

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-989

MEDICAL REVIEW(S)

JAN 6 2000

Dental Officer's Review of NDA 20-989
Resubmission

Drug:

Cevimeline hydrochloride capsules (cis-2'-methylspiro{1-azobicyclo [2.2.2] octane 3,5' -[1,3] oxathiolane} hydrochloride, hydrate (2:1)

Sponsor:

Snow Brand Pharmaceuticals, Inc.

Pharmacologic Category:

Cholinergic

Proposed indication:

Treatment of symptoms of dry mouth _____
_____ in patients with
_____ Sjögren's syndrome

Serial Number: AZ

Submission date: November 11, 1999

Received date: November 12, 1999

Review date: December 23, 1999

PDUFA date: January 12, 2000

Project Manager: Olga Cintron

Reviewer: Fred Hyman

Information to Sponsor:

Yes

No

Background and Regulatory History

The sponsor, Snow Brand Milk Products, Ltd. opened IND _____

At the time that the IND was opened, the drug was named _____ ("cevimeline" was not used until the NDA was opened). The sponsor then opened IND _____ in March, 1995 to test the same drug, which it named SNI-2011 in these trials, for relief of symptoms of Sjögren's syndrome.

There is already one drug that has been approved for relief of symptoms of Sjögren's syndrome. Salagen (pilocarpine), also a cholinergic parasympathomimetic agent with predominant muscarinic action, was approved in February, 1998 for treatment of symptoms of dry mouth in subjects with Sjögren's syndrome.

On August 27, 1999, the Agency issued an approvable letter to SnowBrand Pharmaceuticals, the sponsor of Cevimeline, for the indication, "treatment of symptoms of dry mouth in patients with Sjögren's syndrome". The sponsor's label that was submitted with the original NDA was revised and sent to the sponsor along with the approvable letter. The approval is contingent upon acceptance of the revised label or of a similar, acceptably revised label. The sponsor met with the Agency on November 3, 1999 to discuss the Agency's rationale for the suggested revisions. In this current submission, the sponsor has proposed changes to the version of the label that accompanied their approvable letter. This review will address the acceptability of each of these revisions. The sponsor has also submitted, in accordance with the terms of the approvable letter,

a safety update. This update includes retabulation of safety data, including results of ongoing trials, reporting of new adverse events, and significant changes or findings.

The following section of this review contains each proposed change to the approvable label and a discussion of the acceptability of the change. Following that, the sponsor's safety update is reviewed. Two versions of the drug label are attached to the review. The first is the label that accompanied the sponsor's submission, with strikeout denoting the agency's requested deletions and underlining denoting the agency's requested additions. The second label is the final approved label to accompany the approval letter.

Proposed Changes:

Revision #1:

The sponsor has suggested deleting the last sentence of the second paragraph of the Clinical Studies section. The paragraph currently states:

A 6-week, randomized, double blind, placebo-controlled study was conducted in 75 patients (10 men, 65 women) with a mean age of 53.6 years (range 33-75). The racial distribution was Caucasian 92%, Black 1% and other 7%. The effects of cevimeline at 30 mg tid (90 mg/day) and 60 mg tid (180 mg/day) were compared to those of placebo. Patients were evaluated by a measure called global improvement, which is defined as a response of "better" to the question, "Please rate the overall condition of your dry mouth now compared with how you felt before starting treatment in this study." Patients also had the option of selecting "worse" or "no change" as answers. Seventy-six percent of the patients in the 30 mg tid group reported a global improvement in their dry mouth symptoms compared to 35% of the patients in the placebo group. This difference was statistically significant at $p = 0.0043$. There was no evidence that patients in the 60 mg tid group had better global evaluation scores than the patients in the 30 mg tid group.

Sponsor's Rationale for Revision #1:

The sponsor states that "Since 30 mg tid is the only dose being pursued in the label and for which data from the clinical studies are being presented, this sentence is no longer relevant and thus we deleted it from the label."

Reviewer's Comment:

The phase 2 trial, which was used as support for the efficacy of the 30-mg dose of cevimeline, is the subject of this section of the label. In order to provide complete information, the trial design and results are included. Because the trial was designed to compare both the 30-mg and 60-mg groups to the placebo, the results would be

incomplete if only the 30-mg comparison to placebo were reported. In addition, since it is possible that clinicians may choose in individual cases to increase the recommended dose of 30 mg to 60 mg, this information should be available in order for them to make an informed decision. The sentence will remain in the final label.

Revision #2

The sponsor has suggested the following revision to the fourth sentence of the third paragraph of the Clinical Studies Section:

from: Statistically significant global improvement in the symptoms of dry mouth ($p=0.0004$) was seen for the 30 mg tid group compared to placebo, but not for the 15 mg group compared to placebo.

to: Statistically significant global improvement in the symptoms of dry mouth ($p=0.0004$) was seen for the 30 mg tid group compared to placebo.

Sponsor's Rationale for Revision #2:

The sponsor states that since only the 30-mg dose is being approved, the results of the 15-mg group is not relevant.

Reviewer's Discussion:

All three of the studies described in the Clinical Studies section, taken together, give a complete picture of the controlled clinical trials; i.e. that the 60-mg dose did not show more improvement over placebo than the 30-mg group, and that the 15-mg group did not provide enough improvement over placebo to be deemed effective. Because a capsule containing 30-mg of drug is the only approved form of cevimeline, there is not a concern about clinicians prescribing a 15-mg dose. Nonetheless, this information is important so that the clinician understands the reasons for the approved dosing regimen. This phrase should remain.

Revision #3:

In the fourth paragraph of the Clinical Studies section, the fourth sentence currently states:

No statistically significant differences were noted in the patient global evaluations. There was a higher placebo response rate in this study compared to the aforementioned studies.

The sponsor wishes to combine these two sentences into the following one for better

clarity:

Reviewer's Discussion:

As was discussed in detail in the initial NDA review, the percentage of subjects who responded positively to 30 mg of cevimeline was similar in all three studies described in this section. The trial described in this paragraph refers specifically to the phase 3 trial in which a statistically significant difference between placebo and drug could not be established. In this instance, the high placebo response was unusual and was a large factor in contributing to the inability to demonstrate a statistically significant improvement of the active drug in this trial. However, combining these two sentences would alter the intended meaning sufficiently to imply that causality has been established - and that the agency agrees that the only reason significance was not established was the high placebo effect. As an alternative, the word "however" can be inserted at the beginning of the second sentence in the original version to link the phrases without implying cause and effect. The approved label will read:

No statistically significant differences were noted in the patient global evaluations. However, there was a higher placebo response rate in this study compared to the aforementioned studies.

Revision # 4

In the Cardiovascular Diseases subsection of the WARNINGS section, the label currently states:

Cevimeline can potentially alter cardiac conduction and/or heart rate.

Sponsor's proposed wording:

Cevimeline can potentially alter cardiac conduction and/or heart rate. Patients with significant cardiovascular disease may potentially be unable to compensate for transient changes in hemodynamics or rhythm induced by EVOXAC™. EVOXAC™ should be used with caution and under close medical supervision in patients with a history of cardiovascular disease evidenced by angina pectoris or myocardial infarction.

Sponsor's rationale:

The sponsor believes that their proposed stronger cardiovascular warning relays the possibility that some patients may demonstrate cardiovascular effects, although this was not documented in cevimeline's clinical trials.

Reviewer's Discussion:

Were the sponsor proposing to reduce the level of severity of this warning, the agency might have concerns. However, the sponsor is voluntarily suggesting a stronger warning. As was discussed in the Adverse Events section of the original NDA submission, it is noted that a 79-year old male subject suffered a myocardial infarction during participation in the active phase of a trial, and subsequently died two months after the event. Although there is no compelling evidence that cevimeline contributed to the event, the investigator could not rule out a relation to the drug. In light of this event, the sponsor may have judged it prudent to strengthen this warning. In addition, Salagen (pilocarpine) - a drug very similar to cevimeline, but more thoroughly studied due to its time in use - already contains this suggested wording about transient changes in hemodynamics or rhythm, making the two labels consistent. This is an acceptable change.

Revision #5

The *Geriatric Use* section in the label that was included with the approvable letter to the original NDA submission reads:

[Redacted]

Special care should be exercised when cevimeline treatment is initiated in an elderly patient, considering the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in the elderly.

Sponsor's proposed Change:

The sponsor proposes to delete the first sentence, and alter the wording of the second sentence to become the first. The last sentence of the paragraph will remain intact. The sponsor's revised section is proposed as follows:

[Redacted]

Special care should be exercised when cevimeline treatment is initiated in an elderly patient, considering the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in the elderly.

Sponsor's rationale:

The sponsor believes that the total enrollment of almost 36% of subjects over 65 in their trials constitutes a sufficient number of older subjects.

