CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022036Orig1s000

MEDICAL REVIEW(S)

MEMORANDUM

DATE: December 2, 2009

FROM: Division Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-036

SUBJECT: Action Memo for NDA 22-036, for the use of Silenor (doxepin HCl) in the treatment of insomnia

NDA 22-036, for the use of Silenor (doxepin HCl) in the treatment of insomnia, was submitted by Somaxon Pharmaceuticals on January 7, 2008. The application was submitted as a 505(b)(2) application, relying on the approved applications for Sinequan (doxepin) capsules and Oral Concentrate, as well as Zonalon (doxepin) Cream. Sinequan is approved and has been marketed since 1969 as an anti-depressant and anxiolytic at doses up to 300 mg/day (usual daily dose of 75-150 mg/day). Zonalon Cream is a topical preparation and is indicated in the treatment of pruritis.

The initial application contained the results of 6 controlled trials. The Agency issued a Complete Response (CR) letter on 2/25/09; the primary reasons for this action were as follows:

Effectiveness

The division primarily considered the evidence purporting to establish substantial evidence of effectiveness for Silenor as a treatment for insomnia characterized by difficulty in maintaining sleep (there were no consistent positive findings on measures of sleep latency). However, we had concluded that there was inadequate subjective evidence of sleep maintenance (as assessed by the subjective [sWASO]) in non-elderly adults at the 6 mg dose. Specifically, although there was objective evidence of an effect (as measured by objective Wake Time After Sleep Onset [oWASO]) on sleep maintenance at days 15 and 29 in non-elderly adults, there was no evidence of a beneficial effect on those nights on a subjective measure of sleep maintenance (sWASO) in this population, the protocol-specified primary nights at which a subjective response was to be measured. There were statistically significant drug-placebo differences on nights 16 and 30 on sWASO in this population at this dose, and on the mean of Nights 15 and 16 and 29 and 30. There were also significant findings on sWASO out to 2 months in elderly adults (in a separate study) at 6 mg, but, as noted in the CR letter, we could not be certain that the effects seen on subjective measures at 6 mg in the elderly were applicable to non-elderly adults (possibly because of the higher plasma levels achieved in the elderly

compared to the non-elderly at this dose, or perhaps related to increased sensitivity to drug effect in the elderly).

Further, we noted that there were significant subjective findings on oWASO in the non-elderly population at 3 mg out to one month, but no significant findings on sWASO in this population after Night 1 (and no robust effect on sWASO in the elderly at this dose). Taken together, the division concluded that there was no clear effect on subjective measures of sleep maintenance at any dose in the non-elderly population.

Safety

The division concluded that there was evidence that Silenor might have been associated with a prolongation of the QT interval of between 5-10 msec. We were aware at the time we issued the CR letter that the sponsor had performed, or was in the process of performing, a thorough QT study, and in the letter we asked the sponsor to submit the results of this study.

The sponsor responded to the CR letter with a complete response on 6/4/09. The response primarily consisted of additional statistical analyses performed in an effort to provide evidence that there were robust effects on subjective measures of sleep maintenance at a 6 mg dose in the non-elderly population. This submission has been reviewed by Dr. June Cai, medical officer, Dr. Abiola Olagundoye, SEALD, the Interdisciplinary Review Team for QT Studies, Dr. Tristan Massie, statistician, Jessica Diaz and Melissa Hulett, Division of Risk Management, and Dr. Ronald Farkas, neurology team leader. In this memo, I will very briefly review the relevant issues, and offer the rationale for the division's action.

As noted above, the sponsor has submitted the results of additional statistical analyses that they believe establish a reliable effect of Silenor 6 mg on sWASO.

Specifically, as discussed by Dr. Massie, the sponsor asserts that the treatment by time interaction is not statistically significant for the 6 mg dose based on a Mixed Model Repeated Measures (MMRM) analysis, on the basis of which they conclude that the average treatment difference over the double-blind period can stand for the difference at the end of the study. On the basis of this new analysis, the sponsor obtains a significant drug-placebo difference. Based on the MMRM, differences between 6 mg and placebo at days 15 and 16 did not reach statistical significance nor did the 6 mg-placebo difference reach significance at Night 29 (see Dr. Massie's Table 6), though the between-treatment contrasts for the average of each two night pair does reach nominal significance (see Dr. Massie's Table 8).

However, according to Dr. Massie, the power of this test to detect an interaction is quite low (43%). For this reason, we cannot with confidence reject the hypothesis that there is no treatment by time interaction.

For example, Dr. Massie notes that the p-value for the interaction test based on the first night of each visit is 0.14. Including all nights for each visit, the p-value for the test of the interaction between time and treatment is 0.27. However, for a test of 90% at the 0.05 significance level, the null hypothesis of no interaction would be rejected if the p-value for the interaction test was <0.54. For a test with 80%, we would reject the hypothesis of no interaction with p<0.33.

In addition, a simple inspection of the data suggests that the treatment effect is not constant over time. In this regard, see Dr. Massie's Figure 1, which depicts the mean sWASO over time (at Nights 1 and 2, 15 and 16, and 29 and 30), and clearly documents the inconstant pattern of responses, especially at the end of the study. In fact, the difference in treatment effect between Nights 29 and 30 is statistically significant. This makes it difficult to reliably estimate the true treatment effect at the end of the study, making comparisons between this (unknown) treatment effect and estimates of the treatment effects at earlier timepoints unreliable.

Further, as Dr. Massie notes, there were likely not sufficient assessments during the 30 days of the study to conclude that the treatment difference was constant at times between assessments.

For these reasons, then, in his view, for an assessment of the drug effect at the end of the study, we must continue to rely on the data at that time point (that is, at Nights 29 and 30; again, the assessment at Night 29 was specified in the protocol as the primary assessment).

In addition, the sponsor also applied an MMRM approach to subjective Total Sleep Time (sTST), their preferred subjective measure of sleep maintenance. Using this analysis, statistical significance was not achieved for either Night 29 or Night 30.

The sponsor asserts that a pre-specified plan for performing the MMRM analysis was followed, though they acknowledge that this plan was proposed after the submission of the NDA (that is, after the data and results of the previous analyses were obviously known).

Finally, Dr. Massie performed calculations to determine the potential size of the interaction that could not be excluded, with an eye to examining whether or not the difference in the size of any treatment effect among timepoints might be sufficiently small to be considered unimportant. As he notes, the findings on the MMRM performed by the sponsor are consistent with a treatment difference on Nights 15 or 29 of about 10 minutes less than on Night 1. This difference is

about 50% of the estimate of the treatment difference at Night 1, a difference that seems non-dismissible.

Safety

The sponsor has submitted the results of a thorough QT study examining doxepin doses of 6 and 50 mg. The QT Review Team has concluded that neither dose is associated with a meaningful increase in the QT interval.

Conclusions

The sponsor has submitted numerous additional analyses that purport to establish a consistent effect of a 6 mg dose of doxepin on subjective measures of sleep maintenance in the non-elderly population out to one month. The statistically significant between-treatment differences that the sponsor presents, however, are as the result of MMRM analyses performed after the original data were known and analyzed. Further, and importantly, the results are based on the presumption that there is a constant treatment effect over time, and that there is no treatment by time interaction. Although the sponsor's formal test for such an interaction did not reach significance, Dr. Massie points out that the power to detect such a difference was very small (43%). Inspection of the data also suggests that the effect may not have been constant over time (and that there were likely not sufficient assessments over the 30 days of the study to permit a conclusion that the effects were constant over time). For these reasons, we cannot accept the sponsor's assertions that the MMRM analyses are appropriate. As a result, I believe that we should rely on the original analyses on which we based our original decision.

I note that Dr. Farkas continued to recommend that the application be approved. He bases this conclusion on his original reasoning, and he acknowledges that the sponsor has presented no new statistical arguments that persuasively counter the reasons for the initial CR action. In short, in his view, no meaningful change in the data package has occurred, and so his original conclusion still applies. I agree that the sponsor has provided no new arguments that adequately address our concerns, as articulated in the original CR letter, and which transmitted my decision to not approve the drug at that time. Although I note Dr. Farkas's recommendation, I have not changed my original views, and, for this reason, will issue the attached CR letter.

Russell Katz, M.D.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22036	ORIG-1	SOMAXON PHARMACEUTICALS INC	SILENOR (DOXEPIN HCL)

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

/s/

RUSSELL G KATZ
12/04/2009

MEMORANDUM

DATE: February 23, 2009

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-036

SUBJECT: Action Memo for NDA 22-036, for the use of Silenor (Doxepin HCl) in the treatment of insomnia

NDA 22-036, for the use of Silenor (Doxepin HCl) in the treatment of insomnia, was submitted by Somaxon Pharmaceuticals on January 7, 2008. The application was submitted as a 505(b)(2) application, relying on the approved applications for Sinequan (doxepin) Capsules and Oral Concentrate, as well as Zonalon (doxepin) Cream. Sinequan is approved and has been marketed since 1969 as an anti-depressant and anxiolytic at doses up to 300 mg/day (usual daily dose of 75-150 mg/day). Zonalon Cream is a topical preparation and is indicated in the treatment of pruritis.

This application contains the results of 6 controlled trials, in which doses of 1, 3, and 6 mg/night were evaluated in various models (transient and chronic) of, and in several populations of patients (non-elderly and elderly adults) with, insomnia. In addition, safety data from these studies are presented.

The application has been reviewed by Dr. June Cai, medical officer, Dr. Tristan Massie, statistician, Dr. Ju-Ping Lai, Office of Clinical Pharmacology, Drs. Houda Mahayni and Sherita McLamore, Office of New Drug Quality Assessment, Dr. Jinhee J. Lee, Division of Medication Error Prevention and Analysis, Dr. Katherine Bonson, Controlled Substance Staff, Dr. Antoine El-Hage, Division of Scientific Investigations, and Dr. Ron Farkas, Acting Neurology Team Leader. In this memo, I will briefly review the relevant effectiveness and safety data, and offer the rationale for the division's action.

Effectiveness

As noted, the application contains the results of 6 controlled trials, as follows:

Study 401

A 4 period cross-over study in non-elderly adults evaluating placebo, doxepin 1, 3, and 6 mg, each dose given for 2 nights. Efficacy was to be determined by the average Wake Time During Sleep (WTDS), measured by polysomnography (PSG) for the 2 nights.

Study 402

A similar design as Study 401 in elderly adults.

Study 501

A parallel group study in non-elderly adults evaluating placebo, doxepin 3 and 6 mg/night for 35 nights. The primary outcome was Waketime After Sleep Onset (WASO) as assessed by PSG.

Study 502

A one night, parallel group study utilizing an advance phase model of transient insomnia, evaluating placebo and doxepin 6 mg. The primary outcome was Latency to Persistent Sleep (LPS) as assessed by PSG.

Study 503

A parallel group study in elderly adults evaluating placebo, 1 and 3 mg/night for 3 months. The primary outcome was WASO, assessed by PSG.

Study 509

A parallel group study in elderly adults evaluating placebo and 6 mg/night for 1 month. The primary outcome was Total Sleep Time (TST), assessed subjectively by patients.

All of the studies, except for Study 509, assessed various sleep-related parameters by both objective and subjective measures. The reviewers describe the times at which the primary measures in each study were to be assessed. In many of the trials, the primary time of assessment was to be at Night 1. This reflects the traditional view that hypnotics must be effective immediately, on Night 1 or 2. However, current standards require that hypnotics be shown to be effective over time (for at least one month). Therefore, despite the protocol specification of Night 1 as the primary time of assessment of drug effect, in my view, the appropriate way to analyze these trials is to examine first the high dose in each study at the nominal study endpoint, and then to examine the drug's effects at earlier time points (there were not significant numbers of discontinuations in these studies; this makes an assessment of drug effect out in time by the last observation carried forward (LOCF) method reasonable (although observed cases [OC] analyses were done as well). Although the reviewers discuss in some detail the protocol specified (and resultant post hoc) analyses, and possible (or perhaps traditionally considered necessary) adjustments for multiple comparisons, I believe it is appropriate to analyze the studies as I have described, without adjustments for multiple comparisons

(because even though the analyses I suggest should be done were mostly post hoc, they are the way all such studies are currently analyzed).

Further, several of the studies evaluated LPS, a measure of the drug's effects on patients' difficulty in falling asleep, in addition to WASO or WTDS, measures of the drug's effects on patients' difficulties staying asleep. The results were also examined.

The analyses demonstrate that there are no consistent effects on sleep latency beyond Night 1, and the effect on Night 1 is not entirely consistent across all studies (see, for example, Dr. Massie's Table 52, page 72 of his review).

With regard to doxepin's effects on sleep maintenance, there was a consistent beneficial effect on Night 1 across studies. The following results were seen in Studies 501, 503, and 509, the studies that examined sleep maintenance beyond one or two nights.

Study 501 (non-elderly adults).

In this study, there were statistically significant differences favoring doxepin 6 and 3 mg over placebo on WASO on Nights 29 (end) and 15, the nights the protocol specified as the nights on which the assessments were to be made. However, there were no statistically significant between-treatment differences for either night for either dose compared to placebo on subjective measures of sleep maintenance (subjective WASO). It should be noted that sleep assessments were done on two nights at each evaluation: Nights 15 and 16, and Nights 29 and 30. Statistically significant differences between doxepin 6 mg and placebo were seen on sWASO on Nights 16 and 30, and for the average of Nights 15 and 16, and for the average of Nights 29 and 30 (the protocol specified assessing WASO on the first night of each assessment).

Study 503 (elderly adults)

There were statistically significant differences between doxepin 3 mg and placebo in WASO on Nights 85, 57, 29, and 15. There was a statistically significant difference on WASO between 1 mg and placebo on Night 85, but not on Nights 57, 29, or 15. There were inconsistent statistically significant differences between doxepin 3 mg and placebo on sWASO (Nights 85 and Night 29) and between doxepin 1 mg and placebo (Night 85 only).

Study 509 (elderly adults)

There were clear statistically significant differences favoring doxepin 6 mg over placebo at all time points on sWASO (Nights 57, 29, 15, and 1). There were no objective measures assessed.

Safety

There were 966 unique subjects exposed to doxepin in this application. Drs. Cai and Farkas describe the adverse events seen with the use of doxepin at the doses proposed. As noted by the reviewers, there is some evidence that Silenor does cause some next day residual effects (and when taken with meals, the Tmax increases from about 3-4 hours to about 6-8 hours), and is associated with some other, not unexpected, adverse events. There are no adverse events, however, that would preclude approval of Silenor (recall that doxepin, in the form of Sinequan, is marketed as an anti-depressant and anxiolytic at doses up to 300 mg/day).

However, as described in some detail by Dr. Farkas, what data we do have is suggestive of a capacity of doxepin to prolong the QT interval at the doses evaluated in these studies.

Specifically, the QT interval was prolonged in several studies submitted. The data displayed below are taken from Dr. Farkas's review, pages 22-23.

In Study 501, EKGs were evaluated at Baseline and in the morning of Day 38, 2½ days after the last dose. The change from baseline in msec QT varied as follows:

	Placebo	3 mg	6 mg
QTcF	.9	3.9	5.1
QTcB	.1	4.2	6.6

In Study 505, in which doxepin was administered with cimetidine, a non-specific CYP inhibitor that induces an approximately 2-fold increase in doxepin levels, EKGs were performed at Baseline and 96 hours after a single dose of doxepin 6 mg. The results are given below in msec:

	Baseline	6 mg
QTcF	396	405
QTcB	406	416

In Study 503, EKGs were evaluated at Baseline and in the morning of the final study day, about 9 hours post-dose:

	Placebo	3 mg	6 mg
QTcF	1.4	4.9	6.3
QTcB	3.0	6.0	5.8

In Study 509, EKGs were evaluated at Baseline and on the Final Study Day :

	Placebo	6 mg
QTcF	-6.7	-2.5
QTcB	-5.5	0.9

As Dr. Farkas also notes, in Study 506, which examined the interaction between doxepin 6 mg and sertraline, a moderate CYP 2D6 inhibitor, EKGs were obtained at baseline and on the final study day. There was no placebo, but the change from baseline in QT interval was about 8-9 msec (the Cmax of doxepin increased about 30% in the presence of sertraline).

As further described by Dr. Farkas, analyses of outliers did not yield a consistent picture. There was an increase in the incidence of outliers with absolute QT intervals of >480 msec on drug compared to placebo (9/720 doxepin-treated subjects vs 3/560 placebo-treated patients), but there was a greater incidence of placebo-treated subjects compared to doxepin-treated patients who met outlier criteria as defined by an increase in QT interval of >60 msec.

COMMENTS

The sponsor has presented the results of 6 randomized controlled trials, 5 in patients with chronic insomnia, and one in healthy volunteers in a model of transient insomnia.

The standard requirements for a demonstration of effectiveness for hypnotics is that the drug in question demonstrate an effect on both objective and subjective measures of some aspect of sleep disturbance (e.g., difficulty in falling asleep, difficulty in staying asleep). Typically, this is required to be shown in the same study, and, also typically, these effects are required to be shown in both non-elderly and elderly adults; these populations are typically evaluated in separate studies. Further, and importantly, hypnotics are generally expected to be effective on the first or second night of administration, but also in extended use, at least out to one month of dosing.

The sponsor has performed 3 studies of at least one month in duration, 1 in non-elderly (one month), and 2 in elderly adults (2 months and 3 months).

