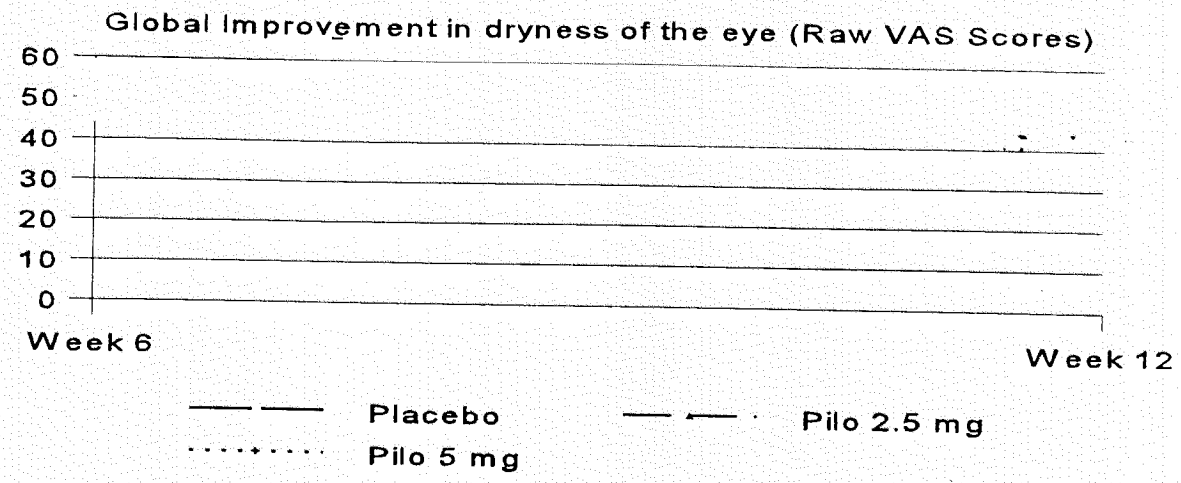
8.1.1.4.2 Efficacy endpoint outcomes

SUMMARY OF EFFICACY RESULTS
INTENT-TO-TREAT COHORT - ENDPOINT ANALYZES

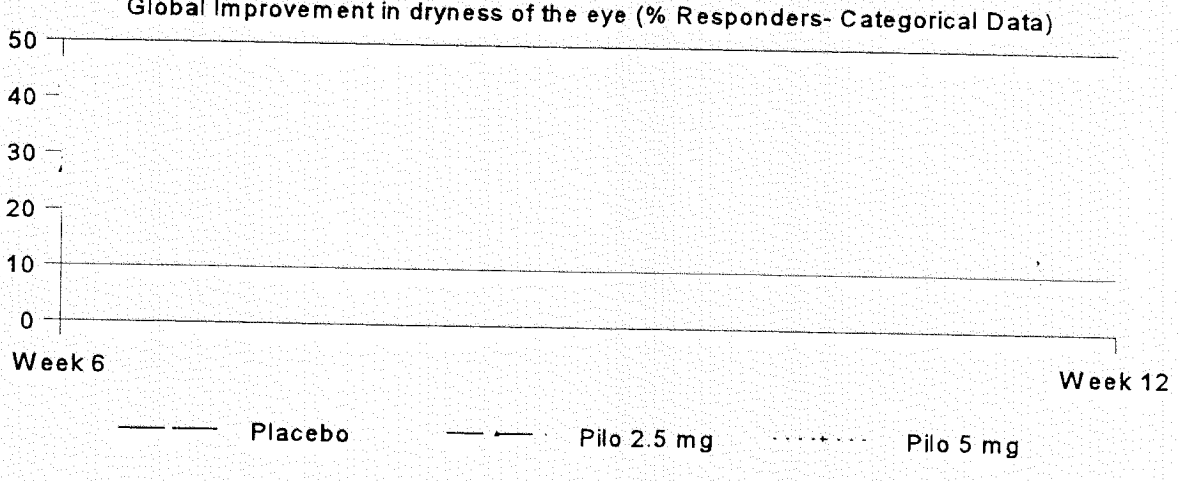
Parameter	Responders			P-value	
	Pilocarpine HCl 2.5 mg	Pilocarpine HCl 5 mg	Placebo	Overall	Placebo vs 5 mg
	% (n)	% (n)	% (n)	≤	≤
Mouth					
Improved global assess. of xerostomia[a]	39.1 (110)	61.3 (119)	31.1 (119)	**.001**	**.001**
Reduced severity of dry mouth.	38.9 (108)	52.9 (119)	37.8 (119)	**.010**	**.019**
Improved mouth comfort	37.0 (108)	52.1 (119)	33.6 (119)	**.002**	**.004**
Decreased use of saliva substitutes	12.7 (110)	21.2 (118)	10.1 (119)	**.014**	**.017**
Improved ability to speak	13.6 (110)	18.6 (118)	10.1 (119)	.068	.059
Improved ability of sleep w/o water	10.0 (110)	27.1 (118)	16.0 (119)	**.005**	**.036**
Eyes					
Improved global assess. of dry eye[a]	30.0 (110)	42.0 (119)	26.1 (119)	**.007**	**.009**
Reduced severity of eye discomfort	25.9 (081)	42.7 (089)	31.8 (088)	.059	.134
Reduced sensitivity to light	17.1 (082)	28.4 (088)	24.7 (089)	.353	.578
Reduced severity of itching of the eyes	18.3 (082)	34.9 (086)	27.3 (088)	.104	.278
Reduced severity of tiredness of the eyes	19.5 (082)	33.3 (087)	25.0 (088)	.109	.225
Reduced severity of redness of the eyes	19.5 (082)	28.7 (087)	27.6 (087)	.591	.866
Reduced feeling that something is in eyes	24.4 (082)	34.5 (087)	34.1 (088)	.649	.956
