CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-989

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEC 22 1999

Clinical Pharmacology/Biopharmaceutics Review

~~Cevimeline Hydrochloride 30mg Capsules~~	**SnowBrand Pharmaceuticals, Inc.**
Exovac®	**San Diego, CA 92121**
Reviewer: A. Noory	**Submission Date:**
NDA 20-989	**November 11, 1999**
Type of Submission: Revised Labeling	

Review of a Revised Labeling

I. Background:

Exovac® (cevimeline hydrochloride) is a quinuclidine derivative of acetylcholine. It is a cholinergic agonist with relatively high specificity for the muscarinic receptors. Cevimeline hydrochloride is indicated for the treatment of symptoms of dry mouth ——— in patients with Sjögren's Syndrome ——— Cevimeline is an agonist that binds with specific muscarinic receptors in various exocrine glands. In this submission the applicant is providing a revised labeling for Exovac®

II. Recommendation:

Please replace the paragraph "Metabolism" under the heading "Pharmacokinetics" with the following.

> 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.

/S/

Assadollah Noory
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm.D (S) 12/22/99

Original: NDA 20-989
CC:
HFD-540/DIV. File
HFD-540/Prj. Mgr./Cintron
HFD-880 (Noory)
HFD-880 (Bashaw)
HFD-880 (Lazor)
(CDR. Attn: Barbara. Murphy)

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ON ORIGINAL

U.S. Food and Drug Administration
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation-III

Team Leader Memo

JUL 8 1999

To: Jonathan Wilkin, M.D., Div. Dir., HFD-540

From: E. Dennis Bashaw, Pharm.D., Team Leader, HFD-880 /S/ 7/8/99

Date: 07/08/99

Re: Cevimeline Capsules, NDA 20-989

Attached is the final review of the pharmacokinetics portion of the cevimeline capsules NDA (20-989). While the review is complete and recommends approval of the application, the reviewer and myself could not come to agreement about one outstanding issue. Rather than engaging in another review cycle, I have exercised my option as a team leader to sign the review with reservations that will be detailed in this memo.

Specifically, in both the recommendation on page 2 and in the review of study II-2 on page 7, Mr. Noory refers to a "dose-response" relationship between dose and saliva secretion. This is based on data from a single study of six individuals, of whom only one had a clear diagnosis of Sjogren's Syndrome. There is a larger response (defined as the amount of saliva excreted during a 2min. observation interval) following a 50mg dose than with a 30mg dose, however, the small number of individuals and the questionable basis of their diagnosis makes the assertion of a dose-response relationship unsupportable in my opinion. I do not dispute that in normal individuals, larger doses of pilocarpine will produce a more pronounced salivary response, the question is, however, "Can this enhancement of salivary flow be reproduced in patients with Sjogren's Syndrome?" The study as designed, powered, and executed is incapable of answering this question.

CC: NDA 20-989(ORIG),
HFD-540/DIV File
HFD-540/Cintron
HFD-880(Bashaw)
HFD-880(Lazor)
CDR. ATTN: B. Murphy

APPEARS THIS WAY
ON ORIGINAL

JUL 8 1999

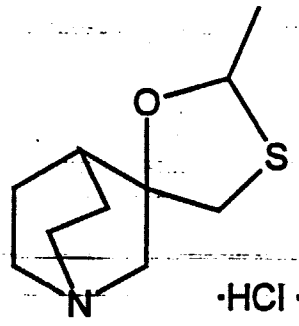
Clinical Pharmacology/Biopharmaceutics Review

Cevimeline Hydrochloride ——— 30mg Capsules	**SnowBrand Pharmaceuticals, Inc.**
Exovac®	**San Diego, CA 92121**
Reviewer: A. Noory	**Submission Date:**
NDA 20-989	**August 26, 1998; January. 7, 1999**
Type of Submission: 1S	**May 24, 1999**

Review of an NDA

I. Background:

Exovac® (cevimeline hydrochloride) is a quinuclidine derivative of acetylcholine. It is a cholinergic agonist with relatively high specificity for the muscarinic M1 and M3 receptors. Cevimeline is also known as SNI-2011, AF102B, FKS-508, and SND-5008. Cevimeline hydrochloride is indicated for the treatment of symptoms of dry mouth ——— in patients with Sjögren's Syndrome ——— Cevimeline is an agonist that binds with specific muscarinic receptors in various exocrine glands. Results of various preclinical studies suggest that cevimeline acts by binding directly to the muscarinic M_3 receptors. This muscarinic agonist is associated with improved glandular ability to increase salivation and lacrimation. The chemical name of cevimeline hydrochloride is cis-2'-methylspiro{1-azabicyclo [2.2.2]octane 3,5'-[1,3] oxathiolane} hydrochloride, hydrate (2:1). The empirical formula for cevimeline hydrochloride is $C_{10}H_{17}NOS \cdot HCl \cdot 1/2H_2O$, with a molecular weight of 244.79. It is a white to off-white crystalline powder and is soluble in water and freely soluble in alcohol. Cevimeline hydrochloride has the following structure:



As part of the human pharmacokinetics and bioavailability portion of this NDA, the applicant has submitted the results of pharmacokinetic studies with in vitro dissolution test.

Synopsis:

Cevimeline hydrochloride binds directly to the muscarinic M_3 receptors and improves glandular secretions associated with glandular dryness. The pharmacokinetic studies submitted adequately describe the pharmacokinetic behavior of the drug in the body. The disposition and metabolic profile of cevimeline has been adequately followed in both normal volunteers and in patients with Sjögren's

Syndrome. Five metabolites, which are considered to have weak pharmacological activity, have been identified. 87% of the drug (parent + metabolites) is eliminated in the urine within 24 hours after drug administration. Capsule formulation has been adequately characterized. It is dose proportional and bioequivalent to the solution and is well tolerated. A food effect study indicated that food has no effect on the extent of absorption, however, Cmax is reduced slightly and Tmax is increased. There is no difference in the disposition of cevimeline in females and males upon single dose administration. Cevimeline has been well tolerated in clinical trials worldwide. Clinical information from supportive studies conducted on patients in Japan demonstrate that there is a linear relationship between the dose and the AUC as well as Cmax as the dose increases from 1mg to 50mg, and that there is a general increase in saliva production. The adverse event profile includes gastrointestinal discomfort (nausea, vomiting, diarrhea, constipation, soft stools and abdominal discomfort), central nervous system effects (dizziness, tremor, and headache), diaphoresis, hypersalivation, and submandibular and parotid swelling. Notable adverse events were present at 30 mg, and they appeared to be dose related, as all patients had adverse events at the maximum tolerated dose.

II. Recommendation:

In support of the pharmacokinetic and bioavailability portion of this NDA the sponsor has submitted the results of six pharmacokinetic studies. Pharmacokinetics of cevimeline upon multiple dose administration has been defined, and the effect of food on the bioavailability of cevimeline has been determined. Additionally, during the review of this NDA a concentration response relation of cevimeline and the secreted saliva was seen. The disposition of cevimeline in males and females were also evaluated. From the Division of Pharmaceutical Evaluation III perspective NDA 20-989 is approvable.

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The Disease:

Sjögren's syndrome is an immunological disorder characterized by dry eyes and dry mouth, and it can include a connective tissue disease. The disease process includes lymphocytic infiltration of glandular tissues that leads to reduction in secretions. About 3 million Americans have dry eye as a consequence of Sjögren's syndrome, and 90% of these patients are women. If untreated, it can affect the skin, lungs, heart, kidneys, muscles, central nervous systems, etc. Primary Sjögren's affects only the eyes or mouth, and secondary Sjögren's occurs with rheumatic disorders sharing certain autoimmune features, for example, rheumatoid arthritis, scleroderma and systemic lupus erythematosus. Prolactin and androgen

levels appear to modulate the lacrimal secretary cell response in Sjögren's syndrome thus providing an explanation for its gender bias.

Environmental and infectious agents and/or their products have been implicated in the pathogenesis of autoimmune diseases, however, there also appears to be a genetic factor. About 20% of the Sjögren's syndrome patients have renal tubular acidosis and in many the renal concentrating ability is decreased. Chronic hepatobiliary disease, as well as pancreatitis, is often associated with Sjögren's Syndrome. Arthritis occurs in approximately 33% of the patients, however, joint symptoms are usually milder. About 20% of the patients with systemic scleroderma also have secondary Sjögren's syndrome.

Treatment for Sjogren's syndrome is primarily symptomatic. Many patients of Sjogren's syndrome are able to treat problems symptomatically, often very successful with corticosteroids. There are several over-the-counter preparations, such as Oral Balance, Xerolube, Replens, and Mouth Kote, which moisten the mouth.

III. Overview of pharmacokinetic section:

The pharmacokinetic/bioavailability studies in this NDA provide sufficient information to adequately characterize the disposition of cevimeline in men, women, patients and the elderly. Five metabolites were identified and quantified in study SNI-2011-001. The metabolites are considered to be pharmacologically weak. About 87% of the dose was found in the urine after 24 hours.
Study SB97US01 illustrated the dose proportionality and bioavailability of single oral doses (15 mg and 30 mg) of cevimeline vs a solution. This study also indicates that there is no statistical difference in the pharmacokinetics of cevimeline in female and male after single dose administration. Study CS-89-1 shows that AUC increases in proportion to the dose (1mg - 50 mg). The food effect study, SB97US02A, shows that the Cmax decreases and Tmax increases but the extent of absorption is unaffected. The dose escalating pharmacokinetic study, R/4800/0002, demonstrated that there may be a difference in the disposition of cevimeline in males and females at higher dose level, however, because of the small sample size one cannot be certain.
The following studies were not reviewed:

Drug Product and Formulation:

The drug product will be marketed in ___ strength that contain ___ 30mg cevimeline anhydrous. The composition of the capsules is shown in the following table.

Ingredient	[redacted]	30 mg
Cevimeline Hydrochloride (AF102B)	[redacted]	[redacted]
Lactose Monohydrate NF	[redacted]	[redacted]
Hydroxypropyl Cellulose, NF	[redacted]	[redacted]
Magnesium Stearate, NF	[redacted]	[redacted]
Total Capsule Fill	[redacted]	[redacted]

Analytical:

Validated assay methodology for the studies are provided for each study. Identification and quantitation of the metabolites of SNI-2011 was carried out using a [redacted] method followed by [redacted]

1. Disposition and Metabolic Profile Study: (Study No. SNI-2011-001)

The objective of this study was to determine the disposition and metabolic profile of ^{14}C-SNI-2011 when administered to six (6) healthy male volunteers. All subjects completed the study. Five metabolites have been identified and quantified in this study. These metabolites were trans-sulfoxide, cis-sulfoxide, N-oxide, glucuronic acid conjugate of SNI-2011, and glucuronic acid conjugate of SNI-2011 trans-sulfoxide. The in vivo pharmacological activity of the metabolites appeared to be weak. The applicant has not determined the relative magnitude of pharmacological activity due to the metabolites.

After 24 hours 87% of total ^{14}C was found in urine. The distribution of the parent and the metabolites of cenimeline are shown in the following table.

Recovery Of Cevimeline And It's Metabolites In Urine After 24 Hours	
Parent (Excreted unchanged)	16.0%
Trans-sulfoxide	35.8%
Cis-sulfoxide	8.7%
Glucuronic acid conjugate of SNI-2011	14.6
Glucuronic acid conjugate of SNI-2011 trans-sulfoxide	7.7%
N-oxide	4.1%

After 168 hours a total of 97.8% of ^{14}C was found in urine and feces (97.3% in the urine and 0.5% in the feces).

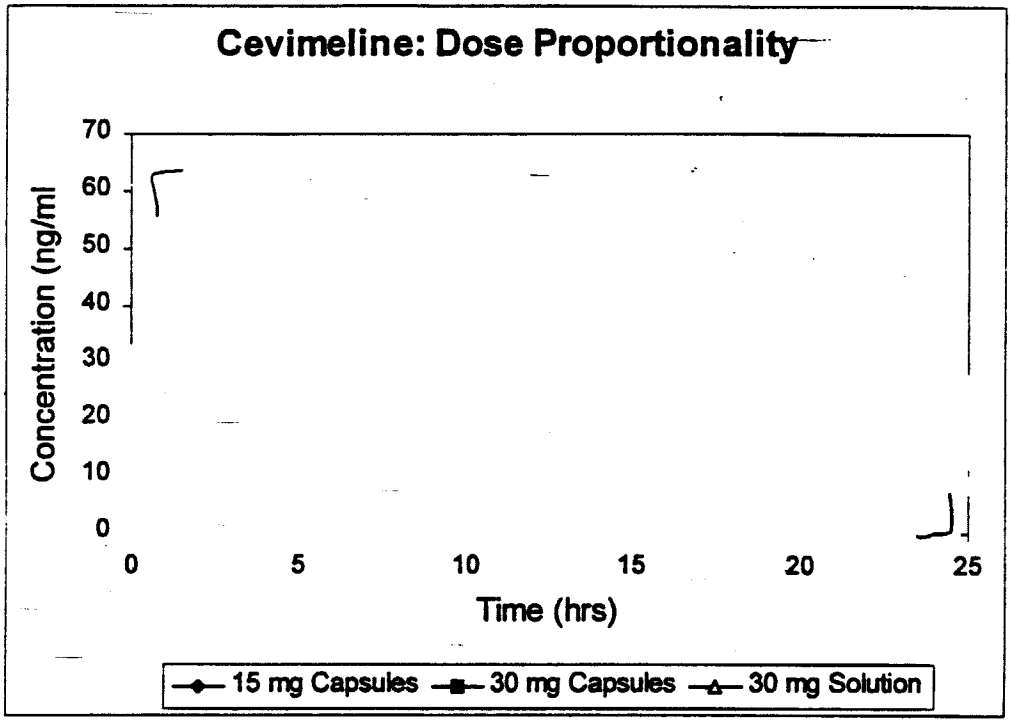
The study summary is located on pages 14-19 of the appendix. The result show that the trans-sulfoxide, cis-sulfoxide, glucuronic acid conjugate of SNI-2011, and glucuronic acid conjugate of SNI-2011 trans-sulfoxide were the major metabolites found in plasma.

