

Recommended Regulatory Action:

The sponsor has successfully demonstrated the safety and efficacy of Salagen® for treatment of the symptoms of dry mouth in patients with Sjögren's syndrome. With modifications to the sponsor's proposed labeling, as was discussed in this review, the product may be approved for marketing for this new indication.

It would be useful for the sponsor to develop trials that would continue to explore some of the questions they had broached but not answered during the two pivotal trials conducted for this application. Successful outcomes in well-controlled trials would result in more precise labeling as well as more information for clinicians and patients.

However, it would be very informative to examine the ocular outcome with the use of Salagen® in individuals with SS to objectively determine the improvement, if any. Similarly, insufficient information was presented in this application to support a dosing higher than 5 mg q.i.d. However, it may be very useful to examine the level of effectiveness that may be achieved at higher dosing, as well as any change in adverse events that may occur. In the first of the two pivotal trials conducted, the sponsor examined a subset of Sjogren's subjects with Rheumatoid Arthritis and noted a trend towards significant effect at a lower dose. This too may be worthy of further examination to uncover whether a lower dose is required in subjects with milder form of the disease.

/s/

2/5/98

Frederick N. Hyman, D.D.S., M.P.H.

cc: Orig NDA
HFD-540/Div File
HFD-540/DD/Wilkin
HFD-540/TL/Kelsey
HFD-540/DO/Hyman/Gilkes
HFD-540/PM/Blay
HFD-540/See
HFD-725/Srinivasan/Farr
HFD-830/Vidra

/ 2/5/98

2/6/98

DEC 31 1997

Medical Officer's Rheumatology Consultation of NDA 20-237/S-007

NDA 20-237
Supplement 7

Submitted date: 12/5/97
Review date: 12/24/97

Sponsor: MGI Pharma, Inc.

Drug: pilocarpine hydrochloride tablets, 5 mg (Salagen®)

Pharmacologic Category: cholinergic

Dosage form/
Route of Administration: oral

Submitted: Amendment 10, S-007
Modified Draft Labeling

Resume: HFD 540 has requested input regarding whether the inclusion criteria in Efficacy Supplement S-007 for Salagen accurately identifies patients with Sjogren's Syndrome (SS). It is noted that in a second amendment (1994) to both protocols (listed below), the requirement for objective assessment of xerophthalmia (i.e. Schirmer's and Rose Bengal tests) were eliminated.

Patients included in trials P92-01 and P92-02:

According to the Inclusion Criteria for trial P92-01 (6.1.d-e; p. 000005) patients were diagnosed with Sjogren's Syndrome if they had:

- d. Residual salivary gland function as demonstrated by unstimulated or stimulated sialometric procedure at the time of screening
- e. Diagnosed with Sjogren's syndrome and having the presence of:
 - 1. Xerostomia (dry mouth symptoms and decreased saliva); and,
 - 2. Xerophthalmia (dry eye symptoms); and,
 - 3. a. Positive autoimmunity with the past year for:

- SS-A and/or
- SS-B and/or
- Rheumatoid Factor and/or
- ANA

AND/OR

- b. Positive labial confirmed by central reading center.

In Appendix C on the following page, the labial biopsy was further described to include "and having a focus score greater than 1 focus/4 mm². However, Appendix C also does NOT contain any questions relating to symptoms of dry eyes or mouth.

Post-amendment questionnaires (p. 000007) designed to describe the ocular and oral symptoms include two VAS questions regarding xerostomia (part I) and four VAS questions regarding xerophthalmia (part II). The xerostomia questions ask the patient to assess oral dryness over the last 7 days and how dry the mouth has been (i.e. does the patient need frequent water or saliva substitutes). The xerophthalmia questions ask patients to compare eye discomfort over the past 7 days as representative of the past 3 months and the severity of eye discomfort including the feeling of a foreign body in the eye.

Inclusion criteria for both protocols also required a negative screen for hepatitis B surface antigen and HIV and the exclusion criteria for protocol P92-01 (only the first three criteria were included in the material submitted for comment) excludes patients with a history of multiple sclerosis.