Reviewer's Discussion

The CFR provides guidelines for Geriatric labeling in 21 CFR 201.57(f)(10) and suggests templates for several different scenarios. One of the proposed inserts describes the situation in which the studies did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently than younger subjects was selected. During the original NDA review, it was decided to use this as a template and modify it to fit the current situation. Although approximately 36% of subjects enrolled in the controlled trials were over 65, this small number (less than 100 with all doses combined), combined with a relatively low incidence of adverse events, does not provide adequate statistical power for conclusions about the age relationship of these events. Refer to the following tables, which summarize the most common adverse events reported in the placebo controlled clinical trials:

Sjögren's placebo-controlled studies; dose = 15 mg

Adverse Events	≤60 years; total n=81		>60 years; total n=59	
	N	%	N	%
Nausea	6	7.4	6	10.1
Increased sweating	3	3.7	4	6.7
Headache	15	18.5	3	5.0
Diarrhea	10	12.3	6	10.1

Sjögren's placebo-controlled studies; dose = 30 mg

Adverse Events	≤60 years; total n=104		>60 years; total n=49	
	N	%	N	%
Nausea	26	25.0	9	18.3
Increased sweating	23	22.1	8	16.3
Headache	22	21.1	10	20.4
Diarrhea	13	12.5	6	12.2

Note that the incidences of reported adverse events are not large enough to form conclusions about the relationship of age to these events. In addition, the pattern differed depending on the dose. For the approved dose of 30 mg, the percentages are very similar for the adverse events between those over 60 and under 60, although the younger group reports a higher incidence in all four of these adverse events. In the 15 mg groups, nausea and increased sweating is higher in the older group, whereas headache is substantially larger in the younger group.

In this current submission, the sponsor requests removal of the first sentence. The sponsor believes that the first sentence would be more correctly used to describe a situation in which almost no experience in individuals over 65 was provided. In all fairness, the sponsor's data gives some assurance that there are no apparent differences between groups; it is simply not conclusive. However, the trials were not large enough to imply that the agency is confident about a lack of differences in the geriatric population. Rather than removing the first sentence, the agency suggests modifying it to the following:

Although clinical studies of cevimeline included subjects over the age of 65, the numbers were not sufficient to determine whether they respond differently from younger subjects.

The remainder of the paragraph is unchanged from the version in FDA's approvable letter.

Revision #6

In the *Management of Overdose* section of the label, it currently states:

Management of the signs and symptoms of acute overdosage should be handled in a manner consistent with that indicated for other muscarinic agonists

Sponsor's proposed wording:

Management of the signs and symptoms of acute overdosage should be handled in a manner consistent with that indicated for other muscarinic agonists: general supportive measures should be instituted.

known if cevimeline is dialyzable.

It is not

Reviewer's Discussion:

The degree of detail in the Management of Overdose section on FDA-approved drug labels is variable. Within the Center, each is considered on a case-by-case basis. On many drug labels, there are specific amounts of recommended antidote drugs and details on supportive medical care. On others, there is a very general statement, or a mention of a recommended drug without amounts or instructions. In general, drugs with a higher potential for overdosage seem to have more detailed instructions. There are three approved drugs that are muscarinic agonists like Cevimeline and have a management of

Overdosage section on their labels. The first one, urecholine injection, is a drug pharmacologically related to acetylcholine, which is used for the treatment of acute postoperative and postpartum urinary retention. Its overdosage section contains very detailed instructions as follows:

OVERDOSAGE

Early signs of overdosage are abdominal discomfort, salivation, flushing of the skin ("hot feeling"), sweating, nausea and vomiting.

Atropine is a specific antidote. The recommended dose for adults is 0.6 mg (1/100 grain). Repeat doses can be given every two hours, according to clinical response. The recommended dosage in infants and children up to 12 years of age is 0.01 mg/kg (to a maximum single dose of 0.4 mg) repeated every two hours as needed until the desired effect is obtained, or adverse effects of atropine preclude further usage. Subcutaneous injection of atropine is preferred except in emergencies when the intravenous route may be employed.

When URECHOLINE is administered subcutaneously, a syringe containing a dose of atropine sulfate should always be available to treat symptoms of toxicity.

The second muscarinic agonist, Salagen, contains a moderate degree of detail in its Management of Overdosage section as follows:

MANAGEMENT OF OVERDOSE

Fatal overdosage with pilocarpine has been reported in the scientific literature at doses presumed to be greater than 100 mg in two hospitalized patients. 100 mg of pilocarpine is considered potentially fatal. Overdosage should be treated with atropine titration (0.5 mg to 1.0 mg given subcutaneously or intravenously) and supportive measures to maintain respiration and circulation. Epinephrine (0.3 mg to 1.0 mg, subcutaneously or intramuscularly) may also be of value in the presence of severe cardiovascular depression or bronchoconstriction. It is not known if pilocarpine is dialyzable.

The third muscarinic agonist listed in the PDR, carbochol ophthalmic solution, has very scant information, as follows:

Overdosage: Atropine should be administered parenterally: (for dosage refer to Goodman & Gilman or other pharmacology reference).

A very detailed overdose section is not recommended as it is not within the jurisdiction of

FDA to oversee the practice of medicine. In addition, there is a concern with being too specific with antidote information in the event that choice of drug may change over time.

To determine the type of overdosing information that the cevimeline label should contain, one should consider the likelihood of overdose and setting in which it could occur. It is highly unlikely that the overdose would occur in the prescribing physician or dentists office; rather the scenario may be a child accidentally swallowing the drug, or a patient misunderstanding the directions on the label at home. An emergency facility, which would treat a patient who received an overdose, would be well-versed in treatment of a muscarinic agonist and not need to rely on the label (The first sentence of this section clearly states that the drug is a muscarinic agonist.). Atropine is a classic, effective treatment for muscarinic agonist overdosing; it is unlikely that it will be not be effective, should a newer drug be developed. The same is true of epinephrine as an effective agent for cardiovascular depression or bronchoconstriction. The sponsor also added "may be of value" to both the atropine and epinephrine to allow for other drug therapy as the attending facility would see fit.

It would be best to remove the dosing range for both the atropine and epinephrine; each situation should be evaluated individually by a trained professional administering the treatment, depending upon the patient and amount of overdose. The insertion of the phrase "if medically indicated" after describing the use of atropine and epinephrine is also recommended to further emphasize the need for individual evaluation. With these changes, the label is acceptable. The management of Overdose section of the approved label will state:

Management of the signs and symptoms of acute overdosage should be handled in a manner consistent with that indicated for other muscarinic agonists: general supportive measures should be instituted. If medically indicated, atropine, an anti-cholinergic agent, may be of value as an antidote for emergency use in patients who have had an overdose of cevimeline. If medically indicated, epinephrine may also be of value in the presence of severe cardiovascular depression or bronchoconstriction. It is not known if cevimeline is dialyzable.

Revision #7:

The Dosage and Administration section of the label currently states:

The recommended dose of cevimeline is 30 mg taken three times a day. There is insufficient safety information for doses greater than 30 mg tid.

The sponsor wishes to remove the second sentence.

Sponsor's rationale:

The sponsor believes that they have sufficient safety information for subjects who received greater than 30 mg tid dosing in the clinical trials.

Reviewer's Discussion

Including the subjects enrolled since the NDA submission, there are a total of 190 subjects who consumed greater than 30 mg tid of cevimeline for 6 months. Of these, 87 received greater than 30 mg tid of cevimeline for 12 months. This is not sufficient to meet the minimum ICH guidelines for demonstrating chronic-use drug safety. The sponsor mistakenly believed that if 300 subjects received 60 mg of cevimeline for any length of time, it met the guidelines. In addition, as is stated in the clinical section of the label, there is insufficient evidence for additional efficacy to support doses greater than 30 mg tid.

This statement should remain in this section in the event that the prescribing clinician decides to increase the dose in subjects who do not respond adequately to the recommended dose. Without a review of an adequate number of subjects on this higher dose, FDA cannot endorse its safety. This information should be available in order for the prescribing clinician to make an informed decision. For a clearer meaning, the phrase _____ should be changed to "to support doses greater than 30 mg". In order to clarify even further to the clinician that additional efficacy at doses greater than 30 mg tid. has not been established, an additional sentence about efficacy is suggested as well. This section of the final label will state:

The recommended dose of cevimeline is 30 mg taken three times a day. There is insufficient safety information to support doses greater than 30 mg tid. There is also insufficient evidence for additional efficacy of cevimeline at doses greater than 30 mg tid.

Proposed Minor Changes:

The following list contains minor changes, which include grammar, spelling, and typographical corrections as follows:

1. The word _____ has been replaced by "trans-sulfoxide" in the metabolism subsection of the Clinical Pharmacology Section. This was a typographical error in FDA's version that was mailed in the approvable letter – the sponsor's spelling is correct.

2. In the *Excretion* subsection of Clinical Pharmacology, the sponsor has added commas to the second and third sentences after the first parenthetical phrase. This grammatical change is acceptable.

3. In the second paragraph of the Clinical Studies section of the label, the third sentence states:

The effects of cevimeline at 30 mg tid (90 mg/day) and 60 mg tid (180 mg/day) were compared to those of cevimeline.

This is a typographical error; the second use of the word "cevimeline" should be replaced by "placebo" as follows:

The effects of cevimeline at 30 mg tid (90 mg/day) and 60 mg tid (180 mg/day) were compared to those of placebo.