2. Dose Proportionality and Bioavailability study: (Study Number SB97US01)

The objective of this study was to compare the rate and extent of absorption of a 15mg capsule, a 30 mg capsule, and 30 mg cevimeline HCl oral solution following a single dose administration. A total of 21 healthy subjects (8 male and 13 female) were enrolled in this single-dose, randomized, three way crossover study. Twenty (20) subjects completed all three periods of the study. One subject withdrew from the study due to sinus pain, congestion, and sore throat and was not included in the data analysis. A summary result is presented in the following table.

Cevimeline: Pharmacokinetic Parameters; N=20; Mean (SE)			
PK-parameter	15mg Capsules	30mg Capsules	30 mg Solution
$AUC_{(0-\infty)}$ (ng*h/ml) 90%CI	210.06 (15.5) 105.8 – 115.9	438.58 (31.74) 101.6 – 111.3	466.39 (33.85) ----------
C_{max} (ng/ml) 90%CI	31.49 (1.88) 98.9 – 109.8	59.94 (3.2) 103.5 – 114.9	65.9 (3.98) ----------
T_{max} (hrs)	1.72 (0.16)	1.75 (0.09)	1.63 (0.13)

A summary of the study and data are located on pages 20-24 of the appendix and the mean plasma concentration time profile is shown in the following figure.

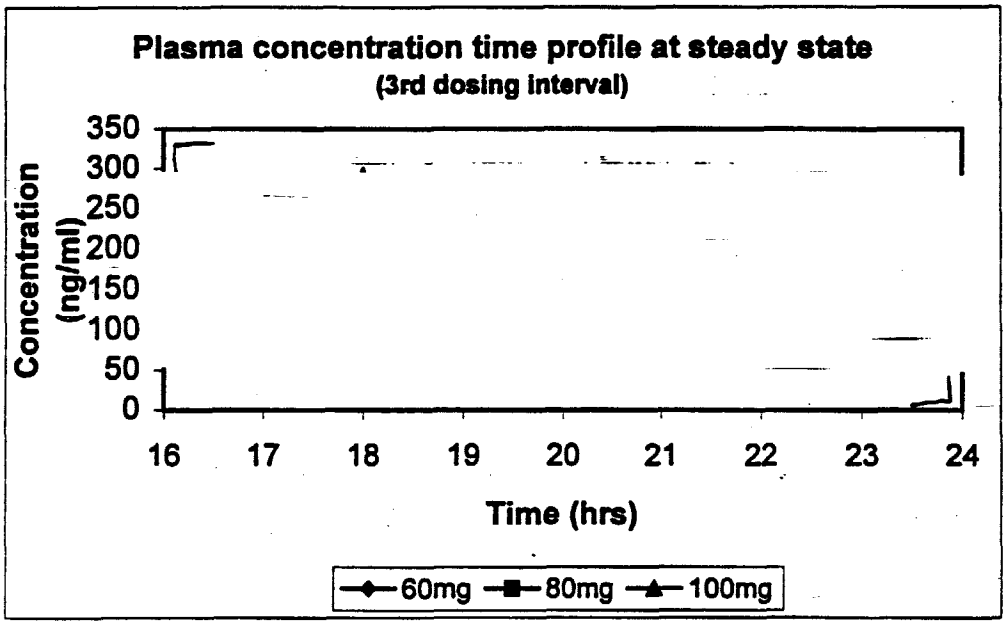


The 30mg capsule and 30mg oral solution were determined to be bioequivalent based on the 90% confidence interval. The 15mg capsule and the 30mg capsule were considered to be dose proportional as evidenced by the magnitude of $AUC_{(0-\infty)}$ and C_{max}. In order to see if there are differences in the pharmacokinetics of cevimeline due to gender, a statistical analysis was carried out. The results show that there is no statistically significant difference in pharmacokinetics of cevimeline in females and men upon single dose administration.

3. Multiple Dose, Dose Escalating study: (Study no. R/4800/0002)

This placebo-controlled, multiple dose, dose escalating tolerance and pharmacokinetics study was conducted to evaluate the pharmacokinetics and tolerance of cevimeline when doses of 60, 80, and 100mg were administered three times a day for 14 days. Twelve (12) subjects completed the study and ten (10) of these subjects participated in more than one dose level. A summary of the study is located on pages 25-

28 of the appendix and the mean plasma concentration time profile at the steady state (hours 16 – 24) is shown in the following figure.

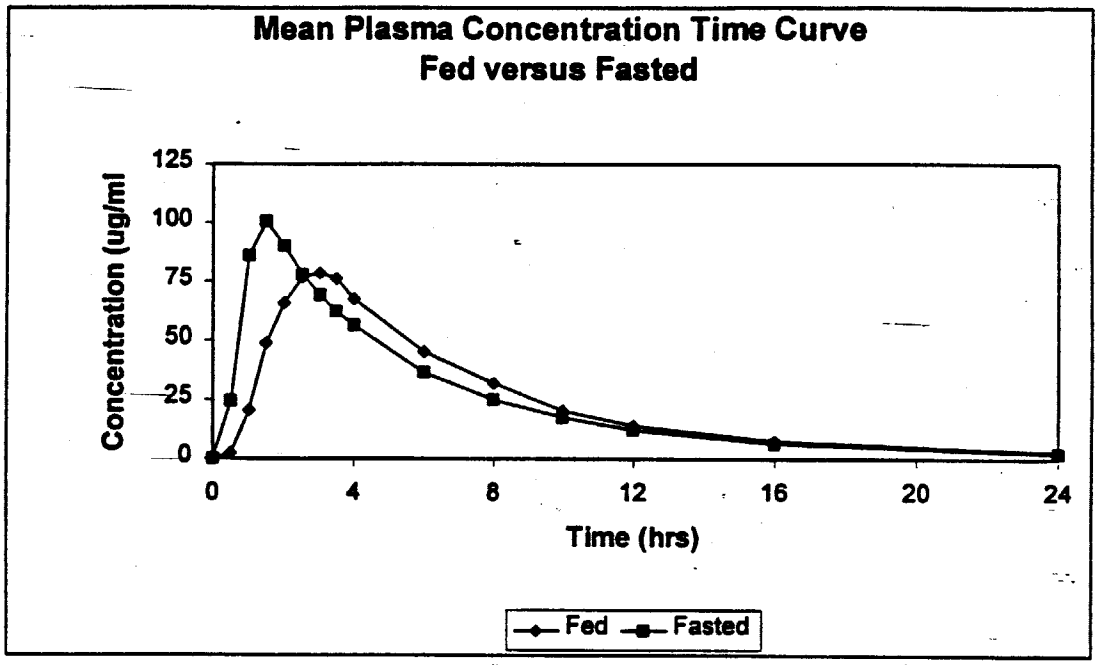


The result of this study showed that there may be a difference in the disposition of cevimeline at the higher doses. A statistical analysis of the data for the 80mg dose level reaveled that there is a statistically significant difference in the extent of absorption (AUCss) of cevimeline in females and males. However due to the small sample size one cannot conclude that this difference seen is factual.

4. Food Effect Study: (Study number SB97US02)

The objective of this study was to compare the rate and extent of absorption of a 30mg cevimeline HCl capsules when given to healthy subjects under fed and fasting conditions. In this two-way crossover study twenty-three subjects were enrolled and twenty-two subjects (9 female and 13 male) completed the study. The standard generic meal was used (Egg McMuffin, 3 Oz. of hash brown, 8 fl. oz. of whole milk, and 6 fl. oz. of orange juice). The summary of the study is located on pages 29-30 of the appendix and the results are shown in the following table and graph.

Effect of Food on Cevimeline; Mean (SE)			
Pk-Parameter	Fed	Fasted	90% C.I.
AUC (0-∞) (ng*h/ml)	581.44 (43.80)	583.05 (52.83)	92.9 – 102.6
C_{max} (ng/ml)	87.39 (14)	104.69 (7.39)	108.3 – 127.1
T_{max} (hr)	2.86 (0.14)	1.53 (0.09)	[redacted]



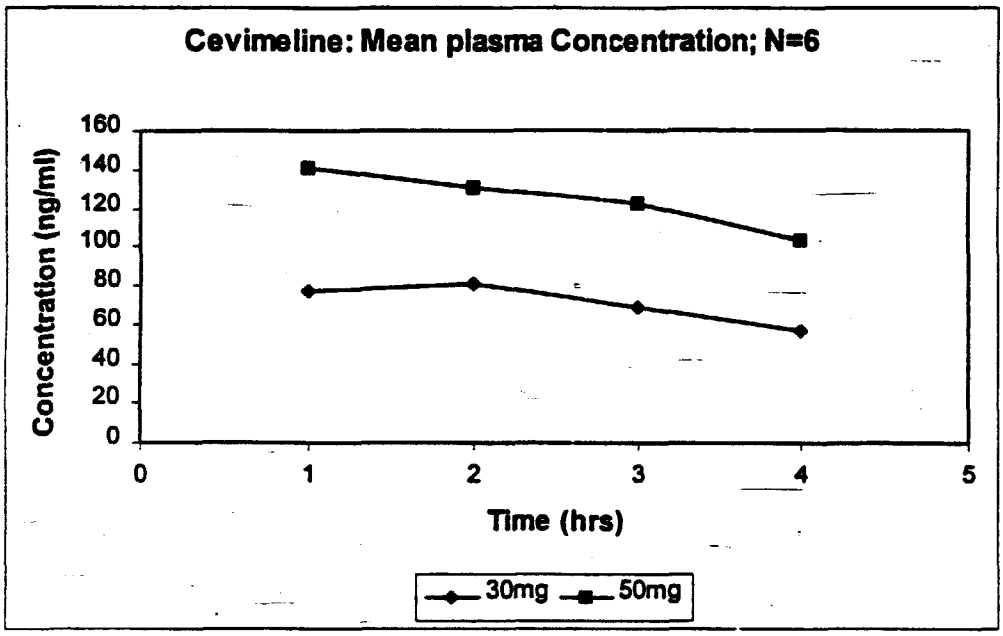
The results of this study show that the AUC remains unchanged, C_{max} is reduced by 17% (from _____ , and the time to peak concentration, T_{max} increased by 87% (from one and half to two and three quarter hour). This difference may not be clinically relevant.