Reduced use of tear substitutes	8.9 (045)	4.9 (041)	6.7 (045)	.640	.722
Change in matting/sticking of the eyes	14.6 (082)	26.7 (086)	19.5 (087)	.147	.260
Improved eye symptoms	31.8 (110)	44.5 (119)	26.9 (119)	**.003**	**.004**
Improved tear flow	23.6 (110)	29.4 (119)	21.0 (119)	.126	.135
Reduced severity of visual blurring	14.6 (082)	32.2 (087)	17.2 (087)	**.006**	**.021**
Reduced severity of discharge in the eyes	11.0 (082)	16.1 (087)	15.9 (088)	.759	.974
Reduced difficulty in focusing to read	15.9 (082)	29.9 (087)	17.1 (088)	**.020**	**.044**
Reduced difficulty in night driving	14.6 (082)	27.6 (087)	16.1 (087)	**.033**	.065
Difficulty focusing after taking study meds	10.9 (046)	11.6 (043)	8.2 (049)	.628	.577
Other					
Change in intensity of nasal dryness	15.9 (107)	37.8 (119)	19.5 (118)	**.001**	**.002**
Change in severity dryness of the skin	22.2 (108)	35.3 (119)	21.0 (119)	**.007**	**.014**
Change in severity of vaginal dryness	23.1 (104)	25.4 (114)	13.5 (111)	.057	**.023**
Change in difficulty in producing mucous	10.2 (108)	13.6 (118)	5.0 (119)	**.043**	**.022**
Salivary Flow					
Increase in Salivary Flow Measured as area under the curve (AUC)	0.11 (108)	0.26 (115)	0.04 (114)	**.001**	**.001**

[a]: Primary analyzes.

Reviewer's Comments: *Most of the ocular variables are not even statistically significant.*



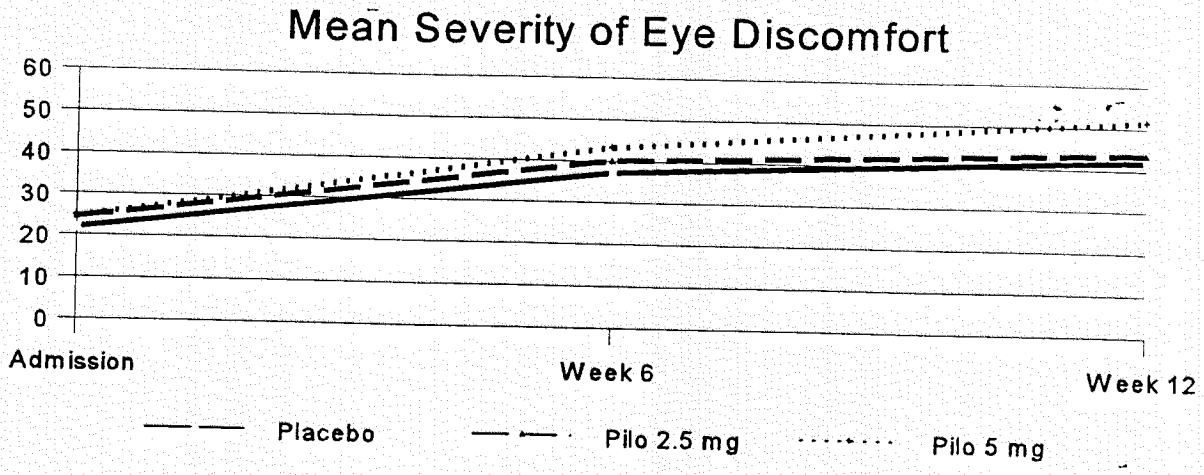
Placebo	52.7	53.8
Pilo 2.5 mg	54	55.5
Pilo 5 mg	57.3	59.2



