TABLE OF NON-PLACEBO-CONTROLLED CLINICAL STUDIES

Protocol Investigators Country	Completion Status (Start and End Dates)	Product Code	Study Design	Treatment	Number of Subjects by Treatment	Age (yr) Range (Mean)	% Male/ Female Race	Duration of Drug Treatment
II-1 Multicenter Japan	Complete Oct 92 – Jun 93	SNI-2011	A multicenter, open-label, gradual dose increase study to examine the safety and effectiveness of cevimeline in the treatment of xerostomia (in particular, hypoptyalism) in subjects with Sjögren's syndrome	Cevimeline HCl 10 mg *t.i.d.* for 2 weeks then 20 mg *t.i.d.* for 2 to 4 weeks then 30 mg *t.i.d.* for 2 to 4 weeks	50	31 - 87 yr (54 yr)	0% M 100% F Race: 50 Asian	6 to 10 weeks
II-4 Multicenter Japan	Complete Apr 94 – Jan 95	SNI-2011	A multicenter, double-blind, randomized, dose-finding study to determine the optimum dose of cevimeline in the treatment of xerostomia in subjects with Sjögren's syndrome	Cevimeline HCl: 2 mg *t.i.d.* 20 mg *t.i.d.* 30 mg *t.i.d.*	 71 73 68	19 - 81 yr (54.5 yr)	1% M 99% F Race: 212 Asian	4 weeks
SB96US03 Multicenter US	At the time of the original NDA submission: Ongoing (Jan 97 – ongoing) (Data cut-off date, 21 Apr 98) At the time of the 120-day safety update: Complete	SNI-2011	A multicenter, open-label, randomized, chronic safety study to examine the safety of cevimeline (15 mg *t.i.d.*, 30 mg *t.i.d.*, and 60 mg *t.i.d.*) in the treatment of xerostomia and in subjects with Sjögren's syndrome	Cevimeline HCl: 15 mg *t.i.d.* 30 mg *t.i.d.* 60 mg *t.i.d.*	362 (total as of data cut-off date)	28 - 75 yr (54.2 yr)	5% M 95% F Race: 326 Caucasian 13 Black 13 Hispanic 7 Asian 3 Other	52 weeks

Study No. II-1

Study No. II-1 was a multicenter, open-label study conducted in Japan to test the safety and effectiveness of a gradually increasing dose of cevimeline in the treatment of subjects with known or suspected Sjögren's syndrome.

Following a 1- to 2-week pre-dosing observation period, all subjects were assigned to receive three courses of treatment: 10 mg cevimeline *t.i.d.* for 2 weeks, 20 mg cevimeline *t.i.d.* for 2 to 4 weeks, and 30 mg cevimeline *t.i.d.* for 2 to 4 weeks. However, in subjects where substantial improvement had been obtained in subjective and objective symptoms, the investigator retained the option to allow the subject to continue the effective dose for the remainder of the study. Saliva volume was measured on the first day of the pre-dosing observation period, on the first day of dosing, and on the last days of each treatment course. Improvement ratings were assigned for salivary secretion, subjective symptoms, and objective findings, and a global improvement rating was assessed for each subject.

The main items collected for statistical analysis were the improvement ratings for salivary secretion, subjective symptoms, and objective findings and the global improvement rating.

Global Improvement Ratings

In Study No. II-1, 55% of the subjects (21/38) were reported to have either remarkable or moderate improvement of their overall condition (based on ratings for salivary secretion, subjective symptoms, and objective findings) following dosing with cevimeline.

Improvement Ratings for Subjective Symptoms

In Study No. II-1, 47% of the subjects (18/38) were reported to show remarkable or moderate improvement in subjective symptoms. The dry mouth symptoms assessed included oral cavity dryness, difficulty in speaking, difficulty in chewing food, and difficulty in swallowing food. All showed significant improvement compared with baseline at the end of treatment with cevimeline ($p < 0.05$).

Salivary Flow

Mean secreted saliva volume increased significantly compared with Baseline at the end of each course of treatment (10 mg, 20 mg, and 30 mg cevimeline *t.i.d.*) ($p < 0.01$).

SECRETED SALIVA VOLUME (G/2 MIN) (STUDY NO. II-1)

Saxon test	Visit				
	Starting day of pre-observation period	Starting day of first course	End day of first course*	End day of second course*	End day of third course*
Mean ± SD	0.89 ± 0.76	0.88 ± 0.76	1.17 ± 1.01	1.60 ± 1.29	1.42 ± 1.19

* Paired t-test vs. starting day of first course, p<0.01.

Adverse Events

Of the 50 subjects evaluable for safety in this study, 17 subjects reported at least one adverse event (17/50; 34%). The most frequently reported adverse event was vomiting, reported for 12% of the subjects (6/50 subjects). Other adverse events reported in this study included perspiration, loss of appetite, uncomfortable feeling, nausea, stomach ache, and headache, all reported for 2 subjects (2/50; 4%). A total of 7 subjects were withdrawn from the study because of an adverse event (7/50; 14%). No serious adverse events were reported during this study.

Study No. II-4

Study No. II-4 was a multicenter, double-blind, randomized, dose-finding study conducted in Japan to determine the optimum dose of cevimeline in the treatment of xerostomia in subjects with known or suspected Sjögren's syndrome.

Following a 2- to 4-week pre-dosing observation period, subjects were randomized to receive 2 mg cevimeline *t.i.d.*, 20 mg cevimeline *t.i.d.*, or 30 mg cevimeline *t.i.d.* for 4 weeks. This dosing period was followed by a 2 to 4 week post-dosing observation period. Secreted saliva volume was measured on the first day of the pre-dosing observation period, on the first day of dosing, on the last day of dosing (Week 4), and at the end of the post-dosing observation period. Subjective dry mouth and dry eye symptoms were also evaluated at these time points. Objective findings of dryness of the oral cavity and dryness of the lips and angle of the mouth were also assessed. Following the completion of dosing and assessments, the investigator provided a global improvement rating for each subject.

The main items collected for statistical analysis were the improvement ratings for salivary secretion, subjective symptoms, and objective findings and the global improvement rating.

Global Improvement Ratings

Thirteen of the subjects receiving 2 mg cevimeline *t.i.d.* who completed the study (13/55; 24%) had a global improvement rating of markedly or moderately improved. This compared with 22 subjects in the 20 mg cevimeline *t.i.d.* group who completed the study (22/55; 40%) and 25 subjects in the 30 mg cevimeline *t.i.d.* group (25/53; 47%) who completed the study. The difference in global improvement ratings for the 2 mg and 30 mg cevimeline *t.i.d.* groups was statistically significant (p=0.006).

Improvement Ratings for Subjective Symptoms

More subjects in the 20 mg cevimeline *t.i.d.* and 30 mg cevimeline *t.i.d.* groups showed marked or moderate improvement in the symptoms of dry mouth (feeling of dryness in oral cavity, feeling of desire for drinking water, difficult to swallow food, and feeling of viscous oral cavity) than did subjects receiving 2 mg cevimeline *t.i.d.*. The differences between the 2 mg and 30 mg cevimeline *t.i.d.* groups in improvement ratings for feeling of desire for drinking water and feeling of viscous oral cavity were statistically significant ($p<0.01$ and $p<0.05$, respectively), favoring the efficacy of the higher dose.

Salivary Flow

Secreted saliva volume was also seen to increase in Study No. II-4. The changes in secreted saliva volume from baseline to the end of dosing were statistically different between the 2 mg and 20 mg cevimeline *t.i.d.* groups (p=0.013) and between the 2 mg and 30 mg cevimeline *t.i.d.* groups (p=0.032), again favoring the enhancement of saliva flow by the higher doses.

SUMMARY OF CHANGES FROM BASELINE[1] IN SECRETED SALIVA VOLUME (G/2 MIN) (STUDY NO. II-4)

Visit	Mean ± SD					
	Cevimeline			p-value (t test)		
	2 mg *t.i.d.*	20 mg *t.i.d.*	30 mg *t.i.d.*	2 mg vs. 20 mg	2 mg vs. 30 mg	20 mg vs. 30 mg
End of dosing	1.20 ± 0.06	1.51 ± 0.10	1.60 ± 0.17	0.013	0.032	0.617

1 Change from Baseline = End of Dosing / (½ x Pre-Dosing Observation + Start of Dosing).

Adverse Events

Twenty-one subjects who received 2 mg cevimeline *t.i.d.* reported at least one adverse event during the study (30%). This compared with 21 subjects in the 20 mg cevimeline *t.i.d.* group (30%) and 20 subjects in the 30 mg cevimeline *t.i.d.* group (32%). The most frequently reported adverse event in this study was nausea (2 mg, 4%; 20 mg, 4%; 30 mg, 13%). Other adverse events reported during this study included abdominal pain, diarrhea, stomach discomfort, and salivary gland pain/salivary abscess enlargement. Ten subjects in the 2 mg cevimeline *t.i.d.* group (15%) discontinued the study prematurely because of an adverse event compared with 11 subjects in the 20 mg cevimeline *t.i.d.* group (16%), and 5 subjects in the 30 mg cevimeline *t.i.d.* group (8%). No serious adverse events were reported during this study.

APPEARS THIS WAY ON ORIGINAL

Study No. SB96US03

Study No. SB96US03 is an ongoing open-label study. The results obtained in this study and discussed within this summary are based on interim data, all data entered into the data base as of the cut-off date of 21 April 1998. Study No. SB96US03 is a multicenter, open-label, chronic safety study designed to examine the safety of cevimeline (15 mg *t.i.d.*, 30 mg *t.i.d.*, and 60 mg *t.i.d.*) in the treatment of xerostomia in subjects with Sjögren's syndrome. Subjects were able to roll over from the double-blind, Phase 3 studies (Study Nos. SB96US02 and SB96US04) and the Phase 2 study (Study No. SB95US01) into this open-label study. In addition, subjects who had not previously been exposed to cevimeline could enroll in the study.

Following successful completion of the screening procedures, eligible subjects received 15 mg cevimeline *t.i.d.* for 2 weeks. Study site personnel contacted the subjects after 2 weeks of treatment to determine if the dosage regimen needed to be increased to 30 mg cevimeline *t.i.d.* to optimize treatment for each subject. Subject visits were scheduled at 4-week intervals from Week 4 through Week 52, with an additional visit at Week 26, to evaluate the safety of the study medication. At each visit, the investigator had the option to change the dosage regimen, based on his or her opinion or that of the subject, to 15 mg cevimeline *t.i.d.*, 30 mg cevimeline *t.i.d.*, or 60 mg cevimeline *t.i.d.* to optimize treatment for each subject.

Reviewer's Comment: In an amendment dated 2/11/97, for the open label study US03, instructions were given to delete the following statement: "All patients will receive 15 mg SNI-2011 t.i.d. for the first 2 weeks of the study. Patients will be assigned study numbers at Week 0." This was done to clarify that no randomization was used for this study.

Assessed in addition to safety evaluations in this open-label, dose-adjusting study are the two objective efficacy parameters: total salivary flow and total lacrimal flow (Schirmer's test). These parameters were measured at screening and at Weeks 12, 26, and 52 of the study. Mean values and change from Baseline at predose and at postdose, based on the data available as of the cut-off date, are summarized descriptively at each visit. Within-visit changes from pre- to postdose are summarized descriptively.

Salivary Flow

Increases in salivary flow from predose to postdose values were observed for all doses administered at each visit.

SUMMARY OF CHANGES IN OBJECTIVE SALIVARY FLOW MEASUREMENTS (ML/MIN) FROM PREDOSE TO POSTDOSE (STUDY NO. SB96US03)[1]

Visit	Cevimeline							
	N	15 mg *t.i.d.*	N	30 mg *t.i.d.*	N	60 mg *t.i.d.*	N	Overall
Week 12	114	0.081 ± 0.140	163	0.119 ± 0.172	52	0.160 ± 0.264	329	0.112 ± 0.181
Week 26	49	0.094 ± 0.122	129	0.139 ± 0.184	73	0.163 ± 0.236	251	0.137 ± 0.192
Week 38	7	0.183 ± 0.370	30	0.143 ± 0.220	9	0.071 ± 0.097	46	0.135 ± 0.229
Week 52	4	0.338 ± 0.243	13	0.116 ± 0.142	10	0.091 ± 0.227	27	0.140 ± 0.203
Final Visit	74	0.131 ± 0.175	170	0.134 ± 0.190	89	0.160 ± 0.247	333	0.140 ± 0.203

[1] Includes data entered in the study data base as of the cut-off date of 21 April 1998.

