sharma et al (1997)	N=36 24.5 (23.3 - 25.7)	N=33 6.1 (4.4 -7.7)	N=30 6.9 (5.4 – 8.4)	N=27 6.2 (4.6 -7.8)	N=25 6.2 (3.9 - 8.6)	N=21 6.2 (4.5 -7.9)	NA	
C90-105 and Drance (1998)	N=11 24.9 (22 to 27.9)	N=11 7 (3.4 -10.6)	N=11 6.2 (2.4 -9.9)	N=11 6.2 (2.4 -10)	N=11 6.9 (2.7 - 11.1)	N=11 4.9 (2.7 -7.1)		

* Mean change from baseline is calculated by subtracting from baseline IOP, the IOP at future visits. Note that the measurements in Vogel et al (1992) represent the maximum diurnal measurements for a day with 5 measurements.

** CI is the 95% confidence interval without adjusting for multiplicity.

***month 0 is the visit at titration of the pilocarpine dose (choice between pilocarpine 2% or 4%).

1.2.2 Induction of miosis

There is overwhelming evidence to support the miotic effect induced by Pilocarpine. Although the effect of the drug on pupil size was rarely precisely quantified, the miotic effect seems clearly visible. This effect is noted and discussed in every single article I reviewed on pilocarpine as a benefit (such as facilitating surgery), as a safety concern (such as reducing vision), or as a potential issue in designing masked studies. Finally, the biological mechanism of pilocarpine to induce miosis seems to be well understood.

A quantification of the short term effect of the drug on pupil size is available in two references I found: Edgar et al (1999) and Webster (1993). These results are summarized in Table 3 and described in more detail in the review. As shown in this table, both studies find that pupil size decreases by about 3mm within one hour after instillation. However, some subjects with glaucoma may not experience any miotic effect.

A quantification of the long term effect of the drug on pupil size is available from three clinical studies submitted by the applicant. These results are summarized in Table 4 below, and shown in more detail in Table 22 and Table 23 in the review. All three studies find that pilocarpine has a significant effect in lowering the pupil size in the first three months. Study C90-105 shows that the miotic effect of pilocarpine may fade over time (after 6 months and up to 2 years), with pupil size going back to baseline or even dilating compared to baseline after 6 months.

Table 3: Summary of results on miosis from short term studies

Study	**Subjects**	**Baseline pupil size (mm) ± SD**	**Pupil size after instillation (mm) ± SD**	**Results on each subject**
Edgar et al (1999)	Healthy volunteers (N=12)	5.49 ± 1.06	2.26 ± 0.49 (60 min after instillation)	All subjects experienced miosis
Webster (1993)	Chronic angle glaucoma (N=20)	5.5	2 (30-40min after instillation)	Seven subjects had dilating pupils (0.3mm to 1.0mm), five subjects had constricting pupils (0.3mm to 2.0mm) and eight subjects remained the same.

Table 4: Pupil size and mean change from baseline in studies C-91-47, C-91-54, and C90-105

Time	Day 14		Day 45		Day 90		NA			
Studies	N	change from baseline (mm)	N	Change from baseline (mm)	N	Change from baseline (mm)				
C-91-47	46	-0.7*	43	-0.8*	37	-0.7*				
C91-54	50	-0.8*	42	-1*	41	-1*				
Time	Month 3		Month 6		Month 12		Month 18		Month 24	
	N	change from baseline (mm)	N	Change from baseline (mm)	N	change from baseline (mm)	N	Change from baseline (mm)	N	Change from baseline (mm)
C-90-105	11	-1.09**		-1.14**	11	0.27	11	0.86	11	1.00

*significant change from baseline at 1% level of significance.
** significant change from baseline (p-value < 0.5%)

1.2.3 (b) (4) acute angle-closure glaucoma

The applicant submitted no evidence to support the indication they are seeking which is (b) (4) acute angle glaucoma. More precisely, the applicant submitted 8 articles to support this indication:

- Kobayashi (1999), Pavlin (1999), and Ritch (1996) do not present any measurements on IOP.

- Lai (1999), Lai (2000), Lam (1998), Lam (2002)a, and Lam (2002)b look at the concomitant effect of timolol 0.5%, pilocarpine 4% and laser surgery on reducing IOP. In all these articles, IOP was measured once before surgery and several times after surgery. None of these articles present both the IOP measurements before instillation of the drug and after instillation of the drug but before surgery occurred.

In addition to the articles submitted by the applicant, I conducted my own search looking at the effect of pilocarpine in subjects undergoing laser iridotomy or laser iridoplasty. Similarly to the issues identified above, the articles from my search either did not measure IOP or measured IOP after drug instillation and after surgery, but not before drug instillation. In summary, I did not find sufficient evidence to support this indication.

*Note that the clinical review team is considering the indication of **management of acute angle closure**. The applicant submitted evidence that pilocarpine is used to manage acute angle-closure glaucoma. Its use in clinical practice will be further described by the clinical review. This effect seems complex as pilocarpine can stop or cause an acute angle closure attack by its miotic effect.*

1.2.4 [redacted] postoperative elevated IOP associated with [redacted] laser surgery

[redacted] I will first summarize my criteria for selection of the studies and their main characteristics. Then, I will outline my reasoning explaining my conclusion for this indication.

From the 6 articles submitted by the applicant and my own literature search, I found 14 relevant publications. Some criteria for selection of the studies in the publication were that each study had to be on subjects undergoing glaucoma laser surgery and had to have measurements of IOP before and shortly after surgery. Additional criteria were that either the study included one arm using pilocarpine alone before or after surgery, or the study included one arm with no treatment before or after surgery or a placebo treatment for another drug. Each study is summarized in detail in the review in Table 12 to Table 21.

A synthesis of the design in these studies is that there is some variation in terms of type of surgery conducted, subjects under consideration for surgery and the type of reported endpoints. Surgeries in these articles were either Argon laser trabeculoplasty (ALT), argon laser iridotomy (ALI) or Nd:YAG laser iridotomy (Nd:YAG) with only one article discussing posterior capsulotomy. Postoperative peak IOP elevation was quantified by comparing IOP before surgery (and after medication) to IOP 1 hour to 3 hours after surgery. Different cut-off points for the within subject difference between the two measurements were used to define a peak or an increase in IOP, these cut-off points were either 0mmHg, 1mmHg, 5mmHg, 10mmHg, 20mmHg, or 30mmHg. Some articles reported the results for several cut-off points, but most only picked a few of these cut-off points. The two most frequent choices of cut-off points were 10mmHg and 5mmHg.

The main studies used to draw my conclusions are the two studies comparing pilocarpine before surgery to no treatment, these studies are Elsas (1991) and Leung and Gillies (1986). I will first

compare and contrast Elsas et al (1991) and Leung and Gillies (1986), then I will compare the findings of these two studies to the remaining studies.

On one hand, Elsas et al (1991) recruited 50 subjects from a narrow population of subjects who have elevated IOP at baseline pre-surgery, who have glaucomatous disc damage and/or visual field defects, who have no previous glaucoma treatment, and who are candidate for laser trabeculoplasty. This study found that pilocarpine 2% solution reduced significantly the number of subject with IOP spikes above 10mmHg after surgery, from 52% (13/25) compared to 12% (3/25) in the no treatment arm. This significance held when looking at other endpoints such as peak above 20mmHg. On the other hand, Leung and Gillies (1986) recruited 64 subjects from a broader population of patients who were under treatment for their open angle glaucoma and were candidates for an argon laser trabeculoplasty. The results for number of subjects with peak above 5mmHg post-srugery are 42% (14/33) for the pilocarpine 4% arm compared to 48% (15/31) in the no treatment arm. The difference is not significant, and this holds when looking at other endpoints such as peak above 30mmHg.

The result on the pilocarpine arm in Leung and Gillies (1986) are not unusually high, and the results in the no treatment arm in this study are not unusually low. The result on the pilocarpine arm of 42% in Leung and Gillies (1986) is similar to the results on the pilocarpine arm in three other studies using the same endpoint (peak above 5mmHg): 46% (46/100) in Krupin et al (1985), 42% (20/47) in Liu et al (2002), and 32% (13/37) in Robin (1989). However, the results on the pilocarpine arm are much larger than the results on the pilocarpine arm of two recent studies: 9% (2/23) in Dapling et al (1994) and 4% (5/114) in Ren et al (1999). The results on the same endpoint (peak above 5mmHg) in the no treatment arm in Leung and Gillies (1986) of 48% are not unusually low, they are in fact higher than in the placebo arm of David et al (1993) of 41% (23/56) and much higher than in the placebo arm result of 27% (19/71) in Shin et al (1996).

The results on the pilocarpine arm in Elsas et al (1991) are unusually low and the results on the no treatment arm seem unusually high as well. The result of 12% on the pilocarpine arm in Elsas et al (1991) is much lower than the rate in other studies with pilocarpine arm using the same endpoint (above 10mmHg): 37% (4/11) in Fernandez-Bahamonde et al (1990), 29% (29/100) in Krupin et al (1985), 32% (13/40) in Robin and Pollack (1984), and 30% (54/182) in Schwartz (1986). The rate in Elsas is higher than the rate of a single study: 3% (1/37) in Robin (1989) which has a similar population than Elsas et al (1991). The results on the no treatment arm in Elsas et al (1992) of 52% is much higher than the placebo arm result of 23% (13/52) in the David et al (1993) study. So, the results in Leung and Gillies (1986) seem more consistent to the results of the other studies than the results in Elsas et al (1991).

In addition, more recent studies seem to have different results than earlier studies. We note that more recent studies such as Dapling et al (1994), Ren et al (1999), and Robin (1989) reported a much lower incidence of peak IOP after surgery in the pilocarpine arm than earlier study. We note also that the placebo arm in the two studies David et al (1993) and Shin et al (1996) also report lower incidence of peak compared to the no treatment arm. After close inspection of the studies, it is still unclear to me which factors are responsible for making the more recent studies different from the earlier studies and whether these factors would affect a possible placebo arm similarly to the pilocarpine arm. It could be that prior use of pilocarpine to manage glaucoma

may reduce the effect of pilocarpine before surgery, This reason may explain the higher rates in earlier studies where more subjects used pilocarpine to manage their glaucoma compared to lower rates in more recent studies where subjects have more drugs available to manage their glaucoma. However, this reason would not imply change of the 'no treatment' or placebo arm over time. It could also be that prior use of any medication to manage glaucoma reduces the occurrence of peaks after surgery for everyone. It could also be that subjects with high IOP at baseline or some damage to their eye are more susceptible to peak elevation post-surgery. Finally, it could be that the type of laser surgeries has changed enough in the past twenty years to give different results. These last three possibilities would explain a reduction of the rate over time for both pilocarpine and placebo arm, although it would still be unknown whether the amount of reduction would be the same in both arms.

2 INTRODUCTION

2.1 Overview

Pilocrapine hydrochloride, the active ingredient of Isopto Carpine, is a muscarinic cholinergic agonist. Pilocarpine hydrochloride is also the active ingredient of several ophthalmic products approved by FDA, those are

- Ophthalmic Medicated Inserts OCUSERT PILO-20 [NDA 017431] and OCUSERT PILO-40 [NDA 017548], which were approved in 1974 for lowering elevated intra-ocular pressure in patients with open angle glaucoma.
- PILOPINE HS® (pilocarpine hydrochloride ophthalmic gel) 4% [NDA 18-796] which was approved by the FDA in 1984 for the control of elevated intra-ocular pressure.

Pilocarpine hydrochloride has been used clinically for the management of elevated IOP since 1876. It is generally no longer used as primary line of therapy for long term management of elevated IOP since there are other drugs with better safety or efficacy profile.

The NDA was submitted under the 505 b(2) pathway, which means that the evidence to support the approval is mainly from published studies. The findings summarized in this review are mostly from published literature submitted by the applicant or found by the reviewer.

2.2 Data Sources

No electronic SAS data sets were submitted in this NDA. Study reports for clinical studies C-90-42, C-91-47, C-91-54, and C-90-105 included raw data in pdf files.
These study reports are available at \\Cdsesub1\evsprod\NDA200890\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\reduction-of-intraocular-pressure\5351-stud-rep-contr

3 STATISTICAL EVALUATION

My statistical evaluation will focus on the efficacy. Please refer to the clinical review for comments on safety.

3.1 Evaluation of Efficacy

Each of the four indications will be reviewed separately in the following subsections.

3.1.1 Reduction of elevated IOP in patients with open angle glaucoma or ocular hypertension

This subsection first describes historical evidence and biological mechanism of this drug, then reviews the evidence submitted by the applicant.

3.1.1.1 Historical background and biological mechanism

The use of pilocarpine clinically to control IOP associated with several types of glaucoma dates back to the 1870s. Three related products, using pilocarpine hydrochloride were approved by FDA in 1970's and 1980's for this same indication. These products are: ophthalmic medicated inserts Ocusert Pilo 20 and Ocusert Pilo 40 approved in 1974 and pilocarpine hydrochloride ophthalmic gel 4% approved in 1984.

