In these studies, 50 STS-treated patients (7.3%) compared with 24 placebo-treated patients (4.5%) discontinued prematurely due to AE(s). Discontinuations due to AEs were dose-related (STS (20mg/20cm2) 7.7% [41/534]; STS (10mg/20cm2) 6.0% [9/151]; and placebo 4.5% [24/535]; FDA Appendix 1, Table A3).

For STS-treated patients, the AE that led to discontinuation most commonly was application site reaction (ASR). ASRs were generally described as locally erythematous and/or pruritic; Most reported ASR were rashes on the application site. Three percent (16/534) of patients in the STS (20mg/20cm2) group discontinued due to ASR, compared with 0.7% (1/151) of patients in the STS (10mg/202) group and none in the placebo group.

The next most common AE leading to discontinuation was anxiety. Anxiety resulted in discontinuation in 0.7% (4/534) of patients in the STS (20mg/20cm2) group, and 0.2% (1/535) of placebo patients and none in the STS (10mg/20cm2) group. No subjects treated with STS discontinued for liver failure, acute renal failure, serious skin reactions, aplastic anemia, or rhabdomyolysis in the controlled clinical studies. No subjects in STS or placebo groups discontinued for orthostatic hypotension.

5.4.1.2 Alzheimer's Disease

Two controlled clinical studies, S9303-E100-94B and S9303-E101-96B were conducted for the indication of Alzheimer's disease.

In study S9303-E100-94B, patients were randomly assigned to STS 8mg, STS 16 mg STS 24 mg and placebo groups. 20% (10/50) STS treated patients discontinued due to AE(s) compared with 5% (1/ 20) placebo-treated patients. See the details of the AEs leading to discontinuation in FDA Table 2 below. The sponsor provided no summary table or narratives for the discontinuations due to AEs in this study.

FDA Table 2. Discontinuations due to AEs in Alzheimer's study S9303-E100-94B

Treatment group	Discontinuations due to AEs	AE
Placebo	5% (1/ 20)	Intermittent orthostasis (n=1)
STS 8 mg	19% (6/31)	Orthostatic/postural hypotension (n=4) Hypotension (n=1) Unstable angina (n=1)
STS 16 mg	21% (3/14)	Orthostatic/postural hypotension (n=2) Hip fracture* (n=1)
STS 24 mg	20% (1/5)	Rash (n=1)

*This patient did not report orthostatic hypotension

In study S9303-E101-96B, nearly 20% of STS-treated and 15.0% of placebo-treated patients discontinued from the study due to an AE. See the details of the AEs leading to discontinuation in FDA Table 3 below.

FDA Table 3. Discontinuations due to AEs occurring in at least 2% of patients and at a frequency at least 2X that of placebo in Alzheimer's study S9303-E101-96B

Discontinuations due to AEs	Treatment	
	STS Treatment % (n/N)	Placebo % (n/N)
Total	19.8 (54/273)	15 (20/133)*
ASR	7.7 (21/273)	1.5 (2/133)
Postural hypotension	2.2 (6/273)	0

* A patient might have more than one AE.

5.4.2 Data Analysis of Discontinuation Due to AEs.

5.4.2.1 Major Depression

The incidence rate of discontinuation due to AEs for placebo is 36 per 100 person years for placebo, 45 per 100 person years for STS (10mg/20cm2), and 62 per 100 person years for STS (20mg/20cm2). The incidence rate of discontinuation due to AEs for STS (20mg/20cm2) and STS (10mg/20cm2) combined is 58 per 100 person years. (See FDA table 4 below.)

FDA Table 4. Rate of discontinuation due to AE by treatment group, pooled placebo-controlled trials in major depression

Treatment	Number of discontinuation due to AEs	Person-Years of exposure	Incidence Rate (per 100 P-Y)	Incidence Density Ratio	95% CI
Placebo	24	67	36	1.0	
STS (10mg/20cm2)	9	20	45	1.3	0.9 - 1.9
STS (20mg/20cm2)	41	66	62	1.7	1.0 - 2.8

FDA Table 4 shows a dose response relationship of STS treatment and discontinuation due to AEs. The incidence of discontinuation due to AEs in the STS (20mg/20cm2) group is statistically significantly higher than that in the placebo group. ASR is the AE that contributed to this significant difference between STS treatment group and placebo group.

5.4.2.2 Alzheimer's Disease

5.4.2.2.1 Study S9303-E101-96B

Fifty-four patients discontinued due to adverse events in the STS treatment group and 20 patients discontinued due to adverse events in the placebo group.

FDA Table 5. Rate of discontinuation due to AE by treatment group, Alzheimer's Study S9303-E101-96B

Treatment	Number of discontinuation due to AEs	Person-Year of exposure	Incidence Rate (per 100 P-Y)	Incidence Density Ratio	95% CI
Placebo	20	92	21.7	1.00	
STS Treatment	54	175	30.9	1.4	0.8 – 2.3

The incidence density ratio comparing the incidence rates of discontinuation due to AE between the two treatment groups is not statistically significant.

5.4.3 Discontinuation due to serious adverse experience

For the controlled clinical trials of major depression, seven patients (STS treatment = 3; placebo=4) discontinued due to serious adverse experiences (sponsor table 6.4). For the uncontrolled clinical trials of major depression, thirteen patients discontinued due to serious adverse experiences (sponsor table 6.9). The sponsor indicated two of the discontinuations (patient 9804/01004 and patient 9806/09009) were possibly related to the STS treatment.

> 9804/01004 (palpitation): This patient, a 20 years old white female, was randomized on 1/25/99 into the double-blind study and completed the study without significant problems. She entered the open-label study on 3/25/99. On 3/26/99, she went to her personal physician with complaints of a flu-like syndrome. He prescribed Claritin-D, without realizing that this was a prohibited medication. The patient took it on the evening of [redacted] at approximately [redacted], the patient contacted the study site complaining of palpitations, described as "fluttering of her heart". She was instructed to remove the patch at this time. The symptoms progressed during early morning, with additional symptoms of sweating and feeling of faintness. The patient's mother reported some unusual muscular activity, which possibly was seizure-related as well. The patient was evaluated at a local emergency room. The patient was stable, had a normal EKG, and was released home with a Holter monitor. The symptoms including palpitations, sweating, and faintness recurred, the patient was hospitalized on [redacted] The opinion of causality possibly related, with the most likely scenario being an interaction between the Claritin-D and STS per the sponsor report.
>
> 9806/09009 (myocardial infarction): This patient, a 64 years old white male, was started on the study medication on 10/14/1999. On [redacted], he developed chest pain, and went to the hospital. He was admitted, and evaluated for a possible cardiac event. The specifics of diagnostic tests and treatment were not known. The patient said that the isoenzymes were positive for a myocardial infarction. The attending physicians recommended a triple vessel coronary artery

bypass grafting procedure. The patient declined the surgery. The investigator's opinion was that this event was possibly related to STS.

5.5 Serious Adverse Experience

5.5.1 Data Description

I reviewed the sponsor's tables listing the serious adverse events (SAEs). The sponsor combined data from all controlled clinical studies in major depression. There were four controlled clinical studies in depression, S9303-E106-96B, S9303-E113-98B, S9303-P9804 and S303-E114. For the Alzheimer's disease indication, the sponsor presented the data by studies.

5.5.1.1 Major Depression

Two STS [20mg/20cm2] patients, one STS [10mg/20cm2] patient, and six placebo patients had SAEs in the controlled clinical studies for major depression. Two placebo and one STS patients made suicide gesture or attempts that were reported as SAEs. There was no other type of SAE that occurred in more than one patient in any treatment group.

No subjects treated with STS developed liver failure, acute renal failure, serious skin reactions, aplastic anemia or rhabdomyolysis in the controlled clinical studies. There were no orthostatic hypotension or related events such as falls reported in the STS treatment group during the controlled or open label clinical studies.

In one of the open label trials in major depression, there was a case of fetal demise, a stillbirth with a cleft palate delivered at 20 weeks. See section 5.6.3.2 "Other Adverse Events of Clinical Interest - Pregnancy".

5.5.1.2 Alzheimer's Disease

5.5.1.2.1 Study S9303-E100-94B

One placebo and eight STS-treated patients had 17 adverse experiences that were considered serious in this study. One (5%) SAE occurred in the placebo group, four (13%) in the STS 8mg group, 10 (71%) in the STS 16mg group, and two (40%) in STS 24mg group. Except for postural hypotension in the STS 16mg group, no individual type of SAE occurred in more than one patient. Because of SAEs related to postural hypotension in the STS 16 mg group, a protocol amendment was made to close down the 16 mg and 24 mg arms of the study.

5.5.1.2.2 Study S9303-E101-96B

Of the patients who received STS, 18.3% (50/273) had one or more SAEs compared with 18% (24/133) of the placebo patients. The most common SAEs were cardiovascular events, with an incidence of 4.4% (12/273) in STS treated patients and 6.0% (8/133) in placebo patients. The most common cardiovascular SAEs were chest pain/angina pectoris, arrhythmia, and congestive heart failure.

FDA Table 6. SAEs in Alzheimer's study S9303-E101-96B occurring in at least 1% of patients and at least 2X the frequency of placebo patients

SAEs	Treatment	
	STS Treatment % (n/N)	Placebo % (n/N)
Skin carcinoma	3.3 (9/273)^ Basal cell Ca (n=7) Bowen disease (n=1) Squamous cell Ca (n=1)	1.5 (2/133) Basal cell Ca (n=1) Other (n=1)
CHF	1.1 (3/273)	0.0 (0/133)

* A patient might have more than one SAE.
^ A single patient (1243/C-B) had a basal cell Ca on the right forehead and a superficial squamous cell Ca over the patch of Bowen's disease on the left cheek

As seen in the table above, nine skin carcinomas (occurring in seven patients) were reported in the STS treatment group compared with two in the placebo group. Of the seven patients on STS, six of the cancers were on the face or head, so it is likely that they were not adjacent to the location of the placement of the STS patch. Narratives for three of the patients reported the patient had a history of skin cancer. The median duration to biopsy of the suspicious lesion was 59 days, with a range of 6-189 days.

There was one hypotension SAE in the in the placebo group, and one postural hypotension/bradycardia SAE in the STS group (Patient 2509). There was one SAE reporting syncope with collapse in the STS group (Patient 2201). One STS patient experienced atrial fibrillation (Patient 2623) and one placebo patient reported seizure.

> Patient 2509, an 84-year-old male, had a history of severely compromised left ventricular function, CHF, and atherosclerotic coronary artery disease. The patient was randomized to receive STS (20 mg/20 cm2) once daily. On Day 162, this patient was transported to the ER after being found on the floor at 4 am. A vertebral compression fracture was found on X-ray and vital sign monitoring revealed decreased blood pressure and pulse. He was hospitalized for observation. The patient had sustained multiple falls, as well as fainting spells and syncope. The fall resulted in severe bruises and hematomas over his face. The patient was discharged on Day 163 with a 24 hour Holter monitor. The fall was attributed to bradycardia and orthostatic hypotension. Holter monitor results confirmed a bradyarrhythmia with AV node Wenchebach second-degree heart block with several prolonged RR intervals. A dual-lead transvenous pacemaker was placed on Day 178, and the patient was discharged on Day 180 in stable condition. In the investigator's opinion, a causal relationship between the fall and the study drug was possible.

Patient 2201, a 68-year-old female, was randomized to receive STS (20 mg/20 cm2) once daily. On Day 250, she stood up, became weak and fell to the floor. She did not lose consciousness. Her blood pressure was 70/40 mmHg, with a heart rate of 72 bpm. When the paramedics arrived, the patient's blood pressure was 68/40 mmHg. The patient was taken to the hospital for observation. An ECG and laboratory values were within normal limits. Study medication was interrupted for one day on Day 251. Concomitant medications included verapamil for hypertension, hydrocortisone cream, 1% topical, and etodolac for osteoarthritis. In the investigator's opinion, a causal relationship between the event and study was possible.

Patient 2623, an 84 –year-old female, was randomized to receive STS (20 mg/20 cm2) once daily. The patient had stopped receiving study drug and withdrew from the study on Day 126 so that she could be treated for depression. Nineteen days later, she had a sudden onset of dizziness/lightheadedness and palpitations and began to hyperventilate. The patient was taken to the ER for evaluation. She had no chest pain, but did have pain in her left arm. An ECG from the ER showed atrial fibrillation, with a rapid ventricular response and an inferolateral ST-T abnormality; the atrial fibrillation was converted following intravenous diltiazem. An ECG taken one hour later showed sinus rhythm with left ventricular hypertrophy. The patient had a normal dipyridamole and thallium stress test, with no evidence of ischemia or infarction. The patient was also ruled out for MI with cardiac enzymes. The patient was diagnosed with paroxysmal atrial fibrillation, and mitral regurgitation. In the investigator's opinion, a causal relationship between the event and study drug was possible.

5.5.2 Data Analysis of Serious Adverse Events

5.5.2.1 Major Depression

The incidence rates of SAEs shown in FDA Table 7 suggest that the risk of SAE in the STS treatment group is substantially less that that of placebo.

FDA Table 7. Rate of SAEs by treatment group, pooled placebo-controlled trials in major depression

Treatment	Number of SAEs	Person-Year of exposure	Incidence Rate (per 100 P-Y)	Incidence Density Ratio
Placebo	6	67	9	1.00
STS (20mg/20cm2)	2	66	3	0.33

5.5.2.2 Alzheimer's Disease

5.5.2.2.1 Study S9303-E101-96B

FDA Table 8 shows that the incidence rate of SAEs in the STS treatment group is greater than that of the placebo group. The IDR of the STS treatment group compared to the placebo group is 1.49, but the rate of SAEs is not statistically significantly different from placebo.

FDA Table 8. Rate of SAE by treatment group, Alzheimer's Study S9303-E101-96B

Treatment	Number of SAEs	Person-Year of exposure	Incidence Rate (per 100 P-Y)	Incidence Density Ratio	95% CI
Placebo	24	92	26.1	1.00	
STS Treatment	76	175	43.4	1.7	1.1 – 2.7

5.6 Adverse Experiences

5.6.1 Data description

5.6.1.1 Major Depression

In the pool of the four controlled clinical studies in major depression, the percentage of patients with one or more AEs was similar in each of the treatment groups: placebo (71.0%, [380/535]), STS (10mg/20cm2) (72%, [110/151]), and STS (20mg/20cm2)(75.7%, [404/534]).

The AEs occurring in the 5% or more of the STS (20mg/20cm2) group included the following: ASR (23%), headache (17.2%), insomnia (9.6%), infection (8.4%), diarrhea (8.2%), and dry mouth (6.6%).

The following table lists that AEs occurring in at least 2% of patients and at an incidence at least 2X that of placebo.

FDA Table 9. Common AEs in four pooled placebo-controlled depression trials occurring in at least 2% of STS patients and at least 2X the frequency of placebo patients

Common AEs	Treatment	
	STS Treatment % (n/N)	Placebo % (n/N)
ASR	23.0 (123/534)	9.7 (52/535)
Insomnia	9.6 (51/534)	4.9 (26/534)
Sinusitis	3.6 (19/534)	0.9 (5/535)
Rash	3.2 (17/534)	1.5 (8/535)

*A patient may have had more than one AE.

5.6.1.2 Alzheimer's Disease

5.6.1.2.1 Study S9303-E100-94B

Sponsor table 6.27 presents incidence by body system and preferred term for all AEs in the STS 8mg and placebo treatment groups. Ninety percent (28/31) of STS 8mg patients

and 60% (12 /20) of placebo patients had an at least one AE during treatment. The AE with the highest incidence was, which occurred in 61% (19/31) of STS 8mg patients and 25% (5/20) of placebo patients. The most common AEs in STS patients included postural hypotension (61%), dizziness (26%), hypotension (23%), and headache (19%). Of these common AEs, postural hypotension, hypotension, and headache occurred at least two times more frequently in the STS group than the placebo group. Syncope occurred in two STS patients (6%) and in no placebo patients.

5.6.1.2.2 Study S9303-E101-96B

Sponsor table 6.29 presents a summary of the occurrence of AEs in the 273 patients who received active treatment with STS (20mg/20cm2) in the study, but did not include placebo incidence. In Table 17 of the clinical study report, the sponsor provided the incidences of AEs in both the placebo and STS groups.

In this 48-week study, 95.2% of the patients in the STS group experienced an AE compared with 89.5% of the placebo group. . Approximately 57% of patients in the STS treatment group experienced an ASR, compared with 8.3% of placebo patients. Slightly more than 10% of patients in both treatment groups experienced rash (13% of STS patients and 10.5% of placebo patients). The sponsor stated that in most cases, these rashes were not considered to be ASRs.

The following table shows the commonly occurring AEs that had an absolute incidence >2% in the STS group and exceeding that in the placebo group by at least twofold. The footnote below the table lists the commonly occurring AEs that had an absolute incidence >2% in the STS group and exceeding that in the placebo group by at least twofold.

It is likely that many of the differences observed are due to chance occurrence in a population that has substantial preexisting morbidity. However, the AEs "ASR" and "postural hypotension" have been identified previously as occurring at an excess in the STS group.

FDA Table 10. Common AEs in Study S9303-E101-96B occurring in at least 2% of STS patients* and at least 2X the frequency of placebo patients^

Common AEs	Treatment	
	STS Treatment % (n/N)	Placebo % (n/N)
ASR	56.8 (155/273)	8.3 (11/133)
Chest pain	5.5 (15/273)	2.3 (3/133)
Postural hypotension	5.1 (14/273)	1.5 (2/133)
Delusions	4.8 (13/273)	1.5 (2/133)
Edema	4.8 (13/273)	2.3 (3/133)
Allergic reaction	3.7 (10/273)	1.5 (2/133)
Flu syndrome	2.9 (8/273)	0.8 (1/133)

Anemia	2.9 (8/273)	0.8 (1/133)
Arrhythmia	2.6 (7/273)	0.8 (1/133)
Rectal hemorrhage	2.2 (6/273)	0.0
Conjunctivitis	2.2 (6/273)	0.8 (1/133)
Prostatic disorder	2.2 (6/273)	0.8 (1/133)

*A patient may have had more than one AE.

^ AEs for which the incidence in placebo exceeded 2% and 2x the incidence in STS included the following (in descending frequency): pain, hypertension, somnolence, dyspepsia, vomiting, anorexia, weight loss, myalgia, joint disorder, fever, vertigo, infection fungal, dehydration, hypercholesterolemia, hypotension, melena, dyspnea, epistaxis, Babinski sign positive

5.6.2 *Data Analysis Of Adverse Events*

5.6.2.1 Major Depression

FDA Table 11. AE rates and IDRs for common AEs occurring at an excess rate in the STS treatment groups compared to placebo of at least 1.5X, pooled placebo-controlled trials in major depression

AE	PBO		STS 20		IDR STS 20/PBO (95% CI)
	n	Rate*	n	Rate*	
All	380	567	404	612	1.1 (0.9, 1.2)
Sinusitis	5	7	19	29	3.9 (1.4, 10.3)
ASR	52	78	123	186	2.4 (1.7, 3.3)
Rash	8	12	17	26	2.2 (0.9, 5.0)
Insomnia	26	39	51	77	2.0 (1.2, 3.2)
Palpitation	9	13	14	21	1.6 (0.8, 3.2)

*Rates are presented per 100 person-years; person-years exposure used to calculate rates were the following: PBO= 67 py, STS 20= 66 py

5.6.2.2 Alzheimer's Disease

5.6.2.2.1 Study S9303-E101-96B

FDA Table 12. AE rates and IDRs for common AEs occurring at an excess rate in the STS treatment groups compared to placebo of at least 1.5X, Alzheimer's Study S9303-E101-96B

AE	PBO		STS 20		IDR STS 20/PBO (95% CI)
	n	Rate*	n	Rate*	

All	389	423	843	482	1.1 (1.0, 1.2)
ASR	11	12	155	89	7.4 (4.0, 13.6)
Postural Hypotension	2	2	14	8	4.0 (0.9, 17.6)
Allergic Reaction	2	2	10	6	2.9 (0.6, 13.2)
Chest pain	3	3	15	9	2.9 (0.8, 10.0)
Fracture	5	5	20	11	2.3 (0.9, 6.1)
Hallucinations	7	8	23	13	1.6 (0.7, 3.7)
Insomnia	7	8	23	13	1.6 (0.7, 3.7)
UTI	19	21	60	34	1.6 (1.0, 2.7)

*Rates are presented per 100 person-years; person-years exposure used to calculate rates were the following: PBO= 92 py, STS 20= 195 py

5.6.3 Other Adverse Events of Clinical Interest

5.6.3.1 Application Site Reactions

5.6.3.1.1 Controlled clinical trials in depression

In the major depression studies, 23% (123/534) of STS 20mg patients compared with 9.7% (52/535) of placebo patients reported an ASR. Within the designation "ASR", the terms "rash" (19.1%), "pruritis" (3.2%), and "maculopapular rash" (1.1%) were reported most frequently. The following table displays the characteristics of the ASR for the controlled clinical studies in major depression, by treatment group.

FDA Table 13. Characteristics of application site reactions, controlled trials in depression

	Placebo N=535 %, (n)	**STS N=534 %, (n)**
Patients with ASR	9.7 (52)	23.0 (123)
Total number of ASR	67	170
Median day of onset of ASR	8	25
Median duration (days)	10	13
Number of occurrences of ASR per patient		
1	78.8 (41)	75.6 (93)
2	13.5 (7)	20.3 (25)
3 or more	7.7 (4)	4.0 (5)
Intensity of ASR:		
Mild	85.1 (57)	71.8 (122)
Moderate-severe	13.4 (9)	28.2 (48)

Treatment required for ASR Medication	6.0 (4)	12.9 (22)

5.6.3.1.2 Cutaneous AEs in controlled depression trial S9303-E114-98B

Because STS is a transdermal drug delivery system, the sponsor examined cutaneous AEs more closely in one controlled trial and two open-label trials in depression. I will describe the findings of the controlled trial S9303-E114-98B in this section.

When a patient reported a cutaneous AE, the investigator was instructed to fill out a special AE form that addressed the following variables: discoloration, palpability of lesion, burning, itching, pain, other characteristics present, dermal response category, time of onset, intensity, relationship to study drug, treatment required, outcome and whether the reaction occurred with every patch application. The dermal response category was coded over a spectrum from 1 "no evidence of irritation" to 7 "strong reaction spreading beyond patch site".

In trial S9303-E114-98B, 17.4% (26/149) of STS (20 mg/20cm2) and 8.9% (13/146) of placebo patients reported at least one cutaneous AE. The following table identifies the major qualities of the ASRs that differed between the STS (20 mg/20cm2) and placebo patients. Note that the denominators in each column are the total number of cutaneous reactions in each treatment group, not the total number of patients in each treatment group.

FDA Table 13A. Characteristics of application site reactions, study S9303-E114-98B

	Placebo N=14	**STS N=29**
Discoloration: Markedly red/pink-deep red/purple	7.1 (1)	17.2 (5)
Palpability of lesion: Moderately palpable-decidedly raised	0.0 (0)	20.7 (6)
Burning: Mild Moderate-severe	0.0 (0) 0.0 (0)	13.8 (4) 10.3 (3)
Pain Mild-moderate	0.0 (0)	17.2 (5)
Other characteristics Blush Swelling	7.1 (1) 0.0 (0)	37.9 (11) 10.3 (3)
Dermal response category Erythema and papules Erythema, edema, and papules	0.0 (0)	20.7 (6) 3.4 (1)
Median time to onset of reaction (days)	2	7

Source: Tables B.6.2.13 – B.6.2.15, Clinical study report S9303-E114-98B

Not only were ASR about twice as common in the STS group, FDA Table 13 above suggests that the ASRs in the STS group were more severe. However, there were a few characteristics of the ASRs that did not differ much between the groups; these included itching, requirement of treatment, and outcome. Sixty to seventy percent of the ASRs were reported to have resolved; although time to resolution was not reported. Fourteen percent (4/29) of the STS patients reporting an ASR discontinued due to this AE compared to none of the placebo patients.

