IV. NDA Clinical Data Sources

A. Primary Development Program

1. Patient Enumeration by Study Type

Phase 1

The original submission to this NDA described 36 Phase 1 studies which involved a total of 630 unique subjects exposed to STS. Since the original submission, three additional Phase 1 trials have been completed:

- P0051 - a PK study of alternate STS application sites.
- P0156 - a study of the effect of STS on the extent of systemic MAO-A and MAO-B inhibition.
- P0201 - a long-term tyramine challenge study.

A total of 72 normal volunteers received STS in these 3 trials.

Phase 2/3

The primary study pool for safety data analyses comprises five short-term, randomized, double-blind, placebo-controlled, parallel group trials. This is designated as Pool A in the sponsor's ISS Amendment and hereafter in this review. The features of these studies are summarized in Table IV-1 below. Safety and efficacy data from the first four trials were submitted in the original submission to this NDA; study P0052 is a new study.

TABLE IV-1
POOL A STUDIES

Study	Duration (weeks)	STS Dose (mg/day)	N_{STS}	$N_{Placebo}$
E106-96B	6	20	89	88
E113-98B	8	20	147	149
P9804	8	20	149	152
E114	8	20 or 10 (fixed)	300	146
P0052	8	20, 30, or 40 (flexible)	132	133
TOTAL			**817**[5]	**668**

[5] Numbers of patients exposed to STS represent the number of patients in the safety population.

The ISS Amendment also describes safety data from the wider pool of all Phase 2/3 trials of STS in major depression, which is designated Pool B. Pool B encompasses the 5 short-term trials mentioned above as well as the following:

- three previously submitted open-label studies of STS in major depression (E106-96B (ext.), P9805, and P9918).
- a newly completed relapse prevention trial (P9806).
- two new ongoing studies in major depression (P0158 and P0204).

A total of 2,036 patients received STS in the trials that comprise Pool B.

An additional 17 patients received STS for major depression in the ongoing open-label compassionate use study P0043.

Finally, a total of 708 patients received STS in studies in other indications (Alzheimer's disease, Parkinson's disease, [redacted] HIV-associated cognitive impairment, and cocaine addiction). Of the 11 trials in other indications, 5 were completed and presented in the original submission and 6 are ongoing or recently completed studies.[6]

Altogether, a cumulative total of 2,761 unique patients has been exposed to STS in Phase 2/3 studies.

All previously submitted studies were summarized in my clinical review dated 2-28-02. All new, recently completed, or ongoing Phase 1 and Phase 2/3 studies are listed and briefly described in **Appendix IV-1** of this review.

2. Demographic Characteristics

The demographic characteristics of patients in Pool A studies are displayed in **Appendix IV-2**. The STS- and placebo-treated patients were comparable in terms of mean age, age range, gender, and race. The vast majority of these patients were under the age of 65 years.

Within Pool B studies, the 2,036 STS patients were slightly older (mean age 44.4 years with 90.3% under the age of 65). A total of 198 patients age 65 and older received STS in

[6] Study ACTG A5090, an NIH study in HIV-associated cognitive impairment, was ongoing at the time of the NA response.

Pool B studies. Otherwise, demography was similar to that in the Pool A studies.

3. Extent of Exposure

Appendix IV-3 enumerates all 2,036 patients in Pool B studies by maximum STS dose and duration of exposure to that dose. Most of these patients (1,576) received a maximum dose of $20mg/20cm^2$. A total of 273 patients received a dose of $40mg/40cm^2$ in depression trials. This dose was received by 157 patients for less than 12 weeks, 116 patients for 12 weeks or longer, and 30 patients for 24 weeks or longer.

B. Published Literature Update

The sponsor provided an update to their previous literature search, which had a cutoff date of May 2000. The cutoff date for this update is September 2003.

Searches were conducted by [redacted] holds a Masters degree in Library and Information Sciences and she has been an information professional since 1987.

Searches were performed using Medline, Biosis Previews, and EMBASE databases. A number of search terms were utilized and are listed under Tab H of the sponsor's 10-29-03 submission. Identified references were then reviewed for relevance by Somerset's medical/scientific team. All articles considered relevant were reviewed in their entirety and summarized under Tab H of the 10-29-03 submission.

Results of this search are presented in **section VII.B.10**.

C. Foreign Regulatory Update

Somerset provided a foreign regulatory update in their 10-29-03 submission to this NDA.

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

V. Clinical Review Methods

A. Items Utilized in Review

Items utilized during the course of this review are listed in **Appendix V-1.**

B. Specific Methods Used to Evaluate Data Quality

The consistency of adverse event documentation for six randomly selected patients who dropped out due to adverse experiences was audited by comparing information across three data sources: the Case Report Form (CRF), narrative summary or dropout line listing summary, and adverse event data listing (ADVERSE.XPT for studies which were integrated electronically or patient data listings from the hardcopy study report for other studies).[7] The results are presented in **section VII.D.**

The coding of adverse event verbatim terms to COSTART preferred terms was audited for all adverse experiences in Pool A studies. The results are provided in **section VII.B.4.**

C. Adherence to Accepted Ethical Standards

All studies in support of this application were conducted in the United States in accordance with Good Clinical Practice regulations (21 CFR Parts 50, 56, and 312) and with applicable, current International Conference on Harmonization guidelines.

D. Evaluation of Financial Disclosure

This submission contains the results of two covered clinical studies as defined in 21 CFR 54.2(e): study P0052 and study P9806. For all principal investigators in these two studies, it was certified 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

[7] The six audited patients were: P0052/23006, P0052/10048, P9806/15011, P9806/22006. P9935/18, and P0044/3188.

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).[8]

VI. Review of New Efficacy Data

A. Short-term Efficacy: Study P0052

Investigators/Sites

Three U.S. centers participated in this trial. The principal investigators were:

1) Alan Feiger, M.D., of the Feiger Health Research Center, Wheat Ridge, CO,
2) Karl Rickels, M.D. and Moira Rynn, M.D., of the University of Pennsylvania, Philadelphia, PA, and
3) Dan Zimbroff, M.D., of the Pacific Clinical Research Medical Group, West Covina, CA.

Objectives

The objectives of this study were to assess the safety and efficacy of STS titrated to doses of 20mg/20cm^2, 30mg/30cm^2, or 40mg/40cm^2 in the treatment of patients with moderate to severe major depressive disorder.

The steady-state pharmacokinetics of selegiline and its metabolites were also assessed.

Patient Sample

This study randomized 265 patients (132 to STS and 133 to placebo). Patients meeting the following inclusion criteria were eligible to participate:

- males and females age 18 and older. Females of childbearing potential were required to have a negative pregnancy test and agree to continuously use medically acceptable birth control during the study.
- capable of giving informed consent.
- a total score of at least 20 on the 17-item HAM-D at screening and baseline.

[8] Certification for the co-principal investigator, Moira Rynn, M.D., at the University of Pennsylvania site in study P0052, was provided in a FAX dated 11-7-03 from the sponsor.

• a score of 4 (moderately ill) or greater on the 7-point CGI severity of illness scale at baseline.
• a DSM-IV diagnosis of major depressive disorder, moderate to severe, based on clinical interview and supported by the semi-structured Mini-International Neuropsychiatric Interview.
• current episode of major depression lasting at least 2 months but not more than 2 years and excluding psychotic features.

Important exclusionary criteria are:

• a significant unstable psychosocial situation that was likely to respond without drug intervention.
• presence of another Axis I condition other than dysthymia (a pre-exiting dysthymic disorder of more than 2 years duration was allowed).
• history of bipolar I disorder or psychotic depression.
• history of substance abuse within 12 months.
• recently initiated or discontinued psychotherapy.
• significant chronic medical conditions, such as unstable angina or poorly regulated hypertension (DBP >100mmHg).
• history of organic CNS illness (e.g., Alzheimer's disease) or epilepsy.
• known lack of response to any MAOI.
• history of hypothyroidism unless taking a stable dose of thyroid medication and asymptomatic for 6 months.
• use of any psychotropic medication within 5 half-lives prior to baseline except for fluoxetine(5 weeks), MAOI's (2 months), oral neuroleptics (60 days), and intramuscular neuroleptics (10 weeks).

Study Design

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

Following a screening period of up to 28 days, patients were randomly assigned to 8 weeks of treatment with STS or a matching placebo patch. STS was begun at 20mg/20cm^2 and, after 2 weeks, if the patient showed definite improvement in the opinion of the investigator, the patient continued on this dose. For patients who did not show definite improvement, the STS dose was increased to STS 30mg/30cm^2 (or the matching 30cm^2 placebo patch for patients assigned to placebo).

After an additional 3 weeks, if there was no improvement, the dose was increased to 40mg/40cm^2 (or matching 40cm^2 placebo patch).

Patients who showed satisfactory improvement at a dose remained at that dose. Patients who had an adverse experience could have their dose level decreased by one level.

The study patches were to be applied to a clean area of skin on the upper torso or upper arm. Application sites were to be rotated on a daily basis. When possible, showering and bathing were to be completed just prior to application of the patch.

Efficacy measures (HAM-D, MADRS, and CGI) were assessed at baseline and at the end of weeks 1, 2, 3, 5, and 8.

Tyramine dietary restrictions were not required under this protocol.

Analysis[9]

The primary efficacy variable is the change from baseline to endpoint in the 28-item HAM-D total score using LOCF methodology. The primary patient population is the modified intent-to-treat population which consists of all randomized patients who received at least one dose of study drug and who had at least one assessment on the primary variable after receiving study drug.

The primary efficacy analysis utilized a two-way ANOVA model with treatment and center as main effects and baseline score as covariate. Treatment-by-center interaction was to be tested using a three-way ANOVA model with treatment, center, and treatment-by-center interaction as main effects. If the interaction term was significantly different from zero at a 0.05 level, this term would be added to the above statistical model and the nature of the interaction would be characterized. There was to be no pooling of centers.

Other variables examined in this review include the change from baseline to endpoint in the MADRS total score, HAM-D item 1, and CGI-severity rating. The same statistical

[9] The analysis plan described in this section is based on the study protocol as amended on 2-8-02 and 6-3-02.

analysis was used for the MADRS. Item 1 of the HAM-D and the CGI-severity score were analyzed as categorical ordinal variables using a Cochran-Mantel-Haenszel Type 2 statistic with center as stratum.

Baseline Demographics

Baseline demographic characteristics are summarized in **Appendix VI-1**. The STS and placebo treatment groups were comparable in terms of mean age, age range, and racial composition. The fraction of males was slightly larger in the placebo group compared to STS (47% vs. 39%).

Baseline Severity of Illness

Mean total scores on the 28-item HAM-D and the MADRS were not substantially different between the STS and placebo groups at baseline:

	STS	Placebo
HAM-D	28.3	28.5
MADRS	29.3	29.2

Additionally, the distributions of CGI-severity scores at baseline were very similar between the two treatment groups (e.g., 65.9% of STS and 69.2% of placebo patients had a score of "moderately ill").

Patient Disposition

In this trial, 265 outpatients were randomized (132 to STS and 133 to placebo). The number of patients remaining in the study by visit in each treatment group is displayed in **Appendix VI-2**. In the end, 76% of randomized STS patients and 80% of placebo patients completed the study.

The overall incidence of dropout was slightly greater in the STS group compared to placebo (24.2% vs. 20.3%). Dropouts are enumerated by reason for discontinuation in **Appendix VI-3**. A relatively small number of patients dropped out due to lack of efficacy: 3.8% of STS patients and 2.3% of placebo patients dropped out for this reason. Several placebo patients were lost to follow up (10.5%).

Dosing Information

The mean daily dose of STS by visit is displayed in **Appendix VI-4**. For the 100 STS patients completing the study, the mean daily dose was 34.7mg.

Concomitant Medications

Overall, 80% of STS and 71% of placebo patients used concomitant medications during this trial.

Sedative/hypnotic agents were the most commonly used psychotropic agents. These were used concomitantly by 14% of STS and 8% of placebo patients.. Otherwise, one STS patient used a concurrent anxiolytic and one used an antidepressant (bupropion); no placebo patients used an anxiolytic or antidepressant.[10]

Efficacy Results

Mean changes from baseline in the 28-item HAM-D, the primary efficacy variable, are displayed in **Appendix VI-5**. At week 8 in the LOCF analysis, STS was superior to placebo (mean changes of -11.1 vs. -8.9, p=0.0327). This finding was even more robust in the observed cases (OC) analysis (-12.8 vs. -9.5, p=0.0053).

Similar results were observed on analysis of the distribution of the HAM-D item 1 scores (**Appendix VI-6**) and on mean change from baseline in the MADRS total score (**Appendix VI-7**). STS was superior to placebo on the CGI-severity scores in the OC analysis but showed only a trend toward superiority in the LOCF analysis (p=0.1010) (**Appendix VI-8**). Results on the CGI-improvement scores (not shown in this review) demonstrated superiority of STS over placebo in both LOCF and OC analyses.

Conclusions

Study P0052 provided evidence of the efficacy of flexible dose STS patches (20mg/20cm^2, 30mg/30cm^2, or 40mg/40cm^2,) compared to placebo in the treatment of major depression.

[10] Patient 10088 received Wellbutrin 100mg tid during the last 10 days of study participation.

B. Longer-Term Efficacy: Study P9806

Investigators/Sites

This trial was conducted at 29 U.S. clinical sites. Principal investigators are listed in **Appendix VI-9**.

Objectives

The study objective was to assess the long-term (up to one year) safety and efficacy of STS versus placebo in patients in remission from an episode of major depression.

Patient Sample

Eligible patients were male or female, 18 years of age or older, and had a diagnosis of DSM-IV major depressive disorder using the Structured Clinical Interview for DSM-IV (SCID). The 17-item HAM-D total score must have been at least 18 at both screening and baseline. Women of childbearing potential were required to have a negative serum pregnancy test at screening and must have agreed to the use of medically acceptable birth control during the trial.

Important exclusion criteria were:

- in regular psychotherapy which could not be discontinued without serious risk.
- uncontrolled congestive heart failure, increasingly frequent angina, recent MI (within 3 months), uncontrolled hypertension, or clinically significant ECG abnormalities.
- history of organic mental illness or epilepsy.
- known lack of response to an adequate course of MAOI treatment.
- post-partum depression.
- hypothyroidism, unless on a stable dose of thyroid medication and asymptomatic for at least 6 months.
- uncontrolled type I diabetes mellitus.
- history of DSM-IV substance abuse within 6 months.
- medical conditions which would interfere with the implementation of the protocol or interpretation of study results.
- treatment with any MAOI within 2 weeks of the start of study treatment with STS.
- use of any psychotropic medication within 5 half-lives prior to baseline except for fluoxetine(5 weeks), oral

neuroleptics (45 days), and intramuscular neuroleptics (10 weeks).
- use of sympathomimetic drugs within 5-half-lives.
- ECT within 90 days.

Study Design

This study consisted of four phases:

- 2-week pre-treatment phase to establish diagnosis and study eligibility.
- 10-week, open label treatment phase with STS 20mg/20cm^2 daily. Assessments were conducted at weeks 2, 4, 6, 8, 9, and 10. Patients who achieved remission at the final visit of this phase (week 10) and did not meet DSM-IV criteria for major depression were randomized to double-blind treatment; this visit was baseline for patients entering the double-blind phase.[11]
- 52-week double-blind treatment phase with either STS 20mg/20cm^2 or placebo. Patients were assessed at weeks 2, 4, 6, 8, 10, 12, 14, 18, 22, 26, 34, 42, and 52 of this phase. Patients who demonstrated a 17-item HAM-D score ≥14 and a CGI-severity score ≥3 with at least a 2-point increase from double-blind baseline and met DSM-IV criteria for major depression at a scheduled or unscheduled visit were required to return for an assessment 2 weeks later to confirm reappearance of depression.[12]
- an open-label rescue phase with STS 20mg/20cm^2 for a maximum of 6 weeks for patients who relapsed during the first 6 months of double-blind treatment.

The study patches were to be applied to a clean area of skin on the upper torso or upper arm at the same time each day and within one hour of removing the previous patch. Application sites were to be rotated on a daily basis. Showering and bathing were to be completed just prior to application of the patch.

Efficacy assessments included the 28-item HAM-D, MADRS, and CGI.

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[11] Remission was defined as a 17-item HAM-D score ≤10 at either week 8 or 9 and at week 10 of the open-label phase. Patients who did not have a HAM-D score ≤10 at either week 8 or 9 were discontinued from the trial.

[12] If it was necessary for a patient to receive alternative medication due to depressive symptoms prior to the required visit 2 weeks later, the patient was discontinued due to "lack of efficacy."

Tyramine dietary restrictions were not required under this protocol.

Analysis

The protocol-specified primary efficacy measure is the between-group comparison of the cumulative proportion of patients experiencing reappearance of depression over the 12 month double-blind treatment phase. Reappearance, or relapse, of depression was defined as a 17-item HAM-D score ≥14 in conjunction with a CGI-severity score ≥3 with an increase in this score of at least 2 points from the double-blind baseline and measured at 2 visits over a 2-week period. Also, reappearance had to be confirmed by the presence of DSM-IV criteria for a major depressive episode.

Although not specifically allowed by the protocol criteria for relapse, the sponsor's efficacy analysis included in the relapse count those patients with confirmatory evidence of relapse at a consecutive visit which occurred at least 11 days after the visit documenting evidence of relapse (i.e., a minimum of 2 weeks minus 3 days). Although this is not precisely consistent with the protocol, I feel this is not unreasonable given windowing conventions for study trials in general and an allowance of ample time to establish that relapse symptomatology was not transient.

The proportions of patients experiencing depression relapse were to be analyzed using a Mantel-Haenszel test stratified by center. The sponsor provided efficacy analyses based on the modified ITT population (defined in the protocol as patients meeting remission criteria at the end of open-label treatment who received at least one dose of double-blind treatment and who had one on-treatment assessment during double-blind treatment), utilizing the above criteria for relapse. For purposes of this review, this is considered the primary efficacy analysis.

The sponsor provided a number of additional analyses based on 1) an ITT population (all randomized patients who received study medication during the double-blind phase), 2) patients with relapse confirmatory visits that occurred as soon as 3 days after the visit documenting evidence of relapse (designated as Type I criteria in the study report), and 3) a expanded definition of relapse (patients meeting the above criteria as well as patients who were

withdrawn from the trial due to lack of efficacy or who had any indication of relapse documented in the CRF (designated as Type II criteria in the study report)). These analyses are not considered in this review since the ITT population, as defined, is not generally accepted as primary for efficacy analyses and the other two analyses were based on changes not formally submitted as protocol amendments.

There is, however, one additional analysis that will be considered here, that is, the Kaplan-Meier analysis of time to reappearance of depression. By protocol, the treatment group difference was to be tested using Cox proportional hazards methods. This analysis is currently considered the standard analytical method for trials of this design.

Baseline Demographics

For the 674 patients who entered the open-label phase of this study, the mean age was 42.9 years (range 18 to 85 years), most (69%) were female, and most (83%) were Caucasian.

Baseline demographic characteristics at the beginning of the double-blind phase are summarized in **Appendix VI-10**. The STS and placebo treatment groups were comparable in terms of mean age, age range, and racial composition. The fraction of males was slightly larger in the placebo group compared to STS (35% vs. 29%).

Baseline Severity of Illness

The 674 patients entering open-label treatment had a mean 28-item HAM-D total score of 30.6 (range 20-58). Most of these patients had a CGI-severity score of 4 (moderate) (46.4%) or 5 (moderately severe)(41.4%). Only 10.4% of these patients were rated as 6 (severely ill).

Mean total scores on the 28-item HAM-D and the MADRS were not substantially different between the STS and placebo groups at baseline for the double-blind period:

	STS	Placebo
HAM-D	7.0	6.7
MADRS	6.4	6.5

Additionally, the distributions of CGI-severity scores at baseline were very similar between the two treatment groups

(e.g., 45.6% of STS and 49.7% of placebo patients had a score of "not ill;" 39.9% of STS and 36.2% of placebo patients had a score of "borderline ill").

Patient Disposition

A total of 675 outpatients enrolled in this trial. Of these, 674 received treatment with STS during the open-label phase.

The open-label phase was completed by 366 patients. Of these, 322 (or 47.7% of the original enrollees) were randomized into the double-blind treatment phase, 159 to STS and 163 to placebo. The most common reason for not randomizing a patient was failure to meet response criteria at the end of open-label treatment (90 patients).

For the 322 patients who were randomized into double-blind treatment, the average length of time in continuous remission prior to randomization (i.e., 17-item HAM-D total score ≤10) was 24.6 days.[13]

During the double-blind phase, 158 patients received STS and 163 received placebo patches. The numbers of patients in the study by visit are displayed in **Appendix VI-11**. By the week 8 visit, only 60% of the STS patients remained in the study and, at week 26, 37% remained. In the end, 21% (N=33) of STS patients and 17% (N=28) of placebo patients completed the double-blind phase.

Dropouts are enumerated by reason for discontinuation in **Appendix VI-12**. In this table, patients who dropped out due to reappearance of depression (by the above criteria) and patients who discontinued due to lack of efficacy are mutually exclusive. In the STS group, 19% of randomized patients discontinued the study due to meeting criteria for reappearance of depression compared to 31% of placebo patients. Smaller proportions of patients dropped out due to lack of efficacy (but not meeting these criteria): 7% of STS patients and 11% of placebo patients. A large fraction of patients in both groups dropped out due to being lost to follow up or withdrawing consent (29% of STS and 30% of placebo patients).

[13] This computation was performed by the statistical reviewer, Dr. Tristan Massie.

A total of 64 patients entered the rescue phase of this study. Of these, 48 (75%) completed this phase.

Concomitant Medications

During the open-label phase of this study, 80% of patients utilized concomitant medications, most commonly analgesics (36%). Thirteen patients (2% of the 674 patients who received STS treatment in this phase) used concomitant antidepressants.

During the double-blind treatment phase, 83% of STS-treated patients and 78% of placebo-treated patients used concomitant medications, most commonly analgesics (33% and 38%, respectively). Concomitant antidepressant agents were taken by 4 (2.5%) of STS patients and 2 (1.2%) of placebo patients.

Efficacy Results

At the end of the open-label treatment phase, 342 of the 645 patients comprising the modified ITT (53%) achieved remission as defined above.

During the double-blind treatment phase, in terms of the protocol-specified primary efficacy measure, the numbers and proportions of patients who met criteria for depression relapse by week 52 of the double-blind treatment phase in the modified ITT population are displayed in **Table VI-1** below. A significantly smaller fraction of STS patients relapsed compared to placebo (14% vs. 24%).

TABLE VI-1
STUDY P9806
PATIENTS MEETING CRITERIA FOR RELAPSE
MODIFIED ITT/DOUBLE-BLIND PHASE

Met Criteria?	STS N=149 n(%)	Placebo N=163 n(%)	p-value[14]
Yes	21 (14%)	39 (24%)	0.0183
No	128 (86%)	124 (76%)	

With respect to the more common analysis of relapse data using Kaplan-Meier methodology, the cumulative rates of relapse at week 52 were 17% in the STS group and 33% in the

[14] Based on a Cochran-Mantel-Haenszel analysis controlled for center.

placebo group. This difference was statistically significant (p=0.0347 using a Cox proportional hazards model). The STS:placebo risk ratio for relapse was 0.564.

The statistical reviewer, Tristan Massie, Ph.D., noted that there were a number of patients who met the scale criteria (HAM-D and CGI) for relapse at some visit and either had no subsequent visit to confirm relapse (32 STS & 22 placebo patients) or had a visit confirming relapse that occurred less than 11 days later (4 STS & 13 placebo patients).

In the case of patients with no confirmatory visit, it is unknown whether these patients would have met the formal criteria for relapse had they undergone an assessment approximately 2 weeks later. Further analysis of these patients revealed that, for 4 STS and 5 placebo patients, the status at the completion of the double-blind phase was considered to be "Relapsed" by the investigator (despite lack of a confirmatory visit); this includes patients who entered the rescue phase of the trial. By protocol, entry into the rescue phase was to be allowed only for patients who met the formal criteria for relapse. Furthermore, another 9 STS and 8 placebo patients were considered by the investigator to have dropped out due to "Lack of Efficacy."