The biological mechanism of the drug to reduce elevated IOP is described in the same fashion in several review articles or book chapters from the past 40 years. For example, there are descriptions of the mechanism in two review articles (Ellis (1971) and Zimmerman (1981)) and a book chapter (Bartlett 2008) which span four different decades. In Ellis 1971: "The ocular hypotensive action of pilocarpine in open angle glaucoma results principally from improved aqueous outflow. The usual explanation for this effect is a pull on the sclera by the ciliary muscle with subsequent widened openeings in trabecular tissue and decreased resistance to aqueous outflow." In Zimmerman (1981): "The effects of pilocarpine on aqueous humor dynamics are complicated and still not completely understood. The primary mechanism for pilocarpine induced intraocular pressure reduction is increased outflow. Parasympathomimetic stimulation contracts the ciliary muscle and produces an inward movement of the scleral spur to which it is attached. This produces a structural change in the trabeculum, permitting an increase in outflow

of aqueous". Finally, in Bartlett (2008) : " although the precise mechanism by which pilocarpine reduces IOP has not been established, the most widely accepted explanation involves direct stimulation of the longitudinal muscle of the ciliary body, which in turn causes the scleral spur to widen the trabecular spaces and increase aqueous outflow."

3.1.1.2 Summary of evidence from clinical studies

The applicant submitted detailed clinical reports of four studies (C-90-42, C-91-47, C-91-54 and C-90-105) as well as a list of 16 publications to support the efficacy indication. There is some overlapping information between these different sources as one of these 16 references (Robin 1996) describes clinical trials C-90-42, C-91-47 and C-91-54 and another reference (Drance 1998) describes clinical trial C-90-105. I first summarize the evidence from the clinical studies conducted by the applicant (and the papers which describe them) and then comment on the studies in the different publications.

Studies C-90-42, C-91-47, C-91-54 and publication Robin 1996

All three studies were multicenter (C-90-42: 6 sites, C-91-47: 9 sites, C-91-54: 6 sites), double masked, active controlled, parallel trials. Studies were conducted from January 30, 1991 to June 19, 1992. Study C-90-42 was a small dose finding study which recruited 76 subjects, while studies C-91-47 and C-91-54 were large pivotal studies which recruited 182 subjects and 186 subjects respectively.

These studies were submitted as part of the NDA submission for betoptic pilo (NDA 20619 approved in 1997). Betoptic pilo is the combination drug of betaxolol 0.25% and pilocarpine 1.75% and the main goal of these studies was to compare the IOP lowering effect of the combination drug to the effect of each of its component: betaxolol 0.25% and pilocarpine 2%.

Patient population:
Subjects recruited in these studies were diagnosed with primary open-angle glaucoma or ocular hypertension and were candidates to use one additional medication adjunctive to a beta blocker. Subjects underwent 3 to 4 weeks run-in of betaxolol 0.25% suspension twice a day, and had an IOP measurements of 23 to 34 mmHg after this run-in period.

Treatment groups and sample sizes:
There were three treatment groups in studies C-91-47 and C-91-54. Each treatment group received 3 to 4 weeks run-in of Betaxolol Suspension 0.25% twice a day (open label). After the run-in period, subjects were randomized to one of these three treatment groups: pilocarpine 2% solution, Betaxolol 0.25% suspension, and the combination of pilocarpine 1.75% and Betaxolol 0.25%. All three treatments were provided three times a day.

Number of visits and measurements at each visit
IOP in the treatment phase was measured on day 14, day 45 and day 90. In study C-90-42, four measurements were taken on 8 AM, 10 AM, 12 PM, 2 PM for C-90-42 on day 14 and day 90 and

only one IOP measurement was taken 8 AM on day 45. In studies C-91-47 and C-91-54, three IOP measurements were taken on day 14 and day 90 at 8 AM, 12 PM, 4 PM and only one IOP measurement was taken at 8 AM on day 45.

Primary endpoint

The primary endpoint was change from baseline, which was calculated for each time of day by subtracting the baseline IOP measurement at 8 AM from the IOP at that time of day. So, this endpoint does not adjust for the diurnal variation in IOP measurement and the treatment effect for all time points after 8AM are confounded with diurnal variation. Since IOP tends to be higher in the morning than in the afternoon, the change from baseline in the afternoon measurements overestimates the treatment effect.

Primary statistical analyses and main findings

The goal of the primary statistical analysis was not to show efficacy of pilocarpine, but rather show superiority of the combination to each of its component in terms of IOP change from baseline.

The primary analysis was a repeated measure analysis of variance at 8AM considering the different days as repeated measures. There were two secondary repeated measures analyses, one at 12 PM and the other at 4PM. The fixed effects in these repeated measures were the investigators, the days, treatment by day interaction, treatment by investigator interaction and baseline IOP measurement. Subject effect was fitted as a random effect.

Results in studies C-91-47 and C-91-54 show that the mean IOP reductions from the combination exceeded the mean IOP reductions from each of the combinations' component. Results from the small exploratory analysis C-90-42 shows similar trends, but the differences were not significant due to small sample sizes.

These statistical analyses were carried out on the intent to treat population, using LOCF to impute missing values. In study C-91-47 182 subjects were recruited and 161 subjects were in intent to treat analysis (54 Combination, 59 Betaxolol, 48 Pilocarpine). In study C91-54, 186 subjects were recruited and 168 subjects were in intent to treat analysis (53 combination, 61 betaxolol, 54 pilocarpine).

Re-analysis of some data for this review

Since the goal of this review, to quantify the effect of pilocarpine, is different from the original goal of the studies, I carried out a different analysis of the results of the studies. My results are shown in Table 1 in the Executive Summary. The endpoint here is IOP change from baseline after the run-in period to 14 days, 45 days and 90 days after treatment on this patient population. The findings in Table 1 suggest that for this patient population and after a run-in period of Betaxolol, pilocarpine still has a statistically significant effect on reducing IOP from baseline. The mean and standard deviation in this table were copied from the study reports and were only available for the per protocol population. Using the mean, sample size and standard deviation of the raw change from baseline data I calculated a confidence interval on each day and for each of the three studies. In pivotal studies C-91-54 and C-91-47, the confidence intervals are strictly

below 0 on all days but day 90 in Study C-91-47. Similar trends of IOP lowering are shown in C-90-42, but for lack of power, most confidence intervals include 0.

Study C-90-105 and Drance (1998)

Study C-90-105 was a small study (69 subjects), randomized, active-controlled, single-center with three parallel arms. The objective of the study was to compare the effect of betaxolol, timolol, and pilocarpine on visual function in primary angle glaucoma patients. The three treatment arms are Betaxolol 0.25% twice daily, Timolol 0.5% twice daily and pilocarpine 2% four times daily. The timolol and betaxolol were masked, whereas the pilocarpine was clearly labeled, as the author considered that "the pupillary effects and frequency of instillation would make masking meaningless". Out of the 69 subjects who were recruited in the study, 14 received pilocarpine 2%. The study ran from June 28th, 1991 to June 13, 1996.

All patients had chronic open-angle glaucoma, which included IOPs 24 mmHg or higher with disc and visual field abnormality. The visual field defects had to include localized scotomata which were not severe enough to preclude reliable psychophysical follow-up and evaluation (mean defect < 10 dB). Patients with glaucoma who have pseudoexfoliation and pigmentary glaucomas could be included. All previous topical therapy had to be discontinued for at least 4 weeks. Patients with a history of ocular trauma, uveitis, inflammatory disease, and recent infections were excluded. A history of retinal disease, intraocular surgery within the past 6 months, or laser trabeculoplasty within the past 3 months were also reasons for exclusion. Current contact lens wearers, patients with a hypersensitivity to betaxolol, timolol, or any components of these medications were excluded. Premenopausal women who were not on a program of birth control, and patients with severe or unstable cardiovascular or pulmonary disease, overt cardiac failure, cerebrovascular disease, chronic renal failure, sinus bradycardia, or more than first-degree heart block were not recruited. The use of systemic glucocorticoids, systemic medication that may affect IOP such as beta agonists and antagonists, calcium-channel blockers, and angioteusin converting enzymes also lead to exclusion.

Visits were scheduled at 3, 6, 12, 18, and 24 months and on each visit IOP was measured. When both eyes of a patient met the inclusion criteria the eye to be studied was randomly selected. Individual IOP measurements at baseline and under treatment were available in the study report submitted by the applicant. These measurements for the Pilocarpine arm are shown in Figure 1 (baseline, month 3 and month 6) and in Figure 2 (month 12, month 18 and month 24). Note that three out of 14 subjects did not have measurements post-baseline. These 3 subjects discontinued the use of the drug due to "unacceptable local side effects" according to the author (Drance 1998). Summary of these results is shown in Table 5. I see in Table 5 that under pilocarpine 2% treatment, IOP is reduced by 5mmHg to 7mmHg from baseline. All these changes in IOP are statistically significant at the 1% significance level using a paired t-test.

Note that in Figure 1 the IOP measurements at baseline were taken anywhere between 8:30 AM and 5:40 PM with only three measurements before 9:30am, whereas the measurements after start of therapy were mostly taken in the morning between 8:30 AM and 9:30 AM. Thus, any individual change from baseline will be due to treatment and diurnal variation of IOP. Since IOP

tends to be higher in the morning than in the afternoon, the treatment effect estimated from this study may be **underestimating** the true treatment effect if all measurements at baseline were taken before 9:30 AM.

PROTOCOL C-90105
TABLE Q
IOP (mmHg), TIME

				BASELINE		MON 3		MON 6	
TREATMENT	INV	PAT	EYE	IOP	IOP TIME	IOP	IOP TIME	IOP	IOP TIME
0.5% TIMOLOL	102	152	OD	12	05:10 PM	18	12:55 PM	16	12:35 PM
0.5% TIMOLOL	102	155	OS	22	04:40 PM	22	12:10 PM	20	12:15 PM
0.5% TIMOLOL	102	156	OS	26	02:40 PM	20	12:45 PM	19	12:35 PM
0.5% TIMOLOL	102	159	OD	24	11:35 AM	19	12:06 PM	16	12:58 PM
0.5% TIMOLOL	102	162	OD	19	12:00 PM	17	12:30 PM	22	12:40 PM
0.5% TIMOLOL	102	163	OS	31	03:10 PM	20	12:35 PM	21	12:44 PM
0.5% TIMOLOL	102	164	OS	24	04:00 PM	16	12:55 PM	21	12:30 PM
0.5% TIMOLOL	102	166	OS	20	12:15 PM	17	12:50 PM	15	12:35 PM
0.5% TIMOLOL	102	168	OS	24	11:25 AM	18	12:40 PM	20	12:30 PM
2.0% PILOCARP	102	101	OD	25	09:40 AM				
2.0% PILOCARP	102	105	OD	23	11:00 AM				
2.0% PILOCARP	102	109	OD	22	03:00 PM	16	10:30 AM	18	09:05 AM
2.0% PILOCARP	102	110	OS	24	08:30 AM	19	09:30 AM	18	09:05 AM
2.0% PILOCARP	102	116	OS	20	02:05 PM	18	09:15 AM	21	11:50 PM
2.0% PILOCARP	102	118	OD	24	12:10 PM	19	11:15 AM	19	09:05 AM
2.0% PILOCARP	102	122	OS	37	09:00 AM	15	08:50 AM	17	08:45 AM
2.0% PILOCARP	102	124	OD	24	09:05 AM	15	09:05 AM	14	09:10 AM
2.0% PILOCARP	102	125	OS	29	04:30 PM				
2.0% PILOCARP	102	128	OD	22	05:30 PM	15	08:30 AM	15	08:35 AM
2.0% PILOCARP	102	132	OD	25	12:00 PM	22	08:35 AM	20	08:25 AM
2.0% PILOCARP	102	133	OD	25	11:50 AM	20	10:05 AM	25	08:40 AM
2.0% PILOCARP	102	137	OD	27	05:40 PM	18	09:15 AM	23	09:30 AM
2.0% PILOCARP	102	140	OS	24	02:20 PM	20	08:35 AM	16	08:49 AM

Figure 1: Results of study C-90-105 on IOP measurements at baseline, month 3 and month 6 for the pilocarpine arm

PROTOCOL C-90105
TABLE Q
IOP (mmHg), TIME (CONTINUED-2)

