

Number of Subjects: An adequate number to ensure that at least 300 evaluable subjects complete the study.

Ages of Subjects: 18 years or older

Inclusion Criteria:

1. Eighteen years of age or older
2. Signed the informed consent form
3. Discontinued use of electrical devices for relief of xerostomia at least 6 weeks prior to xerostomia screening procedures
4. Residual salivary gland function as demonstrated by unstimulated or stimulated sialometric procedure at time of Screening
5. Diagnosed with SS and having the presence of:
 - a. Xerostomia; and
 - b. Xerophthalmia; and
 - c.
 1. Positive autoimmunity within the past year for:
SS-A and/or
SS-B and/or
Rheumatoid Factor; and/or
ANA

AND/OR,

2. Positive labial biopsy confirmed by central reading center.

Reviewer's Comment: There is variation in the definition of Sjögren's syndrome. In the Appendixes that accompany each protocol, a definition of Diagnostic Criteria for SS is stated. Appendix C, which accompanies Study 92-01, requires dry mouth and either presence of autoantibodies or a positive labial biopsy. In Appendix D, neither dry eyes nor dry mouth is listed as a diagnostic criterion - the presence of autoantibodies or positive labial biopsy alone is sufficient. These do not fit any accepted definition. In addition, it is unclear how the sponsor determines xerostomia and xerophthalmia. Although a VAS questionnaire is administered for determining both dry eyes and dry mouth, neither the score required for entry into the trial, nor for fulfilling the definition of SS is stated (See Discussion section of this review for further details).

6. Use of any medication which produces dry mouth such as anti-cholinergics, tricyclic antidepressants, antihistamines was discontinued at least 7 days prior to admission to study.
7. Negative screening results for the following laboratory tests:
 - Serum pregnancy test for females of childbearing potential
 - Hepatitis B surface antigen test

HIV

8. Completion of all screening procedures
9. Willing and able to comply with the protocol

Exclusion Criteria:

1. History of multiple sclerosis
2. Uncontrolled, clinically significant cardiovascular/cardiorenal disease
3. Uncontrolled, clinically significant pulmonary disease
4. Active hepatobiliary disease, active pancreatic disorders, or clinically significant hepatic disease
5. Active asthma
6. Diabetes mellitus - insulin dependent
7. Active peptic ulcers, inflammatory bowel disease, colostomy, or ileostomy
8. Clinically significant ocular disease including, but not necessarily limited to :
 - a. Narrow angle glaucoma or the potential for miosis-induced increase in intraocular pressure.
 - b. Peripheral retinopathies.
 - c. History of retinal detachment, or a condition predisposing to retinal detachment
 - e. Other condition for which ocular pilocarpine would be excluded.
9. Anticipated use of any of the following medications, whether by prescription or over the counter, during the course of this study:
 - a. Use of medications which produce dry mouth symptomatology (e.g., anticholinergics, tricyclic antidepressants, antihistamines)
 - b. Beta blockers
 - c. Pilocarpine for ophthalmic indications
10. Hypersensitivity to pilocarpine
11. Use of any investigational agent within 30 days prior to or during the course of this study.
12. A lactating female or female of childbearing potential who is not using medically acceptable contraceptive methods throughout the study.

Study Design:

A multi center, randomized, double-blind, placebo-controlled trial in which subjects are assigned a placebo, a 2.5 mg q.i.d. dose, or a 5.0 mg q.i.d. dose.

Study Procedures:

Screening

All screening procedures are to be completed within 14 days of admission to the study. These

- 1) placebo q.i.d.
- 2) 2.5 mg Salagen tablets q.i.d.
- 3) 5.0 mg Salagen tablets q.i.d.

