SUMMARY OF CHANGES FROM BASELINE IN SUBJECTS' VISUAL ANALOGUE SCALE (MM) ASSESSMENT OF DRY MOUTH SYMPTOMS AT ENDPOINT (STUDY NO. SB95US01)

Symptom	Mean ± SD			p-value			
	Placebo	Cevimeline 15 mg *t.i.d.*	Cevimeline 30 mg *t.i.d.*	Overall	P vs. 30 mg	P vs. 60 mg	30 mg vs. 60 mg
Feeling of mouth	-15.3 ± 22.4	-25.6 ± 23.8	-22.7 ± 19.7	0.3271	0.1738	0.2158	0.8887
Dryness of mouth	-16.5 ± 23.1	-28.0 ± 22.9	-30.5 ± 21.9	0.0999	0.0943	0.0431	0.7225
Dryness of tongue	-15.8 ± 28.0	-24.0 ± 26.9	-26.5 ± 24.9	0.5593	0.3636	0.3330	0.9542
Ability to speak without drinking	-7.7 ± 16.6	-14.9 ± 17.9	-20.4 ± 25.0	0.3095	0.2389	0.1472	0.7803
Ability to chew and swallow food	-14.9 ± 20.5	-21.3 ± 18.7	-19.6 ± 19.4	0.4040	0.1858	0.3741	0.6441
Ability to sleep	-3.4 ± 16.5	-15.4 ± 15.5	-9.5 ± 15.3	0.0587	0.0180*	0.2583	0.1865

* values are those that are statistically significant at $p < 0.05$. Note that all of the significant differences in this chart are due to the placebo being superior to the 15 mg group.

Secondary outcome variables

Salivary Flow

The salivary flow was measured 90 minutes after the drug was given and was compared with predose values. Only measurements of unstimulated flow were considered. At each visit, salivary flow increased following dosing, with greater increases observed in the active groups compared with placebo, as shown in the following table.

SUMMARY OF CHANGES IN OBJECTIVE SALIVARY FLOW MEASUREMENTS (ML/MIN) FROM PREDOSE TO POSTDOSE (STUDY NO. SB95US01)

Visit	Mean ± SD			p-value			
	Placebo	Cevimeline 30 mg *t.i.d.*	Cevimeline 60 mg *t.i.d.*	Overall	Pla vs. 30 mg	Pla vs. 60 mg	30 mg vs. 60 mg
Week 2	0.052 ± 0.085	0.218 ± 0.184	0.268 ± 0.268	0.0008	0.0055	0.0003	0.3177
Week 4	0.038 ± 0.069	0.190 ± 0.193	0.288 ± 0.291	0.0033	0.0323	0.0009	0.1580
Week 6	0.010 ± 0.063	0.196 ± 0.183	0.223 ± 0.292	0.0028	0.0063	0.0015	0.5022
Final Visit	0.015 ± 0.064	0.194 ± 0.179	0.258 ± 0.310	0.0008	0.0072	0.0003	0.2414

As was noted in the global evaluation for these subjects, although both doses demonstrated a significant improvement in salivary flow, there was no significant difference in salivary flow between the 30 mg group and the 60 mg groups.

Use of Artificial Saliva and Fluid Intake

Overall, there was a greater reduction from baseline in the use of artificial saliva and in fluid intake for patients who received active drug compared with those who received placebo. At all visits after Week 0, more patients in the 60 mg SNI-2011 tid group decreased their use of artificial saliva than did patients in the other treatment groups (Table 6.2) At Endpoint, 19% of the patients in the 60 mg SNI-2011 tid group decreased use of artificial saliva compared with 4% of the patients in the 30 mg SNI-2011 group and no patients in the placebo group (p=0.0549). The difference between the placebo and 60 mg SNI-2011 tid groups in the numbers of patients decreasing their use of artificial saliva at Endpoint approached significance (p=0.0674).

At Endpoint, 58% of the patients in the 60 mg SNI-2011 tid group reported decreased use of artificial saliva compared with 40% of the patients in the 30 mg SNI-2011 tid group and 44% of the patients in the placebo group.

There were no significant differences among treatment groups in the numbers of patients who decreased fluid intake at any visit.

Adverse Events

No subject in any of the three treatment groups reported a serious adverse event. However, eighteen subjects who received placebo reported at least one adverse event during the study (78%). This compared with 22 subjects in the 30 mg cevimeline *t.i.d.* group (88%) and 27 subjects in the 60 mg cevimeline *t.i.d.* group (100%).

The most frequently reported adverse events during the study were increased sweating, nausea, and headache. One subject in the placebo group (4%) discontinued the study prematurely because of an adverse event compared with 4 subjects in the 30 mg cevimeline *t.i.d.* group (16%) and 9 subjects in the 60 mg cevimeline *t.i.d.* group (33%).

INCIDENCE OF ADVERSE EVENTS REPORTED BY ≥10% SUBJECTS IN ANY ONE TREATMENT GROUP (STUDY NO. SB95US01)

	Placebo (N=23)		Cevimeline 30 mg *t.i.d.* (N=25)		Cevimeline 60 mg *t.i.d.* (N=27)	
Adverse Event	**N**	**%**	**n**	**%**	**n**	**%**
Sweating increased	2	8.7	4	16.0	18	66.7
Nausea	0	0	5	20.0	14	51.9
Headache	6	26.1	9	36.0	8	29.6
Rigors	1	4.4	1	4.0	8	29.6
Diarrhea	3	13.0	3	12.0	6	22.2
Dyspepsia	1	4.4	4	16.0	6	22.2
Dizziness	2	8.7	2	8.0	5	18.5
Abdominal pain	1	4.4	1	4.0	5	18.5
Vomiting	0	0	4	16.0	4	14.8
Tremor	0	0	1	4.0	3	11.1
Constipation	0	0	0	0	3	11.1
Saliva increased	0	0	0	0	3	11.1
Skin cold clammy	0	0	0	0	3	11.1
Micturition frequency	0	0	3	12.0	2	7.4
Upper respiratory tract infection	2	8.7	5	20.0	2	7.4
Nervousness	3	13.0	0	0	1	3.7
Sinusitis	1	4.4	3	12.0	1	3.7
Myalgia	2	8.7	3	12.0	1	3.7

Based upon the lack of significant improvement in either global assessment of dry mouth, or salivary flow, and the higher adverse event profile established with the 60 mg group compared to the 30 mg group, the sponsor chose to eliminate the 60 mg dose in the phase 3 trials. Refer to the discussion section of this review for further comments about dose selection.

Phase 3 Trials

Study SB96US02

Protocol Design

This section is a summary of the sponsor's protocol as conducted. The procedures reported in the NDA were compared to the proposed plan as presented in the IND submission, prior to its conduct. All changes to the original protocol were submitted to the IND prior to starting the trials as protocol amendments and are noted at the end of this section.

Phase 3

Title: A Double-Blind, Randomized, Placebo-Controlled Study of SNI-2011 (15 MG and 30 mg *t.i.d.*) Vs. Placebo in Sjögren's Syndrome Patients with Xerostomia

Objectives:

To compare the effectiveness of two doses of SNI-2011 (15 mg *t.i.d.* and 30 mg *t.i.d.*) with placebo on the subject's subjective global evaluation of dryness of the mouth, the eyes, and overall).

To compare the effectiveness of two doses of SNI-2011 with placebo on the subject's subjective assessment of specific symptoms of dry mouth and dry eyes and on the objective measures of total salivary flow and tear flow (Schirmer's test) in Sjögren's syndrome patients with xerostomia

To compare the safety of two doses of SNI-2011 with placebo over a period of 12 weeks in Sjögren's syndrome patients with xerostomia

Principal Investigators and Associated Study Sites:

TABLE A INVESTIGATORS AND INVESTIGATIONAL SITES

SITE NUMBER	NAME OF INVESTIGATOR	ADDRESS OF INVESTIGATIONAL SITE	TOTAL NUMBER OF SUBJECTS ENROLLED
02	Andrew Baldassare, MD	522 N. New Ballas Rd., Suite 240 St. Louis, MO 63141	5
03	Herbert Baraf, MD	Arthritis and Rheumatism Association, P.A. 2730 University Blvd. West Room 310 Wheaton, MD 20902	8
06	Jane Box, MD	Arthritis Clinic 1001 Blythe Blvd., Suite 403 Charlotte, NC 28203-5866	12
08	Steve Carsons, MD	Physician and Rheumatologist 222 Station Plaza No. Suite 430 Mineola, NY 11501	1
10	Stanley Cohen, MD	Metroplex Clinical Research Center 5939 Harry Hines Boulevard Suite 441 Dallas, TX 75235	13
11	Ronald Collins, MD	Columbia Arthritis Center, P.A. 1711 Saint Julian Place Columbia, SC 29204-2409	13
13	John Condemi, MD	AAIR Research Center 919 Westfall Bldg. B Rochester, NY 14618	16
14	Paul Dalgin, MD	Medical Associates of Stamford 1100 Bedford Street Stamford, CT 06905-5301	15
17	Thomas Dykman, DDS, PhD	Fayetteville Diagnostic Clinic 3344 Futrall Drive Fayetteville, AR 72703	11
19	Robert Ettlinger, MD, FACP	Cedar Medical Center 1901 S. Cedar Street Suite 201 Tacoma, WA 98405-2303	7
20	Rose Fife, MD	Indiana University School of Medicine 550 N. University Blvd., Room 2201 Indianapolis, IN 46202	12
23	Alan Friedman, MD	University of Texas Medical School 6431 Fannin, MSB 5270 Houston, TX 77030	7
44	Oscar Gluck, MD	Phoenix Center for Research Clinical 6707 N. 19th Avenue Suite 201 Phoenix, AZ 85015	13
26	Allan Goldman, MD	Rheumatic Disease Center 2015 E. Newport, #409 Milwaukee, WI 53211-2949	1

SITE NUMBER	NAME OF INVESTIGATOR	ADDRESS OF INVESTIGATIONAL SITE	TOTAL NUMBER OF SUBJECTS ENROLLED
18	Kathryn Hobbs, MD	University of Colorado Health Sciences Center Department of Rheumatology Box B-115 4200 9th Avenue Denver, CO 80262	4
28	Richard A.H. Jimenez, MD	Clinical Research Management 21600 Highway 99 Suite 240 Edmonds, WA 98602-8047	9
31	Michael Keller, MD	Michael I. Keller, MD, Inc 5555 Reservoir Drive. Suite 202 San Diego, CA 92120	5
61	Philip Mease, MD	Minor James Clinical Research Center 515 Minor Avenue Suite 170 Seattle, WA 98104	2
34	Brent Mohr, MD	Health Advance Institute 900 East Colfax South Bend, IN 46617	1
36	Edward Morris, MD	Health Trends Research LLC 1838 Greene Tree Road Suite 300 Baltimore, MD 21208	8
40	Ann Parke, MD, PhD	University of Connecticut Health University of Rheumatology MC 1310 263 Farmington Farmington, CT 06032	10
41	Dianne Petrone, MD	Research Associates of North Texas Division of Arthritis Centers of Texas 712 N. Washington #200 Dallas, TX 75246	20
57	Joel Rutsrein, MD, FACP, PA	Arthritis Diagnostic and Treatment Center 10130 Huebner Road San Antonio, TX 78240-1372	0
49	Robert Wilkins, MD	Advanced Research Management 600 Broadway Seattle, WA 98122	1
50	John Zuzga, Jr., DO	Chicago Center for Clinical Research 515 N. State Street Suite 2700 Chicago, IL 60610	2
24	Norman Gaylis, MD	100 NW 170th Street Suite 105 North Miami Beach, FL 33189	1
45	Wayne H. Tsuji, MD	Minor and James Medical 1229 Madison Street, Suite 1500 Seattle, WA 98104	0
TOTAL NUMBER OF SUBJECTS			197