				MON 12		MON 18		MON 24	
TREATMENT	INV	PAT	EYE	IOP	IOP TIME	IOP	IOP TIME	IOP	IOP TIME
0.5% TIMOLOL	102	131		24	12:44 PM	24	12:20 PM		
0.5% TIMOLOL	102	131	OS	24	12:44 PM	24	12:20 PM		
0.5% TIMOLOL	102	136							
0.5% TIMOLOL	102	136	OS						
0.5% TIMOLOL	102	139		15	12:15 PM				
0.5% TIMOLOL	102	139	OD	15	12:15 PM				
0.5% TIMOLOL	102	141	OD	14	12:30 PM	15	12:55 PM	21	12:10 PM
0.5% TIMOLOL	102	145	OD	20	12:16 PM	18	12:35 PM	21	12:30 PM
0.5% TIMOLOL	102	147	OD	18	12:40 PM	17	01:00 PM	20	12:30 PM
0.5% TIMOLOL	102	149	OS	13	11:30 AM	14	01:05 PM	14	12:15 PM
0.5% TIMOLOL	102	150	OS	20	12:00 PM	19	12:40 PM	14	12:20 PM
0.5% TIMOLOL	102	152	OD	17	12:50 PM	15	01:40 PM	16	12:35 PM
0.5% TIMOLOL	102	155	OS	18	12:20 PM	20	10:15 AM	22	01:15 PM
0.5% TIMOLOL	102	156	OS	21	01:35 PM	23	12:50 PM	24	04:15 PM
0.5% TIMOLOL	102	159	OD	17	01:15 PM	17	04:30 PM	20	12:20 PM
0.5% TIMOLOL	102	162	OD	26	12:10 PM	21	12:15 PM	20	12:17 PM
0.5% TIMOLOL	102	163	OS	19	12:10 PM	20	12:30 PM	19	12:20 PM
0.5% TIMOLOL	102	164	OS	19	02:25 PM	18	12:55 PM	19	01:10 PM
0.5% TIMOLOL	102	166	OS	15	12:25 PM	16	12:45 PM	20	12:30 PM
0.5% TIMOLOL	102	168		22	04:10 PM	20	12:10 PM		
0.5% TIMOLOL	102	168	OS	22	04:10 PM	20	12:10 PM		
2.0% PILOCARP	102	101							
2.0% PILOCARP	102	101	OD						
2.0% PILOCARP	102	105							
2.0% PILOCARP	102	105	OD						
2.0% PILOCARP	102	109	OD	15	09:00 AM	18	08:35 AM	17	09:30 AM
2.0% PILOCARP	102	110	OS	20	09:00 AM	20	08:15 AM	20	09:10 AM
2.0% PILOCARP	102	116	OS	18	08:35 AM	17	08:32 AM	15	08:20 AM
2.0% PILOCARP	102	118	OD	22	08:35 AM	16	08:40 AM	15	08:45 AM
2.0% PILOCARP	102	122	OS	17	08:30 AM	12	09:05 AM	27	08:05 AM
2.0% PILOCARP	102	124	OD	18	08:45 AM	19	08:43 AM	23	08:45 AM
2.0% PILOCARP	102	125							
2.0% PILOCARP	102	125	OS						
2.0% PILOCARP	102	128	OD	13	08:35 AM	18	09:03 AM	21	08:35 AM
2.0% PILOCARP	102	132	OD	21	08:35 AM	21	08:19 AM	19	08:45 AM
2.0% PILOCARP	102	133	OD	26	08:50 AM	22	08:25 AM	23	08:40 AM
2.0% PILOCARP	102	137	OD	16	09:30 AM	18	09:35 AM	18	09:10 AM
2.0% PILOCARP	102	140	OS	20	08:32 AM	17	08:40 AM	22	08:40 AM

Figure 2: Results of study C-90-105 on IOP measurements at month 12 and month 18 and month 24 for the pilocarpine arm

Table 5: Selected results from study C-90-105 on IOP and IOP change from baseline. N=11 subjects.

	Baseline	Month 3	Month 6	Month 12	Month 18	Month 24
Mean IOP (mmHg)	24.91	17.91	18.73	18.73	18.00	20.00
SD of IOP (mmHg)	4.41	2.39	3.35	3.61	2.68	3.69
Mean IOP change from baseline (mmHg)	NA	-7.00	-6.18	-6.18	-6.91	-4.91
SD of IOP change from baseline (mmHg)		5.44	5.58	5.69	6.33	3.30

Studies described in publications

I give in this section a general summary of the publications presented by the applicant, then focus on the two most relevant publications for this indication: Vogel et al (1992) and Sharma and Gupta (1997)) to quantify the effect of the drug.

The applicant submitted 16 publications from the past 20 years to support this indication. I already summarized the findings from two of these publications above since these two publications overlapped with the studies conducted by the applicant, so the summary here focuses on the remaining publications. Vogel et al (1992) and Sharma and Gupta (1997)) were selected as most relevant because they quantify the long term (2 years) effect of pilocarpine alone.

The study designs in these publications were diverse in terms of types of glaucoma, length of follow-up, dosage of pilocarpine used, and whether pilocarpine was used as primary line of care for management or glaucoma. Some studies quantified the short term effect of pilocarpine alone on IOP while other quantified the effect over a two year period. Most studies are on subjects with open angle glaucoma or ocular hypertenstion, however Bergea et al (1992) and Bergea et al (1994) present results on subjects with simplex or capsular glaucoma. The IOP lowering effect was quantified in a short time frame in Thygesen (1990) for pilocarpine 4% within 2 hours, in Zadok et al (1994) for pilocarpine 4% within 4 weeks, in Sihota et al (1996) for pilocarpine 1% within 12 hours, in Geyer et al (1997) for pilocarpine 4% within 6 hours, and in Toris et al (2001) for pilocarpine 2% within 8 days. Two studies presented each in Vogel et al (1992) and Sharma and Gupta (1997) quantified the effect of pilocarpine 2%-4% alone over a two year period. The six month study in Diestelhorst 2000 quantify the combined effect of pilocarpine as a second line therapy after timolol fails to adequately lower IOP whereas the study by Anastasios et al (2001) quantifies the effect of pilocarpine as third line therapy after timolol 0.5% and dorzalamide 2% fail to adequately lower IOP. Bergea et al (1995a, 1995b) and Laibovitz (1996) have very little IOP assessments and mostly safety data on pilocarpine arm.

Regardless of design, all publications showed statistically significant (below 1% level of significance) IOP reduction from baseline of pilocarpine hydrochloride arm which further supports the approval of this indication.[1]

Vogel et al (1992)

Seven investigators entered a total of 189 patients with primary open-angle glaucoma into this study. After a pretreatment washout period of 7 days, measurements of IOP were taken along other measurements of interest.

Admission criteria included: (1) IOP of 22 mmHg or greater in one or both eyes on at least 1 of 5 measurements taken (approximately 9:00, 10:30, 12:00, 14:30, and 16:30 hours) on the same day after a washout period of at least 7 days taking no glaucoma therapy; (2) open anterior chamber angles; and, (3) a visual field defect recorded by the Octopus Program 32, which showed a depression of three or more contiguous test points greater than 5 dB below "normal" values for the patient's age as determined by the Octopus or greater than 5 decibels (dB) below adjacent contiguous points. Patients were excluded if they had: (1) a history of severe ocular trauma or intraocular surgery; (2) a corneal ulcer, ocular infection, or herpetic keratitis within 3 months of the study start; (3) a history of angle-closure or secondary glaucoma; (4) bronchial asthma or chronic obstructive pulmonary disease; greater than first degree heart block, uncompensated heart failure, or bradycardia of significant degree; (5) any disease other than open-angle glaucoma producing visual field loss; (6) concomitant medications known to affect IOP; (7) pregnant or nursing women or women of childbearing potential not using adequate means of contraception

Patients were started on either 0.25% timolol twice daily or 2% pilocarpine four times daily according to the random allocation schedule. Patients entered a dose adjustment period, IOP was measured after 2 weeks, and the concentration of the drug was increased (to either timolol 0.5% or pilocarpine 4%) if IOP lowering was insufficient (i.e. if the IOP was above 22 mmHg). If the drug concentration was increased, the patient had a further IOP examination 2 weeks later. Patients were examined every 4 months throughout the 2-year study.

The analysis of efficacy data was performed using a "worse" eye approach. If both eyes were being treated in the study, the eye with the lower mean visual field score at study entry was used in the analysis. If both eyes were being treated and had equivalent mean scores, the right eye was used in the analysis. A partial diurnal curve consisting of 5 IOP measurements spanning 7.5 hours was collected al each visit. The maximum of these five measurements was used as the response variable.

[1] When mean and standard deviation of change from baseline were provided, testing was conducted using a paired t-test controlling for IOP the measurements being made on the same subject/eye. When mean and standard deviation of change from baseline were not provided but the mean and standard deviation of raw IOP were available at baseline and after treatment, testing was conducted using a two sample independent t-test. The two sample independent t-test does not control for the IOP measurements being made on the same subject/eye. However, since the within subject treatment effect (baseline and treatment) seem to outweigh the between subject variability, we do not expect the two tests (pairwise t-test and standard t-test) to give different results.

Within both treatment groups, there was a significant decrease in both the maximum diurnal IOP and in the range from study start (the first day of treatment after a washout period) compared with month 0 (the day of the baseline visual field examination, which was at the end of the dose adjustment period).

Table 6: Selected results from Vogel et al (1992)

	IOP	SD	N	Change from baseline	pooled sd
Baseline	27.9	5.1	45		
0 month	20.5	3.1	45	7.4**	4.22
4 months	20.8	2.8	41	7.1**	4.11
8 months	21.6	4	31	6.3**	4.58
12 months	21.3	3.4	26	6.6**	4.33
16 months	20.8	2.5	26	7.1**	4.02
20 months	21.7	2.4	24	6.2**	3.99
24 months	21.9	2.7	20	6**	4.08

** significant at 0.5% significance level

Sharma and Gupta (1997)

Thirty eight patients at the ophthalmology outpatient of the Postgraduate Institute of Medical Education and Research, Chandigarh with recent diagnosis of POAG were entered into the study. Criteria for inclusion into the trial were as follows: (i) IOP more than 21 mmHg on two occasions or on the same at two hour intervals between 8.00 AM and 5.00 PM with Goldmann applanation tonometer (2) Cup-disc ratio greater than 0.4, pallor of neuroretinal rim and/or generalized thinning of neuroretinal rim, polar notching; (3) glaucomatous field loss using Topcon automated perimeter. Eye with the first of these three criteria along with either on both of the second and third criteria were included in this study.

Once inclusion criteria for primary open angle glaucoma had been satisfied, one eye of every patient was treated with Argon laser Trabeculoplasty (ALT) and the other eye with medical therapy, pilocarpine 2% every 8 hours. The treatment assignment was not randomized, but rather done in alternating fashion. Patients with even numbers received ALT in the right eye and pilocarpine (2%) in the left eye and patients with odd numbers received ALT in the left eye and pilocarpine (2%) in the right eye. Treatment to both eyes was initiated simultaneously. In case of delay in performing ALT, pilocarpine 2% every 8 hours was started and later discontinued on the day ALT was performed.

Table 7: Selected results from Sharma and Gupta (1997)

	IOP	SD	N	change from baseline	pooled sd
Baseline	24.47	3.51	36	NA	
3 months	18.42	3.1	33	6.05**	3.32
6 months	17.59	2.31	30	6.88**	3.03

12 months	18.29	2.45	27	6.18**	3.10
18 months	18.24	5.58	25	6.23**	4.47
24 months	18.27	2.22	21	6.2**	3.10

**significant at 0.5% significance level

3.1.2 Indication 2: (b) (4) acute angle-closure glaucoma

I first describe the use of pilocarpine for acute angle closure described in review articles and book chapters. Then, I comment on the indication sought by the applicant for (b) (4) (b) (4) acute angle closure glaucoma (ACCG).

The effect of pilocarpine on acute angle closure seems complex. Through its miotic effect, pilocarpine is sometimes described as a treatment, and at other times as an aggravating factor or as a trigger to angle closure. In Zimmerman (1981): "Pilocarpine is used to lower intraocular pressure in open angle glaucoma and to break acute angle closure attacks. For this latter use, concentrations of 2% or less are of sufficient strength to stimulate the desired miosis and terminate the attack. Stronger concentrations, which break down the blood-aqueous barrier and further shallow the anterior chamber can lead to permanent peripheral synechiae and permanent angle closure". From the book Chapter by Ritch (1999): "The author's preferred approach to control and break an attack of AACG is as follows: Oral isosorbide and one or more topical aqueous suppressants are administered. Intravenous acetazolamide can be given according to the physician's preference. The patient is then placed supine to permit the lens to fall posteriorly with vitreous dehydration. The eye is reassessed after 1 hour. IOP is usually decreased, but the angle usually remains appositionally closed. One drop of pilocarpine 4% is given and the patient is re-examined 30 minutes later. If IOP is reduced and the angle is open, the patient may be treated medically with topical low-dose pilocarpine, aqueous suppressants, and cotticosteroids, until the eye quiets and laser iridotomy may be performed. However, if IOP is unchanged or elevated and the angle remains closed, lens-related angle closure should be suspected, further pilocarpine is withheld, and the attack is broken by argon laser peripheral iridoplasty (ALPI**)".** Further in the same book chapter: "Prolonged miotic treatment in eyes with open-angle glaucoma and narrow angles may lead to pupillary block and angle-closure glaucoma. Zonular relaxation leads to anterior lens movement and increased lens thickness in combination with increased pupillary block produced by pilocarpine. When miotic-induced angle closure occurs, the approach to treatment should be determined by assessing the medications necessary to control the glaucoma. Dipivefrin or epinephrine may cause mild pupillary dilation, potentially worsening pupillary block. If a patient is taking dipivefrin or epinephrine, its discontinuation may be enough to open the angle and allow the patient to continue taking miotics, presuming IOP remains under control. If the patient has been treated with miotics alone, substitution of aqueous suppressants may suffice. If the patient requires miotics for IOP control, then laser iridotomy is warranted. If the angle remains appositionally closed or spontaneously occludable after laser iridotomy, ALPI is indicated to prevent progressive damage to, or further appositional and/or synechial closure of, the angle. If, after iridoplasty, some of the angle still remains appositionally closed, low-dose pilocarpine, such as 2%, at bedtime often suffices to maintain the patency of the angle".

(b) (4)

The applicant submitted 8 articles to support this indication:

- Kobayashi (1999), Pavlin (1999), and Ritch (1996) do not present any measurements on IOP.

- Lai (1999), Lai (2000), Lam (1998), Lam (2002)a, and Lam (2002)b look at the concomitant effect of timolol 0.5%, pilocarpine 4% and laser surgery on reducing IOP. In all these articles, IOP was measured once before surgery and several times after surgery. None of these articles present IOP measurements before instillation of the drugs and after instillation of the drugs, before surgery occurred.

