

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-237/S-007

STATISTICAL REVIEW(S)

JAN 20 1998

CLINICAL/STATISTICAL REVIEW AND EVALUATION

NDA/DRUG CLASS: 20-237/SE1-007

NAME OF DRUG: SALAGEN Tablets (Pilocarpine Hydrochloride)

APPLICANT: MGI Pharma, Inc.

INDICATIONS: Xerostomia (dry mouth) in Patients
With Sjogren's Syndrome

TYPE OF REVIEW: Clinical/Statistical

DOCUMENTS REVIEWED: Studies: P92-01 and P92-02

MEDICAL REVIEWER: Fred Hyman, D. D. S., M. Ph./HFD-540

STATISTICAL REVIEWER: Shahla S. Farr, M.S./HFD-725

I. INTRODUCTION

The purpose of this supplement is to extend the indication for the use of the currently marketed 5 mg Salagen Tablets (Pilocarpine Hydrochloride) to include the treatment of xerostomia (dry mouth) & keratoconjunctivitis sicca (dry eye) in patients with Sjogren's syndrome.

Sjogren's syndrome is an immunologic disorder characterized by progressive destruction of the exocrine glands leading to oral mucosal and conjunctival dryness (sicca syndrome). The disease can occur by itself, or in association with other autoimmune diseases. Sjogren's syndrome is most common in women in the fifth or sixth decade of life. FDA's Office of Orphan Product Development has estimated that the patient population with this syndrome is 100,000.

Pilocarpine Hydrochloride (HCI) is the chief alkaloid obtained from the leaflets of South American shrubs of the genus Pilocarpus. The use of pilocarpine HCI for many decades as a topical ophthalmic drug, and more recently in clinical trials as an oral dosage to alleviate xerostomia, has provided substantial evidence of its risks for use in human subjects. Pilocarpine HCI (Salagen Tablets) has been shown to be safe and effective for the treatment of xerostomia resulting from radiation damage to salivary glands.

II. REVIEW

The sponsor has submitted three clinical studies in which four different strengths of tablets were used, along with placebo for 12 weeks. Two of these trials are considered pivotal which are the focus of this review. Table I lists the two pivotal studies:

Table I
Summary of Studies

Study # (# of Centers)	Study Design, Duration	Treatment Arm (n)	N	Endpoint
P92-01 (17)	Multicenter, Randomized, Placebo- Controlled, Double-Blind (12 weeks)	1) Salagen 2.5 mg qid (121) 2) Salagen 5 mg qid (127) 3) Placebo qid (125)	373	Global Improvement of Xerostomia using VAS: <45 mm: Worsen, No Resp. 45-55 mm: No Change, No Resp. >55 mm: Improve, Resp.
P92-02 (15)	Multicenter, Randomized, Placebo- Controlled, Double-Blind (12 Weeks)	1) Salagen 5 mg qid 6 weeks/ Salagen 7.5 mg qid 6 weeks (128) 2) Placebo qid (128)	256	Global Improvement of Xerostomia using VAS: <45 mm: Worsen, No Resp. 45-55 mm: No Change, No Resp. >55 mm: Improve, Resp.

Note: Originally this NDA was submitted by the sponsor for two indications, xerostomia (dry mouth) and keratoconjunctivitis sicca or xerophthalmia (dry eye). However, the indication for the dry eye was found not to be approvable by the division of ophthalmic. Therefore, according to the division director of ophthalmic products there will be no need for statistical analysis.

The two studies were similar in terms of the primary efficacy variables, patient population, sample size and statistical methodology.

Primary & Secondary Efficacy Variables:

One primary efficacy variable was evaluated at endpoint: "Global Improvement of Xerostomia (dry mouth)". Endpoint was defined as the last available post-baseline observation for each subject. The subjects ranked the change in dryness on the 100 mm visual analogue scale (VAS). A rating of <45 mm was defined as worsened or no response, 45-55 mm indicated no change or no response, and scores of >55 mm were defined as improvement or response. Based on these definitions, subjects were categorized as responders (improved) or non-responders (no change or worsened). In this review, both the continuous (VAS) and the binomial (Responder vs. Non-Responder) version of the variable are analyzed and presented for Week-6, Week-12 and Endpoint.

The sponsor has submitted approximately twenty variables as their secondary endpoints. However, this is not acceptable by the FDA. The FDA recommends a maximum of three additional parameters as the secondary endpoint variables. Depending on the number of treatment comparisons to be performed, and the degree of correlation between the variables, an appropriate adjustment in the α level has to be made. This would be a high price to pay for these comparisons. Therefore, after discussions with the medical officer, it was decided to report the

results of the most important and most meaningful parameter: "Severity of Dry Mouth" as the only secondary endpoint variable.