For the cases where relapse was confirmed earlier than 11 days later, these visits were distributed throughout the first 10 days after the visit at which scale criteria were met and it seems reasonable to count these patients (4 in the STS group and 13 in the placebo group) as relapses.

By protocol, patients meeting scale criteria at a visit "**must** return to the clinic 2 weeks later" (bolding in the protocol) to confirm reappearance of depression. Thus, it clearly was the sponsor's intention that all such patients be reassessed 2 weeks later to confirm relapse. The fact that this did not happen in these 71 cases is presumed to be beyond the sponsor's direct control. Nonetheless, in keeping with the spirit of the protocol, an effort was made to determine how many of these patients should reasonably be enumerated as relapses.

Although, to be conservative, all 71 patients could be counted as relapses, this may not be entirely valid since some of these patients may have dropped out for reasons not related to poor therapeutic response (e.g., a severe adverse event or relocation from the site area). However,

it does seem reasonable to enumerate as relapses the 9 patients with a documented status of "Relapse," the 17 patients who dropped out due to lack of efficacy, and the 17 patients who had confirmation of relapse prior to day 11.

The efficacy results were recomputed after enumerating these 43 patients as relapses. Then, relapses comprised 26% (39/149) of the STS group and 40% (66/163) of the placebo group. The differences between STS and placebo were statistically significant: p=0.0044 by the protocol-specified CMH test and p=0.0158 by comparison of the Kaplan-Meier survival curves using a Cox proportional hazards model.

Conclusions

I have carefully considered the sponsor's analysis, as specified in the study protocol, as well as an alternative analysis, described above, that utilizes a more liberal approach to enumerating relapses. Both analyses indicate that STS 20mg/20cm^2 daily was superior to placebo in increasing the time to relapse and reducing the risk of relapse during a 52 week follow-up period in patients who had been in remission an average of 25 days prior to randomization.

C. Summary of Data Pertinent to Important Clinical Issues

1. Predictors of Response

For the pool of the 5 short-term, placebo-controlled depression studies, the sponsor computed the mean change from baseline in the 17-item HAM-D score within gender, age, and race subgroups. The results are displayed in Appendix **VI-13**.

There were differences in the placebo-adjusted mean changes in the HAM-D_{17} between demographic subgroups. Females showed a larger response than males, older patients showed a larger response than younger patients, and Caucasians showed a larger response than non-Caucasians, in whom placebo patients actually fared better than STS patients. All of these intergroup differences were less than 2 points.

It is notable that the unadjusted changes for STS were remarkable consistent (almost all in the range of -8 to -9 points) and that the differences in adjusted means were, in large part, attributable to differences in the placebo responses. For instance, in the non-Caucasian subgroup, the STS change was second largest in magnitude among all subgroups (-8.662); however, since the placebo change was the largest (-9.103), the adjusted change indicates that placebo was superior to drug. Given that large placebo responses are not uncommon in antidepressant drug trials, I find it difficult to conclude that there is a substantial difference in efficacy between demographic subgroups.

2. Size of Treatment Effect

The placebo-adjusted mean change from baseline to endpoint in the 28-item HAM-D in study P0052 was -2.2 (LOCF). In the other positive short-term efficacy trial in this development program (study E106-96B), the primary measure was the 17-item HAM-D and the placebo-adjusted mean change from baseline to endpoint for this variable was -2.6.[15] These changes are not large but are comparable to the changes observed in clinical trials with other approved antidepressant agents.

3. Choice of Dose

The sponsor did not perform any multiple fixed dose efficacy trials except for study E114, which studied STS doses of 10mg and 20mg. The results of this trial were negative and data on the primary efficacy measure (mean change in the HAM-D_{17}) suggested no major difference between the two doses. Thus, no conclusions regarding dose-response can be made at this time.

4. Duration of Treatment

Study P9806 demonstrated that continuation of STS in patients who experienced remission after 10 weeks of treatment significantly increased the time to relapse and reduced the risk of relapse compared to placebo over a 52 week follow-up period.

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[15] Interestingly, the placebo-adjusted mean change from baseline for the 17-item HAM-D for study P0052 was only -1.3; this intergroup difference was not statistically significant (p=-0.1338).

D. Conclusions Regarding Efficacy

The development plan for STS in the treatment of depression included a total of 5 short-term, placebo-controlled studies and one longer-term relapse prevention trial. Results from 4 of the short-term studies were submitted and reviewed under the original submission to this NDA.[16]

Appendix VI-14 summarizes the efficacy results for the 5 short-term trials at the final visit of double-blind treatment for the modified ITT populations. At least 70% of the modified ITT populations remained in-study at the final visit in each trial. Two of these studies, E106-96B and P0052, provided strong evidence of the acute efficacy of STS in the treatment of depression in outpatients; E106-96B utilized a fixed daily dose of 20mg/20cm^2 whereas the latter study used flexible doses of either 20mg/20cm^2, 30mg/30cm^2, or 40mg/40cm^2.[17] The remaining 3 studies (E113-98B, P9804, and E114-98B) were negative. None of these trials included an active control arm to determine assay sensitivity and the reasons for negative efficacy results are unclear. Nonetheless, the evidence provided by the 2 positive studies is felt to be sufficient to demonstrate the efficacy of STS in the acute treatment of major depression.

Study P9806 demonstrated the efficacy of STS 20mg/20cm^2 daily versus placebo in significantly increasing the time to relapse and reducing the risk of relapse of major depression in remitted outpatients followed over a 52 week period.

VII. Review of New Safety Data

A. Methodology of the Safety Review

This evaluation of the safety of STS consisted of the following five approaches:

1) an assessment of serious adverse events (deaths and non-fatal SAE's) from:

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[16] See the Review and Evaluation of Clinical Data dated 2-28-02.
[17] Studies E106-96B, P0052, and P9806 all enrolled outpatients only; no inpatients were studied in these trials. This information was obtained verbally from Melissa Goodhead, of Somerset Pharmaceuticals, on 12-15-03.

a) the pool of all depression studies (Pool B, as defined in **section IV.A.1,** plus the compassionate use study P0043 with a cut-off date of 4-30-03),
b) studies in other indications,
c) Phase 1 studies, and
d) the 10-29-03 safety update to 3 ongoing studies. In the original NA response, the cut-off date for serious adverse events in three ongoing studies (P0158, P0204, and P0043) was 4-30-03. In this Safety Update, all remaining data for serious adverse events in study P0158 are provided since that study was completed shortly after the submission of the NA response. For the other two studies in this update, cut-off dates for serious adverse events are 9-1-03 (study P0204) and 10-17-03 (study P0043).

Each adverse event was classified by the investigator as serious or non-serious. Serious adverse events were defined as any fatal or immediately life-threatening experience, any permanent or substantially disabling experience, any experience that requires or prolongs inpatient hospitalization, or any congenital anomaly. Events were also to be classified as serious if the event suggests a significant hazard, contraindication, side effect, or precaution. It should be noted that serious adverse event data previously submitted and reviewed under the original submission of this NDA are not repeated in this review.

2) an evaluation of adverse events that led to dropout, common adverse events, application site reactions, laboratory findings, vital sign data, and ECG findings from the primary safety database (Pool A as defined in **section IV.A.1**). These findings are compared to those from study P0052, in which higher mean doses of STS were utilized (roughly 28-35 mg/day), in contrast to the other 4 Pool A studies, which generally used an STS dose of 20mg/day.

3) a review of the results from two Phase 1 safety-related studies, specifically P0201 (tyramine challenge following long-term STS exposure) and P0046 (phenylpropanolamine interaction study).

4) discussion of the results of the sponsor's literature search to identify important safety findings from published articles.

B. Safety Findings

1. Deaths

All Depression Studies (Pool B + P0043)

There were no deaths in any depression study as of 4-30-03.

Studies in Other Indications

Among the 6 new studies in other indications, there was one new death: in the NIH-HIV study (ACTG A5090) that studied two STS doses (10mg/20cm2 and 20mg/20cm2) versus placebo in the treatment of HIV-associated cognitive impairment, one patient died after 8 weeks of blinded treatment due to cardiovascular disease. No further details were provided.

Phase 1 Studies

There were no deaths in the 3 newly completed Phase 1 studies.

Safety Update (10-29-03)

No deaths were reported in the safety update.

2. Non-Fatal Serious Adverse Events

All newly reported non-fatal serious adverse events in STS-treated patients are listed by patient and study in **Appendix VII-1**. All new SAE's in placebo-treated patients are listed in **Appendix VII-2**.

I examined the Narrative Summary for each of these patients. Three of these SAE's are considered possibly related to STS treatment:

- Patient 10088 in study P0052 was a 55 y.o. male who was hospitalized after taking an overdose of diet pills containing ephedrine and 400mg of nortriptyline while wearing two STS 40mg/40cm^2 patches. He was also in possession of a prescription for bupropion 100mg tid. The patient required significant supportive care, including paralyzing agents and endotracheal intubation. He was discharged 10 days later. In the opinion of the investigator, the patient experienced a **serotonin syndrome**

most likely due to an interaction between STS and other ingested agents.

• Patient 10002 in study P0158 was a 34 y.o. female who received STS, up to 40mg/40cm^2 per day, for approximately 15 weeks when treatment was discontinued due to lack of efficacy. During the next week, depressive symptoms worsened and, a week after stopping STS 40mg/40cm^2, she began taking venlafaxine 75 mg/day. Two hours after the first dose, she experienced anxiety, agitation, weakness, diaphoresis, tachycardia, muscle rigidity, and shivering. In the emergency room, she exhibited myoclonic jerks and hyperreflexivity with a pulse of 133 bpm; blood pressure and temperature were WNL. This reaction was felt to be a **serotonin syndrome** and she was hospitalized and treated with iv fluids and diazepam. This event reportedly lasted 31 days after which she recovered fully.

The sponsor conducted a search for cases of possible serotonin syndrome within study Pool B.[18] No other cases possibly indicative of serotonin syndrome were identified.

• Patient 10006 in study P0158 was a 42 y.o. female who experienced a **manic episode** at a dose of 40mg/40cm^2 per day following a total of approximately 10 weeks of STS treatment. She continued STS treatment at lower doses for about the next 2 months and manic symptoms persisted. STS was then discontinued. She was hospitalized for 5 days and subsequently recovered.

The reporting rate for adverse events coded as manic reactions across all Pool B studies was 0.4% (8/2036). In the short-term, placebo-controlled depression studies (Pool A), the rate among STS patients was 0.2% (2/817) versus 0.1% (1/668) among placebo patients.

In addition to the cases listed in the above appendix, 3 patients who received blinded treatment in study NIH-HIV experienced adverse events classified as serious: asymptomatic lipase elevation (2X ULN), right arm paresthesia, and neutropenia (ANC=517). All 3 patients continued treatment despite these events. No further information on these patients was provided.

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[18] The search methodology is described in detail on pages 191-192 of the updated ISS.

3. Dropouts due to Adverse Events

Table VII-1 below displays the proportion of patients in the pool of the 5 short-term, placebo-controlled depression studies (Pool A) who dropped out by reason for dropout and treatment group.

TABLE VII-1
POOL A
ENUMERATION (%) OF DROPOUTS BY REASON

	STS N=817	Placebo N=668
Total Dropouts	207 (25%)	154 (23%)
Adverse Experience	58 (7%)	24 (4%)
Withdrawn Consent	30 (4%)	47 (7%)
Lost to Follow-up	50 (6%)	36 (5%)
Non-compliance	14 (2%)	9 (1%)
Other[19]	55 (7%)	38 (6%)

Only two adverse events led to dropout in ≥1% of STS-treated patients in Pool A: application site reaction (ASR) and depression. The rates of dropout due to these events are displayed in **Table VII-2** below.

TABLE VII-2
POOL A
AE's LEADING TO DROPOUT IN ≥1% OF STS PATIENTS

	STS N=817	Placebo N=668
Application Site Reaction	16 (2%)	0 (0%)
Depression	9 (1%)	10 (2%)

In study P0052, where higher mean doses were utilized, only one adverse event led to dropout in at least 1% of the STS patients: application site reactions led to dropout in 2% (2/132) of STS- and 0% (0/133) of placebo-treated patients.

In the pool of all depression trials (Pool B, N=2036), only two adverse events led to dropout in at least 1% of the STS-treated patients: application site reactions (3%) and insomnia (2%).

I examined the listing of all treatment-emergent adverse events that led to dropout in Pool B.[20] I discovered none

[19] Includes lack of efficacy, protocol violation, and pregnancy.

that, in my judgement, appeared to represent a significant safety hazard possibly related to STS.

4. Common Adverse Events

Appropriateness of Study Pooling

The primary safety database to assess common adverse findings is Pool A, which is comprised of 5 short-term, placebo-controlled, 6- or 8-week studies of STS in depression. Characteristics of these studies are summarized in **Table IV-1** above. Four of the 5 studies employed fixed doses of STS (10 or 20 mg/day) while the fifth study, P0052, utilized flexible dosing (20, 30, or 40 mg/day). Although it was decided that Pool A is reasonable, the findings from this pool will be compared to those in study P0052 alone to evaluate whether the higher mean doses in this trial produced any significant difference in the safety profile of STS.

Coding of Adverse Events

In the original submission of this NDA, serious problems were detected in the coding of verbatim adverse event terms to preferred terms, including: 1) coding under the wrong preferred term, 2) splitting of similar verbatim terms under several different preferred terms, and 3) lumping of dissimilar verbatim terms under the same preferred term. Thus, in the 3-25-02 NA letter, we requested that the sponsor perform a recoding of verbatim terms and provide us with a revised coding dictionary.

Somerset reviewed the COSTART coding of all AE verbatim terms in the original ISS database. They indicate that they have addressed inconsistencies and consensus coding was achieved via a team of coders, with recoding of verbatim terms as necessary.

The new coding conventions were utilized to recode adverse event data from the updated depression study pool (Pool B and, by inclusion, Pool A), all SAE's from the original submission, and adverse experiences from study E101-96B, a placebo-controlled study in patients with Alzheimer's disease reported in the original submission. Safety data from the latter trial was presented separately in the

[20] Updated ISS Table 5.30.

original safety review (dated 3-14-02) because this study was not deemed to be poolable with the depression studies.

Among the 8 deaths discussed in the original NDA, recoding resulted in a change in the COSTART preferred terms in only two cases:

- Patient 1239 in study E101-96B, CNS Neoplasia was recoded to Carcinoma (placebo patient).
- Patient 04006 in study E109-97B, Septic Shock was recoded to Shock (STS patient).

For non-fatal serious adverse events presented in the original NDA, recoding produced the preferred term changes summarized in **Appendix VII-3**. Most of these changes appeared, on face, to be reasonable. Seven of these changes, as indicated in the appendix, were further evaluated by comparison with the patient's Narrative Summary. All were deemed to be acceptable.

In study E101-96B, the reporting rates of 4 of the most common events differed by greater than 1.0% among STS patients. These changes are summarized in **Table VII-3** below.

TABLE VII-3
STUDY E101-96B
DIFFERENCES IN REPORTING RATES AFTER AE RECODING

	Original Coding		Revised Coding	
	STS	Plac	STS	Plac
ASR	56%	8%	43%	7%
Rash	14	11%	26%	11%
Dizziness	17%	14%	15%	14%
Pain	10%	19%	11%	20%

Finally, I audited the coding of verbatim adverse event terms to COSTART preferred terms for all adverse events that were reported in Pool A studies (N=3285 AE codings) from the electronic file AE.XPT for the updated ISS. No remarkable coding problems were noted.

Common, Drug-Related Adverse Events

Appendix VII-4 displays all adverse events in study Pool A which were reported by at least 2.0% of the STS-treated patients. Only one event is considered common and drug-

related: application site reaction (ASR), reported in 23.5% of STS patients and 11.5% of placebo patients.[21] Please see **section VII.B.5** below for further discussion of ASR's.

In study P0052, which utilized higher mean doses, there were 5 adverse events considered common and drug-related. These are listed in **Table VII-4** below.

TABLE VII-4
COMMON, DRUG-RELATED ADVERSE EVENTS IN STUDY P0052

BODY SYSTEM/PREFERRED TERM	STS N=132	PLACEBO N=133
Application Site Reaction	40.2%	20.3%
Insomnia	30.3%	14.3%
Diarrhea	9.8%	3.8%
Pharyngitis	6.1%	2.3%
Back Pain	5.3%	2.3%

Effect of Demographic Characteristics on AE Reporting Rates

The sponsor performed a subgroup analysis of the influence of demography on adverse event reporting rates within Pool A. This entailed a computation of the STS:placebo odds ratio within each subgroup for those events reported by at least 2% of patients.[22] Then, the homogeneity of the odds ratios across the subgroups was done to detect any statistically significant differences between subgroups (alpha=0.0500). Results were provided in the 10-29-03 submission to this NDA.

There were 5 significant findings, which are summarized in **Table VII-5** below.

[21] That is, reported in at least 5% of drug patients at a rate at least twice that in the placebo group.
[22] Demographic variables and subgroups were: gender (male vs. female), age (<50 years vs. ≥50 years), and race (Caucasian vs. non-Caucasian).

TABLE VII-5 SIGNIFICANT DEMOGRAPHIC EFFECTS ON AE REPORTING RATES POOL A STUDIES[23]					
	Males		Females		p-value
	STS N=304	Placebo N=256	STS N=513	Placebo N=412	
Accidental Injury	3.6%	1.2%	2.1%	3.4%	0.0289
ASR	16.1%	14.5%	27.9%	9.7%	0.0001
	<50		≥50		p-value
	STS N=592	Placebo N=506	STS N=225	Placebo N=162	
Rash	3.4%	2.4%	4.4%	0.0%	0.0315
	Caucasian		Non-Caucasian		p-value
	STS N=682	Placebo N=577	STS N=135	Placebo N=91	
Constipation	1.5%	2.8%	3.0%	0.0%	0.0355
ASR	23.9%	9.7%	21.5%	23.1%	0.0012

STS increased the risk of accidental injury among males while slightly lowering the risk among females.

Females appeared to have greater dermal sensitivity to transdermally delivered selegiline than males. Also, non-Caucasians appeared to have greater sensitivity to the non-selegiline components of the patch and less sensitivity to transdermally delivered selegiline than non-Caucasians.

STS increased the risk of rash among older patients more so than among younger patients.

STS increased the risk of constipation in non-Caucasians while lowering the risk among Caucasians.

Adverse Event Dose-Relatedness

Dose-relatedness of adverse event reporting rates cannot be reliably determined since there are no studies with multiple fixed doses of STS within therapeutic range.

[23] Percentages indicate reporting rates. P-values are derived from a Breslow-Day Chi-Square test for homogeneity of odds ratios across subgroups.

5. Application Site Reactions (ASR's)

The application sites for study drug patches were assessed for skin reactions during each clinical study. These assessments were performed by non-dermatologist physician-investigators, many of whom were psychiatrists. These reactions were described as adverse experiences in the Case Report Forms in terminology of the investigator's choice.

In Pool A studies, ASR's were reported in 23.5% (192/817) of STS patients and 11.5% (77/668) of placebo patients. None of these ASR's were classified as serious. Almost all ASR's were considered mild or moderate in severity. Of the 5 STS patients with ASR's graded as severe, 4 occurred in patients who had received a maximum STS dose of 30mg or 40mg. ASR's led to dropout in 2.0% of STS patients and in no placebo patient in Pool A studies.

In study P0052, the incidence of ASR's was approximately double that for Pool A studies in both the STS and placebo groups (40.2% and 20.3%, respectively). These data suggest that ASR's may be related not only to selegiline dose but also to the other components in the patch.

Detailed descriptions of the ASR's were recorded in study P0052. Most of the STS patients with ASR's (74%) were described as minimal or definite erythema. Another 18% had erythema and papules, definite edema, or erythema, edema, and papules. One STS patient experienced a vesicular eruption. Dropout due to ASR's occurred in 2% of STS patients and no placebo patients. ASR's were observed with every application for 50% of the events in STS patients and 67% of the events in placebo patients. Over half of the ASR's (59%) required no treatment. Medication used to treat ASR's consisted most commonly of preparations containing corticosteroids.

In the broader depression study pool (Pool B), ASR's were reported in 29.9% (608/2036) of STS patients. None of these were classified as serious. As in the Pool A studies, almost all were graded as mild or moderate in intensity. Severe ASR's were reported in 18 patients, 12 of whom had received a STS maximum dose of 30mg or 40mg. ASR's led to dropout in 3.1% of STS patients in Pool B.

6. Laboratory Data

Laboratory Assessments

Routine laboratory assessments (hematology, chemistry, urinalysis) were performed at screening and final on-therapy visit in the 5 short-term, placebo-controlled depression trials (Pool A).

Potentially Clinically Significant Laboratory Changes

Criteria for potentially clinically significant (PCS) changes in laboratory values are found in **Appendix VII-5**. **Appendix VII-6** displays the proportions of patients in study Pool A who met these criteria at some time during treatment. For each variable, the number of patients at risk excludes those who met that criterion prior to study treatment. Also, variables for which no STS patient met the criterion are omitted.

The proportion of patients meeting a PCS criterion was significantly greater for STS patients versus placebo (alpha=0.10) for only one laboratory variable: 3.0% of STS patients and 0.8% of placebo patients experienced a high total T_4 level during treatment (p=0.02). There were no significant differences for high T_3 or high or low TSH levels. A similar finding was observed in the original NDA safety database and it was felt that no definitive conclusions could be drawn without knowing the free T3 and T4 levels.

To follow-up on this finding, Somerset was requested to assay free T_4 (FT4) levels in future trials in the NA letter. In response, they did amend two protocols to measure FT4 levels:

- in the double-blind study P0052, most of the patients had completed the study at the time of the protocol amendment and the window of stability for stored serum samples was exceeded for most of the specimens. The study report contains the week 8 results for FT4 on 47 patients (26 treated with STS and 21 treated with placebo). Baseline values were not available but mean values at week 8 were 1.0 ng/dL (SD=0.1) for both STS and placebo patients. None of the observed values were outside reference range (0.7-1.9 ng/dL).

• in the open-label study P0204, both baseline and on-treatment determinations of FT4 were obtained in 139 STS-treated patients. According to the interim safety report for this trial, there was only a small change from baseline: mean FT4 of 1.1 ng/dL at baseline and 1.3 ng/dL at end of study, for a mean change of +0.2 ng/dL. There were no values outside the normal reference range.

These data, although based on a limited number of patients, do suggest that the elevations in total T_4 are likely to be due to increased protein-bound hormone and not FT4.

PCS laboratory data from study P0052 was remarkable for only one finding: among males, 13% (6/45) of STS patients and no placebo patients (0/47) were found to have RBC's in their urine (p=0.01). Four of these 6 patients received 40 mg/day and 2 received 20 mg/day at the time of the abnormality. There was no significant difference between STS and placebo among female patients in study P0052 nor among males or females in study Pool A with respect to urine RBC's. In study P0052, urinary tract infections were reported in 2% of both STS and placebo patients; hematuria was reported by only one (0.8%) STS-treated patient. The clinical significance of this finding is unknown.

Mean Change from Baseline in Laboratory Values

Appendix VII-7 displays the mean changes from baseline to end of study for laboratory variables in study Pool A.

A number of the changes are statistically significantly different between the STS and placebo treatment groups (alpha=0.10). However, the magnitude of each change is small and none, in my judgement, is clinically significant.

Similar findings were observed in study P0052.

Dropouts due to Laboratory Abnormalities

No patients in Pool A studies prematurely discontinued study participation due to a laboratory test abnormality.

7. Vital Sign Data

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 all 5 Pool A studies. In studies E106-96B and E114, supine and standing blood pressure and heart rate were measured; in study P0052, sitting and standing blood pressure and heart rate were measured; and in studies E113-98B and P9804, only sitting blood pressures and heart rates were measured.

Clinically Notable Vital Sign Changes

Clinically notable changes in vital sign measures are defined in **Appendix VII-8**.