5. Pharmacokinetic study in Patients with Sjogren's Syndrome: (Study No. II-2)

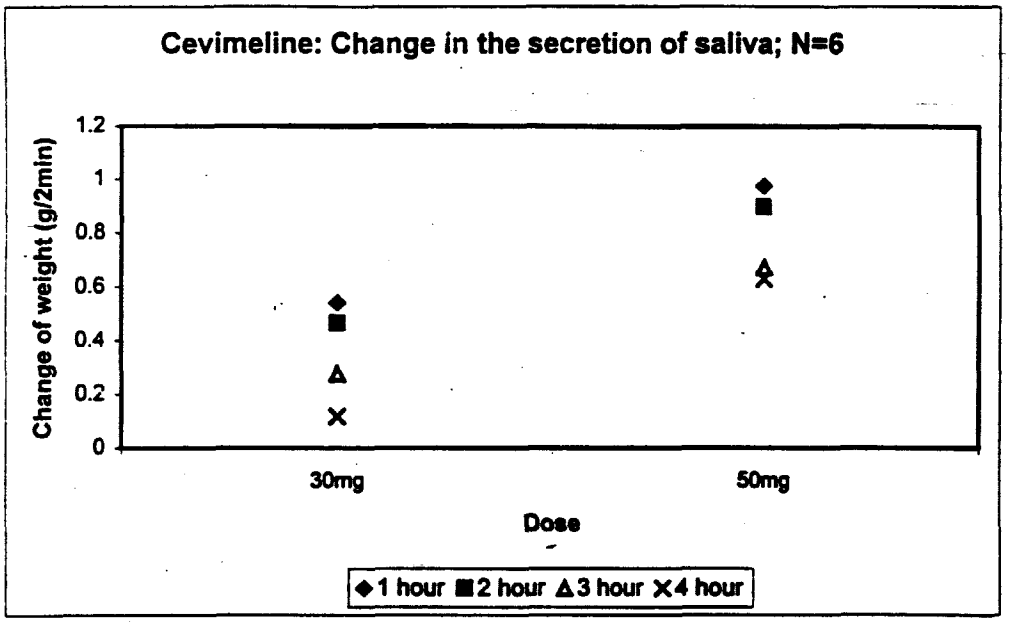
This study examined the pharmacokinetic and pharmacodynamic relationship between secreted saliva volume and the administered dose of 30mg and 50mg of cevimeline to patients with Sjögren' s syndrome. Six female patients (one patient with certainty and 5 patients suspected of Sjögren' s syndrome) were enrolled in the study. For measurements of saliva secretion the Saxon test, where a gauze pad is placed in the mouth for 2 minutes to absorb the secreted saliva, was done at pre-dosing, and 1, 2, 3, 4, 8 and 24 hours post-dosing. A summary study is located on pages 31-35 of the appendix. The following table contains the mean plasma concentration of cevimeline and corresponding amount of saliva secreted.

Mean Plasma Concentration and Amount of Saliva Secreted (N=6)				
Time (hrs)	30 mg Capsule		50 mg Capsule	
	Plasma Conc. (ng/ml)	Amount of Saliva (g/2min)	Plasma Conc. (ng/ml)	Amount of Saliva (g/2min)
0	0	1.44 ± 1.17	0	1.31 ± 1.54
1	76.7 ± 26.9	1.98 ± 1.50	141.2 ± 66.9	2.29 ± 2.00
2	80.8 ± 28.5	1.91 ± 1.45	130.4 ± 30.3	2.21 ± 1.71
3	68.6 ± 26.8	1.72 ± 1.45	122.2 ± 33.4	1.98 ± 1.49
4	57.0 ± 21.9	1.56 ± 1.29	103.7 ± 31.8	1.94 ± 1.55
8	29.0 ± 13.7	1.74 ± 1.46	57.4 ± 32.1	1.69 ± 1.39
24	3.7 ± 2.4	1.53 ± 1.43	6.4 ± 5.0	1.68 ± 1.73

The graph below shows the mean plasma concentration of cevimeline in the first four hours for both 30mg and 50mg capsules.



In order to see any relation between the dose administered and the effect, namely the amount of saliva secreted, the pre-dose values were subtracted from each of the measurements made. The graph below shows this relationship.

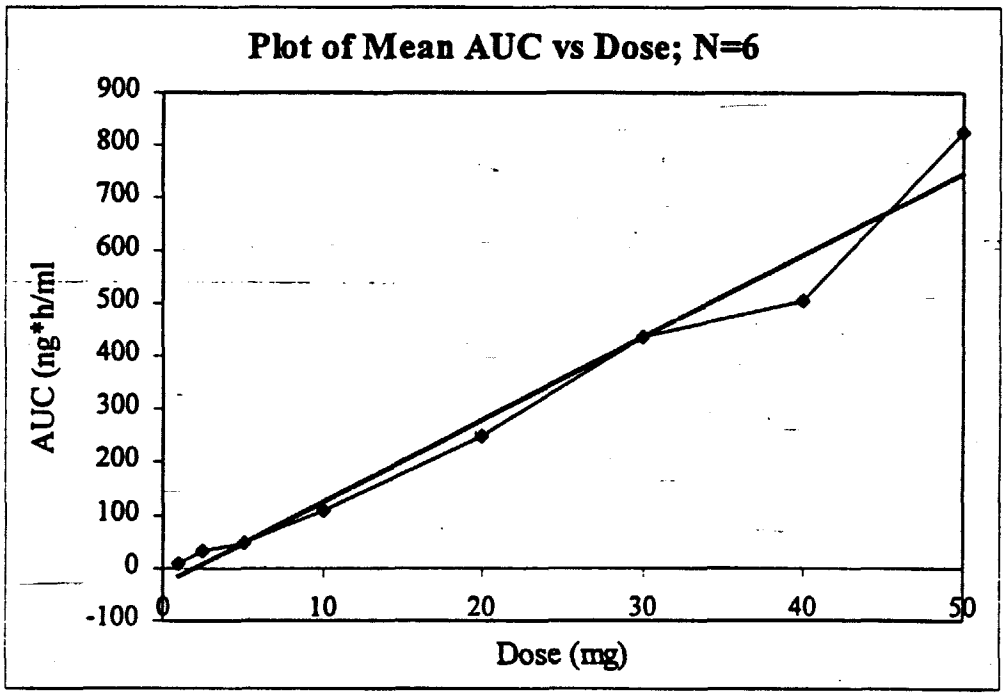


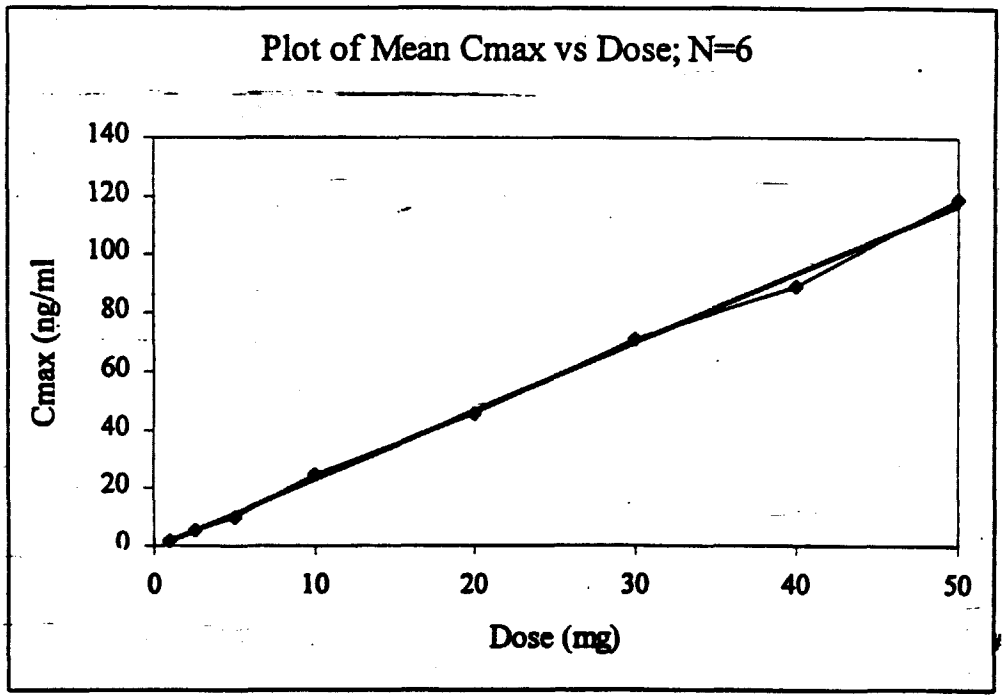
The results of this study indicate that there is a dose response relationship between cevimeline and the amount of saliva secreted.

Supportive Study:

6. Single and Multiple Dose Pharmacokinetic Study: (Study Number CS89-1)

This phase I clinical trial was conducted in 1989 at [redacted] The results of this study were published in J. Clin. Ther. Med. 6, 1990. This study was conducted in single dose and multiple dose administrations. A multiple dose study, R/4800/0002, provided the information upon multiple dose administration, therefore this review will only focus on the single dose phase of the study. The objective of the study was to investigate the tolerance of cevimeline in healthy male subjects. The study consisted of eight (8) groups with eight subjects per group (6 for cevimeline and 2 for placebo). A total of 34 healthy male subjects participated in this trial. Most of the subjects were included in more than one group. Doses of 1, 2.5, 5, 10 20, 30, 40, and 50mg were administered and pharmacokinetic parameters were determined. A summary of the study is located on pages 36-37 and graphs of AUC and Cmax versus dose are shown below.





This study demonstrates that there is a linear relationship between the dose and the AUC, as well as Cmax, as the dose increases from 1mg to 50mg upon single dose administration.

IV. In Vitro Metabolism: (Study number M98-014)

This study was carried out to determine the potential for SNI2011 to inhibit human liver cytochrome P450 enzymes lA2, 2A6, 2C9, 2C9, 2D6, 2E1, and 3A4. The following probe substrates were used to investigate the inhibitory potential of SNI2011 on the respective enzymes: phenacetin for CYPlA2; coumarin for CYP2A6; tolbutamide for CYP2C9; S-mephenytoin for CYP2C19; dextromethorphan for CYP2D6; chlorzoxazone for CYP2E1; and testosterone for CYP3A4. The activity of each CYP45O enzyme was determined in hepatic microsomes in the presence and absence of SNI2011.

The result of this study are located on pages 38-39 of the appendix. It appears that none of the CYP450 activities were inhibited by SNI2O11.

V. Dissolution:

The dissolution test was carried out using [redacted] The results of these tests are located in the appendix pages 40-44. The dissolution medium selected was [redacted] and the clinical and commercial batches were tested using the following test condition.

Apparatus [redacted]
Paddle speed [redacted]
Dissolution Medium [redacted]

The following graph is the profile of the clinical and the commercial batches.

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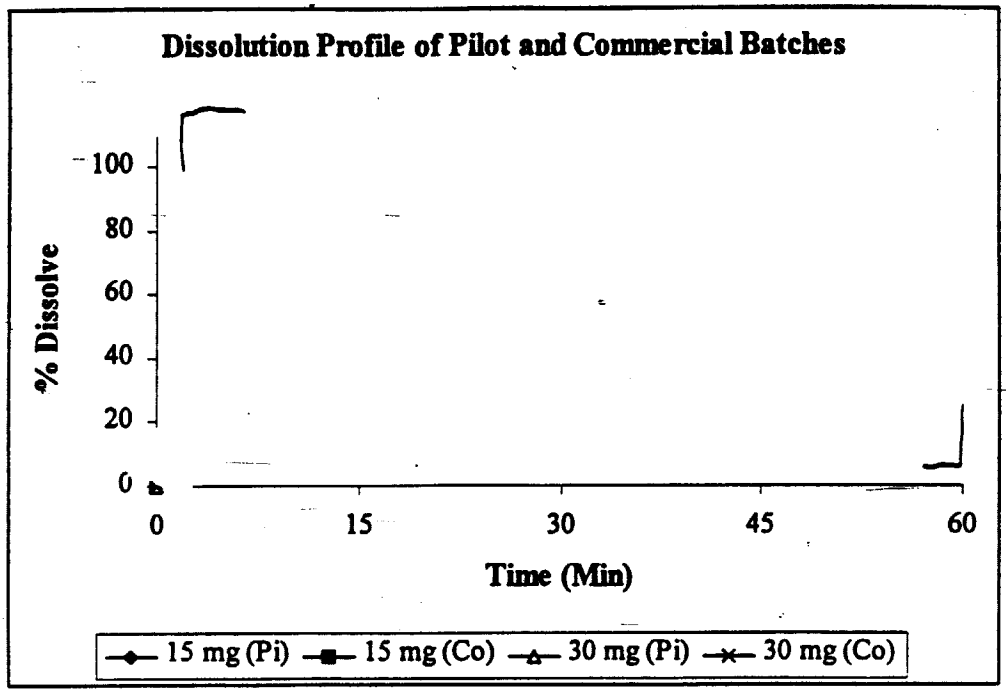

The dissolution method and the specification is acceptable.

Apparatus
Paddle speed
Dissolution Medium
Specification

VI. Labeling Recommendation:

A. Under heading "Pharmacokinetics and Metabolism" of the CLINICAL PHARMACOLOGY section the following changes are recommended:

1 Absorption: delete the first two sentences and replace with After administration of a single 30 mg capsule, cevimeline was rapidly absorbed with a time to peak concentration of 1.5 to 2 hours. No accumulation of active drug or its metabolites was observed following multiple dose administration. Also change the last sentence to: Single oral doses across the clinical dose range are dose proportional.

2 Additionally remove the paragraph on

3 Distribution: Remove the paragraph and replace it with: Cevimeline has a volume of distribution of approximately 6L/kg and is <20% bound to human plasma proteins. This suggests that cevimeline is extensively bound to tissues, however, the specific binding sites are unknown.

4 Metabolism: Remove the paragraph and replace it with: Isozymes CYP2D6 and CYP3A3/4 are responsible for the metabolism of cevimeline. After 24 hours

5 Excretion: Remove the paragraph and replace it with: The mean half-life of cevimeline is 5+/-1 hours. After 24 hours 84% of a 30 mg dose of cevimeline was excreted in urine. After seven days 97% of the dose was recovered in the urine and 0.5% was recovered in the feces.