Placebo	26.9	29.1
Pilo 2.5 mg	26.8	33.3
Pilo 5 mg	41.4	45

Reviewer's Comments:

As seen above, although there is a statistically significant difference in the percentage of responders, the raw scores are very similar and are not clinically significant. The definition of responders is not consistent with the definitions commonly accepted for dry eye studies.

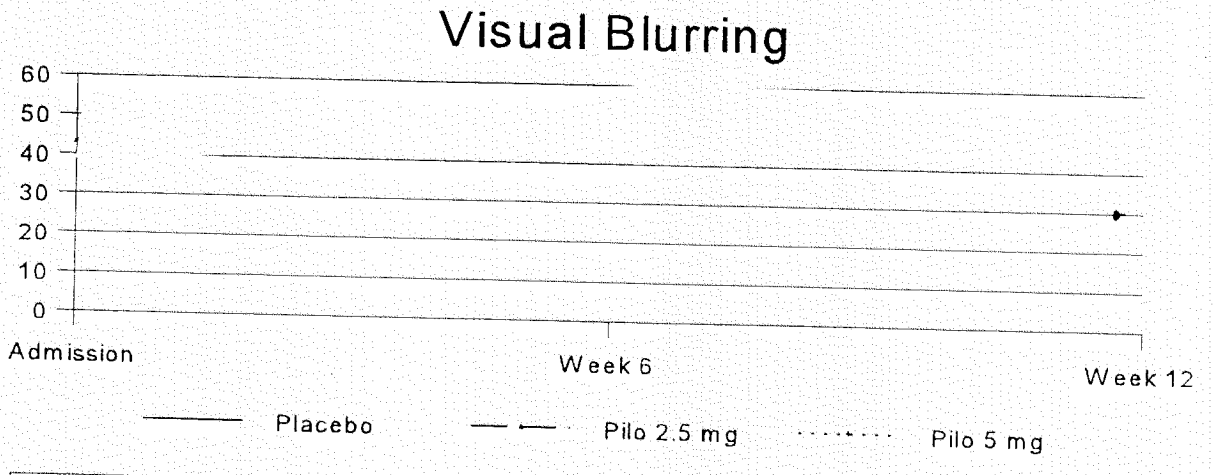


Placebo	21.02	37.24	42.06
Pilo 2.5 mg	24.42	40.08	43.7
Pilo 5 mg	24.68	43.27	51.45

Reviewer's Comments:

1. *The number of patients evaluated at admission is relatively low (i.e., n=62 for placebo, n=57 for Pilo 2.5mg, n=64 for Pilo 5mg). The number of patients evaluated at week 6 and week 12 for each group was approximately 100 in each group at each time point. Baseline evaluations should have been available for all patients.*

2. *The differences between groups is minimal, although the difference at week 12 is statistically significant (p=.025), it is not considered clinically significant.*



Placebo	42.58	51.15	51.5
Pilo 2.5 mg	43.29	53.91	51.44
Pilo 5 mg	39.84	49.72	57.03

Conclusions:

1. The study failed to ensure that patients with "dry eye" signs and symptoms were enrolled.

2. There were no objective criteria upon which to evaluate the treatment.

3. Differences observed in the symptoms are not considered clinically significant.

4. The lack of evaluations for all patients at baseline is unexplained.

5. The definition used for "responder" is not considered by this reviewer to be acceptable.

8.1.1 Reviewer's Trial #2 Sponsor's protocol # P92-02

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Evaluation of Pilocarpine HCl for the Treatment of Xerostomia and Xerophthalmia Associated with Sjögren's Syndrome (Dose Adjustment Study)

Protocol No. MGI 647.94.P92-02; **Report No.** MGI 647.94.CR96-02

Objectives

To assess the efficacy of pilocarpine HCl tablets administered orally as a treatment for the symptoms of xerostomia and xerophthalmia associated with Sjögren's syndrome, and

To evaluate the safety of orally administered pilocarpine HCl tablets in subjects with Sjögren's syndrome.

