Cevimeline for the Treatment of Xerostomia in Patients With Sjögren Syndrome

A Randomized Trial

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Background: Cevimeline hydrochloride is a cholinergic agent with muscarinic agonist activity prominently affecting the M1 and M3 receptors prevalent in exocrine glands. We evaluated the safety and efficacy of cevimeline in the treatment of xerostomia in patients with Sjögren syndrome.

Methods: Seventy-five patients with Sjögren syndrome and associated salivary gland dysfunction were enrolled in a double-blind, randomized, placebo-controlled trial at 8 university- and office-based outpatient clinical facilities in the United States. Eligible study participants were randomized to receive 30 mg of cevimeline 3 times daily, 60 mg of cevimeline 3 times daily, or placebo for 6 weeks. Subjective responses were determined using global patient evaluation and visual analog scales. Salivary flow was measured objectively.

Results: Sixty-one participants completed the study. Patients in both cevimeline groups had significant improvement in dry mouth, as indicated by symptoms, salivary flow, and use of artificial saliva, compared with the placebo group. The drug was generally well tolerated, with expected adverse events resulting from the drug’s muscarinic agonist action. Fourteen patients withdrew from the study because of adverse events, the most frequent being nausea.

Conclusions: Therapy with cevimeline, 30 mg 3 times daily, seems to be well tolerated and to provide substantive relief of xerostomia symptoms. Although both dosages of cevimeline provided symptomatic improvement, 60 mg 3 times daily was associated with an increase in the occurrence of adverse events, particularly gastrointestinal tract disorders. Use of 30 mg of cevimeline provides a new option for the treatment of xerostomia in Sjögren syndrome.

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PATIENTS AND METHODS

INCLUSION CRITERIA

Patients aged 18 to 70 years with a primary or secondary diagnosis of Sjögren syndrome and associated lacrimal and salivary gland dysfunction were included. Women of child-bearing age were required to have a negative pregnancy test result and to use an accepted method of birth control or be surgically sterile.

A clinical diagnosis of primary Sjögren syndrome was defined as follows: (1) at least 1 positive response to ocular and oral symptom yes/no questions; (2) lacrimal and salivary gland dysfunction; and (3) positive anti-Ro/SS-A or anti-La/SS-B antibodies, rheumatoid factor, or antinuclear antibodies.

Secondary Sjögren syndrome was defined as follows: (1) at least 1 positive response to either ocular or oral symptom yes/no questions; (2) lacrimal and salivary gland dysfunction; (3) positive anti-Ro/SS-A or anti-La/SS-B antibodies, rheumatoid factor, or antinuclear antibodies; and (4) positive antinuclear antibodies, rheumatoid factor, or other evidence of accompanying rheumatoid arthritis or other connective tissue disease.

Lacrimal dysfunction was defined as abnormal Schirmer test results (≤5 mm in 5 minutes) for both eyes. Salivary dysfunction was defined as unstimulated whole saliva collection of 1.5 mL or less in 15 minutes.

EXCLUSION CRITERIA

Patients with enlarged salivary glands (with or without pain); those who were suspected of having physical closure of the salivary glands or who had a known surgical closure of the lacrimal punctum (permanent or temporary closure); and those with external opthalmic disease (viral, bacterial, or fungal infection), diabetic keratits, or neutrophilic corneal disorder were excluded. Patients with a significant history of cardiovascular, gastrointestinal tract, psychiatric, pulmonary, or renal disease were excluded. Patients with acute iritis, narrow-angle glaucoma, or preexisting retinal disease were excluded. Patients taking or having taken any other investigational new drug (an entity not registered for use) within the past 30 days or who were due to receive such a drug during this study were excluded. Patients taking any anticholinergic agents or other medications known to affect salivation or lacrimation were excluded. Patients who were unwilling or unable to comply with the protocol or who had a history of radiation therapy as the cause of salivary gland dysfunction were excluded.

PROTOCOL

Patients were enrolled at 8 university- and office-based outpatient clinical facilities in the United States. Before initiation of the study, the protocol was approved by local institutional review boards. The study was completed according to the guidelines of Good Clinical Practice and was conducted in full compliance with the World Medical Association Declaration of Helsinki and its most recent amendments.

