Reviewer's comment: The other pivotal trial's protocol states that the subject will be given, with 6 oz of water, one tablet of test article from the assigned bottle and that study personnel will observe the subject for 90 minutes following the administration of this dose to watch for the appearance of any adverse experiences.

7. Post-dose vital signs will be taken.
8. Sialometry will be conducted at 30 minutes, 45-minutes and 60-minutes post dose.

Reviewer's Comment: The first pivotal trial states that sialometry will be conducted at 30 minutes, 60-minutes and 90-minutes post dose. When queried about the change, the sponsor responded that the peak salivary flow of 60 minutes was estimated from phase 1 pharmacodynamic data, which examined radiation-induced xerostomia. The sponsor set the testing times for the first pivotal study, 92-01, to center around 60 minutes. In anticipation that the peak flow for the patient population being tested in these trials is less than 60 minutes, the second study was centered around 45 minutes as an anticipated peak time.

9. 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.
10. 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 table 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 similar to those of Visit 1. One difference is that during Visit 2, the study personnel will review the subject's diary, and collect the bottles of test article given out at Visit 1. The other change is that all subjects will receive new study medication. Those subjects on 5.0 mg Salagen will receive 7.5 mg tablets Salagen (still blinded), and those on placebo will receive another placebo (also still blinded). If the subject cannot tolerate the increased dose, (s)he can return to the clinic and will be placed on the previous dose for the remainder of the study.

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 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 was measured using a 100 mm visual analogue scale. 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 ability to swallow food without drinking*

- Change in the use of saliva substitutes
- Change in the ability to speak
- Change in the severity of discomfort of dentures (for denture wearers only)*

Reviewer's comment: These secondary efficacy variables are slightly different than the list contained in the first protocol. The two variables with asterisks are not in the prior protocol's list. In addition, the prior protocol contains "Change in the difficulty in producing mucous", which this list does not contain.

These additional efficacy variables 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.

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 prates (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.

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.

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

Study P92-02

	Placebo		Pilocarpine HCl		P-value
	n	%	n	%	≤
Global improvement in xerostomia					
Week 6	121	22.3	121	46.3	0.0001
Week 12	110	30.9	111	61.3	0.0001
Endpoint	123	27.6	122	57.4	0.0001

Additional Outcome Variables
Study P92-02

	Placebo		Pilocarpine HCl		P-value
	n	%	n	%	≤
Severity of dryness of the mouth					
Week 6	122	33.6	122	45.1	0.0661
Week 12	110	45.5	112	57.1	0.0799
Endpoint	123	42.3	122	54.9	0.0488
Severity of discomfort of the mouth					
Week 6	121	33.9	122	49.2	0.0164
Week 12	109	37.6	112	61.6	0.0004
Endpoint	122	33.6	122	60.7	0.0001
*Change in severity of discomfort of the dentures					
Week 6	37	29.7	34	32.4	0.7106
Week 12	34	35.3	28	39.3	0.6528
Endpoint	39	33.3	35	42.9	0.3274
Change in the use of saliva substitutes					
Week 6	122	18.0	121	35.5	0.0024
Week 12	110	20.0	111	53.2	0.0001
Endpoint	123	18.7	122	50.8	0.0001
Change in the ability to speak w/o water					
Week 6	122	20.5	121	35.5	0.0098
Week 12	110	22.7	112	46.4	0.0002
Endpoint	123	20.3	122	45.1	0.0001
Change in the ability to sleep w/o water					
Week 6	122	19.7	121	38.0	0.0019
Week 12	110	23.6	112	45.5	0.0007
Endpoint	123	21.1	122	43.4	0.0002
*Change in the ability to swallow food without drinking water					
Week 6	119	19.3	118	39.8	0.0007
Week 12	108	17.0	111	46.0	0.0001
Endpoint	121	15.7	122	45.9	0.0001

The two variables with asterisks are not in the prior protocol's list. In addition, the prior protocol contains "Change in the difficulty in producing mucous", which this list does not contain.