There has been considerable discussion in the various reviews about the appropriate statistical analyses of these studies, given that for most of them, the primary outcome was to be assessed at Night 1, and measures of sleep latency were to be assessed prior to measures of sleep maintenance at times after Night 1. Given the usual statistical rules, if a particular outcome does not reach

statistical significance at a given time point (for example, sleep latency), subsequent outcomes cannot be analyzed (for example, measures of sleep maintenance after Night 1). My view, however, is that the primary outcomes in essentially all of these studies were measures of sleep maintenance, and patients were required to have sleep maintenance difficulties to enroll in the studies. For this reason, I believe it is reasonable to inspect the results of analyses of the primary maintenance outcomes, independent of the results on the sleep latency measures (almost all of which do not reach statistical significance at any dose). Further, as I noted earlier, I believe it is reasonable to examine the results first at the latest time points, and then "work backwards" in time in evaluating the effects of doxepin on sleep maintenance. In addition, the effects of the highest dose in any study should be examined first, at all time points, and then the same should be done for the lower doses in any given study. The fact that this approach is largely post hoc in these studies is no bar to proceeding in this way; it is the way all modern studies of hypnotics are analyzed, and the fact that this is our choice, not the sponsor's makes it, in my view, acceptable. Finally, when approached in this manner, I do not believe that corrections to the alpha are necessary.

Given this position, the results can be briefly summarized.

There is clear evidence of an effect of doxepin 6mg on objective measures of sleep maintenance out to one month in Study 501. However, the evidence of an effect of 6 mg doxepin nightly on subjective measures of sleep maintenance is somewhat less clear. We do not have clear evidence of such an effect in Study 501, the only study that examined both objective and subjective effects of 6 mg nightly. Specifically, there were no statistically significant differences between 6 mg and placebo in Study 501 on nights 15 and 29. However, significant differences were seen on Nights 16 and 30, and on the average of Nights 15 and 16 and Nights 29 and 30. Further, there were significant differences between 6 mg and placebo at all time points (out to 2 months) on subjective measures in the elderly in Study 509. I agree with Dr. Farkas that these results, taken as a whole, suggest that doxepin 6 mg given nightly, is effective in the treatment of sleep maintenance difficulties, but I also note that this seems to be somewhat less compelling data than we would typically have for most hypnotics. In this regard, I note that the clear subjective findings in the elderly could possibly be the result of the slightly higher plasma levels of doxepin seen in the elderly (although we do not have completely adequate data to establish this difference) and/or an increased sensitivity of elderly patients to a given plasma level/dose of doxepin.

There is clear evidence of an effect of doxepin 3 mg on objective measures of sleep maintenance out to 1 month in non-elderly adults (Study 501) and out to 3 months in the elderly (Study 503). However, there is no evidence of a subjective benefit of 3 mg in non-elderly adults, and a very inconsistent effect out to 3 months in the elderly. For these reasons, I do not believe that the sponsor has demonstrated an adequate effect of a dose of 3 mg dose of doxepin.

Finally, although there are nominally statistically significant treatment differences between 1 mg and placebo at 3 months on both objective and subjective measures of sleep maintenance in the elderly, these effects are inconsistent and do not establish 1 mg as an effective dose.

For these reasons, I do not believe that the sponsor has established substantial evidence of effectiveness for doxepin as a hypnotic for patients with sleep maintenance difficulties, at any dose. Of course, the data are suggestive at 6 mg nightly, and the sponsor should be asked to make the case that this, or any other dose, is effective.

I do not believe that the statistically significant findings at Night 1 on both objective and subjective measures of sleep maintenance for both 3 and 6 mgs is adequate evidence to support approval either as an initial dose, or as a dose for one night of treatment. As I noted above, hypnotics are required to be effective for at least one month, even though patients may not take a hypnotic every night (that is, even though chronic intermittent use may "mimic" a series of repeated single night uses).

With regard to safety, as I noted earlier, no adverse effects were noted that would preclude approval. However, the suggestion that doxepin may prolong the QT interval is of concern.

As noted earlier, the estimate of the degree of QT prolongation seen in several studies varied, but ranged from a difference between drug and placebo in the change from baseline from 3-4 msec to up to 10 msec. What makes these changes of potential concern is that EKGs were obtained long (sometimes days) after Tmax. Whether or not the changes are, in fact, drug-related, is certainly open to question, but an increase of some degree does appear to be consistent, and dose related. It is unclear why such an effect should occur in some cases several days after a last dose of doxepin; one possible explanation might be that the changes are due to a metabolite (the nordoxepine metabolite has a T1/2 of about 30 hours). However, at this time, the explanation for the finding is obscure. Nonetheless, the finding appears to exist (even though, again, the finding could be spurious, given the vagaries of the way the data were collected, and especially that some studies did not employ placebo), and cannot, in view my, be dismissed without further explanation. Doxepin is known to be associated with cases of torsades de pointes, but, as noted earlier, there is a long marketing history of doxepin at much higher doses than those studied here without an overwhelming signal attributable to QT prolongation and its consequences. Nonetheless, data on the QT prolonging effects of any dose of doxepin have not been submitted. We have, however, commented on a protocol for a thorough QT study for doxepin fairly recently. However, we do not know if that study has been done, and certainly no data from this study have been submitted to this application.

In my view, before this application can be approved, the sponsor must adequately address our concerns about the potential for doxepin to prolong the QT interval to a clinically meaningful degree.

For the reasons stated above, therefore, I will issue a Complete Response letter in which we will ask the sponsor to address our concerns about both effectiveness and safety, as described above.

Russell Katz, M.D.

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/s/

Russell Katz
2/25/2009 08:42:51 AM
MEDICAL OFFICER

Cross Discipline Team Leader Review

Date	Feb 12, 2009
From	Ronald Farkas, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA	22-036
Applicant	Samaxon Pharmaceuticals
Date of Submission	January 7, 2008
PDUFA Goal Date	February 27, 2009
Proprietary Name / Established (USAN) names	Silenor / Doxepin HCl
Dosase forms / Strength	1 mg, 3 mg, 6 mg tablets
Proposed Indication(s)	Treatment of Insomnia
Recomended:	Complete response

1. Introduction

Silenor (doxepin HCl) is being developed by Somaxon Pharmaceuticals under section 505(b)(2) for the treatment of insomnia in adult (18-64 years old) and elderly (65 years of age or older) patients. To support the application, the sponsor is referencing safety and efficacy information FDA relied on for approval of NDA 016-798 (Sinequan® Capsules), NDA 017-516 (Sinequan® Oral Concentrate), NDA 020-126 (Zonalon® 5% Cream), published literature, and data generated by the sponsor. Doxepin has been marketed in the U.S. by Pfizer since 1969. Oral doxepin as Sinequan® is indicated for depression and anxiety. Topical doxepin as Zolalon® is indicated for treatment of pruritis.

2. Background

Doxepin is a tricyclic antidepressant with sedating effects. While doxepin binds to a number of CNS targets at the doses used for anxiety and depression, at low doses the sponsor believes that doxepin mainly antagonizes histaminergic H_1 receptors, thereby inducing drowsiness and sleep, similar to the mechanism of currently approved over-the-counter antihistamine sleep aids.

Sinequan labeling indicates that the usual dose range of doxepin for depression or anxiety is 75- to 150 mg/day, up to 300 mg/day. These doses are roughly 10- to 100-fold higher than doses of doxepin studied in the present application for sleep: 1 mg and 3 mg in elderly subjects, and 3 mg and 6 mg in adults.

The sponsor's development program attempted to demonstrate the efficacy and safety of Doxepin for both sleep onset and sleep maintenance endpoints. Doxepin seemed particularly promising for sleep maintenance, an aspect of insomnia in which new treatment options are needed. The sponsor notes that

many drugs currently approved or used off-label for treatment of insomnia are not effective in promoting sleep maintenance, and that some drugs that are effective in sleep maintenance (e.g. longer-acting benzodiazepines) are associated with undesirable effects including next-day sedation and the risk of tolerance and dependence.

3. CMC

Dr. Sherita McLamore was the primary reviewer, and Dr. Ramjesh Sood was the secondary reviewer. Both recommend the approval of Silenor under the conditions specified in the package insert, with no recommendation for phase 4 commitments, agreements, or risk management steps.

4. Nonclinical Pharmacology/Toxicology

This review is pending.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Ju-Ping Lai was the primary reviewer, and Dr. Veneeta Tandon was the secondary reviewer. Both recommend approval provided the sponsor agrees with the following phase 4 requirements:

- An *in-vivo* drug interaction study with a potent CYP 2C19 inhibitor.
- An *in-vivo* drug interaction study with a potent CYP 2D6 inhibitor.

Five phase 1 clinical pharmacology studies involving 104 healthy subjects were conducted, leading to the following major conclusions by Dr. Tandon:

- Dose proportionality: Over the proposed Silenor doses (1, 3, and 6 mg) doxepin and nordoxepine (the major metabolite) exposures were dose-proportional (Study SP-0405) to the lower limits of the assay. About 30% higher proportional Cmax and AUC occurred with 50 mg Sinequan dosing (Study SP-0507), thus in part confirming the much lower exposure to doxepin provided by Silenor.

- Drug interactions:
  - Depression is a common comorbidity in insomnia patients. Therefore, coadministration of antidepressants such as selective serotonin reuptake inhibitors (SSRIs) with doxepin would be anticipated. To investigate this interaction, the sponsor coadministered the SSRI sertraline (a weak CYP 2D6 inhibitor) with doxepin. Sertraline increased the AUC and Cmax of doxepin by about 1/3rd, with no effect on steady-state concentrations of sertraline (Study SP-0506).
  - The sponsor also examined the effect of the non-specific CYP 450 inhibitor cimetidine on doxepin metabolism. CYP 2C19 mediates formation of the major metabolite of doxepin, nordoxepin. Cimetidine increased doxepin AUC and Cmax about 2-fold (Study SP-0505).

> The clinical pharmacologists conclude, and I concur, that the maximum dose of doxepin should be 3 mg when coadministered with cimetidine, which will result in blood levels simlar to those from the maximum recommended dose of 6 mg.

CDTL: Dr. Lai concludes, and I concur that the effects of CYP 2C19 and CYP 2D6 inhibition on Silenor metabolism have not been adequately described, and that studies examining the effects of potent inhibitors of these metabolic enzymes should be required in phase 4. Until the results of these studies are known, I believe that Silenor can be safety marketed through labeling, based on low initial dosing, escalation of dosing titrated to individual response, and inclusion of warnings regarding potential drug interactions.

- Food Effect: A high fat meal increased silenor AUC by 41% and Cmax by 15%, and delayed Tmax from 3-4 hours to 6-8 hours postdose (Study SP-0504).

Dr. Lai notes that these changes in AUC and Tmax could affect the onset and maintenance of drug effect, and increase the likelihood of next day residual effects. She further notes that in the five phase 2 and 3 studies conducted in the sleep laboratory, Silenor was administered at least 3 hours after the evening meal, while in the single at-home study, instructions related to drug administration after a meal were not given. She therefore recommends that Silenor not be taken within 3 hours of a meal.

CDTL: In study SP-0504, fed state resulted in a large delay in Tmax, from 3-4 hours post-dose in fasted state to 6-8 hours post-dose in fed state. This delay is of concern because Tmax in the fed state essentially coincides with wake time, suggesting increased risk of next-day residual drug effects. This concern is strengthened by Study SP-0506, which in addition to examining the interaction of doxepin and sertraline, also included pharmacodynamic assessments of doxepin throughout the day after morning dose in the fasted state (assessments: Digit Symbol Substitution Test [DSST], Symbol Copying Test [SCT], and Visual Analogue Scale [VAS] ratings of sleepiness). The maximum PD effect of Silenor was strongly correlated with doxepin Tmax at 3 hours, and residual PD effect was detected until doxepin blood levels decreased to about 0.6 ng/ml, at 8 hours post-dose. In fed state in study 0504, doxepin blood level did not decrease to 0.6 ng/ml until about 10 hours after dosing. Considering the data from the two studies, there appears to be a high risk of next-day residual effects for at least several hours after awaking if Silenor is taken on a full stomach.

On the supposition that a 3-hour interval between a meal and Silenor dosing approximates dosing on an empty stomach, Dr. Lai suggests that the risk of next-day residual effects can be decreased by specifying in the label that Silenor should not be taken within 3 hours of a meal. I concur with this approach, but note that in patients with delayed gastric emptying a 3-hour delay before dosing may not replicate the PK profile of the fasted state.

Intrinsic Factors

- Age: No new studies were conducted, but published studies indicate that clearance of doxepin decreases by about one third from age 20 to age 75.
- Gender: Mean Cmax and AUC of doxepin in pooled phase 1 studies were 16% and 8% higher, respectively, in females.

CDTL: I concur with Dr. Lai's conclusion that these differences are not likely to be clinically significant.

- Race: In pooled phase 1 studies, Cmax and AUC were higher for the 11 African-Americans versus 84 Caucasians, by 50% and 18% respectively. Given the small sample size and high variability in PK, these differences may have occurred by chance.

CDTL: I concur with Dr. Lai's conclusion that these differences are not likely to be clinically significant, particularly in the context of the individualized dosing of Silenor, starting with lower doses and escalating as clinically indicated.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Cai was the clinical reviewer for both efficacy and safety, and Dr. Massey was the statistical reviewer for this application.

Efficacy Standard

The following is my interpretation of the efficacy standard for sedative-hypnotics:

- To support a marketing claim in insomnia, the Division has considered it necessary for the sponsor to provide independently substantiated evidence of efficacy in improving either sleep latency or sleep maintenance, but not both. Positive findings on both a subjective and an objective endpoint are necessary (for either latency or maintenance). The requirement for positive findings on the subjective endpoint is designed to support the clinical meaningfulness of the objective endpoint. Evidence must be presented for both immediate efficacy (first nights of use), and sustained efficacy (use over months) since hypnotics are typically used on an intermittent and chronic basis.
  CDTL: I agree with this standard.

- For purposes of fulfilling the legislative requirement for independent substantiation of efficacy findings, the Division has accepted as a 'positive study' investigations in which only a subjective endpoint or an objective endpoint was examined.
  CDTL: I agree with this standard.

- Due to concern about possible age-related differences in the efficacy (and safety) of sleep drugs, the Division has additionally required positive efficacy findings in both adults <65 years old, and in elderly subjects > 65 years old, for both objective and subjective endpoints. Demonstration of efficacy in insomnia, particularly in sleep maintenance, in the elderly is important since a large proportion of the target population with chronic insomnia is elderly, and these elderly typically experience more sleep maintenance difficulties than younger adults. There has been some question, however, about what type of data is required to fulfill this requirement.
  CDTL: My interpretation is that the legislation supports the Division's requirement for evidence of efficacy on these 4 endpoints (objective and subjective in adults and elderly) but

only within the usual standard of independent substantiation, which in this context is 2 adequate and well-controlled trials. My interpretation is that efficacy in adults and elderly does not represent two distinct claims, but rather two aspects of a single claim, and as such does not require more than 2 adequate and well-controlled trials. Instead, I consider 'supportive evidence' to be adequate to address the Divisions concerns about efficacy differences that may exist based on age.

Dr. Massey concludes that the clinical studies as analyzed by FDA's usual hierarchical approach to sleep studies appear to provide, but perhaps not unequivocally, sufficient evidence to support efficacy for the 3 mg and 6 mg doses of Silenor for a claim in sleep maintenance. In part Dr. Massey's concern, as discussed below, derives from the fact that if the studies are analyzed by the sponsor's prespecified statistical analysis plan, 2 of the 3 long-term studies would not be considered positive.

Dr. Cai concludes that sufficient evidence for approval is not provided for Silenor in any sleep maintenance or initiation endpoint.

Efficacy Studies

To support efficacy the sponsor primarily relied on the results of the following long-term studies:

- **Study 501**
  - a 1 month, objective (polysomnography [PSG]) and subjective, randomized, double-blind, placebo-controlled, parallel-group study designed to assess the efficacy and safety of two dose levels of doxepin, 3 mg and 6 mg, in adults (mean age about 45 years) with primary insomnia and sleep maintenance difficulties.
  - 229 subjects randomized, 89% completed the study, with no clear evidence of non-random dropout.
- **Study 509**
  - a 1 month, subjective only, outpatient, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to assess the efficacy and safety of 6 mg doxepin, in elderly subjects (mean age about 70) with primary sleep maintenance insomnia.
  - 255 subjects randomized, 93% completed the study, with no clear evidence of non-random dropout.
- **Study 503**
  - a 3 month, objective (PSG) and subjective, randomized, double-blind, placebo-controlled, parallel-group study designed to assess the efficacy and safety of two dose levels of doxepin, 1 mg and 3 mg, in elderly subjects (mean age about 70) with primary insomnia and sleep maintenance difficulties.
  - 240 subjects randomized, 89% completed the study, with no clear evidence of non-random dropout.

The sponsor conducted 3 additional short-term phase 2 studies that provide supporting evidence of efficacy.

- **Study 401 and 402**
  - Double-blind, randomized, placebo controlled, multicenter, 4 period crossover studies in adults (401) and elderly (402) of two consecutive nights each of dosing of placebo, 1 mg, 3 mg, or 6 mg doxepin.

- **Study 502**
  - A 1 night Double-blind, randomized, placebo controlled, multicenter, parallel group, single dose study of 6 mg Silenor in a phase-advance model of transient insomnia.

In the phase 2 and 3 studies, subjects were required to have at least a 3-month history of DSM-IV defined primary insomnia with sleep maintenance difficulties at the initial screening visit: ≥60 minutes of Wake After Sleep Onset (WASO) and ≤6.5 hours of Total Sleep Time (TST) on at least 4 of 7 consecutive nights prior to PSG Screening.