When postdose salivary flow measurements were compared with Baseline values, increases in salivary flow were observed for all doses at all visits. As with the comparison of pre- and postdose measurements, there did not appear to be consistent relationship in the extent of the enhancement of salivary flow with the dose of cevimeline administered.

Satisfaction with dose

Subject satisfaction was recorded as a basis for possible dose adjustment. Subject and investigator satisfaction with current dose are summarized at each visit by specific reason for dosage change. Less than half of the subjects were satisfied with the dose of cevimeline they were receiving at Week 4 (41%). All subjects at this visit who were dissatisfied with the dose of medication wanted to increase the dose (59.3%). The proportions of subjects who were satisfied with the dose of study medication that they were receiving increased at subsequent visits. By Week 20, 88% of the subjects were satisfied with the dose. This level of satisfaction remained consistent throughout the remainder of the study (90% to 96%), indicating that subjects had become stabilized at a particular dose level, generally at a dose of 30 mg cevimeline *t.i.d.*.

Investigator satisfaction with dose mirrored that of subject satisfaction throughout the study with 59% of the subjects receiving a rating of investigator satisfaction at Week 4. Subsequently, the proportion of subjects for whom the investigators were satisfied with the prescribed dose increased. At Week 20, the investigators were satisfied with the dose prescribed for 88% of the subjects. This level of satisfaction remained consistent throughout the remainder of the study (90% to 96%).

Adverse Events

As of the data base cut-off date of 21 April 1998, 62% of subjects receiving 15 mg cevimeline *t.i.d.*, 76% of subjects receiving 30 mg cevimeline *t.i.d.*, and 131 subjects receiving 60 mg cevimeline *t.i.d.* (80%) reported at least one adverse event during the study.

INCIDENCE OF ADVERSE EVENTS (STUDY NO. SB96US03)[1]

	Cevimeline		
	15 mg *t.i.d.*	30 mg *t.i.d.*	60 mg *t.i.d.*
Number of subjects evaluable for safety	362 (100.0%)	316 (100.0%)	164 (100.0%)
Number subjects with at least one adverse event	224 (61.8%)	241 (76.2%)	131 (79.8%)
Number of subjects with no adverse events	138 (38.1%)	75 (23.7%)	33 (20.1%)
Number of subjects with serious adverse events	8 (2.2%)	8 (2.5%)	4 (2.4%)
Number of subjects discontinued due to adverse event	18 (5.0%)	6 (1.9%)	10 (6.1%)

[1] Includes data entered in the study data base as of the cut-off date of 21 April 1998.

The most frequently reported adverse events during the study were increased sweating, nausea, and headache.

INCIDENCE OF ADVERSE EVENTS REPORTED BY ≥10% SUBJECTS IN ANY TREATMENT GROUP (STUDY NO.SB96US03)[1]

	Cevimeline					
	15 mg *t.i.d.* (N=362)		30 mg *t.i.d.* (N=316)		60 mg *t.i.d.* (N=164)	
Adverse Event	N	%	n	%	N	%
Sweating increased	19	5.2	61	19.3	63	38.4
Nausea	36	9.9	43	13.6	24	14.6
Sinusitis	30	8.2	36	11.3	13	7.9
Diarrhea	37	10.2	31	9.8	10	6.1
Headache	40	11.0	35	11.0	7	4.2
Upper respiratory tract infection	25	6.9	36	11.3	6	3.6

[1] Includes data entered in the study data base as of the cut-off date of 21 April 1998.

Thirty-three patients discontinued the study due to adverse events; five were mild in severity, 20 were moderate and eight were severe. ~~Most were~~ gastrointestinal or nervous system disorders. The eight severe adverse events leading to discontinuation were abdominal pain, rash, depression, joint dislocation, granulocytopenia, vertigo, LE syndrome and increased sweating.

Serious Adverse Events and Deaths

Twenty-four patients were listed by the sponsor as experiencing serious adverse events while participating in the study. These events included 4 reports of cancer, 2 reports of pneumonia, and individual reports of bronchitis, respiratory tract infection, bone marrow suppression, traumatic hip injury, hyperglycemia, leg abscess, concussion, depression, shoulder injury, appendectomy, fever of unknown origin, gastrointestinal distress, herpes zoster, cellulitis, diverticulitis, kidney infection, blurry vision, and pruritic rash occurring during hospitalization for viral gastroenteritis. Although the investigators only listed the blurry vision and pruritic rash as events possibly related to study drug, it is not possible to conclusively rule out most of the other reported events. Because all subjects were on active drug in this open label study and the incidence of these reports is low, it is difficult to judge the relationship. No deaths occurred during the study.

Integrated Safety

Studies Included in the Integrated Safety Database

Formal safety analyses were performed on an Integrated Safety Database comprised of data from four Sjögren's syndrome studies (SB95US01, SB96US02, SB96US03, and SB96US04) [redacted] At the time of the 120-day safety update, safety data on an addditional 165 subjects from ongoing open label studies were submitted. A discussion of the safety update is in a separate section of the review following this one.

The safety measurements assessed in the studies conducted in support of this NDA include adverse events, clinical laboratory evaluations, medical history, physical examinations, vital sign assessments, and 12-lead ECGs. [redacted] were also conducted in the Sjögren's placebo-controlled studies. At all study visits, subjects had the opportunity to report any adverse events experienced since the previous visit. An adverse event was defined as any untoward medical occurrence experienced by a subject, regardless of its causal relationship to the study medication. Serious adverse events were defined as those events resulting in death, disability, incapacitation, hospitalization, or prolongation of hospitalization. Any event that was immediately life threatening was considered serious. All cancers and laboratory abnormalities of major clinical concern to the investigator were serious. All adverse events, regardless of severity and relationship to study drugs, were reported and documented. Adverse events were coded using the World Health Organization Adverse Reaction Terms (WHO-ART) coding dictionary.

The sponsor summarized adverse events (the number and percentage of subjects experiencing an event) by body system and preferred term. Statistical comparisons of adverse events were performed based on 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. Laboratory tests included: 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, Hb, Hct, total erythrocyte count, total leukocyte count, with differential, platelet count, urinalysis, and occult blood.

Subject Disposition

For all studies included in the Integrated Safety Database, a total of 882 subjects were enrolled and exposed to at least one dose of either cevimeline or placebo. Of these, 651 subjects received cevimeline and 231 received placebo. Including the subjects who were submitted in the 120-day safety update, as per an agreement at the End-of-Phase 2 meeting, a total of 351 subjects received a dose of 30 mg (the proposed dose of the drug) or greater for 6 months or more. For the subjects in the cevimeline groups there was a 32.8% dropout compared with 13.4% dropout rate in the placebo groups.

SUBJECT DISPOSITION – INTEGRATED SAFETY DATABASE STUDIES

Study Group	Dose Level	Enrolled[1]	Exposed[2]	Discontinued Early[3]		Completed 6 months[4]	Completed 12 months[4]
		N	N	N	%	N	N
All Studies	Placebo[5]	231	231	31	13.4	49	0
	15 mg	314	440	57	12.9	41	1
	20 mg	168	204	8	3.9	0	0
	30 mg	147	404	47	11.6	107	19
	40 mg	0	190	17	8.9	33	6
	60 mg	22	361	82	22.7	96	16
	80 mg	0	66	37	56.0	22	8
	All active	651	754	248	32.8	299	50
	Overall[6]	882	882	279	31.6	348	60
Sjögren's Placebo Controlled	Placebo	164	164	21	12.8	0	0
	15 mg	140	140	26	18.5	0	0
	30 mg	153	153	27	17.6	0	0
	60 mg	27	27	9	33.3	0	0
	All active	320	320	62	19.3	0	0
	Overall[6]	484	484	83	17.1	0	0
Sjögren's All Active	15 mg	381	440	57	12.9	41	1
	30 mg	147	404	47	11.6	107	19
	60 mg	22	186	31	16.6	51	8
	Overall	550	550	135	24.5	199	28

SUBJECT DISPOSITION – INTEGRATED SAFETY DATABASE STUDIES

Study Group	Dose Level	Enrolled[1]	Exposed[2]	Discontinued Early[3]		Completed 6 months[4]	Completed 12 months[4]
		N	N	N	%	N	N

1 Number of subjects presented by initial dose level except All Active studies where number of subjects are presented by initial active dose level.

2 Number of subjects exposed to dosage any time during study. "All Active" = Total number exposed to any active dose.

3 Number of subjects discontinued early by dose level at discontinuation. The percentages are based on the number of subjects exposed to the dosage.

4 Exposure time summed across dosage; presented by dose level at completion milestone.

5

6 "Overall" =Exposure time on all doses including placebo.

Subjects dropped out at a rate that was directly proportional to the dose, both in the Sjögren's syndrome trials Overall, in the short-term studies, higher percentages of subjects in the 60 and 80 mg groups discontinued due to adverse events. The discontinuation rates due to adverse events among the lower dosage groups (15 mg, 20 mg, 30 mg, and 40 mg cevimeline) were comparable to that for the placebo group (2.9%). However, in open-label long-term studies these differences among dose groups were not very prominent.

Adverse Events Incidence

Adverse events occurring in subjects with ≥1% incidence by body system for the placebo-controlled studies in subjects with Sjögren's syndrome is presented below. Although safety data was reviewed and discussed for both the Sjögren's the focus of the remainder of this section will be the adverse events associated with subjects in the Sjögren's trials. Because the proposed indication for the drug is Sjögren's syndrome, it is more relevant to review in detail the adverse events associated with Sjögren's syndrome subjects.

In general, of all adverse events occurring at a ≥1% incidence by body system, the incidence of adverse events reported for the placebo group was similar to the incidence reported for the other groups. However, for adverse events affecting the gastrointestinal system, the skin and appendages, and the body as a whole, the incidences of adverse events were higher among the drug groups compared with the placebo group. Incidences of adverse events occurring at a ≥1% incidence by body system for subjects with Sjögren's syndrome in the placebo controlled studies are presented below.

ADVERSE EVENTS WITH ≥1% INCIDENCE BY BODY SYSTEM:
SJÖGREN'S PLACEBO-CONTROLLED STUDIES

Body System WHO-ART Preferred Term	Dose Level at Onset											
	Placebo (N = 164)		15 mg *t.i.d.* (N = 140)		30 mg *t.i.d.* (N =153)		60 mg (N = 27)		All Active (N = 320)		Overall (N = 484)	
	n	%	n	%	n	%	n	%	n	%	n	%
Total incidence	125	76.2	105	75.0	131	85.6	26	96.3	262	81.8	387	79.9
Body as a whole – general disorders	13	7.9	21	15.0	19	12.4	12	44.4	52	16.2	65	13.4
Fatigue	2	1.2	2	1.4	4	2.6	2	7.4	8	2.5	10	2.0
Hot flushes	0	0	3	2.1	2	1.3	2	7.4	7	2.1	7	1.4
Rigors	2	1.2	0	0	3	1.9	8	29.6	11	3.4	13	2.6
Central and peripheral nervous system disorders	40	24.3	24	17.1	44	28.7	13	48.1	81	25.3	121	25.0
Dizziness	12	7.3	6	4.2	7	4.5	5	18.5	18	5.6	30	6.2
Headache	33	20.1	18	12.8	32	20.9	8	29.6	58	18.1	91	18.8
Tremor	0	0	1	0.7	1	0.6	3	11.1	5	1.5	5	1.0
Gastrointestinal disorders	55	33.5	52	37.1	73	47.7	21	77.7	146	45.6	201	41.5
Abdominal pain	11	6.7	13	9.2	11	7.1	4	14.8	28	8.7	39	8.0
Constipation	2	1.2	3	2.1	2	1.3	3	11.1	8	2.5	10	2.0
Diarrhea	17	10.3	16	11.4	19	12.4	6	22.2	41	12.8	58	11.9
Dyspepsia	14	8.5	9	6.4	9	5.8	5	18.5	23	7.1	37	7.6
Nausea	13	7.9	12	8.5	35	22.8	14	51.8	61	19.0	74	15.2
Saliva increased	1	0.6	1	0.7	6	3.9	3	11.1	10	3.1	11	2.2
Vomiting	4	2.4	2	1.4	7	4.5	4	14.8	13	4.0	17	3.5
Hearing and vestibular disorders	1	0.6	1	0.7	2	1.3	1	3.7	4	1.2	5	1.0
Heart rate and rhythm disorders	1	0.6	4	2.8	2	1.3	0	0	6	1.8	7	1.4
Musculoskeletal system disorders	20	12.2	21	15.0	11	7.1	1	3.7	33	10.3	53	10.9
Skeletal pain	3	1.8	7	5.0	4	2.6	0	0	11	3.4	14	2.8
Psychiatric disorders	10	6.1	4	2.8	8	5.2	2	7.4	14	4.3	24	4.9
Reproductive disorders, female	1	0.6	3	2.1	1	0.6	0	0	4	1.2	5	1.0
Resistance mechanism disorders	4	2.4	4	2.8	4	2.6	0	0	8	2.5	12	2.4
Respiratory system	51	31.1	44	31.4	45	29.4	5	18.5	94	29.3	145	29.9
Coughing	5	3.0	8	5.7	7	4.5	2	7.4	17	5.3	22	4.5
Rhinitis	9	5.4	9	6.4	11	9.1	0	0	23	7.1	32	6.6
Secondary terms	9	5.4	4	2.8	8	5.2	2	7.4	14	4.3	23	4.7