The proportions of patients who met these criteria during Pool A studies are displayed in **Appendix VII-9**. For most vital sign variables, the differences between STS and placebo were not statistically significant (alpha=0.10). But the difference was significant for two measures:

- 3.0% of STS patients and 1.5% of placebo patients experienced a low systolic blood pressure (p=0.06).
- 5.0% of STS and 2.8% of placebo patients experienced a notable decrease in body weight (p=0.03).

Also, a larger proportion of STS patients were found to have a notable orthostatic change in blood pressure (≥10 mmHg decrease in mean BP) compared to the proportion in the placebo group (9.8% vs. 6.7%; p=0.12). The sponsor indicates that these occurrences did not occur at any consistent timepoint during treatment. Lower percentages of patients had a notable orthostatic drop in mean blood pressure and either hypotension or postural hypotension reported as an adverse event or another event potentially associated with orthostatic hypotension (1.1% of STS and 0.3% of placebo patients; p=0.12).[24] **Appendix VII-10** presents the reporting rates of adverse events possibly related to orthostatic hypotension in Pool A studies. The proportion of STS patients experiencing an event was

[24] Events considered potentially associated with orthostatic hypotension were amblyopia, dizziness, accidental injury, spontaneous bone fracture, syncope, and vertigo.

significantly greater than that in the placebo group for only one event, vertigo (1.2% versus 0.1%; p=0.03).

In study P0052, 6.2% (8/129) of STS and 0.0% (0/128) of placebo patients experienced a low standing systolic blood pressure (p=0.007). No other significant findings were observed.

About 8.5% of STS and 7.0% of placebo patients experienced an orthostatic change in mean blood pressure by the above referenced criterion in study P0052 (p=0.7). This is not substantially different from the findings in Pool A, where 9.8% of STS and 6.7% of placebo patients met the criterion. Approximately 3.8% of STS and 0.8% of placebo patients reported postural hypotension as an adverse event in P0052. The STS:placebo odds ratio for reports of postural hypotension as an adverse event was considerably higher in study 0052 versus Pool A (5.2 vs. 1.9); these odds ratios were not significantly different, however (p=0.4350; Breslow-Day test for homogeneity of odds ratios).[25]

Mean Change from Baseline in Vital Sign Readings

Mean changes from baseline in vital sign measurements in Pool A studies are summarized in **Appendix VII-11**.

The only remarkable finding was a mean change in body weight of -1.2 lbs among STS patients versus a gain of +0.3 lbs in the placebo group (an intergroup difference of 1.5 lbs.).

Mean vital sign changes in study P0052 were more notable and are depicted in **Appendix VII-12**. There were larger differences between STS and placebo with respect to mean changes from baseline in sitting and standing systolic blood pressure (mmHg):

	STS	Placebo
Δ sitting SBP	-4.3	-1.2
Δ standing SBP	-5.7	-0.8

The larger differences may reflect the higher mean doses utilized in this trial.

[25] Breslow-Day testing was performed by Dr. Yeh-Fong Chen.

The mean change in weight was similar to that seen in the larger Pool A: a decrease of about 1.5 lbs relative to placebo.

Dropouts due to Vital Sign Abnormalities

In Pool A, 0.4% (3/817) of STS and 0.0% (0/668) of placebo patients dropped out due to hypertension (p=0.26). One of these patients was receiving STS 40 mg/day in study P0052 at the time of dropout.

Search for Cases of Possible Hypertensive Crisis

The sponsor conducted a search of the depression clinical trials database for any occurrence of hypertensive crisis associated with the use of STS.[26] The database encompassed 2036 STS patients and 831 placebo patients.

They indicate that there were no cases judged to be representative of hypertensive crisis. However, they did identify one case which suggested an interaction between STS and albuterol resulting in elevated blood pressure:

- Patient 10079 in study P0158 had taken STS for about 17 weeks when she began treatment with albuterol inhaler for shortness of breath. A few days later, she experienced an acute episode of severe headache, sweating, stiff neck, and palpitations. This episode resolved spontaneously within 15 minutes and she went to work, where her blood pressure was recorded as 170/100 (baseline 146/94). She stopped albuterol and, 2 days later, was discontinued from the trial. Her last STS dose was 30 mg/day. Her blood pressure was 171/109 at termination.

Given her duration of previous treatment with STS without similar blood pressure elevation, a role for STS itself seems less likely. It is not clear to what extent this event is attributable to albuterol versus an interaction between albuterol and STS. Nonetheless, an interaction cannot be ruled out. Also, it is notable that the labeling for albuterol inhalation products does advise extreme caution when these are used with MAOI's or within 2 weeks of stopping MAOI's since such use can potentiate the effect of albuterol on the cardiovascular system.

[26] The methodology for this search is described in detail on pages 179-180 of the updated ISS.

8. ECG Data

ECG Assessments

In the Pool A studies, 12-lead ECG's were performed at screening, mid-treatment, and at the end of treatment except for studies E113-98B and P0052, which did not perform mid-treatment ECG's.

The ventricular rate was recorded in all 5 studies. However, the PR, QRS, and QTc intervals were recorded in only 3 of these trials (E106-96B, E114, and P0052).[27]

Potentially Clinically Significant ECG Changes

Criteria for potentially clinically significant (PCS) ECG changes are displayed in **Appendix VII-13**.

The proportions of patients in Pool A studies who met these criteria are depicted in **Appendix VII-14**. The proportion of patients with PCS changes was greater in the STS group compared to placebo for only 2 parameters:

- increased heart rate (0.5% in the STS group and 0.3% in the placebo group).
- increased PR interval (1.3% in the STS and 0.3% in the placebo group).

Neither of these differences was statistically significant (p=0.7 and 0.3, respectively).

No STS-treated patient in any Pool A study had a QTc greater than 480 msec.

In study P0052, there were no significant differences between STS and placebo in the fraction of patients meeting PCS ECG criteria for heart rate or PR, QRS, or QTc intervals.

Mean Change from Baseline in ECG Parameters

Appendix VII-15 presents the mean changes from baseline to end of study in ECG measurements for patients in Pool A studies. Changes were small and not considered clinically significant.

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[27] The method utilized for correcting the QT interval was not specified.

Mean changes observed in study P0052 were likewise small and deemed clinically insignificant.

Dropouts due to ECG Abnormalities

There were no dropouts due to ECG abnormalities in Pool A studies.

9. Phase 1 Safety-Related Studies

Study P0201 (Long-Term Tyramine Challenge Study)

This study was conducted to address our concern that longer durations of STS exposure may produce greater pressor effects with tyramine.

Study Design
This was a single center, open-label, multiple dose, six period study of tyramine pressor doses after the administration of oral tyramine to non-obese, healthy male volunteers, age 18-60, before and during long-term treatment with STS 40mg/40cm^2.

Period 1 (Days 1-3) and Period 2 (Days 8-10) allowed for baseline determination of cardiovascular sensitivity to oral tyramine in fasting subjects.

Periods 3 (Days 41-43), 4 (Days 71-73), and 5 (Days 101-103) examined response to tyramine in the fasted state during STS treatment.

Period 6 (Days 104-106) evaluated the pressor response to tyramine in the fed state during STS treatment. This was added to the original protocol as an optional study period, according to Protocol Amendment #4 submitted 10-15-02.

STS administration began on Day 11 and continued through Day 106. Dosing consisted of STS 40mg/40cm^2 throughout this 96 day interval. Patches were placed on the torso after washing and drying the skin area at 8:00 (±1 hour) each day and removed after 24 hours.

Use of concomitant medications, including vitamins and food supplements, was excluded by protocol. With respect to fasting measurements, subjects were required to fast for at least 8 hours prior to tyramine administration and 4 hours

post-administration. In period 6, the tyramine dose was administered mid-way through a standardized meal.[28]

Tyramine Challenge
During each period, the tyramine pressor dose was determined through a series of 3 tyramine challenges performed 24 hours apart according to a prespecified algorithm. The tyramine pressor dose (TYR30) was defined as the minimal dose of tyramine required to produce a sustained increase in systolic blood pressure (SBP) of 30 mmHg or more.[29]

Based on published studies, the sponsor states that an ED_{50} for 450mg of tyramine has been reported to produce an increase in SBP of at least 30 mmHg in healthy, non-medicated patients. Thus, a starting dose of 400mg of tyramine was selected for baseline assessments in this study. Lower doses were selected for challenges performed during STS exposure.

The algorithms for tyramine dosing during each study period are displayed in **Appendix VII-16.**

Thirty minutes prior to each tyramine dose, each subject assumed a semi-recumbent position. After 5 minutes, a series of 3 blood pressure and heart rate measurements were done 3 minutes apart using a ambulatory blood pressure monitor. The systolic readings had to be within 7 mmHg of the previous reading and a maximum of only 10 mmHg difference among the 3 consecutive systolic readings was allowed; otherwise, blood pressure readings were repeated until these criteria were met. The average of the 3 blood pressure values was considered the baseline value.

After each tyramine dose, blood pressure was measured every 5 minutes for 2 hours and every 15 minutes from 2 to 6 hours post-dose.[30] Subsequent readings and therapeutic interventions (e.g., labetolol) at any time were at the discretion of the investigator. If the systolic blood

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[28] The meal consisted of 3 pancakes, 2 eggs, hash browns, 2 strips of bacon, a biscuit, and 8 ounces of orange juice.
[29] During the baseline periods, however, the TYR30 was defined as the average of the 3 tyramine pressor doses for each period.
[30] Except in Period 6 where, to allow for a possible delay in tyramine absorption in the fed state, BP was assessed every 5 minutes for 4 hours and every 15 minutes from 4 to 6 hours post-dose.

pressure increased by greater than or equal to 30 mmHg compared to the baseline value for 3 consecutive readings, that dose was considered the TYR30.

Study Results
A total of 25 subjects were enrolled, 24 received tyramine, and 20 received STS; 18 received STS for at least 33 days. Eleven subjects completed the study according to the original protocol (Periods 1-5) and an additional 8 subjects completed the original protocol as well as the optional Period 6 (under fed conditions).

There were no deaths and only one serious adverse event during the study: Subject 001 experienced jaundice and markedly elevated transaminases on Day 49. Diagnostic tests indicated acute hepatitis B infection, which was not felt to be related to the study drug. Four other subjects discontinued due to adverse events: first-degree heart block during a Period 4 tyramine challenge (Subject 008), orthostatic hypotension with two episodes of syncope resulting in lacerations (Subject 016), contact dermatitis (Subject 021), and rash with facial, lip, and tongue swelling (Subject 022).

The observed mean tyramine pressor doses for each Period are presented for all subjects in **Appendix VII-17**.[31] The largest and statistically significant decline in fasting mean tyramine pressor dose occurred between Periods 1/2 and Period 3 (from 575mg to 84mg; $p<0.0001$). The decline between Period 3 and 4 was much smaller (from 84mg to 66mg). There was a small increase between Period 4 and 5 (from 66mg to 88mg). A similar pattern of effects are seen in an examination of the 11 completers (see **Appendix VII-18**).

The mean reduction in tyramine pressor dose in Period 6 (under fed conditions) was less than in the fasted state (see **Appendix VII-19**). In the 8 subjects who completed all 6 Periods, the mean Period 5 tyramine pressor dose was 64mg versus 172mg in Period 6 ($p<0.0023$).

Under fasted conditions, pressor doses as low as 25mg were seen in study P0201. Under fed conditions, the minimum observed pressor dose was 75mg.

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[31] For individuals where a TYR30 was not achieved, the highest administered tyramine dose was used in calculations.

These data suggest that the cardiovascular pharmacodynamic effect of tyramine was much greater after 30 days of STS treatment compared to pre-treatment and that this effect remained stable over the 30 to 90 day STS treatment period.

An alternative manner of examining tyramine challenge data is to compute the tyramine sensitivity factor (TSF). The TSF is the ratio of the tyramine pressor dose observed at baseline to that observed on drug. The TSF calculation corrects for individual differences in baseline pressor dose. Corresponding TSF data are displayed in **Appendix VII-20**. Again, the TSF appears not to change substantially across Periods 3, 4, and 5. Also, the TSF at Period 6, under fed conditions, is considerably lower than during the preceding 3 fasting periods on STS.

Leonard Kapcala, M.D., the Medical Officer assigned to oral selegiline, has considerable experience reviewing tyramine challenge studies and performed some additional analyses on the data from this study. Specifically, since a typical tyramine-rich meal contains 40mg of tyramine, he examined the proportions of patients who exhibited a TYR30 close to or below 40mg. His data are presented in **Table VII-6** below. Although no patients in the fed state (Period 6) had a pressor dose close to 40mg, it is notable that a substantial proportion of patients under fasting conditions (Periods 3-5) had a pressor dose of 50mg or under and, after 30 days of STS treatment (Period 3), almost one-fourth of the patients had a pressor dose of 25mg.

TABLE VII-6
NUMBER (%) OF PATIENTS WITH LOW TYRAMINE PRESSOR DOSES

	Study Period				
	1&2 (N=18)	3 (N=18)	4 (N=14)	5 (N=11)	6 (N=8)
TYR30 ≤50mg	0(0%)	11(61%)	7(50%)	5(45%)	0(0%)
TYR30 =25mg	0(0%)	4(22%)	2(14%)	0(0%)	0(0%)

In addition, I compared these data to data obtained under fasting conditions in previous studies that were reviewed in the initial submission to this NDA. Remarkably, the mean pressor dose in study P0201 after 30 days of STS exposure was lower than that observed in a previous study of shorter duration (10 days) with the 40mg patch reviewed in the initial safety review (84mg versus 198mg) and considerably less than the pressor dose after 9 days of oral selegiline 5mg bid (357mg), which is marketed without

dietary restrictions.[32] The mean pressor dose for tranylcypromine, the active control in the previous trial, was 10mg; that for fluoxetine, the negative control, was 408mg. As expected, the TSF in P0201 was considerably higher than that observed in the previous study for STS and fluoxetine (11.5 vs. 3.5 and 1.4, respectively) but less than that for tranylcypromine (40). Of course, differences between studies are difficult to interpret with certainty and it is unfortunate that study P0201 did not include treatment arms with positive and negative controls.

The sponsor contends that the data obtained during the fed state provide a more "real world" indication of the amount of tyramine in food that must be ingested to produce a hypertensive event. But, it is not clear that the standardized meal that was served to these subjects with tyramine in Period 6 provides a reasonable representation of food consumption that might occur in depressed patients using STS. For example, if a patient were to ingest cheese and wine on an empty stomach, conditions may more closely resemble those of a fasted state (Periods 3, 4, and 5) than those observed in Period 6. Although the minimum pressor dose in the fed state (75mg) is above 40mg, the margin of safety is not large and may be significantly reduced in many patients likely to be treated with STS after approval due to factors such as increased cardiovascular sensitivity, concomitant medications, and higher plasma levels of selegiline compared to the healthy volunteers studied in this trial.

The sponsor argues that over 2,000 depressed patients have been safely treated with STS in clinical trials in the absence of dietary restrictions, including over 400 patients using the 30mg or 40mg patch, without a single occurrence of hypertensive crisis. I do not find this argument very persuasive, however. Most of these patients were not closely monitored for blood pressure changes and the extent to which they consumed moderate to large amounts of tyramine in their diets is unknown.

Interestingly, there have been rare reports of hypertensive reactions with ingestion of tyramine-containing foods in patients taking recommended doses of oral selegiline.[33] Given the dose-related loss of MAO selectivity with selegiline and the fact that STS produces much higher

[32] See page 44 of the 3-14-02 safety review.
[33] See the WARNINGS section of Eldepryl labeling.

plasma levels of selegiline than equivalent oral selegiline doses, reports of hypertensive reactions with ingestion of tyramine-containing foods during STS therapy can be expected.

Additionally, a point raised by Dr. Kapcala in his analysis of these data is the wide intrasubject variability in tyramine pressor doses that was observed between the 2 baseline periods (see **Table VII-7** below). It is remarkable that over 50% of the subjects exhibited a difference in TYR30 between the 2 baseline periods of at least 100mg and 17% had a difference of at least 200mg; one subject had a difference of 300mg. These data suggest that patients in clinical settings are also likely to exhibit wide variation in their response to tyramine. Therefore, it seems prudent to demand a wide margin of safety before omitting dietary restrictions from STS labeling.

TABLE VII-7
VARIATION IN BASELINE TYR30 DOSES

Difference Between Two Baseline Tyramine Pressor Doses (TYR30) (Periods 1&2)	**N(%)** N_{total}=18
0 mg	8 (44%)
100 mg	7 (39%)
200 mg	2 (11%)
300 mg	1 (6%)
≥100 mg	10 (56%)
≥200 mg	3 (17%)
>300 mg	0 (0%)

For these reasons, I feel that dietary restrictions should be exercised during and for 2 weeks after STS therapy.

Study P0046 (Phenylpropanolamine Interaction Study)

Summary data for this study were reviewed in the original safety review of this NDA. Due to some blood pressure elevations of potential clinical concern, we asked the sponsor to submit the full study report for our review. The review below is based on the full study report submitted on 4-5-02.

Study Design
This was an open-label, single-center investigation of the pharmacokinetics, pharmacodynamics, and safety of STS 20mg/20cm^2 and phenylpropanolamine (PPA) given alone and in

combination. The study was conducted in non-obese, healthy male volunteers, age 18-45.

The trial was conducted in 3 phases:

- PPA alone: PPA 25mg was given at 8:00 on Day 1. On Day 2, PPA 25mg was given every 4 hours for 24 hours (6 doses). Doses were at least 1 hour before or 2 hours after meals.
- STS alone: STS 20mg/20cm2 was applied to the upper torso at 8:00 daily and removed 24 hours later on Days 5-11.
- PPA plus STS: PPA 25mg and STS 20mg/20cm^2 were co-administered at 8:00 on Day 12. On Day 13, STS 20mg/20cm^2 was applied at 8:00 and PPA 25mg was given every 4 hours for 24 hours beginning at 8:00.

Blood pressure was monitored using a [redacted] blood pressure monitor. Thirty minutes prior to each PPA dose on Days 1, 2, 3, 12, 13, and 14, each patient assumed a semi-recumbent position and, 5 minutes later, a series of blood pressure measurements was taken at 3 minutes intervals. Measurements were repeated until 3 consecutive readings were within 7 mmHg of the previous reading and all 3 were within 10 mmHg of each other. The mean of those 3 readings was taken as the baseline for that dosing period.

On Days 1 and 12, blood pressure measurements were obtained every 10 minutes from the time of dosing until 4 hours post-dose. On Days 2, 3, 13, and 14, blood pressure was measured every 10 minutes for 2 hours after dosing and then every 30 minutes until the next baseline measurements.

Subjects were not to take concomitant medications (either prescription or OTC) without prior permission from the investigator. Alcohol, caffeine/xanthine-containing drinks or food, any type of wine, and grapefruit juice were prohibited within 24 hours of study entry.

Study Results

Eleven patients completed all 3 phases of the trial. There were no deaths and only one serious adverse event: Subject 08 experienced a dislocated shoulder during the second study phase and was discontinued due to a requirement for prohibited concomitant medication for that condition.

The mean maximum changes in systolic and diastolic blood pressure and heart rate are displayed in **Appendix VII-21**. Most of the differences between the corresponding PPA and

(PPA+STS) means were not statistically significant and there was no clear pattern of differences. For example, in terms of systolic blood pressure, only the post-dose values after the single PPA dose on Days 1 and 12 were significantly different, with a greater mean maximum change with co-administration (+17 mmHg with PPA and +24 mmHg after PPA + STS; p=0.08). However, after the second and third doses of PPA during multiple dosing on Days 2 and 13, the mean maximum changes after PPA alone were numerically greater than with the combined administration.

There were 4 subjects who met predetermined criterion for a pressor response (i.e., three consecutive systolic BP readings at least 30 mmHg above the pre-dose baseline value). These patients are summarized in **Appendix VII-22**. Three of the 4 subjects experienced a pressor response while taking PPA with STS; the fourth had a pressor response after PPA alone. The increases in systolic BP were in the range of 41-46 mmHg. According to the sponsor, none of these findings was associated with adverse events and none required clinical intervention.

Pharmacokinetic data from this trial revealed no major effect of STS on the pharmacokinetic characteristics of PPA.

In sum, this study produced no clear evidence of a pharmacodynamic interaction between PPA and STS in terms of mean maximal changes in blood pressure and heart rate. Also, there was no substantial effect of STS on PPA pharmacokinetics. However, the higher incidence of pressor responses with combined exposure suggests that some patients who receive both drugs concurrently may experience large increases in systolic blood pressure.

10. Results of Literature Search Update

The methodology for the sponsor's updated literature search is described in **section IV.B.**

A total of 2,186 articles were identified and, of these, 80 were reviewed in their entirety by Somerset's medical/scientific team. Among the papers reviewed in detail, 41 were felt to contribute relevant data. These are listed and summarized under Tab H of the 10-29-03 submission to this NDA. With the exception of two studies

in major depression, investigations involved the administration of oral formulations of selegiline.

Somerset states that, in all studies reviewed, selegiline was well tolerated and no information emerged that represented additional safety concerns for individuals receiving recommended doses of selegiline. No unexpected side effects or previously unknown toxicities of selegiline were revealed.

C. Adequacy of Exposure and Safety Assessments

The sponsor has adequately responded to the safety concerns conveyed in our 3-25-02 NA letter.

In our 5-2-02 meeting with the sponsor, we concurred that a total of 150-200 patients exposed to STS doses of $30mg/30cm^2$ or $40mg/40cm^2$ for at least 3 months would provide adequate exposure for safety assessment at these higher doses. In Pool B studies, it appears that a total of 227 patients have been exposed to one of these doses for at least 12 weeks (see **Appendix IV-3**).

In general, safety assessments were adequate. The only remarkable deficiency is the lack of free T_4 (FT4) levels in an adequate number of patients under placebo-controlled conditions. Nonetheless, the data provided by the sponsor from studies P0052 and P0204 do provide some reassurance that the observed increases in T_4 are likely to be due to an increase in bound T_4 and not free T_4.

D. Assessment of Data Quality and Completeness

An audit of adverse event documentation, which is described in **section V.B**, revealed no discrepancies among CRF's, narrative summaries or dropout line listing summaries, and adverse event data listings.

It appears that the sponsor has appropriately addressed our concerns regarding the coding of adverse experiences in the original submission. An audit of adverse event coding to COSTART terms in study Pool A, which is described in **section VII.B.4**, revealed no remarkable errors or inconsistencies.

E. Summary of Safety Findings

This safety review revealed the following notable findings:

- application site reactions (ASR's) are common, drug-related events, occurring in 40% of STS and 20% of placebo patients treated in the short-term, flexible dose trial P0052 which utilized STS doses of 20mg/20cm^2, 30mg/30cm^2, or 40mg/40cm^2. Most ASR's were mild or moderate in severity and consisted of erythema, edema, and/or papules. None were considered serious. In this study, 2% (2/132) of STS patients (and no placebo patients) prematurely discontinued due to ASR's. Over half of ASR's required no treatment. See **section VII.B.5** for further discussion of ASR's.
- there were a greater number of common, drug-related adverse experiences in study P0052, which utilized higher mean doses of STS, than in the pool of all short-term, placebo-controlled, depression trials (Pool A), where mean doses were considerably lower. In Pool A, ASR's were the only common and drug-related events. In study P0052, the following were common and drug-related: ASR's, insomnia, diarrhea, pharyngitis, and back pain. See **section VII.B.4** for further details.
- tyramine pressor doses decreased considerably within the first month of treatment with STS 40mg/40cm^2 per day in study P0201. However, there were no further appreciable decreases after the second and third months of such treatment. Nonetheless, the apparent margin of safety observed in this study was not large. I feel that dietary restrictions should be exercised during and for 2 weeks after STS therapy. Please see **section VII.B.9** for further information and discussion.
- Study P0046, which examined the potential for STS to potentiate blood pressure and heart rate elevation secondary to phenylpropanolamine (PPA), produced no clear evidence of a pharmacodynamic interaction between PPA and STS in terms of mean maximal changes in blood pressure and heart rate. There was no substantial effect of STS on PPA pharmacokinetics. However, there were a greater number of patients with pressor responses during combined STS plus PPA exposure compared to either drug alone, suggesting that some patients who receive both drugs concurrently may experience large increases in systolic blood pressure. See **section VII.B.9** for further details.
- There were two cases of possible serotonin syndrome classified as serious adverse events: one occurred when a supratherapeutic dose of STS was taken with an overdose of

nortriptyline and ephedrine and the second when venlafaxine was taken a week after discontinuing STS. Please see **section VII.B.2** for details. These cases suggest that some patients may experience serious adverse events due to pharmacodynamic interactions between STS, on the one hand, and sympathomimetic drugs, TCA's, or SNRI's, on the other hand.