B. Under heading "Drug Interaction" of the PRECAUTIONS section the following change is recommended:

1 Drug Interaction: Replace the last sentence with: In an in vitro study, cytochrome P450 isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4 were not inhibited by exposure to cevimeline.

/S/ 7/8/99

Assadollah Noory
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm.D. /S/ 7/8/99 w/ reservation
see attached cover memo dated 7/8/99

Original: NDA 20-989
CC:
HFD-540/DIV. File
HFD-540/Prj. Mgr./Cintron
HFD-880 (Noory)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-344 (Viswanathan)
(CDR. Attn: Barbara. Murphy)

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Appendix

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NDA # 20-989 Submission Date: August 26,1998 Volumes: 1.34, 1.34, & 7.1
Study Type: Mass-balance, clinical pharmacology Study # SNI-2011-001
Study Title: A single dose study of the bioavailability, absorption, and excretion of ^{14}C-SNI-2011 in healthy male volunteers

Clinical Investigator/ Site: [redacted]

Analytical Investigator Site: [redacted]

Study Date: 27 January 1997 - 24 February 1997

Study Objective: The objective of this study was to determine the disposition and metabolic profile of. ^{14}C-SNI-201 1 when consumed once by six normal, healthy, male volunteers.

Study Design:
Single Dose: X Multiple Dose: Randomized: Washout Period:
Cross-Over: Parallel: Other Design: single-center, open-label
Fasted: X Post dosing: 4 hours fast
Food Study: Food Type:

Study Subjects: Six (6) healthy male subjects between the ages of 18 and 45 were enrolled in this study. All subjects completed the study.

Subject Breakdown

No. Of Subj.	Gender	Mean Age (yr.)	Range (yr.)	Mean Weight (kg)	Range (kg)
6	Male	31.5	24 - 43	Not reported	Not reported

Treatment

Treatment	Dose	Dosage Form	Strength	Mfg. Lot #	Batch Size
^{14}C-SNI-2011	Oral	Not reported	30mg (200μCuries)	CP-2059-2	Not reported

Sampling Times

Plasma: Two 10ml of blood samples were collected prior to and following the treatment at 0.5, 1, 2, 3, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours after dose administration.

Urine: Urine was collected at intervals of (-2 – 0), (0 - 4), (4 - 8), (8 - 12), (12 - 24), (24 - 48), (48 - 72), (72 - 96), (96 - 120), (120 - 144), and (144 - 168) hours after dose administration.

Fecal: All fecal samples were collected prior to and for a period of one week after the dose administration.

Assay Method: [redacted]

Assay Sensitivity:

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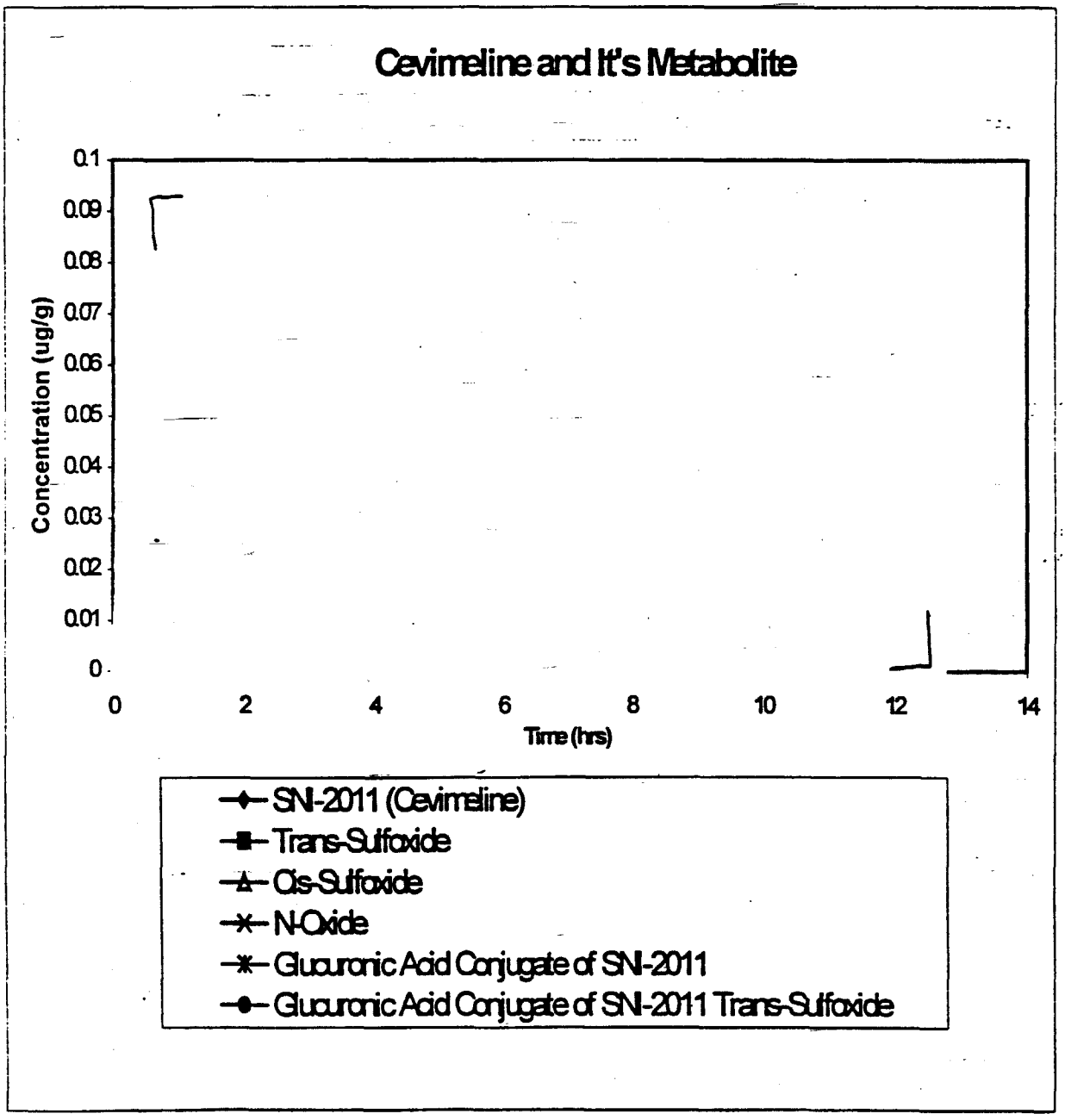
Cevimeline (SNI-2011) and It's Metabolites; Mean (SD)						
Pharmacokinetic Parameters	**SNI-2011**	**Trans-sulfoxide**	**Cis Sulfoxide**	**N-Oxide**	**glucuronic Acid conjugate of SNI-2011**	**Glucuronic acid conjugate of SNI-2011 trans-sulfoxide**
AUC $_{(0-t)}$ (µg.hr/g)	2.38 (0.56) N=6	0.29 (0.11) N=6	0.03 (0.02) N=5	0.01 (0.01) N=3	0.23 (0.18) N=5	0.52 (0.35) N=6
AUC $_{(0-\infty)}$ (µg*hr/g)	2.59 (0.52) N=6	0.41 (0.10) N=4	———	———	———	———
C_{max} (µg/g)	0.20 (0.03) N=6	0.08 (0.06) N=6	0.01 (0.01) N=6	0.01 (0.01) N=6	0.04 (0.02) N=6	0.07 (0.04) N=6
T_{max} (hr)	2.01 (0.63) N=6	1.58 (0.92) N=6	1.81 (1.31) N=5	1.19 (0.80) N=3	4.20 (2.17) N=5	6.17 (4.54) N=6



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confidential

commercial

information

Table 1. Percent of Radioactive Dose in Urine and Feces at Specified Intervals Postdose for Male Subjects (Group 1) Following a Single Oral Dose of ^{14}C-SNI-2011 (30 mg/subject) (Percent of Radioactive Dose)

Collection Interval (Hours)	Subject Number 1	2	3	4	5	6	Mean	SD
				Urine				
0-4							37.3	6.03
4-8							21.0	2.01
8-12							13.9	1.39
12-24							14.5	3.26
24-48							7.67	1.57
48-72							1.85	0.39
72-96							0.62	0.12
96-120							0.25	0.05
120-144							0.12	0.02
144-168							0.05	0.01
Subtotal	98.9	99.6	104	89.1	94.9	97.9	97.3	4.93
				Feces				
0-24							0.05	0.06
24-48							0.22	0.20
48-72							0.12	0.10
72-96							0.04	0.03
96-120							0.02	0.01
120-144							<0.005	NA
144-168							ND	NA
Subtotal	0.34	0.37	0.36	0.44	0.29	0.94	0.46	0.24
Total	99.2	100	104	89.6	95.2	98.8	97.8	4.93

ND Not detected.
SD Standard deviation.
NA Not applicable.

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ON ORIGINAL

Table 3. Urine Profile Distribution from — Analysis (Percent of Dose) for Subjects 1 Through 6.

Subject Number	% of Dose [a]	Radioactivity Detected From TLC (% of dose) SNI-2011	trans-Sulfoxide	cis-Sulfoxide	Sulfone	N-oxide	Unknown 1	Unknown 2
				0-24 Hours				
1								
2								
3								
4								
5								
6								
Average		16.0	35.8	8.7	NA	4.1	14.6	7.7
SD		6.6	10.4	1.3	NA	0.8	6.8	1.9
				48 Hours				
1								
2								
3								
4								
5								
6								
Average		0.6	1.8	0.4	NA	0.3	2.8	2.0
SD		0.3	0.5	0.2	NA	0.2	1.1	0.3

a 0-24 Hour values obtained by adding 4 hour through 24 hour % of dose.
ND Not detected.
SD Standard deviation.
NA Not applicable.

APPEARS THIS WAY
ON ORIGINAL

Total 14C Urine Cumulative Excretion Data
Snow Brand Milk Products Co. Ltd.
Study Drug: 14C-SHI-2011 (Protocol No. SHI-2011-001)
Arithmetic Mean of Cumulative Excretion (%)
Versus Time (CV%) in 6 Subjects

Time	Reference Treatment A
0	0.0000 (%)
4	37.3500 (16.11%)
8	58.3500 (8.42%)
12	72.2333 (5.49%)
24	86.7667 (4.73%)
48	94.4300 (4.92%)
72	96.2833 (5.08%)
96	96.9033 (5.05%)
120	97.1550 (5.04%)
144	97.2717 (5.04%)
168	97.3233 (5.04%)

Total 14C Feces Cumulative Excretion Data
Snow Brand Milk Products Co. Ltd.
Study Drug: 14C-SHI-2011 (Protocol No. SHI-2011-001)
Arithmetic Mean of Cumulative Excretion (%)
Versus Time (CV%) in 6 Subjects

Time	Reference Treatment A
0	0.0000 (%)
24	0.0533 (117.2%)
48	0.3120 (61.96%)
72	0.4400 (51.35%)
96	0.4740 (51.32%)
120	0.4860 (52.69%)
144	0.4880 (52.23%)
168	0.4880 (52.23%)

NDA # 20-989 Submission Date: August 26,1998 Volumes: 1.31 – 1.32
Study Type: Dose proportionality and bioavailability Study # SB97US01
Study Title: A Single-dose, Randomized, Open-label, Three-way Crossover Study Comparing Cevimeline Hydrochloride Administered as a 15mg Capsule, a 30mg Capsule, and as 30mg Oral Solution to Healthy Volunteers under Fasting Conditions

Clinical Investigator:
Site:

Analytical Investigator
Site:

Study Date: 13 October 1997 - 11 December 1997

Study Objective: The objective of this study was to compare the rate and extent of absorption of a 15 mg cevimeline HCl capsule, a 30 mg cevimeline HCl capsule, and 30 mg cevimeline HCl oral solution (15 mL) when given to healthy subjects under fasting conditions.

Study Design:
Single Dose: X Multiple Dose: Randomized: X Washout Period: 7 days
Cross-Over: X Parallel: Other Design:
Overnight Fast: X Post dosing: 4 hours fast
Food Study: Food Type:

Study Subjects: A total of 21 healthy subjects participated in this study and 20 subjects completed the study. Subject number 018 withdrew consent because of sore throat, congestion, and sinus pain.

Subject Breakdown

No. Of Subj.	Gender	Mean Age (yr.)	Range (yr.)	Mean Weight (lb)	Range (lb)
13	Female	34.7	18 - 50	142.8	111 – 186
8	Male	32.8	19 - 49	187.4	152 - 211

Treatment

Treatment	Dose	Dosage Form	Strength	Lot #	Batch Size
A	Oral	Capsules	15mg	H6K10	Not reported
B	Oral	Capsules	30mg	H6K14	Not reported
C	Oral	Solution	30mg	0602	Not reported

Sampling Times

Plasma: 10ml of blood samples were collected prior to and following the treatment at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, and 24 hours after dose administration.