The inclusion criteria (6.1 c-e, p. 000013) and questions (p. 000014) for trial P92-02 are similar to P92-01 though not exact since they only look at unstimulated salivary gland function and there are fewer questions addressing the symptoms of xerostomia and xerophthalmia. Furthermore, Appendix D (p. 000017) does NOT contain inclusion of any signs or symptoms for xerostomia or symptoms of xerophthalmia.

Reviewer's comment:

Any discussion of SS needs to address the problems that have existed in terms of the classification criteria for this syndrome. It is recognized, for example, that SS exists in a primary and secondary form (the latter including the characteristic "sicca complex" of keratoconjunctivitis sicca and xerostomia plus clinical features of another well-defined autoimmune disease such as rheumatoid arthritis) and that important exclusions need to be made for diseases that may mimic these sicca symptoms (such as HIV or hepatitis B or C). This lack of established diagnostic criteria for SS has complicated understanding not only the incidence of primary SS but also interpretation of results of

treatment with particular pharmacologic agents in clinical trials. This deficiency of accepted criteria has also hindered understanding the incidence of associated diseases such as lymphoma, multiple sclerosis, and dementia.

Consequently, efforts have been made to establish classification criteria and currently there are at least three including the "San Diego" criteria (Fox RI, Saito I: Criteria for Diagnosis of Sjogren's syndrome. *Rheum Dis Clin North Am* 20: 391-407, 1994); the "European" criteria (Vitali C, et al.: Preliminary criteria for the classification of Sjogren's syndrome-Results of a prospective concerted action supported by the European community. *Arthritis Rheum.* 36: 340-347, 1993. Also, *Ann Rheum Dis.* 53: 637-647, 1994); and the "San Francisco" criteria (Daniels et al. *Arthritis Rheum.* 37: 869-877, 1994).

The European criteria (**Appendix I**, attached) have recently been adopted by the American College of Rheumatology (ACR). As can be seen, primary SS is divided into "probable" and "definite" SS based upon whether three or four of the six criteria are fulfilled, respectively. These criteria resulted from analysis of data from 22 centers and 11 countries with a total of 246 patients with primary SS and 201 with secondary SS. Among the eye tests, Schirmer's test and the rose bengal score were the most reliable diagnostic features. In terms of salivary gland evaluation, scintigraphy, parotid sialography, minor salivary gland biopsy, and unstimulated and stimulated whole saliva collection were not helpful in the diagnosis. These criteria are considered less stringent than the San Diego criteria (**Appendix II**, attached) which require objective evidence of keratoconjunctivitis sicca and xerostomia along with autoimmunity including a minor salivary gland biopsy which includes a focus score of ≥ 2 based on an average of four evaluable lobules (and so differs from the biopsy as described in the European criteria).

In the information supplied by the sponsor, they note that entrance criteria for both Protocols P92-01 and P92-02 restricted ocular entrance requirements to symptomatic measures only and that the "Fox criteria for diagnosing Sjogren's syndrome by themselves were never addressed in the October 8, 1992 FDA/MGI meeting", however, the ocular assessments were included in the 1992 protocols.

Clearly, neither protocol fulfilled the San Diego criteria. What is not as clear is whether the statement (e-mail dated Dec. 19, 1997, quote of Ms. Gallagher) that "The majority of patients (580/629; 92.2%) entered into our Sjogren's studies meet the European criteria". Part of this confusion results from statement (p. 000002, amendment) that "The diagnosis criteria for Sjogren's syndrome for the two pivotal trials are stated in **Appendixes C...and D...** of Protocol P92-01 and P92-02, respectively". As noted above, these appendixes appear to be a subset of the Inclusion Criteria and if followed alone (i.e. without the other requirements as stated in the Inclusion Criteria of both protocols) **would clearly not fulfill even the European criteria** of SS. Therefore, the remainder of this discussion will assume that patient

entry was based on the Inclusion Criteria and NOT the Appendixes C and D (see above).