I conducted my own search of articles looking at the effect of pilocarpine in subjects undergoing laser iridotomy or laser iridoplasty. Similarly to the issues identified above, the articles from my search either did not measure IOP or measured IOP after drug instillation and after surgery, but not before drug instillation. In summary, although there is evidence suggesting the use of pilocarpine in acute angle closure glaucoma, (b) (4)

Note that the clinical review team considered the indication of ***'management of acute angle closure glaucoma'*** *instead of the indication sought by the applicant of* (b) (4) *acute angle-closure glaucoma'. Since it is unclear to me how the management of acute angle closure glaucoma can be assessed and quantified, I leave it to the clinical review team to comment on this indication.*

3.1.3 Indication 3: Prevention of (b) (4) postoperative elevated IOP associated with (b) (4) laser surgery (b) (4)

(b) (4)
(b) (4).

(b) (4)
I will first summarize my criteria for selection of the studies and their main characteristics. Then, I will outline my reasoning explaining my conclusion for this indication.

From the 6 articles submitted by the applicant and my own literature search, I found 14 relevant publications. Some criteria for selection of the studies in the publication were that each study had to be on subjects undergoing glaucoma laser surgery and had to have measurements of IOP before and shortly after surgery. Additional criteria were that either the study included one arm

using pilocarpine alone before or after surgery, or the study included one arm with no treatment before or after surgery or a placebo treatment for another drug. Among these 14 studies, five studies were submitted by the applicant. Those are: Elsas et al (1991), Dapling et al (1994), Fernandez-Bahamonde and Alcaraz-Michelli (1990), Liu et al (2002), Ren et al (1999) . In addition, nine studies found through reviewer's search are: Leung and Gillies (1986), Robin (1989), Krupin et al (1985), Robin and Pollack (1984), Schwartz et al (1986), Ofner et al (1984), Brown et al (1985), David et al (1993), and Shin et al (1994). The list of studies with pilocarpine can be split in four different groups depending on when pilocarpine was administered and to what it was compared to:

1- Studies comparing pilocarpine (before surgery) to a "no treatment" group: Elsas et al (1991), and Leung and Gillies (1986). Note that I did not find any study comparing pilocarpine to placebo, so this group is the most important group to estimate the treatment effect of pilocarpine. Design synopsis and summary results for these two studies are shown in Table 12 and Table 13.
2- Studies comparing pilocarpine (before surgery) to other drugs or other drug combinations: Dapling et al (1994), Fernandez-Bahamonde and Alcaraz-Michelli (1990), Liu et al (2002), Ren et al (1999) and Robin (1989). Design synopsis and summary results are shown in Table 14 and Table 15.
3- Studies with one or multiple arms all using pilocarpine before surgery: Krupin et al (1985), Robin and Pollack (1984), Schwartz et al (1986). Design synopsis and summary results are shown in Table 16 and Table 17
4- Studies comparing pilocarpine after surgery to no treatment: Ofner et al (1984) and Brown et al (1985). Design synopsis and summary results are shown in Table 18 and Table 19.

In addition to the pilocarpine studies, we have two studies with a placebo arm: David et al (1993) and Shin et al (1994) which are shown in Table 20 and Table 21.

As shown in Table 12 to Table 21, study population varied. All subjects and eyes included in the studies were candidates for laser surgery. The reason for the surgery varied from study to study, it was primary open angle glaucoma (POAG), primary angle closure glaucoma (PACG), chronic angle closure glaucoma (CACG), senile cataract extraction, or exfoliated glaucoma with disc damage and/or visual defects. The type of surgery also varied from study to study, it was either Nd:YAG iridotomy, argon laser iridotomy, argon laser trabeculoplasty (180 or 360 degrees), or Nd:YAG posterior capsulotomy. Pilcoarpine concentration used also varied from 1% to 4%, with most frequent concentrations being 2% or 4%.

This indication is hard to quantify as the endpoint measured in the studies varied widely. Some studies used change from baseline before the surgery as an endpoint, while most studies used number of subjects who experienced an IOP spike after surgery as an endpoint. The definition of spike varied as well, a spike was defined as 'any increase from baseline' (i.e. change above 0 mmHg), increase above 5mmHg, increase above 10mmHg, or increase above 20mmHg. Some spikes of above 30mmHg were observed in some studies as well.

I first summarize the results of the two studies comparing pilocarpine against the no treatment arm, then I discuss the additive effect of pilocarpine to apraclonidine in two studies, and finally discuss the pilocarpine effect quantified in all the other studies.

Results of pilocarpine against no treatment arm

As shown in Table 12 and Table 13, the two studies Elsas et al (1991) and Leung and Gillies (1986) compare pilocarpine 2% or 4% to "no treatment", they were conducted on different population, have different endpoints and different results. More precisely, **Elsas et al (1991)** shows a very significant effect of IOP reduction post-laser trabeculoplasty of pilocarpine 2% applied one hour before surgery against the no treatment arm for eyes with 'severe' untreated glaucoma. I label these eyes as 'severe' untreated glaucoma because the study included eyes with exfoliated glaucoma, simple glaucoma, high baseline IOP baseline, with glaucomatous disc damage and/or visual field defects and no previous glaucoma treatment. This study found that of 12% (3/25) of subjects in pilocarpine 2% arm experienced an IOP peak above 10mmHg in the few hours after surgery, compared to 52% (13/25) in the no treatment arm. This difference is highly statistically significant using a chi-square test. The change in IOP from baseline was of 2.4mmHg with standard deviation of 4.4mmHg in the pilocarpine 2% arm compared to 12.8mmHg with standard deviation of 11.2mmHg in the no treatment arm. In contrast, **Leung and Gillies (1986)** fails to show a significant effect of IOP reduction post-laser trabeculoplasty of pilocarpine 4% applied before surgery compared to a no treatment arm for eyes with open angle glaucoma. This study found that 42% (14/33) of subjects in pilocarpine 4% arm experienced an IOP peak above 5 mmHg in the few hours after surgery, compared to 48% (15/31) in the 'no treatment' arm. The mean change in IOP from baseline was of a 3.2mmHg with standard deviation of 6mmHg in the pilocarpine 4% arm compared to a mean of 4.9mmHg with standard deviation of 6.5mmHg in the 'no treatment' arm.

The following quotes from Leung and Gillies (1986) and Robin (1989) may explain the different results between Elsas et al (1991) and Leung and Gillies (1986). In Leung and Gillies (1986): **Copyright Material** . This quote suggest that the association between baseline IOP and endpoint may explain the difference between the results of Elsas et al (1991) and Leung and Gillies (1986). In Robin (1989) : "patients undergoing chronic pilocarpine therapy at the time of ALT did not benefit as much from pilocarpine 4% prohylaxis". This quote may also also explain the difference between Elsas et al (1991) and Leung and Gillies (1986). It suggests that pilocarpine may work better on a pilocarpine-naïve population than on patients who are already receiving pilocarpine to manage their elevated IOP.

Additive effect of pilocarpine to apraclonidine 1%

In Dapling et al (1994) pilocarpine 4% is compared to apraclonidine 1% and to the combination of pilocarpine and apraclonidine 1% for subjects undergoing laser trabeculoplasty, where apraclonidine is an approved drug for this indication. When comparing the effect of the apraclonidine 1% arm alone to the combination, I see that pilocarpine 4% has a significant additive effect to apraclonidine 1% in reducing IOP elevation after surgery.

Results of pilocarpine arm across multiple studies

There is a lot of heterogeneity of results when comparing the pilocarpine 1%, 2%, or 4% effect in different studies using the same endpoint. As shown in Table 8, the percent of spikes above baseline go from 39% (9/23) in Dapling et al (1996) to 68% (34/50) in Krupin et al (1985). As shown in Table 9, the percent of eyes with spikes above 5mmHg from pre-surgery goes from 4% in Ren (1998) to 46% (23/50) in Krupin et al (1985). Finally, as shown in Table 10, the percent of eyes with spikes above 10mmHg from pre-surgery goes from 3% (1/37) in Robin et al (1989) to 36% (4/11) in Fernandez-Bahamonde and Alcaraz-Michelli (1990).

There is no easy explanation for these discrepancies. However, note that the effect of the pilocarpine arm is the lowest in the more recent studies especially Dapling et al (1996) and Ren et al (1999). One possible explanation is that in both of these studies subjects who would undergo surgery were instructed to continue their regular glaucoma medication until before surgery, hence their baseline IOP before surgery may have been more under control than in earlier studies and this may in turn have lowered the incidence of spikes overall. Another possible explanation is that in earlier studies, subjects undergoing surgery may have already been using pilcoarpine to manage their elevated IOP[2] which in turn may have made them less responsive to the drug. These two possible explanation are simple post-hoc conjectures.

[2] For instance, from Robin and Pollack (1984) we read that "all patients were also using varying strengths (1%-4%) of pilocarpine hydrochloride prior to surgery and throughout the study period"

Comparing Leung and Gillies (1984) to other studies

The result on the pilocarpine arm in Leung and Gillies (1986) are not unusually high, and the results in the no treatment arm in this study are not unusually low. As shown in Table 9, result on the pilocarpine arm of 42% in Leung and Gillies (1986) is similar to the results on the pilocarpine arm in three other studies using the same endpoint (peak above 5mmHg): 46% (46/100) in Krupin et al (1985), 42% (20/47) in Liu et al (2002), and 32% (13/37) in Robin (1989). However, the results on the pilocarpine arm are much larger than the results on the pilocarpine arm of two recent studies: 9% (2/23) in Dapling et al (1994) and 4% (5/114) in Ren et al (1999). As shown in Table 11, results on the same endpoint (peak above 5mmHg) in the no treatment arm in Leung and Gillies (1986) of 48% are not unusually low, they are in fact higher than in the placebo arm of David et al (1993) of 41% (23/56) and much higher than in the placebo arm result of 27% (19/71) in Shin et al (1996).

Comparing Elsas et al (1991) to other studies

The results on the pilocarpine arm in Elsas et al (1991) are unusually low and the results on the no treatment arm seem unusually high as well. As shown in Table 10, the result of 12% on the pilocarpine arm in Elsas et al (1991) is much lower than the rate in other studies with pilocarpine arm using the same endpoint (above 10mmHg): 37% (4/11) in Fernandez-Bahamonde et al (1990), 29% (29/100) in Krupin et al (1985), 32% (13/40) in Robin and Pollack (1984), and 30% (54/182) in Schwartz (1986). The rate in Elsas is higher than the rate of a single study: 3% (1/37) in Robin (1989) which has a similar population than Elsas et al (1991). As shown in Table 11, results on the no treatment arm in Elsas et al (1992) of 52% is much higher than the placebo arm result of 23% (13/52) in the David et al (1993) study. So, the results in Leung and Gillies (1986) seem more consistent to the results of the other studies than the results in Elsas et al (1991).

Table 8: Results of pilocarpine arm for any IOP increase from pre-surgery

Study	Laser surgery	Pilocarpine concentration	subjects with spikes	sample-size	Spike rate
Krupin 1985-A	ALI	2% or 4%	33	50	66%
Krupin 1985-B	ALI	4%	34	50	68%
Robin 1984-A	NdYAG	1%, 2% or 4%	13	20	65%
Robin 1984-B	ALI	1%, 2% or 4%	12	20	60%
Robin 1989	ALT	4%	21	37	57%
Dapling 1994	ALT	4%	9	23	39%

ALI: Argon laser iridoplasty
NdYAG: Nd:YAG laser iridoplasty
ALT: argon laser trabeculoplasty

Table 9: Results of pilocarpine arm for IOP increase above 5mmHg from pre-surgery

Study	Laser Surgery	Pilocarpine concentration	subjects with spikes	sample-size	Spike rate
Krupin 1985-A	ALI	2% or 4%	23	50	46%
Krupin 1985-B	ALI	2% or 4%	23	50	46%
Liu 2002	Nd:YAG	4%	20	47	42%
Leung 1986	LT	4%	14	33	42%
Robin 1989	ALT	4%	12	37	32%
Ren et al 1999	ALT	4%	5	114	4%
Dapling 1994	ALT	4%	2	23	9%

ALI: Argon laser iridoplasty
NdYAG: Nd:YAG laser iridoplasty
ALT: argon laser trabeculoplasty

Table 10: Results of pilocarpine arm for IOP increase above 10mmHg from pre-surgery

Study	Laser surgery	Pilocarpine concentration	subjects with spikes	sample-size	Spike rate
Fernandez-Bahamonde 1990	ALI	4%	4	11	36%
Krupin 1985-A	ALI	2% or 4%	12	50	24%
Krupin 1985-B	ALI	2% or 4%	17	50	34%
Robin 1984-A	Nd:YAG	1%-4%	6	20	30%
Robin 1984-B	ALI	1%-4%	7	20	35%
Schwartz 1986	Nd:YAG	2%	54	182	30%
Elsas 1991	PLT	2%	3	25	12%
Robin 1989	ALT	4%	1	37	3%

ALI: Argon laser iridoplasty
NdYAG: Nd:YAG laser iridoplasty
ALT: argon laser trabeculoplasty
PLT: primary laser trabeculoplasty

Table 11: Results on placebo or no treatment arms for peak above 5mmHg or peak above 10mmHg

Study	Laser surgery	peak	Arm	Subjects with spikes	Sample Size	Spike rate
David 1993	ALT	5mmHg	vehicle of brinominide	23	56	41%
Shin 1996	ALT	5mmHg	vehicle of fluorometholone	19	71	27%
Lung 1986	LT	5mmHg	no pretreatment	15	31	48%
Elsas 1991	PLT	10mmHg	no pretreatment	13	25	52%
David 1993	ALT	10mmHg	vehicle of brinominide	13	56	23%

Table 12: Studies Comparing Pilocarpine (before surgery) to no treatement. Design synopsis.