Skin and appendages disorders	17	10.3	13	9.2	34	22.2	20	74.0	67	20.9	84	17.3
Sweating increased	4	2.4	7	5.0	31	20.2	20	74.0	58	18.1	62	12.8
Special senses	3	1.8	2	1.4	1	0.6	0	0	3	0.9	6	1.2
Urinary system disorders	11	6.7	11	7.8	18	11.7	3	11.1	32	10.0	43	8.8
Micturition frequency	3	1.8	2	1.4	5	3.2	2	7.4	9	2.8	12	2.4
Vascular (extra-cardiac) disorders	1	0.6	0	0	2	1.3	2	7.4	4	1.2	5	1.0
Flushing	1	0.6	0	0	2	1.3	2	7.4	4	1.2	5	1.0
Vision disorders	15	9.1	11	7.8	10	6.5	4	14.8	25	7.8	40	8.2
White cell and reticuloendothelial disorders	3	1.8	5	3.5	3	1.9	2	7.4	10	3.1	13	2.6
Lymphadenopathy	3	1.8	2	1.4	4	0.6	2	7.4	5	1.5	8	1.6

Notes: n is patient adverse event incidence. A patient is counted at most once in each cell.
N is total number of patients exposed to the dosage at any time during the study

Deaths

One subject died during the active phase of the studies and two subjects died following completion of the study. The subject who died during the active phase of the trial was a 70-year old male with previously undiagnosed triple-vessel disease, who died following a myocardial infarct. The investigator assessed the event as possibly related to the study drug. Of the other two subjects, one died from complications of multiple myeloma and the other from pancreatitis. Both causes of death were judged to be unrelated to the study medication.

Serious Events

Of the subjects with Sjögren's syndrome included in the Integrated Safety Database, 10 subjects receiving 15 mg cevimeline *t.i.d.* experienced a serious adverse event (2%), 10 subjects receiving 30 mg cevimeline *t.i.d.* experienced a serious adverse event (2%), and 4 subjects receiving 60 mg cevimeline *t.i.d.* experienced a serious adverse event (2%). These incidence rates were identical to that seen for subjects receiving placebo (2%). Overall, a total of 24 subjects with Sjögren's syndrome who received cevimeline and were included in the Integrated Safety Database reported a total of 42 serious adverse events. Of these 42 serious adverse events, twenty-three were reported as severe, fifteen were reported as moderate, and four were reported as mild in severity. Serious adverse events occurred in six patients in the body-as-a-whole group, manifested as chest pain, fever, edema, syncope, traumatic injury, and increased therapeutic response. Five serious events occurred in three patients in the respiratory system disorders group, manifested as bronchitis, chronic obstructive airway disease, coughing, pneumonia, and upper respiratory tract infection. Three events occurred in four patients in the gastro-intestinal system disorder group, manifested as diverticulitis, GI hemorrhage, and nausea. Surgical interventions included repair of hip prosthesis, and rotator cuff repair. Four events occurred in two patients in the resistance mechanism disorders group manifested as cellulitis of the right leg, Herpes Zoster, and infection of both the right leg and large toes. Three events occurred in three patients in the urinary system disorder group, manifested as kidney infection, incontinence, and nephrotic syndrome. Three events occurred in three patients in the central and peripheral nervous system disorder group, manifested as loss of consciousness, multiple sclerosis, and vestibular vertigo. Two events occurred in two patients in the neoplasm group, manifested as basal cell carcinoma. Additional serious adverse events included endocrine disorder, white cell disorder, heart rate and rhythm disorder, metabolic and nutritional disorder, musculoskeletal disorder, platelet, bleeding and clotting disorder, female reproductive disorder, and psychiatric disorder.

Although the investigators only listed two of these serious events as events possibly related to study drug - blurry vision in one subject and pruritic rash in another - it is not possible to conclusively rule out most of the other reported events.

Relationship of Adverse Events to Drug

In overall incidence, increased sweating was the most common adverse event, followed by nausea, headache, diarrhea, dizziness, and dyspepsia.

Dose response relationships were seen for increased sweating, nausea, diarrhea, abdominal pain, vomiting, micturition frequency and anorexia.

There were no statistically significant differences between placebo and 15 mg dose for any adverse event category except headache. Statistically significant differences existed between placebo and 30 mg for micturition frequency. Statistical differences were seen between placebo and 60 mg for diarrhea, dizziness, dyspepsia, abdominal pain, increased saliva, and tremor.

Vital Signs

There were no apparent dose-related changes from baseline to endpoint for the majority of the vital signs. For the Sjögren's syndrome placebo-controlled studies, no apparent dose-related effect was visible in any of the vital signs. Clinically significantly low values were seen in 3% of 15 mg, 3% of 30 mg, and 6% of the 60 mg subjects. Clinically significantly high values in the same category were seen in 2% of 15 mg, 3% of 30 mg, and 4% of 60 mg subjects.

ECG

No apparent dose-related changes from Baseline to Endpoint were found in the ECG results. No apparent dose-dependent shifts from normal to abnormal were noticed for subjects in the Sjögren's syndrome studies. [redacted] Overall, no apparent drug or dose-dependent changes in ECG were seen in these subjects.

Physical Examination

Physical examination did not reveal significant changes as a result of the drug in [redacted] the Sjögren's syndrome [redacted]

No difference was seen between the placebo and active groups except for lymphadenopathy (placebo 1%, all active subjects 3%) and musculoskeletal system disorders (3% placebo, 5% for all active subjects) in the Sjögren's syndrome studies. For the long-term Sjögren's syndrome studies, the medication did not cause any more visible changes from baseline than were seen in the Sjögren's syndrome placebo-controlled studies.

[redacted]

Clinical Laboratory

Clinical laboratory tests were performed during the screening and during each visit after study medication was distributed. These tests included: 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, Hb, Hct, total erythrocyte count, total leukocyte count, with differential, platelet count, urinalysis, and occult blood. During the phase 2 study (SE95US01), blood was collected at baseline and weeks 2, 4, and 6. During both phase 3 trials, blood was collected at screening and weeks 3, 6, 9, and 12. Subjects enrolled in the open label studies were sampled every 4 weeks from week 4 through week 52.

Two tables that follow have been created to summarize the sponsor's submitted data. The first table consists of a list of each laboratory parameter measured, and the number of subjects whose values ~~fell~~ outside the normal range for each of these parameters. The second table that follows includes only the numbers of subjects who had normal values for each parameter at baseline and developed out-of-normal values at endpoint. (This table was created from the data in the sponsor's SAS tables that plotted the baseline lab values against the endpoint lab values.) Unlike the first table, which does not distinguish newly out-of-range lab values from existing ones, the second table provides an incidence of abnormal lab values that developed over the course of the trial in subjects who entered with normal lab values. Comparison of the active doses to placebo and examination for dose response or unusual patterns in both of these tables is very useful to determine abnormalities.

A third table has been copied directly from the sponsor's submission, and is entitled, "Number Of Patients with Potentially Clinically Significant (PCS) High or Low Values." The sponsor chose values that they believed were sufficiently out-of-range of the normal laboratory values to be of clinical consequence. Generally, these values were approximately three times the normal range. (For example, "PCS high" for total cholesterol is ≥300 mg/dL whereas normal laboratory range is under 200 mg/dL; PCS for ALT, AST, and GGT is ≥3 x ULN). Although this table cannot stand alone to support safety, it is useful as an adjunct to the two above tables to determine if any extreme lab values may have been created by the use of cevimeline in greater proportion than the placebos or with any sort of dose response. The first half of the table includes subjects from all placebo controlled Sjogren's studies, which were of up to 26 weeks duration and had a placebo group for comparison. The lower half of the table includes subjects from the open label Sjogren's study, which was one year in duration and had no placebo group for comparison.

A discussion of the results from these tables can be found in the *Safety* subsection of the *Discussion* section of this review.

Number of subjects in all Sjogren's trials who had out-of normal laboratory values at any visit

The following table of out-of-normal laboratory values includes data from subjects enrolled in the phase 2 study, which was of 6-weeks duration, the two phase 3 trials, both of 12-weeks duration, and the open-label studies, which were of 12 months duration. Although the placebo column of this table does not include data from the open-label studies, the laboratory values should not be affected to any appreciable extent by the lack of blinding in the studies.

The numbers and ~~percentages are listed~~ for each dose level and the placebo to highlight any patterns of abnormal values – either more abnormal values in the drug group than in the placebo group, or a dose-response pattern. Parameters that showed a high overall prevalence include elevated total cholesterol and elevated triglycerides, which is not unexpected. With respect to the relationship between test drug and out-of-normal laboratory values, note that for each parameter, at least one of the active groups had a lower percentage of out-of-normal laboratory values than the placebo with very few exceptions. Those exceptions, which include calcium, potassium, hemoglobin, and red cell count will be examined ~~more~~ closely for causal relationship between the out-of-normal value and active drug. Low calcium occurred in none of the placebo subjects, but 2, 4, and 1 of the subjects in the 15, 30, and 60-mg groups, respectively. The lack of dose response and small number of affected subjects does not support a drug-related event. Similarly, the pattern of response in the reports of low potassium does not raise a serious concern; the differences are insignificant between groups and there is no clear evidence of a dose-response. A lower percentage of placebo subjects demonstrated both higher and lower than normal hemoglobin values. In support of the drug not causing this effect, not only are these differences insignificant between groups, but it is not biologically plausible that the same drug would cause both an elevation and lowering of hemoglobin. Low Red Cell count shows up as of lower percentage in the placebo group than the other groups; however, the other doses show a reverse dose response for this lab parameter, which does not support an effect from the drug.