Number of Subjects: 210 were scheduled to have been enrolled

Ages of Subjects: 18-75 years of age, inclusive

Screening Questionnaire

Some of the inclusion and exclusion criteria are contingent upon answers to the study entry questionnaire, in which the potential subjects were asked the following questions regarding dryness of the mouth and eyes:

1. How would you describe the severity of your dry mouth symptoms over the past few days?

   ☐ No symptoms ☐ Mild ☐ Moderate ☐ Severe

2. Have you had a daily feeling of dry mouth for more than 3 months?

   ☐ Yes ☐ No

3. Have you had recurrent or persistently swollen salivary glands as an adult?

   ☐ Yes ☐ No

4. Do you frequently drink liquids to aid in swallowing dry foods?

   ☐ Yes ☐ No

5. How would you describe the severity of your dry eye symptoms over the past few days?

   ☐ No symptoms ☐ Mild ☐ Moderate ☐ Severe

6. Have you had daily, persistent, troublesome dry eyes for more than 3 months?

   ☐ Yes ☐ No

7. Do you have a recurrent sensation of sand or gravel in the eyes?

   ☐ Yes ☐ No

8. Do you use tear substitutes more than 3 times a day?

   ☐ Yes ☐ No

Inclusion Criteria

Patients were required to meet the following criteria to be enrolled in the study:

1. Patient was between 18 year and 75 years old, inclusive, and had given informed consent to participate in the study

2. Patient, if female and of childbearing potential, was required to have a negative pregnancy test result at screening

3. Patient, if of childbearing potential, was using an accepted method of birth control (e.g., oral contraceptives; intrauterine contraceptive device; diaphragm or condoms in combination with contraceptive cream, jelly, or foam) or was surgically sterile

4. Patient had documented diagnosis of mild-to-moderate primary or secondary Sjögren's syndrome (i.e., lacrimal and salivary gland dysfunction, with or without connective tissue disorder), using the American Rheumatism Association's Diagnostic Criteria as follows:

Primary Sjögren's

- At least one positive response to each of the ocular and oral symptom Yes/No questions

- Salivary and lacrimal gland dysfunction (Salivary dysfunction is defined as the collection of ≤1.5 mL over a 15-minute period and lacrimal dysfunction is defined as a Schirmer's test result, with topical anesthesia, of ≤ 5 mm.)

Reviewer's comment: According to the protocol, at the screening examination only, saliva collection will be assessed without stimulation and, if no saliva is produced, the dorsolateral tongue surface will be stimulated with 2% citrate solution every 30 seconds for 2 minutes. This differs from other accepted classification criteria for Sjögren's syndrome, in which unstimulated saliva only is measured.

- Positive anti-Ro/SS-A, anti-La/SS-B antibodies, rheumatoid factor (RF), and/or documented history of such in patient's medical records, and/or positive anti-nuclear antibodies (ANA) of 1:160 or greater at the time of screening as indicated on the laboratory assessment performed at the screening visit

Secondary

- At least one positive response to either the ocular or oral symptom Yes/No questions on the study entry questionnaire

- Salivary and lacrimal gland dysfunction (Salivary dysfunction is defined as the collection of ≤1.5 mL over a 15-minute period and lacrimal dysfunction is defined as a Schirmer's test result, with topical anesthesia, of ≤ 5 mm.)

- Positive anti-Ro/SS-A, anti-La/SS-B antibodies, RA, and/or ANA antibodies and/or documented history of such in the patient's medical records

- Positive ANA of 1:160 or greater at screening as indicated on the laboratory assessments performed at the screening visit and/or RF antibodies or other evidence of accompanying rheumatoid arthritis or other connective tissue disease

Reviewer's Comment: It is not clear how secondary Sjogren's differs from primary based upon these definitions. Refer to the discussion section of this review for details.

Documentation of prior positive glandular lip biopsy may also have been used to diagnose primary or secondary Sjögren's syndrome.

Exclusion Criteria

Any patient meeting any of the following criteria was not allowed to enter the study:

1. Patient answered "severe" in Questionnaire A, and had null values for both tear and salivary flow measures.

2. Patient had acutely enlarged salivary glands (with or without pain).

3. Patient had suspected physical closure of the salivary glands.

4. Patient had any external ophthalmic disease (viral, bacterial, or fungal infection), diabetic keratitis, or neutrophilic corneal disorder.

5. Patient had a history of significant cardiovascular disease and might be unable to compensate for transient changes in hemodynamics (angina or myocardial infarction) or rhythm induced by cholinergic agents.

6. Patient had a history of significant pulmonary obstructive disease currently requiring chronic medication other than an occasional (<4 days) use of an inhaled sympathomimetic.

7. Patient had a current gastroduodenal ulcer at the time of enrollment or had one within the past year.

8. Patient had acute iritis, narrow-angle (angle-closure) glaucoma.

9. Patient had a history of underlying psychiatric illness that, in the opinion of the investigator, could impair the patient's ability to make a global evaluation of his or her signs and symptoms.

10. Patient had a history of nephrolithiasis or cholelithiasis (Patients who had undergone a cholecystectomy might be enrolled in the study).

11. Patient was taking or had taken any other investigational new drug (a chemical entity not registered for use) within the last 30 days or was due to receive such a drug during this study.

12. Patient was taking any anticholinergic agents or other medications known to alter xerostomia.

Reviewer's Comment: A complete list of salivary altering medication was included with the protocol. These include drugs that increase salivation such as cholinergic stimulants, cholinesterase inhibitor ophthalmic preparations, and direct-acting miotic ophthalmic preparations; as well as drugs that decrease salivation such as anticholinergics, antihistamines, antidepressants, antiarrhythmics, and antipsychotics.

13. Patient had a recent history (within 12 months) of chronic alcoholism or drug abuse.

14. Patient was unwilling or unable to comply with the protocol.

15. Patient had a history of radiation therapy affecting the salivary glands.

Study Design: Multicenter, double-blind, randomized, parallel-group

Study Procedures

Study SB96US02 is a multicenter, double-blind, randomized, parallel-group study which was conducted to compare the efficacy and safety of two doses of SNI-2011 (15 mg *t.i.d.* and 30 mg *t.i.d.*) and placebo in the treatment of xerostomia in subjects with Sjögren's syndrome. A total of 210 subjects were to have been enrolled in this study: 70 per each of three treatment groups. A sample size of 70 subjects per treatment group was expected to be sufficient for detecting statistically significant differences among the three treatment groups.

The following paragraph outlines the study procedures; for a complete list of events at each visit, refer to the chart on the following page.

The screening exam, which was conducted from 5 to 12 days prior to the first visit, included a medical history, physical examination, clinical laboratory tests[1], ECG, vital signs, ophthalmologic examination, total salivary flow measures, Schirmer's test, Dry mouth and

1 The following clinical laboratory tests were performed during the screening and during each visit after study medication was distributed: Serum chemistry: glucose, sodium, potassium, chloride, urea nitrogen, creatinine, uric acid, phosphorus (inorganic), calcium, total cholesterol, triglycerides, protein, albumin, globulin, alkaline phosphatase, SGOT (AST), SGPT (ALT), GGT, total bilirubin, LDH, serum amylase; Hematology: Hb, Hct, total erythrocyte count, total leukocyte count, with differential, platelet count; Urinalysis: specific gravity, pH, glucose, bilirubin, protein, ketones, leukocytes, occult blood. During the screening visit only, screening for autoimmune antibodies (Ro/SS-A, la/SS-B, ANA, RA) and a serum pregnancy test were performed.

eyes symptom VAS questionnaire, and study entry questionnaire. The subjective and objective measures of salivary flow and tear flow were measured at screening to confirm eligibility as well as to establish baseline values. Following successful completion of the screening procedures, eligible subjects were randomized to receive 15 mg SNI-2011 *t.i.d.*, 30 mg SNI-2011 *t.i.d.*, or placebo for 12 weeks. At Week 0 (Visit 1) subjects received their first dose of study medication and completed a VAS questionnaire on symptoms before receiving their assigned treatment and again after dosing. The subjects completed a global evaluation survey one hour after dosing. In addition, vital signs were measured and adverse events monitored both before and one hour after receiving study medication. These procedures were repeated at the scheduled visits during Weeks 0, 3, 6, 9, and 12. In addition, laboratory tests were repeated prior to taking the medication at visits during week 3, 6, 9, and 12. A 12-lead ECG was performed during the Week 6 visit, prior to receiving study medication, and again at the week 12 visit, both pre and post medication. Total salivary flow measures and Schrimer's test were performed during Visit 3 (Week 6) and Visit 5 (Week 12) both pre and post medication.

Chart of Study Procedures

	Day –12 to – 5	Week 0		Week 3		Week 6		Week 9		Week 12	
Visit	Screening	Visit 1		Visit 2		Visit 3		Visit 4		Visit 5	
Assessment		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Informed consent	X										
Medical history	X										
Physical examination	X										x
Autoimmune antibodies (Ro/SS-A, La/SS-B, ANA, RA)	X										
Study entry questionnaire	X										
Dry mouth and eyes symptom questionnaire (VAS)	X	x	x	X	x	x	X	x	x	x	x
Total salivary flow measures	X					x	X			x	x
Schirmer's test	X					x	X			x	x
Ophthalmologic examination	X										x
Subject's global evaluation			x		x		X		x		x
Clinical laboratory tests[2]	X			X		x		x		x	
Serum pregnancy test	X										
12-lead ECG	X					x				x	x
Vital signs	X	x	x	X	x	x	X	x	x	x	x
Study medication		x		X		X		x		x	
Monitor adverse events		x	x	X	x	x	X	x	x	x	x

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ON ORIGINAL

2 Refer to narrative section of Study Procedures section (two pages prior) for a complete list of laboratory tests.

Withdrawal of Subjects from Therapy or Assessment

The investigator was allowed to withdraw a subject from the study if he or she:

1. experienced a serious or intolerable adverse event

2. had laboratory safety assessments that revealed clinically significant hematological or biochemical changes from the baseline values

3. developed, during the course of the study, symptoms or conditions listed in the exclusion criteria

4. continuously consumed medications which were contraindicated during the course of the study

5. experienced a clinically significant deterioration due to progression of the primary disease, regardless of cause

6. incurred a protocol violation such as failure to comply with the specified dosage regime or failure to comply with the visit schedule

7. requested an early discontinuation due to
   a) a clinical event for which the investigator did not consider removal from the study to be necessary,
   b) perceived insufficient therapeutic effect,
   c) perceived sufficient therapeutic effect, or
   d) other (non-specific) subject-initiated cause.

The investigator was allowed to withdraw a subject from the study in the event that Snow Brand Pharmaceuticals, Inc. terminated the study.

Treatments Administered

Subjects were randomized to received placebo, 15 mg Cevimeline hydrochloride, or 30 mg Cevimeline hydrochloride *t.i.d.* for 12 weeks. Subjects were instructed to take the medication at the following times of day: 6 to 8 AM (first dose), 1 to 3 PM (second dose), and 7 to 9 PM (third dose).

Identity of Investigational Product(s)

White gelatin No. 3 capsules containing placebo, 15 mg SNI-2011, or 30 mg SNI-2011 plus

excipients, each identical in appearance, were provided by Snow Brand Pharmaceuticals, Inc. Yamanouchi Shaklee Pharma manufactured the capsules.

Subjects were randomly assigned to receive one of the following treatments three times a day for 12 weeks.

Lot Numbers of Capsules Used in Each Phase 3 Trial

	Placebo group	15-mg group	30-mg group
Trial SB96US02	H6K01	H6K02, H6K09 and H6K10	H6K03, H6K12, H6K13, and H6K14
Trial SB96US04	H6K01	H6K02, H6K09 and H6K10	H6K03, H7J01, H6K13, and H6K14

Reviewer's Comment: Note that one of the lots of the 30 mg capsules has replaced another as follows: In study SB96US04, lot H7J01 replaced lot H6K12. This is discussed later in this review as a potential explanation for difficulties in demonstrating efficacy in the second phase 3 trial.