5.6.3.2 Pregnancy

During the clinical development program of STS, 12 pregnancies were reported; four occurred during controlled clinical trials in depression and eight occurred during open-label trials in depression.

Of the four pregnancies reported in the controlled trials, one STS patient (E113/00724) and two placebo patients (E113/00105 and E113/00422) reported their pregnancies as adverse events; each of these patients elected to terminate her pregnancy. A second STS patient (E113/00724) did not report her pregnancy as an AE, but did identify it as her reason for discontinuing from the study. She intended to carry her pregnancy to term, but the pregnancy outcome was unknown because she was lost to follow-up.

In the open-label trials, six pregnancies were reported as AEs and two were not. FDA Table 14 below lists these eight pregnancies with their outcomes. Patients E106/05003 and 9918/01225 received STS (20mg/20cm2) during the RCT; all patients received STS (20mg/20cm2) in open-label treatment.

FDA Table 14. Pregnancies reported during open-label trials in depression

Patient ID	**Outcome**
9806/24006	Terminated pregnancy
9806/25028	Terminated pregnancy
9918/01225	Pregnancy not reported as an AE; patient discontinued due to pregnancy- outcome unknown
E106/05003	Delivered healthy infant at term
9806/29016	Reported pregnancy at end of trial- had a negative pregnancy test at that time; subsequently delivered healthy infant at term
9806/02013	Delivered healthy infant at term
9806/21014	Delivered healthy infant at term
9806/18014	Delivered stillborn child with cleft palate at 20 weeks

The stillborn child with a cleft palate delivered at 20 weeks was reported as an SAE.

> A 29 yo woman with a history of hypothyroidism, chronic bronchitis, and a positive baseline tox-screen for cannabinoids began open-label treatment with STS 20mg/20cm2. About nine weeks later the patient discontinued from the trial after testing positive on a home pregnancy test. Around 18 weeks of gestation, the patient saw her OB for a routine check-up and was told everything was "okay". About two weeks later on a routine ultrasound no fetal heart tones were detected. A week

later labor was induced and the stillborn was delivered. The fetus was described as "macerated" and with the presence of a cleft palate. During the pregnancy the patient received two courses of amoxicillin and one course of amoxicillin clavulanate for a sinus infection, bronchitis, and strep throat, respectively.

5.6.3.3 Sexual dysfunction

Sexual dysfunction was assessed in the clinical trials in major depression at the baseline and final visits. The self rating MED-D scale includes 12 items representing three symptom complexes: depression, sexual activity, and somatic complaints. Each symptom complex is measured by the sum of its component items (rated on a scale of 1-5, such that the score can range from 5 [not at all] to 25 [severe]). The sexual activity complex (items 5-9) was used for assessing sexual dysfunction. In the NDA submission, I was unable to locate the actual items 5-9 intended to assess the sexual activity symptom complex

In the controlled trials in depression, there was a mean decrease in MED-D score in each treatment group (STS 20mg/20cm2: -1.8; placebo: -1.1)

5.6.3.4 Suicide

In the pool of placebo-controlled trials in depression, one patient on STS 20mg/20cm2 and two patients on placebo reported suicidal ideation. The verbatim term suicidal ideation was mapped to the preferred term suicide attempt.

When considering the pool of all trials in depression including an STS 20mg/20cm2 treatment arm, ten STS patients and three placebo patients "experienced suicidal behavior or had an intentional drug overdose". Three intentional overdoses (one each of zolpidem, aspirin, and alcohol) occurred in STS treated patients.

It would be useful for the sponsor to calculate the rates of suicidal ideation and suicide attempt using the person-time exposure in each treatment group.

6 Phase I safety

The sponsor identified 325 subjects in the STS PK/Safety/Drug interaction population across 36 Phase I studies (Section 8, p.124232). The sponsor pooled and analyzed the data from 18 of the 36 studies, which included 210[3] subjects (Section 8, p.123897). The sponsor decided to present separately the safety data for the tyramine challenge studies (n=10) and an irritation and contact allergenicity study since these studies addressed

[3] The Section 8 text identified 210 subjects included in the pooled analysis. Table 2.5 identifies 211 enrolled subjects. This apparent discrepancy results because Subject 05 from study S9303-P0046 was excluded from the safety analysis- did not receive study medication (Section 8, p.123900).

specific safety questions. The sponsor excluded from the pooled analysis the seven remaining Phase I studies because the studies either used different prototype formulations of the STS or they were conducted by an outside institute (Section 8, p.124231). For the safety data from the non-pooled studies, the sponsor provided narrative summaries for each individual study.

The following table is copied from the ISS, and identifies the 18 studies pooled in the sponsor's Phase I safety analysis.

Table 2.3. Phase I Studies Included in Pooled Analysis of Safety Data

Study Number	Brief Study Description
Pharmacokinetic and Bioavailability Studies	
S9303-P9807	Steady State Crossover Study of STS (10mg/20cm^2) and STS (20mg/20cm^2)
S9303-P9808	Single Dose Duration Study
S9303-P9809	Single Dose IV/PO/Dermal Crossover Study
S9303-P9923	Steady State Crossover Study of STS (10mg/20cm^2) and STS (20mg/20cm^2)
Drug Interaction Studies	
S9303-P9919	Warfarin Drug Interaction Study
S9303-P9920	Alprazolam Drug Interaction Study
S9303-P9921	Risperidone Drug Interaction Study
S9303-P9922	Olanzapine Drug Interaction Study
S9303-P9925	Levothyroxine Drug Interaction Study
S9303-P9926	Ibuprofen Drug Interaction Study
S9303-P9927	Alcohol Drug Interaction Study
S9303-P9928	Pseudoephedrine Drug Interaction Study
S9303-P9931	Ketoconazole Drug Interaction Study
S9303-P9933	Carbamazepine Drug Interaction Study
S9303-P0046	Phenylpropanolamine Drug Interaction Study
Special Population Studies	
S9303-P9811	Pharmacokinetics of STS in Renally Impaired Subjects
S9303-P9812	Pharmacokinetics of STS in Hepatically Impaired Subjects

6.1 Sponsor's approach to summarizing safety data in pooled Phase I trials

The pooled Phase I studies included open label trials, crossover trials, and trials administering STS alone and with other medications. The sponsor presented AE data from Phase I trials using a number of treatment based groupings. Data obtained during treatment periods with STS alone are presented as one treatment group. This "STS alone" group includes crossover studies using only STS (treated as though they were single treatment arm studies), and studies where STS was administered with placebo. Data from non-STS treatment periods are combined and presented as the "non-STS" treatment group. Data from studies using STS concomitantly with another medication are presented as the "STS+other" medication group. Data from all treatment periods for each subject are also combined to summarize the overall safety data for each subject. In the sponsor's analysis, subjects from crossover trials or multiple treatment period trials can appear in more than one group since the analysis classifies by treatment and not subject (Section 8, p.123924). The sponsor did not analyze pooled Phase I lab or vital sign data.

6.2 Deaths in Phase I Trials

The sponsor reported that there were no deaths in the pooled Phase I studies.

6.3 Serious Adverse Events in Phase I Trials

The sponsor identified two subjects from the 18 pooled Phase I trials who experienced SAEs. One subject (S9303-P0046, #8) dislocated his shoulder in a bicycle accident. The second event is summarized below.

> Subject **S9303-P9811, #10**, a 51 year old white male, developed vomiting and dehydration 21 days after receiving the final STS treatment. The subject was hospitalized and recovered two days later. The sponsor did not have details from the hospitalization and noted that the subject was lost to follow up.

One other SAE was identified from a non-pooled Phase I study. That event is summarized below.

> Subject **S9303-029-95B, #02/DMB**, a 70 year old female, awoke on study day 5 with palpitations and was found to be in atrial fibrillation with a rate of 160 bpm. She was treated in an emergency department with IV diltiazem and converted to normal sinus rhythm. She discontinued from the study. The sponsor noted that she admitted to experiencing two similar events prior to enrolling in the study.

6.4 Discontinuations due to AEs in Pooled Phase I trials

One subject discontinued from one of the pooled Phase I trials. That event is summarized below.

> Subject **S9303-P9923, #05**, a 30 year old male receiving STS alone, experienced dizziness on day 2 and withdrew for this event on day 4. The sponsor did not note if the subject had blood pressure abnormalities or characterize the event further.

6.5 Treatment Emergent AEs in Pooled Phase I trials

As explained above, the sponsor presented the treatment emergent AEs by treatment group. Using this approach, subjects can appear in more than one group depending on the number of treatments administered during their trial. The sponsor calculated the AE risk by dividing the number of subjects with an event by the number of subjects in the treatment-based group (ISS, p.123926).

Seventy-three percent (155/210) of subjects in Phase I trials experienced at least one adverse event. The sponsor reported that 54% (105/194) of subjects receiving STS alone reported an AE compared to 49.6% (63/127) receiving STS+other medication, and 44.1% (60/136) not receiving STS (ISS, p.124237).

The following table summarizes the treatment emergent adverse events occurring in at least 5% of any of the treatment based groups.

FDA Table 15. Treatment Emergent AEs Occurring in at least 5% of any Treatment Group, Pooled Phase I Studies

AE	STS alone (n=194)		Non-STS (n=136)		STS+other (n=127)		Total (n=210)	
	%	n	%	n	%	N	%	n
Headache	16.0%	31	11.0%	15	9.4%	12	24.3%	51
Dizziness	7.7%	15	8.8%	12	4.7%	6	14.3%	30
Application site	11.3%	22	0	0	7.1%	9	13.8%	29
Nausea	6.2%	12	2.2%	3	5.5%	7	9.5%	20
Rash	7.2%	14	0	0	3.9%	5	9.0%	19
Somnolence	3.1%	6	14.0%	19	6.3%	8	13.8%	29
Pain	4.6%	9	1.5%	2	3.9%	5	7.6%	16
Asthenia	1.5%	3	5.9%	8	3.9%	5	6.2%	13
Pharyngitis	4.1%	8	0	0	3.9%	5	6.2%	13

Data from sponsor's Table 12.8, Section 8, p.124238

To look for infrequent but potentially important AEs, I reviewed sponsor's Table B.12.3.2, Section 8, p.126966-126978, which included all treatment emergent AEs from the pooled Phase I trials. Table B.12.3.2 included one syncope AE in an STS alone subject, one face edema AE in an STS+other subject, and one exfoliative dermatitis in an STS alone subject. There were no events suggestive of hepatic failure, renal failure, rhabdomyolysis, or aplastic anemia in this table.

6.5.1 Application Site Reactions

The sponsor included an analysis of application site reactions that occurred in the pooled Phase I studies. The sponsor explained that since AEs coded to application site reaction represented a diverse group of events, these AEs were assigned a second preferred term to capture specific reactions (redness, rash, itch, etc.).

Almost 14% (29/210) of the pooled Phase I subjects experienced an application site reaction with most of these events occurring in the STS alone treatment group (22/29). Using the second preferred term classification, the most commonly observed application site reaction in the STS alone group was rash (73%, 16/22), followed by pruritis (18%, 4/22). Application site reactions also included one of each of the following preferred terms: accidental injury, pain, parasthesia, skin discoloration, urticaria, and vesiculobullous rash.

The sponsor explained that one application site reaction was considered moderate intensity with the remainder classified as mild intensity. One subject required treatment (hot pack) and all subjects with a recorded outcome were considered recovered. The sponsor did not explore other characteristics of application site reactions such as dose response, time to event, or persistence/resolution with continuing treatment (Section 8, p.124241).

6.5.2 Orthostatic Hypotension

The sponsor provided an analysis of orthostatic hypotension in the pooled Phase I studies. Orthostatic events were not determined using supine and standing pulse and blood pressure measurements, but instead were identified using AE data. The sponsor first identified subjects with an AE of hypotension. These events were further reviewed to determine if consistent with orthostasis. In the sponsor's analysis, hypotension was considered to be consistent with orthostasis if the subject also had one or more of the following AEs: amblyopia, asthenia, ataxia, confusion, coordination abnormal, dizziness, gait abnormal, syncope, tachycardia, vertigo, or vision abnormal.

The sponsor identified three subjects who met their criteria for orthostatic hypotension, and all were in the "non-STS" treatment group and were not receiving STS at the time of the event. Orthostatic hypotension events occurred in two subjects (Study S9303-P9922, #9 and #10) who were receiving only olanzapine at the time. Both subjects experienced symptoms of hypotension and dizziness, with coincident decline in BP of at least 10mmHg. The third subject (#12) identified with orthostatic hypotension experienced the event during the alcohol alone treatment period of study S9303-P9927 (Section 8, p.124243).

7 Safety- ongoing clinical trials

As of the cutoff date December 31, 2000, there were six ongoing studies using STS; they are listed in the following table:

FDA Table 16. Ongoing STS studies included in the original Emsam NDA

Study Number	Phase	Study Name
S9303-P9937	II	OL study in —
S9303-P9935	II	OL study in —
S9303-P9806	III	DB study in relapse of MD
S9303-P9918	III	OL extension study in MD
S9303-E109-97B	III	DB study in PD
S9303-P9917	III	OL extension study in PD

OL=open label; DB=double blind;
MD=major depression; PD=Parkinson's disease

7.1 Deaths

Two patients died during ongoing clinical studies, one patient each from trials S9303-E109-97B and S9303-P9917 in Parkinson's disease.

9303-P9917/ Patient 06010/V-S, a 76-year old Caucasian female, had a history that included diabetes, mitral valve prolapse, swelling of feet, appendicitis, osteoporosis, incontinence, anteroseptal infarction, stress, insomnia, high BP, irregular heart beat, arm fracture and head trauma secondary to

MVA. She completed 12 weeks of double-blind treatment with STS (15 mg/15 cm^2) on 20 October 1999 and then continued to receive the STS (15 mg/ 15 cm^2). Study drug was stopped on approximately, November 21, 1999. Or — she was hospitalized for symptoms of dyspnea on exertion and at rest and worsening of shortness of breath over the prior 48 hours and was clinically diagnosed with acute myocardial infarction. Concomitant medications included diltiazem HCL, fosinopril, and furosemide for high BP, carbidopa/levodopa for Parkinson's disease, metformin and glipizide for diabetes, fluoxetine for stress, and alprazolam for sleep. The patient died on — — due to acute myocardial infarction.

9303-E109-97B Patient 04006/MEC, a 62-year old Caucasian female, with a history that included heart murmur and rash on chest, received double-blind treatment with STS (15 mg/15 cm2) on October 30, 1997. Study drug was discontinued on — after the patient was seen in the emergency room for generalized urticaria and shortness of breath, treated and then released, on — On — the patient was hospitalized for septic shock, an SAE considered severe in intensity and not related to study drug. Other concomitant medications included pramipexole for Parkinson's disease, diphenhydramine hydrochloride for rash, naproxen sodium for sciatica pain, and steroids for rash. The patient was initially stabilized but arrested and could not be resuscitated. The patient died on — with sub-investigator reporting cause of death as septic shock.

7.2 Serious Adverse Events

Among the ongoing clinical trials, 22 SAEs were reported. Of these 22 events, 11 occurred in the depression relapse prevention trial S9303-P9806, seven occurred in the double blind study in PD S9303-E109-97B, and four occurred in the open label extension study in PD S9303-P9917.

7.2.1 S9303-P9806

Eleven SAEs reported among eight study participants included the following events: surgery for abdominal hernia; multiple injuries secondary to MVA; uncontrolled hypertension; accelerated hypertension; right abdominal mass and possible uterine fibroid and possible bowel obstruction; atrial fibrillation; bowel obstruction; acute dystonic reaction. Two of these events may have represented hypertensive reactions to the drug.

13026/GMS "uncontrolled hypertension"- A 71 year old WF had a multiple year history of HTN. About two months after starting on STS 20mg, the patient was noted to have a BP of 170/100. She was discontinued for the worsening of her baseline hypertension (the narrative did not describe the baseline BP, or what antihypertensive medications she was taking at baseline.)

14008/CLE "accelerated hypertension" – A 51 year old WF had a multiple year history of HTN and was taking atenolol at baseline. After eight weeks of open label therapy of STS 20mg, the patient was randomized to DB therapy that happened to be STS 20mg. Four days later the patient experienced a one hour episode of chest pain and shortness of breath for which she was hospitalized. She was ruled out for an MI, but was noted to have a BP of 160/114 in the emergency department. Her antihypertensive was switched to amlodipine and she was discharged.

7.2.2 S9303-E109-97B

Seven SAEs reported in seven patients included the following events: herniated discs, septic shock (see section 6.1), orthostatic symptoms requiring hospitalization, chest pain, left hip fracture, prolapsed uterus requiring surgery, and fractured femur secondary to a fall.

The two patients who had falls resulting in hip fractures had been randomized to placebo; however, the patient hospitalized for orthostatic symptoms was treated with STS 15 mg.

> 06004/AMI "orthostatic symptoms requiring hospitalization" – A 74 yo WM had a history of an old silent MI. About nine weeks after starting DB STS 15mg, the patient was hospitalized for "lightheadedness". The study drug was discontinued two days prior to hospitalization, but the symptoms did not resolve for about four days after hospitalization.

7.2.3 S9303-P9917

Four SAEs reported in four patients included acute MI (see section 6.1); third degree heart block; aspiration pneumonia, and left hemispheric transient ischemia attack.

8 Evaluation of the potential interaction between STS and sympathomimetic amines

8.1 Rationale for conduct of tyramine challenge studies

As mentioned in the introduction to this review, selegiline is a selective, irreversible inhibitor of MAO-B. It also inhibits the "A" isoform of the MAO enzyme in a concentration-dependent manner.

Despite evidence of efficacy in depression, non-selective inhibitors of MAO generally have not been utilized as first line treatment for depression due to safety concerns. These safety concerns arise from the risk of hypertensive reactions associated with the ingestion of sympathomimetic amines such as tyramine in food[4] and the OTC decongestants (e.g., pseudoephedrine and phenylpropanolamine) in the presence of MAO inhibition. At the oral doses of selegiline required for antidepressant efficacy (30-60 mg), there is a risk of hypertensive reactions following ingestion of sympathomimetic amines. The sponsor developed the STS to achieve adequate levels of brain MAO-A inhibition without the systemic side effects. In order to assess the risk of hypertensive reactions in STS-treated patients exposed to sympathomimetic amines, the sponsor conducted out a battery of different types of pertinent studies. The sponsor maintains that

8.2 Sponsor's Summary of Data and Overall Conclusion

A total of 212 healthy subjects were enrolled into safety studies employing varying safety assessment approaches. The sponsor concluded that multiple dose studies with the STS (20 mg/20cm2) demonstrated a small increase in sensitivity to oral tyramine that they

[4] This is often referred to as the "cheese effect" due to high amounts of tyramine in aged cheese.

deemed clinically non-significant. Additionally, subjects treated to steady state with OTC sympathomimetic decongestants/appetite suppressants did not experience clinically significant changes in cardiovascular measures during concomitant steady-state treatment with the STS (20 mg/20 cm2) compared with pseudoephedrine HCL or phenylpropanolamine HCL treatment alone. Finally, intravenous administration of cocaine to non-dependent, experienced cocaine users treated to steady state with STS (20 mg/20 cm2) demonstrated no changes in cardiovascular measures or other physiological measures associated with sympathetic nerve function compared with cocaine alone.

8.2.1 Tyramine Challenge

Tyramine acts indirectly to mimic the effects of sympathetic nerve stimulation through the release of neuronal stores of norepinephrine. When administered systemically, the cardiovascular actions of tyramine mimic the actions of norepinephrine, including vascular constriction, an increase in ventricular rate, and an increase in cardiac contractility. Normally dietary tyramine is inactivated in the liver, intestinal mucosa, and the adrenergic neuron. When MAO is inhibited, tyramine exerts its effects in sympathetic nerve terminals.

A pressor response to tyramine is generally defined as an increase in systolic blood pressure of >=30mmHg over baseline. In a fasting state, it takes 500 mg of encapsulated tyramine to produce such a response. However, in the presence of substantial (80%) MAO inhibition, ingestion of only 10 mg of encapsulated tyramine would be needed to achieve the pressor response defined above.

A tyramine pressor test, or tyramine challenge, is a method to assess cardiovascular interactions between MAO inhibitor drugs and tyramine. Typically, this test involves monitoring systolic BP and heart rate in response to tyramine prior to and following treatment with the MAO inhibiting drug. A rise of 30 mmHg above baseline is generally considered the end point, and a response greater than 60 mmHg above baseline is generally terminated by administering an α-adrenoceptor blocking agent such as phentolamine or labetalol. The minimum dose of tyramine required to elevate SBP 30 mmHg above baseline is referred to as the Tyramine Pressor Dose 30 (TYRPD30) or simply the "pressor dose".

The sponsor conducted a number of tyramine pressor test studies, assessing the effect of a range of doses of STS, as well as positive and negative controls. The tyramine was administered as a liquid or encapsulated powder because a typical tyramine-rich meal (40 mg) would not provide enough tyramine to reach the pressor dose. The table below summarizes the average baseline "pressor dose" (based on two baseline measurements made 24 hours apart), the "active" pressor dose measured after the achievement of steady state levels of the MAO inhibitor, and the Tyramine Sensitivity Factor (TSF). This last measure is the ratio of the baseline "pressor dose" to the active "pressor dose".

The experience of 47 patients exposed to STS 20 mg for 9-10 days were pooled together from studies S9303-P9932, S9303-P9940, and S9303-P9941, and the results for this pool

are seen in the first row. In these studies no patient reached the blood pressure endpoint at a tyramine dose less than 200 mg. The results in the table below show that the TSF ratio for tranylcypromine, the nonselective MAO inhibitor functioning as a positive control, is 20-fold higher than that for STS 20mg, the dose intended for marketing. Even at double the STS dose intended for marketing, the TSF ratio is 12-fold lower than the positive control. Probably the most reassuring finding in these studies was the observation that the TSF ratio for the marketed dose of oral selegiline was basically the same as that for STS 20, and that dose of oral selegiline has been marketed without dietary restriction for over a decade.

FDA Table 17. Tyramine challenge results before and after steady state dosing of active agents.

	Mean Tyramine Pressor Dose			
	Daily dose/ duration	Baseline average*	Active	TSF Ratio
Pooled^ STS 20mg (N=47)	20mg/ 9-10 d	507 +/- 106	298 +/- 105	1.8 +/- 0.5
STS 30 mg (N=10)	30mg/ 10d	470 +/- 178	210+/- 88	2.4 +/- 0.7
STS 40 mg (N=12)	40mg/ 10d	588 +/- 117	198+/- 98	3.5 +/- 1.3
Oral selegiline (N=21)	5mg BID/9 d	529 +/- 115	357 +/- 147	1.7 +/- 0.8
Tranylcypromine (N=10)	30 mg/ 8 d	400 +/- 71	10 +/- 0	40 +/- 7.1
Fluoxetine (N=12)	60 mg/ 48 d	533 +/- 91	408 +/- 131	1.43 +/- 0.6

Data source: V152, section 8 table 2, page 000315
*Calculated from two baseline measurements
^ S9303-P9932, S9303-P9940, and S9303-P9941

8.2.1.1 Dose-response relationship

The data in FDA table 17 above show a dose-response effect of the STS dose on the TSF ratio. The sponsor acknowledges this dose-response relationship but dismisses the higher TSF at STS 40 mg as being clinically unimportant, relative to that observed with the non-selective MAO inhibitor tranylcypromine.