4. In the fourth paragraph of the Clinical Studies section, the last sentence states, "However, the 30 mg tid group showed a statistically significant increase in salivary flow from pre-dose to post-dose compared to placebo (p=0.0017)." Due to the change made in revision #3 in the prior section of this review, the word "however" is redundant and should be eliminated from this sentence.
5. In the Pregnancy Category section, the sponsor suggests a minor change to the statement as currently written. The sponsor believes that substitution of 60 kg for — kg as the human weight will correct a typographical error. The pharmacologist concurs.

Current statement:

Cevimeline was associated with a reduction in the mean number of implantations when given to pregnant Sprague-Dawley rats from 14 days prior to mating through day seven of gestation at a dosage of 45mg/kg/day (approximately — times the maximum recommended dose for a — g human when compared on the basis of body surface area estimates).

The revised statement would be:

Cevimeline was associated with a reduction in the mean number of implantations when given to pregnant Sprague-Dawley rats from 14 days prior to mating through day seven of gestation at a dosage of 45mg/kg/day (approximately — times the maximum recommended dose for a 60kg human when compared on the basis of body surface area estimates).

6. In the *Nursing Mothers* section, the sponsor changed the first sentence, "It is not known whether this drug is secreted in human milk." to "It is not known - this drug is secreted in human milk." This minor grammatical change does not alter the meaning and is acceptable. The sponsor also added the trademark symbol to "Evoxac", which is acceptable.
7. In the Adverse Reaction section, there are two tables that provide a side-by-side comparison between the 30-mg cevimeline group and the placebo group of the adverse events reported. The footnote at the bottom of the first table refers to the "n" in the cevimeline group and currently reads "n is the total number of patients exposed to the dose at any time during the study." The footnote at the bottom of the second table also refers to the "n" in the cevimeline group and currently reads "n is the total number of patients exposed to the _____ at any time during the study." The sponsor wishes to change the second table's footnote to "n is the total number of patients exposed to the dose at any time during the study." to be consistent with the first table. This change is acceptable.
8. The sponsor was inconsistent with the spelling of Sjögrens. In four separate areas of the Adverse Events section, the umlaut was omitted on the "o". It has been corrected in the following locations of the Adverse Reactions section: the first sentence; introduction to the first table; introduction to the second table; the first sentence of the last paragraph.
9. Under How Supplied, the sponsor has changed two sentences. In the first section, they added the word _____ to their description. In the second section, they changed the storage instructions to match the approved wording in the container label, which they feel is better. The chemistry reviewer agrees with the revised storage instructions, but does not concur with the sponsor about adding _____ to the description.

The following is the revised acceptable wording:

EVOXAC™ is available as white, hard gelatin capsules of cevimeline hydrochloride containing 30 mg of cevimeline imprinted with _____ . It is supplied in child resistant bottles of 100 capsules (NDC XXXXX) and 500 capsules (NDC YYYYYY).

Store at 25°C (77°F) excursion permitted to 15° - 30° C (59° -86° F)

EDA-Initiated Changes:

1. The chemical formula listed in the label's *Description* section is missing a hyphen between octane and 3. The correct formula is cis-2'-methylspiro {1-azabicyclo [2.2.2] octane-3, 5' - [1,3] oxathiolane} hydrochloride, hydrate (2:1).
2. The paragraph "Metabolism" under the heading "Pharmacokinetics" in the sponsor's label currently states:

Metabolism: Isozymes CYP2D6 and CYP3A3/4 are responsible for the metabolism of cevimeline. After 24 hours ~~of the dose was recovered~~ ~~of the dose as glucuronic acid conjugate and 4% of the dose as N-oxide of cevimeline.~~ Cevimeline did not inhibit cytochrome P450 isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4.

In the Biopharmaceutics review, the reviewer has recommended replacing the paragraph with the following revised one.

Metabolism: Isozymes CYP2D6 and CYP3A3/4 are responsible for the metabolism of cevimeline. After 24 hours 86.7% of the dose was recovered (16.0% Unchanged, 44.5% as cis and trans-sulfoxide, 22.3% of the dose as glucuronic acid conjugate and 4% of the dose as N-oxide of cevimeline). Approximately 8% of the trans-sulfoxide metabolite is then converted into the corresponding glucuronic acid conjugate and eliminated. Cevimeline did not inhibit cytochrome P450 isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4.

3. The pharmacology reviewer has recommended the following changes to the *Carcinogenesis*, *Mutagenesis*, *Impairment of Fertility* and *Pregnancy Category* sections:

In the Carcinogenesis section, the following sentences were changed as noted: -

A statistically significant increase in the incidence of adenocarcinomas of the uterus was observed in female rats that received cevimeline at a dosage of 100mg/kg/day (approximately ~ 8 times the maximum human exposure based on comparison of AUC data).

Cevimeline did not adversely affect the reproductive performance or fertility of male Sprague-Dawley rats when administered for 63 days prior to mating and throughout the period of mating at dosages up to 45mg/kg/day (approximately - 2 times the maximum recommended dose for a 60kg human following normalization of the data on the basis of body surface area estimates).

The numerical changes were made due to a recalculation based upon a maximum approved dose of 30 mg tid, rather than the sponsor's originally proposed — mg tid. The sentence about — was removed to be consistent with CDER policy.

In the Pregnancy section, the following sentence was changed as noted due to the recalculation for maximum dose as described above:

Cevimeline was associated with a reduction in the mean number of implantations when given to pregnant Sprague-Dawley rats from 14 days prior to mating through day seven of gestation at a dosage of 45mg/kg/day (approximately — times the maximum recommended dose for a 60kg human when compared on the basis of body surface area estimates).

Safety Update

Safety Status Prior To This Submission

The original NDA review examined all aspects of safety including serious adverse events, deaths, dropouts, physical exam results, laboratory normality shifts, and relationship of events to gender, age or race. At the time that the original NDA submission was filed, a total of 882 subjects were enrolled and exposed to at least one dose of either cevimeline or placebo. Of those, 651 subjects received cevimeline and 231 received placebo. The 120-day safety update was submitted to the NDA on December 23, 1998. Including the subjects who were submitted in the 120-day safety update, a total of 351 subjects received a dose of 30 mg (the proposed dose of the drug) or greater for 6 months or more. Of these, 141 subjects received a dose of 30 mg or more for 12 months.

In all of the trials, serious adverse events occurred with a small incidence (2%) and were similar in incidence in the groups that received 15mg drug, 30 mg drug, 60 mg drug or placebo. As was described in the original NDA review, since this drug is a muscarinic agonist, an expected pattern of adverse events was observed consistently in all trials. In overall incidence, increased sweating was the most common, followed by nausea, headache, diarrhea, dizziness, and dyspepsia. Of the serious adverse events reported in the original NDA, it is clear that many, such as traumatic injuries and cancer, were unrelated to the study medication. Of the four subjects who died only one had a possible relationship: a 79-year old man with previously undiagnosed triple vessel disease who died two months after suffering a myocardial infarction (A statement of caution appears in the Warning section of the label regarding cardiovascular disease). There was no consistent pattern of increased incidence of abnormalities in physical examination or laboratory values in active groups versus placebo. Nonetheless, the label notes one unusually high ALT and two high AST values for completeness of the Adverse Events section.

Information Contained in Current Submission

The current submission contains an update since the 120-day safety update. The cutoff date of the four month safety update was October 5, 1998. At that time, Study SB96US03, an open-label study, which was primarily composed of subjects who were rolled over from one of the Phase 2 or Phase 3 trials, was still ongoing. There are only five subjects in this final update on whom no safety data was collected at the time of the 120-day safety update.

With the additional subjects who completed the ongoing study SB996US03 since the cut-off reporting date for the NDA submission, a total of 359 subjects received a dose of 30 mg or greater for 6 months or more. Of these, 224 subjects received a dose of 30 mg or more for 12 months. Of the 157 who were on doses at 60 mg or higher for at 6 months or more, 81 completed 12 months on a dose of 60 mg or higher.

There were four reports of serious adverse events since the 120-day update, which included shoulder impingement, thoracic outlet syndrome, adenocarcinoma, and squamous cell carcinoma, all from open label study SB96US03. There were no deaths reported during this reporting period. The first serious adverse event involved a 52-year old female subject who underwent surgery for impingement syndrome of the left shoulder approximately 9 months after taking the first dose of cevimeline. The subject remained on the study for the full 12 months. A 51-year old woman developed thoracic outlet syndrome six months after beginning study drug; she was hospitalized for a scalenectomy and remained on cevimeline after the surgery. A 46-year old woman completed the study with one year of drug therapy; shortly after the study ended, she received a diagnosis of intraductal adenocarcinoma. A fourth subject on the open-label study reported the serious adverse event of a squamous cell carcinoma. The lesion was removed four months into the study. The subject remained on cevimeline and completed the 12-months study. There is no indication that any of these four serious events is causally related to cevimeline.