The following procedures will be performed at this visit:

1. Collect samples for urinalysis, chemistry and hematology
2. Vital signs and weight will be recorded.
3. Test article will be dispensed for the next study interval.
4. Diary will be dispensed to the subject.
5. Questionnaires will be administered.
6. Conduct a pre-dose sialometry to establish a baseline salivary flow rate.
7. The subject will be given, with 6 oz of water, one tablet of test article from the assigned bottle. This is to be the only substance taken by the subject until all study procedures have been completed. Study personnel will observe the subject for 90 minutes following the administration of this dose to watch for the appearance of any adverse experiences.
8. Post-dose vital signs will be taken.
9. Sialometry will be conducted at 30 minutes, 60-minutes and 90-minutes post dose.
10. The subject will be instructed to self-administer the test article and record any missed or lost doses, adverse experiences, and answer the questions in the diary.
11. The subject will set up an appointment for the same period of day as Visit 1. The subject will be instructed to take the test article on the day of Visit 2, based on the time of day for that appointment as follows: Morning visit: first tablet of the day to be taken at the clinic; afternoon visit: first tablet of the day taken at home, second tablet of the day to be taken at the clinic, with the first tablet at least 3 hours prior to the second dose.
12. The subject will be instructed to bring their diary, and all test article bottles with them on Visit 2.

Visit 2

Study Visit 2 will occur 42 days (± 7 days) from Visit 1 at the same time of day as Visit 1. The procedures performed at Visit 2 are identical to those of Visit 1. In addition, during Visit 2, the study personnel will review the subject's diary, and collect the bottles of test article given out at Visit 1:

Visit 3

Study Visit 3 will occur 42 days (± 7 days) from Visit 2 at the same time of day as Visits 1 and 2. The procedures performed at Visit 3 are identical to those of Visit 2, except that no new medication will be dispensed at Visit 3. In addition, during Visit 3, an interval medical history

and physical examination will be conducted, and all test articles and diaries will be collected.

Statistical Plan:

Efficacy analysis will include a primary analysis, which is based on the intent-to-treat patient cohort at endpoint, which includes all patients who received at least one dose of study medication and have at least one efficacy assessment after the first dose. A secondary analysis will be conducted on a cohort of evaluable patients. Safety analyses will include all patients who took at least one dose of study medication. The primary efficacy variable will be analyzed for consistency across subgroups by gender, race, and age.

Efficacy Analysis

The primary analysis of efficacy will be based on an endpoint analysis using the evaluations at Week 12. For those subjects who withdraw prior to Week 12, the last evaluation will be used, which the sponsor refers to as "endpoint". Endpoint is defined by the sponsor as "the last available post-baseline observation for each patient.". Separate analyses will also be done on the evaluations from Week 6 and Week 12. The comparison of interest will include an overall test for treatment effect as well as 5 mg versus placebo.

The sponsor divided the efficacy variables into three categories: Symptoms of dryness, Salivary flow, and Ocular Assessments.

A. Symptoms of Dryness

1. Primary efficacy variable

The primary efficacy variable will be global improvement in xerostomia at endpoint, which is to be measured using a 100 mm visual analogue scale. This self-assessment requests that the subject, "Please rate your present condition of dry mouth (xerostomia) compared with your condition at the start of this study. Consider the changes to your dry mouth and other symptoms related to your dry mouth that have occurred since you have taken this medication." Response to the visual analogue scale will be categorized as worsening/non-responder (< 45), no change/non-responder (45 - 55), or improvement/responder (> 55). The treatment groups will be compared using non-parametric methods.

2. Additional efficacy variables for the mouth

The following additional efficacy variables for the mouth will be reviewed:

- Change in the ability to sleep without water

- Change in the severity of dryness
- Change in the severity of discomfort of the mouth
- Change in the difficulty in producing mucous
- Change in the use of saliva substitutes
- Change in the ability to speak without water

Severity of dryness, discomfort of the mouth, and difficulty producing mucous were measured on a 100 mm VAS. Change from-baseline scores will be computed at Week 6, Week 12, and endpoint by subtracting the baseline score from each available post-baseline score. Subjects having an improvement (increase) of ≥ 25 mm will be classified as responders. Subjects having an improvement of < 25 mm will be classified as non-responders. The responders/non-responders will be summarized and analyzed.