Mean Adjusted AUC for Whole Salivary Flow

	Placebo (g/min)			Pilocarpine HCl (g/min)			p-value
	n	mean	SD	n	mean	SD	
Admission	122	0.00	0.0674	122	0.16	0.2635	≤ 0.0001
Week 6	116	0.01	0.0772	113	0.15	0.2217	≤ 0.0001
Week 12	101	0.01	0.0654	108	0.22	0.3150	≤ 0.0001
Endpoint	118	0.01	0.0638	117	0.22	0.3124	≤ 0.0001

The preceding three tables summarize the results of pivotal trial 92-02. 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 for all endpoints tested at Week 6. However, because the Week 12 and Endpoint measurements were made after the subjects on the 5 mg dosing regimen were placed on 7.5 mg dosing, results other than those from Week 6 are not supportive of efficacy. One may also recognize that the p-values presented with the additional endpoint variables in the second table are the sponsor's calculations, which do 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.

Demographics

A total of 629 subjects were enrolled in the two pivotal clinical trials, 373 in Study P92-01 and 256 in Study P92-02. The demographic profile of subjects is listed in the table below. The mean age was between 55 and 56 years, and overall 4.8% men and 95.2% women were enrolled. In 92-02, there were significantly more males in the pilocarpine group than in the placebo group, and the mean height was significantly greater (probably due to the larger number of males). A calculation by the statistical reviewer verified that gender was not determined to be interactive with treatment group, and the disproportionate number of women did not skew the outcome. In both studies, the predominance of females was consistent with the general population of Sjögren's syndrome patients. The sponsor did not consider any of the demographic differences great enough to introduce significant bias into the outcome of the analyses.

Baseline Demographic Characteristics

Baseline Characteristic		No. 92-01			No. 92-02	
		2.5 mg (n=121)	5.0 mg (n=127)	Placebo (n=125)	Pilocarpine (n=128)	Placebo (n=128)
Sex n (%)	Male	5 (4.1)	4 (3.2)	7 (5.6)	**11 (8.6)***	**3 (2.3)***
	Female	116 (95.9)	123 (96.9)	118 (94.4)	**117 (91.4)***	**125 (97.7)***
Age (years)	Minimum					
	Maximum					
	Mean	54.0±12.5	55.4±13.7	54.6±13.6	55.4±13.3	57.8±13.0
Race n (%)	Caucasian	96 (79.3)	104 (81.9)	97 (77.6)	117 (91.4)	116 (90.6)
	Black	1 (0.8)	3 (2.4)	5 (4.0)	7 (5.5)	7 (5.5)
	Oriental	20 (16.5)	14 (11.0)	18 (14.4)	0 (0)	1 (0.8)
	Other	4 (3.3)	6 (4.7)	5 (4.0)	4 (3.1)	4 (3.1)
Anthro-pometric	Height (in)	63.6±2.90	63.8±3.08	63.9±2.99	64.5±2.93	63.8±2.70
	Weight (lb)	145.4±33.5	147.9±32.3	144.9±32.3	153.5±30.83	152.0±38.16

*Statistically Significant Difference Between Groups

Subgroup analysis

No discernible adverse event associations were noted for interactions of pilocarpine HCl and concomitant medications, race, gender, medical histories, or vital signs. However, there was a trend in the elderly population (>65 years of age) towards higher incidences of urinary frequency and diarrhea (twice placebo) and for dizziness (three times placebo).

The protocol of the first pivotal trial, P92-01, stratified subjects by rheumatoid arthritis (RA) status to balance the groups with respect to that variable. The sponsor also statistically analyzed the results of the RA subset of the subjects. The NRA (non-rheumatoid arthritis) group constitutes a major (82%) portion of the entire subject population in this study, so a separate NRA analysis was not conducted. Whereas the overall results demonstrated that the effect of the 2.5 mg strength Salagen is similar to that of placebo, and the 5 mg dose demonstrates efficacy over both groups, within the RA group, the effect of pilocarpine is as follows: 13% of subjects were responders in the placebo group, 61% were responders in the 2.5 mg group, and 50% were responders in the 5 mg group. Further analysis of the RA group showed that the effect of pilocarpine 5 mg is statistically significant compared to placebo; the 2.5 mg to placebo comparison was not made, as this was not a part of the protocol's statistical

plan. The overall comparison was not statistically significant ($p \leq 0.0980$) because the 2.5 and 5 mg outcomes were so similar, coupled with the small subset sample size. However, the treatment-by-RA status interactions at Week 6, 12, and Endpoint were statistically significant ($p \leq 0.0299$), allowing for the conclusion that the RA group benefited more from the pilocarpine HCL 2.5 mg dose than the NRA group. However, since no explanation of the effect was provided, RA status maybe a proxy for some other related factor (e.g., less severe dry mouth symptoms) which shows better response at lower levels of drug. Therefore, it is recommended that a statement be placed in the label, acknowledging a lack of understanding of the clinical relevance of this finding.