8.2.1.2 Duration-response relationship

Due to suggestions in the medical literature that the selectivity of selegiline for MAO-B inhibition may wane with time, associated with a more effective inhibition of MAO-A, the sponsor explored the effect of the duration of STS treatment on the tyramine pressor dose, with the goal of demonstrating chronic safety.

FDA Table 18. Tyramine challenge results before and after steady state dosing of STS 20mg, by duration of STS treatment

		Mean Tyramine Pressor Dose			
Study	Duration	N	Baseline average	Active	TSF Ratio
Pooled^	9-10 d	47	507 +/- 106	298 +/- 105	1.8 +/- 0.5
S9303-037-97B	21d	8	600 +/- 0	263+/- 119	2.8 +/- 1.5
S9303-P0045	33d	12	483 +/- 139	204+/- 86	2.9 +/- 1.5

^ S9303-P9932, S9303-P9940, and S9303-P9941

As FDA Table 18 shows above, the "active" pressor dose falls with each 11 day interval increase in STS treatment. The fall in "active" pressor dose is reflected in an increase in the TSF ratio; although the fall between 21 and 33 days is more striking than the corresponding increase in TSF ratio. It would have been more reassuring if the sponsor had conducted an additional study that prolonged the exposure duration another few weeks, to see if the changes in "active" pressor dose and TSF ratio leveled off. Given that an average treatment duration for an episode of major depression approaches six months, I don't think that findings displayed above going out to one month unequivocally assure chronic safety with regard to interaction between tyramine and STS.

One patient each in the 21 and 33 day studies reached the end point after a 50 mg dose of tyramine. The sponsor attempts to explain each of these occurrences away. In the 21 day study, the patient was rechallenged a few months later and required a 100 mg dose of tyramine at that time to reach the end point. In the 33 day study, the patient was not rechallenged, but further review of his records showed a low dose of tyramine required to reach the endpoint at baseline (around 300 mg, which was about 200 mg less than the other patients). Although the sponsor dismisses each of these patients as outliers, the fact that these patients did respond with end point SBP at relatively low doses of tyramine attests to the actuality that these responses occur.

8.2.1.3 Effect of encapsulated tyramine administered with a meal

The tyramine challenge studies described above were performed in fasting subjects. The sponsor utilized this approach because earlier studies where encapsulated tyramine was administered along with a meal led to substantial variability in pressor doses. A small study of untreated patients (S9303-P9816, N=4) demonstrated that those receiving encapsulated tyramine **with a meal** required, on average, 1.5-2 times the tyramine dose to reach the end point as untreated **fasting** patients. The sponsor interprets this finding to mean that the safety margin is even greater than that demonstrated in the tyramine challenge studies discussed above, because in clinical practice, patients will be receiving tyramine in food.

8.2.1.4 Effect of tyramine-rich meal on vital signs

In study S9303-9802, twelve subjects received 100 mg and 320mg of tyramine as tyramine-rich foods (mainly cheese) at breakfast and dinner, respectively. Vital signs were monitored following these meals at baseline (day 1) and after steady-state treatment with STS (day 13). None of the subjects reached the pressor response end point following STS treatment, although one subject did reach the end point following the breakfast meal on the baseline day.

8.2.2 Other sympathomimetic amines

8.2.2.1 Pseudoephedrine (PSE)

In study S9303-P9928, twelve subjects each underwent three treatment periods: 1) PSE 60 mg TID alone; 2) STS 20 mg alone; or 3) PSE+STS. In table 9 (V152, section 8, page 000332), the sponsor provided the mean SBP, DBP, and heart rate recorded at the end of each treatment period. There was a minimal change in each of the vital sign parameters between the PSE and PSE+STS treatment periods, suggesting that concurrent administration of PSE during STS therapy (or vice versa) confers no additional cardiovascular risk.

8.2.2.2 Phenylpropanolamine (PPA)

In study S9303-P0046, eleven subjects each underwent three treatment periods: 1) PPA 25mg 6x/day alone; 2) STS 20 mg alone; or 3) PPA+STS. In table 10 (V152, section 8, page 000333), the sponsor provided the mean maximum change from baseline for SBP, DBP, and heart rate recorded after a single PPA dose or six PPA doses at the end of treatment periods 1 and 3. Out of a total of 14 PPA doses per subject, each of four subjects achieved a pressor end point after one PPA dose; these pressor responses reached 42-46 mmHg and did not require rescue treatment with labetalol. The sponsor asserts that these events were "deemed random, clinically non-significant occurrences".

Mean maximum change from baseline in SBP, DBP, and heart rate after initial (1^{st}) PPA dose and after last (6^{th}) PPA dose was provided in Table 10 (section 8, page 000333). There were increases of mean SBP and DBP of 8-10 mmHg between the PPA and PPA+STS treatment periods, although these differences did not reach statistical significance. The sponsor claims that these changes were not clinically significant.

8.2.2.3 Cocaine

As a result of a Cooperative Research and Development Agreement between the sponsor and NIDA, two studies have been conducted to examine the physiologic effects of intravenous cocaine administration concurrent with STS therapy. In NIDA study 98-2, 12 non-dependent, experienced cocaine users had physiological parameters measured in response to intravenous cocaine infusion prior to and following seven days of treatment with STS 20mg. There was no substantial difference in peak effect (measured as mean change from baseline) or time to peak effect for SBP, DBP, or heart rate between the baseline and on-STS treatment cocaine infusions (see sponsor table 11, V152, section 8, page 000334).

In NIDA study 9906, 12 non-dependent, experienced cocaine users had physiological parameters measured in response to intravenous cocaine infusion during a 7-day treatment with a placebo patch and a 10 day treatment with STS 20mg. The increase in heart rate and blood pressure observed following cocaine infusion was not altered by treatment with STS 20 mg. Comparison of the physiologic response to cocaine infusion between the placebo patch and STS suggested a diminished cardiovascular response in the presence of STS.

9 120 Day Safety Update

The 120 day safety update includes additional safety information from the six ongoing trials that were included in the original NDA. In addition to these studies, this update includes safety data from five new trials. The cutoff date for new data is July 1, 2001. All eleven trials are listed in the following table (the new studies are below the double line):

FDA Table 19. Ongoing and new STS studies included in the 120 day safety update

Study Number	Phase	Study Name
S9303-P9937	II	OL study in [redacted]
S9303-P9935	II	OL study in [redacted]
S9303-P9806	III	DB study in relapse of MD
S9303-P9918	III	OL extension study in MD
S9303-E109-97B	III	DB study in PD
S9303-P9917	III	OL extension study in PD
S9303-P0051	I	Alternate application site study
S9303-P0156	I	Systemic MAO-A/MAO-B inhibition study
S9303-P0044*	II	OL extension in [redacted]
S9303-P0043*	III	Compassionate use in MD
NIDA-1019*	III	DB study in the treatment of cocaine dependence

*Trial is ongoing as of 7/1/01 cut-off date.
OL=open label; DB=double blind; [redacted]
MD=major depression; PD=Parkinson's disease

9.1 Deaths

No new deaths are reported in any of the 11 studies.

9.2 Serious Adverse Events

No new SAEs are reported in any of the 11 studies.

9.3 Discontinuations due to AEs

Discontinuations due to AEs were not reported for ongoing trials and completed trials whose databases hadn't been locked (S9303-P9806-reappearance DB, S9303-P9917). Among the remaining six trials, 11.8% (153/1297) of patients discontinued due to AEs. The sponsor did not summarize the specific AEs leading to discontinuation in the various trials listed in the table below, so I can't comment whether they were similar to those in the original NDA submission.

FDA Table 20. Incidence of discontinuation due to AE in ongoing and new STS studies included in the 120 day safety update

Study Number	Phase	New D/C due to AE* % (n/N)	Total D/C due to AE % (n/N)
S9303-P0051	I	3.7 (1/27)	3.7 (1/27)
S9303-P0156	I	0 (0/25)	0 (0/25)
S9303-P9937	II	17.6 (3/17)	6.9 (3/49)
S9303-P9935	II	15 (3/20)	15 (3/20)
S9303-P9806- relapse OL	III	8.6 (15/175)	11.1 (75/675)
S9303-P9918	III	0 (0/5)	15.5 (48/310)
S9303-E109-97B	III	12 (23/191)	12 (23/191)

*These percentages and denominators differ from those in Table 4.1, p. 000020 of the 120-day safety update (and in the far right column above) because I calculated the risk of discontinuation due to AE by taking the new discontinuations as the numerator and the newly enrolled patients as the denominator. This contrasted the sponsor's approach which was to take the total number of study participants as the denominator.

9.4 Adverse Experiences in Phase III trials

9.4.1 Depression

In the open label portion of the relapse prevention study S9303-P9806, the most common AEs occurred at a similar frequency as in the original NDA database; these AEs included ASR, headache and insomnia. In the open extension study S9303-9918, ASR, headache, and insomnia were also the most common AEs, although the frequencies were slightly lower.

In the open label portion of the relapse prevention study, the incidence of ASR was 30.5% compared to 18.4% in the open extension study. This difference probably stems from the fact that patients particularly sensitive to the ASR would have dropped out during the preceding RCT, leaving those in the open extension less likely to have a problem with ASR.

9.4.2 Parkinson's disease

In the double-blind study, S9303-E109-97B, the most frequent treatment emergent AEs included dizziness, accidental injury, and postural hypotension. The sponsor did not break out the incidences by treatment group.

10 Laboratory Data

10.1 Lab Assessments

Routine laboratory assessments (hematology, chemistry, urinalysis) were done at screening and final on-therapy visit in the placebo-controlled depression studies. Study E106-96B evaluated these parameters at week 3 also. Serum chemistry parameters

included thyroid function tests, i.e., total T_3, total T_4, and TSH; free T_3, free T_4, and resin T_3 uptake were not assayed.

10.2 Potentially Clinically Significant Lab Changes

The sponsor identified patients in the depression study pool who experienced a notable test result by utilizing the criteria listed in table A.2.2.

The proportions of patients treated with 20mg/20cm^2 STS and with placebo who met these criteria at some point on-treatment are provided in table A.2.3. Denominators exclude patients with a notable value at baseline. Only those tests for which at least one STS 20mg/20cm^2 patient had a notable value on-therapy are listed.

There was a statistically significant difference (alpha=0.10) between STS and placebo in the proportion of outliers for high total T_4 levels: 2.8% (10/360) of the STS patients had a notably elevated total T_4 level versus 0.8% (3/381) in the placebo group (p=0.04, Mantel-Haenszel Chi-Square).[5]

Thyroid function data for the 10 STS patients with elevated total T_4 levels were examined in more detail to detect any significant patterns of concurrent changes in total T_3 or TSH levels. These data are displayed in table A.2.4 and were reviewed with the assistance of Leonard Kapcala, M.D., an endocrinologist in the Division of Neuropharmacological Drug Products. These patients had no substantial changes in T_3 levels and only two patients had remarkable decreases in TSH (patients E114/OA007 and E114/OA391).

There were no statistically significant differences for any other thyroid function variable. Only one STS patient experienced a high total T_3 (1/361 or 0.3% versus no placebo patients). Additionally, slightly greater proportions of placebo patients experienced either high TSH or low TSH.

Hyperthyroidism was reported as a treatment-emergent adverse event in 2/685 STS patients, one patient in the 10mg/20cm^2 group and one in the 20mg/20cm^2 group. No placebo patient was reported as experiencing hyperthyroidism.

Hypothyroidism as a treatment-emergent event was reported in one placebo patient and in no STS patients.

While these data suggest that STS may be associated with an increase in free T_4 levels in a small proportion of patients, there is no clear pattern of accompanying changes in total T_3 or TSH levels and it is possible that these findings may be related to an increase in protein-bound T_4 as opposed to free T_4. Dr. Kapcala felt that no definitive conclusions could be drawn from these data and he suggested that a more complete evaluation of this concern in future studies include free T_3 and T_4 levels.

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[5] As further information, among the patients treated with STS 10mg/20cm^2, 4/137 (2.9%) had a notably increased T_4.

Otherwise, no other findings were deemed to be clinically important.

10.3 Mean Change from Baseline in Lab Values

Table A.2.5 displays the mean change from baseline to last visit for laboratory parameters within the pool of placebo-controlled depression studies.

There was a slightly higher mean change in total T_4 (thyroxine) in the STS 20mg/20cm^2 group compared to placebo (+0.410 versus –0.003 mcg/dl). Free T_4 levels would have been helpful but were not obtained in these trials. Also, there was a higher mean change in TSH in the drug group versus placebo (+0.167 versus +0.042 mIU/L). However, it is noted that the within-group variability for these measures (standard deviation) was considerably larger than the between-group difference (three-fold for T_4 and seven-fold for TSH).

This consideration and the absence of free thyroxine levels do not reasonably permit the inference that STS is associated with an increase in free T_4 levels.

The mean changes in total T_3 were very small for both drug and placebo (-0.001 and +0.007 ng/ml, respectively).

Otherwise, no differences were deemed to be clinically important.

10.4 Dropouts due to Lab Abnormalities

In the placebo-controlled depression pool, there were no premature discontinuations due to laboratory abnormalities.

10.5 Summary of Laboratory Data from Study E101-96B

Routine chemistry, hematology, and urinalysis testing were done at screening, baseline, and at 6 week intervals during the 48 week period of treatment. Thyroid profiles (T_3, T_4, TSH) were performed only at screening.

Examination of mean changes from baseline to endpoint and proportions of patients with changes from the normal range to abnormal at study endpoint revealed no clinically important differences between STS and placebo in this study.[6]

Two patients dropped out due to laboratory abnormalities. Both patients were in the STS treatment group: an 80 year old male discontinued treatment after 85 days due to thrombocytopenia and a 77 year old male dropped out after 34 days of therapy due to an

[6] Data may be found in section 8.3.4 of the study report (vol 1.354).

increase in BUN and creatinine. There were no dropouts for laboratory abnormalities in the placebo group.

11 Vital Sign Data

11.1 Vital Sign Assessments

Blood pressure, heart rate, and (except for study E106-96B) temperature were evaluated at screening, baseline, and at each visit during study treatment in the placebo-controlled depression trials. In studies E106-96B and E114, supine and standing blood pressures and heart rates were measured, which allowed for detection of orthostatic changes in blood pressure and heart rate. In studies E113-98B and P9804, only sitting blood pressures and heart rates were measured.

11.2 Potentially Clinically Significant Vital Sign Changes

The sponsor identified patients from the pool of placebo-controlled depression trials who experienced a clinically notable vital sign change by the criteria listed in table A.2.6.

The proportions of patients treated with 20mg/20cm^2 STS and with placebo who met these criteria at some point on-treatment are provided in table A.2.7. Only those measures for which at least one STS 20mg/20cm^2 patient had a notable value on-therapy are listed.

There was a statistically significant difference between STS and placebo for a notable orthostatic blood pressure change: 11.9% (27/226) of STS patients and 5.7% (13/228) of placebo patients met this criterion at some point (p=0.02).

Of the 27 STS patients meeting the criterion for an orthostatic blood pressure change, about one-half (13) met the criterion in the first 2 weeks of treatment. The same was true for the 13 placebo patients who met the criterion.

There was also a difference in the incidence of low diastolic blood pressure, with 1.2% (6/511) of STS patients and no placebo patients (0/519) meeting this criterion (p=0.01).

11.3 Mean Change from Baseline in Vital Sign Measures

Table A.2.8 displays the mean change from baseline to last visit for vital sign measures within the pool of placebo-controlled depression studies.

A comparison of the STS 20mg/20cm^2 and placebo treatment groups revealed no clinically significant differences for any vital sign measure, including mean orthostatic change in systolic blood pressure, diastolic blood pressure, or heart rate.

11.4 Dropouts due to Vital Sign Abnormalities

In the placebo-controlled depression pool, there were two patients in the STS 20mg/20cm^2 group who dropped out due to hypertension. No placebo patients dropped out for a vital sign abnormality. The proportion of patients dropping out due to hypertension was not significantly different between the two groups (0.4% vs. 0.0%, p=0.2).

11.5 Summary of Vital Sign Data from Study E101-96B[7]

In this study, supine and standing blood pressure and heart rate were measured at screening, baseline, every two weeks to week 12, then every three weeks to week 24, then every six weeks to week 48.

There were no significant differences between STS and placebo with respect to mean changes in supine systolic blood pressure, supine diastolic blood pressure, or standing diastolic blood pressure.

However, mean decreases from baseline in standing systolic blood pressure were significantly greater for STS patients compared to placebo patients at several time points. For drug, the reductions were in the range of 2 to 11 mmHg versus 1 to 5 mmHg in the placebo group.

Orthostatic decreases in systolic blood pressure (supine minus standing BP) tended to be significantly greater in the STS group versus placebo, particularly from week 4 onward. The mean differences for drug were in the range 4 to 7 mmHg versus –1 to 3 mmHg for placebo. For STS at these visits, 6% to 12% of STS patients had an orthostatic difference of at least 20 mmHg compared to 1% to 4% of placebo patients. There were no remarkable orthostatic differences in diastolic blood pressure.

There were no clinically important mean changes from baseline in supine or standing heart rate in STS versus placebo patients.

Patients in both the STS and placebo treatment groups experienced increases in heart rate in the standing position versus supine on average. There were no clinically meaningful differences between the groups. Also, there were no consistent differences between drug and placebo in terms of the proportion of patients with an orthostatic increase in heart rate of 20 bpm or more.

Postural hypotension was reported as an adverse event in 5.1% (14/273) of STS patients and 1.5% (2/133) of placebo patients in this trial (p=0.08, Mantel-Haenszel Chi-Square).

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[7] These data are found in Appendices B.61-B.73 of the study report (volume 1.358).

A greater proportion of patients in the STS group dropped out due to postural hypotension than patients in the placebo group: 2.2% (6/273) vs. 0.0% (0/133).

12 Electrocardiographic (ECG) Data

12.1 ECG Assessments

In the placebo-controlled depression studies, 12-lead ECGs were performed at screening, mid-treatment, and at the end of treatment except for study E113-98B, which did not perform mid-treatment ECGs.

The ventricular rate was recorded in all four studies. However, the PR, QRS, and QTc intervals were recorded in only two of these trials (E106-96B and E114). The sponsor did not specify the method of correction of the QT interval.

12.2 Potentially Clinically Significant ECG Changes

The criteria used to identify patients with clinically notable ECG results were as follows:

Heart rate	<50 bpm or >100 bpm
PR interval	>0.210 sec
QRS duration	>0.120 sec
QTc interval	>0.440 sec

The proportions of patients treated with 20mg/20cm^2 STS and with placebo who met these criteria at some point on-treatment are provided in table A.2.9.

There was a small but significantly higher proportion of STS 20mg/20cm^2 patients who experienced a high ventricular rate compared to placebo (0.9% (4/457) vs. 0.0% (0/458); p=0.06, 2-tailed Fishers exact test). The highest recorded ventricular rate in the STS group was 104 bpm, which is only slightly higher than cut-off rate of 100 bpm.

Eight STS 20mg/20cm^2 patients had a QTc greater than 0.440 sec. The maximum QTc recorded for any STS patient was 0.480 sec.

12.3 Mean Change from Baseline in ECG Values

Table A.2.10 displays the mean change from baseline to final visit for ECG parameters within the pool of placebo-controlled depression studies.

There were no clinically significant differences between the STS 20mg/20cm^2 and placebo treatment groups.

12.4 Dropouts due to ECG Abnormalities

There were no premature discontinuations in the placebo-controlled depression studies due to ECG abnormalities.

12.5 Summary of ECG Data from Study E101-96B

In this trial, 12-lead EKG's were done at screening, baseline, and every six weeks during 48 weeks of treatment.

An analysis of patients with notable specific ECG findings was not performed for this study.

Mean ventricular rates for STS were generally 3 to 5 bpm higher than those in the placebo group.

There were no substantial differences between the STS and placebo treatment groups during the study for mean PR interval, QRS interval, or QT interval.[8]

One STS-treated patient (Patient 0728) dropped out due to bradycardia on day 53 of treatment (42 bpm vs. 49 bpm at baseline). Otherwise, there were no dropouts due to ECG abnormalities.

Otherwise, the evaluation of laboratory, vital sign, and ECG data in this NDA is adequate to assess these domains of safety in support of Selegiline Transdermal System.

13 Summary of Important Laboratory, Vital Sign, and ECG Findings

In the pool of two placebo-controlled depression studies, 11.9% (27/226) of the STS 20mg/20cm^2 patients and 5.7% (13/228) of the placebo patients experienced orthostatic hypotension (defined as a change of at least 10mmHg in mean blood pressure between supine and standing positions).[9] This difference is statistically significant (p=0.02). About 50% of the patients with orthostatic hypotension in each group had this experience in the first 2 weeks of treatment.

No patients in this study pool dropped out due to orthostatic hypotension. Syncope, an adverse experience often related to orthostatic hypotension, was reported in only one STS 20mg/20cm^2 patient within this pool.

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[8] These data are found in Appendix B.82 of the study report (volume 1.359).

[9] As further information, 8.0% (12/150) of the STS 10mg/20cm^2 patients experienced orthostatic hypotension.

In the Alzheimer's disease study (Study E101-96B), postural hypotension was reported as an adverse event in 5.1% (14/273) of STS patients and 1.5% (2/133) of placebo patients (p=0.08, Mantel-Haenszel Chi-Square). A greater proportion of patients in the STS group dropped out due to postural hypotension than patients in the placebo group: 2.2% (6/273) vs. 0.0% (0/133).

It is of interest to note that in an early pharmacokinetic study using patches to deliver selegiline in healthy males for 2 weeks (protocol S9303-020-95B), the 6 subjects in the high dose group (receiving the equivalent of 32mg of selegiline per day) began to experience severe orthostatic hypotension on day 5 of the study (decrease in DBP by 50% and doubling of heart rate). One subject dropped out on day 10 due to headaches and lightheadedness on standing while the remaining 5 subjects were discontinued on day 12 as a precautionary measure due to orthostatic hypotension.[10] This information suggests that the orthostatic hypotension observed with selegiline is dose-related.

In conclusion, it appears that STS is associated with orthostatic changes in blood pressure compared to placebo. This is not surprising since postural hypotension is a very common adverse event associated with previously approved MAOI antidepressants. Elderly patients with Alzheimer's disease may be more sensitive to this adverse effect.

14 Review of Systems

14.1 Cardiovascular

The sponsor's studies examining the cardiovascular implications of the interaction with sympathomimetic amines are evaluated extensively in section 7 of this review, and the findings discussed in section 14.2. Briefly, at the range of doses studied (STS 20-40 mg for 9-10 days), the data from the tyramine challenge studies suggest that dietary restriction of tyramine is not necessary with STS. However, the issue of long term safety is not fully addressed given the fall in the tyramine pressor dose with longer duration of use (up to 33 days). Additionally, the safety of the use of phenylpropanolamine in the presence STS was not fully supported by the summary data presented.