Method of Assigning Subjects to Treatment Groups

Subjects were assigned at random, in the order in which they were enrolled into the study, to receive their allocated treatment according to a computer-generated randomization schedule prepared by ———— prior to screening. All test medication were blinded to both the subject and the investigator. Randomization was allocated using a block size of six. A global allocation of blocks to investigator sites was employed.

Selection and Timing of Dose for Each Subject

Subjects were asked to take the study medication at approximately the same times each day: 6 to 8 A.M. (first dose); 1 to 3 P.M. (second dose); and 7 to 9 P.M. (third dose). Subjects were instructed to refrain from taking one of their regularly scheduled doses on Visit days. Subjects with morning visits refrained from taking their morning dose until predose assessments were completed at the clinic. Subjects with afternoon visits refrained from taking their afternoon dose until predose assessments were completed at the clinic.

Blinding

All study medication used was made to appear indistinguishable. Both the investigators and the subjects were blinded to treatment assignment.

Concomitant Medication

If a subject had been receiving a drug, or drugs, for some period of time prior to the

commencement of the study, as a matter of absolute necessity for the treatment of a medical condition, then such medication was permitted for the duration of the study, at the discretion of the investigator. It was the responsibility of the investigator to ensure that all changes in medication for a subject already on medication, or the commencement of medication during the study for a subject not initially on such medication at the study commencement, were recorded in full in the case report form in a manner corresponding to the entries in the subject's hospital records.

The use of artificial saliva and tears was allowed during the study. Subjects were provided with daily diaries on which to collect information regarding the use of artificial saliva and tears, other medications, and liquid intake.

Prohibited Medication

Use of any anticholinergic agents or other medications known to alter xerostomia was prohibited throughout the study. Had it become necessary to use a prohibited medication during the course of the study, the subject would have been immediately withdrawn from the study and relevant details recorded on the case report form.

Treatment Compliance and Study Drug Accountability

Doses of medication other than the test medications were recorded as they were taken in the subjects' daily diaries. In addition, subjects returned all unused medication at the end of the study for an assessment of compliance.

It was the responsibility of the investigator to maintain accurate records of receipt of all test articles, including when and how much of each test article was dispensed to and used by each individual subject in the study. Reasons for departure from the expected dispensing regimen were also recorded. A Drug Dispensing Form was provided for this purpose. At the conclusion of the study, quantities of drug were reconciled with the dispensing documents, and the remaining drug was returned to the sponsor, or as otherwise indicated.

Primary Efficacy Variables

The primary efficacy endpoints in this study as stated in the protocol prior to commencing the trial were "the subjects' subjective global evaluation of the mouth, of the eyes, and overall." The subjects' global evaluation rated the overall condition of dry mouth, the overall condition of dry eyes, and the subjects' overall feeling toward his or her overall dryness condition compared with before the study as "worse," "no change," or "better."

Below are the questions that were asked by the sponsor as "global":

4. Please rate the overall condition of your dry mouth now compared with how you felt before starting treatment in this study.

   ☐ Worse ☐ No change ☐ Better

5. Please rate the overall condition of your dry eyes now compared with how you felt before starting treatment in this study.

   ☐ Worse ☐ No change ☐ Better

6. Please rate your overall feeling toward your overall dryness condition now compared with how you felt before starting treatment in this study.

   ☐ Worse ☐ No change ☐ Better

7. Please rate your overall feeling about continuing therapy for dryness symptoms with this investigational drug.

   ☐ Would definitely continue ☐ Might continue ☐ Would not continue

8. How many times per day have you used artificial saliva in the last few days?

   _____ per/day

9. How many times per day have you used artificial tears in the last few days?

   _____ per/day

Reviewer's Comment: "Global questions 4,5, and 6 are not stated as being either primary or secondary outcome variables. It is unclear why the sponsor has included them – one must assume for their own information only. Therefore, the results of these questions will not be discussed in this review.

Secondary Efficacy Variables

The secondary outcome variables include both the subject's subjective assessment of specific symptoms of dry mouth and dry eyes and the objective measures of total salivary flow and tear flow.

Total salivary flow was measured at each visit prior to dosing and at a minimum of 90 minutes after dosing. At each collection, the subject was instructed not to swallow but to allow the saliva to collect in the mouth for up to 5 minutes. The subject then expectorated the contents

of the mouth into a collection tube. The collection period lasted for a total of 15 minutes after which the collection tube was sealed and weighed. Since the specific gravity of saliva is approximately 1, the flow was recorded in mL/min.

Using a series of visual analogue scales, the subject evaluated the subjective secondary measures, which are shown below. For the subjective salivary measures, feeling of the mouth, dryness of the mouth, and dryness of the tongue were rated between "comfortable" and "extremely uncomfortable" and ability to speak without drinking liquids, ability to chew and swallow foods, and ability to sleep were rated between "easy" and "very difficult."

Feeling of the mouth	Comfortable	Extremely uncomfortable
Dryness of the mouth	Comfortable	Extremely uncomfortable
Dryness of the tongue	Comfortable	Extremely uncomfortable
Ability to speak without drinking liquids	Easy	Very difficult
Ability to chew and swallow foods	Easy	Very difficult
Ability to sleep	Easy	Very difficult

Artificial saliva use, artificial tear use, and average daily fluid intake in the last few days prior to a visit were recorded at each visit. These results and the changes from baseline were summarized descriptively by visit as well as at the endpoint. For testing purposes, the results of these parameters were categorized as "decrease," "no change," or "increase" from baseline.

Reviewer's Comment: The labeled guides at either end of the scales are not well-balanced. For the first three, either the right side should say "uncomfortable" or the left side should

state, "extremely comfortable." For the last three, either "very easy" should substitute for "easy" or difficult should substitute for "very difficult" for the same reason. As currently written, even a modest improvement may result in a significant movement to the left due to this imbalance.

Safety Variables

The incidence of adverse events during the study and changes in laboratory test results, vital sign measurements, ECGs, and physical and ophthalmologic examinations were the primary safety variables in this study.

Statistical Plan:

Efficacy Analysis

A closed-family, step-down procedure to protect alpha levels was adopted (Tamhane, Hochberg, Dunnett. Multiple Test Procedures for Dose Finding. *Biometrics* 52, 21-37. March 1996.) The procedure is designed to identify the least significant dose. Under this method, first the analysis between 30 mg *t.i.d.* vs. placebo is performed, at the alpha=0.05 significance level. Only if that comparison achieves significance does one proceed to examine the analysis between 15 mg *t.i.d.* verses placebo, also at alpha=0.05. Due to this alpha-level adjustment procedure for multiple testing, the p-value from the test between placebo and 15 mg *t.i.d.* is only presented if the p-value from the corresponding test between 30 mg *t.i.d.* and placebo achieved significance.

Subjects providing evaluations at the baseline visit and at one or more post-baseline visits were included in the efficacy analysis. The primary efficacy variables were the subject's subjective global evaluations of dryness of the mouth, dryness of the eyes, and overall dryness. These categorical measures were analyzed using contingency table analysis methods.

All patients who were dispensed drug but dropped out prior to an efficacy evaluation were considered as "Worse" in the primary endpoint analyses. Of primary interest was change from baseline (Week 0 visit predose assessment, if available, or screening assessment) to the final assessment. For each patient, the last non-missing postdose observation was carried forward (LOCF) in the analyses. The primary timepoint was the Final Value (LOCF) or the Final Visit (last available on treatment visit where both pre- and postdose values were collected).

The secondary efficacy variables included assessments of the specific symptoms of dry mouth and dry eyes and the objective measures of salivary flow and tear flow. Change from baseline were analyzed for these secondary efficacy variables, including an analysis of change from

baseline at each visit, and an endpoint analysis based on the last available visit assessment. ANOVA techniques were to be used for these analyses, unless the underlying assumptions for ANOVA were found to be inappropriate (e.g., homogeneity of variance), in which case alternative methods or transformations were to be used. (Refer to statistics review for details.)

Safety Analysis

Adverse events (the number and percentage of subjects experiencing an event) were summarized by body system and preferred term. Statistical comparisons of adverse events were performed based upon the differences among dosage groups or subject subgroups in the incidence of adverse events. For the Sjögren's syndrome placebo-controlled studies, comparisons were made between placebo and each active dose, as well as between placebo and all active doses combined for: overall adverse events, adverse events related to study drug, and adverse events resulting in discontinuation of study drug. Between-treatment comparisons of the differences in proportions of subjects with adverse events were performed for the Sjögren's syndrome placebo-controlled studies.

Clinical laboratory tests, physical and ophthalmologic examination, vital sign measurements, and changes in 12-lead ECG values were summarized with descriptive statistics and analyzed for significance of within-treatment change from baseline.

Change from baseline at assessment timepoints and at end point were analyzed for statistical significance by treatment group, using a paired t-test or a signed rank test, as appropriate. For safety assessments based on the change from Baseline to Endpoint, Endpoint was defined as the last non-missing, on-treatment observation for each subject.

Amendments to Protocol SB96US02

The following amendments were made to the originally proposed protocol.

1. Originally, the inclusion criteria stated that "the patient is over 18 years old and under 70 years old". This was formally changed on June 11, 1997 in a protocol amendment to "the patient is between 18 and 75 years old, inclusive."

2. In the definition of Primary Sjögren's in the inclusionary criteria of the original protocol for SB96US02, it stated the following: "Positive anti-Ro/SS-A, anti-La/SS-B antibodies, rheumatoid arthritis (RA), and/or documented history of such in patient's medical records." This was changed to: "Positive anti-Ro/SS-A, anti-La/SS-B antibodies, rheumatoid factor (RF), and/or documented history of such in patient's medical records, and/or positive anti-nuclear antibodies (ANA) of 1:160 or greater at the time of screening as indicated on the laboratory assessment performed at the screening visit."

3. Under the definition of Secondary Sjögren's, the original protocol stated, "Positive ANA and/or RA antibodies and/or other evidence of accompanying rheumatoid arthritis or other connective tissue disease." It was revised to "Positive ANA of 1:160 or greater at screening as indicated on the laboratory assessments performed at the screening visit and/or RF antibodies or other evidence of accompanying rheumatoid arthritis or other connective tissue disease."

4. Under the exclusion criteria, the original protocol stated: "Patient was suspected to have physical closure of the salivary glands or surgical closure of the lacrimal punctum (permanent or temporary closure)." It was modified to "Patient had suspected physical closure of the salivary glands."

5. Under the exclusion criteria, the original protocol stated "The patient has a significant history of gastrointestinal disorders (hepatic, pancreatic, gastroduodenal ulcers, or hyperspastic bowel diseases). It was formally shortened in a submission dated April 3, 1997, for both phase 3 trials and the open-label trial to "Patient had a gastroduodenal ulcer at the time of enrollment or had one within the past year."

6. Initially, the primary efficacy analysis was to include both objective and subjective endpoints. After meeting with the division for an End-of-Phase 2 meeting, the objective measures were changed to secondary efficacy variables. Initially, the following was proposed:

   "Subjects providing evaluations at the baseline visit and at one or more post-baseline visits will be included in the efficacy analysis of the three treatment groups. When deemed appropriate, transformation of continuous measurements will be used (e.g. logarithmic transformation). Changes form baseline will be analyzed. Pairwise comparisons will be used. The comparisons at each post-baseline visit will be based on available measurements. There will also be a final value analysis based on the last visit measurement.

   The primary efficacy variables will be the subjective measurement of the subject's global evaluation and the changes in objective measure of salivary flow from predose to postdose. The subjective dry mouth and eyes symptom assessment will be analyzed using analysis of variance. If underlying assumptions for analysis are deemed inappropriate, e.g. non-homogeneity of variances, then alternative methods will be used. The categorical measurements such as subjective global evaluation will be analyzed using contingency table data analysis."

An amendment dated 2/11/97 changed the analysis to the following:

Patients providing evaluations at the baseline visit and at one or more post-baseline visits will be included in the efficacy analysis. The primary efficacy variables will be the patient's subjective global valuations of dryness of the mouth, dryness of the eyes, and overall dryness. These categorical measures will be analyzed using contingency table analysis methods.