Change in the use of saliva substitutes, change in the ability to speak without water, and change in the ability to sleep without water were measured on a scale of increased, stayed the same, decreased. Based on the three-point scores, subjects will be classified as responders (decreased) or non-responders (stayed the same or increased).

Reviewer's Comment: One would expect to see an underestimate of the difference between groups with this method of evaluation. Due to the placebo effect, one would expect most subjects to report a positive effect, which would result in many false positive responses, washing out the true effect between groups. Nonetheless, if this is the case, it will result in error on the side of conservatism in approving the drug for efficacy.

3. Additional efficacy variables

Additional variables such as global improvement of the eye symptoms, severity of eye matting/sticking, and severity of eye discomfort will be evaluated.

B. Salivary Flow

Another measure of efficacy is the sialometry evaluation. Sialometry will be done at baseline and at each of the follow-up visits. At each visit, unstimulated whole saliva will be measured at pre-dose and at 30, 60, and 90 minutes post-dose. The measurements at each visit will be summarized by calculating an area under the curve based on the change from pre-dose. Area under the curve will be calculated using the trapezoidal rule. The treatment groups will be compared at each visit using a linear model. Effects for site and site-by-treatment interaction will be included in the model if sample sizes within each site are sufficient.

The following analyses will be performed:

- Change AUC values at baseline will be analyzed to examine the first-dose effect.

- Raw rates (Time 0) saliva measurements will be analyzed for change-from-baseline and treatment effect at each time to examine long-term trough effects.
- AUC change-from-baseline values will be analyzed to examine short-term effects across time. If the analysis of long-term trough effects indicates a significant sustained increase in flow, change-from-baseline will be based on the raw AUC. Otherwise, change-from-baseline will be based on change AUC.

Comment: In the protocol, it is stated that at baseline, some subjects may need citric acid stimulation to produce saliva, but how these subjects will be analyzed is not discussed.

When queried, the sponsor stated that the citric acid was only used for certain subjects during screening, and never for saliva measurements during the active phase of the trial. The sponsor further stated that since so few patients required the stimulated salivary procedure during 92-01 screening, this step was eliminated from screening in the other pivotal trial, 92-02.

C. Ocular Assessments

Initially, this protocol included objective ocular assessments (Schirmer and Rose Bengal) as measures of efficacy. These assessments were discontinued as stated in the protocol amendment. Results from Schirmer and Rose Bengal testing collected prior to the protocol amendment will be summarized.

Global improvement of the eye symptoms, severity of eye matting/sticking, and severity of eye discomfort will be evaluated.

Reviewer's Comment: The proposed label contains claims of improvement in miscellaneous outcome measurements such as dryness of skin and vaginal dryness. However, these outcome variables were not mentioned in the protocol.

Because the sponsors believe that there is a possibility that those SS patients suffering from rheumatoid arthritis may represent a population whose course of disease may be different from other SS subjects, the subjects were stratified based on the presence or absence of rheumatoid arthritis during group assignment.

Safety Analysis

Safety will be evaluated from reported adverse experiences, changes in clinical laboratory values, changes in vital signs, changes in physical examination results, and changes in ECG results. Adverse experiences will be coded using the COSTART coding dictionary. Subject incidence rates will be calculated and analyzed by treatment group, body system, and specific term.

Results:

Primary Outcome Variable
Summary of Global Improvement in Symptoms of Dry Mouth

	Placebo		Pilocarpine HCl				P-value	
	n	%	2.5 mg		5 mg		Overall	Placebo vs 5 mg
	n	%	n	%	n	%		
Week 6	118	31.4	108	36.1	119	58.8	≤ 0.0001	≤ 0.0001
Week 12	111	32.4	102	42.2	109	61.5	≤ 0.0001	≤ 0.0001
Endpoint	119	31.1	110	39.1	119	61.3	≤ 0.0001	≤ 0.0001

Note: Within the RA subgroup, the effect of pilocarpine 2.5 mg dose appears to be much better than that of placebo and similar to that of the 5 mg dose (Refer to the subgroup analysis section of this review for further discussion).