Number and percentage of subjects in all Sjogren's trials (placebo-controlled and open-label) who had out-of-reference laboratory values at any visit

Analyte	Laboratory reference range		Dose Level							
			Placebo N = 161		15 mg N = 284		30 mg N = 382		60 mg N= 163	
			n	%	N	%	n	%	n	%
ALT (SGPT)	0-48 U/L	High	7	4.4	9	3.2	20	5.2	9	5.6
ALBUMIN	3.2 – 5.0 g/dL	Low	0	0	1	0.4	2	0.5	0	0
		High	0	0	0	0	1	0.3	0	0
ALKALINE PHOSPHATASE	M & F (Ages 20-99): 20-125 U/L	Low	1	0.6	1	0.4	0	0	0	0
		High	5	3.1	12	4.2	16	4.2	5	3.1
AMYLASE, SERUM	30-170 U/L	Low	16	10.0	13	4.7	31	8.2	18	11.0
		High	11	6.9	13	4.7	30	7.9	16	9.8
AST (SGOT)	0-42 U/L (3-64 y) 0-55 U/L (65+ y)	High	8	5.0	9	3.2	14	3.7	7	4.3
BILIRUBIN, TOTAL	0 – 1.3 mg/dL	High	0	0	5	1.8	5	1.3	0	0
CALCIUM	8.5-10.3 mg/dL	Low	0	0	2	0.7	4	1.1	1	0.7
		High	7	5.0	14	5.0	13	3.6	6	4.1
CHLORIDE	95-108 mEq/L	Low	1	0.6	2	0.7	4	1.1	1	0.6
		High	27	16.8	37	13.0	55	14.4	21	12.9
CHOLESTEROL, TOTAL	<170 mg/dL (3-19y) <200 mg/dL (20+ y)	High	81	50.3	135	47.4	205	53.7	73	44.8
CREATININE	0.7-1.4 mg/dL	Low	13	8.1	20	7.0	19	5.0	9	5.5
		High	3	1.9	6	2.1	6	1.6	1	0.6
GGT	<75 U/L (65+y) <65 U/L (M,13-64y) <45 U/L (F, 13-64y)	High	14	8.8	24	8.6	40	10.5	15	9.2
GLOBULIN	2.2-4.2 g/dL	Low	2	1.2	1	0.4	2	0.5	0	0

			Dose Level							
Analyte	**Laboratory reference range**		**Placebo N = 161**		**15 mg N = 284**		**30 mg N = 382**		**60 mg N= 163**	
			n	**%**	**N**	**%**	**n**	**%**	**n**	**%**
		High	19	11.8	32	11.3	52	13.6	27	16.6
GLUCOSE	70-115 mg/dL (13-49y)	Low	18	11.2	15	5.3	31	8.1	8	4.9
	70-125 mg/dL (50+ y)	High	16	10.0	42	14.9	38	10.0	11	6.8
LACTIC DEHYDROGENASE	<250 U/L (3-64y) <270 U/L (65+ y)	High	3	1.9	6	2.1	9	2.4	2	1.2
PHOSPHORUS	2.5-4.5 mg/dL (13-64y)	Low	2	1.4	5	1.8	7	1.9	2	1.4
	2.1-4.3 mg/dL (65+ y)	High	19	13.7	26	9.1	46	12.6	14	9.5
POTASSIUM	3.5-5.3 mEq/L	Low	3	1.9	7	2.5	13	3.4	5	3.1
		High	6	3.7	5	1.8	7	1.8	1	0.6
PROTEIN, TOTAL	6.0-8.5 g/dL (13-64y)	Low	1	0.6	1	0.4	0	0	0	0
SERUM	5.8-8.1 g/dL (65+y)	High	16	9.9	25	9.0	40	10.5	18	11.0
SODIUM	135-146 mEq/L	Low	6	3.7	10	3.6	17	4.5	4	2.5
		High	0	0	4	1.4	3	0.8	0	0
TRIGLYCERIDES	< 200 mg/dL	High	46	28.6	67	23.4	99	25.9	31	19.0
UREA NITROGEN	7-25 mg/dL (13-64y)	Low	4	2.5	7	2.5	7	1.8	2	1.2
	7-30 mg/dL (65+y)	High	6	3.7	3	1.1	8	2.1	2	1.2
URIC ACID	M: 4.0-8.5 mg/dL	Low	28	20.1	51	18.3	74	20.3	24	16.3
	F: 2.5-7.5 mg/dL	High	5	3.6	5	1.8	12	3.3	4	2.7
BASOPHILS	<2.0 %	High	6	3.7	8	2.8	13	3.4	4	2.5
EOSINOPHILS	<7.0%	High	28	17.4	34	12.3	54	14.2	19	11.7
HEMATOCRIT	M: 18-64y: 41.0-50.0% M: 65+y: 36.0-49.0%	Low	24	14.9	42	14.7	55	14.4	26	16.0
	F: 18-64y: 35.0-46.0% F: 65+y: 33.0-46.0%	High	5	3.1	3	1.1	11	2.9	3	1.8

			Dose Level							
Analyte	**Laboratory reference range**		**Placebo N = 161**		**15 mg N = 284**		**30 mg N = 382**		**60 mg N= 163**	
			n	**%**	**N**	**%**	**n**	**%**	**n**	**%**
HEMOGLOBIN	M: 18-64y: 13.8-17.2% M: 65+y: 11.8-16.8% F: 18-64y: 12.0-15.6% F: 65+y: 11.1-15.5%	Low	24	14.9	60	21.3	69	18.1	31	19.0
		High	0	0	1	0.4	3	0.8	3	1.8
LYMPHOCYTES	16.0 – 46.0%	Low	26	16.2	55	19.6	72	18.9	22	13.5
		High	8	5.0	11	3.9	18	4.7	7	4.3
MONOCYTES	<12.0%	High	14	8.7	20	7.1	31	8.1	9	5.5
NEUTROPHIL, SEGS	40.0 – 75.0%	Low	4	2.5	7	2.5	15	4.0	4	2.5
		High	23	14.3	50	17.7	77	20.3	19	11.7
PLATELET COUNT	130,000-400,000 per CUMM	Low	9	5.6	12	4.3	15	3.9	6	3.7
		High	2	1.2	6	2.2	8	2.1	1	0.6
RED CELL COUNT	0 – 3 per HPF	Low	2	1.2	11	3.9	12	3.2	3	1.8
		High	31	19.3	49	17.4	64	16.8	28	17.2
WHITE CELL COUNT	M: 0 – 5 per HPF F: 0 – 10 per HPF	Low	28	17.4	45	16.1	69	18.1	33	20.3
		High	5	3.1	15	5.4	23	6.0	3	1.8

Number of subjects with normal baseline and abnormal endpoint laboratory values

In the preceding table, no distinction was made between subjects who entered the trial with out-of-normal values and those who developed out-of-normal values throughout the course of the trial. The following table provides an incidence of abnormal lab values that developed over the course of the trial in subjects who entered with normal lab values. Of note in this table, the incidences are very low for all parameters. Although a few of the subjects show laboratory values that have a lower incidence in the placebo group than for the other doses (ALT, calcium, creatinine, glucose, phosphorus, potassium, sodium, total serum protein, hemoglobin, platelet count, and white cell count), none of the differences between groups are significant and none show a clear dose response.

Note: The sample size in the following table is slightly smaller than that of the proceeding table, because it was created from data in the original NDA submission. The preceding table was created from data submitted in a more recent submission in which the sponsor included additional subjects from the four-month safety update.

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Number and percentage of subjects in all Sjogren's trials (placebo-controlled and open-label) whose baseline laboratory value was normal (within the laboratory reference range) and endpoint value was abnormal

			Dose Level							
Analyte	Laboratory reference range		Placebo N = 161		15 mg N = 181		30 mg N = 313		60 mg N= 161	
			n	%	n	%	n	%	n	%
ALT (SGPT)	0-48 U/L	High	1	0.6	3	1.6	5	1.6	2	1.2
ALBUMIN	3.2 – 5.0 g/dL	Low	0	0	0	0	1	0.3	0	0
		High	0	0	0	0	0	0	0	0
ALKALINE PHOSPHATASE	M & F (Ages 20-99): 20-125 U/L	Low	0	0	1	0.5	0	0	1	0.6
		High	1	0.6	2	1.1	0	0	0	0
AMYLASE, SERUM	30-170 U/L	Low	4	2.7	1	0.6	2	0.6	2	1.4
		High	2	1.3	2	1.2	6	2.0	2	1.4
AST (SGOT)	0-42 U/L (3-64 y) 0-55 U/L (65+ y)	High	1	0.6	3	1.7	1	0.3	3	1.8
BILIRUBIN, TOTAL	0 – 1.3 mg/dL	High	0	0	1	0.5	1	0.3	0	0
CALCIUM	8.5-10.3 mg/dL	Low	0	0	0	0	4	1.3	0	0
		High	0	0	2	1.1	3	1.0	2	1.4
CHLORIDE	95-108 mEq/L	Low	0	0	1	0.5	0	0	1	0.6
		High	6	3.9	10	5.7	13	4.4	5	3.3
CHOLESTEROL, TOTAL	<170 mg/dL (3-19y) <200 mg/dL (20+ y)	High	9	10.5	11	10.5	13	7.9	6	7.1
CREATININE	0.7-1.4 mg/dL	Low	3	1.9	0	0	7	2.3	0	0
		High	0	0	1	0.5	5	1.6	1	0.6

			Dose Level							
Analyte	Laboratory reference range		Placebo N = 161		15 mg N = 181		30 mg N = 313		60 mg N= 161	
			n	%	n	%	n	%	n	%
GGT	<75 U/L (65+y) <65 U/L (M,13-64y) <45 U/L (F, 13-64y)	High	2	1.3	3	1.7	3	1.0	2	1.3
GLOBULIN	2.2-4.2 g/dL	Low	0	0	1	0.6	1	0.3	0	0
		High	4	2.7	4	2.4	2	0.7	1	0.7
GLUCOSE	70-115 mg/dL (13-49y)	Low	4	2.5	0	0	11	3.6	4	2.6
	70-125 mg/dL (50+ y)	High	2	1.2	7	4.0	7	2.3	4	2.6
LACTIC DEHYDROGENASE	<250 U/L (3-64y) <270 U/L (65+ y)	High	1	0.6	0	0	2	0.6	1	0.6
PHOSPHORUS	2.5-4.5 mg/dL (13-64y)	Low	0	0	1	0.5	2	0.7	2	1.4
	2.1-4.3 mg/dL (65+ y)	High	7	5.3	4	2.3	10	3.6	4	2.8
POTASSIUM	3.5-5.3 mEq/L	Low	0	0	2	1.1	2	0.6	2	1.2
		High	2	1.2	0	0	3	0.9	1	0.6
PROTEIN, TOTAL	6.0-8.5 g/dL (13-64y)	Low	1	0.6	1	0.6	0	0	0	0
SERUM	5.8-8.1 g/dL (65+y)	High	1	0.6	3	1.8	4	1.3	2	1.4
SODIUM	135-146 mEq/L	Low	1	0.6	6	3.3	3	0.9	6	3.8
		High	0	0	0	0	0	0	1	0.6
TRIGLYCERIDES	< 200 mg/dL	High	5	3.7	3	1.9	15	5.4	7	5.3
UREA NITROGEN	7-25 mg/dL (13-64y)	Low	1	0.6	2	1.1	2	0.6	1	0.6
	7-30 mg/dL (65+y)	High	2	1.2	0	0	1	0.3	1	0.6
URIC ACID	M: 4.0-8.5 mg/dL	Low	5	4.0	7	4.3	13	5.0	5	3.7
	F: 2.5-7.5 mg/dL	High	2	1.6	0	0	1	0.3	0	0
BASOPHILS	<2.0 %	High	2	1.2	1	0.5	0	0	0	0
EOSINOPHILS	<7.0%	High	5	3.3	4	2.3	16	5.5	7	4.8

Analyte	Laboratory reference range		Dose Level: Placebo N = 161 n	Placebo %	15 mg N = 181 n	15 mg %	30 mg N = 313 n	30 mg %	60 mg N= 161 n	60 mg %
HEMATOCRIT	M: 18-64y: 41.0-50.0% M: 65+y: 36.0-49.0% F: 18-64y: 35.0-46.0% F: 65+y: 33.0-46.0%	Low	8	5.6	6	3.6	12	4.3	8	5.4
		High	1	0.6	0	0	1	0.3	1	0.6
HEMOGLOBIN	M: 18-64y: 13.8-17.2% M: 65+y: 11.8-16.8% F: 18-64y: 12.0-15.6% F: 65+y: 11.1-15.5%	Low	7	4.9	13	8.0	17	6.2	11	7.6
		High	0	0	1	0.6	0	0	0	0
LYMPHOCYTES	16.0 – 46.0%	Low	8	5.4	10	6.1	16	5.8	6	4.2
		High	2	1.3	4	2.4	3	1.1	3	2.1
MONOCYTES	<12.0%	High	3	1.9	2	1.1	8	2.6	4	2.5
NEUTROPHIL, SEGS	40.0 – 75.0%	Low	2	1.3	2	1.2	3	1.1	1	0.7
		High	13	8.6	10	6.1	13	4.8	5	3.7
PLATELET COUNT	130,000-400,000 per CUMM	Low	2	1.3	5	2.8	6	1.9	1	0.6
		High	0	0	1	0.5	3	1.0	1	0.6
RED CELL COUNT	0 – 3 per HPF	Low	0	0	0	0	2	0.7	0	0
		High	0	0	0	0	0	0	0	0
WHITE CELL COUNT	M: 0 – 5 per HPF F: 0 – 10 per HPF	Low	10	6.9	6	3.9	10	3.7	6	4.4
		High	0	0	2	1.3	7	2.6	1	0.7

Number of Patients with Potentially Clinically Significant High or Low Values

The following table, which was provided by the sponsor, contains a distribution of subjects in whom laboratory values were identified by the sponsor as "possibly clinically significant" which was set at lab values approximately three times the range of normal. This table is valuable in that it includes subjects with lab values that were substantially above or below the normal values. Although this table does not distinguish between those subjects who entered with high values as opposed to developing the high values throughout the course of the trial, it is noteworthy that there is no significant difference between the values in the active groups over the placebo, nor is a dose response observed for any of the parameters.