The secondary efficacy variables will be the assessments of the specific symptoms of dry mouth and dry eyes and the objective measures of salivary flow and tear flow (using Schirmer's test). Change form baseline will be analyzed for these secondary efficacy variables. There will be an analysis of change form baseline at each visit, and an endpoint analysis based on the last available visit assessment. ANOVA techniques will be used for these analyses. If the underlying assumptions for ANOVA are found to be inappropriate (e.g., homogeneity of variance, then alternative methods or transformations will be used.

Reviewer's Comment: According to the sponsor, these protocol changes were all made prior to breaking the blind. All of these changes are acceptable; however, amendments #2 and 3, which change the definitions of primary and secondary Sjogren's syndrome, are not clear. Refer to the discussion section of this review for further explanation.

Results

Baseline Characteristics

The table on the following page shows the baseline characteristics of the subjects enrolled in this trial.

Baseline Characteristic		SB95US02		
		15 mg (n=65)	30 mg (n=62)	Placebo (n=70)
Sex n (%)	Female	61 (93.8)	59 (95.2)	67 (95.7)
	Male	4 (6.2)	3 (4.8)	3 (4.3)
Age (years)	Minimum	23	32	31
	Maximum	73	74	74
	Mean	54.2± 12.4	54.6± 10.8	54.3± 10.6
Race n (%)	Caucasian	59 (90.8)	56 (90.3)	65 (92.9)
	Black	2 (3.1)	3 (4.8)	1 (1.4)
	Hispanic	4 (6.2)	1 (1.6)	3 (4.3)
	Asian	0 (0)	2 (3.2)	0 (0)
	Other	0 (0)	0 (0)	1 (1.4)
Diagnosis of Sjögren s Syndrome	Primary	36 (55.4)	35 (56.5)	43 (61.4)
	Secondary	29 (44.6)	27 (43.5)	27 (38.6)

All three groups are comparable in their baseline characteristics. A larger percentage of subjects assigned to placebo had primary Sjögren's syndrome compared to the 15 mg or 30 mg groups, but it was not a statistically significant difference.

SEVERITY OF DRY MOUTH AT BASELINE: STUDY SB96USO2

	SNI-2011							
	Placebo (N=70)		15 mg t.i.d. (N=65)		30 mg t.i.d. (N=62)		Total (N=197)	
SEVERITY	N	%	N	%	n	%	n	%
Mild	15	21.4	13	20.0	25	40.3	53	26.9
Moderate	39	55.7	34	52.3	28	45.2	101	51.3
Severe	14	20.0	18	27.7	9	14.5	41	20.8
Missing	1	1.4	0	0.0	0	0.0	1	0.5
No symptoms	1	1.4	0	0.0	0	0.0	1	0.5

Of note in the comparison between groups of the severity of dry mouth at baseline is that the 30 mg group is skewed towards milder symptoms. Refer to the discussion section of this review for the potential effect of this finding on efficacy results.

Primary Outcome variable

SUBJECT GLOBAL EVALUATION OF DRY MOUTH – SB96US02

	Better (%)			No Change (%)			Worsening (%)		
		SNI-2011			SNI-2011			SNI-2011	
Evaluation Visit	Placebo	15 mg	30 mg	Placebo	15 mg	30 mg	Placebo	15 mg	30 mg
Week 0	27.9	29.7	37.7	69.1	68.8	62.3	2.9	1.6	0.0
Week 3	43.1	46.6	67.3	56.9	51.7	32.7	0.0	1.7	0.0
Week 6	37.7	50.0	74.5	55.7	48.2	25.5	6.6	1.8	0.0
Week 9	39.3	48.1	73.5	55.7	50.0	24.5	4.9	1.9	2.0
Week 12	39.3	43.1	68.8	60.7	51.0	31.3	0.0	5.9	0.0
Final Value	37.1	44.6	66.1	57.1	47.7	33.9	5.7	7.7	0.0

	p-value			
	Overall	Placebo vs. 15 mg	Placebo vs. 30 mg	15 mg vs. 30 mg
Week 0	0.1471	ND	0.1119	0.2606
Week 3	0.0114*	0.7940	0.0122*	0.0247*
Week 6	0.0001*	0.1459	0.0001*	0.0178*
Week 9	0.0006*	0.2319	0.0008*	0.0301*
Week 12	0.0069*	0.6778	0.0041*	0.0050*
Final Value	0.0007*	0.6216	0.0004*	0.0056*

ND = Not Done
*values indicate significance at $p < 0.05$.
The primary timepoint was the Final Value (LOCF) or the Final Visit (last available on treatment visit where both pre- and postdose values were collected).

The sponsor's three primary outcome variables were global assessments of mouth dryness, eye dryness, and overall dryness. The global evaluations were performed at each visit one hour following administration of the study medication. These data were summarized as the percentage of subjects who reported feeling better, worse, or feeling no change at the time that the evaluations were made compared to the percentages reporting the same at baseline for each of the three variables. Because "overall dryness" is not a meaningful endpoint that would be allowed on the label (See earlier "Regulatory History" section of this review), those results will not be presented in this review. The remainder of the *Results* section in this review will only discuss the outcome measurements that pertain to the dry mouth indication.

At each visit, more subjects who received active drug reported a response of "better" in the subject global evaluation of dry mouth than subjects who received placebo. The difference among treatment groups in the numbers of subjects reporting responses of "better", "no change", and "worse" was statistically significant at every time point except Week 0, the visit

during which subjects took their first dose of test medication. At the Final Value 45% of the subjects who received 15 mg SNI-2011 *t.i.d.* and 66% of the subjects who received 30 mg SNI-2011 *t.i.d.* reported a response of "better" compared with 37% of the subjects who received placebo (p=0.0007). At no point during the trial did the 15 mg group achieve a significantly better global evaluation than the placebo group. At the pre-determined point that the primary efficacy endpoint was defined, which the sponsor calls "Final Value" (each subject's endpoint postdose reading), there was a statistically significant difference between the placebo and the 30 mg group (p=0.0004) and the 15 mg and 30 mg groups (p=0.0056). Specifically, at each visit:

At Week 3 visit, 47% of the subjects who received 15 mg SNI-2011 *t.i.d.* and 67% of the subjects who received 30 mg SNI-2011 *t.i.d.* reported a response of "better" compared with 43% of the subjects who received placebo (p=0.0114). At Week 3 there was also a statistically significant difference between the placebo and the 30 mg group (p=0.0122) and the 15 mg and 30 mg groups (p=0.0247).

At Week 6 visit, 50% of the subjects who received 15 mg SNI-2011 *t.i.d.* and 75% of the subjects who received 30 mg SNI-2011 *t.i.d.* reported a response of "better" compared with 38% of the subjects who received placebo (p=0.0001). At Week 6 there was also a statistically significant difference between the placebo and the 30 mg group (p=0.0001) and the 15 mg and 30 mg groups (p=0.0178).

At Week 9 visit, 48% of the subjects who received 15 mg SNI-2011 *t.i.d.* and 74% of the subjects who received 30 mg SNI-2011 *t.i.d.* reported a response of "better" compared with 39% of the subjects who received placebo (p=0.0006). At Week 9 there was also a statistically significant difference between the placebo and the 30 mg group (p=0.0008) and the 15 mg and 30 mg groups (p=0.0301).

At Week 12 visit, 43% of the subjects who received 15 mg SNI-2011 *t.i.d.* and 69% of the subjects who received 30 mg SNI-2011 *t.i.d.* reported a response of "better" compared with 39% of the subjects who received placebo (p=0.0069). At Week 12 there was also a statistically significant difference between the placebo and the 30 mg group (p=0.0041) and the 15 mg and 30 mg groups (p=0.0050).

In all visits subsequent to Week 0, the 30 mg group had a statistically significant improvement compared to placebo in the global evaluation of dry mouth. For the 15 mg group, although the differences were not statistically significant compared to placebo, a better efficacy was evident regarding the global evaluation of dry mouth, as a higher percentage of subjects were responding "better".

Refer to the Discussion section of this review for comments on these results.

Secondary Outcome Variables

Secondary outcome variables include additional subjective measures of dry mouth as measured on a VAS as well as objective measures of salivary flow.

Subjective Measures

SUMMARY OF CHANGES FROM BASELINE IN SUBJECTS' VISUAL ANALOGUE SCALE (MM) ASSESSMENT OF DRY MOUTH SYMPTOMS AT ENDPOINT (STUDY NO. SB96US02)

Symptom	Mean ± SD			p-value			
	P	Cevimeline					
		15 mg *t.i.d.*	30 mg *t.i.d.*	Overall	P vs. 15 mg	P vs. 30 mg	15 mg vs. 30 mg
Feeling of mouth	-12.2 ± 30.2	-13.4 ± 27.5	-22.3 ± 30.0	0.0816*	0.8752	0.0428*	0.0613
Dryness of mouth	-15.0 ± 33.4	-17.7 ± 25.5	-27.0 ± 30.4	0.0904*	0.7121	0.0389*	0.0880
Dryness of tongue	-11.8 ± 30.8	-16.8 ± 24.2	-21.9 ± 31.5	0.1908	0.4034	0.0693	0.3158
Ability to speak without drinking	-6.2 ± 26.7	-12.5 ± 25.8	-17.3 ± 22.4	0.0426*	0.1538	0.0125*	0.2827
Ability to chew and swallow food	-13.7 ± 26.6	-11.9 ± 24.5	-16.4 ± 24.8	0.5370	0.9301	0.3511	0.3164
Ability to sleep	-0.3 ± 23.9	-7.0 ± 24.7	-9.5 ± 28.5	0.1875	0.2003	0.0780	0.6264

*values are significant at $p < 0.05$

The first VAS assessments were completed at baseline prior to subjects receiving their first dose of test article. One hour after dosing, VAS assessments were repeated. This same pattern of VAS assessments prior to dosing and one hour after dosing was performed during the visits of Weeks 3, 6, 9, and 12. The following symptoms of dry mouth were assessed: feeling of mouth, dryness of mouth, dryness of tongue, ability to speak without drinking, ability to chew and swallow food, and ability to sleep. Subjects were asked to make a mark along a 100 mm line labeled at each end with the worst outcome on the right (i.e., "extremely uncomfortable") and the best on the left (i.e., "comfortable"). Each of these six variables associated with subjective feelings of dry mouth can be examined for significant changes throughout the trial.

None of the differences in the parameters between the 15 mg and the placebo group were significant. The differences in values between the baseline value (pre-dose Week 0) and the last visit (Final value post-dose) are shown in the table above. Note that significantly (or borderline significantly) greater improvement in all of these parameters except for the ability to chew and swallow food was observed in those subjects receiving 30 mg of the drug when

compared to those subjects receiving placebo. See the discussion section of this review for an analysis of these findings.

The sponsor also examined changes from baseline for each of these subjective variables at each visit. Care must be exercised in reaching any conclusions from the p-values that are reported in the following section. Because there were five visits during the course of the trial with both pre and post-dose measurements recorded, a total of ten p-values are given for each comparison. Four comparisons are made at each timepoint, i.e., overall, placebo vs. 15 mg, placebo vs. 30 mg, and 15 mg vs. 30 mg, giving a total of 40 comparisons per variable. The sponsor made no adjustments in p-values for the multiple comparisons.

Feeling of the mouth

When the change from Baseline in the assessment of feeling of the mouth was compared among the treatment groups at each visit, there was a statistically significant improvement in two of the 40 comparisons. At Week 12, the improvement from baseline in the 30 mg group was significantly greater than the improvement from baseline of the placebo group (p=0.0472). At the endpoint measurement, the improvement from baseline in this same variable was greater in the 30 mg SNI-2011 *t.i.d.* group than the placebo group (p=0.0428). None of the differences in improvements between the placebo and 15 mg groups were significant.