Otherwise, the sponsor has adequately responded to the safety concerns conveyed in the 3-25-02 NA letter.

There were no safety findings that would, in my opinion, preclude approval of STS in the daily doses of $20mg/20cm^2$, $30mg/30cm^2$, or $40mg/40cm^2$ for the treatment of major depression.

VIII. Dosing, Regimen, and Administrative Issues

In the 3 positive efficacy trials (E106-96B, P0052, and P9806), STS patches were applied to either the upper torso or upper arm. It is not known whether these two sites produce bioequivalent exposures to selegiline.

Based on Dr. Kavanagh's assessment, it does appear that application to the upper buttock produces higher, non-bioequivalent sele60giline concentrations compared to the upper torso and upper thigh; the latter do appear to produce bioequivalent exposures.

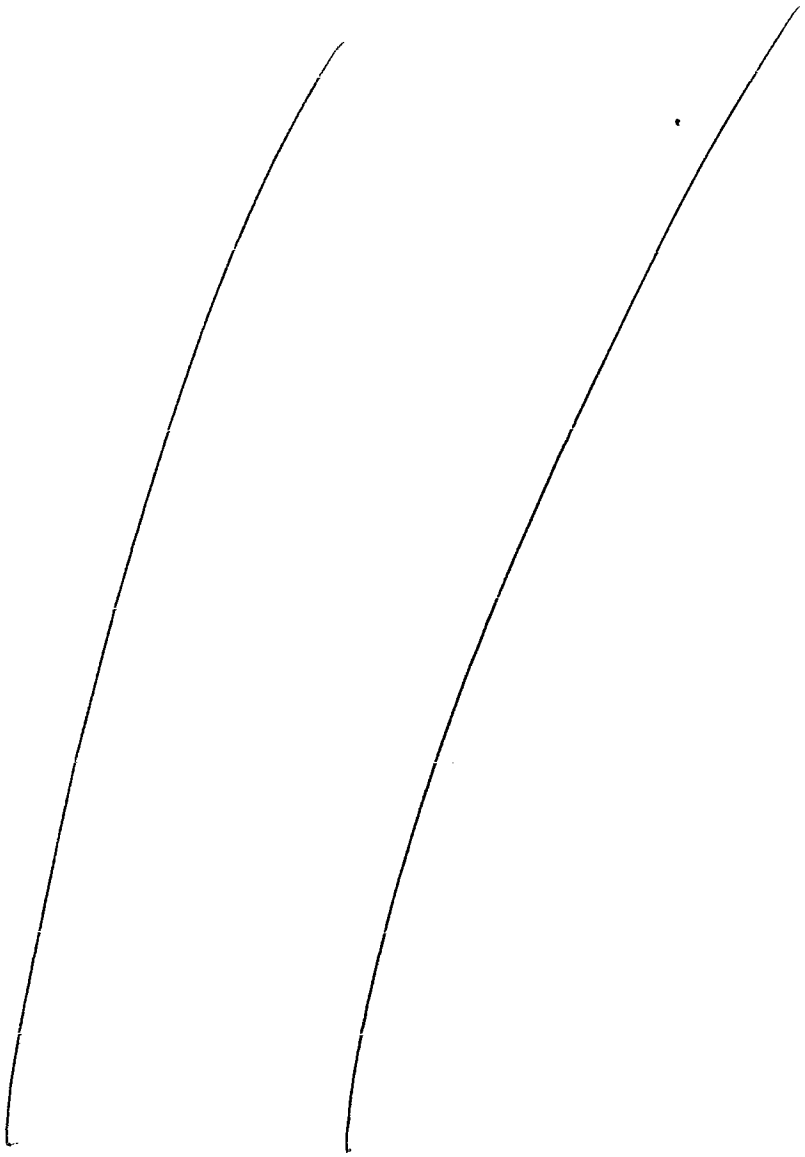
The sponsor is proposing that STS patches be applied to the upper torso, upper thigh, Strictly speaking, such advice is not supported by available data. It is reasonable to advise administration to the upper torso or upper arm since these sites were used in the key efficacy trials; also, application to the upper thigh is reasonable given bioequivalence to the upper torso site. should not be recommended.

Additionally, as discussed in **section VII.B.9**, I am reluctant to recommend approval of STS without typical MAOI dietary restrictions.

IX. Review of Proposed Labeling

The following labeling review is based on the clinical portions of the sponsor's Final Proposed Labeling dated

7-25-03.[34] In addition to the changes discussed below, it is suggested that the sponsor prepare a Medication Guide in accordance with 21 CFR 208.20 to insure that each patient is provided with information regarding a tyramine-restricted diet.



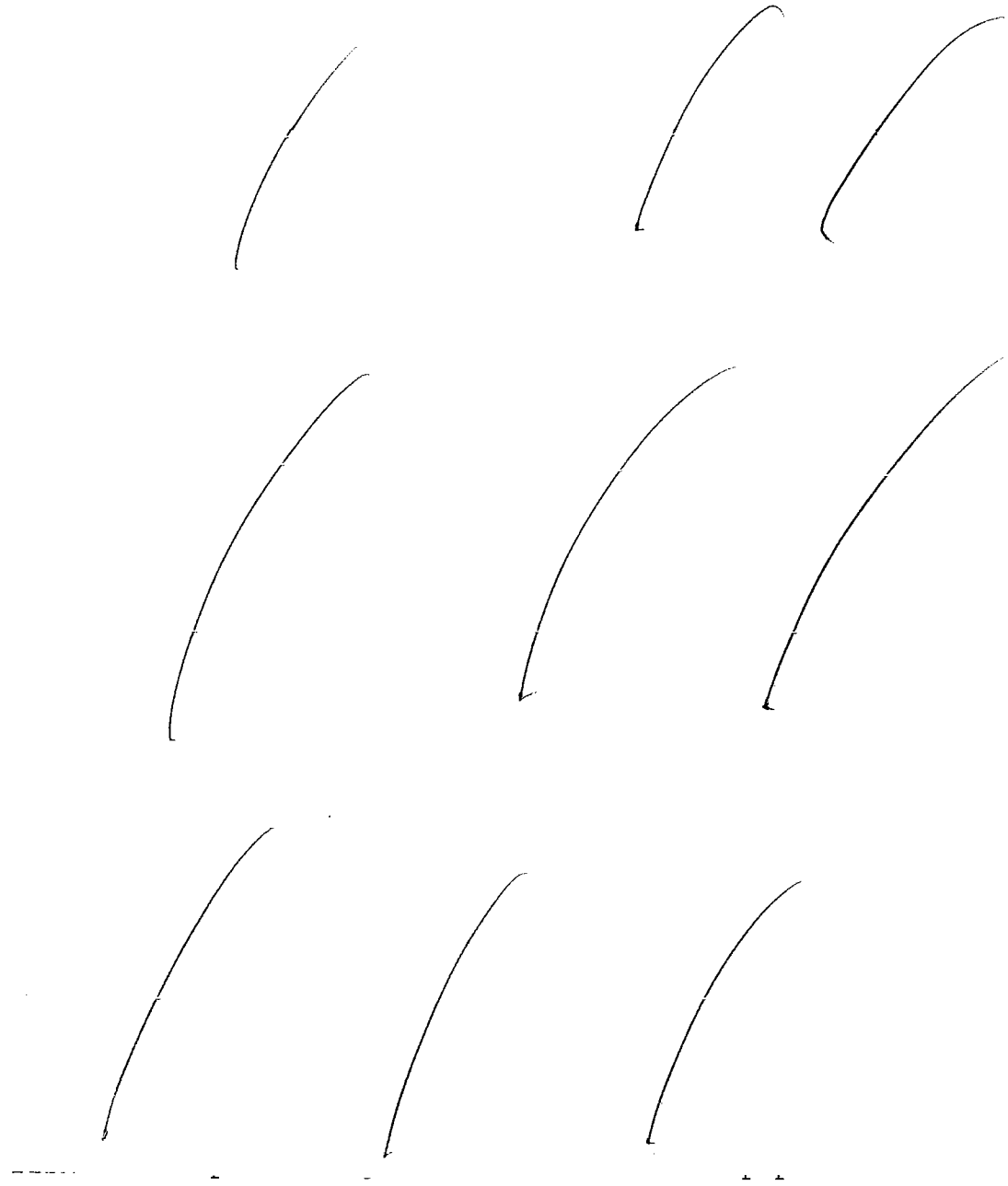
[34] This labeling was submitted in hardcopy in the 7-31-03 submission and received electronically as a WORD document from the Project Manager, Dr. Bates, on 10-20-03.

7 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process



X. Conclusions and Recommendations

The sponsor has presented adequate information to show that STS is reasonably safe and efficacious in the acute and longer-term treatment of major depression in 20mg/20cm^2, 30mg/30cm^2, and 40mg/40cm^2 patches.

From a clinical standpoint, it is recommended that this application be approved with the labeling changes delineated in **section IX** above and a Medication Guide in accordance with 21 CFR 208.20 to insure that each patient is provided with information regarding a tyramine-restricted diet.

Gregory M. Dubitsky, M.D.
December 16, 2003

cc: NDA 21-336
HFD-120/Division File
HFD-120/GDubitsky
/TLaughren
/PAndreason
/DBates

SECTION XI
APPENDICES

APPENDIX IV-1 TABLE OF NEW STUDIES	
PHASE 1 TRIALS	
P0051	Randomized, open-label, 6-way, 3-treatment, 3-period crossover study of the selegiline pharmacokinetics of alternate STS application sites. N=27 normal volunteers. STS 20mg/20cm^2 daily for 30 days.
P0156	Open-label, parallel group study of MAO-A and MAO-B inhibition. N=25 normal volunteers. STS 20mg/20cm^2, 30mg/30cm^2, or two 20mg/20cm^2 daily for 10 days.
P0201	Open-label, oral tyramine challenge study during long-term STS treatment. N=25 normal volunteers. STS 40mg/40cm^2 daily for 96 days; encapsulated tyramine 12.5 to 700mg.
PHASE 2/3 TRIALS	
Short-term, Placebo-Controlled Studies in Major Depression	
P0052	Double-blind, placebo-controlled, parallel group study. N=265. Flexible dose STS 20mg/20cm^2, 30mg/30cm^2, or 40mg/40cm^2 daily for 8 weeks.
Long-term, Relapse Prevention Studies in Major Depression	
P9806	10 weeks of open-label treatment with STS 20mg/20cm^2 daily followed by randomization and up to 52 weeks of double-blind treatment with 20mg/20cm^2 or placebo. N=675.
Open-label, Ongoing in Major Depression	
P0158	52 week open-label extension to study P0052 with identical dosing. N=191.
P0204	Open-label study of flexible dose STS 20mg/20cm^2, 30mg/30cm^2, or 40mg/40cm^2 for 16 weeks. N=152 elderly and non-elderly patients.
Ongoing, Compassionate Use Study in Depression	
P0043	Open-label, compassionate use of STS 20mg/20cm^2 in depressed patients.
Studies in Other Indications	
E109-97B	Double-blind, placebo-controlled, 12-week study of STS 15mg/15cm^2 in 191 patients with late-stage Parkinson's disease.
P9937	Open-label, ascending dose study in [redacted] STS 10mg/20cm^2 for 4 weeks then STS 15mg/15cm^2 for 4 weeks. [redacted] TS 15mg/15cm^2 for 4 weeks then STS 20mg/20cm^2 for 4 weeks.

APPENDIX IV-1 TABLE OF NEW STUDIES	
P0044	Open-label 15-week extension to [redacted] study P9937. N=27. [redacted] STS 10mg/20cm^2 or STS 15mg/15cm^2. [redacted] . STS 15mg/15cm^2 or STS 20mg/20cm^2.
NIH-HIV ACTG A5090	Double-blind, placebo-controlled, 24-week study of STS 10mg/20cm^2 or 20mg/20cm^2 in 28 patients with HIV-associated cognitive impairment. Ongoing at the time of NA submission.
P9935	Open-label study of STS 20mg/20cm^2 daily for 12 weeks in 20 patients [redacted]
NIDA-1019	Double-blind, placebo-controlled, 8-week study of STS 20mg/20cm^2 in 300 patients with cocaine addiction.

APPENDIX IV-2 POOL A DEMOGRAPHIC CHARACTERISTICS			
		STS N=817	**Placebo N=668**
AGE	Mean (yrs)	41.3	41.6
	Range (yrs)	17-70	18-68
	% <65 yrs	99.4%	99.3%
	% ≥65 yrs	0.6%	0.7%
GENDER	% Male	37.2%	38.3%
	% Female	62.8%	61.7%
RACE	% Caucasian	83.5%	86.4%
	% Black	6.9%	4.5%
	% Asian	0.9%	1.3%
	% Hispanic	6.5%	6.4%
	% Other	2.3%	1.3%

APPENDIX IV-3 POOL B: PATIENT ENUMERATION BY MAXIMUM DOSE AND DURATION				
Duration (weeks)	**All STS**	**Maximum Dose[36]**		
		10mg/20cm^2	**20mg/20cm^2**	**30mg/30cm^2 or 40mg/40cm^2**
<12	**1238**	103	1005	130
≥12, <24	**538**	0	378	160
≥24, <48	**205**	0	150	55
≥48	**55**	0	43	12
Total	**2036**	**103**	**1576**	**357**

[36] Patients are enumerated by their maximum dose and duration of exposure to that dose.

APPENDIX V-1 ITEMS UTILIZED IN THE REVIEW	
Submission Date	**Items Reviewed**
4-5-02	P0046 Study Report
7-31-03	Proposed labeling Financial disclosure information P0052 Study Report P9806 Study Report P0201 Study Report Updated Integrated Safety Summary Case Report Forms
8-18-03	Case Report Tabulations (electronic datasets)
10-29-03	Response to request for information (including safety update)

APPENDIX VI-1 STUDY P0052 BASELINE DEMOGRAPHIC FEATURES (ALL RANDOMIZED PATIENTS)		
	STS N=132	**Placebo N=133**
AGE (years)		
Mean	41.8	41.6
Age Range	19-70	18-68
GENDER		
% Males	39.4%	47.4%
% Females	60.6%	52.6%
RACE		
% Caucasian	80.3%	81.2%
% Black	4.5%	4.5%
% Asian	0.8%	1.5%
% Hispanic	9.1%	9.8%
% Other	5.3%	3.0%

APPENDIX VI-2 STUDY P0052 NUMBER (%) OF PATIENTS IN STUDY BY VISIT		
	STS	Placebo
Total Randomized	132 (100%)	133 (100%)
Week 1 Visit	123 (93%)	121 (91%)
Week 2 Visit	122 (92%)	119 (90%)
Week 3 Visit	121 (92%)	115 (87%)
Week 5 Visit	109 (83%)	110 (83%)
Study Completers	100 (76%)	106 (80%)

APPENDIX VI-3 STUDY P0052 ENUMERATION (%) OF DROPOUTS BY REASON FOR DROPOUT[37]		
	STS	Placebo
Total Number of Dropouts	32 (24%)	27 (20%)
Adverse Event	9 (7%)	3 (2%)
Lack of Efficacy	5 (4%)	3 (2%)
Noncompliance	6 (5%)	3 (2%)
Lost to Follow up	2 (2%)	14 (11%)
Withdrew Consent	7 (5%)	2 (2%)
Protocol Violation	1 (1%)	1 (1%)
Other	2 (2%)	1 (1%)

APPENDIX VI-4 STUDY P0052 MEAN DAILY STS DOSE BY VISIT[38]		
	N	Mean STS Dose (mg)
Week 1 Visit	123	20.0
Week 2 Visit	122	20.0
Week 3 Visit	121	28.6
Week 5 Visit	109	29.4
Week 8 Visit	100	34.7

[37] Percentage denominators are the total number of randomized patients in that treatment group.
[38] Data submitted in an 11-7-03 FAX.

APPENDIX VI-5: STUDY P0052 MEAN CHANGE FROM BASELINE IN HAM-D_{28} TOTAL SCORE (MODIFIED ITT)												
Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 5		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Last Observation Carried Forward Analysis												
STS	129	28.3	123	-2.6	128	-4.2	129	-5.8	129	-9.2	129	-11.1
Placebo	128	28.6	121	-2.7	128	-3.8	128	-5.9	128	-7.1	128	-8.9
Two-sided p-values for pairwise comparisons												
STS vs. P	0.6150		0.8507		0.5492		0.9699		0.0255		0.0327	
Observed Cases Analysis												
STS	129	28.3	123	-2.6	122	-4.3	121	-6.2	109	-9.7	100	-12.8
Placebo	128	28.6	121	-2.7	119	-3.9	115	-6.3	110	-7.9	110	-9.5
Two-sided p-values for pairwise comparisons												
STS vs. P	0.6150		0.8507		0.5472		0.9331		0.0749		0.0053	

APPENDIX VI-6: STUDY P0052
HAM-D ITEM 1 (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	0	0	20	16	105	81	4	3	28	22	42	33	28	22	30	23	1	1
Plac	0	0	0	0	19	15	106	83	3	2	19	15	29	23	29	23	47	37	4	3
Two-sided p-values for pairwise comparison of distributions																				
STS/P	0.8797										0.0023									
Observed Cases Analysis																				
STS	0	0	0	0	20	16	105	81	4	3	25	25	38	38	23	23	14	14	0	0
Plac	0	0	0	0	19	15	106	83	3	2	19	17	24	22	27	25	38	35	2	2
Two-sided p-values for pairwise comparison of distributions																				
STS/P	0.8797										0.0001									

APPENDIX VI-7: STUDY P0052 MEAN CHANGE FROM BASELINE IN MADRS TOTAL SCORE (MODIFIED ITT)												
Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 5		Week 8	
	N	Mean	N	Δ	N	Δ	N	Δ	N	Δ	N	Δ
Last Observation Carried Forward Analysis												
STS	129	29.3	123	-1.8	128	-3.4	129	-5.0	129	-9.0	129	-11.6
Placebo	128	29.3	121	-2.4	128	-3.2	128	-5.0	128	-6.3	128	-8.6
Two-sided p-values for pairwise comparisons												
STS vs. P	0.8306		0.2743		0.08327		0.9871		0.0160		0.0193	
Observed Cases Analysis												
STS	129	29.3	123	-1.8	122	-3.4	121	-5.3	109	-9.6	100	-13.6
Placebo	128	29.3	121	-2.4	119	-3.2	115	-5.3	110	-6.9	110	-9.2
Two-sided p-values for pairwise comparisons												
STS vs. P	0.8306		0.2743		0.7866		0.8719		0.0356		0.0017	

APPENDIX VI-8: STUDY P0052 DISTRIBUTION OF CGI SEVERITY SCORES AT WEEK 8 (MODIFIED ITT)							
TX Group	**CGI Improvement Category**	**LOCF Analysis**			**OC Analysis**		
		N	**%**	**p-value**	**N**	**%**	**p-value**
STS (N=129)	Normal, not ill	21	16	0.1010	19	19	0.0234
	Borderline ill	16	12		15	15	
	Mildly ill	26	20		22	22	
	Moderately ill	47	36		36	36	
	Markedly ill	19	15		8	8	
	Severely ill	0	0		0	0	
Placebo (N=128)	Normal, not ill	14	11		14	13	
	Borderline ill	16	13		15	14	
	Mildly ill	19	15		17	16	
	Moderately ill	59	46		49	45	
	Markedly ill	19	15		14	13	
	Severely ill	1	1		1	1	

APPENDIX VI-9 STUDY P9806 PRINCIPAL INVESTIGATORS	
Jay Amsterdam, M.D.	Neil Kaye, M.D.
Jeffrey Apter, M.D.	Louis Kirby, M.D.
Gregory Asnis, M.D.	Glen Koch, M.D.
Vernon Barksdale, M.D.	Theodore Lefton, M.D.
Barry Baumel, M.D.	James Lu, M.D.
Alex Bodkin, M.D.	Robert McMullen, M.D.
John Carman, M.D.	Charles H. Merideth, M.D.
Jesse Carr, M.D.	Margarite Nunez, M.D.
Amal Chakraburtty, M.D.	Jorg Pahl, M.D.
Joseph Fanelli, M.D.	David Sack, M.D.
R. James Farrer, M.D.	Mary Simonson, M.D.
James Hartford, M.D.	Kenneth Sokolski, M.D.
Scott Hoopes, M.D.	Leslie Taylor-VanHouton, M.D.
Rakesh Jain, M.D., M.P.H.	Kenneth Weiss, M.D.
Ethan Kass, D.O.	---

APPENDIX VI-10 STUDY P9806 BASELINE DEMOGRAPHIC FEATURES (SAFETY POPULATION AT START OF DOUBLE BLIND PHASE)		
	STS N=158	**Placebo N=163**
AGE (years)		
Mean	42.3	43.9
Age Range	19-73	18-81
GENDER		
% Males	28.5%	35.0%
% Females	71.5%	65.0%
RACE		
% Asian	0.6%	1.2%
% Caucasian	82.3%	82.2%
% Black	5.1%	5.5%
% Hispanic	8.2%	8.6%
% Other	3.8%	2.5%

APPENDIX VI-11 STUDY P9806/DOUBLE-BLIND PHASE NUMBER (%) OF PATIENTS IN STUDY BY VISIT		
	STS	Placebo
Total Randomized	159 (100%)	163 (100%)
Total Treated	158 (99%)	163 (100%)
Week 2 Visit	146 (92%)	160 (98%)
Week 4 Visit	134 (84%)	143 (88%)
Week 6 Visit	112 (70%)	112 (69%)
Week 8 Visit	96 (60%)	106 (65%)
Week 10 Visit	86 (54%)	87 (53%)
Week 12 Visit	76 (48%)	78 (48%)
Week 14 Visit	71 (45%)	69 (42%)
Week 18 Visit	64 (40%)	65 (40%)
Week 22 Visit	61 (38%)	56 (34%)
Week 26 Visit	58 (37%)	54 (33%)
Week 34 Visit	48 (30%)	34 (21%)
Week 42 Visit	40 (25%)	35 (22%)
Study Completers	33 (21%)	28 (17%)

APPENDIX VI-12 STUDY P9806/DOUBLE-BLIND PHASE ENUMERATION (%) OF DROPOUTS BY REASON FOR DROPOUT[39]		
	STS	Placebo
Reappearance of Depression	30 (19%)	51 (31%)
Other Discontinuations (total)	96 (60%)	84 (52%)
Adverse Event	21 (13%)	10 (6%)
Lack of Efficacy	11 (7%)	18 (11%)
Noncompliance	9 (6%)	3 (2%)
Lost to Follow up	25 (16%)	19 (12%)
Withdrew Consent	21 (13%)	30 (18%)
Protocol Violation	1 (<1%)	1 (<1%)
Other	8 (5%)	3 (2%)

[39] Percentage denominators are the total number of randomized patients in that treatment group. Patients who dropped out for reappearance of depression and patients enumerated under "Other Discontinuations" are mutually exclusive.