NUMBER OF PATIENTS WITH POTENTIALLY CLINICALLY SIGNIFICANT HIGH OR LOW VALUES

Analyte		Dose Level							
		Placebo		15 mg		30 mg		60 mg	
		n	%	n	%	n	%	N	%
Sjögren's Placebo Controlled									
Serum Amylase	PCS High	0	0	0	0	1	0.68	0	0
AST (SGOT)	PCS Low	0	0	0	0	1	0.67	0	0
Chloride	PCS Low	0	0	1	0.73	0	0	0	0
	PCS High	0	0	1	0.73	0	0	0	0
Total Cholesterol	PCS High	4	2.48	4	2.92	1	0.67	0	0
GGT	PCS High	2	1.25	1	0.73	2	1.34	2	9.52
Glucose	PCS High	3	1.86	4	2.92	3	2.01	1	4.76
Potassium	PCS Low	0	0	2	1.46	0	0	0	0
	PCS High	1	0.62	1	0.73	0	0	0	0
Total Serum Protein	PCS High	5	3.11	7	5.11	7	4.70	1	4.76
Triglycerides	PCS High	25	15.53	11	8.03	25	16.78	2	9.52
Urea Nitrogen	PCS High	3	1.86	0	0	2	1.34	0	0
Uric Acid	PCS High	2	1.44	0	0	2	1.60	0	0
Eosinophils	PCS High	4	2.48	2	1.46	6	4.05	1	4.76
Hematocrit	PCS Low	4	2.48	2	1.46	7	4.73	0	0
Hemoglobin	PCS Low	2	1.24	0	0	1	0.68	0	0
Lymphocytes	PCS Low	3	1.86	8	5.84	7	4.73	1	4.76
Monocytes	PCS High	0	0	1	0.73	0	0	0	0
Neutrophil, SEGS	PCS High	0	0	1	0.73	0	0	0	0
Platelet Count	PCS Low	1	0.62	0	0	0	0	0	0
Red Cell Count	PCS High	31	19.25	28	20.44	26	17.57	7	33.33
White Cell Count	PCS Low	9	5.59	8	5.84	6	4.05	1	4.76
	PCS High	0	0	1	0.73	0	0	0	0
Sjögren's All Active									

NUMBER OF PATIENTS WITH POTENTIALLY CLINICALLY SIGNIFICANT HIGH OR LOW VALUES

Analyte		Dose Level							
		Placebo		15 mg		30 mg		60 mg	
		n	%	n	%	n	%	N	%
Alkaline Phosphatase	PCS High	NA	NA	0	0	1	0.26	1	0.61
Serum Amylase	PCS High	NA	NA	0	0	1	0.26	0	0
AST (SGOT)	PCS High	NA	NA	2	0.72	1	0.26	2	1.23
Total Bilirubin	PCS High	NA	NA	2	0.71	0	0	0	0
Chloride	PCS Low	NA	NA	1	0.35	1	0.26	1	0.61
	PCS High	NA	NA	1	0.35	1	0.26	1	0.61
Total Cholesterol	PCS High	NA	NA	6	2.11	7	1.83	1	0.61
Creatinine	PCS High	NA	NA	1	0.35	0	0	0	0
GGT	PCS High	NA	NA	6	2.14	7	1.83	5	3.07
Glucose	PCS Low	NA	NA	1	0.35	1	0.26	1	0.61
	PCS High	NA	NA	10	3.55	8	2.09	1	0.61
Lactic dehydrogenase	PCS High	NA	NA	0	0	0	0	1	0.61
Potassium	PCS Low	NA	NA	2	0.70	1	0.26	0	0
	PCS High	NA	NA	2	0.70	1	0.26	0	0
Total Serum Protein	PCS High	NA	NA	9	3.24	14	3.66	7	4.29
Triglycerides	PCS High	NA	NA	29	10.25	56	14.66	16	9.82
Urea Nitrogen	PCS High	NA	NA	1	0.35	4	1.05	0	0
Uric Acid	PCS High	NA	NA	3	1.08	6	1.65	0	0
Eosinophils	PCS High	NA	NA	4	1.45	12	3.15	4	2.45
Hematocrit	PCS Low	NA	NA	9	3.15	12	3.15	7	4.29
Hemoglobin	PCS Low	NA	NA	0	0	2	0.52	0	0
Lymphocytes	PCS Low	NA	NA	15	5.34	20	5.25	6	3.68
Monocytes	PCS High	NA	NA	1	0.35	0	0	0	0
Neutrophil, SEGS	PCS High	NA	NA	2	0.71	2	0.53	0	0
Platelet Count	PCS Low	NA	NA	1	0.36	4	1.05	1	0.61
	PCS High	NA	NA	0	0	1	0.26	0	0
Red Cell Count	PCS High	NA	NA	49	17.38	64	16.80	28	17.18
White Cell Count	PCS Low	NA	NA	12	4.29	17	4.46	9	5.52
	PCS High	NA	NA	2	0.71	2	0.52	0	0

NA = Not Applicable
PCS = Potentially Clinically Significant

APPEARS THIS WAY
ON ORIGINAL

Because the ALT values are an important measure of potential liver dysfunction, a review of the line listings for this parameter was conducted. Of the subjects with ALT values that go over the normal limit during at least one visit during the trial, there is no noticeable pattern which links increase in dose to increase in ALT values. Half of the subjects (53%) who had at least one ALT value greater than the normal laboratory range remained high for the remainder of the trial and half (47%) returned to normal. Of note, however is one subject who had an extremely high level of ALT. This subject, a 45 year-old female, was enrolled in the open label trial, SB95US03, at a dose of 15 mg and remained on that dose throughout the trial. She had a beginning ALT value of 45, (within the normal range), increased to 272 at Week 4, decreased to 69 at Week 9, increased again to 571 at Week 17, and returned to normal, 26, at Week 22. This subject had Sjogrens syndrome secondary to lupus erythematosus. On, and was receiving multiple medications. In addition to the test drug, she received prednisone, plaquenil, premarin, furosemide, klor-con, doxycycline, hydrocodone, cephalexin, famivir, and cytoxin during the course of the trial. She was discontinued from the study at Week 22 for cytoxin-induced neutropenia. In addition to her elevated ALT, the AST level also rose in the same pattern although not as great as follows: Normal at baseline (33), 112 at Week 4, normal at Week 9 (39), 194 at Week 17 and normal at Week 22 (20). Her GGT rose from 52 at baseline to 154 at Week 4, 229 at Week 9, 3060 at Week 17 and 350 at Week 22 (normal values 0-42). Her total cholesterol is also of note, which rose from 315 at baseline to a high of 860 at Week 17 before returning to 253 at Week 22.

Since the AST is closely related to ALT, AST abnormal values were also examined in greater detail and the following items are of note: In two subjects, both enrolled in the second phase 3 trial (SB95US04) and continuing into the open-label portion of the trial, unusually high values were reached as the drug was raised. The first subject, a 46-year old female, was assigned to the 15 mg dose, and her AST levels remained normal throughout the placebo-controlled portion of the trial. When the subject continued in the open label portion of the trial, however, she raised her dose to 30 mg for 10 weeks which was accompanied by a steady increase in AST, although it did not go above the upper limits of normality until Week 38 at which point it registered 101. At Week 38, she raised her dose to 60 mg and her AST at the following visit (Week 27) increased further to 133, at which point the trial ended. Also of note is that her ALT, although never going above the ULN, also increased steadily after being raised to the 30 mg dose and ended at Week 47 at 48, the upper limit of normal. Alkaline phosphatase, total bilirubin, GGT and all other labs were normal throughout the trial.

The other subject was a 60-year old female who also was enrolled in the second phase 2 trial, at the 15 mg dose, and continued into the open-label portion. She too raised her dose to 30 mg during the open-label continuation of the trial and then increased to 60 mg briefly and dropped back to 30 mg by the last visit. The AST began normally at 26, remained there throughout the subject being on the 15 mg dose, and then increased to 63 when the subject increased the dose to 30 mg. When the dose was increased to 60 mg, the AST reached 139, and when the dose was lowered to 30 mg, the AST decreased to 106. The ALT values also followed a similar pattern in this subject, beginning at 15 and exceeding the upper limits of normality when the subject was taking the 30 mg dose, and reaching the peak at the 60 mg dose. Alkaline phosphatase, total bilirubin, GGT and all other labs were normal throughout the trial.

Two other subjects had at least one significantly elevated AST reading. The first, a 54 year old female, was enrolled in trial SB95US02 and then continued with the open label study. She was assigned the 30 mg dose during the placebo-controlled portion of the trial, and had normal lab values that descending regularly from 38 to 19, at the trial's end. When she enrolled in the open label trial, the subject decreased to a 15 mg dosing and had a value of 162 at Week 31 of the trial, only to return to 44 (within normal limits) by the last visit at week 35. The ALT followed an identical pattern, although the subject began the trial with a value of 48 which was borderline high, and decreased as the trial continued with the exception of week 31, when the ALT jumped to 198. At the last visit, during Week 35, the ALT dropped to 54. Alkaline phosphatase and total bilirubin followed the same pattern in this subject. The other subject, a 33 year-old female who was taking a 30 mg dose of drug during the second placebo-controlled trial (SB95US04), had an AST reading that began slightly elevated (43 at baseline), increased to 141 at Week 6 and decreased to 33 at Week 10 and ended the trial at Week 13 with a value of 32. The subject did not continue with the open-label continuation of the trial. ALT followed a pattern identical to AST, with a baseline reading of 47 (borderline high) and increasing to 182 at Week 6 only to return to 33 at Week 13. There were no abnormalities in alkaline phosphatase, total bilirubin, or any other laboratory values.

Refer to the *Discussion* section of this review for the significance of these findings and *Labeling* section for recommended labeling changes.

Concomitant Medication

There were no apparent differences in the numbers of patients taking concomitant mediations among treatment groups. The most frequently taken concomitant medications were ophthalmologic preparations and estrogens.

Safety Update

The 120-day safety update was submitted to the NDA on December 23, 1998. Prior to submission of this NDA, the sponsor anticipated that the one-year, open-label US trial, SB96US03, would not yet completed by the time of the NDA filing. At the End-of-Phase-2 meeting between the sponsor and FDA, it was agreed that additional data could be included in the 120-day safety update and used for further support of the drug's safety.

With the additional subjects who completed the ongoing study SB996US03 since the cut-off reporting date for the NDA submission, a total of 351 subjects received a dose of 30 mg or greater for 6 months or more. Of these, 141 subjects received a dose of 30 mg or more for 12 months. Of the 154 who were on doses at 60 mg or higher for at 6 months or more, 57 completed 12 months on a dose of 60 mg or higher.

There were eight reports of serious adverse events during this time, including osteomyelitis, carcinoma, depression, mastectomy, a lump in the breast, wrist fusion, thrombocytopenia and two reports of osteomyelitis. There were no deaths reported during this reporting period.

The additional data did not produce any significant changes in the incidenceof adverse events from the data submitted during the original NDA submission.

Also included in the safety update was the final report on the numbers of dropouts from this study. Of the 428 subjects initially enrolled, 44 (10.2%) dropped out while on the 15 mg dose, 38 (10.3%) dropped out while on the 30 mg dose and 36 (17.6%) dropped out while on the 60 mg dose. The overall dropout rate for this trial is 27.5%. For each dose level, the most frequent reasons for discontinuation were adverse events and patient decision, in that order. Further elaboration of the term "patient decision" was not provided.