Dryness of mouth:

When the change from Baseline in the assessment of dryness of the mouth was compared among the treatment groups at each visit, there was a statistically significant improvement in three of the 40 comparisons. At Week 12, the improvement from baseline in the 30 mg group was significantly greater than the improvement from baseline of the placebo group (p=0.0132). At the endpoint measurement, the improvement from baseline in this same variable was greater in the 30 mg SNI-2011 *t.i.d.* group than the placebo group (p=0.0389). None of the differences in improvements between the placebo and 15 mg groups were significant.

Dryness of tongue

When the change from Baseline in the assessment of dryness of the tongue was compared among the treatment groups at each visit, there was a statistically significant improvement in four of the 40 comparisons. At Weeks 3, 6, 9 and 12, the improvement from baseline in the 30 mg group was significantly greater than the improvement from baseline of the placebo group (p=0.0358, 0.0379, 0.0325, and 0.0322, respectively). None of the differences in improvements between the placebo and 15 mg groups were significant.

Ability to speak without drinking

When the change from Baseline in the assessment of ability to speak without drinking was compared among the treatment groups at each visit, there was a statistically significant improvement in two of the 40 comparisons. At Week 12, the improvement from baseline in the 30 mg group was significantly greater than the improvement from baseline of the placebo group (p=0.0407). At the endpoint measurement, the improvement from baseline in this same variable was greater in the 30 mg SNI-2011 *t.i.d.* group than the placebo group (p=0.0125). None of the differences in improvements between the placebo and 15 mg groups were significant.

Ability to chew and swallow food

Examination of this variable yielded no statistically significant differences between any of the groups.

Ability to sleep

This variable was only measured at the pre-dose assessment for each visit, resulting in a total of 20 comparisons. When the change from Baseline in the ability to sleep was compared among the treatment groups at each visit, there was a statistically significant improvement in two of the 20 comparisons. At Week 9, the improvement from baseline in the 30 mg group was significantly greater than the improvement from baseline of the placebo group (p=0.0322). At Week 12, the improvement from baseline in this same variable was greater in the 30 mg SNI-2011 *t.i.d.* group than the placebo group (p=0.0461). None of the differences in improvements between the placebo and 15 mg groups were significant.

Improvement from baseline generally favored the treatment groups compared to the placebo for the other parameters where no statistically significant differences were found. Refer to the Discussion section of this review for significance of results, including the multiple comparison issue.

Comparison of pre and post dose

A comparison was also performed between changes in these secondary outcome variables during each visit, between the VAS result prior to administration of medication and one hour afterwards. There were no statistically significant differences among treatment groups for the changes between predose and postdose assessments in most of the visits. The table below provides the comparisons during the final visit.

SUMMARY OF CHANGES FROM PREDOSE TO POSTDOSE IN SUBJECTS' VISUAL ANALOGUE SCALE (MM) ASSESSMENT OF DRY MOUTH SYMPTOMS AT FINAL VISIT (STUDY NO. SB95US02)

Symptom	Mean ± SD			p-value			
	P	Cevimeline					
		15 mg *t.i.d.*	30 mg *t.i.d.*	Overall	P vs. 15 mg	P vs. 30 mg	15 mg vs. 30 mg
Feeling of mouth	-6.9 ± 17.0	-3.9 ± 18.2	-6.1 ± 17.4	0.6169	0.3493	0.8618	0.4626
Dryness of mouth	-9.2 ± 19.0	-5.3 ± 16.2	-7.0 ± 16.1	0.4070	0.1807	0.5185	0.5044
Dryness of tongue	-7.0 ± 17.5	-5.4 ± 16.5	-8.0 ± 16.1	0.6939	0.6134	0.7081	0.3954
Ability to speak without drinking	-3.0 ± 15.4	-4.7 ± 14.3	-3.8 ± 15.2	0.5165	0.3597	0.8516	0.2872
Ability to chew and swallow food	-7.5 ± 14.8	-2.1 ± 14.0	-5.2 ± 16.9	0.4890	0.2896	0.3255	0.9456

No statistically significant differences between predose and postdose values for any of the variables were noted among treatment groups at final visit. Examination of the predose and postdose comparisons at the other visits showed one significant outcome - at Week 6, there was a statistically significant improvement from predose to postdose between the placebo and 15 mg cevimeline groups in the ability to speak without drinking (p=0.0416). However, as was noted in the prior section of this review in which changes from baseline were reported for each visit – a large number of comparisons are being made for each symptom studied. With four comparisons per visit (overall, placebo vs. 15 mg, placebo vs. 30 mg, and 15 mg vs. 30 mg), and a comparison at each of the five visits plus the final value, 24 comparisons are being made for each symptom. Refer to the discussion section for comments on how this influences the results.

Salivary Flow Measurement

Salivary flow was measured at baseline, the Week 6 visit, and the Week 12 visit. For the Week 6 and Week 12 visit, two salivary flows were recorded – one prior to dosing and the other at a minimum of 90 minutes after dosing. The table below reports the mean salivary flow at each of the visits. At week 6 and week 12, the change between the pre and post dose values is calculated. P-values were calculated for the following comparisons: overall, placebo vs. 15 mg, placebo vs. 30 mg, and 15 mg vs. 30 mg. At both the Week 6 and Week 12 visits, the increase in postdose over predose values in the 15 mg group was greater than the change in the placebo group. Also at both visits, the increase in postdose values was greater in the 30 mg group than the 15 mg group. Although the 15 mg group's improvement from predose was superior to placebo's, the difference was not statistically significant at either time point.

SALIVARY FLOW MEASUREMENT in ml/min - SB96US02

		Mean ± SD			ANOVA p-value			
			SNI-2011					
Visit	Assess -ment	Placebo	15 mg t.i.d.	30 mg t.i.d.	Overall	Placebo vs. 15 mg	Placebo vs. 30 mg	15 mg vs. 30 mg
Screen	Baseline	0.067 ± 0.074	0.059 ± 0.077	0.075 ± 0.071				
Week 6	Predose	0.088 ± 0.103	0.11 ± 0.139	0.156 ± 0.211				
	Postdose	0.112 ± 0.139	0.173 ± 0.205	0.284 ± 0.373				
	Change	0.023 ± 0.054	0.060 ± 0.129	0.129 ± 0.191	0.0011*	0.1483	0.0002*	0.0217*
Week 12	Predose	0.099 ± 0.142	0.082 ± 0.092	0.169 ± 0.212				
	Postdose	0.143 ± 0.175	0.134 ± 0.153	0.290 ± 0.416				
	Change	0.041 ± 0.095	0.050 ± 0.080	0.115 ± 0.284	0.0824	0.4980	0.0278*	0.1359
Final Visit*	Predose	0.095 ± 0.138	0.090 ± 0.104	0.165 ± 0.213				
	Postdose	0.132 ± 0.168	0.138 ± 0.156	0.277 ± 0.402				
	Change	0.037 ± 0.091	0.047 ± 0.077	0.112 ± 0.273	0.0246*	0.3074	0.0068*	0.0933
Final Value*	Postdose	0.132 ± 0.168	0.138 ± 0.156	0.277 ± 0.402				

The primary timepoint was the Final Value (LOCF) or the Final Visit (last available on treatment visit where both pre- and postdose values were collected).
* values are significant at $p < 0.05$

The change from baseline to each visit's predose and postdose value was also computed and compared among groups in order to help adjust for the differences in baseline values for each group (Refer to the table below). P-values were then computed for the comparisons between the 15 mg and 30 mg group to the placebo group of improvements in salivary flow between the baseline and post-dose measurements. At both visits, the improvement in salivary flow in the 30 mg group was significantly greater than the improvement in salivary flow in the placebo group. The 15 mg group showed an improvement in salivary flow that was significantly greater than the improvement in salivary flow in the placebo at the Week 6 visit, but identical improvements were seen at the Week 12 visit.

SUMMARY OF CHANGE FROM BASELINE* TO POSTDOSE IN OBJECTIVE SALIVARY FLOW (ML/MIN) MEASUREMENTS – SB96US02

		Mean ± SD						
			SNI-2011		*ANOVA p-value			
Visit	Assessment	Placebo	15 mg t.i.d.	30 mg t.i.d.	Overall	Placebo vs. 15 mg	Placebo vs. 30 mg	15 mg vs. 30 mg
Week 6	Predose	0.018 ± 0.094	0.054 ± 0.123	0.083 ± 0.201				
	Postdose	0.042 ± 0.126	0.113 ± 0.182	0.219 ± 0.355	0.0001	0.0190	0.0001	0.0570
Week 12	Predose	0.030 ± 0.131	0.022 ± 0.065	0.096 ± 0.192				
	Postdose	0.073 ± 0.162	0.073 ± 0.122	0.216 ± 0.394	0.0097	0.9743	0.0175	0.0157
Final Value	Postdose	0.064 ± 0.155	0.078 ± 0.133	0.205 ± 0.380	0.0035	0.6091	0.0070	0.0195

*Change from Baseline = Post-Baseline – Baseline Value
Data extracted from end-of-text Table 8.2.

Refer to the discussion section of this review for comments about the significance of these salivary flow results.

Use Of Artificial Saliva And In Fluid Intake

Overall, there was a greater reduction from baseline in the use of artificial saliva and in fluid intake for subjects who received 30 mg of Cevimeline tid compared with those who received placebo. At all the Weeks (3, 6, 9, and 12) higher percentages of patients in the 30 mg Cevimeline tid group decreased their use of artificial saliva than patients in the other treatment groups, but the differences were not found to be statistically significant. By Week 12, 13% of the patients in the 30 mg Cevimeline tid group decreased use of artificial saliva compared with 10% of the patients in the 15 mg group and 11% of the patients in the placebo group

Adverse Events

The adverse events profile for this first phase 3 trial will be examined in detail in this section of the review. There will be an identical section in this review following the results section of the second phase 3 trial in which the adverse events for that trial will be presented. In this way, the adverse events can be examined separately to uncover any potential differences in profile between trials. Generally, the label of an approved drug provides only one adverse events profile for the drug which is based upon the integrated results for all relevant trials. Therefore, a separate section of this review will present the integrated safety report, which will include not only a combined adverse events presentation, but also the results from the physical examinations and laboratory testing conducted during all trials. That section of this

review will follow the open label studies section.

Subjects received three doses of study medication per day for 12 weeks. Of the 197 subjects enrolled in this trial, 70 subjects took placebo, 65 subjects were assigned to the 15 mg *t.i.d.* dosage, and 62 subjects took the proposed dose of 30 mg *t.i.d.*.

Incidence of Adverse Events

Of the 197 subjects enrolled in this study, 162 (82%) were reported to have experienced at least one adverse event (See table below). At least one adverse event was experienced in 89% of the subjects in the 30 mg group, followed by 82% in the 15 mg group and 77% in the placebo group. A low incidence of serious adverse events occurred for all treatments: placebo (3%), 15 mg (2%), and 30 mg (2%). Subjects discontinued due to an adverse event are lowest in the placebo group (4%), followed by 15 mg (14%) and 30 mg (16%) treatments. Drug-related adverse events occurred more frequently in the 30 mg group (48%), followed by 15 mg (31%) and placebo (26%) groups. The number of subjects experiencing an adverse event considered severe in intensity was comparable between treatments: placebo (10%), 15 mg (8%), and 30 mg (10%).

INCIDENCE OF ADVERSE EVENTS – SB96US02

	Placebo	SNI-2011	
		15 mg *t.i.d.*	30 mg *t.i.d.*
Number of subjects evaluable for safety	70 (100.0%)	65 (100.0%)	62 (100.0%)
Number subjects with at least one adverse event	54 (77.1%)	53 (81.5%)	55 (88.7%)
Number of subjects with no adverse events	16 (22.9%)	12 (18.5%)	7 (11.3%)
Number of subjects with serious adverse events	2 (2.9%)	1 (1.5%)	1 (1.6%)
Number of subjects discontinued due to adverse event	3 (4.3%)	9 (13.8%)	10 (16.1%)
Number of subjects with drug-related adverse events	18 (25.7%)	20 (30.8%)	30 (48.4%)
Number of subjects with an adverse event of severe intensity	7 (10.0%)	5 (7.7%)	6 (9.7%)

Data extracted from end-of-text Table 10.1.