Going down the list of the European criteria **regarding symptoms**, item 1 (**ocular symptoms**) would appear to be **fulfilled** in a general sense by the questionnaires of protocol P92-01 and to a lesser extent in P92-02, but it is difficult to judge **this since** this European criterion is a categorical (yes/no) question vs. the VAS submitted by the sponsor and it is not stated in the information submitted what VAS score constitutes inclusion. Item 2 (**oral symptoms**) would also appear to be **fulfilled** in a general sense by P92-01 (p.000007) and again to a (much) lesser extent in P92-02 (p. 000014); there persists the difficulty of extrapolation of the VAS scales.

Regarding the European criteria for **signs**, clearly item 3 (**ocular signs**) is **NOT fulfilled** in either protocol. Item 4 (**histologic features**) may or may not have been fulfilled by patients in either protocol since this item may be substituted by item 6 (**autoantibodies**) as specified in the protocols (i.e. AND/OR). For purposes here, it is assumed that either item 3 or 6 of the European criteria has been **fulfilled** in both protocols. Finally, item 5 (**salivary gland involvement**) again **may, or may not, have been fulfilled** in these protocols since under the Inclusion Criteria xerostomia is defined as "dry mouth symptoms and decreased saliva" which may not be the same as demonstrating residual salivary gland function (6.1.d, P92-01); it is not specified in the information included for review what tests were employed to determine if the salivary glands were involved.

Given the various caveats outlined above, it would appear that patients in the protocols for S-007 fulfilled three (items 1, 2, 4 or 6) of the six criteria according to the European classification of SS. Depending upon how **item 5** was addressed in the trials, this also may have been fulfilled and this point **should be clarified**. Therefore, it would appear that there patients qualified as being described as **probably** having primary SS, but not definitely (this classification also imposes the limitation that the autoantibody testing must include only positive anti-Ro/SS-A and anti-La/SS-B). However, it is **unclear how many patients may have had secondary SS or other conditions that needed to be excluded**. In this regard, reference is made to the modified draft labeling which states under the section of Sjogren's syndrome patients (trial 92-01) that "However, the subgroup of patients with rheumatoid arthritis tended to improve in global assessments at 2.5 mg and 5 mg (10-20 mg/day)". It should also be noted that the European criteria for SS would not be considered an "orphan" indication.

Conclusions:

Hopefully, by the lengthy discussion to this point, it is apparent that the patients described in these protocols at best meet any criteria in a **minimal** way. Most problematic is the deletion of the ocular signs component (Schirmer's and rose bengal testing) since these are hallmarks of objective information necessary to confirm the ocular symptoms; i.e. there may be other explanations for the patient's symptoms. It would seem important, therefore, to relay this distinction to both potential patients and their physicians in the **labeling**.

Assuming that items 5 and 6 were not addressed in a way to say patients had definite primary SS, labeling could then reflect this by saying something like "Patients in these studies best fit the classification of probable primary, or secondary, Sjogren's syndrome".* (* According to the ACR Criteria for the Classification of Sjogren's syndrome as adapted from Vitali C.....); the designation of definite could be substituted if appropriate. In other words, it may be necessary to specifically identify (and agree to) which criteria is being used to diagnose SS and then determine if Salagen has successfully treated those patients who meet the diagnostic criteria; the labeling could then reference the criteria used.

/S/

(James Witter, M.D., Ph.D. Medical Officer)

JEH 12-31-97

cc: NDA 20-237
HFD-550
HFD-540
HFD-550/MO/Witter

APPENDIX I

Criteria for the Classification of Sjögren's Syndrome*

1. Ocular symptoms

Definition. A positive response to at least one of the following three questions:

- (a) Have you had daily, persistent, troublesome dry eyes for more than 3 months?
- (b) Do you have a recurrent sensation of sand or gravel in the eyes?
- (c) Do you use tear substitutes more than three times a day?