Statistical Analysis Plan

Dr. Massey notes that the sponsor's prespecified analysis plans for the long-term studies do not support drug efficacy without inflating type I error. In contrast, if testing had followed the Division's recommendations for hierarchical testing of endpoints, adequate evidence of drug efficacy would seemingly have been shown by combining data from studies 501, 503, and 509. The Division recommended the following hierarchical testing:

1. Objective sleep maintenance endpoint (WASO) at the highest dose and last study time point, followed by testing at earlier time points.
2. Subjective sleep maintenance endpoint (sWASO) at the highest dose and last study time point, followed by testing at earlier time points.
3. Objective and subjective sleep latency endpoints tested similarly, from highest dose and last study point to lower dose and earlier time points.

Dr. Massey describes the sponsor's analysis plan for these studies as follows:

- For study 501, the sponsor based the key hypothesis on the first night, but did specify a clear hierarchy for testing additional hypotheses, thus leaving no way to evaluate later time points without inflating type 1 error.
- For study 503, the sponsor specified a hierarchy of testing of objective WASO at each visit followed by subjective total sleep time (sTST) a measure that does not differentiate between effects on sleep latency and maintenance. This was followed by testing of LPS and sleep efficiency. For 3 mg versus placebo, sTST was not significant (p=0.09), such that sWASO could not be tested without inflating type 1 error.
- For study 509, in contrast, the sponsor specified total sleep time as the primary measure, which was positive, so sWASO could also be measured in that study without inflating type 1 error.

CDTL: My interpretation is that analysis of the studies according to the Division's usual hierarchical method, while not strictly pre-specified, adequately represents the results that would have been obtained with a properly selected pre-specified plan. As a result, I conclude that the analysis as conducted by Dr. Massey does not unacceptably inflate type 1 error.

[redacted] (b) (4) . This endpoint, however, is considered by the Division to be a sleep maintenance outcome that is largely reflected in WASO, and that is essentially a measure of WASO in the period immediately before lights on. In addition, the division does not consider that sleep maintenance in any given subset of the night (in this case immediately before lights on) has been demonstrated to be a clinically significant endpoint separate from the general concept of sleep maintenance.

Efficacy Findings

Dr. Massey's analysis of statistical significance for WASO is shown in Table 1.

Table 1: Key Studies and Endpoints

Study	Endpoint	Dose Group	P-Values as Compared to Placebo				
			Night 85	Night 57	Night 29	Night 15	Night 1
401(Phase 2 Crossover, Adult)	WASO	6					<0.0001
402 (Phase 2 Crossover, Elderly)	WASO	6					<0.0001
501 (Adult)	WASO	6			0.0007	0.0011	<0.0001
		3			0.0173	0.0025	<0.0001
	sWASO	6			0.6282	0.2016	0.0004
		3			0.6483	0.1512	0.0003
502 (Transient Insomnia, Adult)	WASO	6					<.0001
	sWASO	6					0.0063
503 (Elderly)	WASO	3	<.0001	0.0029	0.0005	0.0069	<0.0001
		1	0.0330	0.1662	0.0878	0.1945	0.0053
	sWASO	3	0.0153	0.5627	0.0296	0.0729	0.0561
		1	0.0037	0.7417	0.0531	0.8571	0.8497
509 (Elderly/ Subjective Only)	sWASO	6		0.0026 (Week 4)	0.0016 (Week 3)	0.0145 (Week 2)	<0.0001 (Week 1)
	sLSO	6		0.6629 (Week 4)	0.4635 (Week 3)	0.4884* (Week 2)	0.1547 (Week 1)

Table 1: Calculations based on observed cases, and on the first of two nights of data from consecutive PSG sessions on nights 1 and 2 ('Night 1' in table), 15 and 16 ('Night 15'), 29 and 30, etc.

My interpretation of the efficacy findings are as follows:

- **Study 509 is a positive study supporting long-term *subjective* efficacy of Silenor 6 mg in sleep maintenance. The study is positive at 4 weeks and all earlier time points for sWASO.**
- **Study 503 is a positive study supporting long-term *objective* efficacy of Silenor 3 mg in sleep maintenance. The study is positive at 3 months and all earlier time points for WASO.**
- ***I conclude that study 509 and 503 satisfy the legislative standard for independent substantiation of efficacy in at least 2 adequate and well controlled trials. Having established this, the studies are then analyzed for 'supportive evidence' of efficacy for the two age groups, 'adult' and 'elderly.'***

- **Study 509 and 503 support subjective (509) and objective (503) efficacy in elderly, as described above.**

- **Study 501, adults:**
  - **The *objective* endpoint, WASO, is positive at the last time point (1 month) and earlier time points for both 6 mg and 3 mg Silenor, supporting long-term objective efficacy of Silenor in adults.**

  - **The subjective endpoint, sWASO, is positive at night 1. Sustained efficacy is supported by numerical, but not statistical superiority at night 15 (placebo, 66 minutes; Silenor 3 mg, 59 minutes; Silenor 6 mg 58 minutes). At night 29, there is essentially no evidence of efficacy for the endpoint as calculated based on night 1 of the 2-night sleep lab session (placebo 59 minutes, Silenor 3 mg 63 minutes, Silenor 6 mg 58 minutes). However, Dr. Massey notes that for the *second* night of recording sWASO is nominally significant for 6 mg (night 16, p = 0.04; night 30, p = 0.0009)[Table 18 of Dr. Massey's review]. Silenor 3 mg is numerically, but not statistically superior to placebo for these 'second night' endpoints. Sleep-laboratory studies are thought to be affected by 'first-night' artifacts[1], suggesting that the second-night data from this study is clinically meaningful, and can be viewed as supportive evidence of long-term subjective efficacy of Silenor in adults.**

    [In addition, while of lesser importance, baseline imbalance may also have contributed to less robust findings of efficacy in drug arms: sWASO was worse for 3 mg (81 minutes) and 6 mg (78 minutes) arms than for the placebo arm (74 minutes).]

    In sum, I conclude that the night 15 numerical superiority of Silenor combined with the night 30 'second night' superiority provide adequate supportive evidence of long-term subjective efficacy in adult subjects in the context of the clear positive findings in subjective endpoints in elderly subjects in study 509.

- ***Having established adequate supportive evidence for efficacy in both adults and elderly, the studies are then analyzed for dose recommendations.***

  - **Findings on night 1 seemingly must be the primary determinant of dosing recommendations for night 1 of clinical use.**

    - **Adults: In study 501 subjective and objective WASO are strongly positive for both 6 mg and 3 mg on night 1. The 3 mg dose therefore appears to be appropriate for initial dosing.**

    - **Elderly: In study 503 objective WASO was positive for both 3 mg and 1 mg on night 1, but subjective WASO was only close to positive (p = 0.06) for 3 mg. Combined with the positive finding in adults in study 501, 3 mg clearly appears**

[1] Toussaint et al., First-night effect in normal subjects and psychiatric inpatients. Sleep 1995;18:463-9.

to be an effective dose for night 1. Evidence supporting efficacy of the 1 mg dose is derived only from study 503. The 1 mg dose is positive for WASO on day 1, and numerically better than placebo on all subsequent time points. I find this evidence, in combination with increased safety concerns related to drug- and disease interactions, adequate to recommend 1 mg as the starting dose in elderly.

- **For subsequent nights, a general trend towards improvement of sleep maintenance in the placebo groups confounds attempts to identify development of tolerance. I recommend that labeling describe dose escalation to clinical effect, but otherwise do not believe that the data support more specific language about efficacy over time.**

- **There is evidence for a dose/response effect in both adults (6 mg vs. 3 mg) and elderly (3 mg vs. 1 mg) at night 1, but evidence weakens in subsequent nights,** (b) (4)

CDTL overall efficacy conclusions
I find Silenor efficacious for improvement of sleep maintenance in adults and elderly, at recommended doses of 1 mg, 3 mg, and 6 mg.

8. Safety

Dr. Cai conducted the primary safety review.

At the EOP2 meeting FDA agreed that given the extensive marketing history of doxepin at much higher doses than proposed for the current indication, including long-term use, additional safety data would not be required, barring any unexpected safety findings in the proposed clinical trials in this patient population.

Silenor Safety Database: 966 unique subjects were exposed to Silenor, in a total of 11 studies. In long term studies of from 1- to 3-months duration, 77 elderly subjects were exposed to 1 mg, 75 adults and 82 elderly subjects were exposed to 3 mg, and 73 adults and 130 elderly subjects were exposed to 6 mg Silenor. Dr. Cai concludes that this is adequate exposure to investigate the safety of Silenor.
CDTL: I concur.

Deaths: Dr. Cai notes that there were no deaths in the development program.

Serious Adverse Events: In 966 doxepin-exposed subjects across the 3 doxepin dose groups, there were 6 subjects who reported a serious adverse event (SAE), all but one of which (patient with chest pain and hypertension) was in the elderly patient subgroup. In the placebo group, 1 subject out of 699 experienced an SAE, multiple traumas from a motor vehicle accident. SAE's were as follows, by subject:

- Cerebrovascular accident (CVA)
- Chest pain (2 episodes) and hypertension (adult)
- Fall and lung adenocarcinoma

    - The patient fell on study day 24 while carrying luggage up stairs. Dr. Cai reports that she apparently did not experience dizziness or loss of consciousness prior to the fall. The time-relationship of the fall to the last dose of study medication was not clear.
- Gastroenteritis
- "Non-cardiac chest pain"
- Pneumonia

Dr. Cai concludes that there is no clear evidence of drug-relatedness for any of the serious adverse events.

CDTL: The drug-exposed population was less than twice as large as the placebo population, yet experience 6-fold as many SAEs (6 vs. 1), raising concern of drug-relatedness. Of particular concern, 3 patients had cardiovascular SAEs (1 patient with CVA, 1 with chest pain and hypertension, and one with 'non-cardiac' chest pain). While all 3 had cardiovascular risk factors or history of cardiovascular disease, patient randomization would be expected to have balanced these risk factors among study arms, such that an excess of events in drug arms would not have occurred. Cardiovascular risks are discussed in more detail under *CDTL Discussion of Key Safety Issues* below.

Withdrawals due to Adverse Events: There were 15 subjects who withdrew due to adverse events, 3 of which were SAEs described above.

CDTL: Each adverse event leading to withdrawal occurred only once, with the exception of anxiety, which occurred twice in the 6 mg doxepin group. Anxiety did not occur in excess as a common adverse event, such that causal relationship to drug remains uncertain. Somnolence, the most common non-serious adverse event, was the cause for withdrawal in only one patient (taking 6 mg), in support of a conclusion that Silenor is relatively well tolerated even in patients experiencing somnolence as an adverse event.

Adverse Events of Special Interest:

Complex Sleep Behaviors and Parasomnias
Dr. Cai notes that there were no cases of complex sleep behavior in the clinical program. A few subjects reported parasomnias, such as nightmares, sleep paralysis, and enuresis. No patient reported sleep walking.
CDTL: In this relatively small development program with mainly short- and intermediate term exposure, absence of cases of complex sleep behavior does not exclude meaningful risk.

Falls and injuries
Dr. Cai reports no excess of falls or injuries in Silenor treated patients.

Somnolence and Sedation
Dr. Cai notes that somnolence, sedation, and related terms such as drowsiness and sleepiness were clearly drug-related and common.

Weight Gain

Dr. Cai concludes that there was no clinically meaningful change in weight associated with Silenor.

Next day residual effects and effects on daytime functioning
Dr. Cai notes that the potential for next-day residual drug effects was mainly measured with tests of psychomotor function and/or alertness using the DSST (digital symbol substitution test), SCT (symbol copying test), and VAS for sleepiness (visual analog scale for sleepiness). No next day driving test was conducted. Dr. Cai notes that the assessments were conducted according to agreements with FDA at the EOP2 meeting.

Dr. Cai notes that in study 501 scores for DSST and SCT were lower in the 6 mg versus 3 mg group, suggestive of next day effects, and that sleepiness was also more evident as measured by VAS. In study 501, she notes no significant difference between groups.

CDTL:
Next day residual effects are an important measure of safety and tolerability for sedative-hypnotics that I conclude should be added to sponsor-proposed labeling.

In the phase 2 studies in adult and elderly subjects (studies 401 and 402), next day residual affects were assessed by DSST, SCT, and VAS for sleepiness, performed predose and 60 minutes after completion of the 8-hour PSG assessments. In addition, single-item VAS questions the evening after dosing assessed next day wakefulness, ability to concentrate, and daytime sense of wellbeing. Silenor was not associated with consistent decreases in next day performance on DSST or VAS for sleepiness, but SCT was worse for all dose groups, although not in a dose-related pattern (Table 2**, adult and elderly combined). In contrast, small but consistent decreases occurred with 3 mg and 6 mg doses in the next evening questionnaire of wakefulness, ability to concentrate, and daytime sense of wellbeing (**Table 3**, adult;** Table 4**, elderly).**

Table 2: Next Day Effects, Phase 2 studies 401 and 402

Table 2.7.4.84 Summary of DSST, SCT, and VAS for Sleepiness: Change from Night 1 to Average of Day 2 and Day 3 (Phase 2 Safety Analysis Set)

Parameter	Placebo (N=139)	Doxepin 1 mg (N=140)	Doxepin 3 mg (N=141)	Doxepin 6 mg (N=141)
DSST	n=139	n=140	n=140	n=141
Mean (SD)	-3.4 (8.45)	-3.2 (7.17)	-2.6 (9.49)	-3.9 (8.08)
Median	-3.0	-2.3	-2.5	-3.5
Min, Max	-41.0, 29.0	-29.5, 16.0	-54.5, 43.0	-35.0, 30.5
SCT	n=139	n=140	n=140	n=141
Mean (SD)	-3.4 (12.58)	-6.1 (11.91)	-5.4 (15.44)	-5.8 (15.18)
Median	-4.0	-6.0	-3.5	-4.5
Min, Max	-36.0, 39.5	-50.0, 21.0	-98.0, 37.0	-61.0, 70.0
VAS for Sleepiness	n=139	n=140	n=140	n=141
Mean (SD)	2.1 (22.06)	2.5 (24.02)	2.5 (25.35)	0.5 (22.98)
Median	-0.5	3.0	2.0	1.0
Min, Max	-56.0, 80.5	-65.0, 65.0	-77.5, 80.5	-66.0, 54.0

Note: A decrease in DSST or SCT scores from predose may represent residual sedation, whereas an increase in VAS for sleepiness score from predose may represent residual sedation.

Source: M5.3.5.3, Reports of Analyses of Data from More than One Study, Table 2.7.1, Table 2.7.2, and Table 2.7.3.

Table 3: Adult Study 401, Subjective Daytime Function

Table 2.7.4.87 Summary Statistics for Subjective Daytime Function (ITT Analysis Set for Study SP-0401)

Parameter	Placebo (N=66)	Doxepin 1 mg (N=66)	Doxepin 3 mg (N=66)	Doxepin 6 mg (N=67)
Wakefulness (mm)[1]	n=65	n=66	n=65	n=65
Mean (SD)	62.0 (22.64)	62.3 (19.51)	56.2 (22.57)	54.1 (22.78)
Median	63.0	65.0	53.0	53.0
Min, Max	9.0, 99.0	11.0, 95.0	3.0, 92.0	12.0, 97.0
p-value[3]		1.0000	0.1177	0.0219
Ability to Concentrate (mm)[2]	n=65	n=66	n=65	n=65
Mean (SD)	68.4 (19.21)	66.3 (18.41)	61.7 (22.21)	63.2 (20.45)
Median	73.0	69.0	65.0	63.0
Min, Max	23.0, 99.0	15.0, 96.0	3.0, 97.0	19.0, 100.0
p-value[3]		0.6678	0.0167	0.0917
Daytime Sense of Well-being (mm)[2]	n=65	n=66	n=65	n=65
Mean (SD)	69.4 (20.26)	67.1 (20.30)	64.8 (21.33)	64.3 (20.55)
Median	72.0	71.0	69.0	66.0
Min, Max	23.0, 99.0	16.0, 100.0	4.0, 98.0	19.0, 98.0
p-value[3]		0.6849	0.1604	0.1350

[1] Wakefulness: 0=very sleepy, 100=wide awake.
[2] Concentration, Well-Being: 0=poor, 100=excellent.
[3] p-value comparing each active treatment versus placebo using Dunnett's test.
Source: SP-0401 CSR Post-text Table 28.2, Post-text Table 29.2, and Post-text Table 30.2.