The additional data did not produce any changes in the pattern or incidence of adverse events from those currently labeled. Laboratory values from the five subjects who were enrolled in the open label trial after the cut-of date for the 120-day safety update were submitted and reviewed. All five of these subjects had at least one laboratory value that was out of the normal range, but none showed any values that were either extremely out of the normal range or a pattern that supported a relationship between the drug and the abnormality. Three subjects showed high cholesterol readings (> 199 mg/dL total cholesterol) over the course of the trial. However, at values that fluctuated from 193 - 247 and with a baseline reading of 220 in the first subject, this finding does not appear to be related to study drug. Similarly, the second subject had a cholesterol measurement of 233 at baseline and fluctuated from 208 to 239 throughout the trial with no pattern. The third subject with elevated cholesterol began with a value of 267 and ranged from 251 to 292 throughout the trial. Another subject had high chloride readings of 109 and 110 mEq/L, with a higher than normal range defined as

108; however, the subject's initial reading was 109, and other readings fluctuated from 104 to 110 throughout the trial - these values are neither excessively high nor in a pattern that evokes concern. The fifth subject had borderline low hemoglobin at 11.0 during the last visit of the trial, with a baseline reading of 11.8. With a normal lower limit of hemoglobin defined as 11.1, neither the initial reading nor the pattern is indicative of a related adverse event. None of these subjects showed abnormal AST or ALT values at any time during the trial.

Conclusions about Safety

The new information presented in this safety update does not raise new concerns about the safety of this drug. The currently proposed label addresses warnings, precautions and adverse events adequately.

**APPEARS THIS WAY
ON ORIGINAL**

The following pages contain the label that accompanied the sponsor's submission, with strikeout denoting the agency's requested deletions and underlining denoting the agency's requested additions. Following that version is a final, unmarked version of the approved label.

26 Page(s) Redacted

Draft

LABELING

AUG 16 1999

**APPEARS THIS WAY
ON ORIGINAL**

**Evoxac™
(Cevimeline hydrochloride)**

NDA #20-989

**Proposed Indication: Treatment of the Symptoms of _____ Dry Mouth
Associated with Sjögren's Syndrome**

Sponsor: SnowBrand Pharmaceuticals, Inc.

**Frederick N. Hyman, D.D.S., M.P.H.
Dental Officer,
Division of Dermatologic and Dental Drug Products,
HFD-540
Center for Drug Evaluation and Research
August 13, 1999**

**APPEARS THIS WAY
ON ORIGINAL**

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Dental Officer's Review of NDA 20-989
Original NDA

AUG 16 1999

Drug: Cevimeline hydrochloride capsules (cis-2'-methylspiro{1-azobicyclo [2.2.2] octane 3,5' -[1,3] oxathiolane} hydrochloride, hydrate (2:1)	Serial Number: 1
	Submission date: August 27, 1998
	Received date: August 28, 1998
Sponsor: Snow Brand Pharmaceuticals, Inc.	Date of draft review completion: June 24, 1999
Proposed indication: Treatment of symptoms of dry mouth, _____ _____ in patients with _____ _____ Sjögren's syndrome	Date of final review completion: July 7, 1999
Pharmacologic Category: Cholinergic	PDUFA date: August 27, 1999
	Reviewer: Fred Hyman
	Project Manager: Olga Cintron

Introduction

Sjögren's syndrome is an immunologic disorder characterized by progressive destruction of the exocrine glands leading to mucosal and conjunctival dryness. Sjögren's syndrome has attracted growing interest and the disease definition has been broadened to encompass multiple immunological and serological abnormalities. The disease can occur by itself (primary), or in association with other autoimmune diseases (secondary). Primary Sjögren's occurs most frequently in women (female-to-male ratio 9:1) in the fifth or sixth decades of life, although it can be seen in all ages, including childhood. The prevalence of primary Sjögren's syndrome is approximately 0.5 to 1.0 percent. In addition to the primary syndrome, 30 percent of patients with autoimmune rheumatic diseases suffer from secondary Sjögren's syndrome.

Although virtually any organ system of the body may be affected in the patient with Sjögren's syndrome, the disease process is usually most striking in the salivary and lacrimal glands, where there is a progressive mononuclear cell infiltrate which generally leads to scarring. Loss of exocrine function accompanying these tissue changes is responsible for many of the clinical manifestations of Sjögren's syndrome, including the profound dryness of conjunctival and mucosal surfaces.

The major clinical symptoms are xerostomia and keratoconjunctivitis sicca. Patients complain of a gritty, dry, burning, or itching sensations in the eyes and severe dryness of the mouth. Lack of saliva may cause oral discomfort, pain, inflammation, dysgeusia, angular cheilitis,

increased caries and periodontal disease. A diagnosis of primary Sjögren's syndrome is usually made when the triad of keratoconjunctivitis sicca, xerostomia, and mononuclear infiltrate and/or serological abnormalities is noted. Xerostomia and/or keratoconjunctivitis may accompany a connective tissue disease, particularly rheumatoid arthritis. This is referred to as secondary Sjögren's syndrome. The differential diagnosis of Sjögren's syndrome includes sarcoidosis, lymphoma, primary amyloidosis, HIV infection, and graft-verses-host disease.

Treatment is geared toward symptomatic relief of mucosal dryness and meticulous oral hygiene and includes artificial tears, ophthalmologic lubricating ointments, nasal sprays of normal saline, moisturizing skin lotions, frequent sipping of water, artificial saliva preparations and oral fluoride treatments.

The sponsor proposes that cevimeline is an agonist that binds with specific muscarinic receptors in various exocrine glands. Cholinergic stimulation of residual major and minor functional salivary gland tissue results in increased salivary secretions. Increased salivary and lacrimal responses may in turn alleviate symptoms of dry mouth and dry eyes.

Background and Regulatory History:

The sponsor, Snow Brand Milk Products, Ltd. opened IND _____

At the time that the IND was opened, the drug was named _____ "cevimeline" was not used until the NDA was opened). The sponsor then opened IND _____ in March, 1995 to test the same drug, which it named SNI-2011 in these trials, for relief of symptoms of Sjögren's syndrome.

An end-of-phase 2 meeting was held between the sponsor and the agency on October 9, 1996. It was agreed at that time that changes in patient global subjective evaluation of improvement in dry mouth and dry eye symptoms (worsening, no change, or improvement) are acceptable primary assessments of efficacy. (For the exact wording of question that was used for the global subjective evaluation, refer to the section of this review that contains the protocol for each clinical trial.) The sponsor anticipated that the one-year, open-label US trial, SB96US03, would not yet completed by the time of the NDA filing. 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.

During the pre-NDA meeting that was held on April 16, 1998, the agency strongly

recommended a change to the sponsor's planned analysis of the primary outcome variable. In the original analysis plan, _____

At this pre-NDA meeting, the definition of the intent-to-treat subjects was changed from including all subjects who were administered at least one dose of study medication and provided at least one post-baseline efficacy evaluation - to including all subjects who were dispensed drug. It was agreed that all subjects who were dispensed drug but dropped out prior to an efficacy evaluation were to be considered as "Worse" in the primary endpoint analyses.

Also at the Pre-NDA meeting, the Division expressed the desire that an alpha-level adjustment be instated, due to multiple testing (placebo vs. 15 mg *t.i.d.*, placebo vs. 30 mg *t.i.d.*). As a result of this advice, a closed-family, step-down procedure was adopted to protect alpha levels (Refer to statistical review for discussion of this method of Tamhane, Hochberg, and Dunnett).

At the time of filing, the NDA's indications included symptomatic relief of _____ dry mouth, _____ from Sjögren's syndrome.

The sponsor's minutes of the end-of-phase 2 meeting have a reference to _____ "as an example of a subjective claim. To clarify this point, a conference call with the sponsor was initiated by the agency on October 15, 1998. The sponsor explained that the _____

Administratively _____ was discussed and dismissed. There would be no benefit to either the Division of Dermatologic and Dental Drug Products _____ or the sponsor to _____ the NDA. Therefore, it was decided that the Division of Dermatologic and Dental Products would oversee and administer the NDA, including the Chemistry

Manufacturing Controls, Pharmacology/Toxicology, and Biopharmaceutics portions as well as the Clinical /Statistical review of the dry mouth indication. In this review, only the "dry mouth" indication is evaluated in detail;

There is already one drug that has been approved for relief of symptoms of Sjögren's syndrome. Salagen® (pilocarpine), also a cholinergic parasympathomimetic agent with predominant muscarinic action, was approved in February, 1998 for treatment of symptoms of dry mouth in subjects with Sjögren's syndrome. The sponsor of Salagen's proposed indication of

Salagen was shown by the sponsor to be safe and effective for "treatment of symptoms of dry mouth in subjects with Sjögren's syndrome" at a dosing of 5 mg q.i.d.

Executive Summary

In this original NDA, the sponsor has submitted data and supporting documents in an attempt to obtain the indication, "treatment of symptoms of dry mouth, _____ in patients with _____ Sjögren's syndrome." The primary efficacy endpoints were the subjects' subjective global evaluation of dryness of the mouth, of the eyes, and overall. The secondary efficacy endpoints were the subjects' self-assessment of specific symptoms of dry mouth and dry eyes and the objective measures of total salivary flow and tear flow. Safety was assessed from vital sign measurements, electrocardiogram (ECG) recordings, physical and ophthalmologic examination results, clinical laboratory test results, and by monitoring the occurrence of adverse events. The conclusion of this review is that this drug can be approved for marketing in the United States for the "dry mouth" indication, _____

In this review, only the dry mouth portion of the indication is reviewed in detail. The use of the term _____ is not an acceptable drug claim, _____

Efficacy

Both placebo-controlled and open-label trials were conducted in subjects with Sjögren's syndrome in support of this NDA. Four placebo-controlled studies were conducted in subjects with Sjögren's syndrome. Three of these studies were conducted in the United States: one phase 2, randomized, double-blind, placebo-controlled study (Study No. SB96US01) and two phase 3, placebo-controlled, randomized, double-blind studies (Study Nos. SB96US02 and

SB96US04).