2. Oral symptoms

Definition. A positive response to at least one of the following three questions:

- (a) Have you had a daily feeling of dry mouth for more than 3 months?
- (b) Have you had recurrent or persistently swollen salivary glands as an adult?
- (c) Do you frequently drink liquids to aid in swallowing dry foods?

3. Ocular signs

Definition. Objective evidence of ocular involvement, determined on the basis of a positive result on at least one of the following two tests:

- (a) Schürmer-I test (≤ 5 mm in 5 minutes)
- (b) Rose bengal score (≥ 4 , according to the van Bijsterveld scoring system)

4. Histopathologic features

Definition. Focus score ≥ 1 on minor salivary gland biopsy (focus defined as an agglomeration of at least 50 mononuclear cells; focus score defined as the number of foci per 4 mm^2 of glandular tissue)

5. Salivary gland involvement

Definition. Objective evidence of salivary gland involvement, determined on the basis of a positive result on at least one of the following three tests:

- (a) Salivary scintigraphy
- (b) Parotid sialography
- (c) Unstimulated salivary flow (≤ 1.5 ml in 15 minutes)

6. Autoantibodies

Definition. Presence of at least one of the following serum autoantibodies:

- (a) Antibodies to Ro/SS-A or La/SS-B antigens
- (b) Antinuclear antibodies
- (c) Rheumatoid factor

Exclusion criteria: preexisting lymphoma, acquired immunodeficiency syndrome, sarcoidosis, or graft-versus-host disease

* For primary Sjögren's syndrome, the presence of three of six items showed a very high sensitivity (99.1%), but insufficient specificity (57.8%). Thus, this combination could be accepted as the basis for a diagnosis of probable primary Sjögren's syndrome. However, the presence of four of six items (accepting as serologic parameters only positive anti-Ro/SS-A and anti-La/SS-B antibodies) had a good sensitivity (93.5%) and specificity (94.0%), and therefore may be used to establish a definitive diagnosis of primary Sjögren's syndrome.

Reprinted from Vitali C, Bombardieri S, Moutsopoulos HM, et al: Preliminary criteria for the classification of Sjögren's syndrome. *Arthritis Rheum* 36:340-347, 1993, with permission of the American College of Rheumatology.

APPENDIX II

*San Diego criteria for Sjögren's syndrome (SS)**

I. Primary Sjögren's syndrome

A. Symptoms and objective signs of ocular dryness

1. Schirmer's test less than 8 mm wetting per 5 minutes, and
2. Positive Rose Bengal staining of cornea or conjunctiva to demonstrate keratoconjunctivitis sicca.

B. Symptoms and objective signs of dry mouth

1. Decreased parotid flow rate using Lashley cups or other methods, and
2. Abnormal findings from biopsy of minor salivary gland (focus score of ≥ 2 based on average of four evaluable lobules).

C. Serologic evidence of a systemic autoimmunity

1. Elevated rheumatoid factor $>1:320$ or
2. Elevated antinuclear antibody $>1:320$ or
3. Presence of anti-SS-A(Ro) or anti-SS-B(La) antibodies.

II. Secondary Sjögren's syndrome

Characteristic signs and symptoms of SS (described above) plus clinical features sufficient to allow a diagnosis of rheumatoid arthritis, systemic lupus erythematosus, polymyositis, scleroderma, or biliary cirrhosis.

III. Exclusions

Sarcoidosis, preexistent lymphoma, human immunodeficiency virus, hepatitis virus B or C, primary fibromyalgia, and other known causes of autonomic neuropathy, keratitis sicca, or salivary gland enlargement.

* Definite Sjögren's syndrome requires objective evidence of dryness of eyes/mouth and autoimmunity including a characteristic minor salivary gland biopsy (criteria IA, IB, and IC). Probable Sjögren's syndrome does not require a minor salivary gland biopsy but can be diagnosed by demonstrating decreased salivary function (criteria IA, IB-1, and IC). Reprinted from Fox and Saito (4), with permission.