Assay Method: was used for determination of SNI-2011 (cevimeline).
Assay Sensitivity:
Assay Accuracy: Expressed as % diff.: Range was from
Assay Precision: %CV range was from

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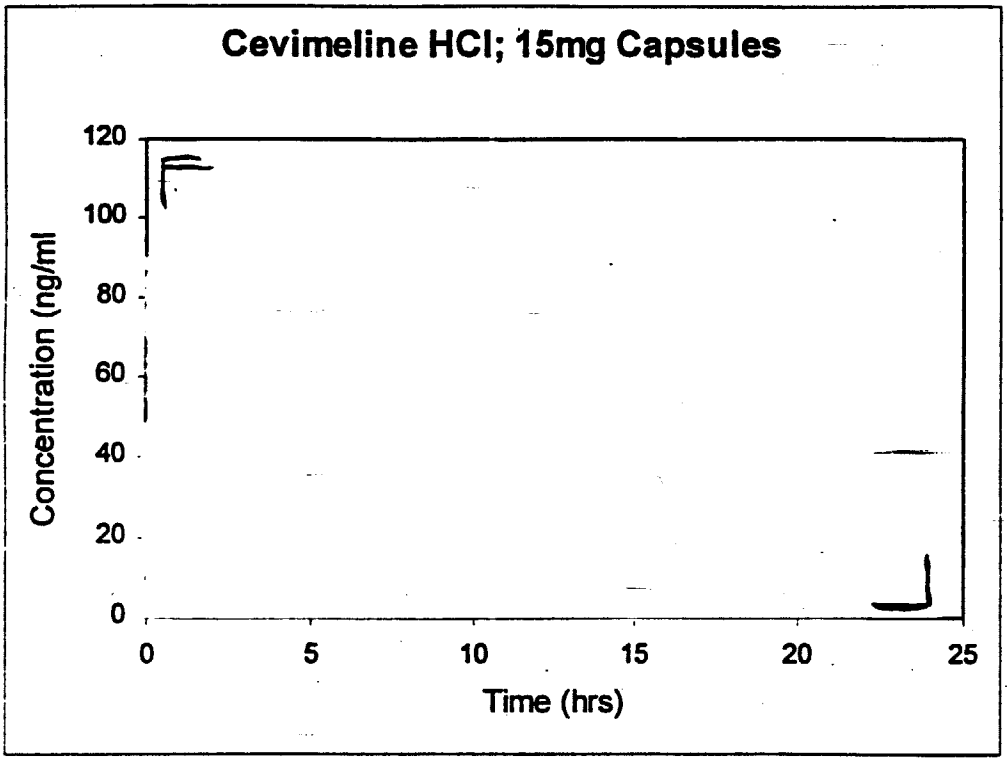
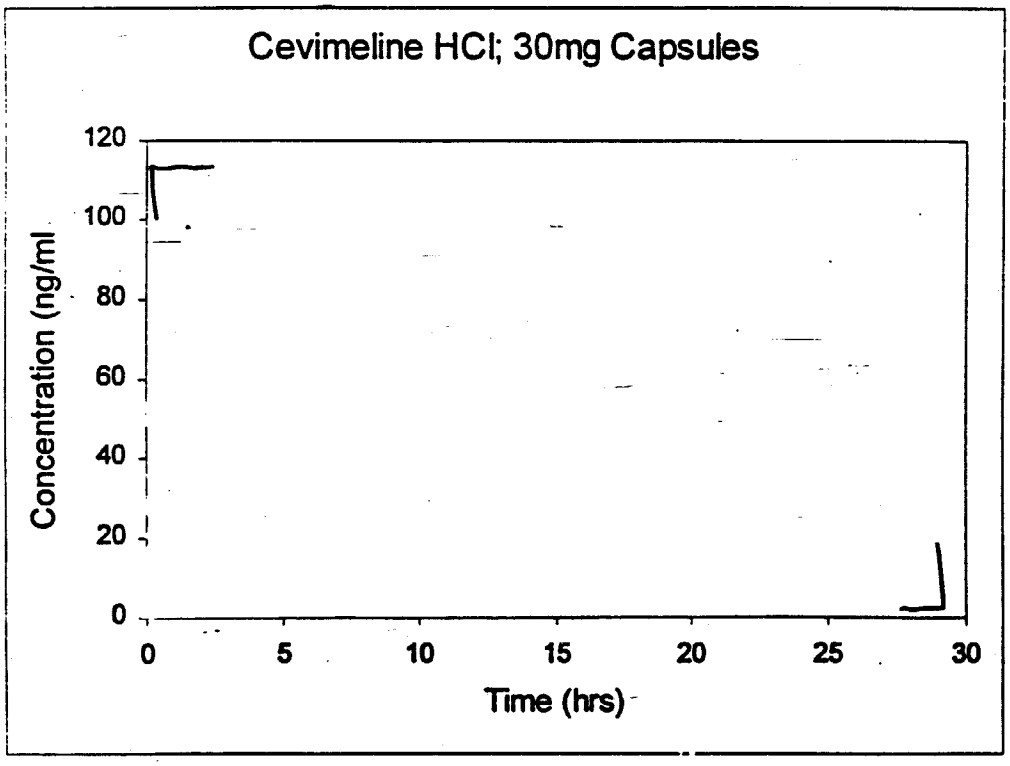
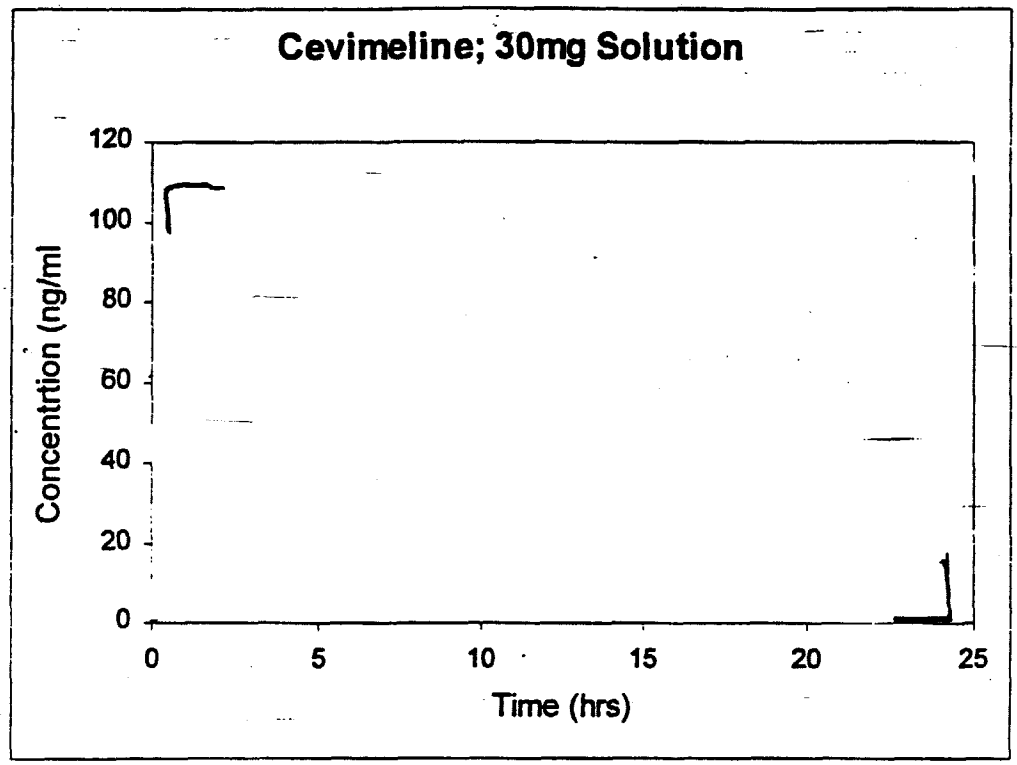
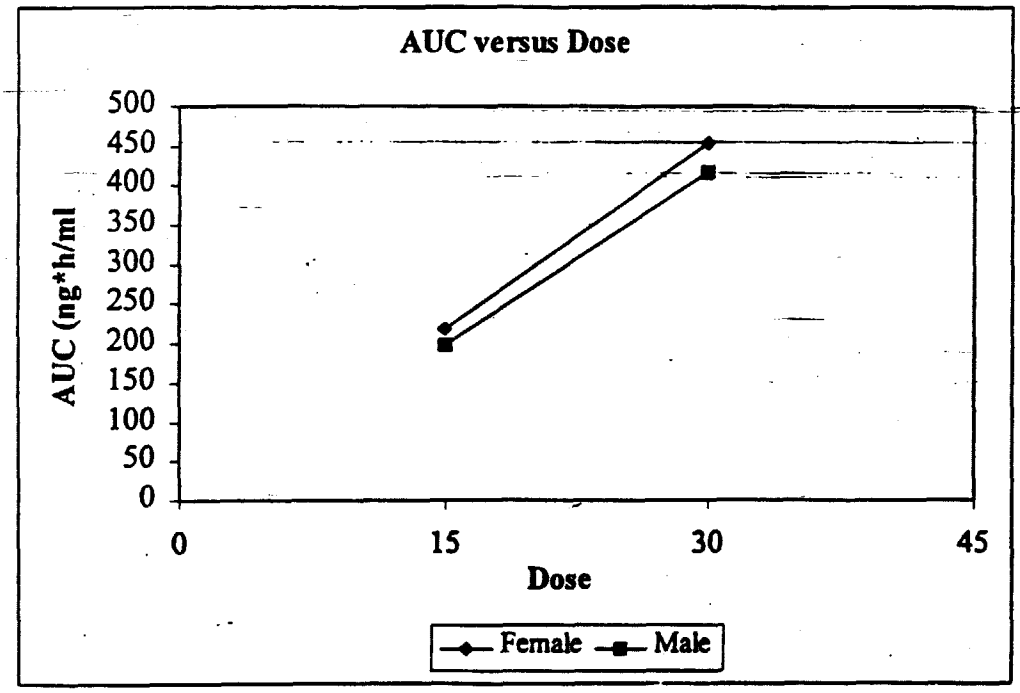
TABLE F. SUMMARY (MEAN ± SE) OF PHARMACOKINETIC PARAMETERS

Parameter	Mean ± SE		
	Treatment A: 15 mg Capsule (N=20)	Treatment B: 30 mg Capsule (N=20)	Treatment C: 30 mg Solution (N=20)
AUC_{0-inf} (hr•ng/mL)	210.06 (15.50)	438.58 (31.74)	466.39 (33.85)
AUC_{0-24} (hr•ng/mL)	198.83 (14.61)	419.14 (29.07)	446.36 (31.25)
C_{max} (ng/mL)	31.49 (1.88)	59.94 (3.20)	65.90 (3.98)
T_{max} (hr)	1.72 (0.16)	1.75 (0.09)	1.63 (0.13)
K_{el} (1/hr)	0.16 (0.01)	0.14 (0.01)	0.14 (0.01)
T1/2 (hr)	4.53 (0.25)	5.06 (0.26)	5.10 (0.22)


Cevimeline HCl; 15mg Capsules
Concentration (ng/ml
120
100
80
60
40
20
0
0
5
10
15
20
25
Time (hrs)


Cevimeline HCl; 30mg Capsules
Concentration (ng/ml
120
100
80
60
40
20
0
0
5
10
15
20
25
30
Time (hrs)


Cevimeline; 30mg Solution
Concentrtion (ng/ml
120
100
80
60
40
20
0
0
5
10
15
20
25
Time (hrs)


AUC versus Dose
AUC (ng*h/ml
500
450
400
350
300
250
200
150
100
50
0
0
15
30
45
Dose
Female
Male

Office of Clinical Pharmacology and Biopharmaceutics
Analysis for Gender Effect

TTEST PROCEDURE

Variable: CL

GEN	N	Mean	Std Dev	Std Error	Variances	T	DF	Prob>|T|
F	13	1.09923077	0.22936367	0.06361404	Unequal	-1.0164	8.2	0.3385
M	8	1.33000000	0.61646457	0.21795314	Equal	-1.2339	19.0	0.2323

'For HO: Variances are equal, F' = 7.22 DF = (7,12) Prob>F' = 0.0032

NDA # 20-989 Submission Date: August 26,1998 Volume: 1.39
Study Type: Multiple Dose, Dose Escalating Study # R/4800/0002
Study Title: A Placebo-Controlled, Multiple Dose, Dose Escalating, Tolerance and Pharmacokinetics Study of AF102B in Healthy Elderly Volunteers

Clinical Investigator [redacted] Analytical Investigator: Not indicated
Site: [redacted] Site: [redacted]

Study Date: From October 5, 1993 through November 10, 1993

Study Objective: The objective of this study was to evaluate the safety, bioavailability and pharmacokinetics of AF1O2B at higher dosage regimens.