Safety

A total of 629 subjects were randomized to participate in two Phase 3 randomized, placebo-controlled studies. Of these 629 subjects, 376 received pilocarpine HCl (121 at 2.5 mg, 255 at 5 mg q.i.d. ((127 at 5 m g q.i.d. in 92-01; and 128 during the first 6 weeks at 5 mg in P92-02)) and 114 at 5 - 7.5 mg. The placebo was administered to 253 subjects in the trials.

The study completion rate at 12 weeks for subjects on pilocarpine HCl was 85.4% and the completion rate of subjects on placebo (87.0%). Of the 629 subjects enrolled in the studies 34 (9.0%) of the pilocarpine HCl group and 17 (6.7%) of the placebo group discontinued from the study due to adverse events, whether or not related to test article. The following table gives a combined summary of reasons for discontinuation from both pivotal trials.

Reason for Discontinuation	Placebo (n=253)		Pilocarpine HCl (n=376)	
	n	%	n	%
Adverse Experience	17	6.7	34	9.0
Lack of Efficacy	1	0.4	1	0.3
Personal/non-compliance	11	4.3	11	2.9
Protocol Violation	0	0.0	2	0.5
Lost to Follow-up	0	0.0	1	0.3
Death	0	0.0	1	0.3
Other	4	1.6	5	1.3
Completed	220	87.0	321	85.4
Total	253	100.0	376	100.0

The following table contains a list of serious adverse experiences reported in both of the pivotal trials. None of the serious events reported were judged by the sponsor as being related to the test medication.

Serious Adverse Experiences in P92-01 and P92-02

Study Group	Treatment Group	Adverse Experience	Withdrew Due to Event (?)
P92-01 (n=7/373)	Placebo	Fever (sepsis)	No
	2.5 mg	Cholelithiasis	No
	2.5 mg	Death - probable pulmonary embolus and clostridium difficile enterocolitis	Yes
	2.5 mg	Peptic ulcer - acute abdominal pain	Yes
	5 mg	Fractured pelvis, mild stroke	Yes
	5 mg	Broken hip and wrist due to fall	Yes
	5 mg	Cholecystitis	Yes
P92-02 (n=10/256)	Placebo	Heat prostration	No
	Placebo	Depression (pre-existing)	No
	Placebo	Pleural effusion secondary to connective tissue disease	No
	Placebo	Stroke	Yes
	5 mg	Depression (pre-existing)	No
	5 mg	Pelvic inflammatory disease	No
	7.5 mg	Myocardial infarction	Yes
	7.5 mg	Uterine fibroids (pre-existing)	No

An open label study (P92-03) was conducted which allowed subjects from the fixed dose pivotal trial to continue P92-01. This open-label study allowed for subjects to titrate their dosage as counseled by the investigator. A total of 212 subjects enrolled in P92-03, which includes 141 subjects who have been on the drug for 6 months as of the submission of the NDA and 69 subjects for 12 months. Only interim information has been provided for this trial. A total of 18 serious adverse experiences have been reported in this ongoing open-label trial to date. Four of the events resulted in subject withdrawal from the study; however, none of these events were considered to be drug related. Because there is no placebo associated with this trial, it is difficult to compare event reporting to background incidence in order to determine relationship to drug consumption. The sponsor was informed at the End-of-Phase 2 meeting that open-label trials are not recommended.