Patient Population, Sample Size & Statistical Methods:

The results of this review are based on the Intent-to-Treat (ITT) population, where ITT includes all subjects who were randomized to the study and were given the study medication, regardless of their use of the dispensed drug. For subjects with no week 12 data available, their week 6 data was carried forward as the last available observation. For subjects with no post baseline data, their baseline value was carried forward.

The sample size was calculated based on an estimated placebo response rate of 30% and active group response rate of 50%. Approximately 100 subjects per treatment group were needed to attain significance at $\alpha=0.05$ with power of at least 80%. These calculations were based on a two-sided, Chi-square test.

Baseline categorical demographic variables (race and sex) were analyzed using Pearson's chi-square test. Continuous demographic variables (age, weight) were analyzed using one-way analysis of variance (ANOVA).

The sponsor has performed a logistic regression model (SAS Proc GENMOD) for their analysis. However, in this review, analyses of responder/non-responder were conducted using a Chi-Squares test. In addition, to investigate the presence of treatment-by-investigator interaction, Cochran Mantel Haenszel test was performed. Also, an analysis of Variance model with treatment, investigator, and treatment by investigator terms was performed on the raw VAS global scores. All inference tests were conducted at $\alpha=0.05$ (two-sided).

Study MGI 647.94.P92-01 (Fixed Dose):

Objective & Design:

The objective of this trial was to assess the efficacy and safety of pilocarpine HCl tablets administered orally as a treatment for the symptoms of xerostomia and xerophthalmia associated with Sjogren's syndrome.

This was a multicenter (17 center), randomized, double-blind, placebo-controlled with three parallel treatment arms: placebo, 2.5 mg pilocarpine HCl or 5 mg pilocarpine HCl administered on a q.i.d. regimen for a 12-week treatment period. Subjects were stratified based on presence or absence of rheumatoid arthritis. The primary dose of interest is pilocarpine HCl 5 mg.

Safety and efficacy evaluations were conducted at baseline (admission) and weeks 6 and week 12.

Demographics & Baseline Characteristics:

A total of 373 subjects were randomized to participate in this study. Of these, 125 received placebo, 121 pilocarpine HCl 2.5 mg and 127 received the 5 mg pilocarpine HCl.

Table II summarizes the demographics and baseline characteristics of these subjects.

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Table II
Demographics & Baseline Characteristics of All Randomized Subjects
Study MGI 647.94.P92-01 (Fixed Dose)

	Whole Population (N=373)	Salagen 5 mg (n=127)	Salagen 2.5 mg (n=121)	Placebo (n=125)	P-Value
Gender (n):					0.6
Male	16 (4%)	4 (3%)	5 (4%)	7 (6%)	
Female	348 (96%)	120 (97%)	114 (96%)	114 (94%)	
Race (n):					0.6
White	288 (79%)	101 (81%)	94 (79%)	93 (77%)	
Black	9 (2%)	3 (2%)	1 (1%)	5 (4%)	
Oriental	52 (14%)	14 (11%)	20 (17%)	18 (15%)	
Other	15 (4%)	6 (5%)	4 (3%)	5 (4%)	
Age (Mean ± Std):	54 ± 13	55 ± 14	54 ± 12	54 ± 13	0.6
Weight (Mean ± Std):	146 ± 33	148 ± 32	147 ± 34	145 ± 33	0.8
Severity of Dry Mouth @ Baseline (VAS) (Mean ± Std):	20 ± 18	19 ± 17	22 ± 20	19 ± 17	0.4
Rheumatoid Arthritis Status (n):					0.9
Yes	71 (19%)	26 (20%)	22 (18%)	23 (18%)	
No	302 (81%)	101 (80%)	99 (82%)	102 (82%)	
Investigator (n):					
LeVeque, Francis G.	37	13	11	13	
Vivino, Frederick B.	28	10	8	10	
Khan, Zafrulla	25	9	8	8	
Salisbury III, Paul L.	37	12	13	12	
Fox, Rober I.	16	5	5	6	
Talal, Norman	13	5	3	5	
Yee, Richard W.	12	4	4	4	
Griffing, W. Leroy	8	2	3	3	
Rhodus, Nelson	17	5	7	5	
Tran-Johnson, Tram	62	20	21	21	
Furst, Daniel	19	7	6	6	
Ellman, Michael	18	6	6	6	
Sreebny, Leo	22	8	7	7	
Meyerowitz, Cyril	15	5	5	5	
Sonis, Stephen	7	3	1	3	
Wolfe, Frederick	12	4	4	4	
Al-Hashimi, Ibtisam	25	9	9	7	

As it is shown in Table II, 96% of the subjects were female and 79% were white.