Postural hypotension, often symptomatic, has been observed during treatment with nonselective MAOIs, and it was observed during the clinical development program of STS. For the controlled clinical trials in major depression, there was no significant difference in the incidence of postural hypotension between the STS and placebo treatment groups based on AE data submitted by the sponsor. However, in the studies in this indication, there was a statistically significant difference between STS and placebo for a notable orthostatic blood pressure change based on vital sign data: 11.9% (27/226) of STS patients and 5.7% (13/228) of placebo patients met this criterion at some point

[10] See the Memorandum of Telephone Conversation dated 3-9-95 by Dr. Balian filed to IND 46,944.

during the trial (p=0.02). (Note: In the vital sign data, postural hypotension was defined by a fall in mean blood pressure[11] of at least 10 mmHg).

In study S9303-E101-96B, a large placebo-controlled trial of STS in Alzheimer's disease patients (mean age = 74 years), 5.1% (14/273) of patients in the STS treatment group compared to 1.5% (2/133) of placebo patients developed postural hypotension. The incidence density ratio 3.3 is clinically important, although not statistically significant. Of the patients who reported postural hypotension, six patients (2.2%) in the STS (20mg/20cm2) group compared with no patients in the placebo group discontinued due to this AE.

In study S9303-E101-96B, chest pain was reported in over 5% of patients and over 2X more frequently in the STS treatment group than in the placebo group. There was an excess of SAEs of "CHF" in the STS group, as well.

Two controlled clinical trials in major depression did not identify a propensity for STS to prolong the QT interval.

14.2 Dermatologic

Since the STS is a transdermal delivery system for selegiline, the sponsor carefully monitored for application site reactions (ASR) and cutaneous AEs throughout the clinical development program. The term "application site reaction" encompasses different types of reactions at the patch site (e.g., redness, rash, itchiness, etc.).

In the controlled clinical trials for major depression, ASR occurred more frequently in STS treatment groups than in the placebo group. The incidence ratio of STS (20mg/20cm2) compared to placebo of 2.4 is statistically significantly higher in STS treatment groups than in the placebo group.

Regarding the quality of the ASR in the controlled trials in depression, in general, those ASRs occurring in the placebo group compared to the STS group were less frequent, occurred earlier and lasted for a shorter duration, had a milder intensity, and required medical treatment less often. In controlled depression trial S9303-E114-98B, ASRs were monitored with a detailed form. Based on the details of the monitoring forms, the ASRs occurring in the placebo group compared to the STS group occurred earlier, had less severe discoloration, were less palpable, were not painful or associated with a burning sensation, had less swelling, and had fewer erythematous papules.

In the controlled clinical trials for Alzheimer's disease (S9303-E101-96B), ASRs were also higher in STS treatment group than in the placebo group. The incidence rate ratio of 6.6 was statistically significant.

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[11] Mean BP =DBP + [(SBP-DBP)÷3]

There was a statistically significant excess of non-melanoma skin cancers in the STS group in the large placebo controlled trial in Alzheimer's disease (S9303-E101-96B). These cancers were identified over the course of the year long study, and were located mainly on the face and head, not adjacent to the location of the STS patch. The excess in the STS group is unexplained, but may be just a chance finding due to the common occurrence of these cancers in the elderly. No skin cancers were reported in the depression trials.

14.3 Neurologic

In the controlled clinical trials for major depression, there was more insomnia reported in the STS (20 mg/20cm2) group than in the placebo group. The rate ratio of 2.0 was statistically significant. The excess frequency of insomnia was not as substantial in the large Alzheimer's trial (RR=1.7); however, insomnia may not be reliably reported in the Alzheimer's disease population and/or it is common in the background population.

No seizures were reported in STS patients in the depression trials.

14.4 Gastrointestinal

Since the STS is a transdermal delivery system for selegiline, it has minimum effects on gastrointestinal system. Diarrhea, nausea and dyspepsia were reported in both treatment groups, but incidence rates of these AEs did not differ importantly between the groups. No liver failure or hepatitis was reported.

14.5 Respiratory

In the controlled clinical trials for major depression, sinusitis was more common in STS treatment groups than in the placebo group. The incidence ratio of 3.9 is statistically significant; however, an examination of the verbatim terms that were coded to the preferred term "sinusitis" and an examination of sinus-related verbatim terms that were coded to preferred terms other than "sinusitis" showed a high degree of variability and inconsistency. Once the verbatim terms are recoded in a consistent manner, we will reexamine the incidence of sinusitis across treatment groups.

14.6 Endocrine

In the controlled clinical trials of major depression and Alzheimer's disease, there was no significant difference in the frequency of endocrine AEs between the STS and placebo treatment groups.

Thyroid function data for the 10 STS patients with elevated total T_4 levels were examined in more detail to detect any significant patterns of concurrent changes in total T_3 or TSH levels. These data are displayed in FDA Table A.3.4. These patients had no substantial

changes in T_3 levels and only two patients had remarkable decreases in TSH. No definitive conclusions could be drawn from these data due to the absence of free T_3 and T_4 levels.

15 Discussion

If STS is shown to be efficacious in the intended indication of use, there is no safety issue that would preclude the approval of this drug product.

15.1 Adverse Event Coding

A major issue that the sponsor will need to address is the inconsistent coding of AE verbatim terms to preferred terms. Dr. Boehm's review of the coding dictionary identified three substantial problems with the AE verbatim coding: potentially miscoded events, potential splitting of similar events, and potential lumping of dissimilar events. Ultimately, it is difficult to know how to interpret any of the data pertaining to adverse events (SAEs, discontinuation due to AEs, and common AEs) given the inconsistencies identified. We would expect that prior to any resubmission, the sponsor would completely overhaul their AE mapping process to ensure that the AE summary data actually reflects what happened to the patients participating in the STS trials.

15.2 Drug-Food/ Drug-drug interactions

Because one of the prominent safety issues with an MAO inhibitor is the risk of hypertensive crises associated with exposure to sympathomimetic amines (either dietary tyramine or OTC decongestants), the sponsor conducted a variety of tyramine challenge studies, as well as drug interaction studies. Probably the most reassuring finding in these studies was the observation that the tyramine sensitivity factor ratio for STS 20mg administered for 10 days is basically the same as that for the marketed dose of oral selegiline (5 mg BID). This finding, coupled with the fact that this dose of oral selegiline has been marketed without dietary restriction for over a decade, supports [redacted] that dietary restriction is not needed with STS. Reflecting its use as a positive control, the results of the tyramine challenge studies showed that the TSF ratio for tranylcypromine, a nonselective MAO inhibitor, was 20-fold higher than that for STS 20mg, the dose intended for marketing. Even at double the STS dose intended for marketing, the TSF ratio is 12-fold **lower** than the positive control.

The question that was not adequately evaluated, though, was the effect of long-term administration of STS on MAO A and B inhibition. In section 7.2.1.2 above, I presented the sponsor's data from the tyramine challenge studies following 10 days, 21 days, and 33 days of STS 20mg treatment. Although the TSF ratio appears to level off between 21 and 33 days, the "active" pressor dose continued to fall between 21 and 33 days. Since most patients will be treated for more than one month, and perhaps up to six months or

longer, it is incumbent on the sponsor to perform a tyramine challenge study after a longer duration of STS treatment. I would suggest at least 60 days, and if the "active" pressor dose is still falling, or the TSF ratio rising, additional studies at longer durations would be required.

The studies conducted by the sponsor to examine the potential interaction between the sympathomimetic drugs pseudoephedrine and cocaine suggested that concurrent administration of these substances with STS would not cause clinically important changes in cardiovascular parameters. The study with phenylpropanolamine was not as reassuring, however. Following seven days of treatment with STS 20 mg, mean maximal changes from baseline for SBP and DBP were in the range of 8-10 mmHg. Although these changes were not statistically significant, they may be clinically significant. We will request that the sponsor submit the full study report for closer review.

15.3 Postural Hypotension

An issue that remains of concern is the frequency of postural hypotension. The large placebo-controlled trial in Alzheimer's disease identified a statistically significant excess of postural hypotension AEs in the STS group, as well as a numerical excess of discontinuations due to postural hypotension in the STS group. Although postural hypotension AEs were not a substantial problem among participants in the placebo-controlled trials in major depression, there was a statistically significant difference between STS and placebo for a notable orthostatic blood pressure change. The mean age of participants in the major depression studies was in the early 40's, with the maximum around 65. The concern that persists is how elderly patients using STS for depression would tolerate the potential side effect of postural hypotension.

15.4 Application site reactions

STS is a transdermal drug delivery system, and in all controlled trials, application site reactions were the most frequently occurring AE in the STS groups. ASRs also led to discontinuation in 3-7% of STS patients compared with 0.7-1.5% of placebo patients. ASRs generally did not qualify as SAEs, though.

16 Conclusion

No conclusions regarding the safety of EMSAM can be drawn until the AE verbatim terms are recoded and reanalyzed.

17 Suggested Follow up Issues

- Prior to any resubmission, the sponsor should completely overhaul their AE mapping process (verbatim to preferred term) to ensure that the AE summary data actually reflect what happened to the patients participating in the STS trials.

- Since most patients will be treated for more than one month, and perhaps up to six months or longer, it is incumbent on the sponsor to perform a tyramine challenge study after a longer duration of STS treatment. I would suggest at least 60 days, and if the "active" pressor dose is still falling, or the TSF ratio rising, additional studies at longer durations would be required.
- The summary data provided by the sponsor to support the safety of concurrent use of phenylpropanolamine with STS is not convincing. We will request that the sponsor submit the full study report for closer review.
- In the depression trials, there was no apparent excess of postural hypotension AEs, despite a finding of excess orthostasis in the STS groups based vital sign measurements. For the controlled trials in depression, following the recoding of the verbatim terms to appropriate preferred terms, the sponsor should review the frequency of AEs potentially related to postural hypotension (e.g., dizziness, falls, fractures, etc) stratified by treatment groups.
- In future studies, free T4 levels should be assayed to determine if STS is truly associated with elevation of T4.

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HFD-120
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18 Appendices

18.1 Appendix 1: Example of rate ratio CI calculation

Discontinuation due to AEs

IDR and its 95% Interval for STS (10mg/20cm2) VS Placebo
(Controlled Clinical Studies in Major Depression)

	D	PT
E	9	20
$\bar{\mathbf{E}}$	24	67

E: STS (10mg/20cm2)
$\bar{E}$: Placebo
D: Discontinuation
PT: Person-Time

IDR= 9÷20/24÷67=1.26

95% Confidence Interval:

$e^{\wedge[\ln(IDR) \pm 1.96(\sqrt{V})]}$

V = 1/a + 1/c= 1/9 + 1/24 =0.153
ln (IDR) = ln(1.26) = 0.23

$e^{\wedge[\ln(IDR) \pm 1.96(\sqrt{V})]} = e^{\wedge[0.23 \pm 1.96(\sqrt{0.153})]}$

Upper Limit $= e^{\wedge[0.621]} = 1.86$
Lower Limit $= e^{\wedge[-0.161]} = 0.85$

Interpretation: The 95% CI contains one. There is no statistical significance.

18.2 Appendix 2: Vital Sign and Lab Data

TABLE A2.1: DEMOGRAPHIC CHARACTERISTICS POOL OF PLACEBO-CONTROLLED DEPRESSION TRIALS			
	STS 10mg/20cm^2	**STS 20mg/20cm^2**	**Placebo**
N	151	534	535
Age (yrs)			
Mean	40.4	41.4	41.7
Range	17-64	18-66	18-65
Age Group			
<60	137 (91%)	508 (95%)	506 (95%)
≥60	14 (9%)	26 (5%)	29 (5%)
Gender			
Male	54 (36%)	198 (37%)	193 (36%)
Female	97 (64%)	336 (63%)	342 (64%)
Race			
White	130 (86%)	446 (84%)	469 (88%)
Black	8 (5%)	42 (8%)	24 (5%)
Hispanic	7 (5%)	34 (6%)	30 (5%)
Other	6 (4%)	12 (2%)	12 (2%)

TABLE A2.2: CRITERIA FOR NOTABLE LABORATORY VALUES PLACEBO-CONTROLLED DEPRESSION STUDY POOL	
Parameter	**Criteria**
Hematology	
Hemoglobin (g/dL)	<0.9 × LLN
Hematocrit (%)	<0.9 × LLN
RBC ($\times 10^{12}$/L)	<0.9 × LLN or >1.1 × ULN
MCV (fl)	<0.8 × LLN or >1.2 × ULN
MCH (pg)	<0.8 × LLN or >1.2 × ULN
MCHC (g/dL)	<0.8 × LLN or >1.2 × ULN
WBC ($\times 10^9$/L)	<2.5 or >15
Neutrophils ($\times 10^9$/L)	<1.0
Eosinophils ($\times 10^9$/L)	>0.7
Platelets ($\times 10^9$/L)	<75 or >700
Blood Chemistry	
Albumin (g/dL)	<2.5
Alkaline phosphatase(U/L)	≥3 × ULN
AST (SGOT)(U/L)	>3 × ULN
ALT (SGPT)(U/L)	>3 × ULN
Bicarbonate (mmol/L)	<18 or >40
BUN (mg/dL)	>30
Calcium (mg/dL)	<7 or >12
Chloride (mmol/L)	<90 or >120
Creatinine (mg/dL)	>2
Glucose (mg/dL)	<50 or >250
LDH (U/L)	>3 × ULN
Phosphorus (mg/dL)	<1.5 or >5.5
Potassium (mmol/L)	<3.0 or >5.5
Sodium (mmol/L)	<130 or >150
Total bilirubin (mg/dL)	>2
Total protein (g/dL)	<0.9 × LLN or >1.1 × ULN
Total T3 (ng/mL)	<LLN or >ULN
Total T4 (mcg/dL)	<LLN or >ULN
TSH (mIU/ml)	<LLN or >ULN
Uric acid (mg/dL)	Female >8.0, Male >10.0
Urinalysis	
Blood	>Trace
Protein	>Trace
Glucose	>Trace
RBC	Female >7, Male >0
WBC	>5

TABLE A2.3:
PROPORTIONS OF PATIENTS WITH NOTABLE LABORATORY VALUES
PLACEBO-CONTROLLED DEPRESSION STUDY POOL[12]

Lab Parameter	STS (20mg/cm^2)			Placebo		
	N_{tot}	n_{not}	%	N_{tot}	n_{not}	%
Hemoglobin (low)	453	2	0.4	465	0	0.0
Hematocrit (low)	455	3	0.6	466	1	0.2
RBCs (low)	452	6	1.3	464	3	0.7
RBCs (high)	452	1	0.2	464	0	0.0
Eosinophils (high)	450	2	0.4	470	0	0.0
MCV (low)	327	1	0.3	338	1	0.3
Potassium (High)	455	2	0.4	472	2	0.4
Bicarbonate (Low)	456	5	1.1	472	2	0.4
Phosphorus (High)	457	1	0.2	472	0	0.0
BUN (High)	457	1	0.2	471	0	0.0
Uric Acid (High)	455	1	0.2	472	1	0.2
Glucose (Low)	455	1	0.22	467	0	0.0
Glucose (High)	455	2	0.4	467	1	0.2
Total T_3 (Low)	361	3	0.8	382	1	0.3
Total T_3 (High)	361	1	0.3	382	0	0.0
Total T_4 (High)	360	10	2.8	381	3	0.8
TSH (Low)	352	5	1.4	371	7	1.9
TSH (High)	352	2	0.6	371	6	1.6
U/A Blood	385	39	10.1	396	35	8.8
U/A Glucose	449	2	0.5	466	2	0.4
U/A WBCs	384	18	4.7	399	32	8.0
U/A RBCs (males)	99	17	17.1	103	18	17.5
U/A RBCs (females)	224	7	3.1	225	14	6.2

[12] Ntot=number at risk excluding those with notable values at baseline.
Nnot=number with notable values on-treatment. %=Nnot/Ntot × 100%.

TABLE A2.4
STS (20mg/20cm^2) PATIENTS WITH ELEVATED TOTAL T_4 LEVELS
PLACEBO-CONTROLLED DEPRESSION STUDY POOL [13]

Patient	Total T_3 (ng/ml) Normal Range 0.59-1.74		Total T_4 (mcg/dl) Normal Range 4.5-12.0		TSH (mIU/ml) Normal Range 0.49-4.67	
	BL	On-TX	BL	On-TX	BL	On-TX
E113/00218	0.81	1.09	7.7	12.7	2.77	1.95
E113/00606	1.04	1.23	9.9	12.4	0.91	0.68
9804/01010	1.05	1.05	11.3	12.7	1.11	0.58
9804/00624	1.01	1.17	8.9	12.9	2.79	2.05
E114/OA007	0.9	1.2	9.0	12.8	1.0	<0.1
E114/OA076	1.0	1.1	10.0	12.4	1.3	0.6
E114/OA087	1.5	1.3	9.6	16.3	2.5	2.3
E114/OA454	0.9	1.0	11.6	15.6	10.2	0.3
E114/OA391	0.8	0.9	10.6	13.4	0.3	<0.1
E114/OA180	1.2	1.1	11.8	13.7	2.2	3.7

[13] Found in Listing D.8.2.2, volume 1.523.

TABLE A2.5
MEAN CHANGE FROM BASELINE TO FINAL VISIT IN LAB PARAMETERS
PLACEBO-CONTROLLED DEPRESSION STUDY POOL

Laboratory Parameter	STS (20mg/cm^2)		Placebo	
	N	Mean Δ	N	Mean Δ
Hematology				
Hemoglobin (g/dL)	456	-0.273	470	-0.126
Hematocrit (%)	456	-0.860	470	-0.351
RBC ($\times 10^{12}$/L)	456	-0.088	470	-0.042
MCV (fl)	328	-0.111	338	+0.094
MCH (pg)	328	-0.039	338	-0.031
MCHC (g/dL)	328	-0.007	338	-0.055
WBC ($\times 10^9$/L)	457	-0.421	471	-0.330
Neutrophils ($\times 10^9$/L)	456	-0.327	470	-0.176
Eosinophils ($\times 10^9$/L)	456	-0.001	470	-0.000
Platelets ($\times 10^9$/L)	449	-2.766	466	+0.052
Blood Chemistry				
Albumin (g/dL)	456	-0.084	472	-0.078
Alkaline phosphatase (U/L)	456	-1.502	472	-0.352
AST (SGOT)(U/L)	456	-0.077	472	-0.436
ALT (SGPT)(U/L)	456	-1.018	472	-0.600
Bicarbonate (mmol/L)	456	-0.226	472	-0.121
BUN (mg/dL)	456	+0.335	472	+0.555
Calcium (mg/dL)	456	-0.119	472	-0.095
Chloride (mmol/L)	456	-0.197	472	-0.049
Creatinine (mg/dL)	456	+0.007	472	+0.004
Glucose (mg/dL)	456	+2.007	472	+3.265
LDH (U/L)	456	+0.822	472	-0.951
Phosphorus (mg/dL)	456	+0.045	472	+0.015
Potassium (mmol/L)	456	-0.023	472	-0.043
Sodium (mmol/L)	456	-0.412	472	-0.146
Total bilirubin (mg/dL)	456	-0.020	471	-0.023
Total protein (g/dL)	456	-0.166	472	-0.111
Total T3 (ng/mL)	369	-0.001	387	+0.007
Total T4 (mcg/dL)	369	+0.410	387	-0.003
TSH (mIU/ml)	365	+0.167	383	+0.042
Uric acid (mg/dL)	456	-0.046	472	0.127
Urinalysis				
Urine pH	454	-0.105	471	-0.028
Urine Specific Gravity	454	+0.002	471	+0.001

TABLE A2.6:
CRITERIA FOR CLINICALLY NOTABLE VITAL SIGNS
POOL OF PLACEBO-CONTROLLED DEPRESSION STUDIES

Vital Sign Measure	Criteria
Systolic BP Low	≤90mmHg and ↓ ≥20mmHg
Systolic BP High	≥180mmHg and ↑ ≥20mmHg
Diastolic BP Low	≤50mmHg and ↓ ≥15mmHg
Diastolic BP High	≥105mmHg and ↑ ≥15mmHg
Orthostatic BP Δ	≥10mmHg ↓ Mean BP[14]
Pulse Low	≤50bpm and ↓ ≥15bpm
Pulse High	≥120bpm and ↑ ≥15bpm
Temperature	>101°F and ↑ ≥2°F
Weight	Change ≥10%

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[14] Mean BP = DBP + [(SBP-DBP)÷3].

TABLE A2.7:
PROPORTIONS OF PATIENTS WITH CLINICALLY NOTABLE VITAL SIGNS
PLACEBO-CONTROLLED DEPRESSION STUDY POOL[15]

VS Parameter	STS (20mg/cm^2)			Placebo		
	N_{tot}	n_{not}	%	N_{tot}	n_{not}	%
Systolic BP Low	511	11	2.2	519	8	1.5
Diastolic BP Low	511	6	1.2	519	0	0.0
Diastolic BP High	511	0	0.0	519	2	0.4
Orthostatic BP Δ[16]	226	27	11.9	228	13	5.7
Pulse Low	511	1	0.2	519	5	1.0
Temperature	511	1	0.2	517	1	0.2
Weight	498	3	0.6	501	0	0.0

TABLE A2.8:
MEAN CHANGE FROM BASELINE TO FINAL VISIT IN VITAL SIGNS
PLACEBO-CONTROLLED DEPRESSION STUDY POOL[17]

Vital Sign Measure	STS (20mg/cm^2)		Placebo	
	N	Mean Δ	N	Mean Δ
Supine Systolic BP (mmHg)	117	-0.8	118	-2.4
Supine Diastolic BP (mmHg)	117	0.0	118	-1.1
Supine Heart Rate (bpm)	117	-0.1	118	-0.7
Standing Systolic BP (mmHg)	117	-1.5	118	-1.0
Standing Diastolic BP (mmHg)	117	-0.1	118	-0.6
Standing Heart Rate (bpm)	117	-0.3	118	0.7
Sitting Systolic BP (mmHg)	200	-1.3	217	-0.9
Sitting Diastolic BP (mmHg)	200	-0.7	217	0.9
Sitting Heart Rate (bpm)	200	0.3	217	0.0
Orthostatic Change SBP (mmHg)	117	-0.5	118	1.3
Orthostatic Change DBP (mmHg)	117	1.2	118	2.5
Orthostatic Change HR (bpm)	117	3.7	118	5.2
Weight (lbs)	496	-1.3	501	0.4
Temperature (°F)	511	0.0	517	0.0

[15] Ntot=number at risk excluding those with notable values at baseline.
Nnot=number with notable values on-treatment. %=Nnot/Ntot × 100%.
[16] Denominators exclude patients with orthostatic hypotension at baseline. Supine and standing blood pressures were obtained in studies E106-96B and E114 only.
[17] Supine and standing blood pressures and heart rates were measured in studies E106-96B and E114. Sitting blood pressures and heart rates were measured in studies E113-98B and P9804.

TABLE A2.9
PROPORTIONS OF PATIENTS WITH CLINICALLY NOTABLE ECG RESULTS
PLACEBO-CONTROLLED DEPRESSION STUDY POOL[18]

ECG Parameter	STS (20mg/cm^2)			Placebo		
	N_{tot}	n_{not}	%	N_{tot}	n_{not}	%
Heart Rate Low	457	2	0.4	458	9	2.0
Heart Rate High	457	4	0.9	458	0	0.0
PR Interval ↑	215	1	0.5	218	1	0.5
QRS Interval ↑	220	0	0.0	217	2	0.9
QTc Interval ↑	199	8	4.0	202	15	7.4

TABLE A2.10
MEAN CHANGE FROM BASELINE TO FINAL VISIT IN ECG PARAMETERS
PLACEBO-CONTROLLED DEPRESSION STUDY POOL

ECG Parameter	STS (20mg/cm^2)		Placebo	
	N	Mean Δ	N	Mean Δ
Ventricular Rate (bpm)	465	0.783	476	1.700
PR Interval (sec)	218	-0.001	218	0.002
QRS Interval (sec)	220	0.000	218	0.006
QTc Interval (sec)	220	-0.002	218	0.003

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[18] Ntot=number at risk excluding those with notable values at baseline.
Nnot=number with notable values on-treatment. %=Nnot/Ntot × 100%.