Study Design

Multicenter, randomized, double-blind, placebo-controlled

Two parallel treatment groups of pilocarpine HCl vs placebo on a q.i.d. regimen: The first 6-week period dosage was pilocarpine HCl 5 mg vs placebo. The dose was escalated to 7.5 mg vs placebo for the second 6-week period.

Safety and efficacy evaluations were conducted at baseline (Admission) and Weeks 6 and 12.

Efficacy variables measured dryness of the mouth and eyes with associated symptoms, and other symptoms of dryness associated with Sjögren's syndrome.

Whole salivary flow was measured pre- and postdose at Admission, Week 6, and Week 12.

Safety was assessed by adverse experience reports, laboratory tests, vital sign measurements, physical examinations, and electrocardiogram readings.

Oral comfort agents and tear substitutes were permitted as needed for symptom relief.

Primary Evaluation Criteria

Two primary efficacy variables were evaluated at Endpoint (Intent-to-Treat [ITT] Cohort)
global improvement of xerostomia (dry mouth)
global improvement of xerophthalmia (dry eyes)

Endpoint was defined as the last available post-baseline observation for each subject. Endpoint analyzes compared the endpoint value to baseline.

Supportive Variables

Unstimulated whole salivary flow was measured at each visit at predose and at 30, 45, and 60 minutes postdose.

Supportive variables assessed were associated with the dryness and discomfort of the mouth and eyes.

Other variables associated with Sjögren's syndrome were assessed: overall dryness, and dryness of the skin, nasal passages, and vagina.

Reviewer's Comments: *No objective criteria have been included.*

Inclusion Criteria

a. Eighteen years of age or older.
b. Signed the approved informed consent form.
c. Xerostomia (dry mouth symptoms and decreased saliva).
d. Xerophthalmia (dry eye symptoms).
e. Residual salivary gland function as demonstrated by unstimulated sialometric procedure at screening.
f. Diagnosed with Sjögren's syndrome and had the presence of
   1. Positive autoimmunity within the past year for
      Sjögren's syndrome A (SS-A) and/or
      Sjögren's syndrome B (SS-B) and/or
      rheumatoid factor and/or
      antibody to nuclear antigens (ANA) and/or
   2. Positive labial biopsy confirmed by central reading source.
g. Negative screening results for the following laboratory tests:
   serum pregnancy test for females of childbearing potential
   hepatitis B surface antigen test
   human immunodeficiency virus (HIV).
h. Completed all screening procedures and deemed an appropriate subject for this study.
i. Willing and able to comply with the protocol.

Exclusion Criteria

a. History of multiple sclerosis.
b. Uncontrolled, significant cardiovascular/renal/pulmonary disease.
c. Active hepatobiliary disease, active pancreatic disorders, or significant hepatic disease.
d. Uncontrolled asthma.
e. Diabetes mellitus, insulin dependent.
f. Active peptic ulcers, inflammatory bowel disease, colostomy, or ileostomy.
g. Clinically significant ocular disease including, but not necessarily limited to:
    1. narrow-angle glaucoma or the potential for miosis-induced increase in intraocular pressure,
    2. peripheral retinopathies,
    3. history of retinal detachment, or a condition predisposing to retinal detachment, or
    4. other condition for which ocular pilocarpine HCl would be excluded.
h. Anticipated use of any of the following medications, whether by prescription or over the counter, during the course of the study:
    1. beta blockers
    2. pilocarpine HCl for ophthalmic indications.
i. Hypersensitivity to pilocarpine HCl.
j. Use of any investigational agent within 30 days prior to or anticipated use during the course of the study.
k. Lactating female or a female of childbearing potential not using a medically acceptable contraceptive method throughout the study.

Reviewer's Comments: *The inclusion and exclusion criteria fail to assure that the correct population was studied.*

Primary Efficacy Variables

The primary efficacy variables were the subject's assessments of global improvement in xerostomia (dry mouth) and xerophthalmia (dry eyes) at Endpoint as measured on a 100 mm VAS. These variables were assessed by subjects at Week 6 and Week 12 and therefore analyzes were conducted for Week 6, Week 12, and Endpoint. For these two variables, the subject ranked the experienced changes in dryness. Based on the 100 mm scale, scores were categorized and summarized as worsened (< 45 mm), no change (45-55 mm), or improved (> 55 mm). Based on these definitions, subjects were categorized as responders (improved) or nonresponders (no change or worsened).