No statistical difference was found among the three treatment arms in regards to the demographics and baseline characteristics variables.

Since centers Griffing (n=8) and Sonis (n=7) were small, for the purposes of the analyses of this review, these two centers were combined.

Clinical Efficacy Analysis & Results:

A total of 119 of the original 127 patients (94%) in the Salagen 5 mg arm, 108 of the 121 subjects (89%) in the Salagen 2.5 mg group and 118 of the 125 subjects (94%) in the placebo group finished the 6 week treatment period.

At the end of the 12th week, 109 (86%) of the 5 mg group, 102 (84%) of the 2.5 mg group and 111 (89%) of the placebo arm had finished the study.

Table III, illustrates the results of the Global Assessment of Dry Mouth based on dichotomous (Yes/ No) data at Week-6, Week-12 and Endpoint.

Table III
Global Assessment of Dry Mouth (dichotomous data)
Study MGI 647.94.P92-01 (Fixed Dose)

Clinical Response	Salagen 5 mg	Salagen 2.5 mg	Placebo	P-Value (All Treats.)	P-Value (5 vs. 2.5 mg)	P-Value (5mg vs. PBO)
Week-6: Responder Non-Responder	70/119= 59% 49/119=41%	39/108=36% 9/108=64%	37/118=31% 81/118=69%	0.001	0.001	0.001
Week-12: Responder Non-Responder	67/109=61% 42/109=39%	43/102=42% 59/102=58%	36/111=32% 75/111=68%	0.001	0.005	0.001
Endpoint (ITT): Responder Non-Responder	73/127=57% 54/127=43%	43/121=36% 78/121=64%	37/125=30% 88/125=70%	0.001	0.001	0.001

As it is seen in Table III, highly statistically significant results were observed when Salagen 5 mg was compared to Salagen 2.5 mg or placebo ($p \leq 0.005$), at Week 6, Week 12 and endpoint.

Controlling for investigator effect did not change the statistical significant results at all the time points ($p=0.001$).

Table IV shows the mean for the Global Assessment of Dry Mouth according to the actual VAScores (continuous data).

Table IV
Global Assessment of Dry Mouth (VAScores, continuous data)
Study MGI 647.94.P92-01 (Fixed Dose)

Clinical Response (Mean ± Std)	Salagen 5 mg	Salagen 2.5 mg	Placebo	P-Value (All Treats.)	P-Value (5 vs. 2.5 mg)	P-Value (5mg vs. PBO)
Week-6	63 ± 19	52 ± 20	52 ± 17	0.07	0.0001	0.0001
Week-12	64 ± 19	53 ± 23	52 ± 21	0.04	0.0001	0.0001
Endpoint (ITT)	63 ± 18	52 ± 21	52 ± 21	0.03	0.0001	0.0001

As it is shown in Table IV, highly statistically significant results were observed between Salagen 5 mg and placebo and Salagen 5 mg and Salagen 2.5 mg ($p=0.0001$). No treatment by investigator interaction effect was observed for all three time points ($p>0.6$).

Secondary Endpoint Variable:

The "Severity of Dry Mouth Was Analyzed" as the secondary variable at each time point. Table V gives the p-values for the analyses.

Table V
Severity of Dry Mouth (VAScores, continuous data)
P-Values
Study MGI 647.94.P92-01 (Fixed Dose)

	(All Treats.)	(5 mg vs. 2.5 mg)	(5 mg vs. PBO)
Week-6	0.09	0.001	0.0004
Week-12	0.2	0.008	0.007
Endpoint (ITT)	0.1	0.02	0.01

As it is shown in table V, statistically significant results were observed in regards to the severity of dry mouth at all time points between Salagen 5 mg and 2.5 mg and also between Salagen 5 mg and placebo treatment arms ($p\leq 0.02$).

Subset Analysis:

Seventy-nine (21%) of the 373 subjects were older than 65 years. No statistical significant difference was observed in regards to the primary endpoint variables for this age group ($p>0.1$). However, the results of the subset analysis for the age category of 65 and younger yielded highly statistically significant results for all the time points and both the categorical and continuous endpoint variables ($p=0.001$).