Study name	Design	Patient population	Type of surgery	Treatment groups	IOP measurements	Key endpoints
Elsas et al 1991**	Prospective, randomized, open label. 50 subjects, one eye per subject.	Exfoliated glaucoma (33), simple glaucoma (17); IOP>=25 mmHg and glaucomatous disc damage and/or visual field defects and no earlier glaucoma treatment	Primary laser trabeculoplasty (360 degrees)	(1)Pilocarpine 2% one hour before surgery (25 eyes) (2) no pretreatment (25 eyes)	1hour before surgery. Post-surgery: + 1hr, + 2hrs, + 4hrs, + 6hr,+ 8hr	mean max pressure increase; IOP increase from pre-surgery >= 10mmHg, >=20mmHg, > 50mmHg
Leung and Gillies 1986	Prospective. 64 subjects, one eye per subject	open angle glaucoma	Laser trabeculoplasty (180 degrees)	(1) Pilocarpine 4% before surgery (33 subjects) (2) no pilocarpine (31 subjects) (2) pilocarpine 1%, on hour before surgery (10 subjects)	Immediately before surgery. After surgery: + 1hr, +2hr	mean rise in IOP >5mmHg; >30mmHg

Table 13: Studies Comparing Pilocarpine (before surgery) to no treatment. Summary of results.

Study name	Treatment groups	Results on IOP spikes	Prelaser IOP mean+/ SD [range]	IOP-post laser (mmHg) Mean ± SD	Change in IOP from Pre-surgery (mmHg) mean ± SD	age	male to female ratio
Elsas et al 1991 **	(1)Pilocarpine 2% (25 eyes)	>=10mmHg: (3/25); >=20mmHg: (0/25);	(1) 34.9 ± 8.1	NA	(1) 2.4 ± 4.4	(1)69±9.9	NA
	(2) no pretreatment (25 eyes)	>=10mmHg: 13/25; >=20mmHg: (8/25)	(2) 33.3 ± 5.6	NA	(2) 12.8± 11.2	(2)71.9±7.1	NA
Leung and Gillies 1986	(1) Pilocarpine 4% (33 subjects)	>5 mmHg: 14/33; >30mmHg: 8/33	(1) 21.4 ± 6.2	NA	(1)+3.2 ± 6.0	NA	NA
	(2) no pilocarpine (31 subjects)	>5mmHg: 15/31; >30mmHg: 9/31	(2) 21.4± 6.1	NA	(2) +4.9 ± 6.5	NA	NA

** reference submitted by applicant

Table 14: Studies comparing pilocarpine to other drugs or other drug combination. Design summary.

Study name	Design	Diagnosis/Inclusion and Exclusion	Type of Surgery	Main drug groups	Time of drug administration	IOP measurement assessments	Key endpoints
Dapling et al 1994 **	randomized. 75 eyes. If both eyes of a subject qualify, first one was entered in the study.	POAG with IOP >=21mmHg. Exclusions: (1) either eye was currently receiving pilocarpine or active ocular infection or inflammation was present (2)Unstable cardiovascular disease (3) patient taking systemic clonidine	Argon laser trabeculoplasty	(1)Apraclonidine 1% (26 eyes)	one hour before surgery and immediately after surgery	Pre-surgery. Post-surgery at +1hr, +2hr and +3hr	IOP values. IOP increase from baseline (any increase, increase above 5mmHg, increase above 10mmHg)
				(2) Pilocarpine 4% (23 eyes)			
				(1) Pilocarpine 4% and Apraclonidine 1% (26 eyes)			
Fernandez-Bahamonde and Alcaraz-Michelli 1990 **	Prospective, randomized, double masked. 22 subjects, one eye per subject	Hispanic with glaucoma: CACG, PACG, significant pupillary block, chronic therapy	Argon laser iridotomy	(1)Pilocarpine alone 4% (11 subjects)	Apraclonidine or placebo:1 hr before surgery and immediately after. Pilocarpine 4%: 30 min before surgery, and then 15 min later.	Pre-surgery, Post-surgery: +1 hr and + 2hrs	IOP elevation from pre-surgery > 10mmHg
				(2) Apraclonidine 1% + Pilocarpine 4% (11 subjects)			
Liu et al 2002 **	Randomized paired design. 47 subjects, both eyes in each subject (each subject receiving both treatment, one in each eye).	PACG requiring bilateral laser iridotomy, with occludable angle. Exclusion: patients with ocular abnormality that might result in secondary angle-closure glaucoma.	Nd:YAG laser iridotomy	(1)Latanoprost 0.005% + pilocarpine 4%	Latanoprost: 45 min prior to pilocarpine. Pilocarpine: pre-operatively	Pre-surgery, Post-surgery: 1-2hrs	IOP pressure rise from pre-surgery >= 6mmHg,
				(2) pilocarpine 4%	Pilocarpine: pre-operatively		

Study name (contd)	Design	Diagnosis/Inclusion and Exclusion	Type of Surgery	Main drug groups	Time of drug administration	IOP measurement assessments	Key endpoints
Ren et al 1999 **	Randomized. 228 subjects, each contributing one eye.	primary open angle glaucoma, bilateral elevation of IOP (>21mmHg before therapy). Exclude: secondary open-angle glaucoma and previous intraocular surgery	argon laser trabeculoplasty (180 degrees)	(1) 1% apraclonidine (114 eyes)	Drug adnimistered 15 min before surgery	measurement at 5 min, 1 hrs ,2 hr post surgery	iop increase from pre-surgery > 1mmHg, >3mmHg, >5mmHg, mean IOP
				(2) 4% pilocarpine (114 eyes)			
Robin 1989	Randomized 4:1:1:1:1, investigator masked, parallel study. 260 subjects, some contributing more than one eye (total of eyes is 360).	Various forms of open angle glaucoma with disk and visual field damage. Poor IOP control despite maximum tolerated medical therapy. Exclusion: patients with asthma, sulpha allergy, unstable cardiovascular disease, allergy to any of the test medications and eyes that had previously undergone argon laser trabeculoplasty	360-degree argon laser trabeculoplasty	(1) apraclonidine 1% (125 eyes)	All drugs were given 1 hour before surgery and immediately following surgery	measured hourly for 3 hours following surgery	IOP elevation from pre-laser value: 1-5mmHg elevation, 6-10mmHg IOP elevation, >10mmHg elevation
				(2) Timolol 0.5% (35 eyes)			
				(3) Pilocarpine 4% (37 eyes)			
				(4) Dipivefrin 0.1% (32 eyes)			
				(5) 250mg oral Acetazolamide (31 eyes)			

Table 15: Studies comparing pilocarpine to other drugs or other drug combination. Summary of results

Study name	Main drug groups	Results on IOP spikes	Prelaser IOP mean+/ SD [range]	IOP-post laser. Mean ± SD [range]	Change in IOP from Pre-surgery: mean ± SD	Age (years): mean ± SD [range]	male to female ratio
Dapling et al 1994 **	(1)Apraclonidine 1% (26 eyes)	(1)any increase: 10/26, >5mmHg: 5/26, >10mmHg:0/26	(1)26.8 ± 4.2	(1)+1hr:24.3±5.9, +2hr:22.3+/6.9; +3hr:21.8±6.9	NA	(1) 72.2 [53-84]	NA
	(2) Pilocarpine 4% (23 eyes)	(2)Any increase: 9/23, >5mmHg: 2/23, >10mmHg: 0/23	(2) 26.5±4.2	(2) +1hr: 26.0±5.1, +2hr: 21.4±5.6, +3hr: 19.0± 5.3	NA	(2) 68.4 [53-86]	NA
	(1) Pilocarpine 4% and Apraclonidine 1% (26 eyes)	(3)Any increase: 2/26, >5mmHg:0/26, >10mmHg: 0/26	(3) 27.4±4.5	(3)+1hr:21.1±5.2, +2hr:17.2+/4.0, +3hr:15.6±4.0	NA	(3) 71.3[46-87]	NA
Fernandez-Bahamonde and Alcaraz-Michelli 1990 **	(1)Pilocarpine alone 4% (11 subjects)	>10mmHg: 4/11;	(1)18.7± 5.3	NA	(1)+1hr: +6.2± 6.4; +2hr: +2.5 ± 5.1;	(1) 63.9±5.7	(1) 4/7
	(2) Apraclonidine 1% + Pilocarpine 4% (11 subjects)	>10mmHg: 0/11	(2)17.4 ± 3.9	NA	(2) +1hr: -1.9 ±7.0 ; +2hr: -3.3± 7.0	(2) 67.3± 5.6	(2)3/8

Study name (contd)	Main drug groups	Results on IOP spikes	Prelaser IOP mean+/ SD [range]	IOP-post laser. Mean ± SD [range]	Change in IOP from Pre-surgery: mean ± SD	Age (years): mean ± SD [range]	male to female ratio
Liu et al 2002 **	(1)Latanoprost 0.005% + pilocarpine 4%	(1)>=6mmHg: 23.4% (11/47) ,	(1) 17.6±4.6	+30min:20.3+/5.4, +1hr 20.1± 5.7, + 2hr: 18.6± 6.6, +3hr: 16.1± 6	change in IOP (1)+30min 2.7± 3.3,+1hr: 2.5±4.8,+2hr:0.8±5.6;+3hr: -0.7± 3.7	65.7±8.8 [50-80]	20/27
	(2) pilocarpine 4%	(2)>=6mmHg: 42.6% (20/47)	(2)16.5 ± 3.9	+30min:20.3+/5.1, +1hr:20.6+/6.3, +2hr: 20.9+/9.0, +3hr: 16.6±5.7	(2) +30min: 3.8 ± 3.4, +1hr: 4.1±4.7,+2hr:4.4±8.1,+3hr:1.2±4.4		
Ren et al 1999 **	(1) 1% apraclonidine (114 eyes)	(1)> 1mmHg: (24/114), >3 mmHg: (17/114), >5mmHg: (10/114)	(1)23.2±4.5,	(1)+5min: 5.1+/5.4, +1hr: 3.3±6.5	NA	(1)68.4±11.4,	43/71
	(2) 4% pilocarpine (114 eyes)	(2) >1mmHg (14/114), >3mmHg(6/114), >5mmHg(5/114 eyes)	(2)21.7±3.5	(2)+5min:4.9± 4.1, +1hr: 3.6± 5.1	NA	(2) 70.3± 10.1	32/82

Study name (contd)	Main drug groups	Results on IOP spikes	Prelaser IOP mean+/ SD [range]	IOP-post laser. Mean ± SD [range]	Change in IOP from Pre-surgery: mean ± SD	Age (years): mean ± SD [range]	male to female ratio
Robin 1989	(1) apraclonidine 1% (125 eyes)	(1) no IOP elevation: 86% (107/125), 1-5mmHg: 11% (14/125), 6-10mmHg: 2% (3/125), >10mmHg: 1%(1/125)	(1)27.2±5.1[22-49]	NA	NA	(1)66.5±12.2[24-92]	55/70
	(2) Timolol 0.5% (35 eyes)	(2) no elevation: 34%(12/35); 1-5mmHg: 34%(12/35); 6-10mmHg: 6% (6/35); >10mmHg: 5% (5/35)	(2)27.6±4.1[23-44]	NA	NA	(2)68.4±10.3[53-92]	15/20
	(3) Pilocarpine 4% (37 eyes)	(3) no elevation: 43% (16/37), 1-5mmHg: 24% (9/37), 6-10mmHg: 30%(11/36), >10mmHg: 3%(1/37);	(3)27.1±5.1[21-50]	NA	NA	(3)67.6±8.9[49-84]	14/23
	(4) Dipivefrin 0.1% (32 eyes)	(4) no elevation: 47% 15/32; 1-5mmHg: 15% 5/32; 6-10mmHg:22% 7/32; >10mmHg:16% 5/32	(4)25.7±3.9[22-36],(	NA	NA	(4)65.5±14[29-86]	16/16

	(5) 250mg oral Acetazolamide (31 eyes)	(5)no elevation: 26% (8/31), 1-5mmHg: 35% (11/31), 6-10mmHg: 26% (8/31), >10mmHg: 13%(4/31)	4)25.9±3.0[22-37]	NA	NA	(5)63.0±13.1[24-79]	,11/20

** reference submitted by applicant

Table 16: Studies using only Pilocarpine before surgery. Design summary.