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Additional Outcome Variables

	Placebo		Pilocarpine HCl				P-value	
	n	%	2.5 mg		5 mg		Overall	Placebo vs 5 mg
	n	%	n	%	n	%		
Severity of dryness of the mouth								
Week 6	119	25.2	106	26.4	118	50.0	≤ 0.0001	≤ 0.0001
Week 12	111	39.6	101	41.6	111	52.3	≤ 0.0443	≤ 0.0590
Endpoint	119	37.8	108	38.9	119	52.9	≤ 0.0105	≤ 0.0189
Severity of discomfort of the mouth								
Week 6	119	28.6	106	27.4	118	44.9	≤ 0.0028	≤ 0.0088
Week 12	110	34.6	102	38.2	111	52.3	≤ 0.0052	≤ 0.0077
Endpoint	119	33.6	108	37.0	119	52.1	≤ 0.0023	≤ 0.0038
Change in the use of saliva substitutes								
Week 6	119	14.3	109	12.8	118	23.7	≤ 0.0279	≤ 0.0628
Week 12	109	10.1	103	13.6	110	20.0	≤ 0.0394	≤ 0.0388
Endpoint	119	10.1	110	12.7	118	21.2	≤ 0.0140	≤ 0.0175
Change in the ability to speak w/o water								
Week 6	119	13.4	109	15.6	118	28.8	≤ 0.0017	≤ 0.0034
Week 12	110	10.0	103	14.6	110	18.2	≤ 0.1062	≤ 0.0793
Endpoint	119	10.1	110	13.6	118	18.6	≤ 0.0684	≤ 0.0586
Change in the ability to sleep w/o water								
Week 6	119	16.0	109	13.8	117	32.5	≤ 0.0004	≤ 0.0028
Week 12	109	16.5	103	10.7	109	26.6	≤ 0.0135	≤ 0.0690
Endpoint	119	16.0	110	10.0	118	27.1	≤ 0.0050	≤ 0.0359
Change in severity of producing mucous								
Week 6	116	4.3	103	8.7	114	11.4	≤ 0.0724	≤ 0.0419
Week 12	105	5.7	101	8.9	106	14.2	≤ 0.0422	≤ 0.0377
Endpoint	119	5.0	108	10.2	118	13.6	≤ 0.0428	≤ 0.0216

Mean Adjusted AUC for Whole Salivary Flow

	Placebo (g/min)			Pilocarpine HCl (g/min)						p-value	
	n	mean	SD	2.5 mg			5.0 mg			Overall	Placebo vs 5 mg
				n	mean	SD	n	mean	SD		
Admission	117	0.02	0.09	110	0.08	0.18	117	0.27	0.39	≤ 0.0001	≤ 0.0001
Week 6	114	0.02	0.10	107	0.11	0.20	114	0.25	0.39	≤ 0.0001	≤ 0.0001
Week 12	108	0.04	0.11	99	0.10	0.19	107	0.25	0.39	≤ 0.0001	≤ 0.0001
Endpoint	114	0.04	0.10	108	0.11	0.19	115	0.26	0.40	≤ 0.0001	≤ 0.0001

The preceding three tables summarize the results of pivotal trial 92-01. A discussion of the meaning of these results is presented in the "Discussion" section of this review. Of note is that for the primary outcome variable, the 5 mg vs placebo comparison is highly significant at all endpoints tested - Week 6, Week 12, and Endpoint. The p-values presented with the additional endpoint variables in the second table are the sponsor's calculations, which does not include adjustment for multiple comparisons. Due to the number of additional endpoint variables presented, a statistical penalty is required. The mean adjusted AUC for whole salivary flow, the subject of the third table produced highly significant differences in salivary flow when 5 mg and placebo groups were compared. The intention of this examination was more directed at gathering pharmacodynamic information than for strict hypothesis testing.