APPENDIX VI-13
DEMOGRAPHIC SUBGROUP ANALYSIS OF EFFICACY
POOL A STUDIES (5 ST, PC DEPRESSION TRIALS)

GENDER				
	Male		Female	
Treatment	STS	Placebo	STS	Placebo
N	295	248	497	399
Mean Δ $HAMD_{17}$	-7.919	-7.722	-8.660	-7.040
STS/Placebo Δ	-0.197		-1.620	

AGE				
	<50		≥50	
Treatment	STS	Placebo	STS	Placebo
N	571	487	221	160
Mean Δ $HAMD_{17}$	-8.184	-7.361	-8.900	-7.119
STS/Placebo Δ	-0.822		-1.782	

RACE				
	Caucasian		Non-Caucasian	
Treatment	STS	Placebo	STS	Placebo
N	662	560	130	87
Mean Δ $HAMD_{17}$	-8.329	-7.021	-8.662	-9.103
STS/Placebo Δ	-1.308		0.442	

APPENDIX VI-14
SUMMARY OF EFFICACY RESULTS FROM SHORT-TERM STUDIES IN MAJOR DEPRESSION
(SIGNIFICANCE OF DRUG/PLACEBO DIFFERENCES AT FINAL DOUBLE-BLIND ASSESSMENT)[40]

Study	STS Dose	HAM-D		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	10 & 20mg	ns	ns	ns	Ns	ns	ns	Ns	ns
P0052	20,30,or 40mg	*	**	*	**	**	**	*	**

[40] ns = not significant (p>0.10)
tr = trend (0.05<p≤0.10)
* = significant (0.01<p≤0.05)
** = highly significant (p≤0.01)
LOCF = Last Observation Carried Forward
OC = Observed Cases
Analyses of HAM-D total score and MADRS data compared mean change from baseline to endpoint.
Analyses of HAM-D item 1 and CGI-improvement data compared the distribution of scores at endpoint.
Significance for study E114-98B based on the overall p-values across 20mg, 10mg, and placebo groups.
The 17-item HAM-D was the primary efficacy variable in all studies except P0052, which used the 28-item HAM-D as the primary variable.

APPENDIX VII-1 STS-TREATED PATIENTS WITH NEWLY REPORTED SERIOUS ADVERSE EVENTS				
Patient ID	**Age**	**Sex**	**Dose (mg/day)**	**SAE Description**
ALL DEPRESSION STUDIES (POOL B STUDIES + P0043)				
P0052/10084	26	F	30	Benign ovarian tumor/cyst requiring laparoscopic surgery & hospitalization
P0052/10088	55	M	40	Possible serotonin syndrome after overdose (STS, nortriptyline, & ephedrine-containing diet pills)
P0052/23006	43	M	20	Overdose (alcohol & OTC sleeping pills)
P0158/10002	34	F	40	Serotonin syndrome: started venlafaxine after stopping STS 1 week earlier.
P0158/10006	42	F	40	Manic reaction
P0158/10110	57	F	30	Hospitalized for severe chest pain lasting 2 days; treated with ASA, NTG, morphine, lidocaine, & Maalox; continued STS throughout.
P0158/30013	57	F	30	Wrist fracture with malalignment
P0158/31028	50	F	30	Appendicitis
P0158/34019	42	F	40	Fractured fibia & tibia after fall
P0158/34021	61	F	20	Hospitalized due to thrombophlebitis; treated with heparin, warfarin.
STUDIES IN OTHER INDICATIONS				
P0044/04191	17	M	20	Congenital hypospadias requiring hospitalization.
NIDA-1019/NS[41]	47	M	20	Hospitalized for tertiary syphilis
NIDA-1019/NS	44	M	20	Hospitalized with suicidal ideation
NIDA-1019/NS	46	Unk	20	Pneumonia possibly due to aspiration

[41] Patient number not specified.

APPENDIX VII-1
STS-TREATED PATIENTS WITH NEWLY REPORTED SERIOUS ADVERSE EVENTS

Patient ID	Age	Sex	Dose (mg/day)	SAE Description
MIDA-1019/NS	49	F	20	Chest pain, hospitalized to R/O MI
NIDA-1019/NS	39	M	20	Acute pancreatitis
NIDA-1019/NS	47	M	20	Hospitalized for a "nervous breakdown" due to work stress
NIDA-1019/NS	55	M	20	Acute tremor after smoking crack
NIDA-1019/NS	36	M	20	Chest discomfort, diaphoresis, dyspnea, radiating paresthesia; MI R/O'd. Cocaine use 2 days prior.
PHASE 1 STUDIES				
P0201/001	51	M	40	Hepatitis B infection
10-29-03 SAFETY UPDATE				
P0043/CU021	Unk	Unk	20	Breast lump, negative biopsy
P0158/10094	37	F	30	Chest pain, arm numbness, nausea; hospitalized to R/O MI; DX: muscular pain.
P0204/04041	Unk	Unk	Unk	Colon cancer, surgery (colostomy)

APPENDIX VII-2
PLACEBO-TREATED PATIENTS WITH NEWLY REPORTED SERIOUS ADVERSE EVENTS

Patient ID	Age	Sex	Dose (mg/day)	SAE Description
ALL DEPRESSION STUDIES (POOL B STUDIES + P0043)				
P0052/20011	37	M	0	Infection in the small intestine, TX with Flagyl.
STUDIES IN OTHER INDICATIONS				
NIDA-1019/NS	49	M	0	Bacterial infection of foot ulcer.
NIDA-1019/NS	51	M	0	Hospitalized for depression, suicidal ideation.

APPENDIX VII-3 RECODED COSTART PREFERRED TERMS FOR NON-FATAL SAE'S			
Patient ID	**TX**	**Original Term**	**Revised Term**
9804/123	Plac	Suicide Attempt	Depression*
9804/509	STS	Suicide Attempt	Depression*
9804/607	Plac	Urinary Tract Disorder	Reaction Unevaluable*
E114/A361	Plac	Suicide Attempt	Depression*
9806/15013	STS	Embolus	Thrombosis
9806/17006	STS	Cerebrovascular Disorder	Cerebral Ischemia
9806/18014	STS	Stillbirth	Cleft Palate Stillbirth
9806/20001	STS	Gastrointestinal Hemorrhage	GI Neoplasia Rectal Hemorrhage
9804/206	STS	Coronary Artery Disorder	Reaction Unevaluable*
9804/310	STS	Breast Neoplasm	Breast Carcinoma
E114/A218	STS	Suicide Attempt	Alcohol Intolerance*
E114/A325	STS	Uterine Disorder	Uterine Neoplasm
E101-96B/419	STS	Peptic Ulcer	Peptic Ulcer Syndrome
E101-96B/609	Plac	CSF Fluid Abnormal	Musculoskeletal Congenital Anomaly*
E101-96B/911	STS	Mental Retardation	Thinking Abnormal
E101-96B/2103	STS	Brainstem Disorder	Cerebral Infarct
E101-96B/2643	STS	Stomach Ulcer Hemorrhage	Gastrointestinal Hemorrhage
E109-97B/3005	Plac	Back Pain	Hernia
E109-97B/11010	STS	Accidental Injury	Pathological Fracture
E109-97B/12008	STS	Uterine Disorder	Uterine Atony
E109-97B/15005	STS	Accidental Injury	Pathological Fracture

* Further evaluated by comparison with the Narrative Summary.

APPENDIX VII-4 ADVERSE EVENT REPORTING RATES (%) IN STUDY POOL A[42]		
BODY SYSTEM/PREFERRED TERM	**STS N=817**	**PLACEBO N=668**
Body as a Whole		
Headache	17.7%	16.5%
Infection	9.3%	10.0%
Pain	3.8%	4.9%
Flu Syndrome	3.2%	2.8%
Accidental Injury	2.7%	2.5%
Back Pain	2.7%	3.9%
Abdominal Pain	2.6%	4.8%
Asthenia	2.6%	3.1%
Cardiovascular		
Palpitation	2.0%	1.8%
Digestive		
Diarrhea	8.9%	7.3%
Nausea	4.8%	5.5%
Dyspepsia	3.9%	2.7%
Nervous		
Insomnia	12.1%	6.7%
Dry Mouth	7.5%	6.3%
Dizziness	5.0%	5.2%
Nervousness	3.7%	3.9%
Somnolence	3.2%	3.0%
Anxiety	2.6%	3.0%
Respiratory		
Pharyngitis	3.1%	2.1%
Sinusitis	3.1%	0.7%
Rhinitis	2.7%	2.5%
Skin		
Application Site Reaction	23.5%	11.5%
Rash	3.7%	1.8%

[42] For adverse events reported by at least 2.0% of STS-treated patients.

APPENDIX VII-5: CRITERIA FOR PCS LABORATORY VALUES	
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

APPENDIX VII-6: POOL A STUDIES PROPORTIONS OF PATIENTS WITH PCS LABORATORY VALUES						
Lab Parameter	STS			Placebo		
	N_{tot}	n_{PCS}	%	N_{tot}	n_{PCS}	%
Hemoglobin (low)	703	3	0.4	564	1	0.2
Hematocrit (low)	704	5	0.7	566	1	0.2
RBC's (high)	701	2	0.3	563	0	0.0
RBC's (low)	701	10	1.4	563	3	0.5
MCV (low)	323	1	0.3	329	1	0.3
WBC (high)	708	1	0.1	570	1	0.2
Eosinophils (high)	699	4	0.6	570	0	0.0
Neutrophils (low)	707	1	0.1	570	0	0.0
SGOT (high)	708	2	0.3	574	0	0.0
Bicarbonate (low)	707	5	0.7	574	3	0.5
BUN (high)	708	2	0.3	573	0	0.0
Chloride (high)	707	1	0.1	574	0	0.0
Chloride (low)	707	1	0.1	574	1	0.2
Glucose (high)	705	3	0.4	569	2	0.4
Glucose (low)	705	2	0.3	569	0	0.0
Phosphorus (high)	708	1	0.1	574	0	0.0
Potassium (high)	705	2	0.3	573	3	0.5
Potassium (low)	705	1	0.1	573	0	0.0
Sodium (low)	707	1	0.1	574	0	0.0
T. Bilirubin (high)	706	1	0.1	571	1	0.2
Total T_3 (high)	496	2	0.4	373	0	0.0
Total T_3 (low)	496	3	0.6	373	1	0.3
Total T_4 (high)	493	15	3.0	372	3	0.8
TSH (high)	481	4	0.8	363	7	1.9
TSH (low)	481	6	1.2	363	7	1.9
Uric Acid (females)	438	2	0.5	354	2	0.6
U/A Blood	613	66	10.8	490	53	10.8
U/A Protein	696	2	0.3	566	5	0.9
U/A Glucose	691	8	1.2	563	3	0.5
U/A WBC's	623	33	5.3	493	39	7.9
U/A RBC's (males)	181	30	16.6	147	21	14.3
U/A RBC's (females)	369	15	4.1	277	21	7.6

APPENDIX VII-7: POOL A STUDIES MEAN CHANGE FROM BASELINE TO FINAL VISIT IN LAB PARAMETERS[43]				
Laboratory Parameter	STS		Placebo	
	N	Mean Δ	N	Mean Δ
Hemoglobin (g/dL)	707	-0.3	568	-0.1 *
Hematocrit (%)	707	-0.9	568	-0.4 *
RBC ($\times 10^{12}$/L)	707	-0.1	568	-0.0 *
MCV (fl)	324	-0.1	329	+0.1
MCH (pg)	324	-0.0	329	-0.0
MCHC (g/dL)	324	-0.0	329	-0.1
WBC ($\times 10^{9}$/L)	708	-0.4	569	-0.3 *
Eosinophils ($\times 10^{9}$/L)	707	-0.0	568	-0.0
Neutrophils ($\times 10^{9}$/L)	707	-0.3	568	-0.2 *
Platelets ($\times 10^{9}$/L)	700	-4.6	564	-0.7
Albumin (g/dL)	708	-0.1	573	-0.1
Alkaline phosphatase(U/L)	708	-1.8	573	-0.4 *
AST(SGOT)(U/L)	708	+0.3	573	-0.1
ALT(SGPT)(U/L)	708	-1.0	573	-0.4
Bicarbonate (mmol/L)	708	-0.1	573	-0.1
BUN (mg/dL)	708	+0.2	573	+0.5 *
Calcium (mg/dL)	708	-0.1	573	-0.1 *
Chloride (mmol/L)	708	+0.1	573	0.0
Creatinine (mg/dL)	708	0.0	573	0.0
Glucose (mg/dL)	708	+2.1	572	+3.9 *
LDH (U/L)	708	+0.8	573	-0.6
Phosphorus (mg/dL)	708	0.0	573	-0.0
Potassium (mmol/L)	708	-0.1	573	-0.1
Sodium (mmol/L)	708	-0.4	573	-0.1 *
Total bilirubin (mg/dL)	708	-0.0	572	-0.0
Total protein (g/dL)	708	-0.2	573	-0.1 *
Total T3 (ng/mL)	504	0.0	378	0.0
Total T4 (mcg/dL)	504	+0.3	378	-0.0 *
TSH (mIU/ml)	499	+0.2	376	0.0
Uric acid (mg/dL)	708	-0.1	573	+0.1 *

[43] * = a statistically significant intergroup difference ($p \leq 0.10$).

APPENDIX VII-8: CRITERIA FOR CLINICALLY NOTABLE VITAL SIGN CHANGES	
Vital Sign Measure	**Criteria**
Systolic BP High	≥160mmHg and ↑ ≥20mmHg
Systolic BP Low	≤90mmHg and ↓ ≥20mmHg
Diastolic BP High	≥100mmHg and ↑ ≥15mmHg
Diastolic BP Low	≤50mmHg and ↓ ≥15mmHg
Orthostatic BP Δ	≥10mmHg ↓ Mean BP w/postural change[44]
Pulse High	≥120bpm
Pulse Low	≤50bpm
Weight	Change ≥5%
Temperature High	>101°F and ↑ ≥2°F

APPENDIX VII-9: POOL A STUDIES PROPORTIONS OF PATIENTS WITH CLINICALLY NOTABLE VS MEASURES						
Lab Parameter	**STS**			**Placebo**		
	N_{tot}	n_{CN}	%	N_{tot}	n_{CN}	%
Systolic BP High	791	8	1.0%	648	8	1.2%
Systolic BP Low	791	24	3.0%	648	10	1.5%
Diastolic BP High	791	7	0.9%	648	6	0.9%
Diastolic BP Low	791	6	0.8%	648	1	0.2%
Orthostatic BP Δ[45]	502	49	9.8%	357	24	6.7%
Pulse High	791	2	0.3%	648	1	0.2%
Pulse Low	791	13	1.6%	648	13	2.0%
Weight Decreased	757	38	5.0%	614	17	2.8%
Weight Increased	757	16	2.1%	614	15	2.4%
Temperature Incr.	791	3	0.4%	646	3	0.5%

[44] Mean BP = DBP + [(SBP-DBP)/3].
[45] Figures for orthostatic blood pressure change exclude patients who met this criterion at baseline.

APPENDIX VII-10 REPORTING RATES OF ADVERSE EVENTS POSSIBLY RELATED TO ORTHOSTATIC HYPOTENSION POOL A STUDIES		
	STS N=817	Placebo N=668
Postural Hypotension	0.9%	0.4%
Hypotension	0.1%	0.0%
Amblyopia	1.1%	0.4%
Dizziness	5.0%	5.2%
Accidental Injury	2.7%	2.5%
Spontaneous Bone Fracture	0.4%	0.3%
Syncope	0.1%	0.0%
Vertigo	1.2%	0.1%

APPENDIX VII-11: POOL A STUDIES MEAN CHANGE FROM BASELINE IN VS MEASURES[46]				
Vital Sign Measure	STS		Placebo	
	N	Mean Δ	N	Mean Δ
Resting Systolic BP (mmHg)	650	-0.8	528	-1.2
Resting Diastolic BP (mmHg)	650	-0.9	528	-0.1
Standing Systolic BP (mmHg)	424	-1.8	297	-1.5
Standing Diastolic BP(mmHg)	424	-1.1	297	-0.3
Resting Pulse (bpm)	647	+0.4	527	+0.6
Standing Pulse (bpm)	424	-0.1	296	+0.3
Weight (lbs)	757	-1.2	614	+0.3
Temperature (°F)	791	-0.0	646	-0.0

[46] Changes were from baseline to week 6 for blood pressure and pulse and from baseline to final visit for weight and temperature.

APPENDIX VII-12: STUDY P0052 MEAN CHANGE FROM BASELINE TO WEEK 8 IN VS MEASURES				
Vital Sign Measure	STS		Placebo	
	N	Mean Δ	N	Mean Δ
Sitting Systolic BP (mmHg)	100	-4.3	110	-1.2
Sitting Diastolic BP (mmHg)	100	-1.2	110	-0.7
Standing Systolic BP (mmHg)	100	-5.7	110	-0.8
Standing Diastolic BP(mmHg)	100	-1.9	110	-1.2
Sitting Pulse (bpm)	100	-0.0	110	-0.2
Standing Pulse (bpm)	100	+0.2	110	+0.3
Weight (kg)	100	-0.7	109	-0.0
Temperature (◦C)	100	+0.0	110	-0.0

APPENDIX VII-13: CRITERIA FOR PCS ECG PARAMETERS	
ECG Parameter	Criteria
Decreased Heart rate	<50 bpm
Increased Heart rate	>100 bpm
PR interval	>0.210 sec
QRS duration	>0.120 sec
QTc interval	>0.440 sec

APPENDIX VII-14: POOL A STUDIES PROPORTIONS OF PATIENTS WITH PCS ECG VALUES						
ECG Parameter	STS			Placebo		
	N_{tot}	n_{PCS}	%	N_{tot}	n_{PCS}	%
Decreased Heartrate	714	4	0.6%	566	11	1.9%
Increased Heartrate	730	4	0.5%	584	2	0.3%
Incr. PR Interval	476	6	1.3%	330	1	0.3%
Incr. QRS Interval	484	3	0.6%	330	2	0.6%
Incr. QTc Interval	443	25	5.6%	304	24	7.9%

APPENDIX VII-15: POOL A STUDIES MEAN CHANGE FROM BASELINE TO END OF STUDY IN ECG MEASURES				
ECG Measure	STS		Placebo	
	N	Mean Δ	N	Mean Δ
Ventricular Rate (bpm)	731	+1.20	586	+1.84
PR Interval (sec)	485	-0.001	331	+0.002
QRS Interval (sec)	486	+0.001	331	+0.003
QTc Interval (sec)	486	-0.002	331	+0.001

APPENDIX VII-16
STUDY P0201 TYRAMINE DOSING ALGORITHMS

PERIODS 1 and 2

Day 1 400 mg tyramine If TYR30 was reached, 200 mg tyramine was administered on Day 2 If TYR30 was not reached, 600 mg tyramine was administered on Day 2			
Day 2 200 mg tyramine If TYR30 was reached, 100 mg tyramine was administered Day 3 If TYR30 was not reached, 300 mg tyramine was administered Day 3		**Day 2** 600 mg tyramine If TYR30 was reached, 500 mg tyramine was administered Day 3 If TYR30 was not reached, 700 mg tyramine was administered Day 3	
Day 3 100 mg tyramine	**Day 3** 300 mg tyramine	**Day 3** 500 mg tyramine	**Day 3** 700 mg tyramine

PERIODS 3, 4, and 5

Day 41 50 mg tyramine If TYR30 was reached, 25 mg tyramine was administered on Day 42 If TYR30 was not reached, 100 mg tyramine was administered on Day 42			
Day 42 25 mg tyramine If TYR30 was reached, 12.5 mg tyramine was administered Day 43 If TYR30 was not reached, 37.5 mg tyramine was administered Day 43		**Day 42** 100 mg tyramine If TYR30 was reached, 75 mg tyramine was administered Day 43 If TYR30 was not reached, 200 mg tyramine was administered Day 43	
Day 43 12.5 mg tyramine	**Day 43** 37.5 mg tyramine	**Day 43** 75 mg tyramine	**Day 43** 200 mg tyramine

PERIOD 6 (tyramine pressor dose ≥ 75 mg during either Period 3, 4, or 5)

Day 101 100 mg tyramine If TYR30 was reached, 50 mg tyramine was administered on Day 102 If TYR30 was not reached, 200 mg tyramine was administered on Day 102			
Day 102 50 mg tyramine If TYR30 was reached, 25 mg tyramine was administered Day 103 If TYR30 was not reached, 75 mg tyramine was administered Day 103		**Day 102** 200 mg tyramine If TYR30 was reached, 150 mg tyramine was administered Day 103 If TYR30 was not reached, 300 mg tyramine was administered Day 103	
Day 103 25 mg tyramine	**Day 103** 75 mg tyramine	**Day 103** 150 mg tyramine	**Day 103** 300 mg tyramine

* Patients who had a tyramine pressor dose of 50mg or less in Periods 3, 4, or 5 started at 50mg in Period 6 and were dosed according to the algorithm for Periods 3, 4, or 5.