Discussion

The sponsor submitted the results of two phase 3 trials, several phase 2 trials, and an open-label trial in support of this NDA. As will be discussed in the following section of this review, although the results of the first phase 3 trial conducted, SB95US02, supports efficacy of the drug, the results of the second phase 3 trial, SB95US04, provides an inconclusive demonstration of effectiveness. In this second trial, the values reported for both the primary outcome variable and the secondary outcome variables are similar to the values in the first trial for each active drug arm. However, in Study SB95US04, due to a placebo group that performed as well as both test drug groups with respect to the primary outcome variables, there is no difference between the dose selected for marketing and the placebo for this outcome. In order to achieve a sufficient demonstration of efficacy for this drug, another well-controlled trial that confirms the first phase 3 trial results is required. Study SB95US01, a phase 2 trial conducted prior to the phase 3 trials, is able to demonstrate a statistically significant improvement in the active drug over the placebo using the same global endpoint measurement as for the phase 3 trials. Therefore, the two trials that will be considered "pivotal" are SB96US02, the first phase 3 trial, and SB95US01, a phase 2 trial. In this section of the review, the results and conclusions from the phase 2 and phase 3 trials will be discussed in depth in order to support a regulatory decision about this drug based upon the totality of the evidence. This will begin with a discussion of the sponsor's arrival at the dose selection, and primary outcome variables, be followed by the phase 3 trials discussion, including the difference in the results, and proceed with a discussion of the phase 2 trial results and their applicability to support Cevimeline's efficacy. The discussion will conclude with an evaluation of the safety findings from all trials conducted.

Dose Selection

In the phase 2 trial (SB95US01), the sponsor tested a 30 mg dose and a 60 mg dose against a placebo. Although both groups showed significant improvement over placebo, no difference in efficacy was demonstrated between the 30 mg and 60 mg dose group as measured by the primary endpoint, subject global evaluation of dry mouth. Since this phase 2 study was not powered to detect a statistically significant difference between the 30 mg and 60 mg groups, it may be misleading to conclude that there was no difference. It is therefore worth examining the actual values and the trend of effect. Four out of the five evaluation visits show that subjects rated the 30 mg dose as better than the 60 mg dose for the primary efficacy variable, the global evaluation. Although these differences are so slight as to be inconclusive as to whether one dose is better than the other, it strongly supports the lower dose being as effective as the higher one. In addition, the adverse events profile showed double the percentage of expected events (increased perspiration, nausea, diarrhea, and abdominal pain) in the 60 mg group as compared to the 30 mg group. The change in salivary flow as measured by a predose to postdose comparison, showed a significant improvement of the 30 mg group compared to placebo, although the increase in flow in the 60-mg group was not significantly greater than the increase in salivary flow in the 30 mg group. Based upon the lack of significant improvement in either the global assessment of dry mouth or salivary flow, and the higher adverse event profile 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. To explore the possibility that a dose even lower than 30 mg *t.i.d.* may be effective, the sponsor designed phase 3 trials to test both a 15 mg dose and a 30 mg dose against a placebo.

The first phase 3 trial conducted with the 15 and 30 mg dosage groups did, in fact, help to confirm the sponsor's conclusion from the phase 2 trial that 30 mg *t.i.d.* was the optimal dose. The 30 mg dose showed significant improvements in salivary flow over placebo as measured by subjective and objective means whereas the 15 mg dose did not show a significant improvement over placebo for either measurement. In addition, the 30 mg dose showed significant improvement over the 15 mg dose in both measures.

Keeping in mind that the clinical trials show group averages and do not account for individual variations in dose requirements, one of the objectives of the open-label study, SB95US03, was to explore dosing, and subject satisfaction at various doses. All subjects were given 15 mg in this trial as their starting dose, and during the first evaluation at Week 4, more than half reported being dissatisfied with this dose, stating that the dose was too low. For the remainder of the trial, subjects were allowed to increase their dose up to 60 mg tid and adjust it during the trial as they saw fit. Of the 251 subjects remaining in the trial at 6 months, 129 (51%) were taking a 30 mg tid dose, 73 (29%) were on the 60 mg tid dose, and 49 (20%) were on the 15 mg tid dose. Over 90% of these subjects reported being satisfied with their dose by this time, with the most popular dose being 30 mg. Comparing the open-label trial to the placebo-controlled trials, "patient satisfaction" as measured in the open-label trial is also a subjective measure not dissimilar from the global assessment of dry mouth. However, before drawing conclusions about the high satisfaction rate reported in the open label trial, it must be considered that in trials SB95US01, SB96US02, and SB96US04, the percentage of subjects on placebo that reported feeling better ranged from 35% - 55%. Therefore, without a placebo group for comparison, it is not possible to draw a conclusion about the effectiveness of the 15 mg group, or the greater effectiveness of the 60 mg group over the 30 mg group, based on satisfaction.

Salivary flow data, a secondary outcome variable in the placebo-controlled trials, was also collected regularly over the course of the open-label trial. All dosing groups reported an increase in salivary flow in the open-label study, but no clear pattern for the 15 mg, 30 mg and 60 mg tid groups emerged. It must also be pointed out that increases were seen in the salivary flow of subjects in the placebo groups of trials SB95US01, SB96US02, and SB96US04. Because the trial is not placebo controlled or blinded, the validity of the results may be compromised since it is difficult to know the impact blinding may have on collection of saliva and recording of the data. Although the high percentage of patient satisfaction and the increases in salivary flow provide some evidence that some patients prefer a dose higher or lower than the 30 mg tid dose, it is difficult to draw definite conclusions from this trial, due to lack of placebo and blinding.

In terms of approving a dose greater than 30 mg tid, there are insufficient numbers of subjects who have been observed with the 45 mg or 60 mg dose for approval. Even including the numbers presented in the 120-day safety update, only 154 were on doses at 60 mg or higher for six months or greater, which is insufficient to meet the minimum ICH guidelines for demonstrating chronic-use drug safety.

The sponsor has proposed ———— and 30 mg capsule for marketing, since they believe that both ——— and 30 mg tid are acceptable dosing regimens. Since only the 30 mg tid dose is being recommended for approval, only a 30 mg capsule would be allowed to be marketed.

Primary Outcome Variables

The sponsor listed global assessments of dry eyes, dry mouth and overall dryness as primary outcome variables. As was discussed earlier in this review, overall dryness is not a meaningful indication and should not have been included in the primary outcome variables. During the discussions that took place between the sponsor and the agency during the End-of-Phase 2 meeting, the focus was on which of the measures being made for dry eyes and dry mouth (subjective and objective) should be primary and which should be secondary. The advice from the agency to make the subjective measures primary was based upon a precedent set with Salagen (pilocarpine), a drug currently approved for the treatment of symptoms of dry mouth,. The first approval for Salagen was issued in 1992 for the indication, "treatment of symptoms of dry mouth from radiation to the head and neck." The medical reviewer assigned to that NDA concluded that, due to the nearly total destruction of saliva-producing cells from head and neck radiotherapy, the improvement in salivary flow attributable to Salagen, although statistically significant, was by itself too small to demonstrate efficacy. The drug was deemed clinically effective primarily because the overwhelming majority of subjects on Salagen reported an improvement in their feeling of mouth dryness that was statistically significant when compared to placebo and measured on a global dryness question similar to the one used in the phase 3 trials for cevimeline.

When the sponsor of Salagen more recently submitted an NDA efficacy supplement to obtain approval for treatment of dry mouth and dry eyes from Sjögren's syndrome, the same logic was applied – that clinically, the most relevant outcome is the subjects' perception of moisture, as measured by polling the subjects at regular intervals throughout the trial. It was felt that the salivary flow by itself does not tell the entire story. If its duration of action is short or if its increase is consistent but of insufficient magnitude to result in a difference to the subject – the clinical significance may be doubtful. Clinical significance was deemed best measured by the subjects' perceptions of comfort over time, i.e., a global perception.

What the sponsor did not address with the agency prior to beginning their phase 3 trials, however, was whether the dry eyes and dry mouth outcomes were both required to be positive or whether either would be acceptable; that is, were the conditions connected by "and" or "or". With the "or" condition, approval could be granted based on either win, although this could affect the statistical interpretation of the results. In the case of the global outcome for dry mouth, however, a statistical adjustment would not affect the conclusions. This is because the first phase 3 trial was highly significant, and an adjustment would not have affected its ability to show significance. The same is true for the phase 2 trial, SB95US01. In the second phase 3 trial, the primary outcome variable for the mouth did not achieve significance without an adjustment, so any further adjustment would not have affected the result. If the "and" condition is assumed, and just the "dry mouth" outcome was successful – can the dry mouth claim stand alone or does the entire trial fail because both eyes and mouth were designated as primary? It must be noted that Salagen was approved with only successful demonstration of efficacy of the dry mouth portion of their primary outcome variables, so cevimeline should presumably be judged in the same manner.

Equivocal Phase 3 Results

Global Assessment

The first phase 3 trial (SB96US02) was successful. The percentage of "better" responses in subjects' global evaluations of dry mouth was greater in all three of the test groups at every visit after baseline (as measured by their response to the question, "Please rate the overall condition of your dry mouth now compared with how you felt before starting treatment in this study."). As is typical of placebo-controlled, blinded clinical trials, the placebo improvement at each visit was in the 30 – 40% range, with 37.1% of the LOCF subjects on placebo reporting "feeling better" at final visit. The 15 mg group reported a greater percentage of subjects feeling better at every visit than the placebo group, but at no point, including the final visit did the difference between the placebo group and the 15-mg group responses approach statistical significance. The 30 mg group produced a greater percentage of subjects who responded "feeling better" at every visit than either the placebo group or the 15 mg group. At each visit after baseline, the difference between the percentage who responded "feeling better" in the 30 mg group and those who responded "feeling better" in the placebo group - as well as the difference between the percentage who responded "feeling better" in the 30 mg and those who responded "feeling better" in the 15 mg group - are both statistically significant. The final LOCF value showed 66.1% of subjects reporting feeling better compared to 37.1% for the placebo ($p = 0.0004$) and 44.6% for the 15 mg group ($p = 0.0056$ for the difference between 44.6% and 37.1%).

In the first phase 3 trial (SB96US02), the improvement in global evaluation of dry mouth is highly significant in the 30 mg group when compared to placebo, occurs consistently at every visit, and shows a highly significant difference when compared to the 15 mg group. These particulars taken together strongly support the efficacy of the 30 mg dose of cevimeline for the indication of dry mouth relief in the first phase 3 trial.

However, the primary efficacy results for the second phase 3 trial (SB96US04) are not as supportive as the first (SB96US02). In this second phase 3 trial, at each of the five visits, the placebo has a greater percentage of "better" responses than the 15 mg group. At two of the five visits, the placebo also has a greater percentage of "better" responses than the 30 mg group. For the three visits that show a greater percentage of "better" responses in the 30 mg group than placebo, including the endpoint value, the differences are not statistically significant.

It is apparent that something unexpected happened in the second trial (SB96US04). In the first trial, SB96US02, the percentage of "better" responses in the 30 mg group is always higher than in both the 15 mg and placebo groups (and the 15 mg group reports a slightly greater number of "better" responses than the placebo group). At the second visit, the differences in "better" responses between the 30 mg group and the placebo group reach statistical significance and remain there throughout the trial. In the second study (Study SB96US04), however, neither the 30 mg group nor the 15 mg group has a significantly better outcome than the placebo. In fact, although the sponsor did not calculate the p value for the difference between 15 mg and placebo as per the statistical protocol, the placebo may be superior to the 15 mg dose.

The actual primary outcome values achieved at each visit in the two trials can also be compared. The 15 mg group in the first phase 3 trial showed results in the primary outcome variable that were very similar in magnitude and pattern to the 15 mg group in the second phase 3 trial. Likewise, the 30 mg group in the first phase 3 trial showed results that were similar in magnitude and pattern to the 30 mg group in the second phase 3 trial. The placebo group in the second study, however, shows significantly higher readings than the placebo group in the first study at every visit.

Phase 2 Trial Results

In the phase 2 trial, SB95US01, values are seen that are very similar to the successful first phase 3 trial with respect to the global evaluation of dry mouth. At endpoint, which was 6 weeks in the phase 2 trial, the results showed 76% of subjects on 30 mg of the drug reporting "better" compared to 35% responding better with placebo. In the first phase 3 trial, at 6 weeks, 75% of the 30 mg group reported feeling "better" compared to 38% of the placebo group. Although the sample size was much smaller in the phase 2 trial than either of the phase 3 trials, the difference between the placebo and 30 mg group was sufficient to result in a highly significant p value at endpoint.