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Pivotal Study P92-02

Protocol Design

Reviewer's comment: The following section is a reiteration of the sponsor's protocol as submitted in the original IND (and included in this NDA submission for completeness). Note that the future tense is used in this section because the protocol was proposed prior to conduct of the trial.

Phase:

3

Title:

A Multi center, Randomized, Double-Blind, Placebo-Controlled Evaluation of Pilocarpine HCl for the Treatment of Xerostomia and Xerophthalmia Associated with Sjögren's Syndrome; Dose Adjustment

Objectives

- a. To assess the efficacy of Salagen Tablets administered orally as a treatment for the symptoms of xerostomia and xerophthalmia associated with Sjögren's syndrome; and,
- b. To evaluate the safety of orally administered Salagen Tablets in patients with Sjögren's syndrome.

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Principal Investigators and Associated Study Site:

Site Number	Principal Investigator	Site Name/Address	Total Number of Subjects Enrolled
01	Robert Ettinger, M.D.	Cedar Medical Center Tacoma, WA	18
02	Norman Gaylis, M.D.	Arthritis & Rheumatic Disease Specialties North Miami Beach, FL	5
03	Bridget Walsh, D.O.	Department of Rheumatology University of Arizona Tucson, AZ	26
04	Harvey Golden, M.D.	Rheumatology Associates Chicago, IL	26
05	Larry Moreland, M.D.	University of Alabama at Birmingham Arthritis Clinical Intervention Program Birmingham, AL	17
06	Athena Papas, D.M.D., Ph.D.	Tufts University School of Dental Medicine Boston, MA	60
07	Michael Charney, M.D.	Denver Arthritis Clinic Denver, CO	21
08	Christopher Wise, M.D.	Division of Rheumatology, Allergy, & Immunology Medical College of Virginia Richmond, VA	20
09	Ann Parke, M.D.	University of Connecticut Health Center Farmington, CT	18
10	Yvonne Sherrer, M.D.	Department of Rheumatology Cleveland Clinic - Florida Ft. Lauderdale, FL	0
11	Thomas Medsger, M.D.	Division of Rheumatology & Clinical Immunology University of Pittsburgh Pittsburgh, PA	24
12	Mark Ginsburg, M.D.	Rheumatology Associates of South Florida Boca Raton, FL	21
Total Number of Subjects			256

Number of Subjects: An adequate number to ensure that approximately 200 evaluable subjects complete the study.

Ages of Subjects: 18 years or older

Inclusion Criteria:

1. Eighteen years of age or older
 2. Signed the informed consent form
 3. Xerostomia
 4. Xerophthalmia
 5. Residual salivary gland function as demonstrated by unstimulated or stimulated sialometric procedure at time of screening
 6. Diagnosed with SS and having the presence of:
 - a. Positive autoimmunity within the past year for:
SS-A and/or
SS-B and/or
Rheumatoid Factor; and/or
ANA
- AND/OR,
- b. Positive labial biopsy confirmed by central reading center.
 7. Negative screening results for the following laboratory tests:
Serum pregnancy test for females of childbearing potential
Hepatitis B surface antigen test
HIV
 8. Completion of all screening procedures
 9. Willing and able to comply with the protocol

Exclusion Criteria:

1. History of multiple sclerosis
2. Uncontrolled, clinically significant cardiovascular/cardiorenal disease
3. Uncontrolled, clinically significant pulmonary disease
4. Active hepatobiliary disease, active pancreatic disorders, or clinically significant hepatic disease
5. Uncontrolled asthma
6. Diabetes mellitus - insulin dependent
7. Active peptic ulcers, inflammatory bowel disease, colostomy, or ileostomy
8. Clinically significant ocular disease including, but not necessarily limited to:
 - a. Narrow angle glaucoma or the potential for miosis-induced increase in intraocular pressure.