Since the majority of subjects were female (96%) and white (79%), subset analyses for gender and race were not found to be necessary.

Study MGI 647.94.P92-02:

Objective & Design:

The objective of this study was to assess the efficacy and safety of pilocarpine HCl tablets administered orally as a treatment for the symptoms of xerostomia and xerophthalmia associated with Sjogren's syndrome.

This was a multicenter (12 center), randomized, double-blind, placebo-controlled with two parallel treatment arms: placebo for a 12-week treatment period & 5 mg pilocarpine HCl for the first 6 weeks, then escalated to 7.5 mg pilocarpine HCl for the second 6 weeks administered on a q.i.d. regimen. Safety and efficacy evaluations were conducted at baseline (admission) and weeks 6 and week 12.

This study does not have a complete 12 week data for the 5 mg dose of Salagen which sponsor requests the approval of. For this reason, the analysis in this review will only include the data for the first 6 weeks of the study for both the treatment arms.

Demographics & Baseline Characteristics:

A total of 256 subjects were randomized to participate in this study. Of these, 128 received placebo, 128 were on pilocarpine HCl 5 mg/7.5 mg.

Table VI summarizes the demographics and baseline characteristics of these subjects.

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Table VI
Demographics & Baseline Characteristics of All Randomized Subjects
Study MGI 647.94.P92-02

	Whole Population (N=256)	Salagen (n=128)	Placebo (n=128)	P-Value
Gender (n):				0.03
Male	14 (5%)	11 (9%)	3 (2%)	
Female	242 (95%)	117 (91%)	125 (98%)	
Race (n):				0.8
White	233 (91%)	117 (91%)	116 (91%)	
Black	14 (5%)	7 (5%)	7 (5%)	
Oriental	1 (0.4%)	0 (0%)	1 (1%)	
Other	8 (3%)	4 (3%)	4 (3%)	
Age (Mean ± Std):	57 ± 13	55 ± 13	58 ± 13	0.1
Weight (Mean ± Std):	154 ± 35	155 ± 32	154 ± 38	0.8
Severity of Dry Mouth @ Baseline (VAS) (Mean ± Std):	18 ± 16	19 ± 17	16 ± 16	0.09
Investigator (n):				
Ettlinger, Robert	18	9	9	
Gaylis, Norman	5	3	2	
Walsh, Bridget	26	13	13	
Gilden, Harvey	26	13	13	
Moreland, Larry	17	8	9	
Papas, Athena	60	30	30	
Charney, Michael	21	11	10	
Wise, Christopher	20	10	10	
Parke, Ann	18	9	9	
Sherrer, Yvonne	0	0	0	
Medsger, Thomas	24	12	12	
Ginsburg, Mark	21	10	11	

The sponsor has not explained as to why investigator Sherrer did not recruit any subjects.

The majority of subjects (95%) were female. No statistical difference was observed among the two treatment groups in regards to the demographics and baseline characteristics variables ($p > 0.05$), except for gender ($p = 0.03$).

For the purposes of the analyses of this review, since center Gaylis (n=5) was small, this center was combined with center Moreland (n=17).

Table VII
Study MGI 647.94.P92-02 (dichotomous data)
@ Week-6

Clinical Response	Salagen (n=128)	Placebo (n=128)	P-Value
Responder	56/121=46%)	27/121=22%	0.001
Non-Responder	65/121=54%	94/121=78%	

As it is shown in Table VII, highly statistically significant results were observed when Salagen was compared to placebo (p=0.001).

Controlling for investigator effect did not change the statistical significant results (p=0.001).

Due to the fact that there was a difference in distribution of the males and females in to the treatment arms, the above analysis was repeated, controlling for gender effect. The results were not different from the previous analyses (p=0.001).

Table VIII shows the mean for the Global Assessment of Dry Mouth according to the actual VA Scores (continuous data).

Table VIII
Global Assessment of Dry Mouth (VAScores, continuous data)
Study MGI 647.94.P92-02
@ Week-6

	Salagen (n=128)	Placebo (n=128)	P-Value
Clinical Response (Mean ± Std)	55 ± 21	48 ± 17	0.004

As it is shown in Table VIII, highly statistically significant results were observed between Salagen and placebo (p=0.004). No treatment by investigator interaction effect (p=0.2) or treatment by gender effect (p>0.5) was observed.

Secondary Endpoint Variable:

The severity of dry mouth at 6 weeks was analyzed as the secondary variable.

Table IX gives the Mean \pm Std as well as the p-value for the analysis.