Table 4: Elderly Study 402, Subjective Daytime Function

Table 2.7.4.88 Summary Statistics for Subjective Daytime Function (ITT Analysis Set for Study SP-0402)

Parameter	Placebo (N=73)	Doxepin 1 mg (N=74)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=74)
Wakefulness (mm)[1]	n=73	n=74	n=75	n=73
Mean (SD)	63.0 (22.34)	66.1 (22.04)	60.2 (21.89)	60.7 (23.05)
Median	71.0	72.5	62.0	67.0
Min, Max	14.9, 97.0	4.0, 98.0	19.0, 99.0	8.0, 98.0
p-value[3]		0.6260	0.5888	0.6684
Ability to Concentrate (mm)[2]	n=73	n=74	n=75	n=73
Mean (SD)	69.7 (18.28)	70.4 (18.28)	67.2 (17.10)	66.4 (18.53)
Median	75.0	76.0	72.0	69.0
Min, Max	26.0, 98.0	24.0, 98.0	22.0, 99.0	19.0, 99.0
p-value[3]		0.8550	0.5713	0.1388
Daytime Sense of Well-being (mm)[2]	n=73	n=74	n=75	n=73
Mean (SD)	71.3 (17.80)	71.3 (17.16)	70.3 (17.31)	68.4 (19.03)
Median	75.0	77.0	75.0	73.0
Min, Max	23.0, 98.0	30.0, 98.0	24.0, 99.0	20.0, 98.0
p-value[3]		0.9966	0.9591	0.2077

[1] Wakefulness: 0=very sleepy, 100=wide awake.
[2] Concentration, Well-being: 0=poor, 100=excellent.
[3] p-value comparing each active treatment versus placebo using Dunnett's test.
Source: SP-0402 CSR Post-text Table 28.2, Post-text Table 29.2, and Post-text Table 30.2.

For the Phase 3 studies, DSST, SCT, and VAS for sleepiness were similarly assessed, but instead of a VAS scale, feeling of drowsiness and ability to function during the day were assessed using an integer scale from 1 (extremely drowsy/unable to function) to 6 (extremely alert/able to function).

In study 501, a 35-day, double-blind, placebo-controlled, parallel group study of Silenor 3 and 6 mg in 221 adults with chronic insomnia, small but consistent decreases in the DSST (Figure 1**) and SCT (**Figure 2**) occurred in the 6 mg group. No change was detected in the next morning VAS for sleepiness (**Figure 3**), or in subjective next day drowsiness or ability to function during the day as measured by single-item 6-point Likert scale**.

Figure 1: Study 501, DSST

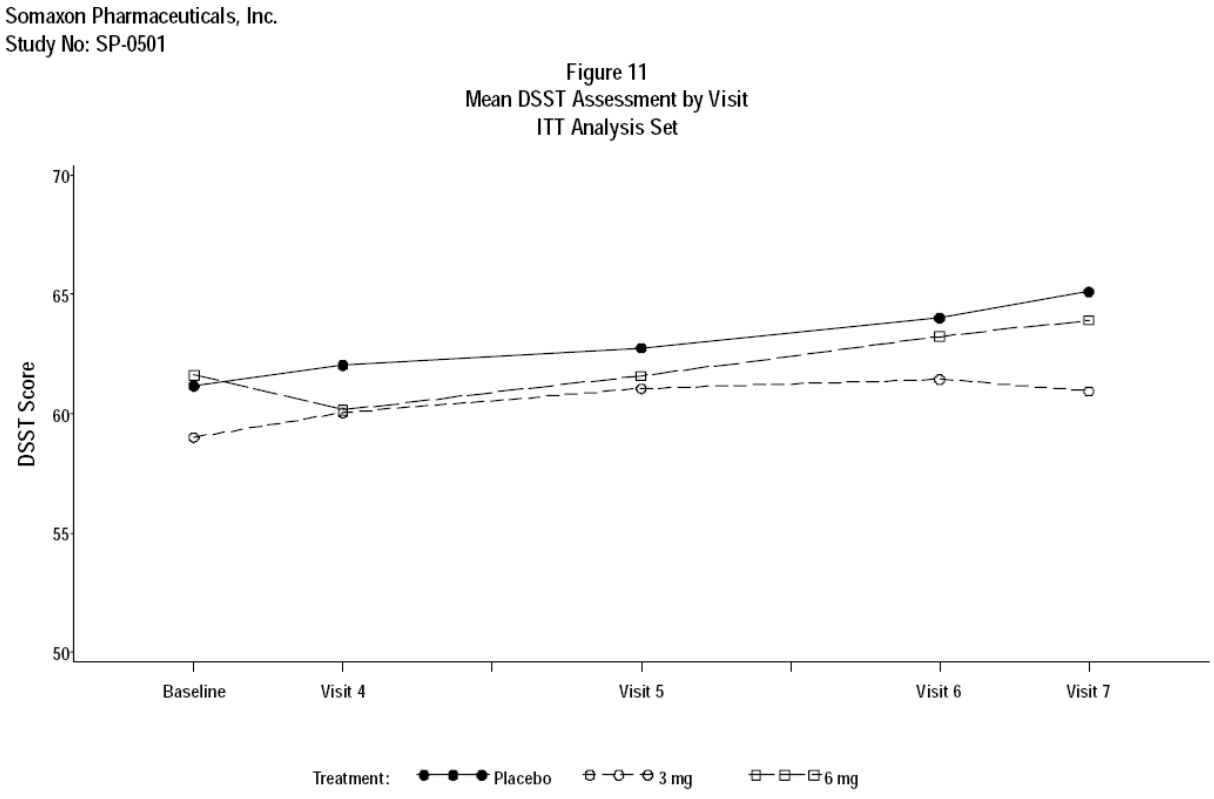
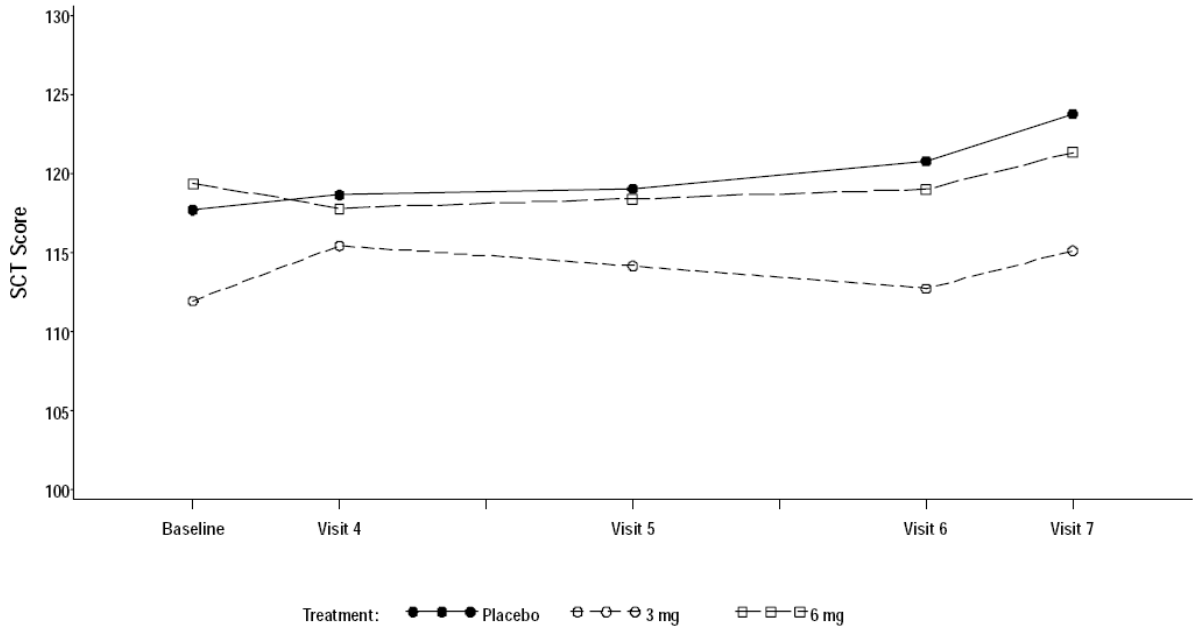


Figure 1:DSST decreases for the 6 mg arm after baseline and remains lower than the placebo arm. At baseline the 3 mg arm was lower than placebo, confounding interpretation, but at later time points (visit 6 and 7) the 3 mg arm decreases relative to placebo, suggesting possible drug effect.

Figure 2: Study 501, SCT

Somaxon Pharmaceuticals, Inc.
Study No: SP-0501

Figure 12
Mean SCT Assessment by Visit
ITT Analysis Set

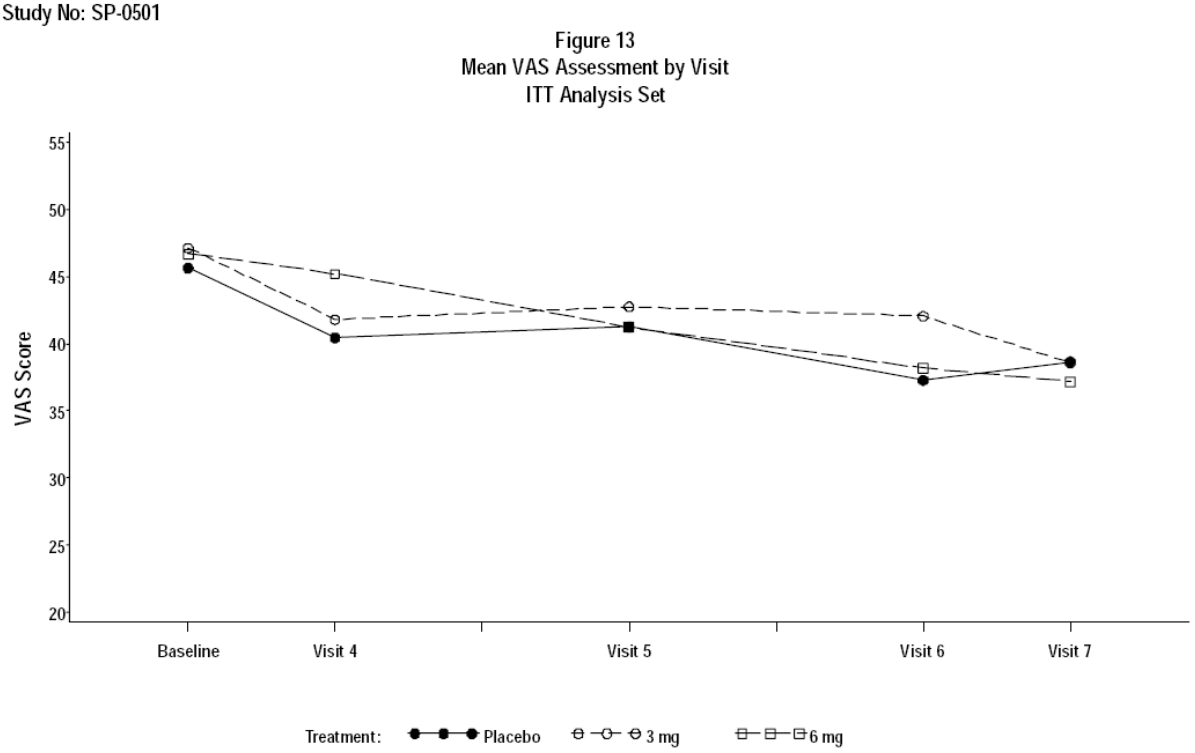


Note: Measurements taken from Days 2 and 3 are averaged. If 1 of the 2 Days has a missing value, the non-missing value is used.
s:\dat\somaxon\sp-0501\sas\programs\g_dsst.sas 02NOV2006 14:52

Figure 2**: Baseline of the 3 mg arm was lower for DSST and SCT than the placebo for unknown reasons, potentially confounding detection of decrease due to that dose. Both the 3 mg and 6 mg arms are consistently numerically worse than the placebo arm.**

Figure 3: Study 501, VAS for Next Day Function

Somaxon Pharmaceuticals, Inc.
Study No: SP-0501



Note: Measurements taken from Days 2 and 3 are averaged. If 1 of the 2 Days has a missing value, the non-missing value is used.
s:\dat\somaxon\sp-0501\sas\programs\g_dsst.sas 02NOV2006 14:52

Figure 3:No meaningful difference was discernable in VAS for next day function.

Study 502 was a one-night, double-blind study of Silenor 6 mg conducted in 565 healthy adult subjects experiencing transient insomnia. SCT and VAS for sleepiness showed modest but statistically significant changes suggestive of residual psychomotor and sedative effects (Table 5**).**

Table 5: Study 502 Tests of Next-Day Effects

Table 38 DSST, SCT, and VAS for Sleepiness – Mean Change in Scores from Night 1 (Predose) to Day 2 (Postdose): Safety Analysis Set

Assessment	Placebo (N=282)	Doxepin 6 mg (N=283)
Digit Symbol Substitution Test (number correct)		
Predose Mean (SD)	59.2 (15.32)	60.9 (13.76)
Postdose Mean (SD)	59.2 (14.34)	59.6 (13.54)
Mean Change (SD)	0.0 (9.81)	-1.3 (9.33)
p-value[1]		p=0.0982
Symbol Copying Test (number correct)		
Predose Mean (SD)	118.8 (27.26)	119.4 (26.11)
Postdose Mean (SD)	117.7 (26.72)	114.7 (26.60)
Mean Change (SD)	-1.1 (19.57)	-4.7 (17.46)
p-value[1]		p=0.0228
Visual Analog Scale for Sleepiness (mm)		
Predose Mean (SD)	27.4 (20.62)	25.0 (18.91)
Postdose Mean (SD)	37.2 (23.07)	39.5 (20.94)
Mean Change (SD)	9.8 (26.12)	14.5 (23.70)
p-value[1]		p=0.0241

[1] p-value for comparing the change from Night 1 to Day 2 between treatments was obtained from an ANOVA model with main effects for treatment and center.

Source: Post-text Table 42.1, Post-text Table 43.1, and Post-text Table 44.1.

In study 503, a 3-month, double-blind, placebo-controlled, parallel group study in 240 elderly subjects with chronic insomnia, Silenor 1 mg and 3 mg arms were comparable to placebo on next morning DSST, SCT, and VAS tested after nights 15, 29, 57, and 85. No change was detected in subjective next day drowsiness or ability to function during the day as measured by single-item 6-point Likert scale, and in fact for many time points both active arms showed improvement versus placebo.

<u>CDTL Discussion of Next Day Residual Effects:</u>

The data above suggest that residual pharmacological effects occur for Silenor. Analysis of dose/response effect is complicated by the fact that elderly subjects received lower doses (1 and 3 mg) than adult subjects (3 and 6 mg), but some evidence suggests that a dose-response effect may occur.

Possibly as a consequence of receiving only the two lower doses in studies that measured residual effects, findings were less consistent in elderly than in adults: residual effects in elderly were detected in study 401 but not in study 503. In any case, the findings in elderly are reassuring that residual effects are likely comparable to those in adults. For both adults and elderly, next day residual effects were of modest size, and appear acceptable for drug approval in terms of patient safety.

Rebound Insomnia

Rebound insomnia was only specifically examined in study 501. Following completion of 35 consecutive nights of double-blind treatment, rebound insomnia was examined during the 2-day Discontinuation Period. All patients were discontinued from study drug and placed on single-blind placebo. Sleep parameters for all patients were then compared to baseline parameters (WASO, LPS, TST). Dr. Cai notes that the study didn't incorporate randomization of the patients to continue or stop the study drug. Dr. Cai considers subjects on placebo during the double-bind phase as inappropriate for comparison to patients on drug during the double-blind phase who were then switched to placebo, and concludes that the study, by design, can't provide meaningful data on rebound insomnia.

CDTL: Only a single, relatively small study in adults examined rebound effects (less than 70 subjects in each treatment arm). However, the limited data suggest rebound insomnia may occur.

Table 6 **shows outliers in study 501 that exceeded baseline by pre-specified objective sleep measures in the 2 nights following the switch of all randomized patients to single-blind treatment with placebo. For the first night after drug withdrawal ('night 36'), there were numerically a higher percentage of outliers for the 3 mg and 6 mg arm for all 3 sleep measures (WASO, LPS, TST), suggesting possible drug-relatedness. This effect was seemingly magnified by examining together the first 2 nights after drug withdrawal ('night 36 and night 37').**

The average values for the sleep measures were improved versus baseline in the withdrawal period for both placebo and study drug arms. The improvement in the placebo arm partly confounds comparison of withdrawal period sleep measures to baseline, but overall is reassuring that Silenor does not cause a large rebound insomnia effect.

I conclude that while data on rebound insomnia is limited, rebound insomia may occur. The effect is likely of modest size, and manageable through appropriate labeling.

Table 6: Rebound Insomnia Outliers

Somaxon Pharmaceuticals, Inc.
Study No: SP-0501

Table 59.2
Rebound Insomnia - Frequency Counts
Safety Analysis Set

PSG Parameter	Criteria	Placebo (N= 73)	Doxepin HCl 3 mg (N= 75)	Doxepin HCl 6 mg (N= 73)
	Number of Patients evaluable for rebound insomnia [1]	N = 67	N = 67	N = 68
WASO (minutes)	Change from Baseline [2] ≥ 35 minutes at Visit 7			
	Night 36	6 (9 %)	10 (15 %)	7 (10 %)
	Night 36 and Night 37	1 (1 %)	1 (1 %)	3 (4 %)
LPS (minutes)	Change from Baseline [2] ≥ 20 minutes at Visit 7			
	Night 36	4 (6 %)	7 (10 %)	8 (12 %)
	Night 36 and Night 37	0 (0 %)	3 (4 %)	2 (3 %)
TST (minutes)	Change from Baseline [2] ≤ -30 minutes at Visit 7			
	Night 36	5 (7 %)	9 (13 %)	6 (9 %)
	Night 36 and Night 37	0 (0 %)	3 (4 %)	2 (3 %)

Table 6: Sleep measures are consistently worse in drug arms, but without clear dose/response effect.

Suicidality

The sponsor conducted an analysis of events in the Silenor development program that might be associated with suicidality. The sponsor used the Columbia Classification Algorithm of Suicide Assessment (C-CASA). 9 patients with adverse events triggered review for potential suicidality. Four subjects identified were in the Placebo group, and 5 in doxepin groups.