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/s/

Judith Racoosin
3/14/02 11:04:34 AM
MEDICAL OFFICER

REVIEW AND EVALUATION OF CLINICAL EFFICACY DATA

Application Information

NDA #:	21-336
Sponsor:	Somerset Pharmaceuticals
Due Date:	March 25, 2002

Drug Name:

Generic Name:	Selegiline Transdermal System
Trade Name:	Emsam

Drug Categorization:

Pharmacological Class:	Monoamine Oxidase Inhibitor
Proposed Indication:	Major Depression
Dosage Forms:	20mg/20cm^2 Patch
Route:	Transdermal

Review Information

Clinical Reviewer:	Gregory M. Dubitsky, M.D.
Completion Date:	February 28, 2002

NDA 21-336
SELEGILINE TRANSDERMAL SYSTEM
TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on Approvability With Respect to Efficacy

There are inadequate data to support the sponsor's claim of antidepressant efficacy. STS has demonstrated convincing evidence of an antidepressant effect in only one of the four key efficacy studies.

Due to an inadequate demonstration of efficacy, it is not recommended that this NDA be approved for the treatment of major depressive disorder.

B. Recommendation on Phase 4 Studies

1. Use in Pediatric Patients with Major Depression

The sponsor has not submitted a plan to evaluate the safety and efficacy of STS in pediatric patients with major depression. If STS is approved for major depression in the future, such a plan will be needed.

2. Safety and Efficacy of Extended Treatment

The sponsor has initiated a long-term, relapse prevention study (P9806) to examine the safety and efficacy of extended STS treatment up to 52 weeks. This study is ongoing at this time. The sponsor should be advised that the results from study P9806 will be required at some point in the future if STS is approved for the treatment of major depression.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Selegiline is an irreversible monoamine oxidase inhibitor (MAOI). This NDA is intended to support a patch formulation of selegiline which will permit transdermal delivery of drug to the systemic circulation, bypassing the gastrointestinal tract and avoiding inhibition of intestinal MAO. This formulation is intended to treat major depression. The proposed trade name for the Selegiline Transdermal System, or STS, is Emsam.

As of the original clinical cut-off date for the NDA (July 20, 2000), the STS clinical development program consisted of 36 Phase 1 studies conducted in healthy volunteers and 17 Phase 2/3 studies in patients.

Among Phase 2/3 trials in major depression, a total of 1,326 patients were exposed to an STS daily dose of 20mg/20cm^2, the dose recommended in proposed labeling. Of these patients, 93 received STS 20mg/20cm^2 per day for at least 24 weeks.

Additionally, a 120-Day Safety Update, submitted on September 26, 2001, reported limited safety information for 6 ongoing studies initiated prior to the original cut-off date and 5 new studies started after that date.

B. Efficacy

The assessment of antidepressant efficacy was based on four short-term, placebo-controlled trials. These are reviewed individually in detail in section VI of the CLINICAL REVIEW.

The primary efficacy measure in all four studies was the change from baseline in the HAM-D_{1-17} total score.

One trial, study E106-96B, was clearly positive on the primary variable as well as on selected secondary variables (HAM-D depressed mood item, MADRS total score, and CGI improvement item.)

The remaining three studies (P9804, E113-98B, and E114-98B) failed to demonstrate statistically significant superiority for STS over placebo on the primary variable.

Overall, only one of the four efficacy studies was positive. This is inadequate evidence to support the sponsor's claim of efficacy in the treatment of major depression.

C. Safety

The review of safety was produced as a separate document and is pending completion at this time. This review was conducted jointly by David Gan, M.D., of the Division Safety Team, and the undersigned (Gregory Dubitsky, M.D.), of the Psychiatric Drug Products Group.

The reader is referred to this safety review for a detailed description of the safety review methods and safety findings.

D. Dosing

All four controlled efficacy trials included a fixed 20mg/20cm^2 dose arm; study E114-98B also incorporated a fixed 10mg/20cm^2 dose arm. One study provided evidence of efficacy for the 20mg/20cm^2 patch administered once daily. There was no evidence to support the 10mg/20cm^2 dose.

To date, other doses have not been adequately evaluated in terms of efficacy.

E. Special Populations

A comparison of the placebo-adjusted changes in the HAM-D_{1-17} total score between demographic subgroups (age, gender, race) and between subgroups defined by baseline severity revealed no clinically important differences. Data may be found in Appendix 23.

CLINICAL REVIEW

I. Introduction and Background

A. Generic and Proposed Trade Name, Drug Class, Proposed Indication, Dose, Regimen, Age Group

The subject of this NDA is a patch formulation of selegiline, a monoamine oxidase inhibitor (MAOI). The trade name proposed by the sponsor is Emsam. The sponsor seeks approval for the treatment of adult patients with major depression utilizing one 20mg/20cm^2 patch daily.

B. State of Armamentarium for Indication

There are currently 19 molecular entities approved in the U.S. for the treatment of major depression. Most of these agents fall into one of the following classes: tricyclics, monoamine oxidase inhibitors (MAOI's), selective serotonin reuptake inhibitors (SSRI's), or serotonin-norepinephrine reuptake inhibitors (SNRI's). There is little evidence to suggest that one class is superior to another in terms of therapeutic effect but there are differences in terms of safety profiles.

Inhibitors of monoamine oxidase (MAO) have been effective as antidepressants but, due to the potential to cause hypertensive crises when certain foods or drugs are ingested, their use has necessitated elaborate dietary and drug restrictions. The rationale for developing transdermal selegiline was to produce an effective antidepressant which did not require such restrictions.

Thus, selegiline transdermal system may represent the first MAOI approved in the U.S. that does not require dietary restrictions.

C. Important Milestones in Product Development

Selegiline HCl was approved as an oral formulation for the adjunctive treatment of Parkinson's disease in 1989. It has since been marketed as Eldepryl in the U.S.

An IND application to develop transdermal selegiline for depression (IND #46,944) was submitted to the Agency on 12-20-94.[1] Depression studies under this IND were initially placed on hold due to concerns about significant orthostatic hypotension reported in an early pharmacokinetic study in healthy volunteers who were administered patches delivering the equivalent of 32mg of selegiline per 24 hours. Furthermore, in a study for Alzheimer's disease, serious adverse events (ischemic stroke and myocardial infarction) occurred in patients with documented orthostasis. Clinical experience with patches delivering considerably lower doses of selegiline was subsequently reviewed and, based on these data, depression studies were permitted to proceed.[2]

A meeting was held with the sponsor on 5-4-98 to discuss the progress of their development program. The following issues were discussed: 1) the need for at least 2 positive studies in depression to obtain approval for that indication, 2) 3) the need for a relapse prevention study, 4) a suggestion to study metabolic enzyme activity in vitro, 5) and 6) a suggestion to obtain dose-response data.

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[2] See the Review and Evaluation of Clinical Data dated 1-4-97 by Dr. Mosholder filed to IND 46,944..

A pre-NDA meeting was held on 6-10-99 to discuss the sponsor's planned NDA submission. The discussion included the following points: 1) applicability of fast track criteria for the NDA, 2) relapse prevention data as a Phase 4 commitment, 3) the number of patients and duration of exposure required for the NDA safety database, 4) acceptability of submitting data from ongoing studies after NDA filing, 5) submission of data from Phase 1 studies using prototype patch formulations, 6) adequacy of data to support [redacted], 7) pharmacology/toxicology requirements, and 8) acceptability of their ADME program. We agreed to provide Somerset with templates for efficacy data to be used in the NDA submission.

On 6-24-99, the sponsor submitted a protocol for a relapse prevention study in depression (S9303-P9806). This protocol was found to be acceptable.[3]

This NDA was submitted on 5-24-01 and received by the Agency on 5-25-01. A filing meeting was held on 7-17-01 and this application was deemed fileable.

A 120-day Safety Update to the NDA was submitted on 9-26-01.

D. Foreign Marketing

Selegiline Transdermal System has not been approved or studied in any country other than the United States.

II. Clinically Relevant Findings from Consultant Reviews

A. Statistical Review and Evaluation

The Statistical Review and Evaluation was performed by Yuan-Li Shen, Dr.PH. Review sign-off within the Division of Biometrics I was completed on 1-25-02.

Overall, this review was consistent with my findings, which are described in section VI. below (the Integrated Review of Efficacy).

[3] This study is ongoing at the time of this review.

B. CDER Controlled Substances Staff

The CDER Controlled Substances Staff (CSS) was consulted to evaluate the abuse potential of transdermal selegiline and the potential for diversion of the drug product to produce illicit drugs, specifically amphetamine and methamphetamine which are hepatic metabolites of selegiline.

The CSS provided their response in a memorandum dated 1-18-02. They indicate that data from the NDA submission, the medical literature, and the Drug Abuse Warning Network (DAWN) database do not suggest concerns related to abuse potential. They are not aware of any reports that oral selegiline, which was approved for marketing in 1989, has been used as the starting material for the synthesis of illegal amphetamines. Furthermore, they opine that because the process for converting selegiline to amphetamine is difficult, it is unlikely that transdermal selegiline would be used for this purpose.

C. DMETS

The Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety was consulted to evaluate the acceptability of the proposed tradename, Emsam.

DMETS responded on 1-24-02 (ODS Consult #00-0159-1). They had no objection to the use of the proprietary name Emsam. However, they did recommend some changes to the product packaging and labeling to minimize potential user error:

Patch Label

Printing the "EMSAM 20" image on the patch itself, as opposed to the removable protective backing, would increase visibility of the patch, making location of the patch and removal easier. (Postmarketing experience with clear transdermal patches has resulted in medication errors.)

Pouch Labeling

The phrase "upper torso" should be revised to [redacted] or "upper torso (below the neck and above the waist)" to facilitate patient understanding.

Carton Labeling

See the above comment regarding the Pouch Labeling.

If space permits, the use of an illustration for handling and applying the patch would enhance patient understanding.

Package Insert

Under PRECAUTIONS/Information for Patients:

- Information should be repeated at the end of the insert in accordance with 21 CFR 201.57(f)(2).
- See the above comment regarding an illustration.
- Increase the prominence of the statement "Do not apply to the same spot on consecutive days" in instruction 2.
- All instructions should be consistent with those on the Carton and Container.
- Increase the prominence of the phrase "Wash your hands" in instruction 6 and 9.

Under DOSAGE AND ADMINISTRATION:

- See the above comment regarding the Pouch Labeling.
- Include the "How to Use Emsam" section from PRECAUTIONS in this section.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics[4]

1. ADME

The selegiline patch formulation was developed to avoid the first-pass effect observed with oral selegiline, thereby producing higher plasma levels of parent drug and markedly reducing levels of the three primary metabolites. Also, the patch administration produces blood levels of drug that are sustained over the 24 hour dosing period.

The 20mg/20cm^2 patch formulation is designed to deliver about 5mg of the applied dose over a 24 hour period.

[4] The Office of Clinical Pharmacology and Biopharmaceutics review is pending completion at this time. The following information was obtained from the sponsor's summary of human pharmacokinetic data contained in the original submission (volume 1.1).

Steady state blood levels of selegiline are achieved in about 5 days. Average steady state trough levels of parent drug are approximately 2,200 pg/ml.

Continuous absorption of selegiline occurs throughout the 24 hour period of patch application. After patch removal, minimal residual drug remains in the skin, generally being non-detectable within 24 hours. After absorption, selegiline is distributed throughout the body, with rapid penetration into the CNS.

In terms of delivered doses, STS demonstrates dose proportionality. There is no evidence of dose dependent excretion or metabolism for transdermally administered selegiline.

At relevant concentrations and pH=7.4, the protein binding of selegiline is about 90%.

Metabolism appears to be the major route of elimination for selegiline. In vivo metabolism studies indicate the presence of three major metabolites of selegiline. After STS 20 mg/20cm^2 administration, R-(-)-methamphetamine is the principal metabolite followed by R-(-)-amphetamine and R-(-)-N-desmethylselegiline. The P450 isoenzymes involved are CYP3A4/5, CYP2B6, CYP2A6, and CYP2C9. The contribution of these metabolites to the overall antidepressant activity of selegiline delivered via STS is believed to be minimal.

Urinary excretion is a minor elimination pathway, accounting for only 0.1% of the applied dose.

2. Pharmacokinetics in Special Populations

In severe renal impairment (creatinine clearance <15 ml/min), there were no significant changes in the pharmacokinetics of selegiline and only minor alterations in the renal excretion of amphetamine and methamphetamine after STS. Since the metabolites lack appreciable pharmacologic activity, no dosage adjustments are likely to be needed in patients with moderate or severe renal impairment.

In eight patients with moderate liver disease (Child-Pugh class A or B) who were administered a single dose of STS 20mg/20cm^2, there were no apparent differences in either the

metabolism or pharmacokinetic behavior of selegiline or its metabolites compared to historical healthy volunteers.

No differences in the disposition of selegiline or its metabolites were noted in elderly patients.

Pharmacokinetic data in young healthy females was compared to that in males after either oral or transdermal selegiline. There were no appreciable differences.

STS dosing with 15mg/15cm^2 per day for 7 days in 12 pediatric subjects (ages 6-14) revealed no major differences in absorption, metabolism, or excretion of selegiline versus normal adult subjects except for some differences in very young subjects. Further studies are ongoing to fully characterize selegiline pharmacokinetics in young subjects.

3. In Vitro P450 Isozyme Inhibition

In vitro, both selegiline and N-desmethylselegiline produced a concentration dependent inhibition of CYP2D6 and CYP3A4/5 at 10 and 25 μM, respectively. At higher concentrations (>100 μM), CYP2C19 and CYP2B6 were also inhibited. Since these concentrations are 3-4 orders of magnitude higher than the concentrations seen clinically with STS (~0.01 μM), in vivo inhibition of cytochrome P450 is not expected.

4. In Vivo Drug-Drug Interaction Studies

A number of drug-drug interaction studies have been conducted. These are summarized below.

- selegiline did not alter the pharmacokinetics of alprazolam (a CYP3A4/5 substrate) and alprazolam did not affect the disposition of selegiline or its metabolites.
- STS had no effect on the pharmacokinetics of risperidone (a CYP2D6 substrate) or its 9-OH metabolite nor did risperidone affect the pharmacokinetics of selegiline.
- there appeared to be no interaction between STS and olanzapine, which is metabolized by CYP1A2 and CYP2D6 and possibly CYP2A6.
- ketoconazole, a potent CYP3A4/5 inhibitor, did not alter the pharmacokinetics of selegiline; there were minor changes in the pharmacokinetics of selegiline metabolites

(increases of 20-40%) which were not deemed to be clinically significant given their low potency relative to the parent drug.

- there was no interaction between STS and ibuprofen, a substrate for CYP2C9.
- S-warfarin is metabolized by CYP2C9 and R-warfarin by CYP3A4. In 10 anti-coagulated individuals, a 7 day course of STS 20mg/20cm^2 had no effect on the pharmacokinetics of either warfarin enantiomer. A minor increase (~2 units) was noted in INR values that was not felt to be clinically significant.
- there was no effect of STS on either the pharmacokinetics or pharmacodynamics of pseudoephedrine.
- single dose levothyroxine pharmacokinetics (measured by T_3 and T_4 levels) were unaffected by a 10 day course of STS 20mg/20cm^2. Levothyroxine did not affect the steady state pharmacokinetics of selegiline or its metabolites except for the Cmax values for N-desmethylselegiline.
- carbamazepine 200mg bid for 14 days and single dose STS produced slight increases in selegiline, amphetamine, and methamphetamine levels in most of 10 subjects, with marked effects in two subjects. There were no effects on N-desmethylselegiline. Changes in selegiline pharmacokinetics were less than 2-fold.
- there was no pharmacokinetic interaction between STS and alcohol. Also, selegiline had no effect on the pharmacodynamic actions of alcohol.
- chronic administration of STS 20mg/20cm^2 had no clinically meaningful effect on either the pharmacokinetics or pharmacodynamics of phenylpropanolamine.

B. Pharmacodynamics

The antidepressant mechanism of action of monoamine oxidase inhibitors is not precisely known. It was originally thought that inhibited breakdown and consequent accumulation of adrenergic amines in the neuron cytoplasm produced a therapeutic action. More recently, it has been discovered that after several weeks of treatment, MAOI's produce effects such as a reduction in the number of β-adrenergic receptors, α_1- and α_2-adrenergic receptors, and 5-HT_1 and 5-HT_2 receptors. These changes are similar to those produced by tricyclic and other antidepressants and

may play an important role in the therapeutic mechanism of MAOI's.[5]

MAO's are classified into two subtypes, MAO-A and MAO-B, depending on substrate specificity and tissue distribution. In humans, intestinal and liver MAO is primarily type A, which is responsible for the catabolism of exogenous amines found in food and drugs (e.g., tyramine). If such amines gain access to the systemic circulation in large amounts, they are taken up by adrenergic neurons and displace norepinephrine, which is then released, causing a hypertensive crisis or the so-called "cheese reaction." For this reason, the ingestion of foods and drugs with a high tyramine content are contraindicated with drugs that inhibit MAO-A.

MAO-B comprises most of the MAO of the brain, where it plays an important role in the catabolism of catecholamines (dopamine, norepinephrine, and epinephrine).

At low plasma levels, selegiline is considered a selective inhibitor of MAO-B. However, higher plasma levels inhibit both MAO-A and MAO-B based on studies of platelet MAO-B activity and urinary MHPG.[6] Current thinking is that an antidepressant effect requires inhibition of both MAO-A and MAO-B in the brain.

The administration of transdermal selegiline produces high plasma levels of drug capable of inhibiting both MAO-A and MAO-B in the brain but without inhibiting MAO-A in the intestine and liver. Thus, in theory, there is no need for food and drug restrictions.

The sponsor examined this issue by conducting a number of clinical studies of the cardiovascular safety of STS. These investigations evaluated the vasopressor effects of tyramine before and after treatment with selegiline delivered via STS, using fluoxetine and tranylcypromine as active controls. Other trials assessed changes in heart rate and blood pressure during treatment with STS given concurrently with sympathomimetic decongestants (pseudoephedrine and phenylpropanolamine) and intravenous

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[5] Krishnan K: Monoamine Oxidase Inhibitors in Textbook of Psychopharmacology. Edited by Schatzberg A and Nemeroff C. Washington, DC, American Psychiatric Press, 1995, pp 184-185.

[6] Platelet MAO activity is a surrogate marker for MAO-B activity and urinary MHPG is a surrogate marker for MAO-A activity.

cocaine. Finally, they point to data from about 1,100 patients who received therapy with STS in clinical trials in the absence of dietary restrictions.

The sponsor asserts that these data indicate that

IV. Description of Clinical Data and Sources

A. Overview of Clinical Data

The NDA clinical database derives from the sponsor's development program for the selegiline transdermal system (STS).

As of the original clinical cut-off date for the NDA (July 20, 2000), the STS clinical development program consisted of 36 Phase 1 studies conducted in healthy volunteers and 17 Phase 2/3 studies in patients.

A 120-Day Safety Update was submitted on September 26, 2001, with a cut-off date of December 31, 2000. This update reported limited data, generally serious adverse events and dropouts due to adverse events, from 6 ongoing studies that were included in the original NDA database as well as from an additional 5 new studies. These studies are not included in the enumerations in the following section.

Appendix 1 summarizes each of the 58 STS studies.

B. Patient Enumeration

1. Phase 1 Studies

Among the 36 Phase 1 studies, 9 were pharmacokinetic or bioavailability studies, 13 were drug interaction studies, 3 were studies in special populations, 10 were tyramine challenge trials, and 1 was an irritation and contact allergenicity study.

The 36 Phase 1 trials encompassed a total of 630 unique subjects exposed to STS. Of these, 469 unique subjects were exposed to STS 20mg/20cm^2. Subjects in Phase 1 studies are enumerated by type of study in Table IV-1 below.

TABLE IV-1: ENUMERATION OF PHASE 1 STUDY SUBJECTS		
Study Type	**Exposed to STS (Total)**	**Exposed to STS ($20mg/20cm^2$)**
Pharmacokinetic/ Bioavailability Studies	166	58
Drug Interaction Studies	156	156
Special Population Studies	32	20
Tyramine Challenge Studies	122	81
Irritation/Allergenicity Studies	154	154

2. Phase 2/3 Studies

There were 11 completed Phase 2/3 trials: 6 were conducted in patients with major depression, 2 in patients with Alzheimer's disease, and 1 study was performed in each of the following three indications: Parkinson's disease, HIV-associated cognitive impairment, and

Among the 6 completed trials in major depression, 4 were acute, multicenter, randomized, double-blind, placebo-controlled studies and 2 were open-label continuation trial of the acute studies.

The safety database for the pool of acute, controlled clinical studies in depression entails a total of 1,220 patients, 685 of whom received STS and 535 of whom received placebo. Among the 685 patients who received STS, 534 received a dose of $20mg/20cm^2$ and 151 received $10mg/20cm^2$.

A total of 533 patients participated in completed trials in indications other than major depression. STS was administered to a total of 374 patients and placebo to 159 patients. Various STS dosage forms were used in these studies. A total of 273 patients, all from the Alzheimer's studies, received STS $20mg/20cm^2$.

Table IV-2 below provides an enumeration of patients in the safety database for various categories of completed Phase 2/3 studies.

TABLE IV-2: ENUMERATION OF PATIENTS IN COMPLETED PHASE 2/3 TRIALS		
Indication/Study Type	**STS**	**Placebo**
DEPRESSION		
Acute, Controlled Trials	685	535
Open Label Studies	338	0
OTHER INDICATIONS		
Alzheimer's Disease	323	153
Parkinson's Disease	25	0
HIV Cognitive Impairment	9	5
[redacted]	17	1

C. Postmarketing Experience

There is no postmarketing experience with Selegiline Transdermal System (STS).

D. Literature Review

Searches of the published literature were conducted by Adis International using a number of databases, to include MedLine, EmBase, and Adis Base to identify all articles on selegiline from the year 1960 to May 2000. Four articles pertaining to studies using selegiline transdermal formulations were identified.[7] The sponsor reported no significant safety or efficacy findings from these trials.

V. Clinical Review Methods

A. Conduct of the Efficacy Review

The efficacy portion of this review was performed by examination of the four acute, placebo-controlled trials in major depression.

B. Overview of Materials Consulted in Review

Items examined during the course of the efficacy review are listed Appendix 2.

[7] Please see volume 1.557, pages 19-20, for a summary of these trials.

See section II. above for a listing of consultative sources of information that were utilized in this review.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Investigations (DSI) inspected three sites from studies in this NDA: sites 01 and 02 from study E106-96B and site 07 from study P9804. For each site, overall data were considered acceptable.

D. Adherence to Accepted Ethical Standards

Somerset Pharmaceuticals states that all sponsored studies were conducted within the United States in accordance with Good Clinical Practice guidelines. Also, the sponsor certifies that it did not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act.

E. Evaluation of Financial Disclosure

For all principal investigators in the four short-term, placebo-controlled efficacy studies in depression, the sponsor certifies that: 1) Somerset has not entered into any financial arrangement whereby investigator compensation could be affected by the outcome of the study as defined in 21 CFR 54.2(a), 2) any investigator required to disclose to the sponsor a proprietary interest in this product or a significant equity interest in the sponsor as defined in 21 CFR 54.2(b) has not disclosed any such interests, and 3) none was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

VI. Integrated Review of Efficacy

A. General Approach to the Review of Efficacy

Evidence to support the sponsor's claim of efficacy in patients with depression rests on four double-blind, placebo-controlled trials. These four studies are the focus of this efficacy review and are listed below.