Study name (contd)	Design	Patient population	Type of surgery	Treatment groups	Time of drug administration	IOP measurements	Key endpoints
Krupin et al 1985	Prospective. 100 eyes	(A) anatomically narrow iridocorneal angles (50 eyes);	Argon laser iridotomy	Pilocparine 2% or Pilocarpine 4%	Before surgery	Pre-laser and Post-laser at 1-2 hrs after surgery	IOP elevation from pre-surgery > 6mmHg and >20mmHg
		(B) chronic angle-closure glaucoma (50 eyes)					
Robin and Pollack 1984	Randomized paired design. 20 subjects (each subject receives both surgeries, one in each eye.)	bilateral primary or chronic angle closure glaucoma	(1)Nd:YAG	(1)Nd:YAG iridotomy, Pilocarpine (1%-4%)	before surgery	observed at an hourly interval for 3 hours following surgery	Any IOP elevation from baseline; IOP elevation from presurgery>=10mmHg
			(2) Argon laser	(2) Argon laser iridotomy, Pilocarpine (1%-4%)			
Schwartz et al 1986	retrospective (180 to 182 eyes)	Acute PACG (42 eyes); CACG (40 eyes); occludable angles (58 eyes); chronic uveitis (5 eyes); intermittent poc (27eyes), fellow eye capable of closure (6 eyes)	Nd:YAG laser iridotomy	pilocarpine 2%	One hour before iridectomy, in three doses, ten minutes apart.	Before surgery. After surgery: +1hr, +2 hr,+ 3hr	IOP increase from pre-surgery: >10mmHg, >15mmHg, >20mmHg

Table 17: Studies using only Pilocarpine before surgery. Summary of results.

Study name (contd)	Treatment groups	Results on IOP spikes	Prelaser IOP mean+/ SD [range]	IOP-post laser. Mean ± SD [range]	Change in IOP from Pre-surgery (mmHg): mean ± SD	age	male to female ratio
Krupin et al 1985	(A) anatomically narrow iridocorneal angles (50 eyes); (B) chronic angle-closure glaucoma (50 eyes)	(A) <=Baseline 17/50; +1 to +5mmHg: 14/50; >= 6mmHg 19/50; >=11mmHg 12/50; >= 20mmHg 5/50	(A) 17.4mmHg ± 3.4 [12-26]	(A)1-2hr: 23.5±3.9[12-54mmHg]	NA	(A)63.6±12.3;	(A) 15/35
		(B)<=Baseline 16/50; +1 to +5mmHg:11/50; >=6mmHg 23/50; >=11mmHg: 17/50; >20mmHg 7/50	(B) 20.9mmHg ± 5 [11-35]	(B)28.2±11.3[11-52 mmHg]	NA	(B) 67.7±13.9	(B)10/40
Robin and Pollack 1984	(1)Nd:YAG	(1) had some IOP elevation: 13/20 ;>=10mmHg: 6/20	NA			mean 66, range [42-83]	6/14
	(2) Argon laser	(2) had some IOP elevation: 12/20 ; >=10mmHg: 7/20; 3 had rise above 20mmHg					
Schwartz et al 1986	Nd:YAG laser iridotomy	>10mmHg: 54 eyes (20%); >15mmHg: 27 eyes (15%); > 20mmHg in 13 eyes (7%)	mean and range 19.6 [6 to 46]	+1hr: 23.0 [8-69]; +2hr: 24.2 [10-52]; +3hr: 22.2 [10-50]	NA		

Table 18: Studies comparing pilocarpine after surgery to no treatment. Design summary

Study name (contd)	Design	Diagnosis/Inclusion and Exclusion	Type of Surgery	Main drug groups	Time of drug administration	IOP measurement assessments	Key endpoints
Ofner et al 1984	randomized, investigator masked. 44 subjects, one eye per subject	undergoing argon laser trabeculoplasty	argon laser trabeculoplasty 180 degrees or 360 degrees	(1) Pilocarpine 4%, (22 subjects)	immediately after surgery	Presurgery. Post-surgery: +1h and +2hrs after surgery	Mean IOP and % of patients with any IOP rise from pre-surgery rise at 1 hour or at 2 hours
				(2) No drop for first two hours post-operatively (22 subjects)			
Brown et al 1985	Prospective, randomized. 30 subjects, one eye per subject	opacified posterior capsule	Q switched Nd:YAG Posterior Capsulotomy	(1) Pilocarpine 4% (15 subjects)	After surgery and every 1 hour until bedtime	Measurement Pre-laser, post-laser (+1hr, +2hr, +3hr, + 4hr, +24h)	IOP elevation from pre-surgery >10mmHg
				(2) Untreated control (15 subjects)			

Table 19: Studies comparing pilocarpine after surgery to no treatment. Summary of results.

Study name (contd)	Main drug groups	Results on IOP spikes	Prelaser IOP(mmHg) mean+/ SD [range]	IOP-post laser. Mean ± SD [range]	Change in IOP from Pre-surgery: mean ± SD	age (years): mean ± SD	male to female ratio
Ofner et al 1984	(1) Pilocarpine 4%, (22 subjects)	Any IOP increase from baseline: + 1hr: 8/22, +2hr: 3/22	(1) 25.1	NA	(1)+1hr: 0, +2hr: -3.6 ±5.1	NA	NA
	(2) No drop for first two hours post-operatively (22 subjects)	Any IOP increase from baseline (2) +1hr: 16/22, +2hr: 13/22	(2) 25.4	NA	(2)+1hr:+3.1, +2hr: +2.4	NA	NA
Brown et al 1985	(1) Pilocarpine 4% (15 subjects)	Pilocarpine 4%:1/15	(1) 14.7± 3.1 [9-20]	+1hr: 16.7± 7.2 [10-39]; +2hr: 15.9±7.4 [9-39]; +3hr : 14.4 ± 7.1 [9-38]	(1) +1hr: 2.0± 7.1; +2hr: 1.1± 7.4; +3hr: -0.3± 7.6	(1) 65± 15	NA
	(2) Untreated control (15 subjects)	untreated control: 10/15	(2) 14.7± 3.5 [10-22]	+1hr : 23.0± 7.7 [12-36] ; +2hr: 23.7± 8.4 [10-39]; +3hr:24.9±10.9 [14-44]	(2) +1hr: 8.3± 6.2; +2hr: 8.9± 6.6; +3hr:10.1 ± 8.8	(2) 68± 16	NA

Table 20: Studies with a placebo arm. Design summary

Study name	Design	Diagnosis/Inclusion and Exclusion	Type of Surgery	Main drug groups	Time of drug administration	IOP measurement assessments	Key endpoints
David 1993	multicenter, double masked, randomized study. 248 subjects, one eye per subject	Undergoing laser trabeculoplasty, at least 21 years old with useful vision in both eyes. Exclusion: patients with prior glaucoma surgery or intraocular surgery were not included.	Argon laser trabeculoplasty	(1)Brinonidine (0.5%) before and after, (2) Brinonidine (0.5%) before, (3) Brinominide (0.5%) after, (4) vehicle before and after.	All medications or placebo vehicles were given 30 to 45 min before and immediately after surgery	Presurgery and within 3 hrs post-surgery	IOP increase from pre-surgery >5mmHg, >10mmHg
Shin 1996	multicenter placebo controlled, parallel comparison study, randomized. 140 subjects, one eye per subject.	POAG or eye with aphakic,pseudoexfoliation, inadequately controlled by maximally tolerated medication. Exclusion: significant ocular trauma, only one eye, allergy or contraindication to corticosteroids or concomitant use of any systemic antiinflammatory medications	Argon laser Trabeculoplasty	(1)0.25% fluorometholone (68 subjects) (2) vehicle (72 subjects)	24hrs before surgery, 4 times a day	Pre-surgery. Post-surgery at +1hr and +3hr	IOP increase from baseline above 5 mmHg

Table 21: Studies with a placebo arm. Summary or results

Study name	Type of surgery	Results on IOP spikes	Prelaser IOP mean+/ SD [range]	IOP-post laser. Mean ± SD [range]	Change in IOP from Pre-surgery (mmHg): mean ± SD	age	male to female ratio
David 1993	Argon laser trabeculoplasty	(1)Brinonidine (0.5%) before and after, (2) Brinonidine (0.5%) before, (3) Brinominide (0.5%) after,	(1)(2)(3) >5 mmHg: 7/183 (4%); >10mmHg 1/183 (0.53%);	(1)23.3 (2)23.9 (3)24.1	mean of maximal IOP change (1) -6.5mmHg, (2) -4.2 (3) -4.2	NA	
		(4) vehicle before and after.	>5mmHg: 23/56 (41%); >10mmH: 13/56 (23%)	(4) 24	(4)+4.2		
Shin 1996	Argon laser Trabeculoplasty	(1)0.25% fluorometholone (68 subjects)	(1) +1hr: 13/68, +3 hr: (15/68)	NA		(1)68.5±10	(1) 35/33
		(2) vehicle (72 subjects)	(2) +1hr: 19/71, +3hr: 11/71			(2)72.4±9.4	(2) 32/40

3.1.4 Indication 4: Induction of Miosis

There is overwhelming evidence to support the miotic effect, or constriction of the pupil induced by Pilocarpine. First, the biological mechanism of pilocarpine to induce miosis seems to be well understood. Second, the miotic effect is noted and discussed in every single article I reviewed on pilocarpine. Finally, when quantified the short term constriction of the pupil induced by pilocarpine is very significant.

The biological mechanism of pilocarpine resulting in pupil constriction is described in the review article by Zimmerman (1981) "After topical application, pilocarpine penetrates the fat/water/fat corneal barrier very well. Miosis begins in 15 to 30 minutes and lasts four to eight hours. Pilocarpine also causes miosis by direct action on the receptors of the papillary sphincter. This miosis may last up to 24 hours. Spasm of accommodation occurs." The biological mechanism is also described in book chapter by Bartlett (2008) " Because of its activity at muscarinic receptor sites on the iris sphincter and ciliary muscles, pilocarpine causes **pupillary constriction** and varying degrees of accommodative spasm, depending on the patient's age. Long term therapy with pilocarpine or other miotics alters iris muscle activity and may cause permanent miosis resulting from loss of iris radial muscle tone and from fibrosis of the sphincter muscle".

The miotic effect is described in all the literature reviewed for this NDA. It is mentioned as either a benefit, for example facilitating surgery as in Krupin et al (1985)[3]. It is often mentioned as a safety concern for example in Diestelhorst (2000) where miosis is reported as an ocular adverse event in 75 out of 106 patients and a reason for withdrawal from the study in 10 out of 35 subjects who withdrew from the study. In all comparative studies, comparing the effect of pilocarpine to other drugs or combination, miosis is mentioned as the reason making masked studies impossible. Thus, if the endpoint is a binary endpoint of clinician's assessment of miotic effect in each study, then 100% of the articles submitted by the applicant or in my own search report this effect.

My own search found only two articles precisely quantifying the short term effect of pilocarpine on pupil size. This effect seems to be more consistent in healthy subjects than in subjects with open angle glaucoma. Edgar (1999) describes a randomized, double-masked, cross over study comparing the effect of pilocarpine, dipivefrin and saline on pupil size (as measured by infra-red pupillometry). The study was conducted on 12 healthy volunteers of 20 to 26 years of age. The paper found that the pupil size decreased from a mean (± SD) of 5.49mm (± 1.06) at baseline to 2.26mm (± 0.49) at 60 minutes after instillation. A close inspection of results for each individual shows that all subject experienced a pupil constriction. The study described by Webster (1993) quantified the pupil constriction on 20 subjects with chronic angle glaucoma under medical therapy, previously undergone trabeculectomy and had glaucomatous field loss, excluding patients on miotic therapy. It finds that the mean pupil size, measured by HFA monitor, decreases from 5.5mm at baseline to 2mm 30-40minutes after instillation of the drug. Although

[3] The quote from Krupin et al (1985) is ""pilocarpine 2% or 4% was administered in all patients prior to laser surgery to have a miotic pupil and the iris under tension"

the mean pupil size decreased, individual responses varied. Seven subjects had dilating pupils (0.3mm to 1.0mm), five subjects had constricting pupils (0.3mm to 2.0mm) and eight subjects remained the same.

The change in pupil size was also reported in long term studies conducted by the applicant. These results and my additional derivations are shown in Table 22 and Table 23. All three studies find that pilocarpine has a significant effect in lowering the pupil size in the first three months. Study C90-105 shows that the miotic effect of pilocarpine may fade over time and repeated exposure (after 6 months and up to 2 years), with mean pupil size going back to baseline or even dilating compared to baseline after 6 months.

Table 22: Pupil size and mean change from baseline in studies C-91-47 and C-91-54

Time	Day 14			Day 45			Day 90		
	N	Mean ± SD (mm)	change from baseline (mm)	N	Mean ± SD (mm)	Change from baseline (mm)	N	Mean±SD (mm)	Change from baseline (mm)
C-91-47	46	2.6 ± 0.8	-0.7*	43	2.5± 0.7	-0.8*	37	2.6 ± 0.7	-0.7*
C91-54	50	2.5±0.9	-0.8*	42	2.4 ± 0.8	-1*	41	2.4±0.8	-1*

*significant change from baseline at 1% level of significance.

Table 23: Pupil size and mean change from baseline in study C90-104

subject id	eye	Baseline	3 months	6 months	12 months	18 months	24 months
109	OD	3	2	1.5	2	6	7
110	OS	3	1.5	1.5	3	4	4
116	OS	5	3	3	4	7	6.5
118	OD	3	2.5	2.5	4	4	4.5
122	OS	3	1.5	1.5	3	3	3
124	OD	4	1	1	3	3	3
128	OD	3	2	2	4.5	4.5	5
132	OD	4	3.5	3.5	3	3.5	3.5
133	OD	4	2	2	6	5	5
137	OD	3.5	4	4	5	4.5	4
140	OS	2.5	3	3	3.5	3	3.5
	Mean ± sd	3.45 ± 0.72	2.36 ± 0.92	2.32 ± 0.96	3.73 ± 1.13	4.32 ± 1.29	4.45 ± 1.33
Summary	mean change from baseline		-1.09**	-1.14**	0.27	0.86	1.00

** significant change from baseline (p-value < 0.5%)

3.2 Evaluation of Safety

Refer to medical officer review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This is a 505 (b) 2 submission, findings were not summarized in special/subgroup populations. Applicant submitted some articles to support the indications for pediatric population. I refer to the clinical review to comment on these publications

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There is overwhelming evidence to support the efficacy of pilocarpine 2% or pilocarpine 4% for induction of Miosis and for reduction of elevated IOP in subjects with open angle glaucoma or ocular hypertension.