APPENDIX VII-17
STUDY P0201
TYRAMINE PRESSOR DOSES - ALL SUBJECTS

Tyramine Pressor Dose	N (subjects)	Mean±Std Dev (mg tyramine)	Minimum (mg tyramine)	Maximum (mg tyramine)
Period 1 (Pre-STS dosing)	18	566.67±113.76	400.0	700.0
Period 2 (Pre-STS Dosing)	18	583.33±115.04	400.0	700.0
Baseline (Mean Period 1 & 2)	18	575.00±92.75	400.0	700.0
Period 3 (30 day Assessment)	18	84.03±69.64[a]	25.0	200.0
Period 4 (60 day Assessment)	14	66.07±45.05[b]	25.0	200.0
Period 5 (90 day Assessment)	11	87.50±60.21[c]	37.5	200.0
Period 6 – Fed Data (94 day Assessment)	8	171.88±92.04[d,e]	75.0	300.0

[a]Statistically different from Baseline (p<0.0001)(N=18)
[b]No difference from Period 3 (p=0.2494) (N=14)
[c]No difference from Period 4 (p=0.2923) (N=11)
[d]Statistically different from Period 5 (p<0.0023) (N=8)
[e]Statistically different from Baseline (p<0.0001)(N=8)
Paired t-tests for all statistical comparisons
Std Dev=standard deviation, N=number of subjects
Data Source: Appendix C, Tables C.1.1, C.1.2, C.1.3, C.1.4 & C.1.7, Appendix G, Listing G.17

APPENDIX VII-18
STUDY P0201
TYRAMINE PRESSOR DOSES - COMPLETERS

Tyramine Pressor Dose	N (subjects)	Mean±Std Dev (mg tyramine)	Minimum (mg tyramine)	Maximum (mg tyramine)
Period 1 (Pre-STS dosing)	11	581.82±116.77	400.0	700.0
Period 2 (Pre-STS Dosing)	11	554.55±112.82	400.0	700.0
Baseline (Mean Period 1 & 2)	11	568.18±90.20	400.0	700.0
Period 3 (30 day Assessment)	11	95.45±75.68[ab]	25.0	200.0
Period 4 (60 day Assessment)	11	71.59±48.44[b]	25.0	200.0
Period 5 (90 day Assessment)	11	87.50±60.21[b]	37.5	200.0

[a]Statistically significant from Baseline (p<0.0001, paired t-test) (N=11)
[b]Repeated measures analysis on within-subject time effect: Period 3, 4 and 5 (p=0.3563) (N=11)
Std Dev=standard deviation, N=number of subjects
Data Source: Appendix C, Tables C.1.8-C.1.11, Appendix G, Listing G.17

APPENDIX VII-19
STUDY P0201
TYRAMINE PRESSOR DOSES - FASTED VERSUS FED

Tyramine Pressor Dose	N (subjects)	Mean±Std Dev (mg tyramine)	Minimum (mg tyramine)	Maximum (mg tyramine)
Period 5 – Fasting Data (90 day Assessment)	8	64.06±27.09	37.5	100.0
Period 6 – Fed Data (94 day Assessment)	8	171.88±92.04[a]	75.0	300.0

[a]Statistically significant from Period 5 (p<0.0023) (N=8)
Paired t-test for statistical comparison
Std Dev=standard deviation, N=number of subjects
Data Source: Appendix C, Tables C.1.12 & C.1.16, Appendix G, Listing G.17

APPENDIX VII-20
STUDY P0201
TYRAMINE SENSITIVITY FACTOR ANALYSES

Table 5.4 Tyramine Sensitivity Factor by Period (All Fasted Subjects Administered the STS and Participating in at least One Tyramine Challenge)

	N (subjects)	TSF±Std Dev	Minimum	Maximum
Period 3 (30 day Assessment)	18	11.46±6.59	2.00	22.00
Period 4 (60 day Assessment)	14	11.36±5.12[a]	2.00	20.00
Period 5 (90 day Assessment)	11	9.32±5.18[b]	2.00	18.67

[a]No difference from Period 3 (p=0.8301) (N=14)
[b]No difference from Period 4 (p=0.4177) (N=11)
Paired t-tests for all statistical comparisons
TSF=Tyramine Sensitivity Factor (Baseline tyramine pressor dose/Period tyramine pressor dose)
Std Dev=standard deviation, N=number of subjects
Data Source: Appendix C, Tables C.2.1-C.2.4, Appendix G, Listing G.17

Table 5.5 Tyramine Sensitivity Factor by Period (Fasted Completers)

	N (subjects)	TSF±Std Dev	Minimum	Maximum
Period 3 (30 day Assessment)	11	10.99±7.74[c]	2.00	22.00
Period 4 (60 day Assessment)	11	10.58±4.98[a,c]	2.00	20.00
Period 5 (90 day Assessment)	11	9.32±5.18[b,c]	2.00	18.67

[a]No difference from Period 3 (p=0.7913) (N=11)
[b]No difference from Period 4 (p=0.4177) (N=11)
[c]Repeated measures analysis on within-subject time effect: Period 3, 4 and 5 (p=0.5272) (N=11)
TSF=Tyramine Sensitivity Factor (Baseline tyramine pressor dose/Period tyramine pressor dose)
Std Dev=standard deviation, N=number of subjects
Data Source: Appendix C, Tables C.2.5-C.2.11, Appendix G, Listing G.17

Table 5.6 Tyramine Sensitivity Factor by Period (Fasted versus Fed)

	N (subjects)	TSF±Std Dev	Minimum	Maximum
Period 5 – Fasting Data (90 day Assessment)	8	11.00±4.56	6.00	18.67
Period 6 – Fed Data (94 day Assessment)	8	4.46±2.13[a]	2.00	7.33

[a]Statistically significant from Period 5 (p<0.0002) (N=8)
Paired t-test for all statistical comparisons
TSF=Tyramine Sensitivity Factor (Baseline tyramine pressor dose/Period tyramine pressor dose)
Std Dev=standard deviation, N=number of subjects
Data Source: Appendix C, Tables C.2.8-C.2.11, Appendix G, Listing G.17

APPENDIX VII-21
STUDY P0046
MEAN MAXIMUM CHANGES IN BLOOD PRESSURE AND HEARTRATE AFTER PPA AND (PPA + STS)

Day[a]	Dose	Maximum Systolic Change (Phenylpropanolamine Alone) Days 1,2,3 Mean (SD) N=11	Maximum Systolic Change (Phenylpropanolamine + STS) Days 12,13,14 Mean (SD) N=11	P-value[b,c]
1	1	16.91(8.37)	24.18(8.61)	0.0758
2	1	19.36(11.24)	23.45(13.76)	0.7105
	2	14.27(10.42)	10.64(8.43)	0.8777
	3	23.73(10.12)	21.27(10.16)	0.4900
	4	13.91(4.59)	18.00(10.66)	0.2345
3	5	15.82(8.30)	17.73(14.79)	0.7336
	6	16.45(9.21)	24.55(12.76)	0.5074

[a]Days 1, 2, and 3 are equivalent to Days 12, 13, and 14 for Treatment III.
[b]One-way repeated ANOVA with baseline data as covariate calculable only for those subjects with data available for Days 1, 2, 3, and 12, 13, 14
[c]Comparison of phenylpropanolamine alone versus combined treatment at each dose
Data Source: Appendix E, Table E.8d, Appendix G, Listing G.9a

Day[a]	Dose	Maximum Diastolic Change (Phenylpropanolamine Alone) Days 1,2,3 Mean (SD) N=11	Maximum Diastolic Change (Phenylpropanolamine + STS) Days 12,13,14 Mean (SD) N=11	P-value[b,c]
1	1	12.91(4.28)	14.27(8.30)	0.3917
2	1	14.18(6.57)	22.00(10.95)	0.0660
	2	15.55(8.59)	16.73(8.70)	0.6047
	3	21.91(8.94)	21.55(8.85)	0.5839
	4	15.36(5.46)	14.91(9.36)	0.8773
3	5	15.82(8.18)	12.82(5.42)	0.2144
	6	15.36(7.26)	25.73(16.64)	0.2371

[a]Days 1, 2, and 3 are equivalent to Days 12, 13, and 14 for Treatment III.
[b]One-way repeated ANOVA with baseline data as covariate calculable only for those subjects with data available for Days 1, 2, 3, and 12, 13, 14
[c]Comparison of phenylpropanolamine alone versus combined treatment at each dose
Data Source: Appendix E, Table E.8e, Appendix G, Listing G.9a

Day[a]	Dose	Maximum Heart Rate Change (Phenylpropanolamine Alone) Days 1,2,3 Mean (SD) N=11	Maximum Heart Rate Change (Phenylpropanolamine + STS) Days 12,13,14 Mean (SD) N=11	P-value[b,c]
1	1	19.55(8.24)	23.00(6.24)	0.3227
2	1	15.82(9.33)	19.73(7.54)	0.1651
	2	14.55(7.55)	7.00(4.86)	0.0639
	3	7.55(3.45)	9.00(6.21)	0.1330
	4	7.55(10.45)	7.09(6.27)	0.2316
3	5	6.09(5.80)	7.18(5.90)	0.8064
	6	13.18(7.74)	17.00(5.55)	0.0246

[a]Days 1, 2, and 3 are equivalent to Days 12, 13, and 14 for Treatment III.
[b]One-way repeated ANOVA with baseline data as covariate calculable only for those subjects with data available for Days 1, 2, 3, and 12, 13, 14
[c]Comparison of phenylpropanolamine alone versus combined treatment at each dose
Data Source: Appendix E, Table E.8f, Appendix G, Listing G.9a

APPENDIX VII-22
STUDY P0046
SUBJECTS MEETING CRITERION FOR A PRESSOR RESPONSE

Subject ID	Day/ Post-dose #	Treatment	Baseline SBP (mmHg)	Maximum SBP of the 3 Consecutive Readings (mmHg)	Maximum Change from Previous Baseline (mmHg)
09	Day 14; Dose 6	STS (20mg/20cm^2) + Phenylpropanolamine	99	141	42
11	Day 14, Dose 5	STS (20mg/20cm^2) + Phenylpropanolamine	140	186	46
12	Day 12, single dose	STS (20mg/20cm^2) + Phenylpropanolamine	115	160	45
14	Day 2, Dose 1	Phenylpropanolamine	103	144	41

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Greg Dubitsky
12/16/03 08:43:40 PM
MEDICAL OFFICER
Draft Labeling to Follow

Thomas Laughren
1/16/04 03:37:48 PM
MEDICAL OFFICER
I agree that this NDA is approvable; see memo to file for more detailed comments.--TPL

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 15, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Non-Approval Action for
Emsam (selegiline transdermal system [STS])

TO: File NDA 21-336
[**Note:** This overview should be filed with the 5-24-01
original submission.]

1.0 BACKGROUND

Selegiline transdermal system [STS] is a patch formulation of seligiline, a monoamine oxidase inhibitor (MAOI) that is currently marketed as Eldepryl (an immediate release capsule for oral administration) as an adjunctive treatment for Parkinson's disease. It is being proposed for the treatment of depression, at a dose of 20 mg (a 20 mg/20 cm2 patch delivers approximately 5 mg of selegiline over a 24 hour period). MAO exists as two isoenzymes, A and B, and these isoenzymes have a role in the catabolism of neurotransmitter amines such as NE, DA, and 5HT. At low concentrations, selegiline is selective for MAO B, but at higher concentrations, it inhibits both A and B. In fact, inhibition of both isoenzymes may be necessary for the antidepressant action of STS, since it was positive in the forced swim test (an animal model for depression) only at doses that inhibited both isoenzymes. Since MAO in the gut wall is also important in the catabolism of certain dietary amines (e.g., tyramine), one concern about MAOI's is their potential to inhibit gut MAO-A, resulting in the "cheese reaction." However, the STS formulation avoids exposure of gut wall MAO-A to selegiline, and apparently "cheese reactions" have not been observed with STS, even without the dietary restrictions that need to be observed with orally administered, nonselective MAOI's. Thus, STS would be expected to have the advantage over other MAOI's marketed in the US for depression (phenelzine, tranylcypromine, and isocarboxizide) of not being associated with the "cheese reaction."

IND 46,944 for the selegiline transdermal system (STS) was originally submitted 12-20-94. Several critical meetings were held during the development of STS:

5-4-98: This was an end-of-phase 2 meeting.
-Several issues were discussed, including: (1) the need for 2 adequate and well-controlled studies, (2) the need to specify a primary outcome (s), (3) the difficulty in establishing , (4) the desirablity of longer term efficacy data and dose/response data, (5) the need for sufficient clinical data to establish . It was noted that separate meetings would be held to discuss pharm/tox and CMC requirements.

6-10-99: This was the first of two pre-NDA meetings.
-Several issues were discussed, including: (1) the need for an ICH size safety database, given the fact that exposure to parent drug is several-fold higher with STS than what is seen with oral form, and (2) a recommendation to do a tyramine challenge study using STS and a nonselective MAOI as a positive control, despite the methodological difficulties of conducting such a study.

3-28-01: This was the second of two pre-NDA meetings.
-Several issues were discussed, including: (1) the sponsor's interest in studying higher doses of STS; we provided general guidance on what types of studies would be needed to support labeling for higher doses, including advice that sufficient additional safety experience would be needed to support the higher doses, (2) the current status of tyramine studies, which appear adequate for the 20 mg/day dose, but would need to be expanded if there was an interest in exploring higher doses.
The original NDA 21-336 for selegiline transdermal system (STS) was submitted 5-24-01. A safety update was submitted 9-26-01.

We decided not to take selegiline transdermal system (STS) to the Psychopharmacological Drugs Advisory Committee (PDAC).

2.0 CHEMISTRY

I am not aware of any CMC issues that would preclude the approvability of this drug.
The nonapproval letter includes a number of issues that need to be addressed at some point prior to final approval.

The proposed name, "Emsam," has been evaluated by DMETS, and they have no objection.

3.0 PHARMACOLOGY

I am not aware of any pharmacology/toxicology issues that would preclude the approvability of this drug. However, the nonapproval letter references our 1-30-02 telcon during which we requested complete electronic datasets for the low and mid dose groups of the rat and mouse carcinogenicity studies. The sponsor agreed to provide these datasets, but it was agreed that these data could be submitted subsequent to the 3-25-02 action date for this NDA, and this deficiency would not be considered a basis for a nonapproval action. The letter also asks the sponsor to address several deficiencies in the genotoxicity data.

4.0 BIOPHARMACEUTICS

With each 20 mg STS patch, approximately 5 mg of selegiline is delivered over 24 hours. Absorption is nonlinear, with Tmax at about 18 hours. Steady state is reached in about 5 to 7 days. There is no indication that metabolites of selegiline, including very small quantities of amphetamine, contribute to the therapeutic effect. Selegiline is cleared through several pathways, making it unlikely that its clearance would be substantially affected by single enzyme inhibitors, and it appears to have little potential for enzyme inhibition of its own. No adjustment of dose is needed in patients with renal impairment or moderate hepatic impairment, or in the elderly. Because of the avoidance of the first pass effect, higher levels of parent drug are seen with the STS formulation than are observed with oral dosing of selegiline.

The pharmacokinetics of selegiline transdermal system (STS) have been adequately characterized and there are no pharmacokinetic deficiencies that would preclude the approvability of this drug.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

There were a total of 4 short-term, placebo-controlled trials of selegiline transdermal system (STS) in major depressive disorder, and these were the focus of the efficacy review for this NDA. These studies were reviewed by Greg Dubitsky, M.D., from the clinical group, and by Yuan-Li Shen, Ph.D. from the biometrics group.

An important issue pertinent to all 4 studies was an attempt by the sponsor to shift, in the study reports, to an analysis plan not included in the protocols for these studies. The accepted standard in this field for the population to include in the efficacy analysis is what is considered a modified intent-to-treat population, i.e., all patients randomized who received at least one dose of assigned treatment and who had both baseline and at least one followup assessment on the primary outcome. In fact, this ITT was specified in the protocols, along with other populations for analysis, e.g., an evaluable subset analysis (i.e., patients who

did not violate the protocol and completed the study), the classical intent-to-treat analysis (i.e., all patients randomized, regardless of whether or not they got assigned treatment), and the observed cases analysis at the last visit. While there was some variation across the 4 protocols regarding precisely which populations were mentioned, they all included the modified ITT population that we usually use as the basis for primary analyses. In fact, it is widely understood that FDA does not accept analyses based on the other populations specified. However, in the study reports for these 4 studies, a different ITT population was used in the primary analysis, i.e., all patients randomized who received at least one dose of assigned treatment and had a baseline assessment, regardless of whether or not they had at least one followup assessment on the primary outcome. Thus, it was a somewhat expanded sample, i.e., one in which patients having only baseline assessments were included, by carrying forward their baseline scores. Importantly, none of the protocols was amended, to my knowledge, to change to this slightly different ITT population for the primary analysis. In the tables to follow in this overview, I will include only the results based on our preferred modified ITT population. It is also important to point out that this subtle change in population matters only for study P9804, where it changes the outcome.

5.1.2 Summary of Studies Pertinent to Efficacy Claims

5.1.2.1 Study S9303-E106-96B

This was a randomized, double-blind, parallel group, 6-week, fixed-dose study (6 US sites) comparing STS (20 mg/20 cm2, qd) and placebo in adult outpatients meeting DSM-IV criteria for MDD. There were roughly 90 patients per each of the 2 groups in the sample analyzed (n=176), with the % completing to 6 weeks ranging from 83 to 88%. The patients were about 60% female, about 93% Caucasian, and the mean age was 42 years.

While the assessments included MADRS, HAMD-28, CGI, and others, the primary outcome was change from baseline to endpoint in HAMD-17 total score, and I will comment primarily on that outcome. As noted above, the sponsor shifted in the study report to a different ITT population than specified in the protocol, however, I will focus on the results based on the protocol specified modified ITT analysis plan. The LOCF analysis was considered primary, but OC was also done. ANCOVA was the statistical model employed, with baseline score as the covariate. The overall analysis for HAMD-17 was significant (p=0.013):

Efficacy Results on HAMD-17 Total Score for E106-96B (LOCF)

	Baseline HAMD-17	**ΔBaseline HAMD-17**	**[P-value(vs pbo)]**
STS 20 mg/20cm2	**22.9**	**-8.7**	**0.013**
Placebo	**23.3**	**-6.1**	

While not described here, results on various secondary endpoints also favored STS over placebo. The sponsor's preferred analysis was essentially the same, since it involved only 1 additional patient being

included in the STS group. Analyses on the HAMD-17 primary outcome including gender, age, or racial group revealed no interactions for these subgroupings.

Comment: Both Drs. Dubitsky and Shen considered this a positive study, and I agree.

5.1.2.2 Study S9303-P9804

This was a randomized, double-blind, parallel group, 8-week, fixed-dose study (16 US sites) comparing STS (20 mg/20 cm2, qd) and placebo in adult outpatients meeting DSM-IV criteria for MDD. There were roughly 145 patients per each of the 2 groups in the sample analyzed (n=289), with the % completing to 8 weeks ranging from 72 to 73%. The patients were about 64% female, about 82% Caucasian, and the mean age was 42 years.

While the assessments included MADRS, HAMD-28, CGI, and others, the primary outcome was change from baseline to endpoint in HAMD-17 total score, and I will comment primarily on that outcome. As noted above, the sponsor shifted in the study report to a different ITT population than specified in the protocol, however, I will focus on the results based on the protocol specified modified ITT analysis plan. The LOCF analysis was considered primary, but OC was also done. ANCOVA was the statistical model employed, with baseline score as the covariate. The overall analysis for HAMD-17 was not significant (p=0.069):

Efficacy Results on HAMD-17 Total Score for P9804 (LOCF)

	Baseline HAMD-17	**ΔBaseline HAMD-17**	**[P-value(vs pbo)]**
STS 20 mg/20cm2	**22.8**	**-8.1**	**0.069**
Placebo	**23.0**	**-6.7**	

The results on HAMD-17 were also not significant at earlier time points. While not described here, results on various secondary endpoints favored STS over placebo in some cases (HAMD-28 and MADRS), but not in others (CGI-S and CGI-I). The sponsor's preferred analysis was positive on HAMD-17 (p=0.046), but as noted, this was not the protocol specified analysis. The sponsor's ITT included 12 additional patients not included in the protocol specified ITT. It should also be noted that both of these p-values, i.e., the 0.046 (sponsor's preferred analysis) and the 0.069 (protocol specified analysis), were based on an additional post hoc change to the statistical model, i.e., the addition of age as a covariate. While the original protocol did apparently permit the addition of age as a covariate, if there was an age imbalance at baseline, amendment 1 to the protocol removed this provision, so age should not have been included in the model. If the analysis is done without age as a covariate, using the protocol specified modified ITT analysis plan, the p-value is 0.084.

Analyses on the HAMD-17 primary outcome including gender, age, or racial group revealed no interactions for these subgroupings.

Comment: Both Drs. Dubitsky and Shen considered this a negative study, and I agree.

5.1.2.3 Study S9303-E114-98B

This was a randomized, double-blind, parallel group, 8-week, fixed-dose study (19 US sites) comparing STS (20 mg/20 cm2, qd), STS (10 mg/20 cm2, qd), and placebo in adult outpatients meeting DSM-IV criteria for MDD. There were roughly 145 patients per each of the 3 groups in the sample analyzed (n=435), with the % completing to 8 weeks ranging from 72 to 75%. The patients were about 66% female, about 87% Caucasian, and the mean age was 41 years.

While the assessments included MADRS, HAMD-28, CGI, and others, the primary outcome was change from baseline to endpoint in HAMD-17 total score, and I will comment primarily on that outcome. As noted above, the sponsor shifted in the study report to a different ITT population than specified in the protocol, however, I will focus on the results based on the protocol specified modified ITT analysis plan. The LOCF analysis was considered primary, but OC was also done. ANCOVA was the statistical model employed, with baseline score as the covariate. The overall analysis for HAMD-17 was not significant (p=0.357, nor were either of the pairwise comparisons of active drug with placebo):

Efficacy Results on HAMD-17 Total Score for E114-98B (LOCF)

	Baseline HAMD-17	**ΔBaseline HAMD-17**	**[P-value(vs pbo)]**
STS 20 mg/20cm2	**23.3**	**-9.2**	**0.569**
STS 10 mg/20cm2	**22.7**	**-9.0**	**0.314**
Placebo	**23.1**	**-8.1**	

The results on HAMD-17 were also not significant at earlier time points. While not described here, results on various secondary endpoints were also uniformly negative. The sponsor's preferred analysis was also negative.

Comment: Both Drs. Dubitsky and Shen considered this a negative study, and I agree.

5.1.2.4 Study S9303-E113-98B

This was a randomized, double-blind, parallel group, 8-week, fixed-dose study (13 US sites) comparing STS (20 mg/20 cm2, qd) and placebo in adult outpatients meeting DSM-IV criteria for MDD. There were roughly 145 patients per each of the 2 groups in the sample analyzed (n=283), with the % completing to 8 weeks ranging from 71 to 77%. The patients were about 61% female, about 82% Caucasian, and the mean age was 40 years.

While the assessments included MADRS, HAMD-28, CGI, and others, the primary outcome was change from baseline to endpoint in HAMD-17 total score, and I will comment primarily on that outcome. As noted above, the sponsor shifted in the study report to a different ITT population than specified in the

protocol, however, I will focus on the results based on the protocol specified analysis plan. The LOCF analysis was considered primary, but OC was also done. ANCOVA was the statistical model employed, with baseline score as the covariate. The analysis for HAMD-17 was not significant (p=0.117):

Efficacy Results on HAMD-17 Total Score for E113-98B (LOCF)

	Baseline HAMD-17	ΔBaseline HAMD-17	[P-value(vs pbo)]
STS 20 mg/20cm2	**23.0**	**-6.6**	**0.117**
Placebo	**22.7**	**-7.8**	

The results on HAMD-17 were also not significant at earlier time points. While not described here, results on various secondary endpoints were also uniformly negative. The sponsor's preferred analysis was also negative.

Comment: Both Drs. Dubitsky and Shen considered this a negative study, and I agree.

5.1.3 Comment on Other Important Clinical Issues Regarding Selegiline Transdermal System (STS) for MDD

Evidence Bearing on the Question of Dose/Response for Efficacy

Of the 4 studies reviewed, only study E114-98B was of fixed dose design, and that was a negative study. Consequently, there is no evidence pertinent to dose response in this program.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of gender, age, and race in E106-96B, the one positive study. There was no indication of differences in response based on these variables, however, there was likely not adequate power to detect such differences.

Size of Treatment Effect

The effect size as measured by difference between drug and placebo in change from baseline in the HAMD-17 observed in study E106-96B, the one positive study, was on the small side, but not unlike that seen in other positive antidepressant trials.

Duration of Treatment

There were no data presented in this supplement pertinent to the question of the longer-term efficacy of STS. It should be noted that the sponsor has initiated a randomized withdrawal trial to explore the longer-term efficacy of STS (P9806), and this trial is ongoing.

5.1.4 Conclusions Regarding Efficacy Data

The sponsor has not, in my view, provided sufficient evidence to support the claim of short-term antidepressant efficacy for STS. Based on earlier discussions with the sponsor, e.g., 3-28-01 preNDA meeting, and on submitted protocols, e.g., 7-9-01 amendment, they are interested in looking at higher STS doses. While the 3 negative trials in this program are uninterpretable, given the lack of an active control for assay sensitivity, the sponsor seems to be considering the possibility that a higher dose is needed to achieve more predictable efficacy.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The safety data for STS, including the original submission, the 9-26-01 safety update, and amendments in response to our requests for additional information, were reviewed by David Gan, M.D., Gerard Boehm, M.D., and Judith Racoosin, M.D., all from the safety group, and Greg Dubitsky, M.D., from the psychopharm group. This review was based on an integrated database (with a cutoff date of 7-1-01 for both the integrated database and also for deaths and other serious events).

Approximately 2000 human subjects were exposed to STS in the sponsor's development program (in the integrated database), including 630 in 36 phase 1 studies approximately 1397 in 13 phase 2-3 studies. The various indications studied in the phase 2-3 studies included depression, Parkinson's disease, [redacted] and HIV-associated cognitive impairment. The total person-time for STS-exposed patients in the phase 2-3 depression program was approximately 86 person-years. Patients in phase 2-3 depression studies were roughly 2/3 female, predominantly Caucasian, and the median age was 42.

5.2.2 Adverse Event Profile for Selegiline Transdermal System (STS)

5.2.2.1 Overview

There were 4 adverse events that emerged as more common for STS than placebo in the controlled trials in depression: application site reaction, insomnia, sinusitis, and rash. Orthostatic hypotension also appears to be a dose-related adverse event. Except for a suggestion of increased total T4 for STS, there was no pattern of laboratory changes. Except for a suggestion of orthostatic BP changes for STS, there was no pattern of vital signs changes. Except for a suggestion of slightly increased HR for STS vs placebo (about 3-4 bpm), there was no pattern of ECG changes.

For the pooled depression studies, the risks for the adverse events that appeared to be drug-related were as follows:

	STS	Placebo
ASR	23.0%	9.7%
Insomnia	9.6%	4.9%
Sinusitis	3.6%	0.9%
Rash	3.2%	1.5%

Given the inconsistent and often erroneous coding of adverse event data, it was not possible to clearly identify what actual conditions accounted for the excess of "sinusitis" in STS patients, however, this will be essential, once the data are recoded.