The sample size for the study was not based on statistical calculations. However, the numbers were deemed adequate to characterize the effect of cevimeline vs placebo. All patients gave written informed consent before eligibility was confirmed. All study participants had a baseline medical history taken and underwent physical and ophthalmic examinations at the screening visit. In addition, clinical laboratory tests, measurement of vital signs, 12-lead electrocardiography, and subjective and objective measurements of salivary and lacrimal flow were performed at the primary screening and after 7 days to establish baseline values.

At the baseline visit (week 0), study participants were randomized using a computer-generated randomization schedule (PPD Pharmaco Inc, Wilmington, NC) to receive one of 3 therapy groups: 23 patients were randomized to receive placebo, 25 to receive 30 mg of cevimeline tid, and 27 to receive 60 mg of cevimeline tid (Figure 1). Most patients enrolled were white (n=69 [92%]) and women (n=65 [87%]) (Table 1). Demographic variables of race and age, mean fluid intake within 24 hours, and number of patients with visual abnormalities were comparable across treatment groups. There was no difference among groups in the number of patients with primary or secondary diagnoses of Sjögren syndrome. Although most patients at baseline had dry mouth and dry eyes of moderate severity, there were no statistically significant differences among treatment groups in the number of patients with mild, moderate, or severe dry mouth and dry eyes.

The study took place between July 6, 1995, and April 11, 1996. Of 129 patients screened, 75 patients met the entry criteria and were randomized to 3 groups. Twenty-three patients were randomized to receive placebo, 25 to receive 30 mg of cevimeline tid, and 27 to receive 60 mg of cevimeline tid (Figure 1). Most patients enrolled were white (n=69 [92%]) and women (n=65 [87%]) (Table 1).
receive either 30 mg of cevimeline hydrochloride 3 times daily (tid), 60 mg of cevimeline hydrochloride tid, or placebo for 6 weeks. All study medication and placebo were provided in white gelatin capsules made to appear indistinguishable. The investigators and participants were masked to treatment assignments. Patients 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 active treatment. Study participants returned to the clinic for evaluation at weeks 2, 4, and 6. At each visit, including the baseline visit, subjective and objective assessments were made before dosing (trough level) and after dosing (peak level).

SUBJECTIVE MEASUREMENTS

The primary efficacy end points were subjective patient assessments, including global patient evaluation to assess improvement in dry mouth. Study participants reported responses of “better,” “no change,” or “worse” compared with baseline (before starting treatment). The global evaluations were performed at each visit (weeks 0, 2, 4, and 6) 1 hour after administration of the study medication. In addition, an uncalibrated 100-mm visual analog scale was used to measure 6 subjective assessments of dry mouth (feeling of mouth, dryness of mouth, dryness of tongue, ability to speak without drinking, ability to chew and swallow food, and ability to sleep). Measured distance along the scale served as the score for these continuous variables. Visual analog scale assessments were carried out before and 1 hour after dosing at each visit.

OBJECTIVE MEASUREMENTS

Secondary efficacy end points included objective measurement of salivary flow and the use of palliative treatments. To measure total salivary flow, patients, who had no gustatory stimulus for a minimum of 90 minutes, were instructed not to swallow and to allow the saliva to collect in the mouth for 5 minutes. Patients then expectorated the contents of the mouth into a collection tube. After the 15-minute collection period, the tube was sealed and weighed.

Throughout the study, participants were provided with take-home questionnaires to record their use of supportive agents, such as artificial saliva, and their fluid intake.

SAFETY

To evaluate safety and toxic effects, clinical laboratory values and findings from 12-lead electrocardiography were recorded at each visit before dosing. Vital signs were recorded before each dose and 1 hour after taking the study medication at each visit. Objective ocular tests, an ophthalmologic examination, and a physical examination were conducted at the screening visit and at the end of the study. In addition, blood and urine samples were collected at each visit for laboratory analysis. Adverse events were documented throughout the study at each visit.

ANALYSES

Efficacy analysis was performed on an intent-to-treat basis. For each of the 4 visits (weeks 0, 2, 4, and 6), data were analyzed for statistical significance, defined as $P<.05$. In addition to analyses by visit week, an end point analysis was performed. End point values were taken from data at the last postdose evaluation for each patient. For patients who completed the study, therefore, week 6 results represent end point values.

The Cochran-Mantel-Haenszel row mean scores statistic was used to analyze significant differences in global patient evaluations and use of supportive treatment among the groups. Analysis of variance was used to detect change from baseline for the visual analog scale and lacrimal and salivary flow measurements. The Fisher exact test was used to assess significant difference in adverse effects across the treatment groups.