MAY 18 1997

Medical Officer's Review of NDA 20-237/S-007
Ophthalmology Consult

NDA #20-237/S-007
M.O. Review #1

Submission: 2/11/97
Review completed: 5/18/97

Trade name: Salagen Tablets
Generic name: Pilocarpine hydrochloride

Sponsor: MGI Pharma, Inc.
Suite 300E, Opus Center
9900 Bren Road East
Minnetonka, MN 55343
612-935-7335

Pharmacologic Category: Cholinergic agonist

Proposed Indication(s): Treatment of symptoms of dry mouth and dry eyes in patients with Sjögren's syndrome.

Dosage Form(s)
and Route(s) of Administration: Oral, 5 mg tablets

NDA Drug Classification: 6 S

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3 **Material Reviewed** - Volume 1, 5-132

6.6 **Proposed Directions for Use**

8 **Clinical Studies**

8.1 **Indication** - Treatment of symptoms of dry eyes

8.1.1 **Reviewer's Trial #1 Sponsor's protocol # P92-01**

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

Protocol No.: MGI 647.94.P92-01 Report No.: 647.94.CR96-01

8.1.1.1 **Objective/Rationale**

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

8.1.1.2 **Design**

Multicenter, randomized, double-blind, placebo-controlled

Three parallel treatment groups: 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.

Safety and efficacy evaluations were conducted at baseline (Admission) and Weeks 6 and Week 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 post-dose at Admission, Week 6, and Week 12. Safety was evaluated by adverse experience reporting, laboratory examination, vital signs measurements, physical examination, and electrocardiogram (ECG). Oral comfort agents and tear substitutes were permitted as needed for symptom relief following implementation of protocol Amendment 2. Prior to the amendment, standardized use of artificial tears was required.

Primary Evaluation Criteria

Two primary efficacy variables were evaluated at endpoint (Intent-to-treat Cohort):

- global improvement of xerostomia (dry mouth)
- global improvement of xerophthalmia (dry eyes)

Endpoint was defined as the last available postbaseline observation for each subject

Supportive Variables

Unstimulated whole salivary flow was measured at each visit predose and at 30, 60, and 90 minutes postdose.

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

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

8.1.1.3 Protocol

8.1.1.3.1 Population

Inclusion Criteria

- a. Eighteen years of age or older.
- b. Signed the approved informed consent form.
- c. Discontinued use of electrical devices for relief of xerostomia at least 6 weeks prior to xerostomia screening procedures.
- d. Had residual salivary gland function as demonstrated by unstimulated or stimulated sialometric procedure at time of screening.
- e. Diagnosed with Sjögren's syndrome and had the presence of
 1. Xerostomia (dry mouth symptoms and decreased saliva); and,
 2. Xerophthalmia (dry eyes symptoms); and,
 3.
 - a) 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
 - b) Positive labial biopsy confirmed by central reading center.
- f. Discontinued use of any medication which produced dry mouth (e.g., anticholinergics, tricyclic antidepressants, antihistamines) at least 7 days prior to admission to study.
- g. Had negative screening results for the following laboratory tests
 - antigen-serum pregnancy test for females of childbearing potential;
 - hepatitis B surface antigen test; and
 - HIV
- h. Had completed all screening procedures and was deemed an appropriate subject for this study.

Exclusion Criteria

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

Protocol Amendments

Three amendments were processed for this study. The first amendment was dated July 14, 1993, and eliminated the need to meet scoring requirements for the Schirmer Tear test and Rose Bengal Stain test and limited the number of centers from which saliva samples would be collected for sialochemical analyzes.

With this amendment, the diagnostic Schirmer and Rose Bengal tests continued to be a part of the screening process. However, if the scores did not meet the required range and all other study requirements were met, the candidates could enter the study but the diagnostic ocular procedures would not be conducted during the study. The questionnaire for the dry mouth and dry eyes and the sialometric procedures continued without change for all study subjects. As a result of this amendment, these diagnostic endpoints were changed from a primary to a secondary endpoint. "The amendment was implemented due to the high ocular screen failure rate for subjects. Failing scores were both below and above the scoring requirements."