Table IX
Severity of Dry Mouth (VAScores, continuous data)
Study MGI 647.94.P92-02

	Salagen	PBO	P-Value
Severity of Dry Mouth (Mean \pm Std)	44 \pm 29	35 \pm 24	0.01

A statistically significant difference was found between the two treatment arms (p=0.01).

Subset Analysis:

Sixty-seven (26%) of the 256 subjects were older than 65 years. No statistical significant difference was observed in regards to the primary endpoint variables for this age group (p>0.1). However, the results of the subset analysis for the age category of 65 and younger yielded highly statistically significant results for all the time points and both the categorical and continuous endpoint variables (p \leq 0.006).

III. CONCLUSION:

The results of the study MGI 647.94.P92-01 indicates the superiority of the Salagen 5 mg over the Salagen 2 mg and placebo (p=0.001) for the *6 week* and the *12 week* time period (per protocol) as well as the *ITT* population in regards to the primary endpoint variable, Global Assessment of Dry Mouth (VAS category and VAS continuous) (p=0.01).

The findings of the second study (MGI 647.94.P92-02) submitted by the sponsor indicates the superiority of the Salagen 5 mg over placebo (p=0.001) for the *6 week* in regards to the primary endpoint variable, Global Assessment of Dry Mouth (VAS category and VAS continuous) (p=0.01).

The secondary variable (Severity of Dry Mouth) also showed statistically significant results for both of the studies, indicating the superiority of the Salagen 5 mg to the 2 mg dose and placebo (p=0.01).

The analysis of subgroups revealed a statistically significant difference between Salagen 5 mg and placebo and also between Salagen 5 mg and Salagen 2.5 mg for subjects 65 years and younger and also for female population. However, no statistically significant results were

observed for the subjects older than 65 and for the male group ($p > 0.05$). This might be due to a small sample size in the older group and the male population.

According to the reviewing medical officer, the data presented by the sponsor did not raise any safety issues to be analyzed and addressed by the statistical reviewer.

Based on results presented in this review, Salagen 5 mg Tablet is safe and effective in the treatment of dry mouth in the subjects who participated in the two clinical trials.

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1/16/98

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Mathematical Statistician, Biometrics IV

01/20/98

concur: R. Srinivasan, Ph.D.
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cc:

Archival NDA 20-237
HFD-540
HFD-540/Dr. Hyman
HFD-540/Dr. Wilkin
HFD-540/Mr. Blay
HFD-725/Ms. Farr
HFD-725/Dr. Srinivasan
HFD-725/Dr. Huque
HFD-344/Dr. Carreras
Chron.

This review contains 12 pages.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-237/S-007

BIOEQUIVALENCE REVIEW(S)

Pilocarpine HCl 5mg tablets
Salagen® Tablets
NDA 20-237 SE1-007
Reviewer: E.D. Bashaw, Pharm.D.
APW

MGI Pharma Inc.
Minnetonka, Minnesota

Submission Date:
Feb. 11, 1998

Review of an Efficacy Supplement

Background

At the present time Salagen® tablets are approved for use in the treatment of xerostoma (dry mouth) associated with radiation therapy in patients with head and neck carcinomas. This efficacy supplement allows for the use of Salagen® tablets to treat patients with Sjogren's syndrome. This syndrome is identified by the presence of a connective tissue disorder (rheumatoid arthritis, scleroderma, SLE, etc.) associated with a deficiency in lacrimal and salivary gland function resulting in symptoms of dry eyes and dry mouth. Sjogren's syndrome is an orphan disease.

Pharmacokinetic Overview

At the present time there is no information available to suggest that Sjogren's syndrome is associated with any metabolic alterations in man. As part of this supplement the applicant used both their marketed product and investigational tablets (similar in formulation and strength to those which were also used in the original NDA). In the original NDA the sponsor demonstrated in vivo bioequivalency between their to-be-marketed formulation and their investigational tablets. At the present time there are not biopharmaceutic issues related to the approval of this efficacy supplement that are outstanding.

Recommendation

As there are no identified pharmacokinetic issues present in this supplement, it is inappropriate for this reviewer to comment on the approvability of this application. This memo was written at the request of the project manager (Roy Blay) to close out the assignment sheet for this product.

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E. Dennis Bashaw, Pharm.D.
Division of Pharmaceutical Evaluation-III

Secondary Review, John Lazor, Pharm.D. *1/14/98*

CC: NDA 20-237 (ORIG),
HFD-540/DIV File
HFD-540/CSO/Blay
HFD-88Bashaw)
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