Of 75 initial patients, 61 completed all visits (Figure 1). All participants to whom study drug was dispensed were included in the intent-to-treat efficacy analysis. One patient in the 60-mg tid group dropped out before an efficacy evaluation; this patient was included (considered as “worse”) in the primary end point analysis and excluded from the other assessments. The following protocol deviations occurred during the study: 1 patient was aged 75 years (outside the range of 18-70 years specified in the inclusion criteria) and no pregnancy test was performed on 2 patients at screening; results of pregnancy tests performed later on these patients were negative. None of these protocol deviations caused the patients to be excluded from the efficacy or safety analyses.

SUBJECTIVE MEASUREMENTS

Patient Global Evaluations

At weeks 0, 2, 4, and 6, statistically significant differences in dry mouth between the placebo group and the 30-mg cevimeline tid group were evident in favor of the active drug ($P = .014$, .011, .011, and .004, respectively). At weeks 0 and 2, there were statistically significant differences in dry mouth between the placebo group and the 60-mg cevimeline tid group favoring the active drug.
At weeks 4 and 6, the differences favoring the active drug at 60 mg tid approached statistical significance ($P \leq .08$). In particular, patients in the 30-mg and 60-mg cevimeline tid groups showed a significantly favorable effect on dry mouth compared with the placebo group at the end point ($P = .004$ and .02, respectively). At the end point, 19 patients receiving 30 mg of cevimeline (76%) and 18 receiving 60 mg of cevimeline (67%) compared with 8 in the placebo group (35%) had a response of “better” when assessed for improvement of dry mouth (Figure 2). There was no significant difference between the 30- and 60-mg cevimeline tid groups at any visit or at the end point.

At the end point, participants receiving 30 mg of cevimeline tid had a statistically significant improvement in dry eyes compared with the placebo group ($P = .007$). Eighteen patients receiving 30 mg of cevimeline tid (72%) vs 7 receiving placebo (30%) had responses of “better” in assessing improvement of dry eyes at the end point (Figure 3). In the 60-mg cevimeline tid group, 14 patients (52%) reported a response of “better” for improvement of dry eyes; however, this was not a statistically significant difference from the placebo group ($P = .10$).

At weeks 2, 4, and 6, a higher percentage of patients receiving active drug reported “better” in their global evaluation for improvement of overall dryness compared with those receiving placebo. By the end point, patients randomized to receive 30 or 60 mg of cevimeline tid had achieved statistically significant improvements in overall dryness compared with the placebo group ($P = .004$ and .03, respectively) (Figure 4).

**Visual Analog Scale**

Overall, there were no statistically significant differences among study groups at predose assessments. However, a trend toward a statistically significant change from baseline was observed between the treatment groups and the placebo group at week 2 for ability to sleep ($P = .08$), burning sensation in the eyes ($P = .05$), and ability to open the eyes in light ($P = .08$).

Comparing changes in predose to postdose assessments at individual visits, a statistically significant difference between treatment groups and the placebo group was observed at week 2 in feeling of the mouth ($P = .02$), dryness of the mouth ($P = .03$), and dryness of the tongue ($P = .04$) (Table 2). In all of these instances, patients treated with cevimeline were more comfortable than those treated with placebo. At week 2, patients treated with 30 mg of cevimeline tid also showed a statistically significant difference in favor of active drug compared with the placebo group in mucus or discharge in the eyes ($P = .01$; 95% confidence interval [CI], −12.95 to −1.14) and burning sensation in the eyes ($P = .001$; 95% CI, −23.53 to −3.65). At the end point, patients in the 30-mg cevimeline tid group compared with the placebo group had a statistically significant difference in favor of the active drug in ability to speak without drinking ($P = .01$; 95% CI, −21.46 to −1.72) and ability to chew and swallow food ($P = .02$; 95% CI, −19.00 to −1.82) (Table 2).

A statistically significant overall difference was detected at the end point among treatment groups in ability to speak without drinking ($P = .04$) and for the sensation of sand in the eyes ($P = .04$) (Figure 5). In each of these cases, patients treated with active drug were more comfortable than patients treated with placebo.

No significant differences were detected among or between treatment groups for the overall feeling of the eyes, dry feeling of the eyes, or ability to open eyes in light.

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**Figure 2.** Patient global evaluation of dry mouth at the end point; tid indicates 3 times a day.