Serious Adverse Events Reported during an Open Label Study (P92-03)

Treatment Group	Adverse Experience	Withdrew Due to Event (?)
2.5 mg q.i.d.	Confusion and lethargy due to overdose of pain medication	No
2.5 mg t.i.d. & 5 mg q.d.	Angioplasty (coronary artery occlusion)	Yes
5 mg t.i.d.	Cholecystectomy (cholelithiasis)	No
	Elective coronary artery bypass graft	No
5 mg t.i.d. & 2.5 mg q.h.s.	Surgical procedure for vaginal prolapse	No
5 mg q.i.d.	Foot ulceration secondary to systemic lupus erythematosus	No
	Pneumonia	No
	Rectal bleeding, cystitis (pre-Existing) and surgical repair of hip	No
	Pneumonia	No
	Flu-like symptoms and acute parotiditis	No
	hysterectomy (cervical dysplasia)	No
	Esophageal ulcers	Yes
	Breast ulcers	No
	Lupus crisis	No
	Elective acid reflux study (pre-existing)	Yes
	Myocardial infarction	No
5 mg 6x/day	Benign brain tumor	Yes
10 mg t.i.d.	Hysterectomy (uterine fibroids)	No

The incidence rates of the most frequently reported adverse experiences in the combined double-blind studies are listed in the following two tables. The first table compares the incidence of adverse experiences between placebo and drug, combining all doses of the drug into one group. The second table specifies the incidence of the individual adverse experiences in groups by assigned dose. The second table includes more adverse experiences due to a larger total sample size, since the 5 - 7.5 mg group is a subset of the 5 mg group. The single most frequently reported adverse experience in the combined studies was sweating, which was reported by 150 (40%) of the subjects taking pilocarpine and 18 (7%) of those on placebo. There were statistically significant treatment differences for sweating, urinary frequency, vasodilation (flushing), chills, and increased salivation. Pharmacologically, pilocarpine stimulates the parasympathetic nervous system, so that these events could be expected.

In addition to the expected events, there were statistically significant differences between treatment groups for the incidences of edema and pruritus. Because of the multiple comparisons involved in the lengthy list of adverse experiences reported, p values must be analyzed with caution. In order to determine if the edema and pruritus are related to pilocarpine use, or a spurious finding, the sponsor performed an evaluation of the dose response with these events. In the case of edema, the 9 reports of subjects with edema can be summarized as follows: 5 subjects (4.1%) on the 2.5 mg dose, 3 subjects (1.2%) on the 5.0 mg dose, and one subject in the 5 - 7.5 mg group (< 1%). Similarly, of the 6 subjects who reported pruritus, 2 (1.7%) were receiving 2.5 mg doses, 3 (1.2%) were receiving 5 mg, and less than 1% were receiving the 5 - 7.5 mg dose. It is unlikely that the edema and pruritus reported in these studies were related to the intake of pilocarpine due to the reverse dose-response trend.

Summary of Incidence of Adverse Experiences (>1%), Studies P92-01 and P92-02

COSTART Specific Term	Placebo (n=253)		Pilocarpine HCL (n=376)		Total (n=629)	p-values
	n	%	n	%		
Sweating	18	7.1	150	39.9	168	≤ **0.0001***
Headache	48	19.0	66	17.6	114	≤ 0.6505
Nausea	23	9.1	46	12.2	69	≤ 0.2161
Flu Syndrome	23	9.1	44	11.7	67	≤ 0.2979
Urinary Frequency	9	3.6	44	11.7	53	≤ **0.0003***
Dyspepsia	18	7.1	30	8.0	48	
Rhinitis	19	7.5	29	7.7	48	
Diarrhea	17	6.7	26	6.9	43	
Vasodilatation	6	2.4	26	6.9	32	≤ **0.0110***
Dizziness	18	7.1	24	6.4	42	
Chills	5	2.0	19	5.1	24	≤ **0.0482***
Abdominal Pain	9	3.6	18	4.8	27	
Sinusitis	13	5.1	16	4.3	29	
Pain	6	2.4	16	4.3	22	
Pharyngitis	12	4.7	15	4.0	27	
Asthenia	5	2.0	13	3.5	18	
Increased Salivation	0	0	12	3.2	12	≤ **0.0041***
Infection	14	5.5	10	2.7	24	≤ 0.0650
Rash	7	2.8	10	2.7	17	
Cough Increased	5	2.0	9	2.4	14	
Blurred Vision	4	1.6	9	2.4	13	
Vomiting	2	0.8	9	2.4	11	
Edema	0	0	9	2.4	9	≤ **0.0132***
Urinary Tract Infection	9	3.6	7	1.9	16	
Lab Test Abnormal	5	2.0	7	1.9	12	
Palpitation	4	1.6	7	1.9	11	
Face Edema	3	1.2	6	1.6	9	
Tachycardia	3	1.2	6	1.6	9	
Glossitis	2	0.8	6	1.6	8	
Pruritus	0	0	6	1.6	6	≤ **0.0435***
Vaginitis	0	0	5	1.4	5	≤ 0.0655
Back Pain	6	2.4	5	1.3	11	
Constipation	4	1.6	5	1.3	9	
Allergic Reaction	1	0.4	5	1.3	6	
Flatulence	0	0	5	1.3	5	≤ 0.0655
Epistaxis,	4	1.6	4	1.1	8	
Tinnitus	5	2.0	4	1.1	9	
Myalgia	4	1.6	4	1.1	8	
Stomatitis	3	1.2	4	1.1	7	
Accidental Injury	2	0.8	4	1.1	6	
Fever	1	0.4	4	1.1	5	
Urinary Incontinence	1	0.4	4	1.1	5	
Somnolence	0	0	4	1.1	4	≤ 0.0998