Study No. SB95US01 was the first clinical trial that was conducted after opening IND for the study of cevimeline for the treatment of dry mouth and dry eyes in subjects with Sjögren's syndrome. Study No. SB95US01 was a multiple-dose, double-blind, placebo-controlled study, which enrolled 60 subjects. Following successful completion of the screening procedures, eligible subjects were randomized to receive 30 mg cevimeline *t.i.d.*, 60 mg cevimeline *t.i.d.*, or placebo for 6 weeks. The primary efficacy endpoints in this study were the patient's subjective global evaluation of dryness (of the mouth, of the eyes, and overall) and the patient's subjective assessment of specific symptoms of dry mouth. Each subject's global evaluation rated the overall condition of dry mouth, the overall condition of dry eyes, and the subjects' overall feeling toward his or her overall dryness condition compared with before the study as "better", "no change", or "worse." The secondary efficacy variables were as follows: the objective measures of salivary flow, the use of artificial saliva, and fluid intake.

Although both groups in this trial 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, patient global evaluation of dry mouth. In fact, in four out of the five evaluation visits, more subjects rated the 30 mg dose as "better" than the 60 mg dose. No significant improvement in any of the visual analogue scale assessments of specific symptoms of dry mouth (including feeling of mouth, dryness of mouth, dryness of tongue, ability to speak without drinking, ability to chew and swallow food, and ability to sleep) was observed in those subjects receiving 60 mg of the drug when compared to those subjects receiving placebo. Only the "ability to sleep" variable showed a significant improvement in the 30 mg group versus the placebo. Although both doses demonstrated a significant improvement in salivary flow, there was no significant improvement in salivary flow between the 30 mg group and the 60 mg groups. Eighteen subjects who received placebo reported at least one adverse event during the study (78%). This compared with 22 subjects in the 30 mg cevimeline *t.i.d.* group (88%) and 27 subjects in the 60 mg cevimeline *t.i.d.* group (100%). Based upon the lack of significant improvement in either global assessment of dry mouth, or salivary flow, and the higher adverse event profile established with the 60 mg group compared to the 30 mg group, the sponsor chose to eliminate the 60 mg dose in the phase 3 trials.

Studies SB96US02 and SB96US04 were both multicenter, double-blind, randomized, parallel-group studies which were conducted to compare the efficacy and safety of two doses of SNI-2011 (15 mg *t.i.d.* and 30 mg *t.i.d.*) and placebo in the treatment of xerostomia _____ in subjects with Sjögren's syndrome. The protocols of these trials were identical. Study SB96US02 enrolled 197 subjects in 25 centers, and SB96US04 enrolled 212 subjects in 25 centers.

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

The secondary outcome variables include both the subject's self-assessment of specific symptoms of dry mouth and dry eyes and the objective measures of total salivary flow and tear flow. Total salivary flow was measured at each visit prior to dosing and at a minimum of 90 minutes after dosing. At each collection, the subject was instructed not to swallow but to allow the saliva to collect in the mouth for up to 5 minutes. The subject then expectorated the contents of the mouth into a collection tube. The collection period lasted for a total of 15 minutes after which the collection tube was sealed and weighed. Since the specific gravity of saliva is approximately 1, the flow was recorded in mL/min.

Using a series of visual analogue scales (VAS) anchored with the terms "comfortable" and "extremely uncomfortable", the subject evaluated the subjective secondary measures that included feeling of the mouth, dryness of the mouth, and dryness of the tongue. Ability to speak without drinking liquids, ability to chew and swallow foods, and ability to sleep were anchored with the terms "easy" and "very difficult."

In Study SB96US02, the percentage of "better" responses in subjects' global evaluations of dry mouth (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.") was greater in all three of the test groups at every visit after baseline. 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's group, but at no point, including the final visit did the difference between the placebo group and the 15-mg group's 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 trial SB96US02, this improvement in global evaluation of dry mouth is highly significant when compared to placebo, occurs consistently at every visit, and shows a highly significant difference when compared to the 15 mg dose. These particulars taken together support the efficacy of the 30 mg dose of cevimeline for the indication of dry mouth relief in the first phase 3 trial.

The primary efficacy results for Study SB96US04 (designated by the sponsor as pivotal), however, are not supportive. Unlike the pattern in SB96US02, where at each visit, the 15 mg dose has a greater percentage of "better" responses than the placebo and the 30 mg dose group has a greater percentage of "better" responses than both the 15 mg and placebo groups, that is not the case in SB96US04. 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. During the three visits that show a greater percentage of "better" responses in the 30 mg group than placebo, including the endpoint value, none of these differences are statistically significant.

Salivary flow was evaluated for improvement as a secondary variable. 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. In Study SB96US02, the baseline salivary flow is comparable in all three study groups, which provides assurance that the individuals in each group were similar with respect to salivation prior to the introduction of the drug or placebo. The differences in this trial 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 Study SB96US04 is similar to that of SB96US02, and is also sufficient to result in a statistically significant salivary flow in the 30 mg group when compared to the placebo.

There are several possible hypotheses for the lack of consistency between the two phase 3 trials in the primary outcome variable. One possibility is incorrect assignment of placebo and drug, but this is most likely ruled out, based upon the pharmacological activity in subjects in the groups. Another possibility is that blinding or randomization, although adequate according to the protocol, may have been violated in the second trial. In particular, the larger number of milder cases in the first phase 3 trial may explain the better outcome of the 30 mg group in that trial.

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's submission of SB95US01 in the NDA application, although not designed as a pivotal trial for efficacy demonstration, was helpful. The conduct was similar enough to the phase 3 trials and number of subjects was sufficient to be 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 capsules were different in the phase 3 trials than those used in the phase 2 trials. Although each of these differences requires some thought about its impact, none preclude applying the results to support approval.

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 apparently 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.

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. 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. Of these, 141 subjects received a dose of 30 mg or more for 12 months.

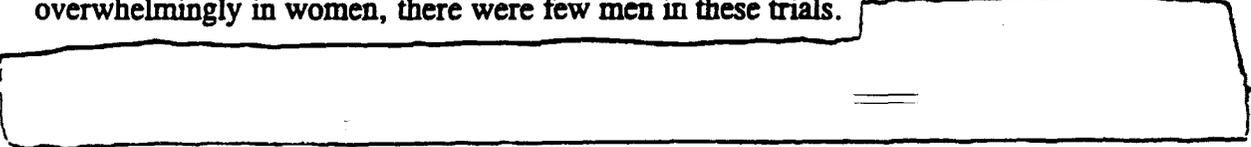
Since this drug is a muscarinic agonist, pharmacologically similar to pilocarpine, an expected pattern of adverse events was observed consistently in all trials. In overall incidence, increased sweating was the most common, followed by nausea, headache, diarrhea, dizziness, and dyspepsia.

Subjects dropped out at a rate that was directly proportional to the dose. For the subjects in the cevimeline groups there was a 32.8% dropout rate 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 due to discontinuation of a more sensitive population or because resistance developed from long-term use:

Serious adverse events 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. The study investigators believe that only two of these serious events have a possible or probable relationship to the study medication. These events were abnormal vision, reported for a subject receiving 30 mg cevimeline *t.i.d.*, and rash, reported for a subject receiving 60 mg cevimeline *t.i.d.*

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 by the sponsor to be unrelated to the study medication.

No gender, age group, or race-related differences were seen within treatment groups 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% female 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 and 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. There were no apparent dose-related changes from baseline to endpoint in the laboratory parameters or in laboratory normality shifts.

Recommended Regulatory Action

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

a meeting with the Agency is strongly recommended to establish agreements prior to conducting additional clinical trials.