CDTL: Doxepin as an antidepressant carries a boxed warning for increased suicidality in children, adolescents, and young adults. The only patient in the doxepin group with an adverse event that appears even potentially related to suicidality was 'cut/scratch left forearm.' In the control group, 2 patients had apparently similar injuries, suggesting no excess of the event from drug. While the data from these studies do not suggest increased suicidality from Silenor, the power to detect such events was small, and the risk can not be excluded based on this data.

Other psychiatric adverse events

As noted above, 2 patients in the 6 mg group discontinued due to anxiety, versus none in the control group. Dr. Cai reports that otherwise only one subject reported depression (6 mg group) and 1 reported elevated mood (3 mg group).

Common Adverse Events:

Dr. Cai examined common adverse events separately for adult and elderly subjects.

Adults: There was 1 long term (1 month) study in adults comparing 3 mg and 6 mg Silenor to placebo. Dr. Cai finds that somnolence and overall infection occurred in 5% or more of drug-treated subjects, and in more than twice as many treated as control subjects, suggesting drug-relatedness. Dr. Cai also notes that nausea and vomiting met these criteria for drug-relatedness in the discontinuation phase.

Elderly:Dr. Cai notes that in study 509, if sedation and somnolence are combined, the incidences in doxepin treatment groups are over 5%, and more than double the incidence in the placebo group. She also notes that psychiatric disorders and dizziness also only appeared in doxepin groups. Dr. Cai notes that in study 503, vascular disorders appeared to be possibly drug-related, with hypertension in 5% of elderly subjects at the 3 mg dose.

CDTL: I reviewed the adverse events in the phase 3 safety analysis set, as listed in 'integrated-safety-data.pdf, table 1.3.3, and find the following frequencies for common adverse events:

Somnolence/sedation: I combined occurrences of somnolence, sedation, lethargy, and sluggishness, resulting in the following frequencies:

Placebo:	12/278 subjects	= 4%
1 mg:	4/77 subjects	= 5%
3 mg:	10/157 subjects	= 6%
6 mg:	20/203 subjects	= 10%

Dizziness, *dry mouth*, and *vomiting* each occurred in 1.5% of subjects in the 6 mg Silenor arm, which rounds to 2%, (b) (4)

Nausea occurred in 2.5% of subjects in the 6 mg Silenor arm, and was added to the common adverse events table in labeling.

Laboratory tests: Dr. Cai concludes that laboratory testing was adequate.

Clinical Chemistry

- *Mean*

Dr. Cai concludes that analysis of mean clinical chemistry data did not reveal clinically significant or likely drug-related abnormalities.

- *Outliers*

Dr. Cai concludes, and that outlier analysis of clinical chemistry data did not reveal clinically significant or likely drug-related abnormalities.

Hematology

- *Mean*

Dr. Cai concludes that there seems to be a decrease of neutrophils in doxepin groups, and of platelets t in some studies, of uncertain clinical meaning.

- *Outliers*

Dr. Cai identifies a number of outliers, of uncertain clinical meaning.

Vital signs and ECG:

Vital Signs

- Mean

Dr. Cai notes that statistically significant, but not clinically meaningful changes in vital signs occurred at some time points in some studies, but that overall, the magnitude of mean changes in vital signs doesn't seem to be clinically meaningful. Dr. Cai notes that the variations in vital signs are larger than the mean changes in most cases, and that no consistent pattern is discernable over time, suggesting that changes are not drug-related.

- Outliers

Dr. Cai did not find clinically meaningful outliers.

ECG

Dr. Cai finds from analysis of QTcB and QTcF confirmation of the risk of QT prolongation and tendency of its worsening from doxepin. She finds this more evident in geriatric patients. She notes that QT effects appeared not to be strictly dose related.

CDTL: Silenor appears to be associated with an average QT prolongation of about 5 ms in the current studies, but importantly, the studies examined QT effect remote from the Cmax of Silenor, raising concern that the QT effect could be even larger at clinically encountered blood (and myocardial) levels.

- **In study 501, ECG was performed during the Initial Screening (baseline) and during the morning of the Final Study Day (Day 38), approximately 2.5 days after administration of the last dose of double-blind study drug on Night 35, or upon early termination. QT effect was about 5 msec, as follows:**

	Placebo	3 mg	6 mg
QTcF:	.9	3.9	5.1
QTcB	.1	4.2	6.6

The half life of doxepin is about 15 hours, and nordoxepin, the major metabolite, 31 hours. QT effect present 2.5 days from dosing may be due to nordoxepin or other metabolites.

- **In study 503, ECGs were performed during Initial Screening (baseline) and during the morning of the Final Study Day (Day 86/ET), approximately 9 hours postdose:**

	Placebo	3 mg	6 mg
QTcF:	1.4	4.9	6.3
QTcB	3.0	6.0	5.8

- **In study 509, ECGs were obtained at screening (Visit 1; baseline) and the Final Study Day (Day 28)**

	Placebo	6 mg

QTcF:	-6.7	-2.5
QTcB	-5.5	0.9

- **Study 505 examined doxepin PK in the presence of the non-specific CYP inhibitor cimetidine. Approximately a two-fold mean increase in Cmax and $AUC_{0-\infty}$ occurred for doxepin. ECG was performed at Screening and <u>96 hours</u> after administration of single dose doxepin 6 mg coadministered with cimetidine 300 mg under fasted conditions. There was no placebo group, limiting interpretability of QT data, but QTcF increased versus baseline by 9 msec, and QTcB increased by 10 msec.**

- **Study 506 examined the PK interaction of Silenor 6 mg and sertraline, finding about 1.3-fold increase in mean doxepin Cmax. ECG was obtained at baseline and final study day. There was no placebo group, limiting interpretability of QT data, but QTcF increased versus baseline by 9 msec, and QTcB increased by 8 msec.**

Outlier analysis provides a less clear picture: for QTcB, there were 9 of 720 doxepin-treated subjects with absolute values >480 ms at the final assessment compared with 3 of 560 placebo patients. However, for >60 ms outliers (by both QTcB and QTcF) there were more outliers in placebo versus doxepin groups.

See additional discussion below under *CDTL Discussion of Key Safety Issues, Cardiovascular Safety*.

Dose dependency of adverse events
Dr. Cai notes that somnolence appeared to be dose related. She also notes that hypertension was more common in the 3 mg than 1 mg dose group. She also notes that nausea occurred in the 6 mg group.

Time dependency for adverse events
Dr. Cai notes that hypertension was seen only in the 3-month elderly study, and that outlier analysis showed that 4 of 6 Cases did not occur until the final study visit.

Race subject-group analysis:
Dr. Cai concludes there is insufficient data to discern a relationship of adverse events to race.

CDTL Discussion of Key Safety Issues:

Cardiovascular Safety

Doxepin has been used in psychiatric indications for decades at doses 10- to 100-fold higher than those found in Silenor. At these higher doses doxepin has been associated with multiple cardiovascular adverse effects including conduction abnormalities, tachycardia, arrhythmias including torsade de pointes, orthostatic hypotension, and possibly congestive heart failure. Topical doxepin (Zonalon) has been approved for about 15 years for management of pruritis in adults with atopic dermatitis or lichen simplex chronicus. Systemic exposure to doxepin from topical application is highly variable, with levels ranging from nondetectable to about 50 ng/mL(Zonalon label), more than 10-fold higher than doxepin exposure from Silenor. Cardiovascular adverse events did not appear to have occurred in the development program for topical doxepin, but only 330 subjects were exposed in apparently short-term clinical studies in support of an indication not to exceed 8 days of use. The Zonalon label does not indicate evidence of cardiac risk from the post-marketing period, but the sensitivity of spontaneous adverse events reporting for unexpected adverse events can be low. I conclude that the reassurance of cardiac safety that can be derived from the clinical experience with topical doxepin is limited, and not adequate of itself to support the cardiovascular safety of Silenor.

Three cardiovascular SAEs were identified in Silenor arms, versus none in placebo, raising concern for drug-relatedness. Dr. Cai identified an excess incidence of hypertension in the 3-month elderly study, raising concern that non-serious cardiovascular events provide a possible mechanism for the drug-relatedness of serious cardiovascular adverse events. Most of the cases of hypertension occurred late in the study, suggesting possible time-dependence of development of hypertension. The other studies in the development program were 1-month or shorter, and while excess hypertension or increased mean blood pressure was not identified, this provides little reassurance of safety if the adverse event is time-dependent, occurring only after several months of exposure. Hypertension is noted in the Sinequan label as an adverse effect to consider when prescribing Sinequan. While none of the above threads of evidence is conclusive by itself, I believe that together sufficient concern is raised about cardiovascular adverse events that Silenor should not be approved unless additional evidence of cardiovascular safety can be presented by the sponsor.

While not clearly related to the adverse events encountered in the Silenor development program, as noted above doxepin has been associated with QT prolongation and other cardiac conduction abnormalities. Doxepin at doses used in depression appears to cause QT prolongation ,[2] and a low micromolar concentrations inhibits HERG potassium channels.[3] In the Silenor development program, ECGs were not done at Tmax, and in fact were often done days after dosing. Despite the low plasma levels of doxepin and nordoxepin at these time points, QT prolongation of about 5 milliseconds seemed to occur. This degree of apparent QT prolongation, together with previous data regarding the pro-arrhythmic potential of doxepin, raises serious cardiovascular safety concerns for Silenor. I believe that Silenor should not be approved unless these concerns can be adequately addressed.

Of note, important exculpatory evidence exists regarding the risk of sudden cardiac death from 'low dose' doxepin. In a large retrospective study of sudden cardiac death in users of cyclic

[2] Baker et al., Electrocardiographic Effects of Fluoxetine and Doxepin in patients with major depressive disorder. J. Clin Psychopharm 1997;17:15-21.
[3] Duncan RS et al., Inhibition of HERG potassium challen by the tricyclic antidepressant doxepin. Biochem Pharmacol 2007;74:425-37.

antidepressants, including more than 10,000 person years exposure to doxepin and about 60,000 person years for all TCAs, no increased risk of sudden cardiac death was found for doses less than 100 mg doxepin-equivalent dose (more than 10-fold higher dose than Silenor).[4] Subgroup analysis of low-dose patients similarly identified no increase in risk in women, who are thought to be at increased risk of drug-induced long QT syndrome and torsades de pointes, or in patients with treated cardiovascular disease, which may increases susceptibility to the proarrhythmic effects of TCAs, or in persons age 65 or older, who have a greater incidence of cardiovascular disease. In contrast, in doses >100 mg, TCA users had a 41% increased risk of sudden cardiac death, with even higher risk in an apparent dose response fashion for TCA use at 200 and 300 mg/day. However, in the absence of more complete data on QT prolongation for low dose doxepin, I do not consider this study to provide adequate evidence of the cardiac safety of Silenor.

Anaphylaxis and Angioedema

The sponsor argues that the antihistaminic mechanism of action of low-dose doxepin suggests that Silenor does not share the potential of other sedative/hypnotic drugs to cause angioedema or anaphylaxis. The sponsor asserts that there were no adverse events in the Silenor development program suggestive of anaphylaxis or anaphylactoid reactions. However, the sponsor notes that the Adverse Event Reporting System (AERS) database contains reports of allergic reaction to doxepin, including anaphylaxis and angioedema. In the sponsor's analysis of AERS reports (amendment 5, 7/31/2008), anaphylaxis and angioedema appeared to be either unrelated to dose, or perhaps inversely related to dose. I therefore recommend that labeling for (b) (4) be included in the Silenor label.

Suicidality

(b) (4)

and conclude that class labeling for antidepressants should be included in the Silenor label.

- (b) (4)

CDTL: The sponsor does not present persuasive evidence that a dose-response effect exists for risk of suicidality from doxepin.

- **The sponsor cites an analysis of AERs reports suggesting that risk of suicidality at <50 mg doxepin may be less than risk at higher doses.**

CDTL: Events related to suicide and suicidality still occurred in the <50 mg group. This seems to suggest that a lower dose limit for risk has not been defined.

- **The sponsor asserts that at low doses doxepin acts mainly on H1 receptors, a different mechanisms of action than in depression, such that Silenor neither carries efficacy in depression, nor increases risks associated with treatment of depression.**

[4] Ray et al., Cyclic antidepressants and the risk of sudden cardiac death. Clin Pharmacol Ther 2004;75:234-41.

CDTL: The mechanism by which antidepressants increase risk of suicidality is unknown. The sponsor makes no persuasive argument about which the mechanisms that may or may not increase risk.

- **The sponsor asserts that the risk of suicidality is present in a younger patient population than will use Silenor, and that in the age group of intended use, antidepressants actually decrease suicidality**

CDTL: An increased risk of suicidality was found in young adults (up to 24 years old). Silenor would be indicated for adults, and would thus include this high risk group. In addition, suicidality labeling should be included to warn about the risks of off-label use in children.

- **The sponsor also notes that adverse events suggestive of increased risk of suicide or suicidality did not occur in the Silenor development program.**

CDTL: Exposure in the Silenor development program was not large enough to exclude a clinically meaningful risk of suicidality-related adverse events.

Abnormal thinking, behavioral changes, and complex behaviors:

The sponsor did not include class labeling in the original submission, on the grounds that these events had not occurred in the Silenor development program. The Division requested that this language be included, and the sponsor submitted a revision of labeling agreeing to include class labeling for sedative-hypnotics.

9. Advisory Committee Meeting

No advisory meeting was held.

10. Pediatrics

No pediatric studies were conducted.

11. Other Relevant Regulatory Issues

- *Division of Scientific Investigations*: Dr. Antoine El-Hage notes in his review that 3 sites were inspected, from the 3 key long-term efficacy studies, and that no significant problems that would adversely impact the data were revealed.
- *Animal carcinogenicity*: In this submission the sponsor included report of an animal carcinogenicity study in transgenic mice that was reviewed by Drs. Mohammad Atiar Rahman and Karl Lin. Their analysis did not show statistically significant positive dose response relationship or increased incidence in the treated group in any of the tested tumor types.

- *Controlled Substance Staff*: Dr. Katherine Bonson reviewed the abuse potential of Silenor, and concludes that doxepin dose not have abuse potential and should not be recommended for scheduling.

12. Labeling

- *Proprietary name*: Dr. Jinhee Lee notes in her review from the Office of Surveillance and Epidemiology / Division of Medication Error Prevention and Analysis (DMEPA), that FDA does not object to the use of the proprietary name Silenor.
- *Container and Carton Labeling*: Dr Jinhee Lee states that the Applicant has changed the container labels and carton labeling according to FDA recommendations.

13. Recommendations/Risk Benefit Assessment

Risk Benefit Assessment

As discussed above under *CDTL Discussion of Key Safety Issues*: *cardiovascular risk*, I conclude that the sponsor has not provided adequate evidence of the cardiovascular safety of Silenor, particularly regarding QT prolongation and the risk of arrhythmia, but also regarding the apparent excess of both serious and non-serious cardiovascular adverse events in the development program. The risk/benefit assessment for Silenor for the indication of insomnia is unfavorable given this potential cardiac risk.

I conclude that the other major risks of Silenor can be adequately mitigated through labeling.

- Worsening of depression and suicide risk : Class labeling for this risk from antidepressants should be added to Silenor labeling

- Abnormal thinking, behavioral changes, and complex behaviors, Serious anaphylactic and anaphylactoid reactions, and Drowsiness: Class labeling for these three risks are included in current sedative-hypnotic labels, and should be included in the Silenor label.

Recommended Regulatory Action

I recommend that Silenor not be approved, and that a Complete Response letter communicating the above safety concerns should be issued to the sponsor.

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

/s/

Ronald Farkas
2/24/2009 01:17:20 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA-22036, 505(b) (2)
Submission Number	000
Submission Code	S
Letter Date	Jan. 30, 2008
Stamp Date	Jan. 30, 2008
PDUFA Goal Date	Feb. 28, 2009
Reviewer Name	June Cai, MD
Review Completion Date	Feb. 3, 2009
Established Name	Doxepin HCl
(Proposed) Trade Name	Silenor
Therapeutic Class	Hypnotics
Applicant	Somaxon Pharmaceuticals
Priority Designation	S
Formulation	Tablets
Dosing Regimen	1mg, 3mg, or 6mg
Indication	Maintenance insomnia Sleep onset insomnia (b) (4)
Intended Population	Adults: 3mg ~ 6mg Elderly: 1mg ~ 6mg

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Considering failure in demonstration of consistent efficacy, inadequate cardiovascular safety profile, and lack of appropriate study for rebound insomnia, I recommend the Division taking a Non-approval action on this NDA.

1.2 Risk Benefit Assessment

Silenor is a very low dose formulation of the antidepressant Sinequan which has been on the market for nearly 40 years. Clinically, Sinequan was used often for depressive patients who couldn't sleep well and the dosage was many times higher than the current study dose of Silenor for sleep.

The number of adverse effects of Sinequan appears to be much lower in this formulation. However, the presence of more cardiac events in the later stage of the longer term study and the inappropriate timing of cardiac risk assessment in this clinical program is concerning. Rebound insomnia was also studied improperly. Moreover, risks of suicidality associated with this compound and sleep complex behavior as a hypnotics can't be totally ruled out despite there appear no cases in the trials of this clinical development program and theoretical mechanisms presented do not support the possible risks. The fact is that the exact factors of the phenomenon are unclear.

1.3 Recommendations for Postmarketing Risk Management Activities

The sponsor has sent in REMS. It is still being reviewed by OSE. However, since I don't consider this drug is appropriate to be approved as sleeping pill according to these data, I don't have recommendation for postmarketing risk management activities.