1) Study E106-96B
2) Study E113-98B
3) Study P9804
4) Study E114-98B

B. Review of Efficacy Data from Adequate, Well-Controlled Studies

1. Study E106-96B

Investigators/Locations

This trial involved six sites, all in the U.S. Study investigators are listed below.

Site	Investigator
01	
02	
03	
04	
05	
06	

Objectives

The primary objective of this study was to assess the safety and efficacy of the Selegiline Transdermal System (STS) in patients with major depression.

Patient Sample

Study participants were male and female patients, ages 18-65, with DSM-IV major depressive disorder, either single episode or recurrent. Patients were required to have a score of 20 or greater on the first 17 items of the 28-item HAM-D at screening. A repeat HAM-D was performed at baseline and this score was not to be ≥20% below that obtained at screening.

Exclusionary criteria included the following:

- primary psychiatric illness other than major depression.
- history of mania or hypomania.
- lack of response of the current episode to two previous antidepressant trials.
- diet from which tyramine-containing foods could not be eliminated.
- psychotropic medication, including antidepressants, within 5 half-lives or 2 weeks, whichever was longer.
- ECT within 90 days.

• positive urine screen for cannabinoids, cocaine, barbiturates, or opiates.

Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel group trial designed to evaluate the safety and efficacy of STS (20mg/20cm^2), administered once daily, for 6 weeks in adult patients with major depression.

There were three study periods:

1) Pre-treatment period consisting of an initial screening visit (day -21 to -8), a visit to further assess study eligibility (day -7), and a baseline visit (day 1). At the day -7 visit, eligible patients began a 7 day single-blind placebo run-in to exclude early placebo responders. On day 1, patients still eligible were randomized in a 1:1 ratio to either STS or placebo.

2) Double-blind treatment period consisting of four visits (days 8, 15, 22, 29, and 43) at which safety, efficacy, and pharmacokinetic parameters were assessed.

3) Post-treatment period of one visit (day 59) for a follow-up safety assessment.

Efficacy measures (HAM-D, MADRS, and CGI) were obtained at baseline and at weeks 1, 2, 3, 4, and 6.

Treatment comprised identically appearing selegiline and placebo 20cm^2 patches. All patients were instructed to apply one patch daily at about the same time each day within a 6 hour window (6AM to 12 Noon). The skin area for application was to be cleaned with soap and warm water and dried before application. The patches were to be applied to the torso or upper arm and the application sites were to be rotated throughout the study.

The following were prohibited throughout the study: tyramine-rich foods, high protein food that has undergone protein breakdown (through aging, fermentation, pickling, smoking, or bacterial contamination), and excessive amounts

of caffeine and chocolate.[8] Patients were provided with dietary counseling and a dietary instruction sheet.

Analysis

The protocol-specified primary efficacy variable was the change from baseline in the first 17 items of the HAM-D ($HAM\text{-}D_{1\text{-}17}$) following 6 weeks of treatment. These data were analyzed using a General Linear Models (GLM) procedure that included baseline measurement, study site, and treatment group as well as a treatment-by-center interaction. If the latter interaction term was not significant, it was dropped from the model.

Other outcomes considered in this review are the change from baseline for the MADRS total score, the HAM-D depressed mood item (item #1), and the CGI change in severity of illness score (i.e., CGI improvement score). The MADRS was analyzed using a GLM procedure as for the $HAM\text{-}D_{1\text{-}17}$ score. The HAM-D depressed mood item and CGI improvement score were summarized as frequency distributions and analyzed as ranked data using the Cochran Mantel-Haenszel procedure controlling for center and baseline.

The sponsor presented efficacy analyses for three different groups of patients, as defined below.

1) Intent-to-Treat (ITT) Population: all randomized patients administered at least one dose of double-blind study drug.
2) Modified ITT Population: all randomized patients who had a baseline visit, received at least one dose of double-blind study drug, and had at least one on-treatment measurement of the primary efficacy variable ($HAM\text{-}D_{1\text{-}17}$).
3) Evaluable Population: patients who completed 6 weeks of therapy minus patients who had a significant protocol deviation. This is essentially a subset of the traditional observed cases dataset.

According to the study protocol, the primary efficacy analysis was to be based on the Evaluable Population.

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[8] Tyramine-rich foods included cheese, wine, liquor, beer, raisins, pickled herring, liver, yeast extract, dry sausage, pods of broad beans, sauerkraut, and yogurt.

ICH guidance states that decisions concerning the analysis set should be guided by two principles: 1) minimization of bias and 2) avoidance of Type I error inflation.[9] Since an analysis of the Evaluable Population, as defined above, is prone to bias (e.g., by virtue of excluding protocol violators and dropouts), it is not felt to be a suitable dataset for the primary efficacy analysis. The use of the ITT population, as defined above, is also felt to be unsuitable since it would include patients missing a baseline HAM-D_{1-17} score or without any on-therapy HAM-D_{1-17} scores. A measurement of the improvement of such patients on the primary efficacy variable is impossible. The only reasonably suitable patient sample for the efficacy analysis is the modified ITT.

I feel that these considerations take precedence over the dataset designation stated in the study protocol. Thus, this review will consider the modified ITT population as the primary efficacy dataset.

A statistically significant difference between treatment groups was declared if the 2-sided p-value was less than or equal to 0.05.

Baseline Demographics

Baseline demographic characteristics are displayed in Appendix 3.

A comparison of the STS and placebo treatment groups by mean age, gender, and race revealed no significant differences.

Baseline Severity of Illness

At baseline, the mean HAM-D_{1-17} score in the STS group was 22.9 (range 20-28) and in the placebo group 23.3 (range 20-35). The maximum score on the HAM-D_{1-17} is 52.

A comparison of the STS and placebo treatment groups at baseline on the mean HAM-D_{1-17} total score and MADRS total score revealed no statistically significant differences (α=0.10).

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[9] See section V.(B.) of ICH Guidance for Industry E9, Statistical Principles for Clinical Trials.

Patient Disposition

This study randomized 177 patients to either STS (N=89) or placebo (N=88). Of these, 88 in each treatment group were included in the modified ITT; one STS patient dropped out of the trial prior to providing any on-therapy data.

A total of 79 STS patients and 74 placebo patients from the modified ITT completed 6 weeks of double-blind therapy (90% and 84% of the modified ITT, respectively). The most frequently reported reason for premature discontinuation was lack of efficacy (6% among STS and 10% of placebo patients).

Protocol Violations

Protocol violations were found for 10 STS patients and 14 placebo patients.[10] These deviations were reviewed and it is considered unlikely that they significantly biased the efficacy results in favor of STS.

Concomitant Medications

At least one concomitant medication was taken during the course of this study by 67 STS patients (76% of the modified ITT) and 62 placebo patients (70%). The most commonly used medication was the analgesic acetaminophen, taken by about 16% of all patients.

One STS patient (2202) did take sertraline for depression during double-blind treatment with STS. The patient started STS therapy and began taking sertraline 50mg qday about 2 weeks later. The patient withdrew consent for study participation and discontinued STS about 2 weeks after starting sertraline. There was also one patient in the placebo group who used sertraline during the study.

It is unlikely that these uses significantly biased the efficacy results of the trial.

Efficacy Results

Efficacy findings on the HAM-D_{1-17} total score, MADRS total score, HAM-D depressed mood item, and CGI improvement score are displayed in Appendices 4, 5, 6, and 7, respectively.

[10] These patients are listed in Supplemental Table 10.1 of the study report.

Mean decreases from baseline on the HAM-D_{1-17} total score, the primary efficacy variable, were significantly greater for the STS group over placebo from week 1 onward in both LOCF and OC analyses except for week 4 in the OC analysis, where there was a strong trend favoring STS (p=0.058).

STS was superior to placebo on the MADRS total score from week 1 onward in both LOCF and OC analyses. The difference at week 6 was highly statistically significant (p=0.005).

A comparison of the distributions of HAM-D depressed mood item scores at week 6 revealed a statistically significant shift toward lower scores for STS over placebo in both LOCF and OC analyses.

Likewise, the distributions of CGI improvement scores at week 6 indicated a significant shift toward lower scores favoring STS over placebo for both LOCF and OC analyses.

Conclusions

Study E106-96B provides solid evidence for the antidepressant efficacy of STS over placebo at a dose of 20mg/20 cm^2 daily for 6 weeks.

2. Study E113-98B

Investigators/Locations

This trial involved 13 sites, all in the U.S. Study investigators are listed below.

Site	Investigator
01	
02	
03	
04	
05	
06	
07	
08	
09	
10	
11	
12	
25	

Objectives

The objective of this study was to assess the safety and efficacy of STS in patients with major depression.

Patient Sample

Study participants were ages 18-65, with DSM-IV major depressive disorder, either single episode or recurrent. Patients were required to have a score of 20 or greater on the first 17 items of the HAM-D. A repeat HAM-D was performed at baseline and this score was not to be more than 20% below that obtained at screening. Females of childbearing potential were required to have a negative serum pregnancy test at screening and to agree to use medically acceptable birth control during the trial.

Exclusionary criteria included the following:

- primary psychiatric illness other than major depression.
- history of mania or hypomania.
- clinically significant finding on physical examination, laboratory test, or ECG.
- clinically significant medical disease or illness.
- lack of response of the current episode to two previous antidepressant trials.
- most psychotropic medication within 5 half-lives or 2 weeks, whichever was longer; fluoxetine within 5 weeks; oral neuroleptics within 45 days; MAOI's within 2 months; or IM neuroleptics within 10 weeks.
- ECT within 90 days.
- positive urine screen for cocaine, barbiturates, opiates, amphetamines, cannabinoids, or benzodiazepines at the screening visit.

Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel group trial designed to evaluate the safety and efficacy of STS ($20mg/20cm^2$), administered once daily, for 8 weeks in adult patients with major depression.

This study consisted of a 3-week pre-treatment period and an 8-week double-blind treatment period.

1) The pre-treatment period consisting of an initial screening visit (day -21 to -8), a visit to further assess study eligibility (day -7), and a baseline visit (day 1). At the day -7 visit, eligible patients began a 7 day single-blind placebo run-in. On day 1, patients still eligible were randomized in a 1:1 ratio to either STS or placebo.

2) The treatment period consisting of five visits (days 8, 15, 29, 43, and 57) at which safety, efficacy, and pharmacokinetic parameters were assessed.

Efficacy measures (HAM-D, MADRS, and CGI) were obtained at baseline and at weeks 1, 2, 4, 6, and 8.

Treatment comprised identically appearing selegiline and placebo $20cm^2$ patches. All patients were instructed to apply one patch daily at the same time each day within a 4 hour window (8AM to 12 Noon). The skin area for application was to be cleaned with soap and warm water and dried before application. The patches were to be applied to the torso or upper arm and the application sites were to be rotated throughout the study.

Analysis

The protocol-specified primary efficacy variable was the change from baseline in the first 17 items of the HAM-D ($HAM\text{-}D_{1\text{-}17}$) following 8 weeks of treatment. These data were analyzed using ANCOVA with treatment and center as main effects and baseline $HAM\text{-}D_{1\text{-}17}$ as a covariate. The treatment-by-center interaction term was computed and if it was not significant ($p>0.10$), it was dropped from the model.

Other outcomes considered in this review are the change from baseline for the MADRS total score, the HAM-D depressed mood item (item #1), and the CGI change in severity of illness score (i.e., CGI improvement score). The MADRS was analyzed using ANCOVA as for the $HAM\text{-}D_{1\text{-}17}$ score. The HAM-D depressed mood item and CGI improvement score were summarized as frequency distributions and analyzed using the Cochran Mantel-Haenszel test controlling for center and baseline scores.

The study protocol, including Amendment 2, states that the efficacy analysis would be performed on the following two patient groups:

1) Intent-to-Treat (ITT) group: all randomized patients who took at least one dose of study drug and had at least one post-baseline measurement of the primary efficacy variable ($HAM\text{-}D_{1\text{-}17}$).
2) Evaluable group: all ITT patients who met all inclusion criteria and had no significant exclusion criteria present.

Neither group was designated as the primary group for the efficacy analysis.

It is notable that the final Clinical Study Report defines slightly different patient populations:

1) Intent-to-Treat (ITT) Population: all randomized patients who took at least one dose of double-blind drug.
2) Modified (ITT) Population: all randomized patients who took at least one dose of double-blind study drug and had at least one on-treatment measurement of the primary efficacy variable ($HAM\text{-}D_{1\text{-}17}$).
3) Evaluable Population: all modified ITT patients who met all inclusion criteria, had no significant exclusion criteria present, had no influential protocol deviations, and completed the study.

It should be noted that the ITT group, as defined in the protocol, corresponds to modified ITT population, as defined in the Clinical Study Report.

Based on the considerations discussed in the analysis section of Study E106-96B above, this review will consider the modified ITT to be the primary population for efficacy analysis.

A statistically significant difference between treatment groups was declared if the 2-sided p-value was less than or equal to 0.05.

Baseline Demographics

Baseline demographic characteristics are displayed in Appendix 8.

A comparison of the STS and placebo treatment groups by mean age, gender, and race revealed no significant differences.

Baseline Severity of Illness

At baseline, the mean HAM-D_{1-17} score in the STS group was 23.00 (range 17-32) and in the placebo group 22.80 (range 17-33).

A comparison of the STS and placebo treatment groups at baseline on the mean HAM-D_{1-17} total score and MADRS total score revealed no statistically significant differences (α=0.10).

Patient Disposition

A total of 453 patients were screened for this trial. This study randomized 297 patients to either STS (N=147) or placebo (N=150). Of these, 137 STS patients and 146 placebo patients were included in the modified ITT.

A total of 104 STS patients and 112 placebo patients from the modified ITT completed 8 weeks of double-blind therapy (76% and 77% of the modified ITT, respectively). The most frequently reported reason for premature discontinuation in both treatment groups was loss to follow-up (10% of STS and 9% of placebo patients).

Protocol Violations

Protocol violations were found for 33 STS patients and 29 placebo patients.[11] These deviations were reviewed and it is considered unlikely that they significantly biased the efficacy results in favor of STS.

Concomitant Medications

At least one concomitant medication was taken during the course of this study by 110 STS patients (80% of the modified ITT) and 105 placebo patients (72%). The most commonly used medications were acetaminophen and ibuprofen, each taken by about 20% of all patients.

[11] These patients are listed in Supplemental Table 10.1 of the study report.

No concomitant antidepressant medication was reported during double-blind treatment in this study.

Efficacy Results

Efficacy findings on the HAM-D_{1-17} total score, MADRS total score, HAM-D depressed mood item, and CGI improvement score are displayed in Appendices 9, 10, 11, and 12, respectively.

Mean decreases from baseline on the HAM-D_{1-17} total score were not significantly greater for the STS group over placebo at any timepoint in either LOCF or OC analyses. In fact, mean decreases in the placebo group were numerically greater than those in the STS group and, at week 4, significantly so.

Similarly, STS was not statistically superior to placebo on mean decreases in the MADRS total score at any timepoint in either LOCF or OC analyses. Again, mean decreases in the placebo group tended to be numerically greater than those in the STS group and, at week 2, significantly so.

A comparison of the distributions of HAM-D depressed mood item scores at week 8 revealed no statistically significant shift toward lower scores for STS over placebo in either LOCF or OC analyses.

Likewise, the distributions of CGI improvement scores at week 8 indicated no significant shift favoring STS over placebo.

Conclusions

Study E113-98B did not demonstrate antidepressant efficacy of STS over placebo at a dose of 20mg/20 cm^2 daily for 8 weeks.

3. Study P9804

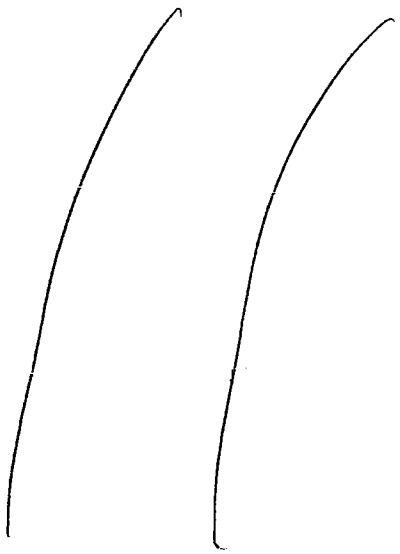
Investigators/Locations

This trial involved a total of 16 sites, all in the U.S. Safety and efficacy data from one site (site 12) could not be audited because all records for this investigator, Dr. [redacted]. Data from the 9 randomized patients at this

site were excluded by the sponsor from most safety and all efficacy analyses.

Investigators for the remaining 15 sites are listed below.

Site	Investigator
01	
02	
03	
04	
05	
06	
07	
08	
10	
11	
25	
26	
27	
28	
29	



Objectives

The objective of this study was to evaluate the safety and efficacy of STS in patients with major depression.

Patient Sample

Study participants were ages 18-65, with DSM-IV major depressive disorder, either single episode or recurrent. Patients were required to have a score of 20 or greater on the first 17 items of the HAM-D. A repeat HAM-D was performed at baseline and this score was not to be more than 20% below that obtained at screening. Females of childbearing potential were required to have a negative serum pregnancy test at screening and to agree to use medically acceptable birth control during the trial.

Exclusionary criteria included the following:

- primary psychiatric illness other than major depression.
- history of mania or hypomania.
- clinically significant finding on physical examination, laboratory test, or ECG.

- clinically significant medical disease or illness.
- lack of response of the current episode to two previous antidepressant trials.
- most psychotropic medication within 5 half-lives or 2 weeks, whichever was longer; fluoxetine within 5 weeks; oral neuroleptics within 45 days; MAOI's within 2 months; or IM neuroleptics within 10 weeks.
- ECT within 90 days.
- positive urine screen for cocaine, barbiturates, opiates, amphetamines, cannabinoids, or benzodiazepines at the screening visit.

Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel group trial designed to evaluate the safety and efficacy of STS ($20mg/20cm^2$), administered once daily, for 8 weeks in adult patients with major depression.

This study consisted of a 3-week pre-treatment period and an 8-week double-blind treatment period.

1) The pre-treatment period consisting of an initial screening visit (day -21 to -8), a visit to further assess study eligibility (day -7), and a baseline visit (day 0). At the day -7 visit, eligible patients began a 7 day single-blind placebo run-in. After the baseline evaluation, patients still eligible were randomized in a 1:1 ratio to either STS or placebo.

2) The treatment period consisting of five visits (days 8, 15, 29, 43, and 57) at which safety, efficacy, and pharmacokinetic parameters were assessed.

Efficacy measures (HAM-D, MADRS, and CGI) were obtained at baseline and at weeks 1, 2, 4, 6, and 8.

Treatment comprised identically appearing selegiline and placebo $20cm^2$ patches. All patients were instructed to apply one patch daily at the same time each day within a 4 hour window (8AM to 12 Noon). The skin area for application was to be cleaned with soap and warm water and dried before application. The patches were to be applied to the torso or upper arm and the application sites were to be rotated throughout the study.

Analysis

The protocol-specified primary efficacy variable was the change from baseline in the first 17 items of the HAM-D ($HAM\text{-}D_{1\text{-}17}$) following 8 weeks of treatment. These data were analyzed using ANCOVA with treatment and center as main effects and baseline measurement and age as covariates.[12] The treatment-by-center interaction term was computed and if it was not significant ($p>0.10$), it was dropped from the model.

Other outcomes considered in this review are the change from baseline for the MADRS total score, the HAM-D depressed mood item (item #1), and the CGI change in severity of illness score (i.e., CGI improvement score). The MADRS was analyzed using ANCOVA as for the $HAM\text{-}D_{1\text{-}17}$ score. The HAM-D depressed mood item and CGI improvement score were summarized as frequency distributions and analyzed using the Cochran Mantel-Haenszel test controlling for center and baseline scores.

The study protocol (including Amendment 1 dated 1-15-99) defined two patient populations for efficacy analysis:

1) Intent-to-Treat (ITT) group: all randomized patients who took at least one dose of study drug and had at least one post-baseline measurement of the primary efficacy variable ($HAM\text{-}D_{1\text{-}17}$).
2) Evaluable group: all ITT patients who met all inclusion criteria and had no significant exclusion criteria present.

Neither group was designated as the primary group for efficacy analysis.

It is of note that the final Clinical Study Report defines slightly different patient populations:

1) Intent-to-Treat (ITT) Population: all randomized patients administered at least one dose of double-blind drug.

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[12] It is noted that the original protocol for this study provided for the inclusion of covariates that were significantly different between treatment groups at baseline. There was a significant difference in age at the 0.10 alpha level ($p=0.073$). However, amendment 1 to the protocol removed this provision. Nonetheless, the sponsor did include age as a covariate in the final efficacy analyses.

2) Modified (ITT) Population: all randomized patients administered at least one dose of double-blind study drug and with at least one on-treatment measurement of the primary efficacy variable ($HAM\text{-}D_{1\text{-}17}$).
3) Evaluable Population: all modified ITT patients who met all inclusion criteria, had no significant exclusion criteria present, had no significant protocol deviations, and completed the study.

It should be noted that the ITT group, as defined in the protocol, corresponds to modified ITT population, as defined in the Clinical Study Report.

A protocol amendment presenting these new definitions could not be found.[13] Hence, it is possible that these definitions were established sometime after completion and unblinding of the trial.

Based on the considerations outlined in the analysis section of Study E106-96B above, this review will consider the modified ITT to be the primary population for efficacy analysis.

A statistically significant difference between treatment groups was declared if the 2-sided p-value was less than or equal to 0.05.

The sponsor indicated that exclusion of the 9 patients at site 12 (see above) did not affect the original power calculation for this study since 9 additional patients were enrolled at other sites.

Baseline Demographics

Baseline demographic characteristics are displayed in Appendix 13.

A comparison of the STS and placebo treatment groups by mean age, gender, and race revealed a statistically significant difference only for mean age at baseline: 41.2 (SD=11.6) years in the STS group and 43.5 (SD=10.0) years in the placebo group (p=0.073). It is doubtful that this difference has clinical significance. Nevertheless, the

[13] A phone call from the sponsor's Director of Regulatory Affairs, Melissa Goodhead, on 2-13-02 confirmed that Amendment 1 was the only amendment to the study protocol.

sponsor did include age as a covariate in the statistical model.

Baseline Severity of Illness

At baseline, the mean HAM-D_{1-17} score in the STS group was 22.8 (range 16-34) and in the placebo group 22.9 (range 17-32).

A comparison of the STS and placebo treatment groups at baseline on the mean HAM-D_{1-17} total score and MADRS total score revealed no statistically significant differences (α=0.10).

Patient Disposition

This study screened 365 patients and randomized 310 patients to either STS (N=153) or placebo (N=157). Of these, 145 STS patients and 144 placebo patients were included in the modified ITT.

A total of 106 STS patients and 109 placebo patients from the modified ITT completed 8 weeks of double-blind therapy (73% and 76% of the modified ITT, respectively). The most frequently reported reason for premature discontinuation in the STS group was loss to follow-up (12% of STS patients). Placebo patients most frequently dropped out for loss to follow-up or withdrawn consent (almost 7% each).

Protocol Violations

Protocol violations were noted for 63 patients (27 randomized to selegiline and 36 to placebo).[14] These deviations were reviewed and it is considered unlikely that they significantly biased the efficacy results in favor of selegiline.