The second Amendment (dated December 29, 1994) eliminated the Schirmer Tear test and Rose Bengal Stain procedures from Screening and the study. "The purpose of this amendment is to eliminate the objective assessment of ocular efficacy from this study. While Schirmer Tear Test and Rose Bengal Test scores will be recorded during screening procedures, these measurements will not be measured during the study nor will the standardized use of artificial tears be required. This amendment was implemented due to the continued high ocular screening failure rate for subjects. Failing scores were both below and above the scoring requirements."

The third amendment (dated May 31, 1996) identified the global question on dryness of the mouth as the primary measure of symptomatic relief of xerostomia rather than the singular question on dryness of the mouth. This amendment occurred prior to securing the database for analyzes.

Reviewer's Comments: *As noted in the protocol amendments, the ocular inclusion criteria were deleted from the protocol. The inclusion and exclusion criteria fail to assure that the correct population was studied. The measurements failed to include objective measures.*

8.1.1.3.2 Endpoints

Primary Efficacy Variables

The primary efficacy variables were the subjects' 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 on a VAS, the experienced change in dryness. Based on the 100 mm scale, scores were categorized as worsened (< 45 mm), no change (45-55 mm), or improved (> 55 mm). Based on these definitions, subjects were categorized as responders (improved) or non-responders (no change or worsened).

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 at each visit 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 non-responders.

Responder/non-responder results were summarized and analyzed.

Mouth variables evaluated using a 100 mm VAS were

- a. severity of dryness in mouth
- b. severity of discomfort of the mouth

Eye variables evaluated using a 100 mm VAS were

- a. degree of improvement in eye symptoms
- b. change in tear flow
- c. severity of eye discomfort
- d. severity of sensitivity to light
- e. severity of visual blurring
- f. severity of discharge/drainage of the eye
- g. severity of itching of the eyes
- h. severity of tiredness of the eyes
- i. severity of redness of the eyes
- j. severity of matting or sticking of the eyes
- k. severity of feeling that something is in the eyes
- l. difficulty in focusing to read
- m. difficulty with driving at night
- n. change in use of tear substitutes

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

For eye efficacy variables measured using a 3-point scale, difficulty with night driving after taking medication and difficulty with reading after taking medication were measured on a scale of more difficulty, no difference or less difficulty, and subjects were classified as responders (less difficulty) or non-responders (no difference or more difficulty).

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

Symptoms of dryness associated with Sjögren's syndromes 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. dryness of the vagina (VAS)
- d. dryness of the nasal passage (VAS)

The 5-point question was analyzed as responder/non-responder: worsened and no change classified as a non-responder; and improved, moderately improved, and significantly improved classified as responders.

Diagnostic Ocular Assessments

Initially, this protocol was intended to include diagnostic ocular assessments (Schirmer Tear Test and Rose Bengal Stain). However, these assessments were discontinued as stated in Amendment 2 due to the continued high screening failure rate on these procedures. Failing scores were both below and above the requirements.

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.* ✓

8.1.1.4 Results

8.1.1.4.1 Populations enrolled/analyzed

SUBJECT ENROLLMENT BY INVESTIGATOR (Placebo = 125, 2.5 mg = 121, 5 mg = 127)

Site Number	Principal Investigators	Total Number Enrolled	Subject Numbers
01	LeVeque, Francis G.	37	
02	Vivino, Frederick B.	28	
03	Khan, Zafrulla	25	
04	Salisbury III, Paul Lee	37	
05	Fox, Robert I.	16	
06	Talal, Norman	13	
07	Yee, Richard W.	12	
08	Griffing, W. Leroy	8	
09	Rhodus, Nelson	17	
10	Tran-Johnson, Tram	62	
11	Furst, Daniel	19	
12	Ellman, Michael	18	
13	Sreebny, Leo	22	
14	Meyerowitz, Cyril	15	
15	Sonis, Stephen	7	
16	Wolfe, Frederick	12	
17	Al-Hashimi, Ibtisam	25	
Total=373			