5.2 Conclusions and Recommendations

There is substantial evidence from the literature to support the efficacy of pilocarpine 2%-4% for the two following indications:

3- Reduction of elevated IOP in patients with open angle glaucoma or ocular hypertenstion
4- Induction of Miosis

There is insufficient evidence to support the efficacy of pilocarpine for the two following indications:

3. (b) (4) acute angle-closure glaucoma
4. Prevention of (b) (4) postoperative elevated IOP associated with (b) (4) laser surgery (b) (4)

Note that the clinical review team considered the indication of ***'management of acute angle closure glaucoma'*** *instead of the indication sought by the applicant of* (b) (4) *. Since it is unclear to me how the management of acute angle closure glaucoma can be assessed and quantified, I leave it to the clinical review team to comment on this indication.*

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7 SIGNATURES/DISTRIBUTION LIST

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Date: May 25th, 2010

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200890	ORIG-1	ALCON INC	PILOCARPINE HYDROCHLORIDE OPHTHALMIC SOLUTION, 1%, 2% AND 4%

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

/s/

RIMA IZEM
05/26/2010

YAN WANG
05/26/2010
see my review.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

M E M O R A N D U M

DATE: May 22, 2010

FROM: Yan Wang, Ph.D.
Statistical Team Leader
Division of Biometrics IV
Office of Biostatistics/OTS

SUBJECT: Statistical team leader's efficacy evaluation of NDA 200890 for pilocarpine hydrochloride ophthalmic solution, 1%, 2%, and 4%

This memorandum evaluates the efficacy evidence of pilocarpine in NDA 200890 for the prevention of post-operative elevated intraocular pressure (IOP) associated with (b) (4) laser surgery (b) (4).

Background: NDA 200890 is a 505b(2) submission. This NDA seeks the approval of pilocarpine hydrochloride ophthalmic solution, 1%, 2%, and 4% for the following four indications:

1. the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension
2. (b) (4) for acute angle-closure glaucoma
3. the prevention of (b) (4) post-operative elevated IOP associated with (b) (4) laser surgery (b) (4)
4. the induction of miosis (b) (4)

The primary statistical reviewer's main conclusions are:

- There is substantial evidence to support the efficacy of pilocarpine 2% and 4% for indications #1 and #4.
- There is insufficient evidence to support the efficacy of pilocarpine for indications #2 and #3.

This review concurs with the primary statistical reviewer's evaluation on the evidence of efficacy for indications #1, #2, and #4.

Indication #3 comprises two-sub indications: (b) (4) and the prevention of post-operative elevated IOP associated with (b) (4) laser surgery (b) (4). For the sub-indication (b) (4)

[redacted] this review concurs with the primary statistical reviewer's conclusion that there is no evidence to support it.

For the sub-indication "the prevention of post-operative elevated IOP associated with [redacted] laser surgery [redacted], there is a difference of opinion between the statistical team leader and the primary statistical reviewer. Based on the following detailed efficacy evaluation, the statistical team leader concludes that there is substantial efficacy evidence to support this indication.

Evaluation of efficacy of pilocarpine for the indication "the prevention of post-operative elevated IOP associated with [redacted] laser surgery i[redacted]

A total of 14 studies from 14 publications are included in the efficacy evaluation for this indication in the primary statistical review (a detailed summary of the study designs is provided in the primary statistical review). Among those, 7 studies either treated all patients with pilocarpine (5 studies) or did not include pilocarpine as a treatment arm (2 studies). These 7 studies are bolded in italics in the Appendix. These 7 studies are not included in this review because they provide little information in ascertaining the pilocarpine treatment effect. The remaining 7 studies are evaluated in detail in this review. The three studies published in 1991-1999 and submitted by the applicant are discussed first, followed by the four studies published in 1984-1989 and identified by the primary statistical reviewer.

Elsas et al. 1991: Pilocarpine to Prevent Acute Pressure Increase Following Primary Laser Trabeculoplasty

This was a randomized study comparing two treatment groups: two drops of pilocarpine 2% one hour before surgery vs. no treatment. Fifty eyes from 50 patients (33 with exfoliative and 17 open-angle glaucoma) were randomized (25 eyes per group). The study eyes did not receive any glaucoma treatment before entering the study. The IOPs were measured before surgery, 1, 2, 4, 6, 8, and 24 hours after surgery.

As shown in Table 1, the pilocarpine treatment effect is highly statistically significant. The post-surgery mean maximum IOP increase is 12.8 mmHg in the no treatment group and 2.4 mmHg in the pilocarpine group; the treatment difference is -10.4 (95% CI: -15, -5.7; p-value < 0.0001) mmHg.

The proportion of eyes with post-surgery IOP rise ≥ 10 mmHg is 52% in the no treatment group and 12% in the pilocarpine group; the treatment difference is -40% (95% CI: -63%, -17%; p-value = 0.0054). The proportion of eyes with post-surgery IOP rise ≥ 20 mmHg is 32% in the no treatment group and 0% in the pilocarpine group; the treatment difference is -32% (95% CI: -50%, -14%; p-value = 0.0040). The proportion of eyes with post-surgery peak IOP ≥ 50 mmHg is 40% in the no treatment group and 4% in the pilocarpine group; the treatment difference is -36% (95% CI: -57%, -15%; p-value = 0.0046).

Table 1: Analysis Result of IOP from Paper by Elsas et al. 1991

IOP measurement (mmHg)	No treatment (N=25)	Pilocarpine 2% (N=25)	Difference (95% CI) P-value*
Pre-surgery Mean (±SD)	33.3 ± 5.6	34.9 ± 8.1	
Post-surgery Mean (±SD) maximum IOP increase	12.8 ± 11.2	2.4 ± 4.4	-10.4 (-15, -5.7) <0.0001
Post-surgery IOP rise ≥ 10 mmHg	13/25 (52%)	3/25 (12%)	-40% (-63%, -17%) 0.0054
Post- surgery IOP rise ≥ 20 mmHG	8/25 (32%)	0/25 (0%)	-32% (-50%, -14%) 0.0040
Post- surgery peak IOP ≥ 50 mmHG	10/25 (40%)	1/25 (4%)	-36% (-57%, -15%) 0.0046

* Calculated by the Reviewer: 95% CI is based on the normal distribution approximation; P-value is based on the two-sample t-test for maximum IOP increase and the Fisher-Exact test for binary endpoints.

Dapling et al. 1994: Influence of Apraclonidine and Pilocarpine alone and in Combination on Post Laser Trabeculoplasty Pressure Rise

This was a randomized study comparing three treatment groups: Apraclonidine 1% (Group A) vs. Pilocarpine 4% (Group B) vs. Combination of both drugs (Group C). Apraclonidine 1% (one drop) was given 1 hour before and immediately after surgery, and pilocarpine 4% (one drop) was given immediately after surgery. Seventy five eyes from 75 patients (26 eyes in Group A, 23 eyes in Group B, and 26 eyes in Group C) were randomized. Study eyes had open angle glaucoma with IOP > 21 mmHg. Patients were excluded if either eye was currently receiving pilocarpine. The study eyes received their regular topical treatments before surgery. The IOPs were measured before surgery, 1, 2, 3 hours after surgery.

As shown in Table 2, when group C is compared with group A, the addition of the pilocarpine treatment to the apraclonidine treatment yields statistically significant effect in lowering IOP during the first three hours after surgery. The lowering IOP effects at 1, 2, and 3 hours post-surgery are: -3.2 (95% CI: -6.4, -0.01; p-value = 0.0490) mmHg, -5.1 (95% CI: -8.3, -1.9; p-value = 0.0021) mmHg, and -6.2 (95% CI: -9.3, -3.1; p-value = 0.0002) mmHg, respectively.

It is noted that apraclonidine 1% is an FDA approved drug for the indication of interest. When the apraclonidine 1% group is compared with the pilocarpine 4% group, the study results indicate that the effect of the pilocarpine 4% treatment in lowering post-surgery IOP is comparable to that of the apraclonidine 1% treatment.

Table 2: Analysis Result of IOP from Paper by Dapling et al. 1994

Mean±SD* IOP (mmHg)	Group A Apraclonidine 1% (N=26)	Group B Pilocarpine 4% (N=23)	Group C Combination (N=26)	Difference (95% CI) P-value* (between groups C and A)
Pre-surgery	26.8 ± 4.4	26.5 ± 4.4	27.4 ± 4.7	
Post-surgery				
1 Hour	24.3 ± 6.2	26.0 ± 5.4	21.1 ± 5.5	-3.2 (-6.4, -0.01) 0.0490
2 Hours	22.3 ± 7.3	21.4 ± 5.9	17.2 ± 4.2	-5.1 (-8.3, -1.9) 0.0021
3 Hours	21.8 ± 7.0	19.0 ± 5.6	15.6 ± 4.2	-6.2 (-9.3, -3.1) 0.0002

* SD, 95% CI, and p-values are calculated by the reviewer using the normal distribution approximation and the two-sample t-test.

Ren et al. 1999: Efficacy of Apraclonidine 1% versus Pilocarpine 4% for Prophylaxis of Intraocular Pressure Spike after Argon Laser Trabeculoplasty

This was a randomized study comparing two treatment groups: one drop of apraclonidine 1% vs. one drop of pilocarpine 4% given 15 minutes before surgery. Two hundred twenty eight eyes from 228 patients who had primary open-angle glaucoma were randomized (114 eyes per group). Patients were allowed to continue their previous chronic glaucoma medications during the study, including apraclonidine and pilocarpine. The IOPs were measured before surgery, 5 minutes, 1 and 24 hours after surgery.

It is noted that apraclonidine 1% is an FDA approved drug for the indication of interest. As shown in Table 3, pilocarpine 4% treatment is at least as effective as apraclonidine 1% treatment in preventing the post-surgery IOP rise. Post-surgery mean IOPs at 5 minutes, 1 hour, and 24 hours were significantly lower than pre-surgery mean IOPs in both apraclonidine and pilocarpine groups (p-value < 0.001 at all time points). The proportions of eyes with IOP spikes greater than 1, 3, and 5 mmHg at 1 hour post-surgery were 21.1%, 14.9%, and 8.8% in the apraclonidine group and 12.3%, 5.3%, and 4.4% in the pilocarpine group (p-value = 0.076, 0.015, and 0.18).

Table 3: Analysis Result of IOP from Paper by Ren et al. 1999

IOP Variable (mmHg)	Apraclonidine 1% (N=114)	Pilocarpine 4% (N=114)	Difference (95% CI) P-value*
Pre-surgery Mean (±SD) IOP	23.2 ± 4.5	21.7 ± 3.5	
Post-surgery Mean (±SD) Change in IOP from Pre-surgery			
5 minutes	-5.1 ± 5.4	-4.9 ± 4.1	0.2 (-1.0, 1.4) 0.7528
1 hour	-3.3 ± 6.5	-3.5 ± 5.0	-0.2 (-1.7, 1.3) 0.7946

IOP Variable (mmHg)	Apraclonidine 1% (N=114)	Pilocarpine 4% (N=114)	Difference (95% CI) P-value*
24 hours	-7.6 ± 5.0	-7.1 ± 4.6	0.5 (-0.7, 1.7) 0.4320
1-hour post-surgery IOP rise > 1 mmHG	24/114 (21.1%)	14/114 (12.3%)	-8.8 (-18.4, 0.8) 0.076
1-hour post-surgery IOP rise > 3 mmHG	17/114 (14.9%)	6/114 (5.3%)	-9.6 (-17.4, -1.9) 0.015
1-hour post-surgery IOP rise > 5 mmHG	10/114 (8.8%)	5/114 (4.4%)	-4.4 (-10.8, 2.0) 0.18

* 95% CI is calculated by the reviewer using the normal distribution approximation; p-values for testing the difference in mean IOP change are calculated by the reviewer based on the two-sample t-test; p-values for testing the binary endpoints are reported in the paper based on the chi-square test.

Ofner et al, 1984: Pilocarpine and the Increase in Intraocular Pressure after Trabeculoplasty

This was a randomized study comparing two treatment groups: one drop of pilocarpine 4% given immediately after surgery vs. no treatment for the first two hours after surgery. Forty four eyes from 44 patients were randomized (22 eyes per group). The IOPs were measured before surgery, 1, and 2 hours after surgery.

As shown in Table 4, the pilocarpine treatment effect of lowering post-surgery IOP is statistically significant (p-value < 0.05). At 1 hour post-surgery, mean IOP change from pre-surgery is 3.1 mmHg in the no treatment group and 0 mmHg in the pilocarpine group; at 2 hours, it is 2.4 mmHg in the no treatment group and -3.6 mmHg in the pilocarpine group.

The proportion of eyes with no IOP rise at 1 hour post-surgery is 36.4% in the no treatment group and 72.7% in the pilocarpine group; the proportion of eyes with no IOP rise at 2 hour post-surgery is 18.2% in the no treatment group and 54.5% in the pilocarpine group.