Four body systems that had differences in occurrence between treatment groups were central and peripheral nervous system, gastrointestinal, skin and appendages, and urinary system. Significant differences between placebo and the 30 mg dose occurred in gastrointestinal ($p = 0.0292$) and urinary system ($p = 0.0298$). Significant differences occurred between the 15 mg and 30 mg doses for central and peripheral nervous system ($p = 0.0406$) and skin and appendages ($p = 0.0196$). All other adverse events occurred in comparable numbers among the three treatment groups with no discernible trends for one treatment having more adverse events than any other. As is typical of cholinergic drugs, cevimeline's adverse event profile is

largely predictable, especially upon closer examination in the following table, which includes reports by incidence of ≥ 4 subjects in any one treatment group, in descending order of occurrence. Many of the frequently reported adverse events were expected due to the expected pharmacological effect of the study medication, e.g., increased sweating, abdominal pain, diarrhea, and nausea. It is noteworthy that statistically significant increases in the frequency of adverse events were uncovered when comparing the 30 mg group to the placebo group for the following: nausea, increased sweating, urinary tract infection, and vertigo. Refer to the discussion section for interpretation of these results.

INCIDENCE OF ADVERSE EVENTS REPORTED BY ≥ 4 SUBJECTS – SB96US02

ADVERSE EVENT WHOART PREFERRED TERM	Placebo N = 70		SNI-2011				Significant Difference	p value
			15 mg *t.i.d.* N = 65		30 mg *t.i.d.* N = 62			
	n	%	n	%	n	%		
Headache	11	15.7	5	7.7	11	17.7		
Nausea	5	7.1	8	12.3	13	21.0	Placebo vs 30 mg	0.0209
Diarrhea	5	7.1	9	13.9	10	16.1		
Sinusitis	11	15.7	3	4.6	8	12.9	Placebo vs 15 mg	0.0346
Sweating increased	1	1.4	3	4.6	11	17.7	Placebo vs 30 mg 15 mg vs 30 mg	0.0011 0.0182
Dizziness	5	7.1	3	4.6	5	8.1		
Pharyngitis	4	5.7	7	10.8	2	3.2		
Upper respiratory tract infection	3	4.3	4	6.2	6	9.7		
Rhinitis	2	2.9	4	6.2	6	9.7		
Abdominal pain	4	5.7	6	9.2	2	3.2		
Urinary tract infection	0	0.0	4	6.2	6	9.7	Placebo vs 30 mg	0.0094
Dyspepsia	3	4.3	3	4.6	3	4.8		
Rash	6	8.6	2	3.1	1	1.6		
Pain	1	1.4	5	7.7	3	4.8		
Conjunctivitis	4	5.7	2	3.1	2	3.2		
Xerophthalmia	4	5.7	3	4.6	0	0.0		
Inflicted injury	3	4.3	1	1.5	2	3.2		
Hypertonia	1	1.4	2	3.1	3	4.8		
Skeletal pain	0	0.0	4	6.2	2	3.2		
Coughing	2	2.9	1	1.5	2	3.2		
Chest pain	1	1.4	3	4.6	1	1.6		
Saliva increased	0	0.0	1	1.5	4	6.5	Placebo vs 30 mg	0.0462

Salivary gland enlargement	1	1.4	2	3.1	2	3.2		
Surgical intervention	3	4.3	1	1.5	1	1.6		
Vision abnormal	3	4.3	0	0.0	2	3.2		
Lymphadenopathy cervical	0	0.0	3	4.6	2	3.2		
Vomiting	1	1.4	2	3.1	2	3.2		
Back pain	2	2.9	1	1.5	1	1.6		
Fever	1	1.4	2	3.1	1	1.6		
Vertigo	0	0.0	0	0.0	4	6.5	Placebo vs 30 mg	0.0462
Sialoadenitis	1	1.4	3	4.6	0	0.0		
Stomatitis ulcerative	1	1.4	1	1.5	2	3.2		
Arthropathy	1	1.4	3	4.6	0	0.0		
Anxiety	3	4.3	0	0.0	1	1.6		
Infection fungal	1	1.4	0	0.0	3	4.8		
Bronchitis	2	2.9	2	3.1	0	0.0		
Micturition frequency	1	1.4	1	1.5	2	3.2		

Severe Adverse Events, Serious Adverse Events and Events Resulting in Discontinuation

Severe adverse events occurred in 29 subjects during the study. Thirteen occurred in the placebo group, 11 in the 30 mg subjects and five in the 15 mg group. The most common severe adverse event was headache with a total of 4 subjects representing all treatment groups, followed by nausea with all 3 subjects in the 30 mg group, and 2 subjects reporting abdominal pain, one in the placebo and one in the 15 mg treatment group. All other adverse events considered severe in intensity occurred a single time.

Four events occurred during this study that met the serious adverse event criteria. Two occurred in placebo subjects and one each occurred in the 15 and 30 mg treated subjects. The two serious adverse events that occurred on placebo were severe shoulder pain secondary to surgery, and a psychiatric disturbance labeled "nervous breakdown." One subject in the 30 mg group reported blurry vision, and an inflamed salivary gland and one subject in the 15 mg group reported an inflamed salivary gland. Although both events resolved without incident and both subjects continued in the trial without further incident, a relationship between medication and these events cannot be ruled out.

A total of 22 subjects (11%) discontinued from the study prematurely because of an adverse event. Three (4%) subjects in the placebo group, 9 (14%) subjects in the 15 mg group, and 10 (16%) subjects in the 30 mg group discontinued from the study. The most frequently reported adverse events causing discontinuation were chest pain and diarrhea. The three chest pain withdrawals occurred in two 15 mg subjects and one 30 mg subject. Both withdrawals due to

diarrhea occurred in 15 mg subjects. There was a single incidence of all other adverse events resulting in trial discontinuation.

Related Events

Sixty-five patients in the 30 mg treatment group, 40 in the 15 mg group, and 33 in the placebo group experienced adverse events that were expected with cholinergic drugs. The most common drug related adverse events in decreasing order were nausea, increased sweating, headache, dizziness, diarrhea, abdominal pain and increased saliva.

Study SB96US04

Protocol Design

The second phase 3 trial, SB96US04, is nearly identical in design to the first phase 3 trial, SB96US02. To avoid repetition in this review, identical sections will be noted, and the reader will be referred to study SB96US02 for details. Sections of P96US04 that are different from US02 will be presented in detail, including an enumeration of the changes.

Phase 3

Title A Double-Blind, Randomized, Placebo-Controlled Study of SNI-2011 (15 MG and 30 mg *t.i.d.*) Vs. Placebo in Sjögren's Syndrome Patients with Xerostomia

Objectives

Same as SB96US02

Principal Investigators and Associated Study Sites:

INVESTIGATORS AND INVESTIGATIONAL SITES

SITE NUMBER	NAME OF INVESTIGATOR	ADDRESS OF INVESTIGATIONAL SITE	TOTAL NUMBER OF SUBJECTS ENROLLED
4	Garry E. Bayliss, MD	Lewis-Gale Clinic 1802 Braeburn Dr. Salem, VA 24153	0
59	Beverly A. Carpenter, MD	Tri-State Arthritis and Osteoporosis Center, P.S.C. 1150 W. 8th St. Suite 120 Cincinatti, OH 45203	1
9	Walter Chase. MD, PA	1301 W. 38th St., #609 Austin, TX 78705	9
12	Julian A. Colton, MD	SYNERGY in Clinical Research, Inc. 6950 Central Avenue, Suite 100 St. Petersburg, FL 33707	8
15	Francis Dega, MD	999 N. Curtis, Suite 512 Boise, ID 83706	25
16	Robin K. Dore, MD	1120 W. La Palma Avenue Suite 7 Anaheim, CA 92801	5
22	Robert I. Fox, MD	Scripps Clinic 10666 N. Torrey Pines Rd. La Jolla, CA 92037	4
25	Harvey E. Golden, MD	Rheumatology Associates 1725 W. Harrison Street, Suite 1039 Chicago, IL 60612	2
55	Maria Greenwald, MD	39700 Bob Hope Drive, Suite 202 Rancho Mirage, CA 92270	1
56	Matthew D. Heller, MD	39 Cross St. #103 Peabody, MA 01960	4
58	Paul F. Howard, MD	AARA 10599 N. Tatum Blvd. Suite F150 Paradise Valley, AZ 85253	11
29	S. Michael Jones, MD	Little Rock Diagnostic Clinic 10001 Lile Drive Little Rock, AR 72205	8
30	Jeffery Jundt, MD	Scott and White Clinic (HMO) 2401 South 31st Street Temple, TX 76508	11
51	Alan J. Kivitz, MD	711 Logan Blvd. Altoona, PA 16602	19
32	Richard B. Lies, MD	Wichita Clinic, P.A. 3311 E. Murdock Wichita, KS 67208	11
52	James Loveless, MD	Medical Center Physicians, P.A. 215 E. Hawaii Avenue Nampa, ID 83686	8

SITE NUMBER	NAME OF INVESTIGATOR	ADDRESS OF INVESTIGATIONAL SITE	TOTAL NUMBER OF SUBJECTS ENROLLED
53	Angela McCain, MD	2205 Williams Trace, Suite 106 Houston, TX 77478	0
33	James McKay, DO	Healthcare Research Consultants 4619 S. Harvard Suite A Tulsa, OK 74135	12
35	Larry W. Moreland, MD	Arthritis Clinical Intervention Program 1717 6th Avenue South, Room 068 Birmingham, AL 35294-7201	10
37	Carter V. Multz, MD	1835 Park Avenue San Jose, CA 95126	8
60	David H. Neustadt, MD	234 E. Gray St., Suite 328 Louisville, KY 40202	6
38	Kenneth M. Nies, MD, F.A.C.P.	23441 Madison Street Suite 340 Torrance, CA 90505	6
42	Charles H. Pritchard, MD	RDAL-Clinical Research Regency Towers, Suite 101 1003 Easton Rd. Willow Grove, PA 19090	4
43	Daniel Small, MD	Sarasota Arthritis Center 3500 South Tamiami Trail Sarasota, FL 34239	15
54	Jon T. Stevenson, MD	Arthritis Northwest W. 105 8th Avenue Suite 120 Spokane, WA 99204	2
46	Frederick B. Vivino, MD	University of Pennsylvania Health System Presbyterian Medical Center 39th & Filbert Streets Medical Arts Building, Suite 107 Philadelphia, PA 19104	8
48	Craig Wiesenhutter, MD	Coeur d'Alene Arthritis Clinic 950 Ironwood Drive Coeur d'Alene, ID 83814	14
TOTAL NUMBER OF SUBJECTS			212

Number of Subjects 210 were scheduled to have been enrolled

Ages of Subjects 18-75 years of age, inclusive

Screening Questionnaire The screening questionnaire is identical to SB96US02's.

Inclusion Criteria

The inclusion criteria are identical to SB96US02's.

Exclusion Criteria

The exclusion criteria are identical to SB96US02's.

Study Design Multicenter, double-blind, randomized, parallel-group

Study Procedures

The procedures are identical to the first phase 3 trial with the exception of the definition of the primary and secondary efficacy endpoints. In the sponsor's IND submission that provided the final protocol for SB96US04, the primary efficacy endpoints were identical to those in SB96US02, i.e., "The primary efficacy variables will be the subject's subjective global evaluations of dryness of the mouth, dryness of the eyes, and overall dryness." However, in the NDA submission, the study report for SB96US04 states under the section "Primary Efficacy Parameters" that the "primary assessments were subject global evaluation of dry mouth and subject global evaluation of dry eyes." And under "Secondary Efficacy Parameters, "Secondary efficacy parameters including overall dryness were analyzed similarly to the dry mouth and dry eye assessments." Because overall dryness is not being evaluated as a meaningful endpoint, the impact of its being classified as primary or secondary will only affect other endpoints in its effect on adjustment for multiple endpoints. Refer to the discussion section of this review for an elaboration of the treatment of these outcomes.