**Figure 3.** Patient global evaluation of dry eyes at the end point; tid indicates 3 times a day.

**Figure 4.** Patient global evaluation of overall dryness at the end point; tid indicates 3 times a day.
OBJECTIVE MEASUREMENTS

In postdose assessments, there was a significant difference in end point salivary flow values from baseline values for both cevimeline groups compared with the placebo group (P = .001 and < .001, respectively). Change in mean salivary flow from predose to postdose was significantly different among the groups at all visits (P ≤ .003).

Table 2. Changes in Predose to Postdose Assessment of Symptoms of Dry Mouth and Dry Eyes Using the Visual Analog Scale

<table>
<thead>
<tr>
<th>Symptom and Visit</th>
<th>Placebo Group</th>
<th>Cevimeline Group</th>
<th>ANOVA P Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 mg tid</td>
<td>60 mg tid</td>
<td>Overall</td>
</tr>
<tr>
<td>Feeling of the mouth</td>
<td></td>
<td></td>
<td>Placebo vs 30 mg</td>
</tr>
<tr>
<td>Week 2</td>
<td>−1.64 ± 12.14</td>
<td>−17.27 ± 15.87</td>
<td>−13.71 ± 19.10</td>
</tr>
<tr>
<td>Week 4</td>
<td>−3.05 ± 12.46</td>
<td>−14.14 ± 19.07</td>
<td>−16.59 ± 20.26</td>
</tr>
<tr>
<td>End point</td>
<td>−6.09 ± 12.62</td>
<td>−15.77 ± 22.14</td>
<td>−19.32 ± 21.47</td>
</tr>
<tr>
<td>Dryness of the mouth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>−13.74 ± 18.44</td>
<td>−21.64 ± 16.87</td>
<td>−27.92 ± 21.04</td>
</tr>
<tr>
<td>Week 2</td>
<td>−4.00 ± 14.84</td>
<td>−20.59 ± 18.21</td>
<td>−16.24 ± 19.49</td>
</tr>
<tr>
<td>Week 4</td>
<td>−3.59 ± 12.59</td>
<td>−15.86 ± 19.71</td>
<td>−17.24 ± 21.66</td>
</tr>
<tr>
<td>End point</td>
<td>−8.27 ± 14.24</td>
<td>−16.59 ± 22.54</td>
<td>−19.95 ± 22.10</td>
</tr>
<tr>
<td>Dryness of the tongue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>−2.64 ± 15.80</td>
<td>−17.41 ± 18.59</td>
<td>−12.19 ± 15.16</td>
</tr>
<tr>
<td>Dryness of the tongue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ability to speak without drinking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>−7.18 ± 14.90</td>
<td>−14.86 ± 10.88</td>
<td>−7.90 ± 11.15</td>
</tr>
<tr>
<td>Week 4</td>
<td>−1.59 ± 10.69</td>
<td>−10.71 ± 16.72</td>
<td>−9.59 ± 14.02</td>
</tr>
<tr>
<td>Week 6</td>
<td>0.19 ± 10.15</td>
<td>−11.90 ± 17.18</td>
<td>−6.33 ± 17.43</td>
</tr>
<tr>
<td>End point</td>
<td>−9.36 ± 10.24</td>
<td>−11.95 ± 16.77</td>
<td>−9.14 ± 20.46</td>
</tr>
<tr>
<td>Ability to chew and swallow food</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>−7.36 ± 12.62</td>
<td>−13.73 ± 11.3</td>
<td>−6.38 ± 11.75</td>
</tr>
<tr>
<td>Week 6</td>
<td>−2.86 ± 4.44</td>
<td>−13.00 ± 15.96</td>
<td>−8.72 ± 17.64</td>
</tr>
<tr>
<td>End point</td>
<td>−2.82 ± 4.34</td>
<td>−13.23 ± 15.61</td>
<td>−10.77 ± 18.63</td>
</tr>
<tr>
<td>Ability to sleep</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>−1.35 ± 11.63</td>
<td>−6.80 ± 13.44</td>
<td>−9.69 ± 14.01</td>
</tr>
<tr>
<td>Week 6</td>
<td>4.24 ± 11.00</td>
<td>−5.95 ± 15.43</td>
<td>−5.33 ± 15.78</td>
</tr>
<tr>
<td>End point</td>
<td>4.23 ± 10.73</td>
<td>−6.50 ± 15.27</td>
<td>−6.95 ± 17.09</td>
</tr>
<tr>
<td>Sand sensation in the eyes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>−5.23 ± 8.21</td>
<td>−12.27 ± 11.00</td>
<td>−5.67 ± 9.97</td>
</tr>
<tr>
<td>Burning sensation in the eyes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>−1.55 ± 14.00</td>
<td>−15.14 ± 15.23</td>
<td>−1.52 ± 19.83</td>
</tr>
<tr>
<td>Week 6</td>
<td>3.24 ± 12.72</td>
<td>−6.19 ± 14.32</td>
<td>−1.83 ± 16.47</td>
</tr>
<tr>
<td>End point</td>
<td>3.45 ± 12.45</td>
<td>−5.77 ± 14.11</td>
<td>−4.45 ± 18.04</td>
</tr>
</tbody>
</table>