- b. Peripheral retinopathies.
 - c. History of retinal detachment, or a condition predisposing to retinal detachment
 - e. Other condition for which ocular pilocarpine would be excluded.
9. Anticipated use of any of the following medications, whether by prescription or over the counter, during the course of this study:
- b. Beta blockers
 - c. Pilocarpine for ophthalmic indications

Reviewer's Comment: The other pivotal trial excluded subjects who use any medication which produces dry mouth such as anti-cholinergics, tricyclic antidepressants, or antihistamines whereas this one did not. When asked about this, the sponsor stated that removal of subjects on these medications resulted in great difficulty in recruiting subjects. The sponsors reasoned that since so many patients with SS were prescribed concomitant medications, that they would enroll these subjects to study the effect of Salagen on them.

10. Hypersensitivity to pilocarpine
11. Use of any investigational agent within 30 days prior to or during the course of this study.
12. A lactating female or female of childbearing potential who is not using medically acceptable contraceptive methods throughout the study.

Study Design: A multi center, randomized, double-blind, placebo-controlled trial in which subjects are assigned either a placebo or active treatment with 5 mg increased to 7.5 mg Salagen.

Study Procedures:

Screening

All screening procedures are to be completed within 14 days of admission to the study. These include:

1. Informed consent.
2. A medical history will be taken and physical examination conducted prior to admission to the study.
3. Vital signs, including temperature, pulse, respiration rate, and blood pressure will be recorded at screening as well as weight.
4. Tests administered will include a 12-lead electrocardiogram, laboratory evaluations, pregnancy test, tests for Hepatitis B and HIV, and immunological screening. Immunological screening tests include tests for Rheumatoid Factor, ANA, SS-A and SS-B; if these tests have been conducted within the past year, the results may be

supplied from laboratories. Blood and urine samples will be collected from potential subjects following a 10-hour (overnight) fast and evaluated for the following:-

Hematology: RBC, hemoglobin, hematocrit, platelets, WBC, ESR, Polys, Lymphocytes, monocytes, eosinophils, and basophils.

Chemistry: Total calcium, inorganic phosphorus, BUN, Uric Acid, glucose, total protein, albumin, chloride, CO₂, total bilirubin, alkaline phosphatase, cholesterol, ALT (SGPT), AST (SCOT), creatinine, potassium, sodium.

Urinalysis: pH, specific gravity, acetone, albumin, glucose, casts/HPF, RBC/HPF, and WBC/HPF

5. A questionnaire will be administered to confirm the presence of dry eye and dry mouth.
6. Residual salivary gland function will be demonstrated by collecting one 5 minute unstimulated whole saliva sample.

Visit 1

Acceptable subjects will return to the study site at the same period of day (morning or afternoon), as occurred at Visit 1.

Note: The prior pivotal trial's protocol (P92-01) included stratification of subjects to either the SS Group with Rheumatoid Arthritis or the SS Group without Rheumatoid Arthritis. This trial (P92-02) did not perform an identification of subjects with Rheumatoid Arthritis.

Subjects will be randomized into one of two treatment groups:

- 1) placebo q.i.d.
- 2) active treatment with 5 mg and 7.5 mg Salagen tablets q.i.d.

Note: At Week 6, all subjects will have their dose escalated: placebo to placebo and active treatment with 5.0 mg Salagen increased to 7.5 mg Salagen. If a subject cannot tolerate the escalated dose, (s)he will be returned to the previous dose for the balance of the study.

The following procedures will be performed at this visit:

1. Collect samples for urinalysis, chemistry and hematology
2. Vital signs and weight will be recorded.
3. Test article will be dispensed for the next study interval.
4. Diary will be dispensed to the subject.
5. Questionnaires will be administered.
6. Conduct a pre-dose sialometry to establish a baseline salivary flow rate.