Study Design:

Single Dose:	Multiple Dose: X	Randomized:	Washout Period:
Cross-Over:	Parallel: X	Sequential: X	Other Design:
Fasted:	Post dosing:		
Food Study:	Food Type:		

Study Subjects: A total of twenty-four healthy elderly subjects were enrolled in this study (18 in the treatment groups and 6 in the Placebo). Twelve (12) of the eighteen (18) subjects in the treatment groups completed the study. Most subjects participated in more than one dosing group.

Subject Breakdown

Treatments	No. Of Subj.	Gender	Mean Age (yr.)	Range (yr.)	Mean Weight (kg)	Range (kg)
AF102B	13	Female	70.8	64 – 77	61.8	54.0 – 75.0
	5	Male	72.8	65 - 82	76.8	69.5 – 85.2
Placebo	4	Female	70.5	67 - 77	64.8	55.5 – 73.5
	2	Male	70.5	68 - 73	85.3	77.0 – 93.5

Treatment

Treatment	Dose (mg)	Dosage Form	Strength	Lot #	Batch Size
AF102B	60 TID	Capsules	1X60 mg	46083-G01	Not Provided
AF102B	80 TID	Capsules	2X40mg	46083-G02	Not Provided
AF102B	100 TID	Capsules	1X40mg + 1X60 mg	[redacted]	[redacted]

Treatment A: Days 1-2: One 40 mg AF1O2B capsule and one placebo capsule (equivalent to 40 mg TID).
Days 3-14: One 60 mg AF1O2B capsule and one placebo capsule (equivalent to 60 mg TID).
Days 15-16: Two 40 mg AF1O2B capsules (equivalent to 80 mg TID).
Days 17-28: One 40 mg AF1O2B capsule and one 60 mg AF1O2B capsule (equivalent to 100 mg TID).
Treatment B: Days 1-28: Two placebo capsules.
Treatment C: Days 1-2: One 60 mg AF1O2B capsule and one placebo capsule (equivalent to 60 mg TID).
Days 3-14: Two 40 mg AF1O2B capsules (equivalent to 80 mg TID).
Days 15-28: One 40 mg AF1O2B capsule and one 60 mg AF1O2B capsule (equivalent to 100 mg TID).
Treatment D: Days 1-28: Two placebo capsules.

Sampling Times

Plasma: Five ml of blood samples were collected prior to and following the dose administration at 1, 2, 3, 4, 8, and 24 hours on days 14 and 28.
Assay Method: [redacted]
Assay Sensitivity: [redacted]
Assay Accuracy: Range was from [redacted]
Assay Precision: %CV range was from [redacted]

Preliminary Report
Study R/4800/0002

Table 6

AF102B Pharmacokinetic Parameters at Steady State Following Oral Administration of AF102B Three Times a Day Every 8 Hours

Parameters	60 mg	80 mg	100 mg
AUC (0-τ) (ng.hr/mL)	1146.1 ± 497.6	1362.1 ± 296.8	1734.7 ± 497.2
Rel. Bio.	110.1%	98.2%	
Cmax (ng/mL)	212.7 ± 78.5	245.2 ± 46.5	325.9 ± 84.8
Rel. Bio.	108.8%	95.6%	
Tmax (Hours)	1.9 ± 0.4	2.3 ± 0.8	2.1 ± 0.6
Kel (hr^{-1})	0.177 ± 0.054	0.245 ± 0.265	0.198 ± 0.142
Half-life (hr)	4.29 ± 1.54	4.81 ± 1.42	3.46 ± 1.95
MRT_{∞} (hr)	6.92 ± 2.39	8.11 ± 2.66	6.34 ± 3.02
CL/f (L/min)	1.04 ± 0.54	1.01 ± 0.18	1.02 ± 0.39
V_z (L)	349.7 ± 97.8	464.9 ± 159.1	358.1 ± 129.5

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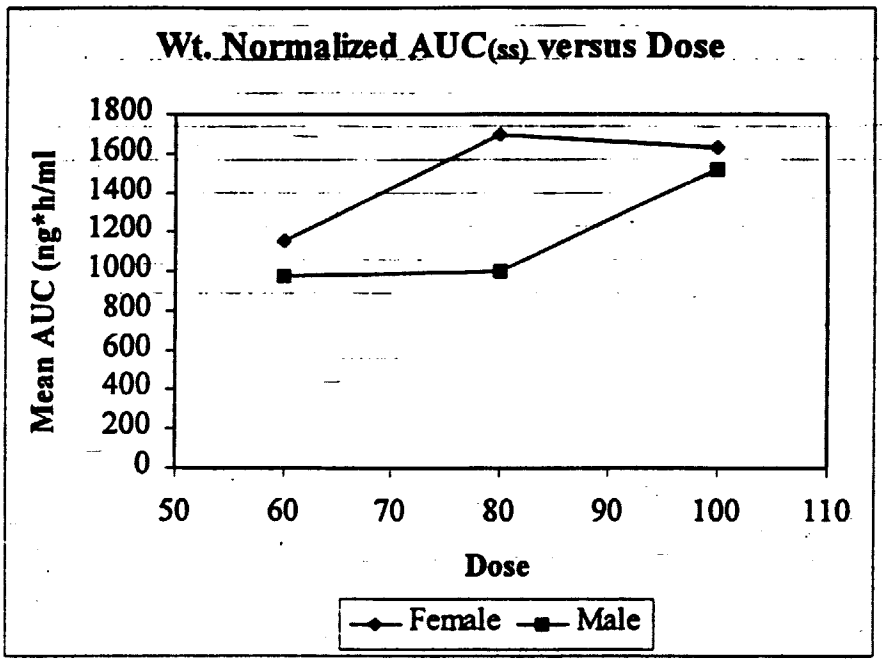
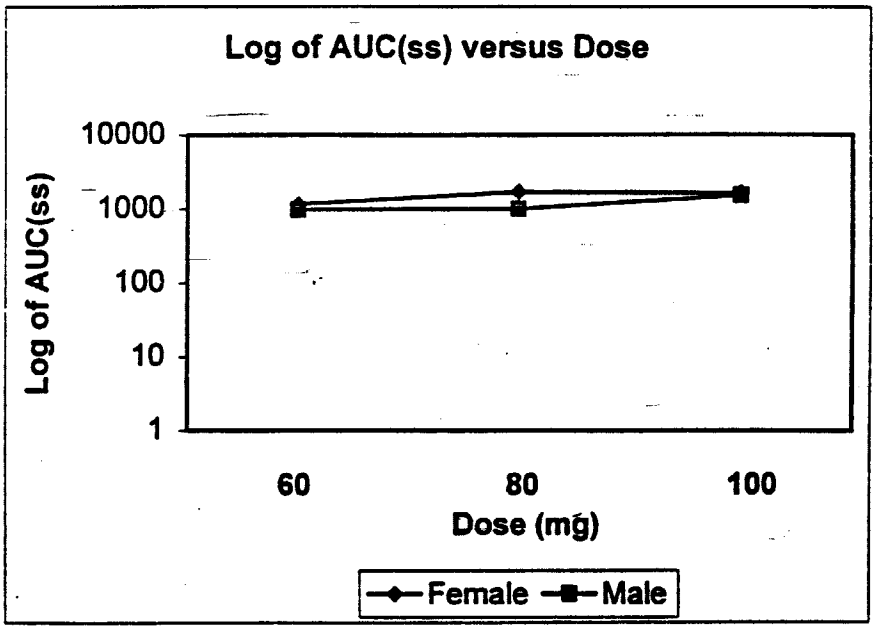

Wt. Normalized AUC(ss) versus Dose
Mean AUC (ng*h/ml
1800
1600
1400
1200
1000
800
600
400
200
0
50
60
70
80
90
100
110
Dose
Female
Male


Log of AUC(ss) versus Dose
Log of AUC(ss)
10000
1000
100
10
1
60
80
100
Dose (mg)
Female
Male

Office of Clinical Pharmacology and Biopharmaceutics
Gender analysis, 80 mg capsules, study R/4800/0002

TTEST PROCEDURE

Variable: LNAUC

GEN	N	Mean	Std Dev	Std Error	Variances	T	DF	Prob>|T|
F	3	7.41983122	0.22408768	0.12937708	Unequal	3.0742	3.9	0.0391
M	3	6.90010821	0.18849427	0.10882721	Equal	3.0742	4.0	0.0371

For HO: Variances are equal, F' = 1.41 DF = (2,2) Prob>F' = 0.8287

NDA # 20-989 Submission Date: August 26,1998 Volumes: 1.33
Study Type: Food Effect Study # SB97US02
Study Title: A Single-dose, Randomized, Open-label, Two-way Crossover Study Comparing Cevimeline Hydrochloride Administered as a 30mg Capsule to Healthy Volunteers under Fed and Fasting Conditions

Clinical Investigator
Site:

Analytical Investigator
Site:

Study Date: 20 October 1997 - 2 December 1997

Study Objective: The objective of this study was to compare the rate and extent of absorption of a 30mg cevimeline HCl capsule when given to healthy subjects under fed and fasting conditions.

Study Design:
Single Dose: X Multiple Dose: Randomized: X Washout Period: 7 days
Cross-Over: X Parallel: Other Design:
Overnight Fast: X Post dosing: 4 hours fast
Food Study: X Food Type: High-fat breakfast

Study Subjects: A total of 23 healthy subjects were enrolled in this study and 22 subjects completed the study. Subject number 19 could not be located and did not complete the study.

Subject Breakdown

No. Of Subj.	Gender	Mean Age (yr.)	Range (yr.)	Mean Weight (lb)	Range (lb)
9	Female	34.1	18 - 44	138.9	111 – 172
14	Male	31.7	20 - 47	168.1	134 - 201

Treatment

Treatment	Dose	Dosage Form	Strength	Lot #	Batch Size
Cevimeline HCl	Oral	Capsules	30mg	H6K14	Not reported

Sampling Times

Plasma: 10ml of blood samples were collected prior to and following the treatment at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, and 24 hours after dose administration.

Assay Method: [redacted] was used for determination of SNI-2011 (cevimeline).
Assay Sensitivity: [redacted]
Assay Accuracy: Range was from [redacted]
Assay Precision: %CV range was from [redacted]

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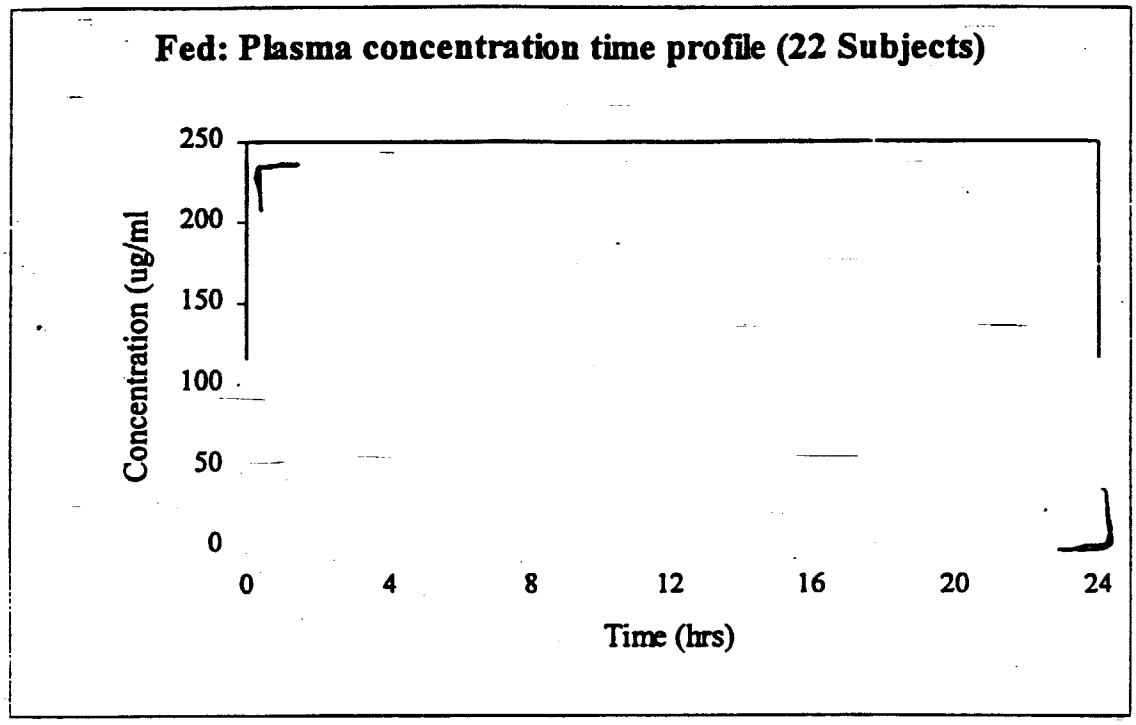
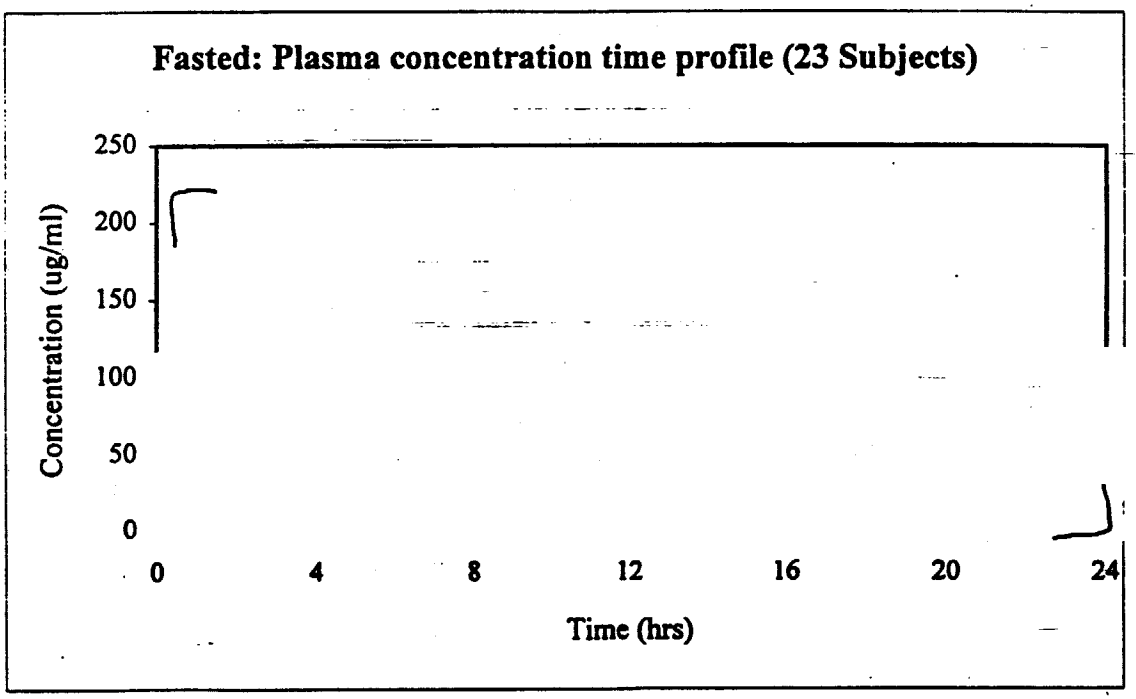
ON ORIGINAL