Statistical Plan

The statistical plan in this trial is identical to the one in trial SB96US02.

Results

Baseline Characteristics

Refer to the following table for a summary of baseline characteristics in trial SB96US04:

CHARACTERISTICS AT BASELINE: STUDY SB96US04				
Baseline Characteristic		15 mg (n=75)	30 mg (n=66)	Placebo (n=71)
Sex n (%)	Female	72 (96.0)	60 (90.9)	69 (97.2)
	Male	2 (2.8)	6 (9.1)	2 (2.8)
Age (years)	Minimum	28	24	30
	Maximum	74	75	74
	Mean	56.4± 11.9	54.6± 12.1	54.9± 11.7
Race n (%)	Caucasian	65 (86.7)	60 (90.9)	63 (88.7)
	Black	2 (2.7)	2 (3.0)	0 (0)
	Hispanic	4 (5.3)	3 (4.5)	5 (7.0)
	Asian	1 (1.3)	0 (0)	2 (2.8)
	Other	3 (4.0)	1 (1.5)	1 (1.4)
Diagnosis of Sjögren's Syndrome	Primary	44 (58.7)	35 (53.8)	43 (60.6)
	Secondary	31 (41.3)	30 (46.2)	28 (39.4)

All three groups are comparable in their baseline characteristics. The ratio of primary to secondary Sjögren's syndrome diagnosis is somewhat lower in the 30 mg group compared to the 15 mg group or placebo group, but it is not a statistically significant difference. The patterns in demographics are comparable to those in the first phase 3 trial.

SEVERITY OF DRY MOUTH AT BASELINE: STUDY SB96US04

	Placebo (N=70)		SNI-2011 15 mg *t.i.d.* (N=65)		SNI-2011 30 mg *t.i.d.* (N=62)		Total (N=197)	
SEVERITY	N	%	n	%	n	%	n	%
Mild	11	15.5	13	17.3	13	19.7	37	17.5
Moderate	40	56.3	39	52.0	34	51.5	113	53.3
Severe	18	25.4	22	29.3	19	28.8	59	27.8
No symptoms	2	2.8	1	1.3	0	0.0	3	1.4

All three groups are comparable with respect to degree of dry mouth at baseline. This differs from the first phase 3 trial in which the 30 mg group had milder disease than the other two groups. Refer to the discussion section of this review for elaboration on the significance of this finding.

Primary Outcome Variable

TABLE 2. SUBJECT GLOBAL EVALUATION OF DRY MOUTH (STUDY NO. SB96US04)

	Better (%)			No Change (%)			Worse (%)		
		Cevimeline			Cevimeline			Cevimeline	
Evaluation Visit	P	15 mg	30 mg	P	15 mg	30 mg	P	15 mg	30 mg
Week 0	33.8	22.7	18.2	62.0	72.0	81.8	4.2	5.3	0.0
Week 3	50.7	41.2	53.4	46.3	55.9	46.6	3.0	2.9	0.0
Week 6	47.7	46.0	58.9	50.8	50.8	39.3	1.5	3.2	1.8
Week 9	57.1	54.1	58.9	42.9	44.3	39.3	0.0	1.6	1.8
Week 12	61.7	40.7	57.1	38.3	59.3	42.9	0.0	0.0	0.0
Endpoint	54.9	36.0	53.0	45.1	62.7	47.0	0.0	1.3	0.0

	p-value			
	Overall	P vs. 15 mg	P vs. 30 mg	15 mg vs. 30 mg
Week 0	0.1418	ND	0.1703	0.7274
Week 3	0.7006	ND	0.4703	0.2339
Week 6	0.2894	ND	0.2840	0.1352
Week 9	0.9861	ND	0.9100	0.4999
Week 12	0.4932	ND	0.6133	0.0568
Endpoint	0.7944	ND	0.8886	0.0311*

ND = not done (placebo vs. 15 mg was only tested if placebo vs. 30 mg was significant, due to alpha level adjustment)
* values are significant at $p<0.05$

As in study SB96US02, subjects in this trial indicated their global evaluation of their dry mouth, dry eyes and overall dryness as "better", "no change" or "worse" at Weeks 0, 3, 6, 9 and 12. Also in this trial, as in SB96US04, the global evaluations were performed at each visit one hour following administration of the study medication. Subjects in all groups indicated that they felt better. The placebo group showed an exceptionally high percentage indicating "better" much higher than the placebo group in study SB96US02. The 15 mg *t.i.d.* and 30 mg *t.i.d.* groups showed improvements that were in line with results from study SB96US02. However, the placebo results were very similar to the 30 mg *t.i.d.* results, negating any statistical significance for the differences between the two groups. Therefore, no difference was demonstrated between the placebo and 30 mg groups for the primary outcome. Refer to the discussion section for comments on this finding.

Secondary Endpoints

Secondary outcome variables include salivary flow as well as VAS subjective measures of specific dry mouth symptoms.

VAS Analogue Scale Assessments

Visual analogue scale assessments were completed prior to and one hour after dosing at

baseline (Week 0) and during the visits of Weeks 3, 6, 9, and 12. The following symptoms of dry mouth were assessed: feeling of mouth, dryness of mouth, dryness of tongue, ability to speak without drinking, ability to chew and swallow food, and ability to sleep. Subjects were asked to make a mark along a 100 mm line labeled at each end with the worst outcome on the right (i.e., "extremely uncomfortable") and the best on the left (i.e., "comfortable"). Each of these six variables associated with subjective feelings of dry mouth were examined for significant changes throughout the trial.

The differences in values between the baseline and the last visit are shown in the table below. Note that no significant improvement in any of these parameters was observed in those subjects receiving 30 mg of the drug when compared to those subjects receiving placebo. Although four of the six parameters show a statistically significant difference in symptoms between the placebo group and the 15 mg group, the results favored the placebo. The overall results of these secondary variables support superiority of the placebo over the 15 mg dose and no difference between the placebo and the 30 mg dose. See the discussion section of this review for further details.

SUMMARY OF CHANGES FROM BASELINE IN SUBJECTS' VISUAL ANALOGUE SCALE (MM) ASSESSMENT OF DRY MOUTH SYMPTOMS AT ENDPOINT (STUDY NO. SB96US04)

Symptom	Mean ± SD			p-value			
	Placebo	Cevimeline					
		15 mg *t.i.d.*	30 mg *t.i.d.*	Overall	P vs. 15 mg	P vs. 30 mg	15 mg vs. 30 mg
Feeling of mouth	-24.3 ± 27.7	-10.7 ± 26.5	-23.9 ± 23.2	0.0072	0.0034*	0.6644	0.0162
Dryness of mouth	-27.2 ± 27.9	-17.0 ± 26.5	-28.2 ± 21.7	0.0357	0.0335*	0.8039	0.0214
Dryness of tongue	-25.1 ± 29.8	-15.3 ± 26.3	-24.5 ± 23.0	0.0853	0.0541*	0.9825	0.0595
Ability to speak without drinking	-18.4 ± 26.8	-11.4 ± 23.7	-18.0 ± 27.9	0.4998	0.2784	0.8961	0.3593
Ability to chew and swallow food	-17.9 ± 26.2	-12.8 ± 23.7	-13.0 ± 27.0	0.4013	0.3373	0.1945	0.7014
Ability to sleep	-10.0 ± 27.8	0.3 ± 27.8	-9.5 ± 22.3	0.0261	0.0111*	0.6471	0.0445

* values are those that are statistically significant at $p < 0.05$. Note that all of the significant differences in this chart are due to the placebo being superior to the 15 mg group.

The sponsor also examined changes from baseline for each of these subjective variables at each visit. In the comparison of the placebo to the 30 mg group, only two of the parameters showed any significant improvement at any timepoint. Feeling of the mouth at week 3 showed a significant improvement as well as dryness of the mouth at week 3. For the comparison of 15 mg to placebo, several of the timepoints showed a statistically significant difference, but all in the wrong direction, i.e., supporting superiority of the placebo to the 15 mg test group. As with trial SB96US02, a total of 40 comparisons were made for each symptom (five visits with a pre and post dose reading each compared in four ways – overall, placebo vs. 15 mg, placebo vs. 30 mg, and 15 mg vs. 30 mg). None of the comparisons are supportive of the active over the placebo.

Pre and Post dose comparisons

No statistically significant differences in changes from predose to postdose were noted among treatment groups at final visit.

SUMMARY OF CHANGES FROM PREDOSE TO POSTDOSE IN SUBJECTS' VISUAL ANALOGUE SCALE (MM) ASSESSMENT OF DRY MOUTH SYMPTOMS AT FINAL VISIT (STUDY NO. SB95US04)

Symptom	Mean ± SD			p-value			
	P	Cevimeline					
		15 mg *t.i.d.*	30 mg *t.i.d.*	Overall	P vs. 15 mg	P vs. 30 mg	15 mg vs. 30 mg
Feeling of mouth	-6.4 ± 13.9	-6.5 ± 12.6	-9.9 ± 17.5	0.7486	0.7112	0.4473	0.6851
Dryness of mouth	-6.7 ± 14.1	-7.8 ± 15.2	-11.0 ± 17.1	0.3314	0.8226	0.1631	0.2372
Dryness of tongue	-7.1 ± 14.5	-7.0 ± 14.7	-11.5 ± 20.5	0.2658	0.9061	0.1391	0.1712
Ability to speak without drinking	-5.3 ± 13.8	-4.5 ± 13.4	-6.2 ± 18.9	0.8385	0.6640	0.8846	0.5739
Ability to chew and swallow food	-5.7 ± 14.4	-6.6 ± 13.5	-7.6 ± 15.1	0.9400	0.8239	0.8956	0.7300

Salivary Flow

Salivary flow was measured at screening (baseline), Week 6 and Week 12. A dose response effect was seen with SNI-2011 at each time point, with 30 mg *t.i.d.* producing a greater effect than 15 mg *t.i.d.*. The 15 mg *t.i.d.* dose produced significantly greater salivary flow than placebo at Week 6, measuring postdose vs. predose, and was nearly significant at Week 12 and Final Visit. The 30 mg *t.i.d.* dose produced significantly greater salivary flow at each time point. Refer to the following table for the exact values:

OBJECTIVE SALIVARY FLOW MEASUREMENT SB96US04

		Mean ± SD						
			SNI-2011		ANOVA p-value			
Visit	Assess-ment	Placebo	15 mg t.i.d.	30 mg t.i.d.	Overall	Placebo vs. 15 mg	Placebo vs. 30 mg	15 mg vs 30 mg
Screen	Baseline	0.059 ± 0.075	0.066 ± 0.099	0.062 ± 0.069				
Week 6	Predose	0.102 ± 0.115	0.097 ± 0.109	0.090 ± 0.104				
	Postdose	0.114 ± 0.144	0.159 ± 0.180	0.209 ± 0.224				
	Change	0.012 ± 0.082	0.063 ± 0.111	0.118 ± 0.165	0.0000*	0.0044*	0.0000*	0.0280*
Week 12	Predose	0.109 ± 0.117	0.106 ± 0.122	0.083 ± 0.091				
	Postdose	0.143 ± 0.137	0.166 ± 0.181	0.218 ± 0.258				
	Change	0.032 ± 0.064	0.059 ± 0.103	0.135 ± 0.193	0.0186*	0.1674	0.0048*	0.1395
Final Visit	Predose	0.104 ± 0.115	0.102 ± 0.119	0.083 ± 0.091				
	Postdose	0.133 ± 0.135	0.156 ± 0.178	0.218 ± 0.258				
	Change	0.029 ± 0.061	0.054 ± 0.100	0.135 ± 0.193	0.0073*	0.1349	0.0017*	0.0896
Final Value	Postdose	0.133 ± 0.135	0.156 ± 0.178	0.218 ± 0.258				

*values are significant at $p < 0.05$
The primary timepoint was the Final Value (LOCF) or the Final Visit (last available on treatment visit where both pre- and postdose values were collected).