2 Introduction and Regulatory Background

2.1 Product Information and Availability of Active Ingredients

Doxepin HCl (1-Propanamine, 3-dibenz [b,e]oxepin-11(*6H*)ylidene-*N*,*N*-dimethyl-hydrochloride) is a white, crystalline powder with a slight amine-like odor. It is widely available in the U.S. It was approved as a dibenzoxepin tricyclic antidepressant (Sinequan® capsule, NDA 16-798, Pfizer) in the US in 1969. Subsequently, Doxepin oral concentrate (NDA 17-516) was approved in 1974. Its topical cream 5% that contains 50mg of Doxepin HCl, Zonalon® (NDA 20-126, Bradley), was

approved for short term treatment of moderate pruiritis associated with atopic dermatitis or lichen simplex chronicus in 1994.

(b) (4)

2.2 Summary of Presubmission Regulatory Activity Related to Submission

The original IND (#67,162) was submitted on June 4, 2004. Subsequently, an EOP2 meeting was held on April 25, 2005 to discuss the development of Phase III studies with Division of Anesthetic Critical Care, and Addiction Drug Products. (Meeting Minutes by the sponsor was dated on May 19, 2005; the Agency Meeting Minutes was dated on May 25, 2005.) The clinical aspects of the discussion are as follows:

1) At least two adequate and well-controlled studies are needed, which means, in addition to the three studies already proposed by the sponsor ("a 35-day adult study, a two-week elderly study, and a transient insomnia"), at least one more adult study is needed to support an NDA submission and approval for the treatment of insomnia.

- One of the adult studies can have subjective outcomes; PSG will be used as the objective measure of one proposed adult study.
- Study duration longer than 35 days are strongly encouraged
- An outpatient study in elderly patients with objective and subjective assessments and more than 35 days of duration was suggested.

2) The proposed assessments of next-day residual effects by the sponsor were acceptable. They include Digit Symbol Substitution Test (DSST), Symbol Copying Test (SCT), and Visual Analog Scale (VAS).

3) *The preferred primary endpoint for insomnia studies in adult patients is objective Wake After Sleep Onset (oWASO)*, however, objective Wake Time During Sleep (oWTDS) can be considered if there is adequate rationale and data. The Agency agreed that *the subjective Total Sleep Time (sTST) is the preferable subjective endpoint for measuring sleep maintenance but requires replication.*

4) *The preferred primary endpoint for transient insomnia is also oWASO,* but Total Sleep Time maybe acceptable if appropriate supporting data are available.

5) Given the extensive experience and exposure with Doxepin HCl at doses much higher than proposed for the current indication, including long-term use, additional safety data would not be required, barring any unexpected safety findings in the proposed clinical trials in this patient population.

In a teleconference of Aug. 11, 2005 (Meeting Minute Jan. 6, 2006), the Division of Neurology Products (DNP) stated that TST is inadequate and WASO is a better indicator of effect on sleep

maintenance. The sponsor agreed. With regard to transient insomnia, the Division stated the need of two adequately developed studies and one must prove an effect on latency, in which the patients should have proven impairment in sleep latency; if properly developed, effects on latency and maintenance can be shown in one study.

The sponsor submitted a teleconference meeting minutes on Aug. 11, 2005 indicating that they understood the following:

a) An endpoint of TST is acceptable if justified and the LPS was also mentioned as a primary endpoint. But WASO was regarded as the preferred endpoint.

b) The Division agreed that sleep latency as a secondary endpoint, evaluated in a subset of patients who have sleep latency problems, from the sleep maintenance studies would support a sleep onset claim. The Division confirmed that a maintenance claim could be achieved in the absence of a sleep onset signal.

A pre-NDA meeting was held on May 31, 2006 with Division of Neurology Products. The sponsor presented the following endpoint summary (see tables below).

Table 1. Studies and Endpoints to Support Sleep Onset

	LPS*	LSO*
0401	X	X
0402	X	X
0501	X	X
0502	X	X
0503	X	X
0509		X

* = Primary efficacy endpoints to support each claim; remaining measures are key secondary endpoints to support each claim.

Table 2. Studies and Endpoints to Support Sleep Maintenance

	WASO*	WTDS	TST	SE	sTST*	sWASO
0401	X	X	X	X	X	X
0402	X	X	X	X	X	X
0501	X	X	X	X	X	X
0502	X	X	X	X	X	X
0503	X	X	X	X	X	X
0509					X	X

* = Primary efficacy endpoints to support each claim; remaining measures are key secondary endpoints to support each claim.

The clinical aspects of the pre-NDA Meeting Minutes are summarized as follows:

1) The Division agreed upon efficacy results from the six studies as described may support the proposed indications but *noted the absence of an outpatient study in non-elderly adults and thus, it may lead to an age restriction (that is a restriction to preclude use in non-elderly adults) in the label since we would lack subjective evidence of efficacy measured as a primary endpoint in this non-elderly population.* The sponsor was advised to submit data from one objective and one subjective study in each of the two populations (adults and elderly) in order to address the possibility of an age restriction in the label, but the Agency may entertain an argument that the indication should not be restricted.

2) We would like complete safety and efficacy information from the pivotal studies at the time of initial NDA filing. The sponsor was advised to present data from the objective studies that would include *hour-by-hour calculations of 1) total wake time (TWT); and 2) number of awakenings after sleep onset (NAASO) at each of the visits where assessed*.

3) For the statistical analysis of the primary and secondary endpoint data, the sponsor was advised to *perform a sequential analysis* demonstrating effect for both primary and secondary endpoints, with *subjective and objective measures* for *sleep latency and sleep maintenance*, *by dose, at Week 1 and at end of treatment*. Such a sequential analysis would require ranking of the endpoints, such that the sequential analysis would end when one of the endpoints fails to reach statistical significance. The objective endpoints must be considered prior to the analysis of the subjective endpoints, for instance, the hierarchy would analyze oWASO and oLPS followed by sWASO and sLPS.

4) As agreed at the EOP2 Meeting, the result of a study in healthy subjects experiencing *transient insomnia would be described in the Clinical Trials section of Silenor Prescribing Information.*

5) With regard to adverse events, the Division agreed to the following: Describe only the adverse effects observed in clinical studies conducted by Somaxon at doses of 1mg, 3 mg, and 6 mg in the Adverse Reactions section of Silenor Prescribing Information; The safety information from higher doses and felt to be dose-related will be described in the over-dosage section; Adverse events felt to be idiosyncratic that occur at higher doses, if any, may be described elsewhere in the labeling.

6) With regard to statistical analyses, the Division reminded the sponsor that persistence of effect on sleep initiation and/or sleep maintenance as a key secondary outcome in objective studies can be considered.

The Division also informed the sponsor that the primary analysis must be an intent-to-treat analysis, including all subjects as randomized, with an appropriate pre-specified imputation method for missing data. – The efficacy analyses proposed by the sponsor which was based on observed data only; missing data not be imputed" will not be accept as the primary analysis. The sponsor was also informed that the analysis plan should specify alternative imputation methods to be used in sensitivity analyses. • The sponsor will revise the primary analysis on the primary and secondary endpoints to specify a rank-ordered analysis that will proceed until one of the endpoints fails to reach statistical significance.

7) Regarding abuse liability issue, the Agency Controlled Substance Staff (CSS) concurs with the sponsor's conclusions that low-dose doxepin has minimal abuse potential and that Silenor tablets should not be scheduled and further testing regarding abuse liability potential for this NDA is unnecessary

On July 19, 2006, the sponsor requested clarifications of the necessity for an additional study and argued that imputation of data would depend on the extent of missing data in studies and that if the rate was low, imputing the missing data for secondary endpoints would not be required.

In response to the sponsor's request, in a correspondence of Sept. 14, 2006, the Division confirmed that additional study in adult patients with subjective endpoints as primary efficacy variable is not required to file an NDA and a step-down analysis approach must be used to analyze. However, the final determination of whether the subjective evidence from Study 501 will be adequate to inform labeling is a review issue.

2.3 Tables of Currently Available Treatments for Proposed Indications

Below is a list of products that have been approved for this indication since 1970.

Table 4. Approved Hypnotics Since 1970

Categories	Drug Names		Significant AEs
Benzodiazepines	Dalmane	flurazepam	Paradoxical effect
	Restoril	temazepam	
	Doral	quazepam	
	Halcion	triazolam	Traveler's amnesia, increased day time anxiety or depression
Nonbenzodiazepines	ProSom*	estazolam	Amnesia, sleep driving, bizarre or complex behaviors, esp. when taken with alcohol and or other CNS depressants; Aggression and other disinhibitive behaviors, changes in mood, perceptions, and thought contents; paradoxical effect
	Ambien	zolpidem	
	Sonata	zaleplon	
	Lunesta	eszopiclone	
	Ambien CR	zolpidem slow release	
	Rozerem	ramelteon	problems in libido, fertility, and menses or galactorrhea

*Brand name manufacturing discontinued by the sponsor, Abbott for commercial reasons.

3 Significant Safety/Efficacy Issues From Other Review Disciplines

3.1 Chemistry Manufacturing and Controls

There was no safety issue with this product. Please see the chemistry review conducted by the Agency Chemistry Reviewer, Sherita McLamore, Ph.D.

3.2 Preclinical Pharmacology/Toxicology

Although doxepin HCl has been on the market for almost four decades, new studies were requested for this new formulation during the pre-NDA meeting. Please see the review of these studies conducted by the Agency Pharm-tox Reviewer, Melissa Banks, Ph.D. As of today, issue such as risk category of reproduction system is still pending (personal communication with Dr. Banks).

3.3 Clinical Pharmacology

This section summarizes PK study results. For detail results of review, please see Biopharmaceutical Science Review conducted by the Agency Reviewer, Ju-ping Lai, Ph.D.

3.3.1 Pharmacokinetics

The sponsor submitted five Phase I studies (Studies # 0405, 0504, 0505, 0506, 0507; See next section Source of Clinical Studies) that devoted to characterize PK parameters of doxepin HCl, its main metabolite, nordoxepin HCl, food effect on this drug, and interactions with cimetidine as well as sertraline (both CYP2D6 inhibitors). The following figures and tables summarize these findings.

Table 5. Descriptive Statistics for Doxepin and Sinequan® PK Parameters (From Study 0507, provided by the sponsor)

Parameter (Unit)	Treatment A (Doxepin 6 mg tablet) N=23	Treatment B (Sinequan® 50 mg capsule) N=24
AUC_{0-t} (ng*h/mL/mg)[1]	2.816 (90.8)	3.933 (83.2)
$AUC_{0-\infty}$ (ng*h/mL/mg)[1]	3.139 (89.2)	4.148 (87.4)
C_{max} (ng/mL/mg)[1]	0.1823 (84.2)	0.2491 (90.3)
T_{max} (h)	3.0 (1.0–6.0)	2.5 (1.0–6.0)
$t_{1/2}$ (h)	16.01 (47.7)	19.13 (28.4)

[1] Derived from dose-normalized plasma concentrations.
The estimates presented are arithmetic mean (CV%) for AUC, C_{max}, and $t_{1/2}$ and median (range) for T_{max}.

These parameters are fairly comparable between these two doses; however, AUC and Cmax were somewhat higher in the high dose Sinequan as expected. Doxepin dose concentration-time profile can be seen in the figure below.

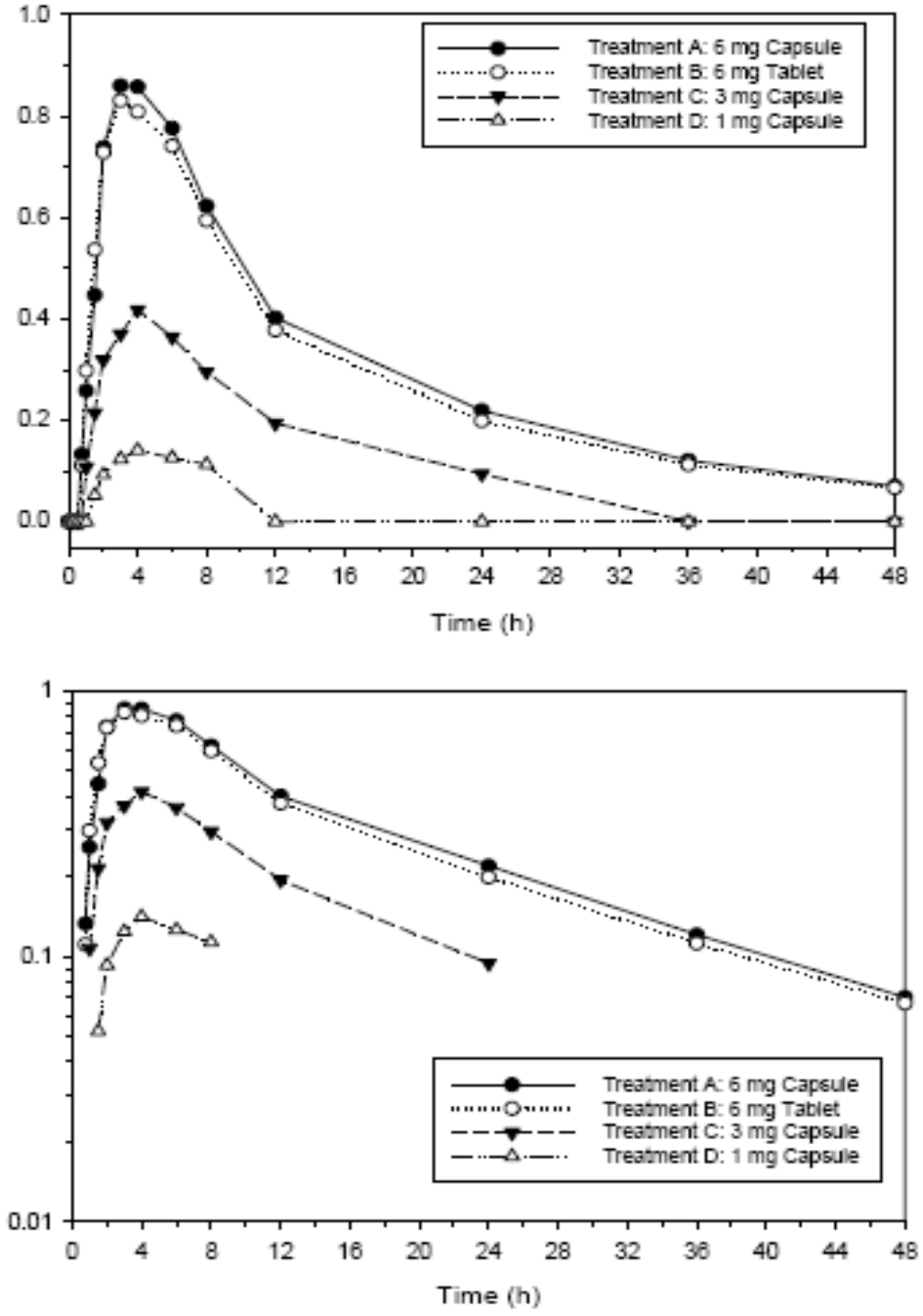


Figure 1. Linear and Logarithmic Concentration-Time Profiles for Doxepin 1 mg, 3 mg, and 6 mg (Study 0405)

There is a food effect on PK of Silenor: Tmax and half life both increased at fed state. (See Table 6)

Table 6. Descriptive Statistics for Food Effect on Doxepin PK Parameters (From Study 0504, provided by the sponsor)

Parameter (Unit)	Treatment A, Fasted (doxepin 6 mg tablet) N=15	Treatment B, Fed (doxepin 6 mg tablet) N=16
AUC_{0-t} (ng*h/mL)	12.57 (85.7)	16.81 (74.0)
$AUC_{0-\infty}$ (ng*h/mL)	14.12 (80.6)	18.55 (70.2)
C_{max} (ng/mL)	0.8544 (63.2)	0.9514 (58.8)
T_{max} (h)	3.0 (1.5–6.0)	6.0 (2.0–6.0)
$t_{½}$ (h)	14.37 (42.2)	16.53 (23.8)

The estimates presented are the arithmetic mean and (CV%) for AUC, C_{max} and $t_{½}$ and the median and (range) for T_{max}.

With Cimetinde AUC and Cmax of Silenor doubled (Table 7); whereas with Sertraline, Cmax of Silenor only slightly increased (Table 8).

Table 7. Descriptive Statistics for Cimetidine Effect on Doxepin PK Parameters From Study 0505, provided by the sponsor

Parameter (Unit)	Treatment A, reference (Doxepin 6 mg) N=24	Treatment B, test (Doxepin 6 mg + cimetidine 300 mg) N=22
AUC_{0-t} (ng*h/mL)	14.28 (93.4)	25.77 (68.0)
$AUC_{0-\infty}$ (ng*h/mL)	15.99 (90.6)	27.67 (67.2)
C_{max} (ng/mL)	0.8645 (57.1)	1.701 (42.6)
T_{max} (h)	4.0 (1.5–6.0)	3.0 (2.0–6.0)
$t_{1/2}$ (h)	15.93 (43.6)	16.79 (26.6)

The estimates presented are arithmetic mean (CV%) for AUC, C_{max}, and $t_{1/2}$ and median (range) for T_{max}.