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Summary Table for Focal Clinical Trials for NDA 20-989

Trial		SB95US01			SB96US02			SB96US04		
Phase		2			3			3		
Status		Completed April 1996			Completed April 1998			Completed March 1998		
Total subjects enrolled in each treatment group	Placebo	23			70			71		
	15 mg dose	None			65			75		
	30 mg dose	25			62			66		
	60 mg dose	27			None			None		
Duration of trial		6 weeks			12 weeks			12 weeks		
Primary Outcome Variable	Definition	Percent of subjects who reported feeling "better" when asked the question: "Please rate the overall condition of your dry mouth now compared with how you felt before starting treatment in this study."								
	Global Assessment of Dry Mouth (at endpoint)	Placebo	30-mg group	60-mg group	Placebo	15-mg group	30-mg group	Placebo	15-mg group	30-mg group
		34.8%	76.0%	66.7%	37.1%	44.6%	66.1%	54.9%	36.0%	53.0%
p-value for comparison of 60-mg to placebo		0.0152*								
p-value for comparison of 60-mg to 30-mg		0.3835								
p-value for comparison of 30-mg to placebo		0.0043*			0.0004*			0.8886		
p-value for comparison of 15-mg to placebo					0.6216			Not calculated as per statistical analysis plan		
p-value for comparison of 30-mg to 15-mg					0.0056* (in favor of the 30-mg dose)			0.0311*		
Secondary Outcome Variable:		Saliva was collected for 15 minutes and a flow rate was calculated in ml./min. The change in the flow rate is the difference between the baseline flow rate and the flow rate one hour after dosing								
Change from baseline to postdose in salivary flow (ml/min) at endpoint		Placebo	30-mg group	60-mg group	Placebo	15-mg group	30-mg group	Placebo	15-mg group	30-mg group
		0.065 ml/min	0.268 ml/min	0.400 ml/min	0.064 ml/min	0.078 ml/min	0.205 ml/min	0.075 ml/min	0.091 ml/min	0.160 ml/min
p-value for comparison of 60-mg to placebo		0.0002*								
p-value for comparison of 60-mg to 30-mg		0.5228								
p-value for comparison of 30-mg to placebo		0.0015*			0.0070*			0.0236*		
p-value for comparison of 15-mg to placebo					0.6091			0.5881		
p-value for comparison of 30-mg to 15-mg					0.0195*			0.0677		
Comments		The failure of trial SB96US04 to demonstrate a significantly greater number of subjects who reported feeling better in their global assessment of dry mouth results from a very effective placebo group.								

*value is statistically significant at p < 0.05

Chemistry and Manufacturing Controls Summary

In general, SnowBrand has been meticulous in their drug substance synthesis, controls, and impurities throughout their submission. Impurities are all well below ——— There is very good documentation throughout the NDA. The synthesis process was changed during development and their comparison between the EP (Existing Process) and AP (Alternate Process) was very good. The drug product specifications, manufacturing processes, and stability data all appear acceptable.

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 were minor differences in the inactive ingredients in the drug used in SB95US01. The chemistry and biopharmaceutical teams jointly concluded that the two drug products were bioequivalent.

Pharmacology/Toxicology Summary

Cevimeline did not demonstrate acute or chronic toxicities in animals. In one-year repeat dose toxicology studies both in rats and in dogs, animals at high-dose exhibited signs of excessive cholinergic stimulation (e.g., salivation, diarrhea, lacrimation, and tremor), as expected for a cholinomemetic drug, but no apparent adverse effects were observed that were not secondary to the expected pharmacodynamic properties of the drug substance.

No developmental effects were observed in teratology studies in rats and rabbits. Cevimeline did not adversely effect the reproductive performance or fertility of rats, although animals in a high-dose test group exhibited a reduction in the mean number of implantations, and a higher number of visceral anomalies in F1 animals (first-generation offspring). In that ("Segment 1") study, the percentage of fetuses with skeletal variations increased in proportion to dosage. However, it is unlikely that these effects would be apparent at clinical dosages.

Cevimeline is apparently not a genetic toxicant; negative results were obtained in an Ames test, a chromosomal aberration study in cultured fibroblasts, a mouse lymphoma study in L5178Y cells, or in a micronucleus assay.

Cevimeline was assessed for carcinogenicity in two-year bioassays in CD-1 mice and F-344 rats. Among female rats, the incidence of uterine adenocarcinoma in animals that received 100mg/kg/day cevimeline HCl was significantly greater than in control animals. No other statistically significant differences in tumor incidence were observed in either species.

Pharmacokinetic Summary

The pharmacokinetics of cevimeline upon single and multiple dose administration have been defined, and the effect of food on the bioavailability of cevimeline has been determined. With food there is some reduction in the C_{max} and some delay in T_{max}, but AUC remains unaffected. During the review of this NDA a concentration response relation between cevimeline and the secreted saliva was evaluated/proposed although final confirmation is not possible at this time. NDA 20-989 is approvable from a biopharmaceutics perspective. See the above note in the CMC summary regarding the 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.

Division of Scientific Investigations Inspection

As a part of FDA's Bioresearch Monitoring Program, The Division of Scientific Investigations directed inspections between April 5 and April-19, 1999 of two sites at which the phase 3 clinical study, SB96US02, was conducted. These inspections are designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected. Except for the non-reporting of an adverse drug event for one subject and minor record-keeping deficiencies, the study was conducted in compliance with federal regulations and good clinical investigational practices.

Clinical Trials:

Both placebo-controlled and open-label trials in support of this NDA were conducted in subjects with Sjögren's syndrome. In this review, the controlled trials will be presented first, including the protocols, results and adverse events profiles for each trial. The open label trials will follow with a similar presentation. An integrated safety summary will include results of physical examination, laboratory findings and combined adverse events from all relevant trials used to support safety. A discussion of the strength and weaknesses of the safety and efficacy data from all these trials will conclude the review.

Controlled Trials

Four placebo-controlled studies were conducted in subjects with Sjögren's syndrome. Three of these studies were conducted in the United States: one Phase 2, randomized, double-blind, placebo-controlled study (Study No. SB96US01) and two Phase 3, placebo-controlled, randomized, double-blind studies (Study Nos. SB96US02 and SB96US04).

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TABLE OF 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
SB95US01 Multicenter US	Complete (Jul 95 - Apr 98)	SNI-2011	A multicenter, double-blind, placebo-controlled, randomized study comparing cevimeline 30 mg <i>t.i.d.</i> and 60 mg <i>t.i.d.</i> with placebo in the treatment of xerostomia — _____ in subjects with Sjögren's syndrome	Cevimeline HCl: 30 mg <i>t.i.d.</i> 60 mg <i>t.i.d.</i> Placebo	25 27 23	33 – 75 yr (53.6 yr)	13% M 87% F Race: 69 Caucasian 1 Black 5 Hispanic	6 weeks
SB96US02 Multicenter US	Complete (Jan 97 - Apr 98)	SNI-2011	A multicenter, double-blind, randomized, parallel-group study comparing the efficacy and safety of cevimeline 15 mg <i>t.i.d.</i> and 30 mg <i>t.i.d.</i> with placebo in the treatment of xerostomia — _____ in subjects with Sjögren's syndrome	Cevimeline HCl: 15 mg <i>t.i.d.</i> 30 mg <i>t.i.d.</i> Placebo	65 62 70	23 – 74 yr (54.4 yr)	5% M 95% F Race: 180 Caucasian 6 Black 8 Hispanic 2 Asian 1 Other	12 weeks
SB96US04 Multicenter US	Complete (Jan 97 - Mar 98)	SNI-2011	A multicenter, double-blind, randomized, parallel-group study comparing the efficacy and safety of cevimeline 15 mg <i>t.i.d.</i> and 30 mg <i>t.i.d.</i> with placebo in the treatment of xerostomia — _____ in subjects with Sjögren's syndrome	Cevimeline HCl: 15 mg <i>t.i.d.</i> 30 mg <i>t.i.d.</i> Placebo	75 66 71	24 – 75 yr (55.3 yr)	5% M 95% F Race: 188 Caucasian 4 Black 12 Hispanic 3 Asian 5 Other	12 weeks

Controlled Phase 2 trials:

SB95US01

Study No. SB95US01 was the first clinical trial that was conducted after opening IND _____ for the study of cevimeline for the treatment of dry mouth _____ in subjects with Sjögren's syndrome. Study No. SB95US01 was a multiple-dose, double-blind, placebo-controlled study. _____

_____ This review will only discuss evaluation of dry mouth symptoms.

Protocol Design

Following successful completion of the screening procedures, eligible subjects were randomized to receive 30 mg cevimeline *t.i.d.*, 60 mg cevimeline *t.i.d.*, or placebo for 6 weeks. Subjective and objective measures of salivary flow were recorded at screening to establish baseline values. Subjects returned to the investigational site for evaluation after 2, 4, and 6 weeks. At each visit, assessments were made prior to dose administration (trough levels) and following dosing (peak levels). The primary efficacy endpoints in this study were the patient's subjective global evaluation of dryness (of the mouth, of the eyes, and overall) and the patient's subjective assessment of specific symptoms of dry mouth.

Each subject's global evaluation rated the overall condition of dry mouth, the overall condition of dry eyes, and the subjects' overall feeling toward his or her overall dryness condition compared with before the study as "better", "no change", or "worse." Using a series of visual analogue scales, the subjects evaluated the other subjective measures. For the subjective salivary measures, feeling of the mouth, dryness of the mouth, and dryness of the tongue were rated between "comfortable" and "extremely uncomfortable" and ability to speak without drinking liquids, ability to chew and swallow foods, and ability to sleep were rated between "easy" and "very difficult."

The secondary efficacy variables were the objective measures of salivary flow, the use of artificial saliva, and fluid intake. Total salivary flow was measured at each visit prior to dosing and at a minimum of 90 minutes after dosing. At each collection, the patient was instructed not to swallow but to allow the saliva to collect in the mouth for up to 5 minutes. The patient then expectorated the contents of the mouth into a collection tube. The collection period lasted for a total of 15 minutes after which the collection tube was sealed and weighed. Since the specific gravity of saliva is approximately 1, the flow was recorded in milliliters per minute.