Fed: Plasma concentration time profile (22 Subjects)
Concentration (ug/ml
250
200
150
100
50
0
0
4
8
12
16
20
24
Time (hrs)


Fasted: Plasma concentration time profile (23 Subjects)
Concentration (ug/ml)
250
200
150
100
50
0
0
4
8
12
16
20
24
Time (hrs)

NDA # 20-989 Submission Date: August 26,1998 Volume: 1.45
Study Type: PK-study in patients with Sjögren's syndrome Study # II-2
Study Title: Examination of Pharmacokinetics and Saliva-Secretary Function of Patients with Sjögren's syndrome when Administered by a Single Oral Dose of SNI-2011.

Clinical Investigator: [redacted] Analytical Investigator: Not indicated
Site: [redacted] Site:

Study Date: From April 1993 through December 1993

Study Objective: The objective of this study was mainly to examine the relationship between secreted saliva volume and pharmacokinetic profile of SNI-2011, when a single dose was administered to patients with Sjögren' s syndrome.

Study Design:
Single Dose: X Multiple Dose: Randomized: Washout Period:
Cross-Over: Parallel: Other Design: single-center, open-label; 30mg dose was administered
Fasted: X Post dosing: and After 3 days the 50mg dose was administered
Food Study: Food Type:

Study Subjects: Six (6) female subjects with Sjögren' s syndrome between the ages of 18 and 45 were enrolled in this study. All subjects completed the study.

Subject Breakdown

No. Of Subj.	Gender	Mean Age (yr.)	Range (yr.)	Mean Weight (kg)	Range (kg)
6	Female	53.8	48 - 68	43.4	35 – 54

Treatment

Treatment	Dose	Dosage Form	Strength	Mfg. Lot #	Batch Size
SNI-2011	Oral	Capsules	30mg 50mg	Not reported	Not reported

Sampling Times

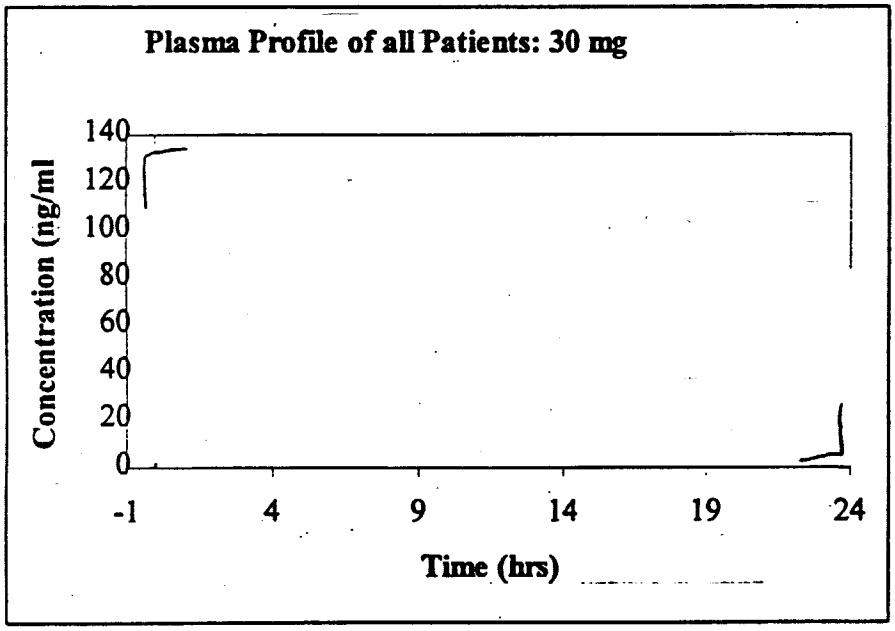
Plasma: Five ml of blood samples were collected prior to and following the dose administration at 1, 2, 3, 4, 8, and 24 hours.

Saliva: Saxon test was done at pre-dosing, and 1, 2, 3, 4, 8 and 24 hours post-dosing.

Assay Method: [redacted]
Assay Sensitivity: [redacted]
Assay Accuracy: Range was from [redacted]
Assay Precision: %CV range was from [redacted]

APPEARS THIS WAY
ON ORIGINAL

Plasma Concentrations of SNI-2011 following Administration of 30 mg of SNI-2011(ng/ml)							
	Time (Hours)						
Patient No.	1	2	3	4	8	24	Cmax
1	[redacted]						
2							
3							
4							
5							
6							
Mean	76.7	80.8	68.6	57.0	29.0	3.7	
S.D.	26.9	28.5	26.8	21.9	13.7	2.4	



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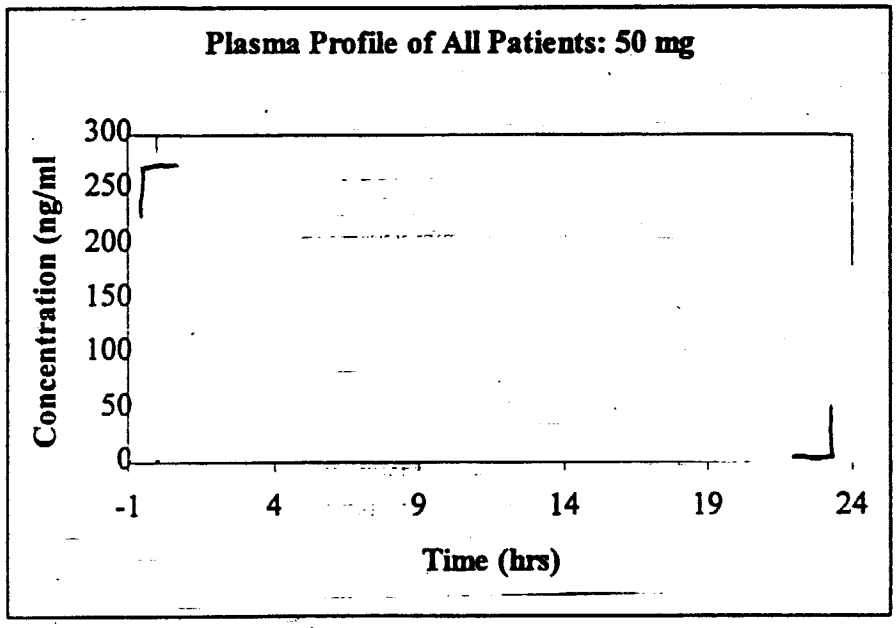
Plasma Concentrations of SNI-2011 following Administration of 50 mg of SNI-2011(ng/ml)							
	Time (Hours)						
Patient No.	1	2	3	4	8	24	Cmax
1							
2							
3							
4							
5							
6							
Mean	141.2	130.4	122.2	103.7	57.4	6.4	
S.D.	66.9	30.3	33.4	31.8	32.1	5.0	



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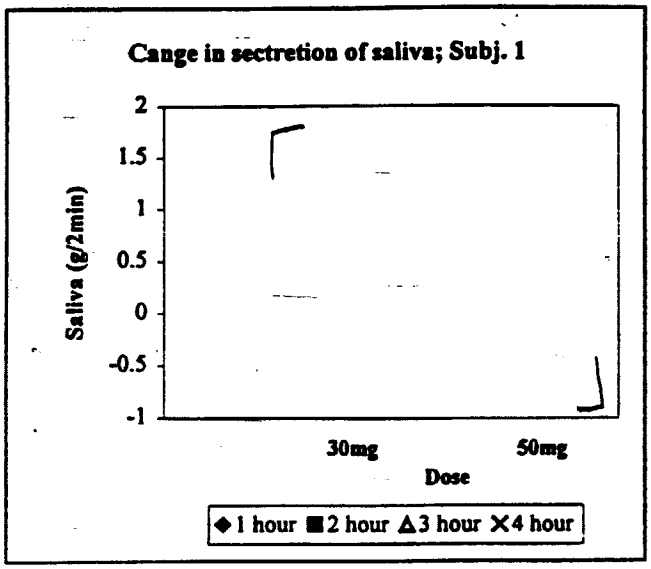
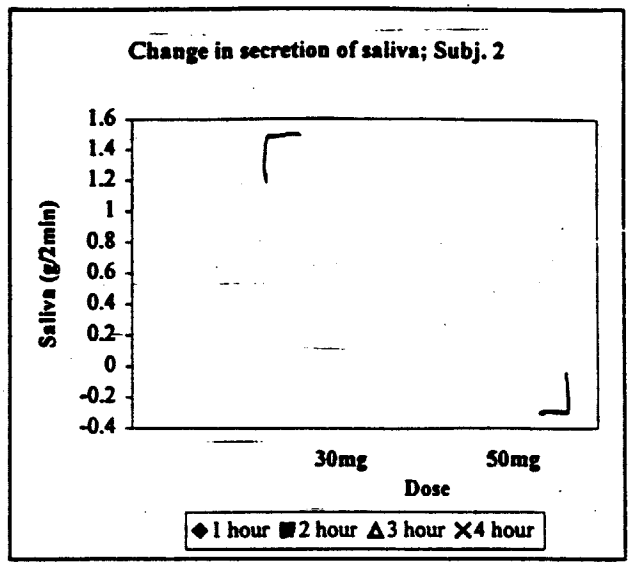
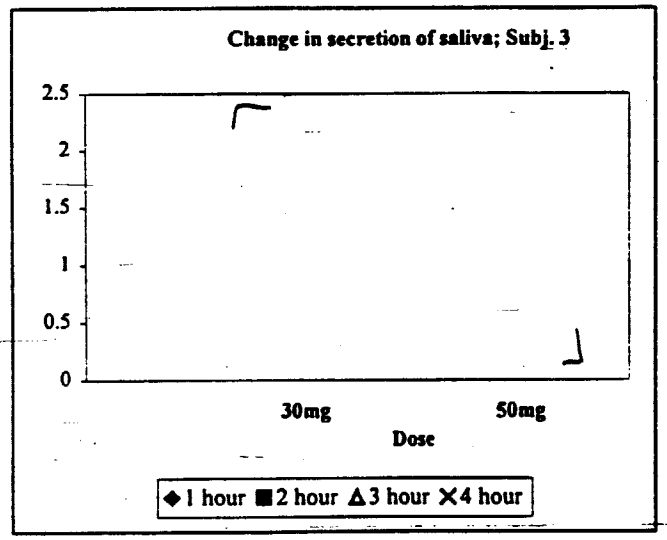
Secreted saliva of patients following the Administeration of 30 mg SNI-2011 (g/2minutes)							
Patient No.	Time after Administraton (hours)						
	0	1	2	3	4	8	24
1							
2							
3							
4							
5							
6							
Mean ±S.D.	1.44 ±1.17	1.98 ±1.50	1.91 ±1.45	1.72 ±1.45	1.56 ±1.29	1.74 ±1.46	1.53 ±1.43