Table 8. Descriptive Statistics for Sertraline Effect on Doxepin PK Parameters From Study 0506, provided by the sponsor

Parameter (Unit)	Treatment A (Doxepin 6 mg) N=24	Treatment C (Doxepin 6 mg + Sertraline 50 mg) N=24
AUC_{0-t} (ng*h/mL)	12.64 (106.3)	14.78 (79.4)
$AUC_{0-\infty}$ (ng*h/mL)	14.40 (98.0)	16.29 (75.1)
C_{max} (ng/mL)	0.9843 (61.7)	1.270 (54.3)
T_{max} (h)	3.0 (1.0–6.0)	2.0 (1.5–6.0)
$t_{1/2}$ (h)	14.42 (33.2)	13.96 (32.2)

The estimates presented are arithmetic mean (CV%) for AUC, C_{max}, and $t_{½}$ and median (range) for T_{max}.

For subgroup analysis, the sponsor reports the following:

- The mean $AUC_{0-\infty}$ and C_{max} were modestly higher for females, a difference that was not considered clinically meaningful. The median T_{max} was equivalent between genders.
- Numbers of subjects within all racial groups were insufficient in PK database to permit a formal analysis. Thus, ethnic differences have not been studied extensively. However, with 11 Blacks and 84 Caucasians, a comparison of these subjects at 6 mg suggested a higher AUC (arithmetic mean 18.5 vs. 15.7 ng*hr/mL) and C_{max} (arithmetic mean 1.36 vs. 0.90 ng/mL) in Black subjects, although the distributions overlapped substantially.
- No PK study was conducted in elderly patients. The sponsor cites one population PK model from the literature that concluded age and body weight as the primary factors influencing steady-state doxepin and nordoxepin concentrations. The model indicated that, on average, clearance was decreased by approximately one third from age 20 to age 75. Additionally, estimates of plasma concentrations resulting from a given dose could also be improved by taking patient weight into account.

The sponsor reports that effects of hepatic dysfunction on doxepin pharmacokinetics have not been studied. Since it is extensively metabolized by hepatic enzyme (CYP 2C19), caution is recommended in the selection of doses for such patients.

3.3.2 Pharmacodynamics

Silenor is an H_1 receptor antagonist. For review of study results, please see the review conducted by the Agency Biopharmaceutical Sciences, Ju-Ping Lai, Ph.D.

4 Clinical Data

4.1 Source of Clinical Studies

4.1.1 Tables of Clinical Studies

The clinical program includes a total of 11 studies that are summarized in the table below. Among them, four are Phase III studies, two Phase II, and the rest five are Phase I studies.

Table 9. Overview of Silenor Phase I Studies

ID	Title of Studies	Design Detail	Subject Dose Exposure		Primary Variables
Phase I			Dose group (subjects)	Total N	
SP-0405	A pilot, Phase I, PK study in healthy volunteers	Single dose, 4-way crossover	Doxepin 1mg (15) Doxepin 3mg (15) Doxepin 6mg (16)	16	PK proportionality bioequivalence
SP-0504	A randomized, open-label study to assess the effect of food on the PK of Doxepin HCl	Single dose, 2-way crossover Fasted/fed states	6mg fasted (15) 6mg fed (16)	16	Food effect on PK
SP-0505	A fixed sequence, open-label study to assess the PK interaction of Cimetidine with Doxepin HCl in healthy adults	Fixed sequence 2 treatments Drug interaction	Doxepin 6mg (24) Cimetidine 300mg (22) Combined doses (22)	24	PK of combined cimetidine and doxepin administration
SP-0506	A single-blind study to assess the PD and PK interaction of Sertraline HCl with Doxepin HCl in healthy adults	Single-Blind Fixed sequence, Double-dummy 3 treatments	Doxepin 6mg (24) Sertraline 50mg(24) Combined doses (24)	24	PK of combined sertraline and doxepin administration
SP-0507	A randomized, open-label study to assess the relative bioavailability of Silenor™ 6mg tablets compared to Sinequan® 50mg capsules	2-way crossover 9-day washout	Doxepin 6mg (23) Sinequan® 50mg (24)	24	Relative bioavailability compared to Sinequan®

The following two tables include Phase II and III studies that are submitted to support efficacy claims.

Table 10. Overview of Silenor Phase II Studies

ID	Title of Studies	Duration, Age	Subject Dose Exposure		Primary Variables
Phase II Studies			Dose group (subjects)	Total N	
SP-0401	A Phase II, randomized, double-blind, placebo-controlled, dose-response Study to assess the efficacy and safety of doxepin HCl in patients with *primary sleep maintenance insomnia*	2 nights Age 18-64 years old	Doxepin 1mg (66) Doxepin 3mg (66) Doxepin 6mg (67) Placebo (66) *4- way/periods crossover 5-12 day washout between periods.	67	Objective WTDS with 8 hours of PSG after each dosing
SP-0402	A Phase II, randomized, double-blind, placebo-controlled, dose-response study to assess the efficacy and safety of Doxepin HCl in *elderly* patients with *primary sleep maintenance insomnia*	2 nights but Age ≥ 65 years old	Doxepin 1mg (74) Doxepin 3mg (75) Doxepin 6mg (74) Placebo (73) *same as SP-0401	76	Objective WTDS with 8 hours of PSG after each dosing

Table 11. Overview of Silenor Phase III Studies

ID	Title of Studies	Duration Age	Subject Dose Exposure		Primary Variables
Phase III Studies			Dose group (subjects)	Total	
SP-0501	A Phase III, randomized, double blind, placebo-controlled, parallel group, multi-center, study to assess the efficacy and safety of Doxepin HCl in primary insomnia patients with *sleep maintenance difficulties*	35 nights Age 18-64 years old	Doxepin 3mg (75) Doxepin 6mg (73) Placebo (73) *Fixed-dose	221	WASO (LPS)
SP-0503	A Phase III, randomized, double blind, placebo-controlled, parallel-group, multi-center, study to assess the long term efficacy and safety of doxepin HCl in primary elderly insomnia patients with sleep maintenance difficulties	85 nights Age ≥ 65 years old	Doxepin 1mg (77) Doxepin 3mg (82) Placebo (81) *Fixed dose	240	WASO (LPS)
SP-0509*	A Phase III, randomized, double-blind, placebo controlled, parallel-group, multicenter outpatient study to assess the efficacy and safety of Doxepin HCl in elderly patients with *primary sleep maintenance insomnia*	28 nights Age ≥ 65 years old	Doxepin 6mg (130) Placebo (124) *Fixed dose	254	sTST at Week 1 (LSO* at Week 1)
SP-0502	A Phase III, randomized, double-blind, placebo controlled, parallel-group multicenter study to assess the efficacy and safety of Doxepin for the treatment of *transient insomnia* in adults	1 night Age 25−55 years old	Doxepin 6mg (283) Placebo (282) *Single dose	565	LPS (sTST at Week 1)

*Key secondary variable

4.2 General Discussions

4.2.1 Phase I Studies

Phase I Studies are summarized below:

SP-0405 is a randomized, four-way crossover, open-label, single dose, PK (bioequivalence) study in 16 healthy adult male subjects aged 18-45 years old. There are two stages with four treatment periods in the study for the following two *objectives*.

- Stage I (Treatment Period 1 and 2): *To assess the bioequivalence of 6mg tablets and 6mg capsules*, subjects were randomly assigned to receive 6mg capsule (Treatment A) and 6mg tablets (Treatment B) in a crossover sequence of A/B or B/A.
- Stage II (Treatment Period 3 and 4): *To characterize the PK profile of Doxepin 1mg and 3mg*, subjects were randomly assigned to receive a 3mg capsule (Treatment C) and 1mg capsule (Treatment D) in crossover sequence of C/D or D/C.

Washout period between two Treatment Periods was six days; Washout period between two Stages was 13 days.

A total of 15 subjects completed study because one subject was discontinued due to tested positive for cocaine abuse. PK blood samples were drawn predose (0 hour), postdose 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours.

Safety evaluation includes reported adverse events (AEs), changes from baseline in physical examinations, electrocardiograms (ECGs), vital signs, and routine laboratory assessments (serum chemistry, hematology, and urinalysis).

SP-0504 is a randomized, two-way crossover, open-label, single dose study with two treatments, Treatment A (fasted) and Treatment B (fed). The *primary objective* is to *assess the effect of food on the PK profile of doxepin HCl in male and female healthy subjects of 18-45 years old*; the secondary objective is to assess safety and tolerability.

A total of 6 male and 10 female subjects were assigned randomly to receive one doxepin HCl 6mg tablet in a sequence of fed/fasted or fasted/fed in the morning – Fasting requires overnight for at least 10 hours prior to study drug administration and for 4 hours post dose. (Fluids were restricted from 1 hour predose to 1 hour postdose with the exception of 240 mL of water taken at the time of dosing.) Fed condition was achieved about 5 minutes after consuming a standardized high-fat, high-calorie breakfast.

After admitted to the study center on Day 0, subjects were given a dose of doxepin HCl 6mg on Day 1, and remained in the study center for 4 nights and 5 days for each treatment period. Since one subject withdrew consent for "personal reason" after Treatment B, only 15 subjects completed

the study. PK samples were collected predose (0 hour), and postdose 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 96 hours (that is up to 4 days). Another dose was given on Day 8 in a different status followed by the same procedures.

The safety and tolerability of doxepin were assessed with reported adverse events (AEs), changes from baseline in physical examinations, electrocardiograms (ECGs), vital signs, and laboratory results (serum chemistry, hematology, and urinalysis).

SP-0505 is an open label drug interaction study with fixed sequence of doxepin HCl 6mg tablets (Treatment A, reference) and the combination with cimetidine 300mg tablets (Treatment B, test) during two treatment periods (Treatment Period 1: Days 1-6; Treatment Period 2: Days 7- 14). The primary objective is to characterize the PK profile of doxepin when administered alone and in combination with cimetidine to healthy subjects. The secondary objective is to study PK of doxepin metabolite desmethyldoxepin (nordoxepin) under the same above treatments and the safety and tolerability of doxepin with such treatment combination.

A total of 9 male and 15 female subjects aged 18-45 years old were enrolled. Study drugs were given in the morning under fasted conditions on Day 1 and then Day 8: On Day 1, all subjects were given doxepin 6mg; On Day 8, subjects received the combination of one dose of doxepin and five doses of cimetidine (two doses on the day before, one dose during, and two doses after doxepin administration). PK samples were collected predose (0 hour), postdose 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 96 hours. The samples were analyzed for doxepin and nordoxepin plasma concentrations (at all timepoints for both Treatment Periods) and for cimetidine plasma concentrations (from 0 through 24 hours postdose following administration of Treatment B during Treatment Period 2).

Evaluation of safety and tolerability of doxepin (administered alone and coadministered with cimetidine) included reported adverse events (AEs), changes from baseline in physical examinations, electrocardiograms (ECGs), vital signs, and laboratory results (hematology, serum chemistry, and urinalysis).

All completed the study treatments except two following subjects: One withdrew from the study during Treatment Period 1 prior to the 36 hour blood draw and another withdrew at the beginning of Treatment Period 2 check-in. (See Section 6.4.5 Drug-Drug Interaction for more details.)

SP-0506 is a single-blind, double dummy drug interaction study with fixed sequence of three treatments: Doxepin HCl with sertraline placebo (Treatment A), sertraline in combination with doxepin placebo (Treatment B), and doxepin with sertraline (Treatment C). Primary objective is to characterize PK and PD profile when doxepin was given alone.

A total of 24 male and female subjects of 18-45 years of age completed the study. On Day 1 (Treatment Period 1), subjects received Treatment A in the morning under fasted conditions. On Days 8–13, subjects returned to the clinic each morning and receive Treatment B, also under fasted

conditions. On the evening of Day 13 (Treatment Period 2), subjects returned and stayed inpatient to receive Treatment B again on Day 14. On Day 15, subjects receive Treatment C.

PK samples were collected at predose (0 hour), postdose 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 96 hours following administration of Treatment A and Treatment C (for doxepin and nordoxepin), and predose (0 hour), postdose 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose following administration of Treatment B and Treatment C (for sertraline).

PD evaluation consists measures of sedation (Digit Symbol Substitution Test [DSST], Symbol Copying Test [SCT], and Visual Analogue Scale [VAS] ratings of sleepiness) were conducted predose (0 hour), and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose following administration of Treatment A (Day 1), Treatment B (Day 14), and Treatment C (Day 15).

The safety and tolerability were assessed by the evaluation of reported adverse events (AEs) and changes from baseline in physical examinations, electrocardiograms (ECGs), vital signs, and laboratory results (hematology, serum chemistry, and urinalysis) throughout the study. (See Section 6.4.5 Drug-Drug Interaction for more details.)

SP-0507 is a randomized, open-label, two-way crossover study with two treatments: Treatment A (doxepin 6mg tablets, test) and Treatment B (Sinequan 50mg capsule, reference). All does were administered in the morning under fasted conditions. The primary goal is to obtain relative bioequivalence of doxepin 6 mg tablets compared to Sinequan® 50 mg capsules in healthy subjects.

A total of 24 healthy male (19) and female (5) adults of age 18-45 years of age were assigned to receive treatment sequence of A/B or B/A. Subjects were admitted to the study center the evening before each drug administration day (Day 0 and Day 9) and remained at the center for approximately 5 days and 4 nights. There is a nine-day washout period in-between treatments.

PK samples were collected predose (0 hour), postdose 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 96 hours following each drug administration for plasma concentrations of doxepin and its primary metabolite, desmethyldoxepin (nordoxepin).

Assessment of safety and tolerability of doxepin was conducted with reported adverse events (AEs) and changes from baseline in physical examinations, electrocardiograms (ECGs), vital signs, and laboratory results (hematology, serum chemistry, and urinalysis) throughout the study. Since Phase II and III studies are efficacy studies. They will be described in detail in Efficacy section.

4.2.2 Phase II Studies

The Phase II studies are no more than 2 nights and since the proposed efficacy are basically covered by Phase III studies, the Phase II studies will be summarized as follows. Statistics will be discussed more in depth in Agency Statistician, Dr. Tristan Messie's Review. Safety will be included in Section 6 Review of Safety.

SP-0401 is a randomized, double-blind, placebo-controlled, 4-period crossover study with three doxepin dose groups (1, 3, and 6mg) and one placebo group.

The primary objective was to evaluate the sleep maintenance effects of the three doses of doxepin HCl relative to placebo in adult patients ≤ 65 years old with primary insomnia. The main secondary objectives were 1) to assess the safety and tolerability of doxepin, 2) to examine the dose response effect of the three doses of doxepin on objective and subjective measures of sleep and conclude minimum effective dose.

Subjects: Male and/or female patients, aged 18 to 64 years, in good general health with at least a 3-month history of DSM-IV- defined primary insomnia, reporting each of the following on 4/7 nights prior to PSG Screening: ≤6.5 hours of total sleep time, ≥60 minutes of wakefulness after sleep onset and ≥20 minutes of latency to sleep onset. Additionally, entry criteria during the Screening PSG Period include: Wake Time During Sleep (WTDS) ≥60 minutes with no PSG Screening night <45 minutes, Total Sleep Time (TST) >240 minutes but ≤ 410 minutes on both PSG Screening nights, Latency to Persistent Sleep (LPS) ≥10 minutes on both PSG Screening nights, <10 periodic limb movements with arousal per hour of sleep on the first PSG Screening night, and <10 apnea/hypopneas per hour of sleep on the first PSG Screening night.

Method: A total of 76 male and female adult patients who met the inclusion criteria were randomized and received study drug. Each patient was expected to participate in four Treatment Periods. Each Treatment Period had two consecutive nights of study drug dosing separated by a 5- or 12-day drug-free interval.

After receiving single-blind placebo for two consecutive nights during the PSG Screening Period, patients were given double-blind study drug for two consecutive nights during each of the four Treatment Periods. Following each study drug administration, patients had eight continuous hours of PSG recording in the sleep center. A 5- or 12- day study drug free interval separated each PSG assessment visit. Efficacy assessments were made at each visit and safety assessments were performed throughout the study to a treatment sequence using a Latin square design.

The primary efficacy assessment was WTDS. Secondary efficacy assessments included Wake After Sleep Onset (WASO), Sleep Efficiency (SE), TST, LPS, and numerous others. All objective efficacy assessments were performed on Night 1 and Night 2, and all subjective assessments were reported on Day 2 and Day 3 of each Treatment Period (or Early Termination, if applicable).

Main Efficacy Results:
Primary: WTDS was significantly decreased at the doxepin 3 mg ($p<0.0001$) and 6 mg ($p=0.0002$) dose levels compared with placebo. WTDS was numerically but not significantly decreased at the doxepin 1 mg dose level.

Secondary: WASO was significantly decreased at the doxepin 1 mg ($p=0.0130$), 3 mg ($p<0.0001$), and 6 mg ($p<0.0001$) dose levels compared with placebo. SE was significantly increased at all three dose levels of doxepin (1 mg, $p=0.0004$; 3 mg, $p<0.0001$; 6 mg, $p<0.0001$) compared with placebo.

TST was significantly increased for all three dose levels of doxepin (1 mg, $p=0.0004$; 3 mg, $p<0.0001$; and 6 mg, $p<0.0001$) compared with placebo. Although there were no significant differences between doxepin and placebo at any dose level for LPS, LPS was numerically decreased, most notably at the 6 mg dose level. WTAS was significantly reduced at the doxepin 6 mg dose level ($p=0.0105$) compared with placebo.

SP-0402 is a similar study to SP-0401 except it was done in elderly patients of 65 years old and above.