The categorized scores and the actual VAS scores were analyzed for treatment differences.

Reviewer's Comments: *The categorized endpoints have not been shown to represent clinically significant differences and are not considered acceptable.*

Supportive Efficacy Variables - Mouth and Eye

Relief of symptoms associated with dry mouth and dry eyes were also evaluated using either a 100 mm VAS or a 3-point categorical question. For VAS questions, the score was computed at Week 6, Week 12, and Endpoint by subtracting the baseline score from each available post-baseline score. Subjects whose calculated scores increased by ≥ 25 mm (improvement) were classified as responders. Subjects whose calculated scores increased by < 25 mm were classified as nonresponders. Responder/ nonresponder results were summarized and analyzed.

Mouth variables evaluated using a 100 mm VAS were severity of:

a. dryness in mouth
b. discomfort of the mouth
c. discomfort of dentures (for denture wearers only)

Eye variables evaluated using a 100 mm VAS were severity of:

a. eye discomfort
b. sensitivity to light
c. itching of the eyes
d. tiredness of the eyes
e. redness of the eyes
f. matting or sticking of the eyes
g. feeling that something is in the eyes

For the efficacy variables measured using the 3-point scale, changes in the use of saliva and tear substitutes were measured on a scale of decreased, stayed the same, or increased, and subjects were classified as responders (decreased) or nonresponders (stayed the same or increased). Changes in the ability to speak, to sleep without water, and to swallow food were measured on a scale of worsened, stayed the same, or improved, and subjects were classified as responders (improved) or nonresponders (stayed the same or worsened).

Supportive Efficacy Variables - Other Symptoms of Dryness Associated with Sjögren's Syndrome

Symptoms of dryness associated with Sjögren's syndrome, other than those associated with the mouth and eyes, were evaluated:

a) overall assessment of symptoms of dryness (referred to as overall dryness) (5-point categorical question)
b) dryness of the skin (VAS)
c) vaginal dryness (VAS)
d) nasal dryness (VAS)

The 5-point question was analyzed as responder/non-responder with worsened and no-change equal to non-responder and improved, moderately improved, and significantly improved equal to responders.

Reviewer's Comments: *The failure to include objective ocular measurements (Schirmer Tear Test and Rose Bengal Stain) is a fatal flaw of the protocol with respect to the proposed ocular claims. In addition, the definition of responders is not consistent with the typical definitions used for dry eye products.*

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ON ORIGINAL

SUBJECT ENROLLMENT BY INVESTIGATOR
(placebo = 128; pilocarpine HCl = 128)

Site Numbers	Principal Investigators	Total Number Enrolled	Subject Number
01	Ettlinger, Robert	18	
02	Gaylis, Norman	5	
03	Walsh, Bridget	26	
04	Golden, Harvey	26	
05	Moreland, Larry	17	
06	Papas, Athena	60	
07	Charney, Michael	21	
08	Wise, Christopher	20	
09	Parke, Ann	18	
10	Sherrer, Yvonne	0	
11	Medsger, Thomas	24	
12	Ginsburg, Mark	21	
		Total = 256	

DEMOGRAPHIC CHARACTERISTICS

	Pilocarpine HCl (N=128)	Placebo (N=128)	P-value
	Mean ± SD (range)		
Age (y)	55.4 ± 13.34	57.8 ± 13.04	0.15
Height (in)	64.5 ± 2.93	63.8 ± 2.70	0.05
Weight (lb)	153.5 ± 30.83	152.0 ± 38.16	0.73
	N (%)		
Race			0.80
Caucasian	117 (91.4)	116 (90.6)	
Black	7 (5.5)	7 (5.5)	
Oriental	0 (0.0)	1 (0.8)	
Other	4 (3.1)	4 (3.1)	
Sex			0.03
Female	117 (91.4)	125 (97.7)	
Male	11 (8.6)	3 (2.3)	