Objectives

- (1) to assess the subjective and objective parameters
- (2) to provide preliminary efficacy measures of SNI-2011, and
- (3) to assess the safety of SNI-2011 in patients with xerostomia

Principal Investigators and Associated Study Sites:

INVESTIGATORS AND INVESTIGATIONAL SITES

NAME OF INVESTIGATOR	ADDRESS OF INVESTIGATIONAL SITE	TOTAL NUMBER OF SUBJECTS ENROLLED
Walter Chase, MD	Medical Park Tower 1301 W. 38th Street Austin, TX 78705	17
Robin Dore, MD	1120 West La Palma Avenue, Suite 7 Anaheim, CA 92801	15
Rose Fife, MD	Indiana University School of Medicine Out Patient Clinical Research Facility 550 N. University Boulevard, Room 1705 Indianapolis, IN 46202	24
John Jandinski, DMD	UMDNJ - Dental School Department of Oral Pathology 110 Bergen Street Newark, NJ 07103	0
Peter Lockhart, DDS	Carolinas Medical Center 1000 Blythe Boulevard Charlotte, NC 28232	2
James Suen, MD	University of Arkansas Medical Sciences 4301 W. Markham Street Little Rock, AR 72205	1
Elizabeth Tindall, MD	10201 SE Main Street #29 Portland, OR 97216	2
Craig Wiesenhutter, MD	950 Ironwood Drive Coeur d'Alene, ID 83814	14

Number of Subjects: 75

Ages of Subjects: 18-75

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Inclusion Criteria

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

1. Patient was over 18 years old and under 70 years old and had given informed consent to participate in the study.

Reviewer's Comment: The sponsor noted that one 75-year old was inadvertently enrolled in the trial.

2. Patient, if female and of child-bearing potential, was required to have a negative pregnancy test.
3. Patient, if of child-bearing potential, was using an accepted method of birth control (e.g., oral contraceptives; intrauterine contraceptive device; diaphragm or condoms in combination with contraceptive cream, jelly, or foam) or was surgically sterile.
4. Patient had documented primary or secondary Sjögren's syndrome (i.e., lacrimal and salivary gland dysfunction, with or without connective tissue disorder):

Lacrimal dysfunction: abnormal Schirmer's test results (≤ 5 mm/5 minutes) for both eyes

Salivary dysfunction: unstimulated whole saliva collection revealing saliva flow of ≤ 1.5 mL/15 minutes

The following definitions of primary and secondary Sjogren's syndrome were used for this trial:

Primary Sjogren's

- At least one positive response to each of the ocular and oral symptom Yes/No questions
- Lacrimal and salivary gland dysfunction
- Positive anti-Ro/SS-A or anti-La/SS-B antibodies (or documented history of such in the patient's existing records), rheumatoid arthritis (RA), and/or anti-nuclear antibodies (ANA)

Secondary Sjogren's

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

- Lacrimal and salivary gland dysfunction
- Positive anti-Ro/SS-A or anti-La/SS-B antibodies (or documented history of such in the patient's existing records), RA, and/or ANA
- Positive ANA and/or RA antibodies and/or other evidence of accompanying rheumatoid arthritis or other connective tissue disease

Exclusion Criteria

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

1. Patient answered "severe" in Questionnaire A, and had null values for both tear and salivary flow measures.
2. Patient had enlarged salivary glands (with or without pain).
3. Patient was suspected to have physical closure of the salivary glands or surgical closure of the lacrimal punctum (permanent or temporary closure).
4. Patient had any external ophthalmic disease (viral, bacterial, or fungal infection), diabetic keratitis, or neutrophilic corneal disorder.
5. Patient had a history of significant cardiovascular disease and might be unable to compensate for transient changes in hemodynamics or rhythm induced by cholinergic agents (angina or myocardial infarction).
6. Patient had a history of significant pulmonary disease (controlled or uncontrolled asthma, chronic bronchitis, or chronic obstructive pulmonary disease [COPD]).
7. Patient had a significant history of gastrointestinal disorders (hepatic, pancreatic, gastroduodenal ulcers, or hypersensitive bowel diseases).
8. Patient had acute iritis, narrow-angle (angle-closure) glaucoma, or pre-existing retinal disease.
9. Patient had a history of underlying psychiatric disease.
10. Patient had a history of nephrolithiasis or cholelithiasis.
11. Patient was taking or had taken any other investigational new drug (a chemical entity not registered for use) within the last 30 days or was due to receive such a drug during

this study.

12. Patient was taking any anticholinergic agents or other medications known to alter xerostomia.
13. Patient had a recent history (within 12 months) of chronic alcoholism or drug abuse.
14. Patient was unwilling or unable to comply with the protocol.
15. Patient had a history of radiation-induced therapy affecting the salivary glands.

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

Study Procedures

This was a multiple-dose, double-blind, placebo-controlled study in subjects with Sjögren's syndrome who presented with both xerostomia _____ Eligible subjects who had given written, informed consent underwent screening procedures including a medical history, physical and ophthalmologic examinations, a 12-lead electrocardiogram (ECG), measurement of vital signs, and clinical laboratory tests.

Baseline subjective and objective measurements of salivary and lacrimal flow were performed at screening and after 7 days (Days -9 to -5) to establish baseline values. Subjects were provided with questionnaires on which to record information regarding fluid intake and the use of artificial saliva and tears.

Subjects were randomized to receive either 30 mg or 60 mg SNI-2011 tid or placebo tid for a 6-week period. They returned to the investigational site for evaluation after 2, 4, and 6 weeks. At each visit, assessments were made prior to dose administration (trough levels) and following dosing (peak levels). Prior to dosing, vital signs were assessed and a 12-lead ECG was recorded. The subjects completed the visual analogue scales in the xerosis questionnaire, and objective measurements of salivary and lacrimal flow were made. In addition, blood and urine samples were collected for laboratory analysis.

One hour after taking the study medication, vital signs were measured and the subjects again completed the visual analogue scales in the xerosis questionnaire. Objective measurements of salivary and lacrimal flow were made approximately 90 minutes after dose administration. In addition, the global subjective improvement questionnaire was completed.

Removal of Subjects from Therapy or Assessment

Subjects were permitted to leave the study at any time if they so wished. In addition, a subject could be withdrawn from the study under any of the following circumstances.

1. A serious adverse event or a significant abnormality/change in laboratory test value occurred (unless the investigator and sponsor judged the adverse event or abnormality to be clinically acceptable).
2. The subject's symptoms worsened.
3. A complication or an accidental symptom occurred (including accidents).
4. The subject withdrew his or her consent.
5. The subject was non-compliant with the protocol.
6. The need for a concomitant medication prohibited by the protocol arose.
7. The principal investigator decided that it was in the best interest of the subject to withdraw from the study.
8. The study was terminated by the sponsor.

Treatments Administered

Subjects were randomized to received placebo, 30 mg SNI-2011, or 60 mg SNI-2011 tid for 6 weeks. Subjects were instructed to take the medication on an empty stomach (at least 1 hour after a meal) and were counseled to avoid high-fat meals during the active treatment study period. Subjects were encouraged to take the medication at the following times of day: 6 to 8 AM (first dose), 1 to 3 PM (second dose), and 7 to 9 PM (third dose).

Identity of Investigational Product(s)

White gelatin No. 3 capsules containing placebo, 30 mg SNI-2011, or 60 mg SNI-2011 plus excipients, each identical in appearance, were provided by Snow Brand Milk Products Co., Ltd.

Subjects were randomly assigned to receive one of the following treatments three times a day for 6 weeks.

- A SNI-2011 30 mg capsule; lot number 46124-G03
- B SNI-2011 60 mg capsule; lot number 46124-G05

C Placebo capsule; lot number 46124-G01

Method of Assigning Subjects to Treatment Groups

Subjects were randomly assigned to receive placebo or 30 mg or 60 mg SNI-2011 tid according to a computer-generated randomization schedule provided by _____ prior to the start of the study.

Selection and Timing of Dose for Each Subject

Subjects were asked to take the study medication at approximately the same times each day: 6 to 8 AM (first dose); 1 to 3 PM (second dose); and 7 to 9 PM (third dose). Subjects were also instructed to take the medication on an empty stomach (at least 1 hour after meals) and to avoid high-fat meals during the study. In addition, all study measures were taken between 8 and 11 AM to avoid known diurnal variation.

Blinding

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

Prior and Concomitant Therapy

Subjects were excluded from the study if they used any anticholinergic agents or other medication known to affect salivation or lacrimation. Use of artificial saliva and tears was allowed.

If it was necessary to take any other medication during the study, the staff at the investigational site was informed and the drug, dose, start and stop dates, and indication for use were recorded in the subject's case report form.

Treatment Compliance

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

Primary Efficacy Variables

The primary efficacy endpoints in this study were the subjective subject assessments. These included the subjects' global evaluation of improvement in dry mouth and dry eye symptoms,

as well as the subjects' evaluation of the overall dryness compared with before starting treatment in this study (defined as "worse," "no change," or "better").

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

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

Worse No change Better

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

Worse No change Better

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

Worse No change Better

Additional primary efficacy variables included the following 12 subjective subject assessments of dry mouth and dry eyes, as measured on a series of uncalibrated 100-mm visual analogue scales: feeling of mouth, dryness of mouth, dryness of tongue, ability to speak without drinking, ability to chew and swallow food, ability to sleep, overall feeling of eyes, dry feeling of eyes, ability to open eyes in light, sand sensation in eyes, mucus or discharge in eyes, burning sensation in eyes.