*Values shown in boldface represent statistically significant treatment differences; tid indicates 3 times a day; ANOVA, analysis of variance; and CI, confidence interval.

Figure 5. Summary of change from predose to postdose in patients’ visual analog scale assessment of selected symptoms at the end point; tid indicates 3 times a day.
and particularly at the last visit, when patients in the cevimeline groups had a change in predose to postdose mean salivary flow of 0.26 mL/min (60-mg group) and 0.19 mL/min (30-mg group) compared with 0.01 mL/min in the placebo group (* P* < .001) (Figure 6). Throughout the study, both cevimeline groups had a greater mean increase in salivary flow for all assessments compared with the placebo group. Increases in salivary flow were most notable in the group receiving 60 mg of cevimeline tid compared with those receiving 30 mg of cevimeline tid. There seems to be a greater effect on salivary flow with increasing dose levels. Table 3 provides a summary of the quantitative salivary flows at the end point.

No significant differences were observed in lacrimal flow among the treatment groups during the study or at the end of the study. For instance, change from pre-dose to postdose in mean lacrimal flow was 0.75 mm/min in the group receiving 60 mg of cevimeline tid, 0.67 mm/min in those receiving 30 mg of cevimeline tid, and 0.71 mm/min in the placebo group at the end point (*P* = .29).

Overall, there was a greater reduction from baseline in the use of artificial saliva and tears and in fluid intake for patients who received active drug compared with those who received placebo. More patients in the 60-mg cevimeline group decreased their use of artificial saliva than in the other groups. At the end point, 5 patients in the 60-mg cevimeline tid group (19%) decreased their use of artificial saliva compared with 1 in the 30-mg cevimeline tid group (4%) and none in the placebo group (Table 4). Ten patients receiving 30 mg of cevimeline tid (40%) and 15 receiving 60 mg of cevimeline tid (58%), compared with 10 in the placebo group (44%), decreased baseline use of artificial tears at the end of the study (Table 4). There were no significant differences among treatment groups at any visit in the number of patients who decreased fluid intake.

### SAFETY

A total of 14 patients withdrew from the study because of adverse events. Nine patients withdrew from the 60-mg cevimeline tid group, 4 from the 30-mg cevimeline tid group, and 1 from the placebo group. All patients receiving 60 mg of cevimeline had at least 1 adverse event reported during the study (Table 5). The most common adverse effects, categorized by body system, were general disorders (body as a whole), gastrointestinal tract disorders, and dermatologic disorders (skin and appendages). The average number of adverse events reported per patient increased with increasing dose (Table 5).

Adverse events reported in 10% or more of patients in any single treatment group are presented in Table 6. Significant differences were noted between the placebo and the 60-mg cevimeline tid groups in the incidence of...
increased sweating ($P<.001$), nausea ($P<.001$), and rigors ($P=.03$). Overall, adverse events were more frequently reported for patients receiving 60 mg of cevimeline tid than in the other treatment groups and thus seem to be dose related. Many of the frequently reported adverse events were those expected on the basis of the pharmacological action of the study medication, for example, increased sweating, increased salivation, and nausea. The most frequently reported adverse event resulting in discontinuation from the study was nausea (Table 7).

There were no apparent dose-related changes in mean laboratory values and vital signs from baseline to the end of the study. Most patients in each treatment group had laboratory values within the reference ranges at baseline and at the end of the study. The serum amylase level was noted to be elevated in 1 patient receiving 60 mg of cevimeline tid.