Concomitant Medications

At least one concomitant medication was taken during the course of this study by 112 STS patients (77% of the modified ITT) and 124 placebo patients (86%). The most commonly used medications were ibuprofen and acetaminophen, taken by approximately 20% of all patients.

[14] These patients are listed in Supplemental Table 10.1 of the study report.

Concomitant antidepressant medication was taken by two placebo patients during double-blind treatment: Patient 1105 began amitriptyline for back pain 3 days before dropping out at week 4 and Patient 1109 began sertraline 10 days before dropping out at week 3.

Neither usage is likely to have biased the study results in favor of selegiline.

Efficacy Results

Efficacy findings on the HAM-D_{1-17} total score, MADRS total score, HAM-D depressed mood item, and CGI improvement score are displayed in Appendices 14, 15, 16, and 17, respectively.

Mean decreases from baseline on the primary efficacy variable, the HAM-D_{1-17} total score, were not significantly different between treatment groups up to and including week 6. At week 8, there was only a trend for superiority of STS over placebo in both LOCF and OC analyses.

STS was superior to placebo on mean changes in the MADRS total score at weeks 4, 6, and 8 in both LOCF and OC analyses. The differences at week 8 were highly statistically significant ($p=0.001$).

A comparison of the distributions of the HAM-D depressed mood item scores at week 8 revealed a statistically significant shift toward lower scores for STS over placebo in the OC analysis with a trend toward a significant difference in the LOCF analysis. There were no significant differences at earlier visits.

The distributions of CGI improvement scores at weeks 6 and 8 indicated a trend favoring STS over placebo in the OC analysis; there were no significant differences or trends in the LOCF analysis at any visit.

Conclusions

Study P9804 failed to demonstrate statistical superiority for STS over placebo on the protocol-specified primary efficacy variable for the modified ITT. Thus, this study must be considered negative despite the superiority demonstrated on the MADRS total score, a secondary variable.

4. Study E114-98B

Investigators/Locations

This trial involved 19 sites, all in the U.S. Study investigators are listed below.

Site	Investigator
01	
02	
03	
04	
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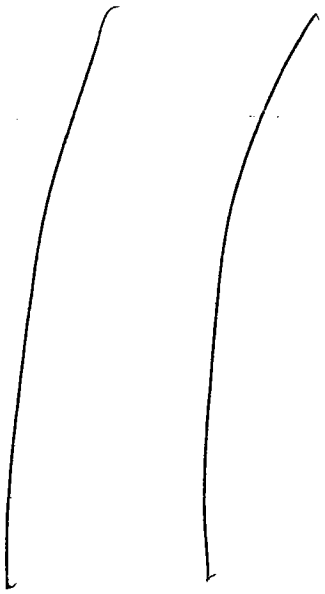

Objectives

The objective of this study was to assess the safety and efficacy of two fixed doses of STS in patients with major depression.

Patient Sample

Study participants were ages 18-65, with DSM-IV major depressive disorder, either single episode or recurrent. Patients were required to have a score of 20 or greater on the first 17 items of the HAM-D and a baseline HAM-D that was not more than 20% below the score at screening. Females of childbearing potential were required to have a negative serum pregnancy test at screening and to agree to use medically acceptable birth control during the trial.

Exclusionary criteria included the following:

- primary psychiatric illness other than major depression.
- history of mania or hypomania.
- clinically significant finding on physical examination, laboratory test, or ECG.
- clinically significant medical disease or illness.
- lack of response of the current episode to two previous antidepressant trials.
- most psychotropic medication within 5 half-lives or 2 weeks, whichever was longer; fluoxetine within 5 weeks; oral neuroleptics within 45 days; MAOI's within 2 months; or IM neuroleptics within 10 weeks.
- ECT within 90 days.
- positive urine screen for cocaine, cannabinoids, amphetamines, benzodiazepines, barbiturates, or opiates at the screening visit.

Design

This was a randomized, double-blind, placebo-controlled, parallel group study.

After screening, patients entered a one-week, single-blind placebo run-in to exclude early placebo responders (Days -7 to -1).

Thereafter, patients underwent a baseline evaluation (Day 1) and were randomized to one of three treatment groups: selegiline 20mg/20cm^2, selegiline 10mg/20 cm^2, or placebo/ 20 cm^2. All were administered as identically-appearing transdermal patches. This treatment was administered once daily for 8 weeks under double-blind conditions.

Efficacy measures (HAM-D, MADRS, and CGI) were obtained at baseline and at weeks 1, 2, 4, 6, and 8.

All patients were instructed to apply one patch daily at the same time each day within a 4 hour window (8AM to 12 Noon). The skin area for application was to be cleaned with soap and warm water and dried before application. The patches were to be applied to the torso or upper arm and the application sites were to be rotated throughout the study.

Analysis

The protocol-specified primary efficacy variable was the change from baseline in the first 17 items of the HAM-D ($HAM\text{-}D_{1\text{-}17}$) following 8 weeks of treatment. These data were analyzed using ANCOVA with treatment and center as main effects and significant baseline measurements as covariates. Linear contrasts were utilized to assess the difference between each dose group and placebo as well as between the two active doses; no multiple comparison adjustments were made. The treatment-by-center interaction term was computed and if it was not significant ($p>0.10$), it was dropped from the model.

Other outcomes considered in this review are the change from baseline for the MADRS total score, the HAM-D depressed mood item (item #1), and the CGI change in severity of illness score (i.e., CGI improvement score). The MADRS was analyzed using ANCOVA as for the $HAM\text{-}D_{1\text{-}17}$ score. The HAM-D depressed mood item and CGI improvement score were summarized as frequency distributions and analyzed using the Cochran Mantel-Haenszel test controlling for center and baseline scores.

The study protocol defined two patient populations for efficacy analysis:

1) Intent-to-Treat (ITT) group: all randomized patients who took at least one dose of study drug and had at least one post-baseline measurement of the primary efficacy variable ($HAM\text{-}D_{1\text{-}17}$).
2) Evaluable group: all ITT patients who met all inclusion criteria and had no significant exclusion criteria present.

Neither group was designated as the primary group for efficacy analysis.

It is of noteworthy that the final Clinical Study Report defines slightly different patient populations:

1) Intent-to-Treat (ITT) Population: all randomized patients who were dispensed double-blind therapy.
2) Modified (ITT) Population: all randomized patients who took at least one dose of double-blind study medication and had at least one on-treatment measurement of the primary efficacy variable ($HAM\text{-}D_{1\text{-}17}$).

3) Evaluable Population: all modified ITT patients who met all inclusion criteria, had no significant exclusion criteria present, and had no influential protocol deviations.

It should be noted that the ITT group, as defined in the protocol, corresponds to modified ITT population, as defined in the Clinical Study Report.

Based on the considerations outlined in the analysis section of Study E106-96B above, this review will consider the modified ITT to be the primary population for efficacy analysis.

A statistically significant difference between treatment groups was declared if the 2-sided p-value was less than or equal to 0.05.

Baseline Demographics

Baseline demographic characteristics are displayed in Appendix 18.

Statistical evaluation of the homogeneity among the three treatment groups at baseline was performed for mean age, gender, and race. This revealed no statistically significant differences.

There was a statistically significant difference in mean body weight among the groups (84kg in the STS 20mg group, 77kg in the STS 10mg group, and 81kg in the placebo group) (p=0.011).

Baseline Severity of Illness

At baseline, the mean HAM-D_{1-17} scores were comparable among the three treatment groups: 23.30 in the STS 20mg group, 22.73 in the STS 10mg group, and 23.06 in the placebo group.

Statistical comparisons of the three treatment groups at baseline for the mean HAM-D_{1-17} total score and MADRS total score revealed no significant differences (α=0.10).

Patient Disposition

This study screened 651 patients and randomized 446 patients to STS 20mg (N=149), STS 10mg (N=151), or placebo (N=146). Of these, the modified ITT included 142 patients in the STS 20mg group, 151 in the STS 10mg group, and 142 in the placebo group.

About three-fourths of the modified ITT patients in each group completed 8 weeks of double-blind therapy (77% of the STS 20mg group, 74% of the STS 10mg group, and 77% of the placebo group). The most frequently reported reason for premature discontinuation was adverse events in the STS 20mg group (11%) and lack of efficacy in the STS 10mg group (9%).

Protocol Violations

Protocol violations were noted for 80 patients (27, 27, and 26 patients randomized to STS 20mg, STS 10mg, and placebo, respectively).[15] These deviations were reviewed and it is considered unlikely that they significantly biased the efficacy results in favor of selegiline.

Concomitant Medications

At least one concomitant medication was taken during the course of this study by 127 STS 20mg patients, 123 STS 10mg patients, and 121 placebo patients. The most commonly used medication was acetaminophen.

Concomitant antidepressant medication was reportedly taken by three patients during this trial: sertraline by one STS 10mg patient, paroxetine by one placebo patient, and fluoxetine by one placebo patient. Additionally, selegiline was taken by one patient in the placebo group for treatment of depression.

These uses are unlikely to have biased the study results in favor of selegiline.

Efficacy Results

Efficacy findings on the HAM-D_{1-17} total score, MADRS total score, HAM-D depressed mood item, and CGI improvement score

[15] These patients are listed in Supplemental Table 10.1 of the study report.

are displayed in Appendices 19, 20, 21, and 22, respectively.

Overall comparisons among the three treatment groups were not statistically significant at any timepoint for any variable in either the LOCF or OC analysis. There was a very weak trend for superiority of the 20mg dose at week 6 (LOCF) on the MADRS total score (p=0.097).

Pairwise comparisons (not shown in the Appendices) revealed only borderline significant findings favoring the 20mg dose over placebo at weeks 6 and 8 on the MADRS and at week 8 on the CGI improvement score, all with the LOCF analysis (p= 0.052, 0.051, and 0.048, respectively). Pairwise comparisons require a multiplicity correction. After such adjustment, these p-values do not reach a level of statistical significance.

Conclusions

Study E114-98B did not demonstrate an antidepressant effect of STS with either the 20mg/20cm^2 dose or the 10mg/20cm^2 dose.

C. Summary of Data Pertinent to Important Clinical Issues

1. Predictors of Response

The sponsor performed subgroup analyses to examine the effects of demographic variables (age, race, gender) as well as baseline severity of illness on the antidepressant response to STS relative to placebo.

The following subgroups were defined:

Gender:	Male vs. Female
Age:	≤40 years vs. >40 years
Race:	White vs. Non-white
Baseline Severity:	HAM-D_{1-17} total score ≤23 vs. >23

Antidepressant response was considered to be the mean change from baseline to final efficacy assessment for the HAM-D_{1-17} total score. This subgroup analysis was applied to

all intent-to-treat patients for the pool of studies E106-96B and P9804.[16]

Data are displayed in Appendix 23. A comparison of the placebo-adjusted antidepressant response between subgroups for each variable revealed no clinically important differences.

2. Size of Treatment Effect

The placebo-adjusted mean change from baseline in the HAM-D_{1-17} total score among STS patients in study E106-96B was -2.63 units (LOCF). This is comparable to changes observed in clinical trials with other approved antidepressant agents.

3. Choice of Dose

All four controlled efficacy trials included a fixed 20mg/20cm^2 dose arm; study E114-98B also incorporated a fixed 10mg/20cm^2 dose arm.

Antidepressant efficacy was demonstrated for the 20mg/20cm^2 transdermal patch only in study E106-96B. Study E114-98B did not demonstrate efficacy for the 10mg/20cm^2 transdermal patch.

4. Duration of Treatment

The one positive efficacy trial, E106-96B, was 6 weeks in duration. Antidepressant efficacy of STS was not demonstrated in the three 8 week trials.

Efficacy studies longer than 8 weeks have not been completed. However, a relapse prevention trial, P9806, is currently ongoing. This trial consists of a 10 week open-label run-in with STS 20mg/20cm^2 followed by randomization of responders to continued drug or placebo for an additional 52 weeks of double-blind treatment.

D. Efficacy Conclusions

Appendix 24 summarizes the efficacy results for the four placebo-controlled efficacy trials in depression at the final visit of the double-blind treatment period for the

[16] These two studies were originally identified by the sponsor as positive efficacy trials.

modified ITT population. At least 70% of the modified ITT populations remained in-study at final visit in each trial.

Study E106-96B was clearly positive, demonstrating superiority of STS over placebo at endpoint for the primary efficacy variable (HAM-D_{1-17} total score) as well as for three other selected secondary variables (MADRS total score, HAM-D item #1, and CGI improvement score).

Studies P9804, E113-98B, and E114-98B did not show superiority of STS over placebo on the protocol-specified primary efficacy measure (HAM-D_{1-17} total score) in the modified ITT populations. Thus, these trials must be considered negative.

In summary, the positive results of a single trial, study E106-96B, do not provide adequate evidence to support the approval of STS for the treatment of major depression.

VII. Integrated Review of Safety

Please see the separate Safety Review.

VIII. Dosing, Regimen, and Administrative Issues

It is not known whether STS doses higher than 20 mg/20cm^2 would be effective or entail a substantially different safety profile.

The following are important issues in using STS patches:

- the application site should be clean and dry.
- application sites should be rotated on a frequent basis.
- heat should not be applied to the patch.
- patches should not be worn for longer than 24 hours.
- patches should be appropriately discarded to prevent the accidental ingestion of residual drug by small children or animals.

IX. Use in Special Populations

A. Gender Effects

There appears to be no effect of gender on antidepressant efficacy measures.

B. Age and Race Effects

There appears to be no effect of age or race on the efficacy measures in depression.

C. Pediatric Program

To date, no studies of the safety and efficacy of STS in the treatment of pediatric patients with major depression have been completed.

Major depression is a common psychiatric condition in children and adolescents. Also, antidepressant efficacy in adults cannot be reliably extrapolated to the pediatric population. Therefore, prior to approval, the sponsor should provide a Phase 4 commitment to complete [redacted] Phase 3 studies of STS in pediatric patients with this disorder.

X. Labeling Review

Since a non-approvable action is recommended, no labeling review was performed.

XI. Conclusions and Recommendations

A. Conclusions

Efficacy evidence is insufficient to support the approval of Selegiline Transdermal System 20mg/20cm^2 for the treatment of major depression.

Completion of the clinical Safety Review is pending at this time.

B. Recommendations

A non-approvable action is recommended based on an inadequate demonstration of efficacy.

It is recommended that the following comments be conveyed to the sponsor:

1) If Selegiline Transdermal System is approved for major depression in the future, the following commitments will be requested: a) to evaluate safety and efficacy in pediatric

patients and b) to submit the results of a longer term relapse prevention trial (such as P9806).

Gregory M. Dubitsky, M.D.
February 28, 2002

cc: NDA #21-336
HFD-120 (Division File)
HFD-120/GDubitsky
/AMosholder
/TLaughren
/DBates

XII. APPENDICES

APPENDIX 1: TABLE OF ALL STUDIES	
Study Type/ Study Number	**Study Description**
PHASE 1 STUDIES	
PHARMACOKINETIC AND BIOAVAILABILITY STUDIES	
S9303-028-95B	Single-dose, 3-way crossover study in 12 males and 12 females, ages 54-76; STS doses = 0.5mg/10cm^2, 10mg/10cm^2, and 15mg/10cm^2.
S9303-029-95B	Parallel group study in 24 males and 24 females, ages 55-77, of one of four daily doses of STS administered for 7 days: 5mg/10cm^2, 10mg/10cm^2, 15mg/10cm^2, or 22.5mg/15cm^2.
S9303-030-95B	Multiple dose, parallel group study in 24 males, ages 19-36, of one of three doses of STS: 5mg/10cm^2, 10mg/10cm^2, or 15mg/10cm^2.
S9303-031-95B	Multiple dose, parallel group study in 18 males, ages 55-78, of one of three daily doses of STS administered for 10 days: 20mg/20cm^2, 30mg/20cm^2, or 7.5mg/5cm^2.
S9303-035-96B	Single dose study in 12 males, ages 18-34, of STS 20mg/20cm^2.
S9303-P9807	Multiple dose, two-way crossover study in 10 males, ages 21-37, of STS 10mg/20cm^2 or STS 20mg/20cm^2, each dose given daily for 10 days.
S9303-P9808	Single dose study in 6 males and 4 females, ages 19-42, of STS 20mg/20cm^2.
S9303-P9809	Single dose, three-way crossover study in 13 males, ages 21-40, of STS 20mg/20cm^2, oral selegiline 10mg, and IV selegiline 10mg/24 hours.
S9303-P9923	Multiple dose, two-way crossover study in 12 males, ages 21-40, of STS 10mg/20cm^2 and 20mg/20cm^2, each dose given daily for 10 days.

APPENDIX 1: TABLE OF ALL STUDIES	
Study Type/ Study Number	**Study Description**
DRUG INTERACTION STUDIES	
S9303-P9919	Warfarin titrated to INR (days 1-10), then maintenance dose (days 11-21) and STS 20mg/20cm^2 per day (days 15-21); in 13 males, ages 20-43.
S9303-P9920	Three-period, three-treatment, six-way Latin square crossover study; STS 20mg/20cm^2 per day, alprazolam 0.5mg tid, and STS 20mg/20cm^2 plus alprazolam 0.5mg tid, each given for 7 days; 11 males and 5 females, ages 21-43.
S9303-P9921	Three-period, six-way Latin square crossover study; STS 20mg/20cm^2 per day, risperidone 1mg bid, and STS 20mg/20cm^2 plus risperidone 1mg bid, each given for 7 days; 6 males and 6 females, ages 19-42.
S9303-P9922	Three-period, three-treatment, six-way Latin square crossover study; STS 20mg/20cm^2 per day, olanzapine 5mg daily, and STS 20mg/20cm^2 plus olanzapine 5mg daily, each given for 10 days; 5 males and 7 females, ages 19-42.
S9303-P9925	Levothyroxine 150 mcg (days 1 and 14) and STS 20mg/20cm^2 per day (days 4-16); in 6 males and 4 females, ages 18-35.
S9303-P9926	Ibuprofen 800mg per day (days 1 and 12) and STS 20mg/20cm^2 per day (days 2-12); in 7 males and 3 females, ages 19-44.
S9303-P9927	Alcohol 0.75 mg/kg or placebo per day (days 1, 2, and 11-13) and STS 20mg/20cm^2 per day (days 3-13); in 16 males, ages 21-45.
S9303-P9928	Pseudoephedrine 60mg (day 1) and 60mg tid (days 2 and 3), STS 20mg/20cm^2 per day (days 4-13), pseudoephedrine 60mg (day 11) and 60mg tid (days 12 and 13); in 9 males and 3 females, ages 19-27.
S9303-P9931	STS 20mg/20cm^2 per day (days 1-14) and ketoconazole 200mg per day (days 8-14); in 5 males and 5 females, ages 20-43.

APPENDIX 1: TABLE OF ALL STUDIES	
Study Type/ Study Number	**Study Description**
S9303-P9933	STS 20mg/20cm^2 (day 1), carbamazepine 200mg bid (days 4-16), then STS 20mg/20cm^2 and carbamazepine 200mg (day 17); in 7 males and 3 females, ages 19-45.
S9303-P0046	Phenylpropanolamine 25mg (day 1), phenylpropanolamine 25mg q4hrs (days 2-3), STS 20mg/20cm^2 per day (days 5-11), phenylpropanolamine 25mg with STS 20mg/20cm^2 (day 12), then phenylpropanolamine 25mg q4hrs with STS 20mg/20cm^2 per day (days 13-14); in 12 males, ages 20.5-44.7).
NIDA 98-2	IV cocaine 0.5 mg/kg/10 minutes then 2 mg/kg/4 hours (day 1), STS 20mg/20cm^2 per day (days 4-12), IV cocaine 0.5 mg/kg/10 minutes then 2 mg/kg/4 hours (day 11); in 11 males and 1 female, ages 22-43.
NIDA 9906	Placebo patch daily (days 1-7), STS 20mg/20cm^2 per day (days 7-17), placebo patch daily (days 17-20); 5 challenges with IV cocaine: 1 challenge during placebo phase, 4 challenges during the STS phase; in 19 males and 2 females, ages 31-49.
SPECIAL POPULATION STUDIES	
S9303-P9811	Single dose study of STS 20mg/20cm^2 in 6 males and 6 females, ages 46-80.
S9303-P9812	Single dose study of STS 20mg/20cm^2 in 6 males and 2 females, ages 41-54.
[illegible]	
TYRAMINE CHALLENGE STUDIES	
S9303-010-94B	Tyramine challenge during single dose application of ¼, ½, and 1 STS 18.3mg/10cm^2 in 15 healthy males, ages 19-30.
S9303-033-96B	Tyramine pressor response after multiple dose (21 day) STS 15mg/15cm^2 and 30mg/20cm^2 daily in 7 male and 11 female healthy elderly volunteers, ages 50-63.

APPENDIX 1: TABLE OF ALL STUDIES	
Study Type/ Study Number	**Study Description**
S9303-037-97B	Tyramine pressor response after multiple dose (19 day) STS 20mg/20cm^2 daily in 10 healthy male volunteers, ages 19-32.
S9303-P9802	Tyramine-enriched meal blood pressure response after multiple dose (13 day) STS 20mg/20cm^2 daily in 16 healthy male volunteers, ages 18-28.
S9303-P9932	Oral tyramine pressor response before and after multiple dose (9 day) STS 20mg/20cm^2 daily in 24 healthy male volunteers, ages 18-52.
S9303-P9940	Oral tyramine pressor response before and after multiple dose (9 day) STS 20mg/20cm^2 daily in 13 healthy male volunteers, ages 18-49.
S9303-P9941	Oral tyramine pressor response before and after tranylcypromine 30mg/day (8 day) or STS 20mg/20cm^2 per day (10 days) in 12 healthy male volunteers, ages 29-36.
S9303-P0045	Oral tyramine pressor response before and after STS 20mg/20cm^2 per day (33 day) in 13 healthy male volunteers, ages 19-50.
S9303-P0048	Oral tyramine pressor response before and after STS 30mg/30cm^2 per day (10 day) in 12 healthy male volunteers, ages 23-60.
S9303-P0050	Oral tyramine pressor response before and during steady-state STS 20mg/20cm^2 ×2 per day (10 days) in 14 healthy male volunteers, ages 20-50.
IRRITATION AND CONTACT ALLERGENICITY STUDIES	
S9303-P9936	Investigation of primary irritation and contact allergenicity of 20mg/20cm^2 per day (days 1-22, 36-40) in 73 male and 81 female healthy volunteers, ages 18-60.
PHASE 2/3 TRIALS	
CONTROLLED STUDIES IN MAJOR DEPRESSION	
S9303-E106-96B	Double-blind, placebo-controlled, parallel group, 6 week study of STS 20mg/20cm^2 per day in 177 patients.