For the subjective salivary measures, feeling of the mouth, dryness of the mouth, and dryness of the tongue were rated between "comfortable" (left side of the scale) and "extremely uncomfortable" (right side of the scale) and ability to speak without drinking liquids, ability to chew and swallow foods, and ability to sleep were rated between "easy" (left side of the scale) and "very difficult" (right side of the scale). Changes from pretreatment baseline values (Week 0 visit predose, if available, or screening) to the postdose Endpoint values were the primary interest for each of the parameters scored using a visual analogue scale. These parameters were assessed at screening and twice at each later visit: prior to and approximately 1 hour after administration of study medication. Measured distance along the scale served as the score for these continuous parameters.

Secondary Efficacy Variables

Secondary efficacy endpoints included objective measurements of lacrimal and salivary flow. Total salivary flow and tear flow were measured at screening and twice at each visit, once prior to dosing and again approximately 90 minutes after dosing. For each collection of total salivary flow, the subject was instructed not to swallow but to allow the saliva to collect in the

mouth for 5 minutes. The subject then expectorated the contents of the mouth into a collection tube. The collection period lasted for a total of 15 minutes after which the collection tube was sealed and weighed. Since the specific gravity of saliva is approximately 1, the flow was recorded in milliliters/minute.

Safety Variables

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

Statistical Plan:

Efficacy Analysis

Efficacy analyses were performed on an intent-to-treat basis. All patients to whom study drug was dispensed were included in the intent-to-treat efficacy analysis. Any subjects who dropped out prior to an efficacy evaluation in this study were considered as "Worse" in the primary endpoint analyses.

For each patient, the last non-missing post-dose observation was carried forward (LOCF) for the Endpoint analyses. Analyses by visit week were performed in addition to Endpoint analyses. For these analyses, the last observation was not carried forward across weeks. The Week 6 results, therefore, represent the endpoint outcome of the patients who completed the study. Endpoint values reflect the results of changes from baseline to postdose at the patients' last visit. Final Visit values present the results of changes from predose to postdose within the patients' last visit for which pre- and postdose data were available.

The primary efficacy parameters were the subjective measurements of dry eye and dry mouth. The Cochran-Mantel-Haenszel (CMH) row mean scores statistic was used to test response ("better than before," "no change," and "worse than before") between treatment groups, stratified by investigator.

Changes from pretreatment baseline values (Week 0 visit predose, if available, or screening) to the postdose Endpoint values were the primary interest for each of the parameters scored using a visual analogue scale as well. The null-hypothesis of equality of mean change between randomized groups was tested overall and on a pairwise basis (via contrasts) using analysis of variance (ANOVA) methods.

In addition to Endpoint values, the change from baseline at both predose and postdose was summarized and analyzed at each visit for these parameters scored using visual analogue scales.

For objective measurements of salivary flow, the mean changes from baseline (screening) to postdose by visit and at endpoint were summarized and analyzed for differences between randomized groups both overall and on a pairwise basis using ANOVA methods.

Safety Analyses

All patients who took at least one dose of study medication and provided safety information were included in the safety analysis.

Adverse events were summarized overall, by body system, and by preferred term. The Fisher's Exact test was used to assess significance of the differences in proportions of patients with adverse events across the treatment groups. The list of patient reasons for early discontinuation of study medication and the adverse events causing discontinuation were summarized. Also, adverse events were summarized separately by severity and relationship to study drug.

Laboratory values at the baseline and Final Visit were summarized using mean, standard error estimate, and minimum and maximum laboratory values. The mean change and mean percent change in the laboratory values from baseline to Final Visit were similarly summarized. When the baseline laboratory value was zero, the mean percent change was treated as missing. The laboratory values were categorized as low, normal, and high, accordingly, if the laboratory value was below the lower limit, within the limits, or above the upper limit of the normal range of the laboratory test, respectively. Shifts in laboratory value classification from baseline to Final Visit were also summarized separately.

Results

Baseline Characteristics

The majority of patients enrolled in this study were Caucasian (92%) and female (87%). This reflects the typical population of patients with Sjögren's syndrome. The demographic variables of race and age were comparable across treatment groups, as is seen in the following table.

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DEMOGRAPHIC SUMMARY: STUDY SB95US01

CHARACTERISTIC	Placebo		SNI-2011				Total	
			30 mg tid		60 mg tid			
	n	%	n	%	n	%	n	%
Number of Patients	23	100.0	25	100.0	27	100.0	75	100.0
Gender								
Female	19	82.6	21	84.0	25	92.6	65	86.7
Male	4	17.4	4	16.0	2	7.4	10	13.3
Race								
Caucasian	22	95.7	23	92.0	24	88.9	69	92.0
Black	1	4.4	0	0	0	0	1	1.3
Hispanic	0	0	2	8.0	3	11.1	5	6.7
Age (years)								
Mean ± SD	55.3 ± 10.2		52.8 ± 12.3		52.9 ± 9.6		53.6 ± 10.7	
Range	33 - 69		34 - 75		33 - 69		33 - 75	

At baseline, there was no noticeable difference in the proportion of patients with diagnosis of primary versus secondary Sjögren's syndrome among treatment groups, as illustrated in the following table.

DIAGNOSIS OF SJÖGREN'S SYNDROME: STUDY SB95US01

DIAGNOSIS	Placebo (N=23)		SNI-2011				Total (N=75)	
			30 mg tid (N=25)		60 mg tid (N=27)			
	n	%	n	%	n	%	n	%
Primary	8	34.8	11	44.0	10	37.0	29	38.7
Secondary	15	65.2	14	56.0	17	63.0	46	61.3

At baseline, the majority of patients (67%) had dry mouth and dry eyes of moderate severity. There was no statistically significant difference in the numbers of patients with mild, moderate, or severe dry mouth and eyes among treatment groups. There were no differences among treatment groups regarding the responses given concerning dry mouth and dry eyes.

SEVERITY OF DRY MOUTH AND DRY EYES AT BASELINE: STUDY SB95US01

SEVERITY	Placebo (N=23)		SNI-2011				Total (N=75)	
			30 mg tid (N=25)		60 mg tid (N=27)			
	n	%	n	%	n	%	n	%
Dry mouth								
Mild	4	17.4	4	16.0	7	25.9	15	20.0
Moderate	19	82.6	17	68.0	14	51.9	50	66.7
Severe	0	0	3	12.0	5	18.5	8	10.7
Missing	0	0	1	4.0	1	3.7	2	2.7
Dry eyes								
No symptoms	0	0	0	0	1	3.7	1	1.3
Mild	5	21.7	4	16.0	3	11.1	12	16.0
Moderate	14	60.9	17	68.0	19	70.4	50	66.7
Severe	4	17.4	3	12.0	3	11.1	10	13.3
Missing	0	0	1	4.0	1	3.7	2	2.7

Primary Outcome Variable

The following table shows the percentage of subjects at each visit who reported feeling better, worse, or unchanged with respect to the global evaluation of their dry mouth and the associated p values.

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GLOBAL EVALUATION OF DRY MOUTH (STUDY NO. S395US01)

Evaluation Visit	Better (%)			No Change (%)			Worse (%)		
	Plac	Cevimeline		Plac	Cevimeline		Plac	Cevimeline	
		30 mg	60 mg		30 mg	60 mg		30 mg	60 mg
Week 0	39.1	72.0	76.9	60.9	28.0	23.1	0.0	0.0	0.0
Week 2	45.5	81.8	81.0	54.5	18.2	19.0	0.0	0.0	0.0
Week 4	50.0	85.7	77.8	50.0	14.3	22.2	0.0	0.0	0.0
Week 6	36.4	81.0	72.2	63.6	19.0	27.8	0.0	0.0	0.0
Endpoint	34.8	76.0	66.7	60.9	24.0	29.6	4.3	0.0	3.7
p-value									
		Overall		Plac vs. 30 mg	Plac vs. 60 mg	30 mg vs. 60 mg			
Week 0		0.0028*		0.0143*	0.0027*	0.6740			
Week 2		0.0078*		0.0114*	0.0160*	0.9411			
Week 4		0.0326*		0.0112*	0.0751	0.5829			
Week 6		0.0173*		0.0035*	0.0569	0.5355			
Endpoint		0.0188*		0.0043*	0.0152*	0.3835			

* values are significant at $p < 0.05$

Although both groups showed significant improvement over placebo, no difference in efficacy was demonstrated between the 30 mg and 60 mg groups as measured by the primary endpoint, subject global evaluation of dry mouth. In fact, in four out of the five evaluation visits, more subjects rated the 30 mg dose as "better" than the 60 mg dose.

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

The differences in values between the baseline and the last visit are shown in the table below. Note that no significant improvement in any of these parameters was observed in those subjects receiving 60 mg of the drug when compared to those subjects receiving placebo. Only the "ability to sleep" variable showed a significant improvement in the 30 mg group versus the placebo. See the discussion section of this review for further thoughts on the clinical utility of these results.

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