Table 4: Analysis Result of IOP from Paper by Ofner et al. 1984

	No treatment (N=22)	Pilocarpine 4% (N=22)	Difference (95% CI) P-value
Pre-surgery IOP Mean (mmHg)	25.1	25.4	
Post-surgery IOP			
Mean Change in IOP at 1 hr	3.1	0	< 0.05[a]
Mean Change in IOP at 2 hr	2.4	-3.6	< 0.05[a]
No IOP rise at 1 hr	8/22 (36.4%)	16/22 (72.7%)	36.4% (9.0%, 64%)[b] 0.0329
No IOP rise at 2 hr	4/22 (18.2%)	12/22 (54.5%)	36.4% (10%, 63%)[b] 0.0269

[a] Provided in the paper. SD values for the IOP measurements were not reported in the paper.

[b] For the binary endpoints, 95% CI and p-value are calculated by the reviewer using the normal distribution approximation and the Fisher-exact test, respectively.

Brown et al, 1985: Effect of Pilocarpine in Treatment of Intraocular Pressure Elevation Following Neodymium: YAG Laser Posterior Capsulotomy

This was a randomized study comparing two treatment groups: pilocarpine 4% immediately after surgery and every hour until bedtime vs. no treatment. Thirty aphakic or pseudophakic eyes from 30 patients with opacified posterior capsules were randomized (15 eyes per group). Patients being treated for pre-existing open-angle glaucoma were included if their IOPs were under good control and if they did not exhibit severe optic nerve damage and visual field loss. The IOPs were measured before surgery, 1, 2, 3, 4, and 24 hours after surgery.

As shown in Table 5, the pilocarpine treatment effect is highly statistically significant during the first four hours after surgery. The treatment differences in the post-surgery mean IOP change from pre-surgery at 1, 2, 3, and 4 hours post-surgery are: -6.3 (95% CI: -11, -1.5; p-value = 0.0096) mmHg, -7.8 (95% CI: -13, -2.8; p-value = 0.0023) mmHg, -10.4 (95% CI: -16, -4.5; p-value = 0.0005) mmHg, and -8.9 (95% CI: -14, -3.5; p-value = 0.0013) mmHg, respectively.

The proportion of eyes with post-surgery IOP rise ≥ 10 mmHg is 66.7% in the no treatment group and 6.7% in the pilocarpine group; the treatment difference is -60% (95% CI: -87%, -33%; p-value = 0.0017). The proportion of eyes with post-surgery peak IOP ≥ 24 mmHg is 93.3% in the no treatment group and 6.7% in the pilocarpine group; the treatment difference is -87% (95% CI: -100%, -69%; p-value < 0.0001).

Table 5: Analysis Result of IOP from Paper by Brown et al. 1985

	No treatment (N=15)	**Pilocarpine 4% (N=15)**	**Difference (95%CI) P-value***
Pre-surgery IOP Mean (±SD) (mmHg)	14.7 ± 3.5	14.7 ± 3.1	
post-surgery IOP Mean (±SD) change from pre-surgery level (mmHg)			
1 hour	8.3 ± 6.2	2.0 ± 7.1	-6.3 (-11, -1.5) 0.0096
2 hours	8.9 ± 6.6	1.1 ± 7.4	-7.8 (-13, -2.8) 0.0023
3 hours	10.1 ± 8.8	-0.3 ± 7.6	-10.4 (-16, -4.5) 0.0005
4 hours	7.5 ± 6.9	-1.4 ± 8.2	-8.9 (-14, -3.5) 0.0013
24 hours	2.5 ± 5.6	-1.8 ± 4.1	-4.3 (-7.8, -0.8) 0.0164
Post-surgery IOP rise ≥ 10 mmHg	10/15 (66.7%)	1/15 (6.7%)	-60% (-87%, -33%) 0.0017
Post-surgery Peak IOP > 24 mmHg	14/15 (93.3%)	1/15 (6.7%)	-87% (-100%, -69%) <0.0001

* Calculated by the Reviewer; 95% CI is based on the normal distribution approximation; P-value is based on the two-sample t-test for maximum IOP increase and the Fisher-Exact test for binary endpoints.

Leung and Gillies 1986: The detection and management of acute rise in intraocular pressure following laser trabeculoplasty

This was a study comparing two treatment groups: pilocarpine 4% given immediately before surgery vs. no treatment. Sixty four eyes from 64 patients who had open-angle glaucoma were included (31 eyes in the no treatment group and 33 eyes in the pilocarpine group). The IOPs were measured before surgery, 1 and 2 hours and in some patients 3, 4, and 24 hours after surgery.

As shown in Table 6, there are no statistically significant differences between the two treatment groups even though the point estimates for the post-surgery highest IOPs are lower in the pilocarpine group than in the no treatment group. The mean changes in the highest post-surgery IOP from pre-surgery level are 4.9 (SD=6.5) mmHg in the no treatment group and 3.2 (SD=6.0) mmHg in the pilocarpine group; the treatment difference is -1.7 (95%: -4.8, 1.37; p-value = 0.2655) mmHg. The proportions of eyes with post-surgery IOP spikes greater than 5 mmHg were 48% in the no treatment group and 42% in the pilocarpine group; the treatment difference is -6% (95%: -30%, 18%; p-value = 0.8020).

It is noted that the pilocarpine treatment effect is small in comparison of the results reported by Elsas et al. 1991 and Dapling et al. 1994. The authors did not mention if this was a randomized study. The authors mentioned that IOPs were not measured for many of the patients at 3 or 4 hours; however, the authors did not comment on the impact of the missing data on the finding. The pre-surgery IOPs are much lower compared to those reported in Elsas et al. 1991 and Dapling et al. 1994. It is not clear whether these lower pre-surgery IOPs were due to the use of chronic concomitant medications for glaucoma, including pilocarpine. The authors did not provide any details on the use of chronic concomitant medications. The authors mentioned that when a patient had an IOP rise to over 30 mmHg at two hours, topical therapy was augmented with timolol or pilocarpine if not already in use; however, the authors did not discuss the impact of these rescue therapies on the finding.

Table 6: Analysis Result of IOP from Paper by Leung and Gillies 1986

IOP measurements (mmHg)	**No treatment (N=31)**	**Pilocarpine 4% (N=33)**	**Difference (95%CI) P-value***
Pre-surgery Mean (±SD) IOP	21.4 ± 6.2	21.4 ± 6.1	
Post-surgery Mean (±SD) Change from highest IOP to pre-surgery	4.9 ± 6.5	3.2 ± 6.0	-1.7 (-4.8, 1.4) 0.2778
Post-surgery IOP rise ≥ 5 mmHG	15/31 (48%)	14/33 (42%)	-6% (-30%, 18%) 0.8020

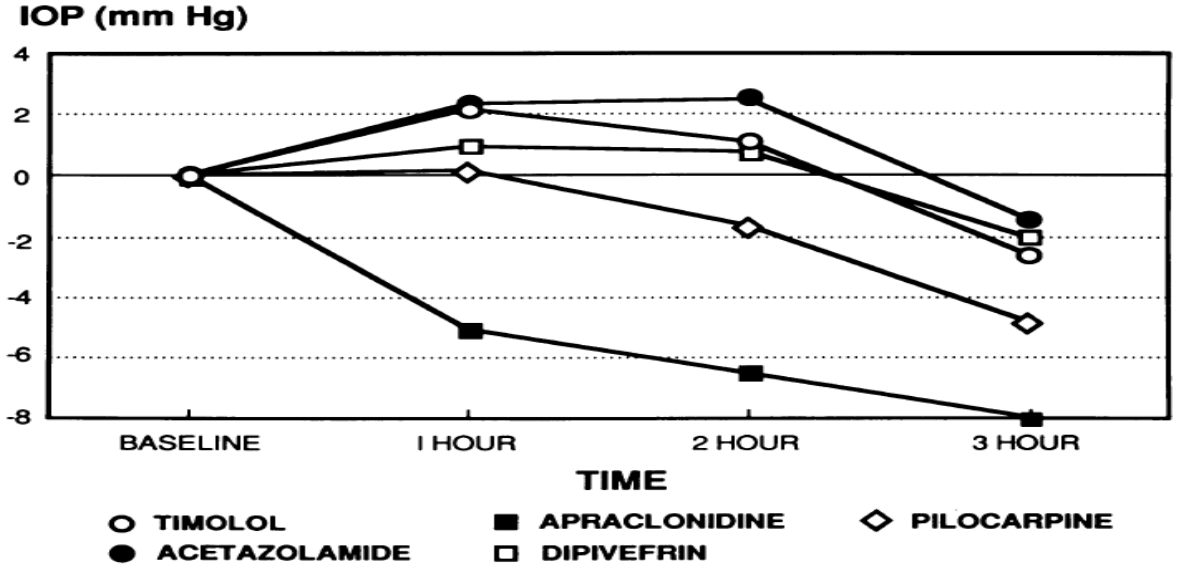
* Calculated by the reviewer: 95% CI is based on the normal distribution approximation, and p-value based on the two-sample t-test for change in IOP and the Fisher-exact test for binary endpoints.

Robin 1989: The Role of Apraclonidine Hydrochloride in Laser Therapy for Glaucoma

This was a randomized study comparing five treatment groups: Apraclonidine 1% vs. Pilocarpine 4% vs. Timolol 0.5% vs. Dipivefrin 0.1% vs. oral acetazolamide 250 mg. All treatments were administered one hour before Argon laser trabeculoplasty. Two hundred sixty eyes from 260 patients were randomized in a 4:1:1:1:1 ratio: 125 in apraclonidine group, 37 in pilocarpine group, 35 in timolol group, 31 in dipivefrin group, and 32 in acetazolamide group. The majority of the study eyes had either chronic open-angle or chronic angle-closure after iridotomy. All study eyes had poor IOP control despite maximum tolerated medical therapy. The IOPs were measured before surgery, 1, 2, and 3 hours after surgery.

As presented in the paper, the following Figure shows that in the pilocarpine group, the mean IOP at 1 hour post-surgery is about the same as pre-surgery IOP; the mean IOPs are reduced about 1.8 mmHg and 4.8 mmHg at 2 and 3 hours post-surgery, respectively. The pilocarpine treatment demonstrates a numerically better performance when compared with the timolol, or dipivefrin, or acetazolamide treatment.

It is noted that the apraclonidine treatment is more effective than the pilocarpine treatment. This may be due to the fact that more eyes in the apraclonidine group received pre-operative chronic pilocarpine therapy than in the pilocarpine group: 74% vs. 54% (p-value < 0.03). The peri-surgery pilocarpine prophylaxis is not fully effective in eyes with chronic pilocarpine use (Ren et al. 1999); on the other hand, eyes already receiving chronic pilocarpine may benefit much more in reducing IOP with the addition of apraclonidine (Dapling et al. 1994).



Conclusions

The efficacy of the pilocarpine treatment for the indication "the prevention of post-operative elevated IOP associated with [redacted] laser surgery [redacted] has been evaluated in 7 studies from 7 publications. Among them, 5 studies demonstrated statistically significant results and the remaining 2 studies showed supporting evidence of a numerical trend favoring pilocarpine over no treatment (Leung and Gillies 1986) and favoring pilocarpine over timolol or dipivefrin or acetazolamide (Robin 1989). Furthermore, the positive conclusion of the primary statistical reviewer on the efficacy evaluation for indication #1 (the reduction of elevated IOP in patient with open angle glaucoma or ocular hypertension) and indication #4 (the induction of miosis) provides additional supporting evidence for the indication of interest.

Thus this review concludes that there is substantial efficacy evidence of pilocarpine 2% and 4% for the indication "the prevention of post-operative elevated IOP associated with [redacted] laser surgery [redacted]

Appendix: A List of 14 Studies Included in the Primary Statistical Review

Studies Identified by Primary Reviewer	Treatment Arms
Ofner et al, 1984 (Randomized Trial)	No treatment vs. 4% pilocarpine immediately after surgery
[redacted] (b) (4)	
Brown et al, 1985 (Randomized 1:1)	No treatment vs. 4% pilocarpine immediately following laser surgery and every hour until bedtime
[redacted] (b) (4)	
Leung and Gillies, 1986	No treatment vs. 4% pilocarpine before surgery
[redacted] (b) (4)	
Robin, 1989 (randomized 4:1:1:1:1)	Apraclonidine 1% vs. Timolol 0.5% vs. Pilocarpine 4% vs. Dipivefrin 0.1% vs. oral Acetazolamide 250mg
[redacted] (b) (4)	
Studies Submitted by Applicant	
[redacted] (b) (4)	
Elsas et al, 1991 (randomized 1:1)	No treatment vs. 2% pilocarpine one hour prior to surgery
Dapling et al, 1994 (randomized 1:1:1)	Apraclonidine 1% vs. Pilocarpine 4% vs. (Apraclonidine 1% + Pilocarpine 4%).
Ren et al, 1999 (randomized 1:1)	Apraclonidine 1% vs. Pilocarpine 4% fifteen minutes before surgery
[redacted] (b) (4)	

Note: The studies bolded in italics are not included in the detailed efficacy evaluation of pilocarpine in the team leader's review.

cc:
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200890	ORIG-1	ALCON INC	PILOCARPINE HYDROCHLORIDE OPHTHALMIC SOLUTION, 1%, 2% AND 4%

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

/s/

YAN WANG
05/27/2010

MOHAMMAD F HUQUE
05/27/2010