The secondary efficacy variables, which include other subjective measures of dryness and salivary flow, will be discussed in the next section. After examining the patterns in the secondary outcomes in both trials, an attempt will be made to offer possible explanations for the difference in results between the two phase 3 trials.

Secondary variables

Both subjective and objective measurements of mouth dryness were used as secondary outcome variables. Salivary flow was measured at different timepoints to produce an objective outcome. In addition, the sponsor chose six subjective measures of dryness of the mouth that are more specific than the global measure as secondary. Salivary flow, the objective measure of dryness, was also measured regularly during each phase 3 trial and the phase 2 trial, SB95US01. In each study, comparisons between groups were made both from the timepoints of immediately prior to and 90 minutes after medication, and from the baseline measurement to the post-dose one. The remainder of this section will discuss the results for the dry mouth variables only.

Subjective

Secondary subjective variables included "feeling of mouth", "dryness of mouth", "ability to speak without drinking", "dryness of the tongue", ability to chew and swallow food", and "ability to sleep." The subjects were asked to rate each on a VAS during each visit. Changes were then compared between groups at different timepoints to look for significance. In the first phase 3 study, none of the comparisons between the placebo group and the 15 mg group resulted in significant improvements from baseline in any of these secondary variables. For the comparison of the placebo group to the 30 mg group, the final value showed "feeling of mouth", "dryness of mouth", and "ability to speak without drinking" to be significantly superior in the 30 mg group at $p < 0.05$; "dryness of tongue" and "ability to sleep" is superior in the 30 mg group with a borderline significance at $p<0.08$. Only the ability to chew and swallow food was not significant at a p value of 0.35. In examining the results at individual visits, there was less consistency demonstrated. Other than the final visit, on average, only one of the other comparisons was significant at any particular visit.

The magnitude of the changes observed for the secondary subjective variables for the 15 mg and 30 mg cevimeline *t.i.d.* groups in the second study was similar to that seen in the first study; however, the changes from baseline for the placebo group were greater in the second study. This effect mirrors the results of the primary outcome comparisons – because there was a strong placebo response, no statistically significant improvements were noted between the 30 mg group and placebo group or the 15 mg group and placebo group.

In the phase 2 study, these subjective variables were regarded along with the global assessment as primary outcome variables. Although the global assessment of dry mouth had a significantly larger number of "better" responders in the test groups compared to placebo, the same subjects did not report a significantly better outcome in the other subjective variables being discussed in this section when comparing either of the test groups with the placebo.

As was discussed in the results section of this review, in addition to the 30 mg vs. placebo comparison, three other sets of comparisons were made (placebo vs. 15 mg, 15 vs. 30 mg, and overall comparison), resulting in a total of 24 comparisons for these secondary variables. At a p value of 0.05, one would expect at least two of the comparisons to reach significance by chance. Furthermore, in the subanalysis during which patterns between visits were examined, even more caution must be used in the interpretation of significant values. 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: 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.

Because neither the second phase 3 trial nor the phase 2 trial could repeat the statistically significant finding of the first phase 3 trial with respect to these subjective variaibles, no conclusions can be reached about them. Therefore, these statements about specific dry mouth symptoms should not be included in the label as the sponsor has proposed.

Comparison of pre and post dose for secondary subjective variables

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. The results section for each phase 3 trial contains a table for this comparison. Neither trial demonstrates any significant differences. This is not unexpected for the subtle changes being examined with these secondary variables (such as ability to more comfortably speak and eat) would be noticed during normal activities of daily living, rather than during an hour-~~long~~ exam in a clinical setting.

Objective: Salivary Flow

Although there were some inconsistencies in the results of salivary flow measurements, the comparison between the 30 mg group and the placebo group demonstrated a statistically significant increase in salivary flow in the 30 mg group in both phase 3 trials as well as the phase 2 trial.

In the first study, the baseline salivary flow is comparable in all three study groups. Pre-dose, at each visit, flow rates for the placebo group and the 15 mg group are approximately the same, indicating that any significant pharmacologic effect from the 15 mg tablet had probably dissipated prior to the next scheduled dosing. The pre-dose salivary flow rate of the 30 mg group, on the other hand, is significantly higher than the 15 mg or placebo group at every visit, indicating that there is still some pharmacologic activity at the higher dose. Note that the pre-dose measure at each visit after baseline for the placebo is consistently approximately 30% higher than the baseline measure. This effect may be explained by the subjects being more experienced with the salivary collection procedure, an increased psychogenic effect increasing saliva production, or raised examiner expectations that are reflected in more aggressive collection of the saliva. Similarly, post-dose readings for the placebo are always higher than pre-dose readings, which may be for the same reasons. However, because the study was blinded and comparisons were always made to the placebo, any bias from this effect should cancel. Mirroring the results of the global assessment measure, the improvements in the 15 mg group are not significantly better than improvements in the placebo at any visit. However, for the 30 mg group, both the pre-dose and post-dose readings were higher than in either the 15 mg or placebo groups. These differences were enough to result in a statistically significantly greater improvement in salivary flow in the 30 mg group than the placebo at all visits, and is supportive of efficacy of the 30-mg dose of this drug.

The pattern of salivary flow for the first study is similar to that of the second study, and is sufficient to result in a statistically significant improvement in the salivary flow in the 30 mg group when compared to the placebo. However, the major difference between the two studies is that the 30 mg group had a lower salivary flow for every predose visit in the second study compared to the first study, and the flow rate never achieved as high a value at the post dose visit in the second study compared to the first study. As in the first study, all three groups in the second study had approximately the same flow at baseline; in fact, the baseline values are very similar to the first study. The placebo predose value increased from baseline at each visit in the second study, beginning at week 6, and stayed at the same level at each subsequent visit. Also, as was seen in the first study the 15 mg group in the second study improved from predose to post dose by about the same amount at each visit. However, compared to the first study, the 30 mg group in the second study had lower pre-dose readings. Nonetheless, this lower predose value and lower post dose value for the 30 mg group still produced a large enough difference to be a statistically significantly greater improvement than seen in either the 15 mg group or the placebo, although the actual flow in the 30 mg group is less in the first study than the second study.

The salivary flow changes in SB95US01, the phase 2 trial, show a similar pattern of magnitude and trend in the comparison of the active groups and placebo over time. Just as the 30 mg groups showed improvement over the 15 mg group and both were significantly greater improvement than the placebo in the phase 3 trials – the 60 mg group showed improvement over the 30 mg group and both were significantly greater improvement than the placebo in the phase 2 trial. There is no evidence in either the phase 2 or phase 3 trials that the salivary flow improvement is decreasing over the duration of the trials.

The summary of change from baseline was a slightly different way in which the sponsor compares salivary flow. Comparing the changes from baseline to postdose is intended to control for the differences in baseline values, which the pre-dose to post-dose comparison does not. Although the patterns are the same in this comparison, all of the values in this analysis are higher, resulting in comparisons that have much better p values since the absolute differences are greater. Although the measurements show that the 30 mg group has a statistically significantly greater salivary flow at all three post-dose comparisons to baselines in both trials, the first trial has far better p values for the differences than the second trial. This is consistent with both the prior salivary flow analyses as well as with the results of the global assessment.

Possible explanation for difference of phase 3 trial results

In trial SB96US02, the difference in theh primary outcome variable between the placebo and 30 mg group is highly significant; whereas in trial SB96US04, there is no difference between these same groups. It would be valuable to explore why this happened and whether the results of the phase 2 trial, SB95US01, can corroborate the results that demonstrated efficacy.

In terms of examining potential problems in either phase 3 trial that would yield invalid results, one can look at potential errors including blinding or randomization inadequacies, unbalanced baseline characteristics, proper production of and assignment of study medication. One can also try to validate the subjective measures by comparing them with the pharmacologic outcomes such as salivary flow and increased sweating in each trial.

In each trial, the groups are demographically similar in terms of age, gender, and race. There is no evidence that the randomization or blinding scheme is flawed , though with predictable adverse events such as sweating being so common in this class of drug, it is likely that many subjects in the trial on active know they are receiving a drug. This would bias the studies towards effectiveness of the drug, but it is unlikely to bias one study over another unless subjects are more likely to discuss these events with other subjects or investigators in one trial over another. With identical protocols, this seems unlikely, but it is always a possibility.

Other baseline characteristics that could affect the outcome, including degree of dryness, diagnosis of primary vs. secondary Sjögren's syndrome were also examined with one potentially confounding finding. As was noted in the results section of this review, the first phase 3 trial, which showed a greater global score improvement in the 30 mg group than the second phase 3 trial, also had a far greater number of subjects with milder disease. Forty percent of subjects had mild disease in the first study's 30-mg group compared to 20% of subjects in the second study's 30-mg group and a lesser number had severe disease at baseline (15% of the 30 mg group's subjects in the first study compared to 30% of the 30 mg group's subjects in the second study. It was observed in the clinical trials for Salagen's supplement for Sjögren's syndrome that pilocarpine has the strongest effects on patients with mild disease. Cevimeline, being pharmacologically similar to pilocarpine, may be expected to perform similarly. This difference between trials in severity at baseline may explain why the second trial had lesser improvements in global outcome, making it more difficult to surpass the placebo's effect.

Because the sponsor used the Last Observation Carried Forward (LOCF) method for treating dropouts as having reported "worse" in response to the global evaluation for their final value, it may also be informative for them to examine how many of the dropouts are from placebo and how many are from the active group. Although this would not explain the greater percentage of "better" responses in the placebo group, the treatment of dropouts in these trials may have resulted in the lesser numbers of "better" responses in the active test groups, especially the 30 mg group. This is due to the high number of discontinuations that are expected in the 30 mg group as a result of adverse events. This would then make the treatment group look worse than it really was, which is conservative, but would be difficult to overcome if there were a high dropout rate. On the other hand, if the placebo group had more dropouts due to lack of effect, it would have been easier for the active group to demonstrate effectiveness since the comparison would show an inflated success in the active.

What is seen is that when asked the global question about mouth dryness at each timepoint compared to baseline, there was a significant improvement in the 30 mg group compared to the placebo in the first phase 3 trial. In the second, no significant difference was demonstrated between placebo and 30 mg dose. The sponsor contends that the lack of a difference is due to a very active placebo group, which is correct. However, it must also be noted that the 30 mg group showed a lesser effect in the second trial compared to the first both in the global measure and the salivary flow. In the first trial, 66% of the 30 mg group improved, compared to the placebo's 37% - this is statistically significant. In the second trial, in the 30 mg group 53% reported feeling better, but the placebo group reported 55%, so there is no difference. We see a combination of the placebo performing much better than expected and the 30 mg group worse in the second trial – had the 30 mg group performed as well in the second trial as the first, it may have been sufficient to be statistically superior to the placebo. It is therefore worth examining further not only why the placebo effect was more pronounced in the second trial, but also why the 30 mg group performed worse. Measures that may provide some insight are differences in the salivary flow and adverse events between trials.

The salivary flow of the placebo groups is very similar in both trials. In both cases, the baseline measure is approximately 0.06 ml/min at baseline. The improvement resulting from being in the trial increases the predose salivary measure at each visit to approximately 0.09 – 0.10 ml/min in the first trials and 0.10 to 0.11 ml/min in the second. The post dose measure in salivary flow for the placebo group is nearly identical in both trials. Of course, variability is also very high in the salivary flow data. This is partly due to the high individual variability that one sees in salivary flow. There may also be a lot of variability because both protocols called for post dose saliva collection "at a minimum of 90 minutes after dosing." This open-ended time frame may allow for different pharmacologic effects depending on how long after 90 minutes the saliva is collected and if this varies by study site. However, it is unlikely that this instruction would bias the outcome, unless the investigators in the second trial were given further instruction that changed their collection time or method.

The fact that the salivary flow data in the second phase 3 trial produces a significant increase in the 30 mg group compared to placebo, along with the expected increase in adverse events in the 30 mg group refutes the hypothesis that the test drug may have been mislabeled and the placebo group received active drug. This is supported by the fact that the adverse events profile showed comparable values in the 30 mg group with 18% of subjects reporting increased sweating in the first trial and 24% in the second trial.