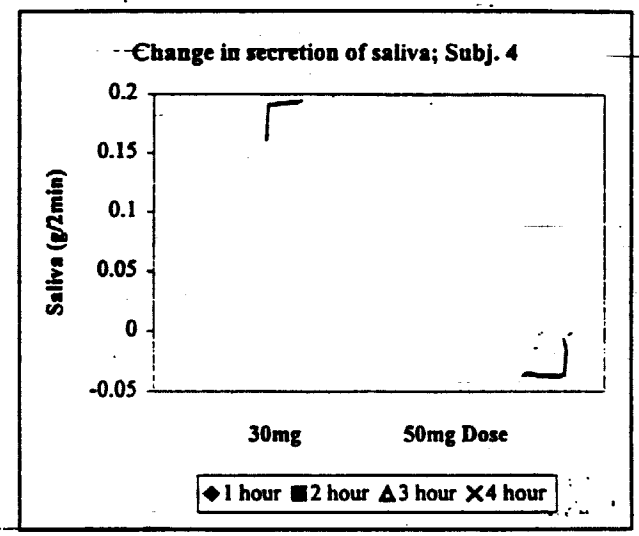
Secreted saliva of patients following the Administeration of 50 mg SNI-2011 (g/2minutes)							
Patient No.	Time after Administration (hours)						
	0	1	2	3	4	8	24
1							
2							
3							
4							
5							
6							
Mean ±S.D.	1.31 ±1.54	2.29 ±2.00	2.21 ±1.71	1.98 ±1.49	1.94 ±1.55	1.69 ±1.39	1.68 ±1.73

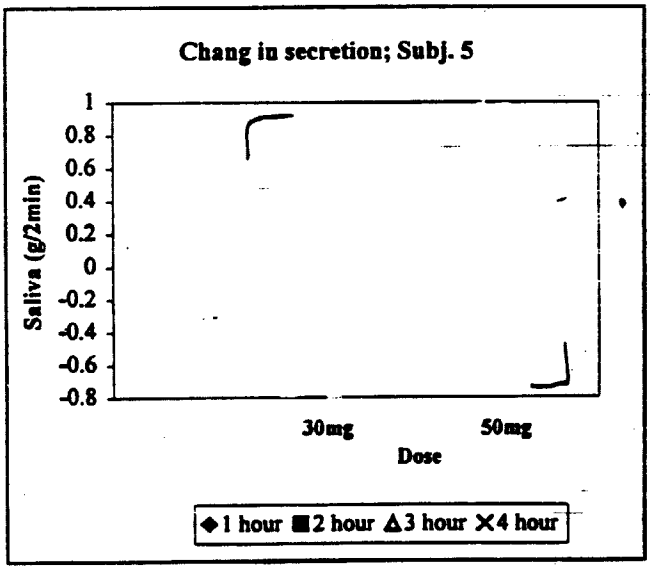
APPEARS THIS WAY
ON ORIGINAL

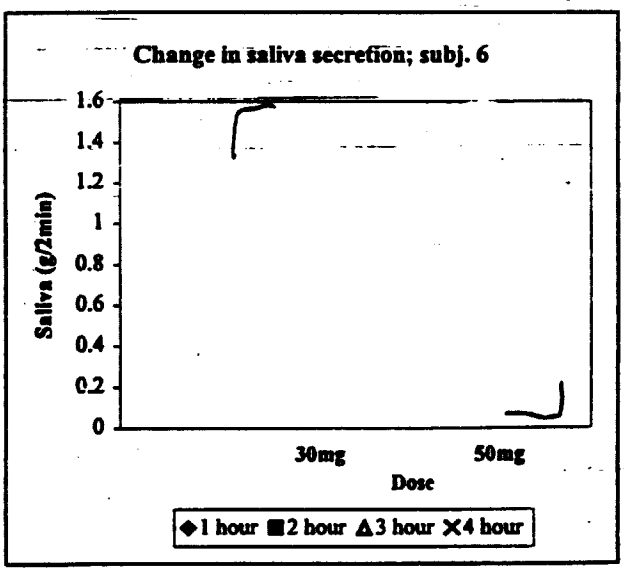

Cange in sectretion of saliva; Subj. 1
Saliva (g/2min)
2
1.5
1
0.5
0
-0.5
-1
30mg
50mg
Dose
◆1 hour ■2 hour △3 hour ✕4 hour


Change in secretion of saliva; Subj. 2
Saliva (g/2min)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
30mg
50mg
Dose
◆1 hour ■2 hour △3 hour ✕4 hour


Change in secretion of saliva; Subj. 3
2.5
2
1.5
1
0.5
0
30mg
50mg
Dose
◆1 hour ■2 hour △3 hour ✕4 hour


Change in secretion of saliva; Subj. 4
Saliva (g/2min)
0.2
0.15
0.1
0.05
0
-0.05
30mg
50mg Dose
◆1 hour ■2 hour △3 hour ✕4 hour


Chang in secretion; Subj. 5
Saliva (g/2min)
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
30mg
50mg
Dose
◆1 hour ■2 hour △3 hour ✕4 hour


Change in saliva secretion; subj. 6
Saliva (g/2min)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
30mg
50mg
Dose
◆1 hour ■2 hour △3 hour ✕4 hour

NDA # 20-989 Submission Date: August 26,1998 Volumes: 1.29
Study Type: single and multiple dose study Study # CS89-1
Study Title: Phase I Study of FKS-508 - Single and multiple dose study

Clinical Investigator: A qualified physician.
Site:

Study Date: 3 October 1988 – 10 April 1989

Analytical Investigator
Site:

Study Objective: The objective of this study was to investigate the tolerance and pharmacokinetics of FKS-508 (cevimeline) when given as single and multiple dose to healthy subjects under fasting conditions.

Study Design:
Single Dose: X Multiple Dose: X Randomized: X Washout Period: One week
Cross-Over: Parallel: X Other Design: (for subjects that were enrolled more than once)
Overnight Fast: X Post dosing: 4 hours fast
Food Study: Food Type:

Study Subjects: A total of 34 healthy Male participated in this study. Subjects were placed in eight (8) treatment groups (Treatment 6 subjects, Placebo 2 subjects). Some of the subjects were placed in more than one dosage group.

Subject Breakdown

No. Of Subj.	Gender	Mean Age (yr.)	Range (yr.)	Mean Weight (kg)	Range (kg)
34	Male	32.2	21 – 43	66.6	49.9 – 82.2

Treatment

Treatment	Dose	Dosage Form	Strength	Lot #	Batch Size
1	Oral	Capsules	1mg	Not Reported	Not Reported
2	Oral	Capsules	2.5mg		
3	Oral	Capsules	5mg		
4	Oral	Capsules	10mg		
5	Oral	Capsules	20mg		
6	Oral	Capsules	30mg		
7	Oral	Capsules	40mg		
8	Oral	Capsules	50mg		

Sampling Times

Plasma: 10ml of blood samples were collected prior to and following the treatment at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dose administration. Additional 28 and 32 hours samples were collected for doses of 30, 40, and 50mgs.

Assay Method: was used for determination of FKS-508 (cevimeline).
Assay Sensitivity:
Assay Accuracy:
Assay Precision: %CV:

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Table 6 Pharmacokinetic parameters at FKS-508 single-dose trial

Dose (mg)	No. of cases	C_{max} (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC$_{0-\infty}$ (ng·hr/ml)	Rate of urinary excretion$_{0-72hr}$ (% of dose)
1	6	1.7± 0.4	1.7±0.5	–	7.3± 4.3	16.4± 3.4
2.5	6	5.5± 0.7	1.5±0.6	3.82±0.60	32.6± 6.5	18.1± 3.9
5	6	9.6± 4.0	1.8±1.0	2.81±0.48	47.5± 18.9	18.0±10.0
10	6	24.3± 8.0	1.2±0.4	2.66±0.66	107.5± 73.8	14.2± 4.8
20	6	45.3±10.0	1.5±0.6	3.55±0.87	249.1± 86.1	23.6± 8.0
30	6	70.9±17.3	1.5±0.6	3.91±1.19	435.7±165.1	18.2± 8.6
40	6	89.0± 9.8	1.0±0.0	3.78±0.31	505.9± 70.4	12.4± 3.9
50	6	118.8±31.6	2.2±0.8	4.34±0.25	824.8±212.2	7.8± 2.5

(Mean±S.D.)

Table 1: Hepatic microsomal activities of phenacetin (CYP1A2) and coumarin (CYP2A6) in male and female human microsomes incubated with SNI2011 at doses of 1, 3, and 10 uM

Control/ Test Article	Conc (uM)	Phenacetin Acetaminophen Production (pmol/mg protein/min)	Phenacetin % Inhibition	Coumarin 7-HC Production (pmol/mg protein/min)	Coumarin % Inhibition
NC	NA	1274±55	0±4	226±11	0±5
CIC	NA	0± 0	NA	0± 0	NA
DDC	100	NA	NA	203± 5	10±3
FUR	20	420±13	67±3	NA	NA
SNI2011	1	1270±62	0±5	210±12	7±6
SNI2011	3	1309±88	-3±7	219± 3	3±1
SNI2011	10	1366±98	-7±7	214± 4	5±2

Values are the mean ± standard deviation of N = 3 samples.
Abbreviations: Conc, concentration; 7-HC, 7-hydroxycoumarin; NC, negative control; NA, not applicable; CIC, chromatographic interference control; DDC, diethyldithiocarbamate; FUR, furafylline.

Table 2: Hepatic microsomal activities of tolbutamide (CYP2C9) and *S*-mephenytoin (CYP2C19) in male and female human microsomes incubated with SNI2011 at doses of 1, 3, and 10 uM

Control/ Test Article	Conc (uM)	Tolbutamide 4-OH TB Production (pmol/mg protein/min)	Tolbutamide % Inhibition	*S*-Mephenytoin 4-OH ME (pmol/mg protein/min)	*S*-Mephenytoin % Inhibition
NC	NA	63±14	0±22	24±2	0± 7
CIC	NA	0± 0	NA	0±0	NA
SFZ	50	8± 0	87± 2	NA	NA
TRAN	20	NA	NA	17±2	30±10
SNI2011	1	69± 3	-10± 4	25±2	-2± 7
SNI2011	3	68± 2	-8± 3	24±3	1±11
SNI2011	10	72± 3	-14± 4	26±1	-7± 5

Values are the mean ± standard deviation of N = 3 samples.
Abbreviations: Conc, concentration; 4-OH TB, 4-hydroxytolbutamide; 4-OH ME, 4-hydroxymephenytoin; NC, negative control; NA, not applicable; CIC, chromatographic interference control; SFZ, sulfaphenazole; TRAN, tranylcypromine.

Table 3: Hepatic microsomal activities of dextromethorphan (CYP2D6) and chlorzoxazone (CYP2E) in male and female human microsomes incubated with SNI2011 at doses of 1, 3, and 10 uM

Control/ Test Article	Conc (uM)	Dextromethorphan DXP Production (pmol/mg protein/min)	Dextromethorphan % Inhibition	Chlorzoxazone 6-OH CZX Production (pmol/mg protein/min)	Chlorzoxazone % Inhibition
NC	NA	83 ± 3	0 ± 3	428 ±20	0±5
CIC	10	0 ± 0	NA	0 ± 0	NA
DDC	10	NA	NA	144 ± 6	66±4
QUIN	1	24 ± 4	71 ±17	NA	NA
SNI2011	1	87 ± 5	-5 ± 6	408±30	5±7
SNI2011	3	90 ± 4	-9 ± 4	389 ± 6	9±2
SNI2011	10	88 ± 1	-6 ± 1	368±31	14±8

Values are the mean ± standard deviation of N = 3 samples.
Abbreviations: Conc, concentration; DXP, dextrorphan; 6-OH CZX, 6-hydroxychlorzoxazone; NC, negative control; NA, not applicable; CIC, chromatographic interference control; DDC, diethyldithiocarbamate; QUIN, quinidine.

Table 4: Hepatic microsomal activities of testosterone (CYP3A4) in male and female human microsomes incubated with SNI2011 at doses of 1, 3, and 10 uM

Control/ Test Article	Conc (uM)	Testosterone 6β-OHT Production (pmol/mg protein/min)	Testosterone % Inhibition
NC	NA	172±18	0±10
CIC	NA	0± 0	NA
KTZ	5	25± 3	86±12
SNI2011	1	189±31	-10±17
SNI2011	3	186±67	-8±36
SNI2011	10	168± 2	2± 1

Values are the mean ± standard deviation of N = 3 samples.
Abbreviations: Conc, concentration; 6β-OHT, 6β-hydroxytestosterone; NC, negative control; NA, not applicable; CIC, chromatographic interference control; KTZ, ketoconazole.

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