* statistically significant

Note: P values are presented only for those terms with an incidence rate of at least 10% in any treatment group or with a p value of 0.10 or less.

Incidence Rates of Adverse Experiences (>1%) - Studies P92-01 and P-92-02 (from Appendix 6 - page 45, vol 132)

COSTART Specific Term	Placebo (n=253)	Pilocarpine HCL 2.5 mg (n=121)	Pilocarpine HCL 5.0 mg (n=255)	Pilocarpine HCL 5 - 7.5 mg (n=114)
	n (%)	n (%)	n (%)	n (%)
Sweating	18 (7.1)	13 (10.7)	101 (39.6)	53 (46.5)
Headache	48 (19.0)	25 (20.7)	33 (12.9)	10 (8.8)
Nausea	23 (9.1)	15 (12.4)	24 (9.4)	8 (7.0)
Flu Syndrome	23 (9.1)	16 (13.2)	22 (8.6)	6 (5.3)
Urinary Frequency	9 (3.6)	13 (10.7)	25 (9.8)	7 (6.1)
Dyspepsia	18 (7.1)	8 (6.6)	17 (6.7)	5 (4.4)
Rhinitis	19 (7.5)	9 (7.4)	18 (7.1)	2 (1.8)
Diarrhea	17 (6.7)	7 (5.8)	15 (5.9)	4 (3.5)
Dizziness	18 (7.1)	6 (5.0)	14 (5.5)	4 (3.5)
Vasodilatation	6 (2.4)	2 (1.7)	22 (8.6)	3 (2.6)
Abdominal Pain	9 (3.6)	9 (7.4)	7 (2.8)	4 (3.5)
Sinusitis	13 (5.1)	3 (2.5)	10 (3.9)	3 (2.6)
Pharyngitis	12 (4.7)	6 (5.0)	6 (2.4)	3 (2.6)
Chills	5 (2.0)	1 (0.8)	11 (4.3)	7 (6.1)
Infection	14 (5.5)	3 (2.5)	4 (1.6)	3 (2.6)
Pain	6 (2.4)	6 (5.0)	10 (3.9)	0 (0)
Asthenia	5 (2.0)	5 (4.1)	6 (2.4)	2 (1.8)
Rash	7 (2.8)	4 (3.3)	5 (2.0)	1 (0.9)
Urinary Tract Infection	9 (3.6)	3 (2.5)	4 (1.6)	0 (0)
Cough Increased	5 (2.0)	4 (3.3)	4 (1.6)	1 (0.9)
Blurred Vision	4 (1.6)	3 (2.5)	5 (2.0)	1 (0.9)
Increased Salivation	0 (0)	0 (0)	7 (2.8)	5 (4.4)
Lab Test Abnormal	5 (2.0)	3 (2.5)	2 (0.8)	2 (1.8)
Back Pain	6 (2.4)	2 (1.7)	3 (1.2)	0 (0)
Palpitation	4 (1.6)	1 (0.8)	5 (2.0)	1 (0.9)
Vomiting	2 (0.8)	2 (1.7)	7 (2.8)	0 (0)
Constipation	4 (1.6)	1 (0.8)	4 (1.6)	0 (0)
Edema	0 (0)	5 (4.1)	3 (1.2)	1 (0.9)
Face Edema	3 (1.2)	4 (3.3)	2 (0.8)	0 (0)
Tachycardia	3 (1.2)	1 (0.8)	4 (1.6)	1 (0.9)
Tinnitus	5 (2.0)	0 (0)	3 (1.2)	1 (0.9)
Epistaxis,	4 (1.6)	1 (0.8)	3 (1.2)	0 (0)
Glossitis	2 (0.8)	4 (3.3)	2 (0.8)	0 (0)
Hypertension	5 (2.0)	0 (0)	2 (0.8)	1 (0.9)
Myalgia	4 (1.6)	2 (1.7)	2 (0.8)	0 (0)
Bronchitis	5 (2.0)	0 (0)	1 (0.4)	1 (0.9)
Chest Pain	4 (1.6)	0 (0)	3 (1.2)	0 (0)
Insomnia	4 (1.6)	1 (0.8)	2 (0.8)	0 (0)
Stomatitis	3 (1.2)	1 (0.8)	3 (1.2)	0 (0)
Accidental Injury	2 (0.8)	0 (0)	1 (0.4)	3 (2.6)
Allergic Reaction	1 (0.4)	3 (2.5)	2 (0.8)	0 (0)
Conjunctivitis	3 (1.2)	0 (0)	3 (1.2)	0 (0)
Depression	3 (1.2)	2 (1.7)	1 (0.4)	0 (0)
Dry Eyes	4 (1.6)	0 (0)	2 (0.8)	0 (0)
Pruritus	0 (0)	2 (1.7)	3 (1.2)	1 (0.9)