5.2.2.2 Specific Adverse Events of Concern for Selegiline Transdermal System (STS), and Other Safety Related Issues

5.2.2.2.1 Abuse Potential

We requested a CSS consult on this NDA, given that amphetamine and methamphetamine are metabolites of selegiline. CSS staff noted that the levels of amphetamine and methamphetamine produced by therapeutic doses of selegiline are not considered to be pharmacologically significant, and the levels would be even lower with the STS formulation due to absence of first pass. In addition, the lower fluctuation of selegiline plasma levels with the STS compared to IR would also argue against an increase in abuse potential. Finally, there is no evidence of abuse with the oral form of selegiline. Thus, CSS does not consider STS to have abuse potential.

5.2.2.2.2 Potential for "Cheese Reaction"

As noted, at low concentrations, selegiline is selective for MAO B, but at higher concentrations, it inhibits both A and B. Since MAO in the gut wall is also important in the catabolism of certain dietary amines (e.g., tyramine), one concern about MAOI's is their potential to inhibit gut MAO-A, resulting in the "cheese reaction." However, the STS formulation avoids exposure of gut wall MAO-A to selegiline. Thus, STS would be expected to have the advantage over other MAOI's marketed in the US for depression (phenelzine, tranylcypromine, and isocarboxizide) of not being associated with the "cheese reaction." The sponsor provided two sources of evidence [redacted] (1) Apparently, "cheese reactions" have not been observed with STS, even without the dietary restrictions that need to be observed with orally administered, nonselective MAOI's. (2) Challenge studies with tyramine, pseudoephedrine, phenylpropanolamine (PPA), and cocaine, using STS doses of 20-40 mg/day for 9-10 days, suggested that there is little risk of a clinically important interaction with dietary tyramine. While the safety group generally agreed that these data [redacted], they noted that the tyramine pressor dose in these challenge studies tended to decrease with longer-duration use (up to 33

days), and has asked that a tyramine challenge study be repeated at 60 days, and at later time points if the pressor dose is still declining at 60 days. The safety group also noted that only summary data were reported for the PPA interaction study, and given that these data were not entirely reassuring (increase in mean maximal BP of 8-10 mmHg), they have asked that the full report be submitted.

5.2.2.2.3 Potential for Interaction with TCA's, MAOI's, and SSRI's

Eledpryl labeling contraindicates the concomitant use of oral selegiline with TCAs and SSRIs, based on reports of serious, and even fatal, cases of hyperthermia and rigidity with these combinations. the proposed labeling for STS

c. Therefore, if STS is ever to be marketed, I think the same contraindication for oral selegiline would be appropriate for STS.

5.2.2.2.4 Hypotension

In a pool of the two depression trials in which orthostatic testing was done, 12% of STS patients vs 6% of placebo patients met criteria for an orthostatic change in blood pressure (a change of at least 10 mmHg supine to standing; p=0.02). None discontinued for orthostatic hypotension and syncope was reported in only 1 STS patient. Orthostatic hypotension was also a drug-related adverse event in the Alzheimer's disease program for STS. Despite the finding of drug-related orthostatic changes, the adverse event data did not reveal an excess of adverse events potentially related to orthostasis (e.g., dizziness, falls, fractures, etc.).

5.2.2.2.5 Application Site Reaction (ASR)

ASR's were the most frequent adverse event in STS exposed patients, and led to discontinuation in 3-7% of patients. However, to my understanding, none of these were classified as serious.

5.2.2.2.6 Thyroid Function

Ten STS patients had elevated total T4 levels, but none had changes in T3, and only 2 had decreases in TSH. The safety group recommended measures of free T3 and T4 in future studies to followup on this finding.

5.2.2.2.7 Sexual Dysfunction

Sexual dysfunction was assessed in the depression trials at baseline and endpoint, as part of the MED-D scale, that apparently has 5 items measuring sexual function. The NDA did not include the scale or the specific items. Rather, data were provided on a summary score for the sexual dysfunction subscale. In a pool of the depression trials, there was apparently actually a slight improvement in sexual function compared to baseline, and compared to placebo [-1.8 for STS vs -1.1 for placebo]. I am not familiar with the MED-D, or with its sensitivity in detecting sexual dysfunction.

5.2.2.2.8 Problems in Coding of Adverse Events

Serious problems were detected in the coding of investigator terms under preferred terms, including: (1) coding under the wrong preferred term, (2) splitting of similar investigator terms under several different preferred terms, and (3) lumping of dissimilar investigator terms under the same preferred term. These problems essentially compromise the entire safety data base, making it necessary to redo the entire coding.

5.2.2.3 Conclusions Regarding Safety of Selegiline Transdermal System (STS)

While there are no safety findings that would preclude the approvability of this application, there are, as noted, several issues that need additional clarification before any final conclusions can be reached about the safety of STS. Importantly, the adverse event data need to be recoded, given the serious flaws in the coding.

5.3 Clinical Sections of Labeling

Since there is agreement that the appropriate action at this point is a nonapproval action, we have not proposed labeling at this time.

6.0 WORLD LITERATURE

The sponsor conducted a literature search and detected only 4 papers regarding STS. They provided a warrant than none contained any information pertinent to the safety of STS.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, STS is not marketed anywhere at this time. We will ask for an update on the regulatory status of STS in the nonapproval letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this application to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 3 domestic sites for STS studies, and it is my understanding that all 3 audits were classified as either VAI or NAI. Thus, the data for these studies were deemed acceptable.

10.0 LABELING AND NONAPPROVAL LETTER

10.1 Labeling

As noted, we have not proposed labeling.

10.2 Foreign Labeling

STS is not marketed anywhere at this time.

10.3 Nonapproval Letter

The nonapproval letter includes an explanation for our conclusion that efficacy has not been demonstrated, along with comments on other parts of the development program that need additional work.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Somerset has not submitted sufficient data to support the conclusion that STS is effective in the treatment of MDD. Thus, I recommend that we issue the attached nonapproval letter.

cc:
Orig NDA 21-336 (Selegiline Transdermal System [STS])
HFD-120
HFD-120/TLaughren/RKatz/JRacoosin/GDubitsky/DGan/DBates

DOC: MEMSLGDP.NA1

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/s/

Thomas Laughren
3/15/02 09:39:59 AM
MEDICAL OFFICER

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21-336**
Sponsor:	**Somerset Pharmaceuticals, Inc**
Drug:	**EMSAM™ (selegiline transdermal system**
Proposed Indication:	**Major Depression**
Material Submitted:	**NDA #21-336, 561 paper volumes** **NDA #21-336, ISS Depression Datasets**
Action Date:	**March 25, 2002**
Date Review Completed:	**March __, 2002**
Reviewers:	**David Gan, M.D., Dr.PH** **Greg Dubitsky, M.D.** **Judith A. Racoosin, MD, MPH** **Gerard Boehm, MD, MPH**

The following DNDP medical officers conducted the NDA safety review:

David Gan, MD, DrPH
- deaths, other serious adverse events, dropouts due to adverse events, common adverse experiences, and review of systems.

Greg Dubitsky, MD
- ECG, lab and vital sign data

Gerard Boehm, MD, MPH
- coding of AE verbatim terms, Phase 1 safety

Judith A. Racoosin, MD, MPH
- safety of oral selegiline, demographics, other adverse events of clinical interest, evaluation of the potential interaction between STS and sympathomimetic amines, ongoing studies, 120-day safety update, discussion, and supervisory editorial/compositional input into Dr. Gan's review

1 Executive Summary

Somerset Pharmaceuticals, Inc. is requesting approval for the use of EMSAM^{TM} (selegiline transdermal system) 20mg/20cm^2 for the treatment of major depression. According to the sponsor, non-clinical studies demonstrated reliable transdermal absorption of selegiline, producing a targeted inhibition of both MAO-B and MAO-A activities in the brain, while maintaining selectivity for MAO-B inhibition in peripheral tissues such as sympathetic neurons, intestinal epithelium, and liver.

The sponsor's Integrated Summary of Safety (ISS) for the selegiline transdermal system (STS 20mg/20cm2) presents safety data from four completed double-blind, placebo-controlled Phase III studies, three open-label continuation treatment studies and an open-label run-in phase of an ongoing double-blind treatment discontinuation study in patients with major depression.

Data from five Phase II/III studies in other indications also are presented in the ISS. These include data from two studies in Alzheimer's disease, one study in Parkinson's disease, one study in HIV-associated cognitive impairment, and one study in [redacted]. In total, the sponsor provided data from 36 phase I studies conducted in volunteer subjects and 13 phase II/III clinical studies conducted in patients.

The review of the adverse event 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.

Tyramine, pseudoephedrine, phenylpropanolamine, and cocaine were evaluated for their potential for causing hypertensive reactions in association with STS because of its MAO inhibiting function. 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.

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.

1.1 Depression studies

In the four controlled clinical studies with total of 1220 patients for the indication of major depression. There were 534 patients treated with STS (20mg/20cm2), 151 patients

treated with STS (10mg/20cm2), and 535 treated with placebo treatment. Mean duration of treatment in the three groups in this pool were comparable across treatment groups with a mean exposure time that ranged from 46 to 49 days. Person-year of exposure was estimated by summing up duration (day) in each exposure category and then converting to person-years. Total STS (10mg/20cm2) exposure is 20 person-years, total STS (20mg/20cm2) exposure is 66 person-years, and total placebo exposure is 67 person-years.

For the indication of major depression, there were no deaths in the RCTs or the uncontrolled (open-label) studies.

In the randomized controlled clinical studies for major depression, 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). The discontinuations due to AEs in the STS (20mg/20cm2) group are statistically significantly higher than that in the placebo group. Application site reaction (ASR) is the AE that contributed to this significant difference between STS treatment group and placebo group.

Nine patients had SAEs in the controlled clinical studies for the indication of major depression, two STS [20mg/20cm2] patients, one STS [10mg/20cm2] patient and six placebo patients. One of the STS 20mg SAEs was a stillbirth with a cleft palate at 20 weeks gestation.

For the controlled clinical studies in major depression, the percentage of patients with one or more AEs was similar in the STS (10mg/20cm2), (72%, [110/151]), STS (20mg/20cm2), (75.7%, [404/534]), and placebo groups (71.0%, [380/535]). ASR, insomnia and sinusitis were significantly higher in STS treatment group than in placebo group.

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 patients had no substantial changes in T_3 levels and only two patients had remarkable decreases in TSH. A more complete evaluation of the potential affect of STS on thyroid function can be addressed in future studies by measuring free T_3 and T_4 levels.

STS was associated with orthostatic changes in blood pressure compared to placebo. In the pool of two placebo-controlled depression studies where orthostatic blood pressure was measured, 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). 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. However, no patients in this study pool discontinued 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.

1.2 Alzheimer's disease studies

There was one other large source of placebo-controlled safety data in the NDA database. In S9303-E101-96B, the 12-month study in Alzheimer's disease, 69.6% (190/273) of STS (20mg/20cm2) patients and 76.7% (102/133) of placebo patients had more than 24 weeks of exposure. Total STS (20mg/20cm2) exposure is 175 person-years. Total placebo exposure is 92 person-years. There was also a smaller placebo-controlled randomized double blind dose ranging study in Alzheimer's disease (S9303-E100-94B).

There were six deaths in studies involving elderly patients with Alzheimer's disease. Of these six deaths, one death occurred in study S9303-E100-94B post-treatment beyond the 30-day follow-up period. The other five deaths occurred in study S9303-E101-96B, three patients were in the STS (20 mg/20 cm^2) group and two were in the placebo group.

In S9303-E100-94B, a small placebo-controlled randomized double blind dose ranging study in Alzheimer's disease, the 16 mg and 24 mg arms of the study were discontinued by protocol amendment due to an elevated frequency of discontinuation in the 16 mg study arm due to postural hypotension. Of the patients in S9303-E101-96B 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, seventy-four patients experienced a total of 100 SAEs. A total of 76 serious adverse experiences were reported in the STS treatment group (sponsor table 6.34). Of the patients who received placebo, 18% (24/133) had at least one SAE.

In study S9303-E101-96B (48-week study), 95.2% of the patients in the STS group experienced an AE and 89.5% of the patients in the placebo group experienced AEs. The incidence of ASR was significantly higher in the STS group than in the placebo group.

In the Alzheimer's disease study S9303B-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).

1.3 Remaining issues to be addressed by the sponsor

- 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.

2 Materials Used in the Review

- NDA # 21-336, 561 paper volumes dated 5/24/2001
- ISS Depression Datasets, 8/3/2001
- Safety update, 9/26/2001
- Coding dictionary datasets, 2/25/02

3 Background

3.1 Development of EMSAM™

Somerset Pharmaceuticals, Inc. is requesting approval for the use of EMSAM™ (selegiline transdermal system [STS]) 20mg/20cm^2 for the treatment of major depression. The sponsor pursued the development of EMSAM™ as a treatment of major depression based on the pharmacological properties of selegiline. Selegiline is a levorotatory acetylenic derivative of phenethylamine. It is commonly referred to in the clinical and pharmacological literature as l-deprenyl. Selegiline is a second-generation monoamine oxidase (MAO) inhibitor. At low oral dosages (up to 5 mg BID), selegiline is a potent, selective, irreversible inhibitor of MAO-B. The selectivity of selegiline for MAO-B arises from a greater affinity for the MAO-B flavin site and a greater reactivity of selegiline from the covalent bond with MAO-B as compared to MAO-A. However, selegiline also inhibits MAO-A in a concentration-dependent manner.

Unlike non-selective MAO inhibitor agents, the sponsor stated that selegiline at doses of approximately 10 mg/day (selegiline HCL) is not associated with the "cheese effect". "Cheese effect " refers to cardiovascular interactions between MAO inhibitor drugs and tyramine (a chemical present in aged cheeses).

Currently, oral selegiline HCL is approved for the treatment of patients with late stage Parkinson's disease receiving levodopa/carbidopa therapy who experience deterioration in the quality of response to this treatment.

At the therapeutic dose for Parkinson's disease patients (5 mg BID), selegiline has no therapeutic efficacy in depression. Oral selegiline has low bioavailability because of extensive first-pass metabolism. Therapeutic efficacy in depression is only achievable at oral doses of approximately 30-60 mg/day; however, at this dose level of selegiline, the cardiovascular safety is compromised when ingested with dietary tyramine or OTC sympathomimetic decongestants.

In order to circumvent the first-pass effect, the sponsor explored the feasibility of transdermal delivery of the dose of selegiline required for antidepressant efficacy. According to the sponsor, non-clinical studies demonstrated reliable transdermal absorption of selegiline, producing a targeted inhibition of both MAO-B and MAO-A

activities in the brain, while maintaining selectivity for MAO-B inhibition in peripheral tissues such as sympathetic neurons, intestinal epithelium, and liver. Tyramine is a common substrate for either isoform of MAO. Preservation of MAO-A activity in intestinal and hepatic tissue sites maintains the normal barriers to entry of bioactive amines associated with the "cheese effect".

3.2 Safety of oral selegiline

Oral selegiline (marketed as Eldepryl ®) is approved for use as an adjunctive treatment of Parkinsonian patients being treated with levodopa/carbidopa who exhibit deterioration of their response to this therapy. The main warning in the Eldepryl labeling cautions against the use of higher than recommended doses (5 mg po BID) due to the non-selective MAO inhibition that occurs at such doses. Ingestion of tyramine-containing foods leads to hypertensive reactions in patients who have non-selective inhibition of MAO A and B.

The Eldepryl labeling also warns against the concomitant use of the drug with tricyclic antidepressants and selective serotonin reuptake inhibitors due to cases of hyperthermia and rigidity sometimes resulting in death occurring in patients who took these classes of drugs with Eldepryl.

Of commonly occurring adverse events associated with Eldepryl use, nausea and dizziness/lightheadedness/fainting occurred most frequently, and at an excess risk of >3X in the Eldepryl group compared to the placebo group.

In section 8.H.16.2, the sponsor sites 11 references that address efficacy of oral selegiline in depression; five of these studies were randomized, double-blinded, and placebo-controlled. These controlled studies found that efficacy was achieved only at the high end of the dosing range, but that all doses were well tolerated. The sponsor asserts that the safety profile of oral selegiline resembled that of the placebo group in these controlled trials. These studies did not identify substantial safety issues; however, it is well recognized that reporting of safety outcomes in papers describing efficacy studies is often inadequate and neglected.[1] Adverse events that were documented included dry mouth,

[1] Ioannidis JPA and Lau J. "Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas." *JAMA* 2001; 285(4): 437-443.

dizziness, headache, insomnia, agitation, anorexia, aggressiveness, hypotension, and anxiety. One hypertensive event was reported following a patient's ingestion of cheese. The sponsor suggests that this event supports the observation that dietary tyramine restriction is needed at the oral doses of selegiline needed for antidepressant efficacy (30-60 mg/day).

3.3 EMSAM™ Preclinical Studies

The sponsor conducted toxicology studies in rats, rabbits and dogs using current STS formulation, pilot formulation of the current STS and intravenous, subcutaneous and oral formulation of selegiline HCL.

According to the sponsor, the toxicity of high doses of transdermal selegiline was similar to the toxicity from high doses of oral selegiline HCL, and represents the extended pharmacological effects that would be expected at high doses. No unique toxicological effects were associated with transdermal selegiline based on animal studies. The sponsor states that, overall, the results from the pharmacology, pharmacokinetic and toxicology studies support the potential efficacy and safety of selegiline delivered via the STS (20 mg/20 cm^2) at the proposed clinical dose and regimen, and indicates that unwanted adverse effects should not occur in humans at the clinical dosage. The toxicity in rats and dogs was limited to reversible dose-related clinical signs (which included CNS signs) and decreased body weights. Dermal irritation was observed at the patch application sites, the sponsor indicated this irritation was caused by the patch itself and not by selegiline.

At targeted doses of up to 75 mg/kg/day, selegiline causes slight toxicity in rats; these doses did not cause adverse effects on fertility or reproductive parameters. The toxicity in rats and dogs was limited to reversible dose-related clinical signs and decreased body weight.

Transdermal selegiline was not teratogenic in rats up to 18 times human exposure or in rabbits at up to 20 times human exposure. In rats, the NOEL (no-effect level) for maternal toxicity after STS (20 mg/20 cm^2) application was 10 mg/kg/day (approximately twice human exposure based upon AUC_{0-24}) and the NOAEL (no observed adverse effect) for developmental toxicity was 30 mg/kg/day (approximately 6 times human exposure based upon AUG_{0-24}). In rabbits, the NOEL for maternal toxicity was 10 mg/kg/day and NOEL for fetotoxicity and teratogenicity was 40 mg/kg/day.

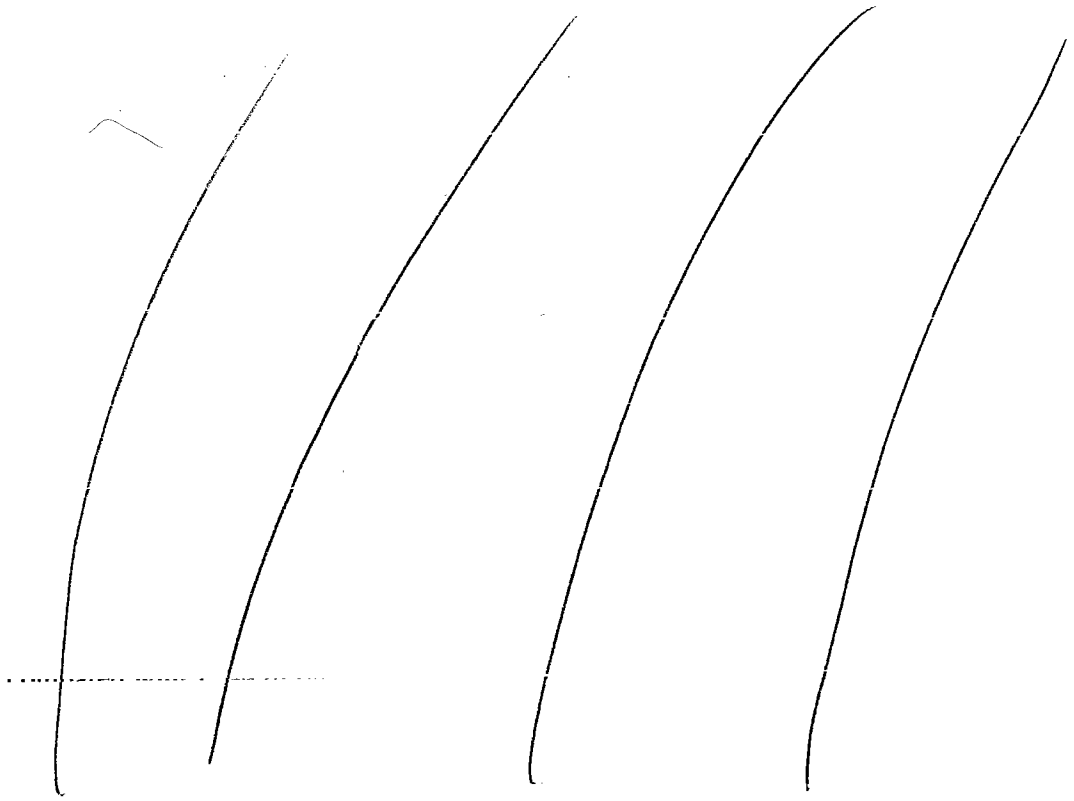
Peri-and post-natal exposure of female rats to selegiline delivered via the STS (20 mg/20 cm^2) in a Segment III study produced no F0 maternal toxicity at 10 mg/kg/day, but did produce F0 maternal toxicity at 30 and 75 mg/kg/day. These doses represented approximately 6 and 17 times the daily human exposure to selegiline via the STS (20 mg/20 cm2), respectively.

The toxicity in the F1 pups was associated with maternal toxicity as well as with oral exposure to high concentrations of selegiline and its metabolites via milk. After peri-and post-natal application of STS (20 mg/20 cm^2) to maternal rats, the NOEL for maternal

toxicity and the NOAEL for developmental toxicity were 10 mg/kg/day (approximately twice the daily human exposure to selegiline via the STS (20 mg/20 cm^2).

The sponsor also conducted a standard battery of in vitro and in vivo mutagenicity studies. The studies show that selegiline does not have mutagenic potential. Selegiline was not carcinogenic in a 78 week mouse dietary carcinogenicity study and a 104 week rat dietary carcinogenicity study.

3.4 Review of Safety Issues Identified in Proposed Labeling



4 Methods of Safety Review

4.1 The Sponsor's Approach to the Safety Analysis

4.1.1 Exposure

The sponsor used the total number of patients in the treatment and placebo groups as the denominator for the calculation of incidence rates. The sponsor did not take into account of the duration of exposure.

4.1.2 Numerator

The sponsor counted the number of patients who had one or more adverse events as the numerator. If a patient experienced more than one episode of an adverse event, the event was counted only once for the numerator.

4.1.3 Data Analysis

The sponsor calculated incidence rates using number of patients who had adverse events as numerator and the total number of the patients in treatment and placebo groups as denominator. Then the sponsor compared the rates of STS treatment group to placebo group. The sponsor did not calculate incidence rate ratios. The sponsor did not perform statistical significance tests or provide a 95% confidence interval for a rate ratio.

4.2 FDA Reviewer's Approach to the Safety Analysis

Although some of the sponsor's studies included a treatment arm of STS dose 10cm/20cm, the intended dose for marketing is 20mg/20cm2. As such, this review will focus on the comparison of the 20mg/20cm2 dose with placebo.

4.2.1 Exposure

I calculated person years of exposure for the treatment and placebo groups as the denominator for the calculation of incidence rates.

4.2.2 Numerator

I counted the number of events in the treatment groups and the placebo groups as numerator. One patient could have experienced an adverse event once or more than once.

4.2.3 Data Analysis

I calculated incidence rates using number of adverse events as numerator and the total person-time in treatment and placebo groups as denominator. Incidence rate ratios were

also calculated comparing treatment group to placebo group. I also calculated the 95% confidence interval to test if the incidence rate ratios are statistically significant.

I limited my analyses of incidence rates to the pool of placebo-controlled trials in depression and Alzheimer's study 29303-E101-96B because these two data sources had sufficient person time exposure to STS and placebo.