EFFICACY EVALUATION OF ITT COHORT AT WEEK 6, WEEK 12, AND ENDPOINT; RAW VAS SCORES

	Placebo			Pilocarpine HCl			
	n	Mean	SD	n	Mean	SD	P-value
Mean global improvement in xerostomia (not change from baseline)							
Week 6	121	48.1	17.13	121	55.2	21.39	**≤0.004**
Week 12	110	50.0	21.65	111	64.6	21.68	**≤0.001**
Mean global improvement in dryness of the eye (not change from baseline)							
Week 6	121	46.7	19.08	121	49.7	20.58	≤0.216
Week 12	111	48.8	21.39	111	58.7	21.77	**≤0.001**
Change from Baseline							
MOUTH							
Severity of dryness of mouth							
Week 6	122	19.4	22.03	122	24.4	26.63	≤0.104
Week 12	110	24.1	25.54	112	34.2	28.07	**≤0.004**
Severity of discomfort of the mouth							
Week 6	121	17.5	24.20	122	25.5	27.41	**≤0.016**
Week 12	109	21.7	26.92	112	32.2	28.34	**≤0.005**
Change in the severity of discomfort of dentures							
Week 6	37	8.3	33.95	34	9.6	35.83	≤0.667
Week 12	34	10.8	40.66	28	12.5	39.67	≤0.499
EYE							
Change in severity of eye discomfort							
Week 6	121	15.9	26.84	122	23.2	27.34	**≤0.037**
Week 12	111	17.0	27.01	111	33.7	28.33	**≤0.001**
Change in sensitivity to light							
Week 6	121	10.9	26.34	121	15.6	26.76	≤0.185
Week 12	110	14.8	25.99	110	19.4	27.91	≤0.214
Endpoint	123	13.8	26.96	122	19.1	27.53	≤0.145
Change in severity of itching of the eye							
Week 6	120	7.9	29.81	121	17.4	28.80	**≤0.013**
Week 12	110	7.5	27.27	110	21.2	29.54	**≤0.001**
Change in severity of tiredness of the eye							
Week 6	119	12.3	27.86	121	16.3	24.72	≤0.255
Week 12	111	17.0	24.93	112	23.1	28.71	≤0.103
Change in severity of redness of the eye							
Week 6	119	5.2	31.09	120	13.9	29.57	**≤0.034**
Week 12	111	6.8	29.33	110	17.5	33.57	**≤0.013**

Change in severity of matting/sticking of the eye							
Week 6	121	5.4	34.66	121	2.0	29.96	≤0.369
Week 12	111	6.3	31.98	112	4.3	31.59	≤0.722
Change in severity of the feeling that something is in the eye							
Week 6	117	12.8	30.04	122	15.8	29.73	≤0.465
Week 12	109	15.3	30.92	112	21.0	33.94	≤0.178
OTHER VARIABLES							
Change in severity of dryness of the skin							
Week 6	118	11.2	27.15	120	9.1	27.53	≤0.439
Week 12	110	13.9	29.02	111	11.5	31.80	≤0.549
Change in severity of vaginal dryness							
Week 6	116	0.1	35.57	110	2.1	34.52	≤0.694
Week 12	107	2.8	39.05	101	1.2	35.96	≤0.703
Change in severity of nasal dryness							
Week 6	120	7.6	33.95	121	6.7	36.62	≤0.782
Week 12	110	8.4	35.42	110	10.0	35.31	≤0.696

Reviewer's Comments:

The differences between groups are not considered clinically significant and did not reproduce the same findings as Study 92-01.

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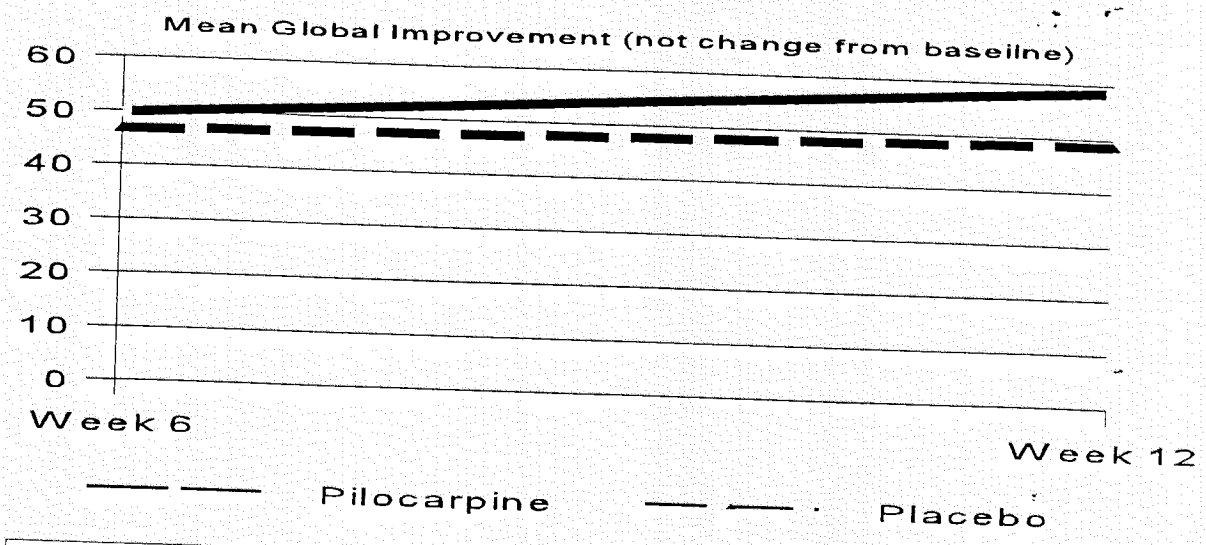
ON ORIGINAL