Dyspnea	3 (1.2)	0 (0)	1 (0.4)	1 (0.9)
Fever	1 (0.4)	2 (1.7)	2 (0.8)	0 (0)
Flatulence	0 (0)	1 (0.8)	3 (1.2)	1 (0.9)
Leg Cramps	3 (1.2)	0 (0)	2 (0.8)	0 (0)
Taste Perversion	2 (0.8)	1 (0.8)	2 (0.8)	0 (0)
Urinary Incontinence	1 (0.4)	0 (0)	4 (1.6)	0 (0)
Vaginitis	0 (0)	2 (1.7)	3 (1.3)	0 (0)
Photosensitivity	3 (1.2)	0 (0)	0 (0)	1 (0.9)
Somnolence	0 (0)	1 (0.8)	3 (1.2)	0 (0)
Gastroenteritis	1 (0.4)	2 (1.7)	0 (0)	0 (0)
Urinary Urgency	0 (0)	0 (0)	3 (1.2)	0 (0)
Viral Infection	1 (0.4)	2 (1.7)	0 (0)	0 (0)
Moniliasis	0 (0)	2 (1.7)	0 (0)	0 (0)

Electrocardiogram findings

Four subjects (1 pilocarpine 5 - 7.5 mg, 1 pilocarpine 5 mg and 2 placebo) had abnormal ECG's that were reported as adverse experiences, none of which were judged related to the test article. A total of 127 subjects had abnormal ECG's at both the screening and end of study visits and 79 subjects had abnormal ECG's at entrance to the study and normal ECG's at the end of the study. Of the 50 subjects who had normal ECG's at baseline and abnormal ECG's at the end of the study, 8 (out of 114 (7.0%) were in the pilocarpine 5 - 7.5 mg strength group, 18 (out of 255 (7.1%) were in the pilocarpine 5 mg group, 8 (out of 121 (6.6%) were in the 2.5 mg pilocarpine group, and the remaining 16 (out of 253 (6.3%) were in the placebo group.

Vital Signs

For both pivotal studies, vital sign measurements were obtained for each subject at screening, admission, Week 6 and Week 12. These measurements included systolic and diastolic blood pressure, pulse, respiration and temperature. In subjects who demonstrated changes in vital sign measurements during the conduct of the trial, no significant difference between the number of subjects in the placebo and test groups was noted that would alert us to an event that is related to pilocarpine use. However, the label will reflect the exact numbers of reports of vital sign changes during the trials in both pilocarpine and placebo group in those events reported with greater than 3% frequency.

Clinical Laboratory Evaluations

For both pivotal studies, laboratory tests were evaluated at screening, admission and at the end of study participation. Laboratory tests were also obtained at Week 6 in study P92-01. No subject discontinued from either study because of a laboratory abnormality. Twenty-two subjects (15/376 (4%) pilocarpine HCL, and 7/253 (3%) placebo) had shifts in laboratory test results and were reported as adverse experiences by the investigator. The following table summarizes these changes.