When change from baseline to postdose was compared among groups, statistically significant differences were noted between placebo and 30 mg at Final Visit (each subject's endpoint postdose reading) (p=0.0070), at Week 6 (p=0.0001), and at Week 12 (p=0.0175). Statistically significant differences were found among the treatment groups in the Final Visit (p=0.0035) as well as in both at Week 6 (p=0.0001) and at Week 12 (p=0.0097). Significant difference was also observed between placebo and 15 mg group at Week 6 (p=0.0190). Refer to the following table for exact values:

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SUMMARY OF CHANGE FROM BASELINE IN OBJECTIVE SALIVARY FLOW (ML/MIN) MEASUREMENTS – SB96US04

		Mean ± SD			ANOVA p-value			
			SNI-2011					
Visit	Assessment	Placebo	15 mg t.i.d.	30 mg t.i.d.	Overall	Placebo vs. 15 mg	Placebo vs. 30 mg	15 mg vs. 30 mg
Week 6	Predose	0.043 ± 0.110	0.032 ± 0.085	0.032 ± 0.078	0.8563	0.9249	0.6614	0.6001
	Postdose	0.055 ± 0.136	0.093 ± 0.149	0.151 ± 0.201	0.0010*	0.1060	0.0019*	0.0621
Week 12	Predose	0.048 ±0.107	0.039 ± 0.084	0.026 ± 0.064	0.4241	0.8285	0.2166	0.3106
	Postdose	0.081 ± 0.120	0.099 ± 0.137	0.160 ± 0.235	0.0302*	0.5280	0.0452*	0.1268
Final Value	Postdose	0.075 ± 0.116	0.091 ± 0.134	0.160 ± 0.235	0.0156*	0.5881	0.0236*	0.0677

Change from Baseline = Post-Baseline – Baseline Value
*values are significant at $p < 0.05$
Final Value = LOCF

Use of Artificial Saliva, and Fluid Intake

There were no statistically significant differences among the treatment groups in the use of artificial saliva or tears, and in fluid intake

Adverse Events

As was discussed in the Adverse Events section of the first phase 3 trial, the adverse events for this second phase 3 trial will be presented in detail in this section of the review. See the section of this review that follows open label studies for a presentation of combined adverse events from all relevant trials.

Incidence of Adverse Events

Of the 212 subjects enrolled in this study, 184 (87%) were reported to have experienced at least one adverse event. At least one adverse event was experienced by 60 (91%) of the subjects in the 30 mg SNI-2011 *t.i.d.* group, followed by 65 (87%) in the 15 mg SNI-2011 *t.i.d.* group and 59 (83%) in the placebo group. There was a low incidence of serious adverse events for all treatments. Drug-related adverse events occurred more frequently in the 30 mg SNI-2011 *t.i.d.* group (58%), and in comparable number of subjects in the placebo (27%) and 15 mg SNI-2011 *t.i.d.* (24%) groups. The number of subjects experiencing an adverse event considered severe in intensity was comparable between treatments of placebo (10%), 15 mg SNI-2011 *t.i.d.* (11%), and 30 mg SNI-2011 *t.i.d.* (9%) doses.

INCIDENCE OF ADVERSE EVENTS – SB96US04

	Placebo	SNI-2011	
		15 mg t.i.d.	30 mg t.i.d.
Number of subjects evaluable for safety	71 (100.0%)	75 (100.0%)	66 (100.0%)
Number subjects with at least one adverse event	59 (83.1%)	65 (86.7%)	60 (90.9%)
Number of subjects with no adverse events	12 (16.9%)	10 (13.3%)	6 (9.1%)
Number of subjects with serious adverse events	2 (2.8%)	1 (1.3%)	1 (1.5%)
Number of subjects discontinued due to adverse event	3 (4.2%)	8 (10.7%)	7 (10.6%)
Number of subjects with drug-related adverse events	19 (26.8%)	18 (24.0%)	38 (57.6%)
Number of subjects with a severe adverse event	7 (9.9%)	8 (10.7%)	6 (9.1%)

Reference end-of-text Table 10.1

More subjects in the 15 mg SNI-2011 *t.i.d.* group experienced significantly more "body as a whole" adverse events than those in the placebo group (p=0.0287), while more subjects in the 30 mg SNI-2011 *t.i.d.* group had skin and appendages disorders than those in the placebo group (p=0.0282). All other adverse events occurred in comparable numbers among the three treatment groups.

The most frequently reported adverse events, i.e., reported by incidence of ≥ 4 subjects in any one treatment group, are presented in descending order in the following table. Many of the frequently reported adverse events were expected due to the pharmacological effects of the study medication, e.g., headache, increased sweating, abdominal pain, and nausea.

INCIDENCE OF AES REPORTED BY ≥ 4 SUBJECTS IN ANY TREATMENT GROUP

ADVERSE EVENT WHO-ART preferred term	Placebo (N = 71)		SNI-2011 15 mg t.i.d. (N = 75)		SNI-2011 30 mg t.i.d. (N = 66)	
	n	%	n	%	n	%
Total incidence	59	83.1	65	86.7	60	90.9
Headache	16	22.5	13	17.3	12	18.2
Nausea[1]	8	11.3	4	5.3	17	25.8
Upper respiratory tract infection	11	15.5	7	9.3	6	9.1
Diarrhea	9	12.7	7	9.3	6	9.1
Abdominal pain	7	9.9	7	9.3	8	12.1
Sweating increased[2]	1	1.4	4	5.3	16	24.2
Dyspepsia[3]	10	14.1	6	8.0	2	3.0
Rhinitis	6	8.5	5	6.7	7	10.6
Sinusitis	6	8.5	8	10.7	4	6.1
Coughing	3	4.2	7	9.3	4	6.1
Urinary tract infection	5	7.0	4	5.3	4	6.1
Pharyngitis	5	7.0	4	5.3	1	1.5
Myalgia	5	7.0	4	5.3	1	1.5
Dizziness[4]	5	7.0	3	4.0	0	0
Edema peripheral	2	2.8	3	4.0	3	4.6
Skeletal pain	3	4.2	3	4.0	2	3.0
Artbralgia	2	2.8	4	5.3	2	3.0
Back pain	4	5.6	2	2.7	2	3.0
Conjunctivitis	1	1.4	3	4.0	3	4.6
Inflicted injury	1	1.4	2	2.7	4	6.1
Pain	3	4.2	3	4.0	1	1.5
Vaginitis	1	1.4	3	4.0	1	1.5
Palpitation	1	1.4	3	4.0	1	1.5
Abscess	1	1.4	3	4.0	0	0
Insomnia	0	0	3	4.0	1	1.5
Vomiting	3	4.2	0	0	1	1.5
Allergic reaction	0	0	4	5.3	0	0
Tooth disorder	0	0	3	4.0	1	1.5

See next page for footnotes to this table.

[1]Nausea had significant differences between placebo and 30 mg (p = 0.0282) and between 15 and 30 mg (p = 0.0007)

[2]Sweating increased had significant differences between placebo and 30 mg (p = 0.0001) and between 15 and 30 mg (p = 0.0013)

[3]Dyspepsia had a significant difference between placebo and 30 mg (p = 0.0222)

[4]Dizziness had a significant difference between placebo and 30 mg (p = 0.0588)

Severe Adverse Events, Serious Adverse Events, and Discontinuations Due to Adverse Events

Twenty-five adverse events were considered by the investigators to be severe. Nine severe Adverse Events were reported for 7 subjects in the placebo group, nine severe adverse events were reported for 8 subjects in the 15 mg SNI-2011 *t.i.d.* group, and seven severe adverse events were reported for 6 subjects in the 30 mg SNI-2011 *t.i.d.* group. The most common severe event was headache with three occurrences, while sinusitis, back pain, and nausea each occurred twice. All other adverse events considered to be severe had a single occurrence.

Four events occurred during this study that met the serious adverse event criteria. Two occurred in subjects in the placebo group, which included urinary incontinence which resolved with surgical intervention, and loss of conciousness. One subject on 15 mg cevimeline was treated for basal cell carcinoma and myocardial infarction, and another subject on 30 mg cevimeline experienced a myocardial infarction. Although it is highly unlikely that the basal cell carcinoma was related to study medication, the relationship between myocardial infarction and the study drug in this trial cannot be ruled out.

A total of 18 subjects (8.5%) discontinued from the study prematurely because of an adverse event. Three (4.2%) subjects in the placebo group, 8 (10.7%) subjects in the 15 mg group, and 7 (10.6%) subjects in the 30 mg SNI-2011 *t.i.d.* group discontinued from the study because of an adverse event. Three subjects in the 30 mg SNI-2011 *t.i.d.* group withdrew from the study due to nausea. One subject in the placebo group and two subjects in the 15 mg SNI-2011 *t.i.d.* group withdrew due to diarrhea while one subject in the placebo group and one subject in the 30 mg SNI-2011 *t.i.d.* group withdrew due to aggravated depression. There was a single incidence of the following: myocardial infarction, increased sweating, increased saliva, gastric ulcer, abscess, purpura thrombocytopenic, urticaria, upper respiratory tract infection, dizziness, and headache.

Relationship of Adverse Events

Based upon the pharmacology of cevimeline, the incidence of expected adverse events was higher in the 30 mg SNI-2011 *t.i.d.* group, but comparable between the placebo and 15 mg SNI-2011 *t.i.d.* groups. The most common drug-related adverse events in decreasing order were increased sweating, nausea, headache, diarrhea, abdominal pain, dizziness, and dyspepsia. The number of reports of increased sweating was 16 (24%) in the 30 mg SNI-2011 *t.i.d.* subjects, compared with 4 (5%) subjects in the 15 mg SNI-2011 *t.i.d.* group and 1 (1%) in the placebo group. Nausea was reported in 14 (21%) subjects in the 30 mg SNI-2011 *t.i.d.* group, 3 (4%) subjects in the 15 mg SNI-2011 *t.i.d.* group and 2 (3%) in the placebo group. Diarrhea was experienced by 4 (6%) subjects in the 30 mg SNI-2011 *t.i.d.* group, 3 (4%) subjects in the 15 mg SNI-2011 *t.i.d.* group and 4 (6%) subjects in the placebo group, and abdominal pain was experienced by 4 (6%) subjects in the 30 mg SNI-2011 *t.i.d.* group and 1 (1%) subject in the 15 mg SNI-2011 *t.i.d.* group.

Open Label Studies

In addition to the controlled clinical trials that were conducted by the sponsor, three open label studies were initiated as well. Two of the trials were conducted in Japan between 1992 and 1995, and the third is a trial of one year's duration conducted in the U.S. The two Japanese trials were phase 2 trials designed to examine safety and effectiveness of the drug and explore optimal dosing. The trial conducted in the United States was designed to supply sufficient subject exposure to the drug to support safety in the NDA. At the time of the NDA filing, the one-year, US trial, SB96US03, was not yet completed, but data on the subjects collected as of April 21, 1998, were submitted. As per an agreement made at the End-of-Phase 2 meeting, the additional data included in the 120-day safety update would be used for further support of the drug's safety. The safety update is discussed in a section of this review following the review of the safety of the original NDA materials.

As with all uncontrolled trials, results must be evaluated with caution. As was observed in the phase 3 trials, particularly trial SB96US04, the placebo effect can be very great; therefore, without a placebo comparison in these open trials, improvements in comparisons to baseline may not be supportive of the drug's efficacy. In addition, subjects were allowed to increase or decrease their dosages, so self-dosing is another confounding element.

In the following section, brief outlines of the study design, results and adverse events will be presented. Refer to the Discussion section of this review for interpretation of these data.