Pilocarpine	49.7	58.7
Placebo	46.7	48.8

Reviewer's Comments: *The observed differences have not been shown to be clinically significant.*

APPEARS THIS WAY
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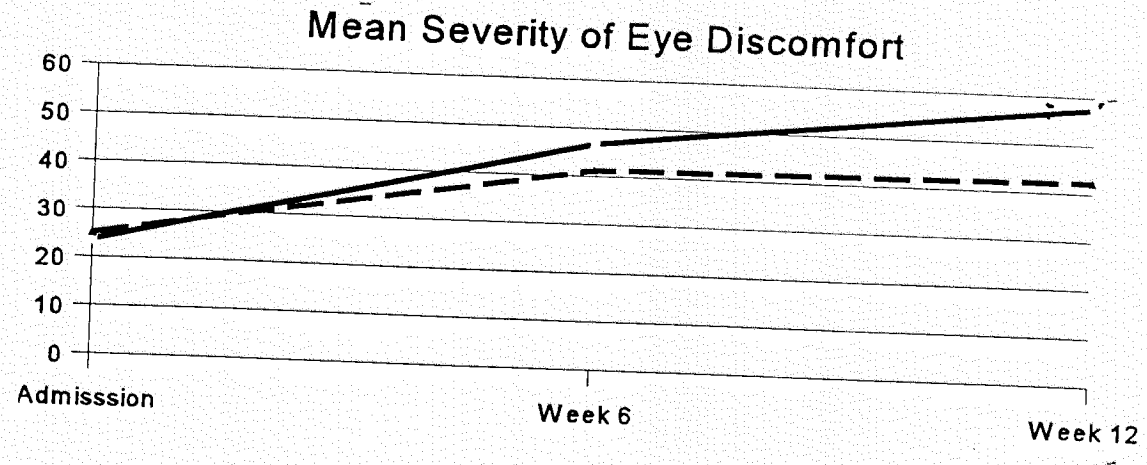
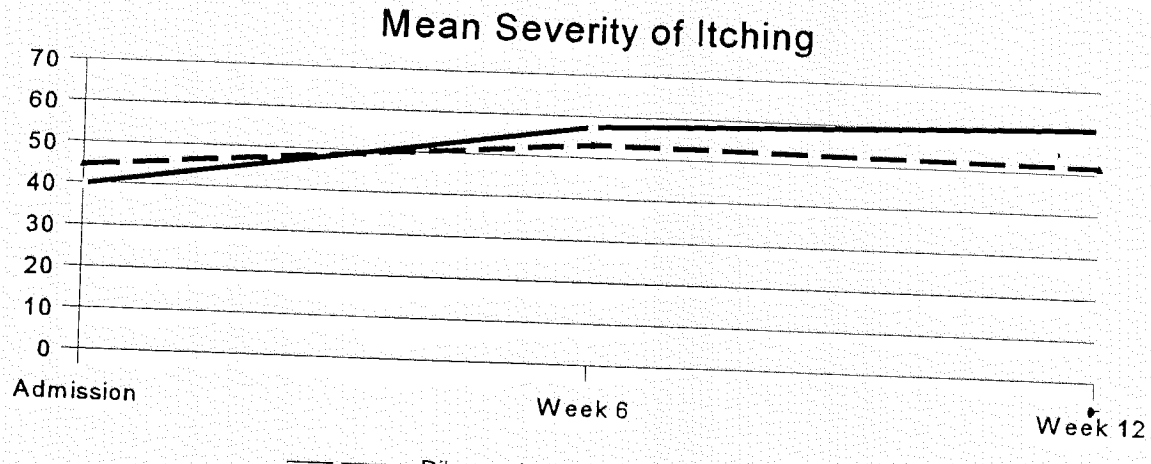