APPENDIX 1: TABLE OF ALL STUDIES	
Study Type/ Study Number	**Study Description**
S9303-E113-98B	Double-blind, placebo-controlled, parallel group, 8 week study of STS 20mg/20cm^2 per day in 297 patients.
S9303-P9804	Double-blind, placebo-controlled, parallel group, 8 week study of STS 20mg/20cm^2 per day in 301 patients (after exclusion of 9 patients from site 12).
S9303-E114-98B	Double-blind, placebo-controlled, parallel group, 8 week study of STS 20mg/20cm^2 or STS 10mg/20cm^2 per day in 446 patients.
OPEN LABEL STUDIES IN MAJOR DEPRESSION	
S9303-E106-96B	12 week open label extension of study S9303-E106-96B; N=137.
S9303-P9805	12 week open label extension of study S9303-E113-98B and study S9303-P9804; N=202.
ALZHEIMER'S DISEASE	
S9303-E100-94B	Double-blind, placebo-controlled, parallel group, 28 week study in 70 patients, ages 60-84. Daily doses: STS 8mg/10cm^2 or STS 16mg/20cm^2 or STS 16mg/20cm^2. Followed by a 56 day extension in 41 patients.
S9303-E101-96B	Double-blind, placebo-controlled, parallel group, 48 week study of STS 20mg/20cm^2 per day in 406 patients, ages 51-85.
OTHER INDICATIONS	
S9303-E110-97B	Double-blind, placebo-controlled, parallel group, 10 week pilot study of STS 15mg/15cm^2 per day in 14 patients
S9303-E112-97B	Open label, 8 week, dose escalation study in Daily doses: STS 5mg/5cm^2 for 2 weeks, then 10mg/10cm^2 for 2 weeks, then 15mg/15cm^2 for 4 weeks.

APPENDIX 1: TABLE OF ALL STUDIES	
Study Type/ Study Number	**Study Description**
S9303-E102-96B	Open label study of STS 30mg/20cm^2 per day for 8 weeks in 25 patients (ages 48-80) with mild to moderate Parkinson's Disease.
ONGOING PHASE 2/3 STUDIES	
S9303-P9918	24 week open label extension of depression studies S9303-E113-98B, S9303-E114-98B, and S9303-P9804; N=305.
S9303-P9806	Relapse prevention study in major depression: 10 week open label lead-in with STS 20mg/20cm^2 per day followed by randomization of responders to STS 20mg/20cm^2 per day or placebo for 52 weeks of double-blind treatment; 682 patients entered the open label lead-in and 321 were randomized to double-blind treatment.
S9303-E109-97B	Double-blind, placebo-controlled trial of STS 15mg/20cm^2 per day in Parkinson's disease; data from 191 patients are complete.
S9303-P9917	Open label extension of study S9303-E109-97B; N=36.
S9303-P9935	12 week, open label study of STS 20mg/20cm^2 per day in 20 patients with [redacted]
S9303-P9937	Open label study in [redacted] 32 patients had been enrolled.
NEW STUDIES REPORTED IN THE 9-26-01 120-DAY SAFETY UPDATE	
Phase 1 Studies	
S9303-P0051	Randomized sequence crossover study of the pharmacokinetic profiles of selegiline when STS 20mg/20cm^2 was applied to three different body sites for 10 days each in 27 healthy volunteers.
S9303-P0156	MAO-A/MAO-B inhibition study using STS in three different dosages (20mg, 30mg, and 40mg; all at 1.0 mg/cm^2) in 25 subjects.

APPENDIX 1: TABLE OF ALL STUDIES	
Study Type/ Study Number	**Study Description**
Phase 2/3 Studies	
S9303-P0043	Ongoing open-label compassionate use study of STS 20mg/20cm^2 in 14 depressed patients.
S9303-P0044	Ongoing open-label extension study of STS 10mg/20cm^2, 15mg/15cm^2, and 20mg/20cm^2 in 27 patients
NIDA-1019	Ongoing double blind study of STS 20mg/20cm^2 in the treatment of cocaine dependence in 4 patients.

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APPENDIX 2: MATERIALS USED IN THE CLINICAL REVIEW		
NDA Volume(s)	**Submission Date**	**Material**
1.1	May 24, 2001	Proposed Labeling NDA Summary Debarment Certification Financial Disclosure
1.210	"	Study Report: E106-96B
1.220	"	Study Report: E113-98B
1.235	"	Study Report: P9804
1.249	"	Study Report: E114
1.505	"	Integrated Summary of Efficacy
T6103	Aug 30, 2001	Efficacy Subgroup Analysis
-	-	IND 46,944 Division File

APPENDIX 3: STUDY E106-96B BASELINE DEMOGRAPHIC CHARACTERISTICS (ALL RANDOMIZED PATIENTS)							
Treatment Group	N	Age (years)		Gender [N(%)]		Race	
		Mean	Range	Male	Female	White	Non-White
STS	89	41.4	19-62	36(40%)	53(60%)	96%	4%
Placebo	88	43.2	20-65	35(40%)	53(60%)	90%	10%

APPENDIX 4: STUDY E106-96B MEAN CHANGE FROM BASELINE IN HAM-D_{1-17} TOTAL SCORE (MODIFIED ITT)												
Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 6	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Last Observation Carried Forward Analysis												
STS	88	22.86	86	-3.91	88	-5.90	88	-7.17	88	-8.17	88	-8.73
Placebo	88	23.30	85	-2.59	88	-4.14	88	-5.43	88	-6.15	88	-6.10
Two-sided p-values for pairwise comparisons												
STS vs. P	0.280		0.048		0.025		0.048		0.040		0.013	
Observed Cases Analysis												
STS	88	22.86	86	-3.91	85	-6.13	76	-7.59	83	-8.65	79	-9.66
Placebo	88	23.30	85	-2.59	86	-4.16	77	-5.58	76	-6.83	74	-7.11
Two-sided p-values for pairwise comparisons												
STS vs. P	0.280		0.048		0.017		0.032		0.058		0.018	

APPENDIX 5: STUDY E106-96B MEAN CHANGE FROM BASELINE IN MADRS TOTAL SCORE (MODIFIED ITT)												
Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 6	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Last Observation Carried Forward Analysis												
STS	88	28.85	86	-3.22	88	-5.25	88	-7.02	88	-8.50	88	-9.77
Placebo	88	29.53	85	-1.11	88	-3.17	88	-4.47	88	-5.55	88	-5.65
Two-sided p-values for pairwise comparisons												
STS vs. P	0.393		0.014		0.041		0.031		0.029		0.005	
Observed Cases Analysis												
STS	88	28.85	86	-3.22	85	-5.47	76	-7.58	83	-9.13	79	-11.1
Placebo	88	29.53	85	-1.11	86	-3.21	77	-4.74	76	-6.39	74	-6.73
Two-sided p-values for pairwise comparisons												
STS vs. P	0.393		0.014		0.035		0.028		0.047		0.005	

APPENDIX 6: STUDY E106-96B HAM-D DEPRESSED MOOD ITEM DISTRIBUTION OF SCORES (MODIFIED ITT)																				
TX	Baseline Score Distribution										Week 6 Score Distribution									
	0		1		2		3		4		0		1		2		3		4	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Last Observation Carried Forward Analysis																				
STS	0	0	2	2	28	32	56	64	2	2	15	17	24	27	25	28	20	23	4	5
Plac	0	0	1	1	18	21	69	78	0	0	6	7	22	25	26	30	29	33	5	6
Two-sided p-values for pairwise comparison of distributions																				
STS/P	0.161										0.030									
Observed Cases Analysis																				
STS	0	0	2	2	28	32	56	64	2	2	15	17	24	27	22	25	17	19	1	1
Plac	0	0	1	1	18	21	69	78	0	0	6	7	20	23	24	27	22	25	2	2
Two-sided p-values for pairwise comparison of distributions																				
STS/P	0.161										0.028									

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APPENDIX 7: STUDY E106-96B DISTRIBUTION OF CGI IMPROVEMENT SCORES AT WEEK 6 (MODIFIED ITT)							
TX Group	CGI Improvement Category	LOCF Analysis			OC Analysis		
		N	%	p-value	N	%	p-value
STS (N=88)	Very much improved	17	19	0.007	17	19	0.035
	Much improved	20	23		20	23	
	Minimally improved	21	24		19	22	
	Unchanged	23	26		19	22	
	Minimally worse	3	3		3	3	
	Much worse	4	5		1	1	
Placebo (N=88)	Very much improved	8	9		8	9	
	Much improved	16	18		14	16	
	Minimally improved	21	24		20	23	
	Unchanged	30	34		27	31	
	Minimally worse	9	10		5	6	
	Much worse	4	5		0	0	

APPENDIX 8: STUDY E113-98B BASELINE DEMOGRAPHIC CHARACTERISTICS (ALL RANDOMIZED PATIENTS)							
Treatment Group	N	Age (years)		Gender [N(%)]		Race	
		Mean	Range	Male	Female	White	Non-White
STS	147	41.04	18-65	56(38%)	91(62%)	80%	20%
Placebo	150	39.79	18-64	59(39%)	91(61%)	85%	15%

APPENDIX 9: STUDY E113-98B MEAN CHANGE FROM BASELINE IN HAM-D_{1-17} TOTAL SCORE (MODIFIED ITT)												
Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Last Observation Carried Forward Analysis												
STS	137	22.94	134	-3.35	137	-4.84	137	-5.98	137	-6.58	137	-6.64
Placebo	146	22.74	143	-3.51	146	-5.47	146	-7.28	146	-7.57	146	-7.81
Two-sided p-values for pairwise comparisons												
STS vs. P	0.493		0.613		0.192		0.045		0.203		0.117	
Observed Cases Analysis												
STS	137	22.94	134	-3.35	134	-4.96	118	-6.40	109	-7.62	104	-7.70
Placebo	146	22.74	143	-3.51	136	-5.57	128	-7.77	121	-8.29	112	-8.88
Two-sided p-values for pairwise comparisons												
STS vs. P	0.493		0.613		0.209		0.046		0.460		0.164	

APPENDIX 10: STUDY E113-98B MEAN CHANGE FROM BASELINE IN MADRS TOTAL SCORE (MODIFIED ITT)												
Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Last Observation Carried Forward Analysis												
STS	137	27.26	134	-2.66	137	-3.89	137	-6.22	137	-7.17	137	-7.22
Placebo	146	26.95	143	-2.91	146	-5.18	146	-7.54	146	-7.75	146	-8.43
Two-sided p-values for pairwise comparisons												
STS vs. P	0.511		0.522		0.054		0.107		0.514		0.188	
Observed Cases Analysis												
STS	137	27.26	134	-2.66	134	-4.04	118	-6.74	109	-8.58	104	-8.76
Placebo	146	26.95	143	-2.91	136	-5.42	128	-8.17	121	-8.55	112	-10.0
Two-sided p-values for pairwise comparisons												
STS vs. P	0.511		0.522		0.048		0.111		0.985		0.311	

APPENDIX 11: STUDY E113-98B HAM-D DEPRESSED MOOD ITEM DISTRIBUTION OF SCORES (MODIFIED ITT)																				
TX	Baseline Score Distribution										Week 8 Score Distribution									
	0		1		2		3		4		0		1		2		3		4	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Last Observation Carried Forward Analysis																				
STS	0	0	2	2	28	20	102	75	5	4	18	13	32	23	31	23	50	37	6	4
Plac	0	0	5	3	31	21	106	73	4	3	15	10	37	25	39	27	54	37	1	1
Two-sided p-values for pairwise comparison of distributions																				
STS/P	0.350										0.810									
Observed Cases Analysis																				
STS	0	0	2	2	28	20	102	75	5	4	18	13	27	20	24	18	31	23	4	3
Plac	0	0	5	3	31	21	106	73	4	3	14	10	34	23	29	20	35	24	0	0
Two-sided p-values for pairwise comparison of distributions																				
STS/P	0.350										0.741									

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APPENDIX 12: STUDY E113-98B DISTRIBUTION OF CGI IMPROVEMENT SCORES AT WEEK 8 (MODIFIED ITT)							
TX Group	CGI Improvement Category	LOCF Analysis			OC Analysis		
		N	%	p-value	N	%	p-value
STS (N=137)	Very much improved	20	15	0.494	20	15	0.752
	Much improved	24	18		20	15	
	Minimally improved	38	28		30	22	
	Unchanged	41	30		26	19	
	Minimally worse	9	7		5	4	
	Much worse	5	4		3	2	
Placebo (N=146)	Very much improved	19	13		19	13	
	Much improved	29	20		27	19	
	Minimally improved	42	29		32	22	
	Unchanged	52	36		32	22	
	Minimally worse	4	3		2	1	
	Much worse	0	0		0	0	

APPENDIX 13: STUDY P9804 BASELINE DEMOGRAPHIC CHARACTERISTICS (ALL RANDOMIZED PATIENTS)							
Treatment Group	N	Age (years)		Gender [N(%)]		Race	
		Mean	Range	Male	Female	White	Non-White
STS	149	41.2	19-64	55(37%)	94(63%)	77%	23%
Placebo	152	43.5	19-65	53(35%)	99(65%)	88%	12%

APPENDIX 14: STUDY P9804 MEAN CHANGE FROM BASELINE IN HAM-D_{1-17} TOTAL SCORE (MODIFIED ITT)												
Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Last Observation Carried Forward Analysis												
STS	145	22.79	137	-4.32	145	-5.74	145	-7.02	145	-7.56	145	-8.08
Placebo	144	22.99	141	-4.03	144	-5.68	144	-6.43	144	-6.74	144	-6.67
Two-sided p-values for pairwise comparisons												
STS vs. P	0.604		0.544		0.742		0.356		0.247		0.069	
Observed Cases Analysis												
STS	145	22.79	137	-4.32	137	-5.77	121	-7.30	111	-8.00	106	-8.80
Placebo	144	22.99	141	-4.03	138	-5.81	124	-6.75	115	-7.24	109	-7.48
Two-sided p-values for pairwise comparisons												
STS vs. P	0.604		0.544		0.946		0.439		0.292		0.096	

APPENDIX 15: STUDY P9804 MEAN CHANGE FROM BASELINE IN MADRS TOTAL SCORE (MODIFIED ITT)												
Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Last Observation Carried Forward Analysis												
STS	145	28.26	137	-4.07	145	-6.60	145	-8.89	145	-9.03	145	-10.2
Placebo	144	28.47	141	-4.04	144	-5.92	144	-6.79	144	-6.86	144	-6.72
Two-sided p-values for pairwise comparisons												
STS vs. P	0.741		0.827		0.312		0.024		0.027		0.001	
Observed Cases Analysis												
STS	145	28.26	137	-4.07	137	-6.63	121	-9.38	111	-9.62	106	-11.2
Placebo	144	28.47	141	-4.04	138	-6.15	124	-7.27	115	-7.79	109	-7.70
Two-sided p-values for pairwise comparisons												
STS vs. P	0.741		0.827		0.509		0.041		0.051		0.001	

APPENDIX 16: STUDY P9804
HAM-D DEPRESSED MOOD ITEM DISTRIBUTION OF SCORES (MODIFIED ITT)

TX	Baseline Score Distribution										Week 8 Score Distribution									
	0		1		2		3		4		0		1		2		3		4	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Last Observation Carried Forward Analysis																				
STS	0	0	4	3	29	20	108	75	4	3	26	18	39	27	39	27	38	26	3	2
Plac	1	1	2	1	23	16	110	76	8	6	14	10	29	20	39	27	57	40	5	4
Two-sided p-values for pairwise comparison of distributions																				
STS/P	0.215										0.062									
Observed Cases Analysis																				
STS	0	0	4	3	29	20	108	75	4	3	22	15	28	19	33	23	23	16	0	0
Plac	1	1	2	1	23	16	110	76	8	6	11	8	25	17	35	24	35	24	3	2
Two-sided p-values for pairwise comparison of distributions																				
STS/P	0.215										0.025									

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APPENDIX 17: STUDY P9804 DISTRIBUTION OF CGI IMPROVEMENT SCORES AT WEEK 8 (MODIFIED ITT)							
TX Group	CGI Improvement Category	LOCF Analysis			OC Analysis		
		N	%	p-value	N	%	p-value
STS (N=145)	Very much improved	22	15	0.157	18	12	0.076
	Much improved	40	28		35	24	
	Minimally improved	41	28		31	21	
	Unchanged	35	24		20	14	
	Minimally worse	6	4		2	1	
	Much worse	1	1		0	0	
Placebo (N=144)	Very much improved	13	9		12	8	
	Much improved	33	23		27	19	
	Minimally improved	40	28		33	23	
	Unchanged	45	31		28	19	
	Minimally worse	11	8		8	6	
	Much worse	2	1		1	1	

APPENDIX 18: STUDY E114-98B
BASELINE DEMOGRAPHIC CHARACTERISTICS
(ALL RANDOMIZED PATIENTS)

Treatment Group	N	Age (years)		Gender [N(%)]		Race	
		Mean	Range	Male	Female	White	Non-White
STS 20mg	149	42.05	19-66	51(34)	98(66)	87%	13%
STS 10mg	151	40.36	17-64	54(36)	97(64)	86%	14%
Placebo	146	40.79	19-63	46(32)	100(68)	89%	11%

APPENDIX 19: STUDY E114-98B
MEAN CHANGE FROM BASELINE IN HAM-D_{1-17} TOTAL SCORE (MODIFIED ITT)

Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Last Observation Carried Forward Analysis												
STS 20mg	142	23.29	140	-3.90	142	-6.04	142	-7.36	142	-8.54	142	-9.18
STS 10mg	151	22.73	142	-3.85	151	-5.93	151	-7.17	151	-8.06	151	-9.02
Placebo	142	23.06	137	-3.60	142	-5.45	142	-6.63	142	-7.73	142	-8.12
Two-sided p-values for overall comparisons												
Overall	0.274		0.747		0.659		0.579		0.629		0.357	
Observed Cases Analysis												
STS 20mg	142	23.29	140	-3.90	136	-6.21	126	-7.81	116	-9.28	109	-10.4
STS 10mg	151	22.73	142	-3.85	150	-5.95	133	-7.37	118	-9.08	112	-10.6
Placebo	142	23.06	137	-3.60	134	-5.79	127	-7.42	116	-9.23	110	-9.96
Two-sided p-values for overall comparisons												
Overall	0.274		0.747		0.803		0.756		0.977		0.597	

APPENDIX 20: STUDY E114-98B MEAN CHANGE FROM BASELINE IN MADRS TOTAL SCORE (MODIFIED ITT)												
Treatment Group	Baseline		Week 1		Week 2		Week 4		Week 6		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Last Observation Carried Forward Analysis												
STS 20mg	142	27.49	139	-3.49	141	-6.09	141	-8.21	141	-10.5	141	-11.2
STS 10mg	151	26.93	142	-3.20	151	-5.97	151	-7.48	151	-8.36	151	-9.58
Placebo	142	27.46	137	-2.96	142	-5.47	142	-6.88	142	-8.38	142	-8.96
Two-sided p-values for overall comparisons												
Overall	0.491		0.647		0.696		0.378		0.097		0.144	
Observed Cases Analysis												
STS 20mg	142	27.49	139	-3.49	136	-6.31	126	-8.89	116	-11.8	109	-13.1
STS 10mg	151	26.93	142	-3.20	150	-5.99	133	-7.83	118	-9.57	112	-11.7
Placebo	142	27.46	137	-2.96	134	-5.84	127	-7.61	116	-10.0	110	-11.1
Two-sided p-values for overall comparisons												
Overall	0.491		0.647		0.826		0.378		0.161		0.303	

APPENDIX 21: STUDY E114-98B
HAM-D DEPRESSED MOOD ITEM DISTRIBUTION OF SCORES (MODIFIED ITT)

TX	Baseline Score Distribution										Week 8 Score Distribution									
	0		1		2		3		4		0		1		2		3		4	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Last Observation Carried Forward Analysis																				
STS20	0	0	5	4	22	16	105	74	10	7	30	21	40	28	31	22	38	27	3	2
STS10	0	0	4	3	29	19	106	70	12	8	27	18	46	31	26	17	50	33	2	1
Plac	1	1	2	1	20	14	111	78	8	6	23	16	35	25	31	22	46	32	7	5
Two-sided p-values for overall comparisons of distributions																				
All	0.953										0.185									
Observed Cases Analysis																				
STS20	0	0	5	4	22	16	105	74	10	7	27	19	35	25	22	16	24	17	1	1
STS10	0	0	4	3	29	19	106	70	12	8	26	17	38	25	21	14	26	17	1	1
Plac	1	1	2	1	20	14	111	78	8	6	23	16	33	23	21	15	30	21	3	2
Two-sided p-values for overall comparisons of distributions																				
All	0.953										0.288									

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APPENDIX 22: STUDY E114-98B DISTRIBUTION OF CGI IMPROVEMENT SCORES AT WEEK 8 (MODIFIED ITT)							
TX Group	**CGI Improvement Category**	**LOCF Analysis**			**OC Analysis**		
		N	**%**	**p-value**	**N**	**%**	**p-value**
STS 20mg (N=142)	Very much improved	33	23	0.156	31	22	0.163
	Much improved	44	31		38	27	
	Minimally improved	28	20		17	12	
	Unchanged	27	19		20	14	
	Minimally worse	7	5		2	1	
	Much worse	3	2		1	1	
STS 10mg (N= 151)	Very much improved	33	22		31	21	
	Much improved	44	29		34	23	
	Minimally improved	28	19		22	15	
	Unchanged	35	23		21	14	
	Minimally worse	8	5		2	1	
	Much worse	3	2		1	1	
Placebo (N=142)	Very much improved	26	18		26	18	
	Much improved	31	22		30	21	
	Minimally improved	35	25		27	19	
	Unchanged	39	28		21	15	
	Minimally worse	9	6		5	4	
	Much worse	2	1		1	1	

APPENDIX 23: SUBGROUP ANALYSIS OF EFFICACY RESPONSE POOL OF STUDIES E106-96B AND P9804				
GENDER				
Subgroup	Male		Female	
Treatment	STS	Placebo	STS	Placebo
N	91	88	147	152
Mean Δ HAM-D	-7.451	-6.341	-8.585	-6.178
STS/Placebo Δ	-1.110		-2.407	
AGE				
Subgroup	>40 years		≤40 years	
Treatment	STS	Placebo	STS	Placebo
N	128	144	110	96
Mean Δ HAM-D	-8.000	-6.014	-8.327	-6.573
STS/Placebo Δ	-1.986		-1.754	
RACE				
Subgroup	White		Non-white	
Treatment	STS	Placebo	STS	Placebo
N	199	213	39	27
Mean Δ HAM-D	-7.894	-6.019	-9.462	-7.963
STS/Placebo Δ	-1.876		-1.499	
BASELINE SEVERITY				
Subgroup	HAM-D >23		HAM-D ≤23	
Treatment	STS	Placebo	STS	Placebo
N	88	88	150	152
Mean Δ HAM-D	-8.966	-6.784	-7.673	-5.921
STS/Placebo Δ	-2.182		-1.752	

APPENDIX 24: SUMMARY OF EFFICACY RESULTS (SIGNIFICANCE OF DRUG/PLACEBO DIFFERENCES AT FINAL DOUBLE-BLIND ASSESSMENT)[17]									
Study	STS Dose	HAM-D_{1-17}		MADRS		HAM-D item 1		CGI improvement	
		LOCF	OC	LOCF	OC	LOCF	OC	LOCF	OC
E106-96B	20mg	*	*	**	**	*	*	**	*
E113-98B	20mg	ns	ns	ns	ns	ns	ns	ns	ns
P9804	20mg	tr	tr	**	**	tr	*	ns	tr
E114-98B	20&10mg	ns	ns	ns	ns	ns	ns	ns	ns

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[17] ns = not significant ($p>0.10$)
tr = trend ($0.05<p\leq0.10$)
* = significant ($0.01<p\leq0.05$)
** = highly significant ($p\leq0.01$)
LOCF = Last Observation Carried Forward
OC = Observed Cases
Significance for study E114-98B based on the overall p-values across 20mg, 10mg, and placebo groups.

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/s/

Greg Dubitsky
2/28/02 03:31:58 PM
MEDICAL OFFICER

Thomas Laughren
3/8/02 03:54:27 PM
MEDICAL OFFICER
I agree that this NDA is not approvable; see memo to file for more detailed comments.--TPL