4.3 Data Audit

4.3.1 Patient accounting issue- study 29303-E100-94B

The sponsor's use of 13 as the denominator for the placebo group in this study is not clearly explained in the study report. According to Table 4.1.1 of the study report "Patient Disposition: All Treatment Groups", 20 patients were randomized to placebo, with 13 completing at least 28 days of treatment. At the same time, 31 patients were randomized to STS 8 mg, with 29 completing at least 28 days of treatment. The sponsor appropriately chose to use 31 as the denominator for the STS 8 mg group, but without explanation, chose 13 for the placebo denominator. What may have happened, although the sponsor does not explicitly state this in the study report, is that for each dosage level of STS, placebo patients were assigned to that same level. Despite the fact that there is no real difference between a placebo 8 mg, placebo 16 mg, or placebo 24 mg patient[2], it appears that the sponsor only included the placebo patients assigned to the 8 mg group in their analysis. The approach seems irrational, so in this review 20 rather than 13 will be used as the placebo denominator for this study.

4.3.2 Data quality

In this NDA application, the sponsor submitted 561 volumes of materials for reviewing. There were some data discrepancies in the summary tables.

- Table 6.1, page 124005, "Summary of Adverse Experiences: Controlled Clinical Studies in Major Depression" listed total of 50 patients discontinued for AEs. It is four less than the sum of the numbers of patients discontinued due to AEs obtained from individual study reports.

- The sponsor's table 5.8, "Patient Disposition: Alzheimer's disease Study S9303-E100-94B "(page 123998), is disorganized and difficult to interpret.

- In table 6.28, "Incidence Rate of Serious Adverse Experiences: Study S9303-E100-94B", (page 124081), the sponsor listed a total of nine serious adverse events. Actually, 17 serious adverse events were reported in 9 patients.

[2] Except perhaps for ASR, since placebo patients in higher dose groups wore larger or additional patches

- In table 6.34, "Non-fatal Serious Adverse Experiences During Double-Blind Treatment: Study S9303-E101-96B", (page 124101-124106) the sponsor listed 50 STS-treated patients (18.3% [50/273]) who had an SAE(s). In table 6.29, "Summary of Adverse Experiences: Total STS (20mg/20cm2) Exposure in Alzheimer's disease Study S9303-E101-96B", the sponsor listed 53 patients (19.4%) in the active treatment group who experienced an SAE.

- In reviewing the SAE of the study S9303-E101-96B, I could not locate the narratives for patients 126, 134, 506, 520, 607, 609, 622, 939, 1008, 1014, 1017, 1239, 1316, 1319, 1532, 2105, 2203, 2210, 2610, 2646, 2653 and 2661. The narratives for these patients were missing from Section 8 of the submission (page 124420 to 124447), containing the SAE narratives for the study.

4.3.3 Review of the Sponsor's Coding of Adverse Event Terms

I reviewed the sponsor's approach to coding AE verbatim terms by using the JMP statistical software package to explore the sponsor's data files that contain the AE verbatim terms and the coded COSTART terms. These coding data files were not included with the original NDA submission and were requested from the sponsor during the NDA review. Specifically, I examined the coding by comparing the AE verbatim terms to the coded COSTART terms to assess the accuracy of the coded term subsuming the identified AE verbatim term. I also looked to see if similar AE verbatim terms were appropriately grouped, to determine if there was inappropriate splitting of similar AEs or grouping of unlike AEs.

I found several examples of what appeared to be inaccurate coding, splitting of similar AE verbatim terms to multiple COSTART terms, and grouping of dissimilar AE verbatim terms under a single COSTART term. Any of these findings could have impacted the interpretability of the risks calculated using the COSTART terms. In the following sections, I provide examples of the identified coding concerns. The following sections are not mean to be a comprehensive listing of all potential coding problems, but serve to provide examples of concerns that could have impaired the ability of the reviewer to accurately describe or detect safety signals in the EMSAM NDA.

4.3.3.1 Potentially miscoded events

I identified instances where AE verbatim terms were mapped to COSTART terms that appeared inaccurate. Below I provide a specific example to illustrate this finding.

Sexual side effects

I identified what appears to be inaccurate mapping of sexual AE verbatim terms. Specifically, the COSTART term Libido decreased appeared to be used inappropriately when comparing the verbatim term to the COSTART term. Libido is defined in Stedman's medical dictionary as conscious or unconscious sexual desire. The sponsor coded verbatim terms such as decreased sexual sensation, delayed orgasm, and difficulty

achieving orgasm to the COSTART term libido decreased. Based on comparison of these verbatim terms to the COSTART terms, the coding appears inaccurate, and could impede the reviewer's ability to examine the relationship between drug and specific sexual side effects.

4.3.3.2 Potential Splitting of Similar Events

In the coding data set, I found instances of coding similar verbatim terms to different COSTART terms. In some cases the exact same verbatim term was coded two or more different COSTART terms. Below, I provide examples of apparent splitting of similar AE verbatim terms. The list is not meant to be a comprehensive catalogue of all such occurrences in the coding data set.

Selected Verbatim terms and their corresponding COSTART terms from the sponsor's coding data sets

Verbatim term	**COSTART term**
Bloated abdomen	Abdo Enlarge
Bloated stomach	Flatulence
Bloating	Flatulence
Cervical Spasm	Hypertonia
Cervical Spasms	Spasm general
Cold Sore	Herpes simplex
Cold Sore mouth	Stomatitis
Blood in Stool	Hem GI
Blood in Stool	Melena
Blurred Vision	Amblyopia
Blurring vision	Vision abnm
Breakthrough bleeding	Metrorrhagia
Breakthrough menstrual flow	Mens dis
Disoriented	Confusion
Disoriented	Thinking Abnormal
Dizzy	Dizziness
Dizzy	Vertigo

4.3.3.3 Potential Lumping of Dissimilar Events

I identified instances of potential lumping of dissimilar AE verbatim terms under a single COSTART term. For example, the COSTART term Infection was used for many verbatim terms including the following: head cold, infection of the left thumb, right ear infection, sinus infection, throat infection, and venereal disease. While all of the verbatim terms suggest an infection AE, this appears to be a collection of dissimilar events. Furthermore, I cannot determine why sinus infection would be including under the Infection COSTART term instead of the Sinusitis COSTART term. Another example of potential lumping of dissimilar AE verbatim terms was the use of the COSTART term Pain. The COSTART term Pain subsumed many verbatim term AEs including the

following: aches, burning in the arms and upper torso, cramping, intestinal pain, maxillary sinus tenderness, stomach cramps, and tooth aches. While all of these events are painful, inclusion under a single COSTART term does not allow a meaningful risk assessment for these individual AEs and could impede detection of a cluster of specific similar AEs.

4.4 Description of the ISS

The sponsor's Integrated Summary of Safety (ISS) for the selegiline transdermal system (STS 20mg/20cm2) presents safety data from four completed double blind, placebo-controlled Phase III studies, three open-label continuation treatment studies and an open-label run-in phase of an ongoing double-blind treatment discontinuation (relapse prevention) study in patients with major depression.

Data from five Phase II/III studies in other indications also are presented in the ISS. These studies include two placebo-controlled studies in Alzheimer's disease, one small dose-ranging study and one large 12 month efficacy study. One study each in Parkinson's disease and were open-label and enrolled 25 and 18 patients, respectively. A study in HIV-associated cognitive impairment was a randomized, double-blinded, placebo-controlled study; however, it enrolled only 14 patients. Because of the small numbers of patients participating in these studies, and the uncontrolled status of two of them, the safety results of these studies will not be discussed further in this review.

The sponsor also included information on deaths and serious adverse events occurring in ongoing trials. Two deaths occurred in ongoing trials in Parkinson's disease; those deaths are described below in sections 4.3.1.3 and 4.3.1.4.

4.4.1 Brief Description of Major Trials

Sponsor's table 2.1 (section 8 page 123892 – 123893) below lists all clinical studies in the sponsor's ISS database.

Sponsor table 2.1

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Table 2.1. Overview of Integrated Summary of Safety Database by Study Pool and Study (Page 1 of 2)

STUDY POOL/ STUDY NUMBER	NUMBER OF CENTERS	PATIENTS RANDOMIZED OR ENTERED##	PATIENTS INCLUDED IN SAFETY POPULATION N (%)	PATIENTS EXCLUDED FROM SAFETY POPULATION N (%)
CONTROLLED CLINICAL STUDIES IN MAJOR DEPRESSION				
S9303-E106-96B	6	177	177 (100.0)	0 (0.0)
S9303-E113-98B	13	297	296 (99.7)	1 (0.3)
S9303-P9804	16	310	301 (97.1)	9 (2.9)
S9303-E114	19	446	446 (100.0)	0 (0.0)
TOTAL	54	1230	1220(99.2)	10 (0.8)
OPEN-LABEL CLINICAL STUDIES IN MAJOR DEPRESSION				
S9303-E106-96B+	6	137	137 (100.0)	0 (0.0)
S9303-P9805#	20	202	201 (99.5)	1 (0.5)
S9303-P9918@	38	305	305 (100.0)	0 (0.0)
S9303-P9806$	29	500	500 (100.0)	0 (0.0)
TOTAL	93	1144	1143(99.9)	1 (0.1)
TOTAL STS EXPOSURE &				
STS 20MG/20CM^2	83	1330	1326(99.7)	4 (0.3)
STS 10MG/20CM^2 FOLLOWED BY 20MG/20CM^2	15	45	45 (100.0)	0 (0.0)
CLINICAL STUDIES IN OTHER INDICATIONS^				
ALZHEIMER'S DISEASE				
S9303-E100-94B	5	70	70 (100.0)	0 (0.0)
S9303-E101-96B	25	406	406 (100.0)	0 (0.0)
TOTAL	30	476	476 (100.0)	0 (0.0)
PARKINSON'S DISEASE				
S9303-E102-96B	3	25	25 (100.0)	0 (0.0)
HIV-ASSOCIATED COGNITIVE IMPAIRMENT				
S9303-E110-97B	3	14	14 (100.0)	0 (0.0)
[redacted]	2	18	18 (100.0)	0 (0.0)
TOTAL PATIENTS IN CLINICAL STUDIES IN OTHER INDICATIONS	-	533	533 (100.0)	0 (0.0)
TOTAL UNIQUE PATIENTS++	-	2263	2253(99.6)	10 (0.4)

\+ OPEN-LABEL EXTENSION OF CONTROLLED STUDY S9303-E106-96B.
\# OPEN-LABEL EXTENSION OF CONTROLLED STUDY S9303-E113-98B AND S9303-P9804.
@ OPEN-LABEL EXTENSION OF CONTROLLED STUDY S9303-E113-98B, S9303-P9804 AND S9303-E114. THIS STUDY WAS ONGOING AT THE TIME OF SUBMISSION, WITH DATA CUTOFF OF 7/20/00.
$ INCLUDES DATA FROM THE FIRST 500 PATIENTS WHO COMPLETED (OR DISCONTINUED FROM) THE 10-WEEK, OPEN-LABEL, RUN-IN PERIOD.
& INCLUDES ALL PATIENTS WHO RECEIVED STS IN ANY CLINICAL STUDY IN MAJOR DEPRESSION, AND INCLUDES EACH PATIENT'S TOTAL CONTINUOUS TREATMENT WITH STS (E.G., STS TREATMENT IN A CONTROLLED STUDY FOLLOWED BY STS TREATMENT IN AN OPEN-LABEL EXTENSION STUDY).
^ DATA OBTAINED FROM FINAL CLINICAL STUDY REPORTS.
++ INCLUDES PATIENTS IN COMPLETED CONTROLLED CLINICAL STUDIES IN MAJOR DEPRESSION, PATIENTS WITH MAJOR DEPRESSION IN STUDY S9303-P9806, AND PATIENTS IN CLINICAL STUDIES IN OTHER INDICATIONS.
PATIENTS WHO EITHER WERE RANDOMIZED TO STUDY TREATMENT, OR ENROLLED TO PARTICIPATE IN THE CLINICAL STUDY.
STS=SELEGILINE TRANSDERMAL SYSTEM
DATA SOURCE: APPENDIX B, TABLE B.2.1.
THE ABOVE FOOTNOTES APPLY TO THIS ENTIRE TABLE.

5 Safety Data and Data Analysis- Phase III trials

5.1 Exposure

5.1.1 Major depression

Extent of exposure in studies of patients with major depression is expressed as mean and/or median number of days on treatment, with the understanding that the patch, either active STS or placebo, was changed daily.

In the four controlled clinical studies, a total of 1220 patients were treated for the indication of major depression. There were 534 patients treated with STS (20mg/20cm2), 151 patients treated with STS (10mg/20cm2), and 535 treated with placebo treatment. Mean duration of treatment in the three groups in this pool was comparable across treatment groups with a mean exposure time that ranged from 46 to 49 days.

FDA Table EXP-MD. Person Years of Exposure: Controlled Clinical Studies in Major Depression

Duration of treatment in Days	Treatment			
	STS (total) (n=685)	STS (10mg/20cm2) (n=151)	STS (20mg/20cm2) (n=534)	Placebo (n=535)
< 3 (fewer than 3 days)	24x1.5 d	0x1.5 d	24x1.5 d	17x1.5 d
≥ 3 (At least 3 days)	3x 5 d	1x5 d	2x5.0 d	8x5.0 d
≥ 7 (At least 1 week)	13x10 d	1x10 d	12x10 d	8x10 d
≥ 14(At least 2 weeks)	70x2 d	21x21 d	49x21 d	43x21 d
≥ 28 (At least 4 weeks)	52x35 d	11x35 d	41x35 d	31x35 d
≥ 42 (At least 6 weeks)	190x49 d	31x49 d	159x49 d	164x49 d
≥ 56 (At least 8 weeks)	333x56 d	86x56 d	247x56 d	254x56 d
Total Person Day	31429	7176	24253	24393
Total Person Year	86	20	66	67

FDA Table EXP-MD above summarizes the extent of exposure to treatment in the four controlled clinical studies in major depression. I estimated person-years of exposure by summing up duration (day) in each exposure category and then converting to person-years. Total STS (10mg/20cm2) exposure is 20 person-years and total STS (20mg/20cm2) exposure is 66 person-years. Total placebo exposure is 67 person years.

5.1.2 Alzheimer's disease

There was one other large source of placebo-controlled safety data in the NDA database. In S9303-E101-96B, the 12-month study in Alzheimer's disease, 69.6% (190/273) of STS (20mg/20cm2) patients and 76.7% (102/133) of placebo patients had more than 24 weeks of exposure. 173 patients had treatment with STS (20mg/20cm2) for 48 weeks or more. This study is not pooled with the four placebo-controlled depression trials for purposes of safety analysis because of the differences in patient diagnosis and age as well as the longer study duration.

FDA Table EXP-ALZ96B. Person Year of Exposure: Alzheimer's Study S9303-E101-96B

Duration of treatment in Weeks	Treatment	
	STS Person week	Placebo Person week

≤ 6 > 6 ≤ 12 > 12 ≤ 24 > 24 ≤ 36 ≤ 36 ≤ 48 > 48 Unknown	22x3 22x9 33x18 15x30 103x42 72x48 6x1	10x3 8x9 11x18 4x30 55x42 43x48 2x1
Total Person Week	9096	4796
Total Person Year	175	92

FDA Table EXP-ALZ96B above summarizes the extent of exposure to treatment in the controlled clinical study (S9303-E101-96B) in Alzheimer's disease. I estimated person-years of exposure by summing up duration (weeks) in each exposure category and then converting to person-years. Total STS (20mg/20cm2) exposure is 175 person-years. Total placebo exposure is 92 person-years.

5.2 Demographics

5.2.1 Major depression

In the pool of placebo-controlled trials in depression, the median age in both the STS 20mg/20cm2 and placebo groups was 42 years old (range 18-66); 95% were younger than age 60. About 63% of patients in both groups were women. The vast majority of patients in these trials were Caucasian (84-88%). The demographic profile of the patients participating in the open-label trials in depression was very similar to that observed in the placebo-controlled trials.

5.2.2 Alzheimer's disease

In study S9303-E101-96B in Alzheimer's disease, the median age in both the STS 20mg/20cm2 and placebo groups was 76 years old (range 51-85); about 20% were age 60-69 and about 80% were age 70-79. Women accounted for just over half the patient population (range 53-59%). The vast majority of patients in these trials were Caucasian (93-96%). The placebo group had a longer median duration of Alzheimer's disease than the STS group (6.0 v. 4.0 years). The demographic profile of the patients participating in trial S9303-E10-94B in Alzheimer's disease was similar to that observed in the larger E101 trial, except that the median duration of Alzheimer's disease was shorter (about 3 years).

5.3 Death

For the indication of major depression, there were no deaths in the RCTs or the uncontrolled (open-label) studies. There were six deaths in studies involving elderly patients with Alzheimer's disease. Of these six deaths, one death occurred in study

S9303-E100-94B post-treatment beyond the 30-day follow-up period. The other five deaths occurred in study S9303-E101-96B; three patients were in the STS (20 mg/20 cm^2) group and two were in the placebo group. In the following paragraphs, I provide clinical details for the NDA deaths, followed by a comparison of mortality risk by treatment.

5.3.1 Description of Deaths

5.3.1.1 Study 29303-E101-96B (Senile Dementia Associated with Alzheimer's Disease)

5.3.1.1.1 STS Group

There were three deaths in the treatment (STS 20 mg/20 cm^2) group. The reported underline causes of death were cardiorespiratory events and stroke.

Patient 0120/MEW , a 73-year old female with no history of heart disease, died of cardiorespiratory failure. The patient was randomized to receive STS (20 mg/20 cm^2) once daily. On Day 46, the patient experienced intermittent abdominal and back pain. On Day 48, the patient had a single episode of emesis in the evening. On Day 49, the patient was clammy and diaphoretic, and was brought to the emergency room. Study drug was stopped on Day 49.

At the hospital, the patient went into cardiorespiratory arrest and required resuscitation. The diagnosis was shock with atrial fibrillation, acute respiratory failure, probable sepsis, possible pancreatitis, and severe renal insufficiency. The patient continued to have hypotension, worsening renal insufficiency with anuria, and rapidly elevating liver functions. The patient expired on Day 50.

Patient 0522/DAM, an 85-year old female died of cardiorespiratory arrest. The patient was randomized to receive STS (20 mg/ 20 cm^2) once daily. Sixteen days after study was stopped, she developed dyspnea that was unsuccessfully treated with albuterol. She was transported to the emergency room and was found to have pyuria, hypoxia, pulmonary rales, tachycardia, and hypertension. A chest X-ray revealed acute pulmonary edema and cardiomegaly (not present on the chest X-ray done one day after study drug was stopped). There were no signs of an acute MI. The patient was treated in the emergency room with oxygen, intravenous furosemide, and nitroglycerin ointment, and transferred to the ICU. Intravenous antibiotics were begun when laboratory results revealed leukocytosis and possible urinary sepsis. Two days later, the patient expired due to acute respiratory deterioration, adult respiratory distress syndrome, cardiopulmonary arrest, congestive heart failure, and possible pneumonitis.

The patient had a history of dyspnea secondary to chronic obstructive pulmonary disease and coronary atherosclerosis. The patient's concomitant medications started prior to study entrance included levothyroxine, aspirin, docusate sodium, and Maalox®.

Patient 0611/F-S, an 83-year old male was randomized to receive STS (20 mg/20 cm^2) once daily. On Day 13, he experienced drooling, facial paralysis, and syncope. These events were not reported to the clinic until Day 15, at which time, the study drug was discontinued and the patient referred to his primary care physician. On Day 17 the patient's condition deteriorated, with seizure-like activity and loss of activities of daily living. Hospitalization was required. The patient expired four days after study drug was stopped.

The patient had a history of heart disease and had a coronary artery bypass graft procedure approximately four years prior to study entry. Concomitant medications included glyburide, finasteride, and Vitamin B-12.

5.3.1.1.2 Placebo Group

There were two deaths in the placebo group. The reported underlying causes of death are motor vehicle accident and breast cancer.

Patient 0607/RBB, a 79-year old female, was randomized to receive placebo once daily. On Day 254, the patient was involved in a motor vehicle accident and died instantly. The patient had no medical history relevant to the event. No details were given for the MVA in the case report form (volume 414).

Patient 1239/FMM, a 79-year old Caucasian female, was randomized to receive placebo. The patient had a history of breast cancer and a benign tumor removed from her left arm. The investigative site noted an increase in the patient's LFTs from approximately 7 months after study entry through study Day 293. A gallbladder/biliary ultrasound revealed multiple masses of mixed echogenicity within the liver, compatible with metastatic disease. Two weeks after the initial ultrasound (study Day 307), the patient started chemotherapy. A CT scan on Day 331 reveled supra and infratentorial metastasis of brain. The CT scan also showed small vessel disease (history compatible with the patient's age) and right frontal calvarial metastases. The patient died on Day 345 at home. Concomitant medications included ibuprofen, 200 mg po qd for arthritis of the back and knees, and levothyroxine sodium, 88 mcg po qd for long-standing hypothyroidism.

5.3.1.2 Study 29303-E100-94B (Senile Dementia Associated with Alzheimer's Disease)

Patient 117, a 77 old Caucasian female with a history of progressive Alzheimer's disease of one year in duration, was randomized to receive STS (8mg). She was receiving no medication other than laxatives. Beginning on Day 11, the patient had mild, intermittent, symptomatic orthostatic hypotension of 30 days duration considered by the investigator to be related to study drug. The patient completed the initial 29 days (Day 29) of treatment but did not enter the open label extension.

On Day 29, the patient was admitted to the hospital. She had not been eating well, her speech had deteriorated, and she was assaultive and withdrawn. On admission, her physical exam revealed normal vital signs, clear lungs, and normal heart tones. However, her gait was unstable and a brain scan showed diminished cerebral perfusion. On Day 33 she was discharged and transferred to a terminal care nursing home. By Day 53, she made no verbal responses, her head and eyes were rotated to the right, her arms and legs had flexion contractures, and there was myoclonic jerking of the wrist, hand, and fingers. By Day 77, she was mute and not functioning. On Day 90, the patient died. An autopsy was not performed. The cause of death on the death certificate was probable Creutzfeldt-Jakob disease (progressive dementia).

5.3.2 Mortality Data Analysis

5.3.2.1 Major depression

There were no deaths in the clinical studies for the indication of major depression.

5.3.2.2 Alzheimer's Disease

There were six deaths in studies involving elderly patients with Alzheimer's disease; one of these deaths, due to probable Creutzfeldt-Jacob disease, occurred in study S9303-E100-94B. I excluded this death from my analysis since this death occurred in post-treatment beyond the 30-day follow-up period. I calculated mortality rates both in selegiline treatment group and placebo group in Study 29303-E101-96B (Senile Dementia Associated with Alzheimer's Disease). Then I calculated a mortality rate ratio using mortality rate of treatment group as a numerator and mortality rate of placebo as denominator. Two of these five deaths occurred in placebo group and three in treatment group. I derived person year exposure from the data provided by the sponsor.
The mortality rate of STS treatment group is 17 per 1,000 person-years compared with 22 per 1,000 person-years in the placebo group. . The mortality rate ratio of the STS treatment group vs. placebo group is 0.77.

FDA Table 1. Mortality Rates by treatment group, Alzheimer's Study 29303-E101-96B

Treatment	Deaths	Person Year	Mortality Rate *	Mortality Rate Ratio
Placebo	2	92	22	1
STS treatment	3	175	17	0.77

* per 1000 person years

5.4 Adverse Events Leading to Discontinuation

5.4.1 Data description

5.4.1.1 Major Depression

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.

All of the controlled clinical studies in depression are multicenter, randomized, double blind, placebo-controlled studies in patients with major depression. The studies included STS (20 mg/20 cm2) STS (10 mg/20 cm2) and placebo. There was a discrepancy of total number of patients who discontinued due to an AE reported in the NDA submission (sponsor table 6.1) and total number of patients who discontinued due to an AE obtained from the individual study reports. There were two patients each in the STS (20mg/20cm2) and placebo groups who discontinued due to AEs that began prior randomized treatment The sponsor stated that the discrepancy was due to these discontinuations for preexisting conditions.