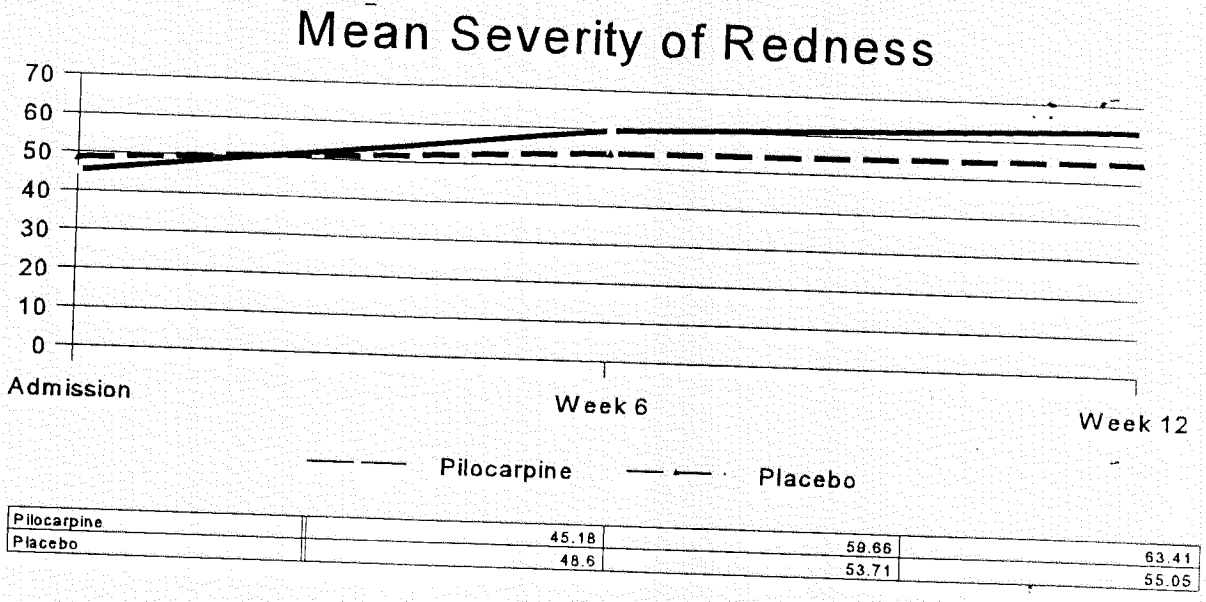
Pilocarpine	23.59	46.78	57.54
Placebo	25.07	41.23	42.28

Reviewer's Comments: *The differences between groups are not clinically significant. A clinically significant difference would be expected to be at least 25 units on this scale.*



Pilocarpine	39.69	57.34	60.76
Placebo	44.55	53.09	51.63

Reviewer's Comments: *The differences both at admission and throughout the study are equivalent and are not considered clinically significant.*



Pilocarpine	45.18	59.66	63.41
Placebo	48.6	53.71	55.05

Reviewer's Comments: *The differences both at admission and throughout the study are equivalent and are not considered clinically significant.*

Conclusions:

1. The study failed to ensure that patients with "dry eye" signs and symptoms were enrolled.
2. There were no objective criteria upon which to evaluate the treatment.
3. Differences observed in the symptoms are not considered clinically significant.
4. The definition used for "responder" is not considered by this reviewer to be acceptable.

Overview of Safety and Efficacy for Ocular Indications:

1. The studies failed to ensure that patients with "dry eye" signs and symptoms were enrolled.

2. There were no objective criteria upon which to evaluate the treatment.

3. Differences observed in the symptoms are not considered clinically significant.

Conclusions and Recommendations

The supplemental application fails to provide support for the treatment of symptoms of dry eyes in patients with Sjögren's syndrome.

/S/

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: HFD-540
HFD-105
HFD-550/Consult File
HFD-340
HFD-540/PHARM/Jacobs
HFD-540/PM/Blatt
HFD-540/DO/Hyman
HFD-550/MO/Chambers