In summary, one phase 3 trial has very strong results and another phase 3 trial is supportive, but is unable to show significant improvement over placebo. This is due to both a very strong placebo response, and a slightly weaker response in the second trial from the 30 mg arm. Possible explanations have been hypothesized for the active arm performing less strongly in the second phase 3 trial, but no firm explanation other than random chance can account for the high placebo effect. Because these two outcomes combined render the second phase 3 trial incapable of demonstrating efficacy, another trial is required to confirm the efficacy of Cevimeline. Fortunately, a placebo control trial was conducted as a phase 2 trial in 1995, SB95US01 that was of sufficient size to demonstrate a statistically significant improvement in the global evaluation of dry mouth.

Use of Phase 2 trial results as pivotal

After thorough review of the two sets of phase 3 trial results, which resulted in one trial that demonstrated efficacy for the primary global outcome and the other that did not, further evaluation is necessary to grant approval. The sponsor submitted SB95US01, their phase 2 study, in the NDA application. Although the sponsor designed the trial primarily for dose-ranging exploration, the conduct of this trial was similar enough to the phase 3 trials and the number of subjects were sufficient to deem it acceptable as a confirmatory trial.

There are differences between the phase 2 and phase 3 trial protocols, which require exploration to determine the comparability of the studies. The phase 2 trial used 30 mg and 60 mg for the test drugs, rather than 30 mg and 15 mg as was done in the two phase 3 trials. Another difference between the phase 2 and phase 3 trials is that in phase 2, more than one subjective measure was used as primary outcome. A third difference is that the phase 2 trial was of 6 weeks duration, rather than 12 as were the phase 3 trials. One final difference is that the inactive components of the drug product were somewhat different in the phase 3 trials than those used in the phase 2 trials. None of these differences are insurmountable in applying the results favorably to support approval.

The use of specific symptoms of dry mouth in addition to the global assessment in the phase 2 trial occurred prior to the end-of-phase 2 meeting, at which time the agency advised use of only the global as a primary endpoint. The Agency views use of multiple endpoints for primary as being less than ideal due to the need to adjust for multiple comparisons in the case of the "or" situation, and the difficulty in satisfying the "and" situation. However, since the phase 2 trial was highly significant, even the maximum adjustment would not result in non-significance of the global outcome comparison.

The use of 6 weeks duration is also not crucial, since there is no set policy for the length of time for xerostomia trials. Twelve weeks was the length of time used for Salagen's phase 3 trials, as well as the phase 3 trials for Cevimeline. Nonetheless, because 6 weeks was sufficient to demonstrate efficacy in the phase 2 trial, 12 weeks of placebo-controlled results were reviewed in the phase 3 trials, and the open label study was of one year's duration, the shorter time in SB95US01 is not a roadblock to approval.

Both phase 3 trials failed to demonstrate effectiveness of the 15 mg dose for subjects, so the 30 mg dose appears to be optimal over the general population tested. Therefore, the 30 mg results from the phase 2 trial are the ones of most interest, and are supportive for approval.

Finally, the difference in formulations is minor and was reviewed by both Chemistry and Biopharmaceutics. The Cevimeline capsules used in the phase 2 trial, SB95US01, were composed of a drug substance that was manufactured using the same process and in the same amount as the capsules used in both phase 3 trials. However, there was a minor difference in the inactive ingredients that made the drug used in SB95US01 not identical to the drug in the phase 3 trials. The chemistry and biopharmaceutical teams jointly concluded that the two drug products were bioequivalent.

Totality of Evidence for Effectiveness

What has been presented in the NDA submission and reviewed thoroughly are three adequate and well-controlled clinical trials for Cevimeline, with two of the trials demonstrating efficacy of the global assessment of dry mouth and one being inconclusive. The two trials that were able to demonstrate significant improvement in primary outcome of the 30 mg group over placebo also showed statistically significant improvements in salivary flow, a secondary outcome variable, in both groups. The inconclusive results from the second phase 3 trial were the result of a very active placebo group, for which no explanation could be provided. Nonetheless, the global assessment values for both the 15 mg group and 30 mg group are very comparable to those of both the other phase 3 trial and the successful phase 2 trial. The salivary flow improvements were statistically significant for the 30 mg group in the inconclusive phase 3 trial and were very similar in value to the other two trials. Based on the success of two well-controlled trials and one additional inconclusive but supportive trial, the totality of evidence provides an adequate demonstration of the effectiveness of 30-mg of Cevimeline to treat the symptoms of dry mouth.

Definition of Primary and Secondary Sjogren's Syndrome

As was noted in the Introduction section of this review, Sjögren's syndrome may be primary or secondary, depending upon the presence of another autoimmune disorder. The question of which definition was used to diagnosis primary versus secondary Sjogren's in the enrolled subjects arose. One of the challenges in doing research for this indication is that there is no single well-defined diagnostic set of criteria for Sjögren's syndrome. The sponsor cited the American Rheumatism Association's Diagnostic Criteria for primary and secondary Sjogren's, but the definition in the protocol may have been incorrectly stated. The sponsor's definition appeared to allow an "or" condition for the Sjogren's being secondary to another autoimmune condition. Upon questioning the sponsor, the sponsor acknowledged that the definition may not have been well stated, but that all of the investigators were well-trained in the diagnosis and treatment of Sjogren's syndrome, and labeled the subjects properly as being primary or secondary Sjogren's. Nonetheless, because there were approximately 25 sites used in each of the phase 3 trials, leaving the definition of SS to each investigator has the potential to provide inconsistent, and possibly invalid results. Dr. Robert Fox, the author of the chapter on Sjögren's syndrome in <u>The Textbook of Rheumatology</u> (*Fourth Edition*: Kelley, W.N. et al, W.B. Saunders Company, Pennsylvania, 1993.) states that "One major problem in describing the clinical spectrum of SS is that there is no uniformly accepted definition for this syndrome."

Because there is insufficient data to state specific findings regarding subjects with either primary or secondary Sjogren's syndrome, it is recommended that the label not include specific statements that split out patients with either primary or secondary Sjogren's syndrome as the sponsor has proposed. Rather, it is desirable to include general labeling of Sjogren's, without specifying primary or secondary.

Safety

For all studies included in the Integrated Safety Database, a total of 882 subjects were enrolled and exposed to at least one dose of either cevimeline or placebo. Of these, 651 subjects received cevimeline and 231 received placebo. International Conference on Harmonization Document E1A ("Guideline on the Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions; Availability") makes the following comment on evaluation of safety: "Available information suggests that most adverse drug experiences first occur, and are most frequent, within the first few months of drug treatment. The number of patients treated for 6 months at dosage levels intended for clinical use, should be adequate to characterize the pattern of adverse drug experiences over time. To achieve this objective, the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5 percent to 5 percent). Usually 300 to 600 patients should be adequate." Including the subjects who were submitted in the 120-day safety update, a total of 351 subjects received a dose of 30 mg tid or greater for 6 months or more. Of these, 141 subjects completed twelve months of treatment with the proposed dose of the drug, 30 mg, or higher.

As was expected with a drug that is a muscarinic agonist, pharmacologically similar to pilocarpine, a consistent pattern of expected adverse events was observed in all trials. In overall incidence, increased sweating was the most common, followed by nausea, headache, diarrhea, dizziness, and dyspepsia.

Subjects dropped out at a rate that was directly proportional to the dose, both in the Sjögren's syndrome trials For the subjects in the cevimeline groups there was a 32.8% dropout compared with 13.4% dropout rate in the placebo groups.
Overall, in the short-term studies, higher percentages of subjects in the 60 and 80 mg groups discontinued due to adverse events. The discontinuation rates due to adverse events among the lower dosage groups (15 mg, 20 mg, 30 mg, and 40 mg cevimeline) were comparable to that for the placebo group (2.9%). However, in open-label long-term studies these differences among dose groups were not very prominent. This may be because of discontinuation of a more sensitive population or because resistance developed from long-term use.

Serious adverse vents occurred with a small incidence (2%) and were identical in incidence in the groups that received 15mg drug, 30 mg drug, 60 mg drug or placebo. Of the serious adverse events, it is clear that many are unrelated to the study medication, such as traumatic injuries and cancer. Nonetheless, it is not possible to rule out a relationship between many of these events and the study drug.

One subject died during the active phase of the studies and two subjects died following completion of the study. The subject who died during the active phase of the trial was a 70-year old male with previously undiagnosed triple-vessel disease, who died following a myocardial infarct. The investigator assessed the event as possibly related to the study drug. It should be noted that the proposed label for this drug warns of drug use in the event of significant cardiovascular disease. Of the other two subjects, one died from complications of multiple myeloma and the other from pancreatitis. Both causes of death were judged to be unrelated to the study medication.

No gender, age group, or racial differences were seen within a treatment group in total incidence of adverse events for the Sjögren's placebo-controlled studies except for the placebo group (81% female vs. 67% male) and 30 mg group (92% females vs. 62% male). No formal studies were conducted to investigate demographic or disease interactions with cevimeline. However, no differences were evident in studies conducted either in the United States or in Japan with respect to racial origin or age. Because Sjögren's syndrome is a disease occurring overwhelmingly in women there were few men in these trials.

There were no apparent dose-related changes from baseline to endpoint for any of the vital signs, or ECG. Physical examination did not reveal significant changes as a result of the drug in either the Sjögren's syndrome Because this drug is a new molecular entity, careful attention was given to the analyses for changes in laboratory parameters as well.

All subjects on any dose of the drug in the placebo-controlled and open-label studies had blood samples collected at baseline, endpoint, and several visits in between. Placebo subjects in the placebo-controlled trial were also sampled for comparison. All subjects with out-of-normal range laboratory values were tabulated and categorized by exposure to drug. This was done for all subjects with any laboratory value out-of-normal, as well as for only those subjects whose values were normal at baseline and whose values fell out of normal at endpoint. A comparison was also made for those subjects whose values were well beyond the boundaries of normal range.

As is typical with most NDA's submitted for review, the database used for examining safety and length of study, although conforming to ICH guidelines, can only be expected to identify adverse events that occur at a rate of approximately 1% or more. Rarer events are often discovered only through adverse drug reaction reports and post-marketing surveillance. Although no patterns of serious adverse events or evidence of drug-related laboratory abnormalities was uncovered in the clinical trials, careful monitoring is recommended, particularly during the first several years of commercial use of a new molecular entity.

Although there is no clear evidence of dose response or significant increases in laboratory values with drug compared to placebo, some of the changes in laboratory values occurred for reasons that cannot be explained and an effect of Cevimeline cannot be ruled out. Many of the patients in these studies who have Sjogren's syndrome also have other autoimmune diseases and received multiple drug therapy. In one subject who was discontinued from one of the trials due to cytoxin-induced neutropenia, there was an extreme elevation in ALT levels. Although the cytoxin or other drugs may have caused the extreme elevation of ALT levels, Cevimeline cannot be ruled out as contributory. Since many individuals have Sjogren's syndrome secondary to lupus or other autoimmune conditions and require the same medications as this patient, a note in the label of this abnormal laboratory chemistry may be warranted. Similarly, as was presented in the *Results* section of this review, two subjects on the drug registered extremely high AST values which increased as the drug dose was increased. Once again, it may be prudent to include this information in the labeling of the drug.

Recommendations to the Sponsor

With changes to the proposed label, Cevimeline is recommended for approval for relief of the symptoms of dry mouth at a dosing of 30 mg t.i.d.

Proposed Labeling

The sponsor's proposed label has been edited to produce a label that is accurate and complies with FDA guidelines. The first of the two versions of the label, beginning on page 115 of this review, shows strikeouts and additions to the sponsor's proposed label in order to achieve this goal. The second version is a "clean" copy of the first with the markings removed for easier reading.

Each of the following comments provides a rationale for the clinical changes to the proposed label, in order of appearance.

34 PAGE(S) REDACTED

Draft

Labeling

Recommended Regulatory Action:

This new drug application for Cevimeline hydrochloride is approved for the treatment of symptoms of dry mouth at a dosing of 30 mg tid.

/S/ 8/13/99
Frederick N. Hyman, D.D.S., M.P.H.

cc: Orig NDA
HFD-540/Div File
HFD-540/DD/Wilkin
HFD-540/TL/Kelsey /S/ 8/13/99
HFD-550/TL/Chambers
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