### Table 5. Incidence of Adverse Effects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo Group</th>
<th>Cevimeline Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 mg tid</td>
<td>60 mg tid</td>
</tr>
<tr>
<td>Patients evaluable for safety, No. (%)</td>
<td>23 (100)</td>
<td>25 (100)</td>
</tr>
<tr>
<td>Patients with $\geq$ 1 adverse event, No. (%)</td>
<td>18 (78)</td>
<td>22 (88)</td>
</tr>
<tr>
<td>Number of adverse events</td>
<td>46</td>
<td>89</td>
</tr>
<tr>
<td>Number of adverse events per patient, mean No.</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

* Tid indicates 3 times a day.
† $P=.02$ (placebo vs cevimeline, 60 mg tid).

Sjögren syndrome remains an incurable disease. Hence, treatment is aimed at providing symptomatic relief and at limiting the damaging local effects of xerostomia and keratoconjunctivitis sicca.1

Typically, patients with Sjögren syndrome have relied on physiological stimulation of salivary flow or the use of saliva substitutes to relieve symptoms of dry mouth. Physiological stimulation with sugarless chewing gum or hard candies can be effective in patients who retain some salivary function, but salivary flow is increased only while the gum or candy is in the mouth. Saliva substitutes do not fulfill all of the functions of natural saliva, and because they are swallowed, the duration of their effect is brief.10

Several investigations have shown that pilocarpine use is beneficial in reducing the symptoms of xerostomia, with the effects of a single dose lasting up to 3 hours.11 Cevimeline, a quinuclidine derivative of acetylcholine, is a novel muscarinic receptor agonist9 and was recently approved by the Food and Drug Administration for the treatment of dry mouth in patients with Sjögren syndrome. Because of its extended 5-hour half-life, cevimeline is taken 3 times daily;12 it seems to have minimal adverse effects at doses of 90 mg/d and is tolerated at doses up to 180 mg/d. The monthly cost of treatment with cevimeline, at the recommended dosage for xerostomia in Sjögren syndrome, is approximately $118.12

Consistent with results of animal models,4,8 this study shows that cevimeline therapy is highly effective in improving the symptoms of dry mouth in patients with Sjögren syndrome. The differences among study groups overall in the number of patients reporting responses of “better,” “no change,” and “worse” were significant in favor of the active drug at all assessments for dry mouth ($P\leq.03$) and at all assessments after week 0 for overall dryness ($P\leq.04$). Furthermore, the difference among treatment groups in change in salivary flow from predose to postdose within each visit was statistically significant at the end point ($P<.001$) and at all other visits ($P\leq.003$). At all assessments, the cevimeline groups had greater mean increases in salivary flow than did the placebo group. The dose of 30 mg of cevimeline tid was well tolerated and provided substantive relief for the duration of the study.

### Table 6. Incidence of Adverse Events Reported by 10% or More of the Patients in Any Single Treatment Group

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo Group (n = 23)</th>
<th>Cevimeline Group (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 mg tid</td>
<td>60 mg tid</td>
</tr>
<tr>
<td>Increased sweating</td>
<td>2 (9)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (26)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Rigors</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (13)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1 (4)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (9)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Tremor</td>
<td>0 (0)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0 (0)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Increased salivation</td>
<td>0 (0)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Cold and clammy skin</td>
<td>0 (0)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Micurition frequency</td>
<td>0 (0)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2 (9)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Nervousness</td>
<td>3 (13)</td>
<td>1 (4)</td>
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<tr>
<td>Sinusitis</td>
<td>1 (4)</td>
<td>3 (12)</td>
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<tr>
<td>Myalgia</td>
<td>2 (9)</td>
<td>3 (12)</td>
</tr>
</tbody>
</table>

* Tid indicates 3 times a day.
† $P<.001$ (placebo vs cevimeline, 60 mg tid).
‡ $P=.03$ (placebo vs cevimeline, 60 mg tid).

### Table 7. Discontinuation Due to Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo Group (n = 23)</th>
<th>Cevimeline Group (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 mg tid</td>
<td>60 mg tid</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cold sweats</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Night sweats</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Laboratory abnormality</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

* Tid indicates 3 times a day.
We conclude from the results of this randomized, double-blind, placebo-controlled, phase II study that cevimeline has therapeutic effects in the treatment of xerostomia in patients with Sjögren syndrome for up to 6 weeks. Further work needs to be done to assess its long-term efficacy and safety and its utility in the treatment of keratoconjunctivitis sicca.

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REFERENCES