Subjects: Male and/or female patients, aged 65 years or older, in good general health with essentially the same DSM-IV diagnostic criteria and PSG screening criteria as those in SP-0401, except periodic limb movements with arousal should be <15 per hour of sleep on the first PSG Screening night, and apnea/hypopneas should be <15 per hour of sleep on the first PSG Screening night.

Method: The primary efficacy assessment was WTDS. Secondary efficacy assessments were Wake After Sleep Onset (WASO), Sleep Efficiency (SE), TST, LPS, as well as the subjective assessments of latency to sleep onset (LSO), subjective total sleep time (sTST), subjective wake after sleep onset (sWASO), and among others. All objective efficacy assessments were performed on Night 1 and Night 2, and all subjective assessments were reported on Day 2 and Day 3 of each Treatment Period (or Early Termination, if applicable).

Main Efficacy Results:
Primary: WTDS was statistically significantly decreased at the doxepin 1 mg ($p=0.0001$), 3 mg ($p<0.0001$) and 6 mg ($p<0.0001$) dose levels compared with placebo in the PP analysis set. The results using the ITT analysis set were consistent with those from the PP analysis set.

Secondary: WASO was statistically significantly decreased at the doxepin 1 mg ($p<0.0001$), 3 mg ($p<0.0001$), and 6 mg ($p<0.0001$) dose levels compared with placebo. SE was statistically significantly increased at all three dose levels of doxepin (1 mg, $p<0.0001$; 3 mg, $p<0.0001$; 6 mg, $p<0.0001$) compared with placebo. TST was statistically significantly increased for all three dose levels of doxepin (1 mg, $p<0.0001$; 3 mg, $p<0.0001$; and 6 mg, $p<0.0001$) compared with placebo.

LPS was numerically decreased at the 3 mg and 6 mg dose levels. WTAS was statistically significantly reduced at the doxepin 3 mg (p=0.0264) and 6 mg (p=0.0008) dose levels and numerically reduced at the doxepin 1 mg dose level, all compared with placebo.

4.2.3 Phase III Studies

Below are descriptions of Phase III study designs. They will be reviewed in detail for efficacy in Section 5 Review of Efficacy and for safety in Section 6 Review of Safety.

Table 12. Descriptions of Phase III Studies

SP-0501	A Phase III, randomized, placebo-controlled, parallel group, multi-center, study to assess the efficacy and safety of Doxepin HCl in primary insomnia patients with *sleep maintenance difficulties*
SP-0503	A Phase III, randomized, double blind, placebo-controlled, parallel-group, multi-center, study to assess the long term efficacy and safety of doxepin HCl in primary elderly insomnia patients with sleep maintenance difficulties
SP-0509	A Phase III, randomized, double-blind, placebo controlled, parallel-group, multicenter outpatient study to assess the efficacy and safety of Doxepin HCl in elderly patients with *primary sleep maintenance insomnia*
SP-0502	A Phase III, randomized, double-blind, placebo controlled, parallel-group multicenter study to assess the efficacy and safety of Doxepin for the treatment of *transient insomnia* in adults

4.3 Review Strategy

The Phase 3 studies will be reviewed individually for clinical efficacy. Main efficacy results will be based on the three long term studies: SP-0501, SP-0503, and SP-0509. Short term Phase 3 study SP – 0502 will be reviewed as part of efficacy.

All eleven studies are included for review of safety (please see review methods in Safety section). Common adverse events will be mainly based on the three long term studies as well.

5 Review of Efficacy

5.1 Study 501 – A Phase III, randomized, double blind, placebo-controlled, parallel group, multi-center study to assess the efficacy and safety of Doxepin HCl in primary insomnia patients with sleep maintenance difficulties

5.1.1 Method

Study design: The subjects were randomized into three treatment groups in a 1:1:1 ratio, which is placebo (72), doxepin 3mg (75), doxepin 6mg (73). The doses were fixed. The duration of double

blind treatment was 35 nights. There were a total of 7 visits from Screening to Final Study Day or Early Termination. Subjects recorded their usual bedtime in a sleep diary between Visit 1 (Screening) and Visit 2 (Nights -13 and -12, PSG Screening) as instructed, from which each subject's median bedtime was determined according to the 7 consecutive nights before Visit 2.

PSG recordings were conducted as part of the screening, 3 times during double blind treatment period (up to Night 29, see below "Double-blind Treatment"), and during the two nights after discontinuation of study drug. Each began at individual subject's median bedtime, approximately 30 minutes postdose, and included continuous 8-hour recordings for two consecutive nights.

- Initial Screening

Initial screening visit (Visit 1) can be any time between Day -27 to -14. If indicated, a seven-day medication washout was pursued during this period.

- PSG Screening

During Visit 2 (Nights -13 and -12) and Visit 3 (Nights -6 and -5), subjects began a single-blind placebo treatment which lasted for up to two weeks (Nights -13 to 0), if eligible for subsequent steps of the study, and participated in two consecutive nights of 8-hour continuous PSG recording each time.

- Baseline

After Visit 3, those who remained eligible for study entry were randomly assigned to one of three treatment groups (placebo, doxepin 3 mg, or doxepin 6 mg).

- Double-blind Treatment

From Visit 4 (double-blind treatment period, which includes Visits 4-6, Nights 1-35), subjects began 35 consecutive nights of treatment. During each scheduled study visit (Visits 4-6, that are Nights 1-2, Nights 15-16, and Nights 29-30), subjects were given a single dose of study drug with 100 mL of water approximately 30 minutes prior to their median bedtime and participated in two consecutive nights of continuous 8-hour PSG recordings in the sleep center. After completing each study visit, subjects were dispensed double-blind study drug and instructed to self-administer study drug with 100 mL of water 30 minutes before bedtime when dosing at home (Nights 3-14; Nights 17- 28; and Nights 31-35). According to the sponsor's response to biopharmaceutical reviewer, there was no specific instruction on timing of food consumption at home.

- Discontinuation Period

During Visit 7 (Nights 36 and 37), subjects received single-blind placebo for two consecutive nights and underwent continuous 8-hour PSG recordings to assess rebound insomnia. Symptoms of withdrawal were assessed using Tyrer's Symptom Checklist (previously known as the Benzodiazepine Withdrawal Symptom Questionnaire). Subjects were discharged from the sleep center on Day 38 (or upon early termination) after completion of all final study-related assessments.

Subjects: A total of 229 male and female subjects of age 18 – 64 years old were randomized.

- Main selection criteria were:
    1. At least a 3-month history of primary insomnia (as defined in DSM-IV-TR)
    2. Reported experiencing the following:

    1) ≥60 minutes of Wake After Sleep Onset (WASO),
    2) ≥20 minutes of Latency to Sleep Onset (LSO), and
    3) ≤6.5 hours of Total Sleep Time (TST) on at least 4 of 7 consecutive nights prior to PSG Screening.

- Major exclusion criteria included following history and conditions:
    1. Had used any investigational drug within 30 days or five half-lives (whichever is longer) prior to Visit 1, or planned to use any other investigational drug during the study.
    2. Were using any of the following medications that could not be discontinued for the purpose of study entry (with the exception of sleep aids, which may have been discontinued at Visit 1): anxiolytics; antidepressants; anticonvulsants; antipsychotics; appetite suppressants; barbiturates; histamine-1 receptor antagonists except for loratadine, desloratidine and fexofenadine; narcotic analgesics; cytochrome P450 (CYP450) 2D6 inhibitors; sedative-hypnotics (other than study drug) or sleep aids (may be discontinued at Visit 1); systemic corticosteroids; theophylline; respiratory stimulants and decongestants; and other drugs known to inhibit doxepin metabolism.
    3. Had symptoms consistent with the diagnosis of any sleep disorder other than primary insomnia (e.g., sleep apnea, narcolepsy, periodic leg movements, and restless leg syndrome).
    4. Had insomnia associated with circadian rhythm disturbances, such as night or rotating shift work or travel across more than four time zones during the 14 days before Visit 1 or during the study.
    5. Had a self-reported intentional napping more than twice per week.
    6. Had a variation in bedtime of more than 2 hours on 5 of 7 consecutive nights as recorded on the sleep diary (maintained for 7 nights immediately prior to PSG Screening [Visit 2]).

- PSG screening criteria for entering double blind treatment are as follows:
    1. Mean WTDS of ≥ 60 minutes from two PSG screening nights, with no night <45 minutes.
    2. Total sleep time (TST) >240 minutes and ≤ 400 minutes on both PSG screening nights.
    3. Latency to persistent sleep (LPS) >10 minutes on both PSG screening nights.
    4. On Night -13, <10 periodic limb movements with arousal per hour of sleep and <10 apnea/hypopneas per hour of sleep.

Concomitant Use of Medications:

The sponsor reports that certain medications (see Exclusion Criteria #2) were strictly prohibited from Visit 1 through the Final Study Day.
Caffeine-containing products were prohibited 6 hours before admission to the study center. Alcohol was prohibited on the day of admission; it was limited to two beverages per day and not within 4 hours of bedtime at home. Fewer than 15 cigarettes or nicotine equivalent was allowed during the study but the usual sleep period.

Protocol deviations: Does not appear to affect efficacy in significant way.

5.1.2 Demographics and Other Disease Characteristics at Baseline

Subject demographic data at baseline are summarized in the following table by the sponsor.

Table 13. Subject Demographics at Baseline: Safety Analysis Set (SP0501)

Variable/Category	Placebo (N=73)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)	Total (N=221)
Age (years)				
Mean (SD)	43.6 (12.31)	45.5 (10.56)	44.2 (11.05)	44.5 (11.30)
Range	(18–64)	(20–64)	(19–63)	(18–64)
Sex [n (%)]				
Male	22 (30%)	17 (23%)	21 (29%)	60 (27%)
Female	51 (70%)	58 (77%)	52 (71%)	161 (73%)
Race/Ethnicity [n (%)]				
White	35 (48%)	33 (44%)	39 (53%)	107 (48%)
Black/African American	25 (34%)	26 (35%)	21 (29%)	72 (33%)
Hispanic	11 (15%)	15 (20%)	10 (14%)	36 (16%)
Asian	1 (1%)	1 (1%)	0 (0%)	2 (1%)
Other	1 (1%)	0 (0%)	3 (4%)	4 (2%)
Weight (kg)				
Mean (SD)	74.4 (13.93)	77.5 (14.54)	77.8 (15.35)	76.6 (14.63)
Range	(52–106)	(47–117)	(51–119)	(47–119)
BMI (kg/m^2)				
Mean (SD)	26.4 (4.54)	27.8 (4.94)	27.4 (4.14)	27.2 (4.57)
Range	(18.2–40.6)	(19.1–41.5)	(19.2–38.0)	(18.2–41.5)

Concurrent Conditions: The sponsor reports that the most common medical history involved a psychiatric condition (62% of subjects), and most of these cases were primary insomnia. "However, recording of the study indication within the Psychiatric category was inconsistent across study centers."

5.1.3 Patient Disposition

A total of 221 of the 229 subjects received the double blind treatment, but only 203 (89%) completed the study.

The most common reason for dropout was noncompliance, 3 (4%) in doxepin 6mg group and placebo group; 2 (3%) in doxepin 3mg group. They were participating in this study at more than one study center. Other reasons included adverse events (also 3%) that were more common in doxepin high dose group. Withdrawing consent and protocol violation were other reasons for dropout.

5.1.4 Analysis and Results

Statistic Method

The Agency provided guidance regarding how the Type 1 error rate should be controlled and suggested the sponsor following a closed-system step-down procedure for interpreting the study results. The system specifies a single comparison at each level (see below), starting with the comparison of the doxepin 6 mg and placebo groups with respect to the primary variable (WASO on Night 1). If the resulting p-value was ≤0.05, the next comparison was to be made, until a non-significant p-value was reached.

- WASO on Night 1 and then Night 29
- LPS on Night 1 and then Night 29
- sTST on Night 1 and then Night 29
- LSO on Night 1 and then Night 29

Only those shown statistically significant differences in the higher dose group were compared for doxepin 3 mg and placebo groups.

Missing data were imputed for LOCF. Pair wise comparisons of each active doxepin treatment group, 3 mg and 6 mg, versus placebo were performed within the context of the ANCOVA model using linear contrasts.

Objective Variables for Sleep Maintenance

The sponsor defined Primary Efficacy Variable as objective WASO on Night 1.

Additional Objective Variables defined by the sponsor are: Wake Time During Sleep (WTDS), TST, Sleep Efficiency (SE) overall, SE by third of the night, SE in the last quarter of the night, SE by hour of the night, Latency to Persistent Sleep (LPS), latency to Stage 2 sleep, Number of Awakenings After Sleep Onset (NAASO), NAASO by hour of the night, Total Wake Time (TWT), TWT by hour of the night, Wake Time After Sleep (WTAS), and sleep architecture

(including percentage and minutes of Stage 1, 2, and 3-4 sleep; percentage and minutes of rapid eye movement [REM] and non-REM sleep; and latency to REM sleep).

Team meeting discussion concluded that oWASO of last PSG will be considered as objective primary variable for sleep maintenance and LPS of last PSG will be considered as objective primary variable for sleep initiation.

- Objective WASO

The table below is provided by the sponsor that shows oWASO results of SP-0501.

Statistically significant improvement was seen from the first night to the end of the study (1 month) at both dose levels. At the end of the month, the result of 6mg group appears more significant than that of 3mg group.

Table 14. Objective WASO at Baseline, Night 1, Night 15, and Night 29: (*LOCF)*
(Provided by the sponsor)

WASO (minutes)	Placebo (N=73)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
Baseline (Mean of Nights -6 and -5)			
Mean (SD)	65.7 (36.78)	67.8 (33.56)	65.0 (33.23)
Median (Range)	62.5 (7.0–193.0)	65.3 (9.3–167.5)	58.8 (2.5–178.0)
Night 1 (Visit 4)			
Mean (SD)	66.8 (49.93)	41.4 (31.51)	36.3 (26.14)
Median (Range)	55.5 (6.5–292.5)	32.5 (3.5–175.5)	29.5 (3.0–126.5)
Diff. of LS Mean (Std. Err.)		-26.0 (5.15)	-30.9 (5.17)
95% CI of LS Mean Diff.		(-36.2, -15.9)	(-41.1, -20.7)
p-value[1]		p<0.0001	p<0.0001
Night 15 (Visit 5)			
Mean (SD)	60.5 (51.90)	44.7 (29.24)	41.7 (29.38)
Median (Range)	45.5 (5.0–300.0)	40.0 (2.0–144.0)	34.5 (3.0–137.5)
Diff. of LS Mean (SE)		-16.9 (5.52)	-18.7 (5.55)
95% CI of LS Mean Diff.		(-27.8, -6.0)	(-29.6, -7.8)
p-value[1]		p=0.0025	p=0.0009
Night 29 (Visit 6)			
Mean (SD)	60.5 (38.75)	47.2 (43.48)	40.7 (37.26)
Median (Range)	51.5 (11.5–171.0)	41.0 (1.5–318.5)	25.0 (5.5–208.0)
Diff. of LS Mean (Std. Err.)		-13.8 (6.09)	-20.7 (6.12)
95% CI of LS Mean Diff.		(-25.8, -1.8)	(-32.8, -8.6)
p-value[1]		p=0.0248	p=0.0009

- Latency Persistent Sleep (LPS)

Table 15 is the result of LPS of SP-0501 provided by the sponsor.

LPS improvement is seen in both doxepin groups compared to placebo on the first night but not afterwards. Thus, it doesn't support objective measure for sleep initiation claim.

Table 15. LPS at Baseline, Night 1, Night 15, and Night 29 (LOCF Method): Post-hoc ITT Analysis of SP-0501

LPS (minutes)	Placebo (N=73)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
Baseline (Mean of Nights -6 and -5)			
Mean (SD)	37.9 (28.38)	35.9 (29.84)	39.1 (34.10)
Geometric Mean	27.6	27.4	25.9
Median (Range)	31.5 (1.8–146.5)	26.8 (5.0–191.5)	30.3 (1.5–194.8)
Night 1 (Visit 4)			
Mean (SD)	44.8 (54.56)	26.7 (23.42)	27.1 (25.42)
Median (Range)	29.0 (2.5–394.0)	17.5 (2.5–103.5)	19.5 (0.5–163.5)
Geometric LS Mean[1]	27.0	18.1	16.7
LS Mean Ratio		0.7	0.6
95% CI of LS Mean Ratio		(0.5, 0.9)	(0.5, 0.8)
p-value[2]		p=0.0047	p=0.0007
Night 15 (Visit 5)			
Mean (SD)	34.0 (39.04)	38.0 (39.61)	31.7 (35.87)
Median (Range)	22.5 (2.0–237.0)	22.5 (1.0–256.0)	17.5 (0.5–170.0)
Geometric LS Mean[1]	20.2	23.7	17.8
LS Mean Ratio		1.2	0.9
95% CI of LS Mean Ratio		(0.9, 1.6)	(0.6, 1.2)
p-value[2]		p=0.3105	p=0.4309
Night 29 (Visit 6)			
Mean (SD)	32.0 (35.32)	28.5 (26.01)	24.6 (21.09)
Median (Range)	17.0 (0.5–204.0)	21.0 (0.5–130.5)	18.5 (1.0–81.0)
Geometric LS Mean[1]	17.8	18.5	16.2
LS Mean Ratio		1.0	0.9
95% CI of LS Mean Ratio		(0.8, 1.4)	(0.7, 1.2)
p-value[2]		p=0.7916	p=0.5622

[1] Analysis was performed on log-transformed data. LS mean values were converted to original scale by taking the anti-log.

[2] p-value comparing each active treatment versus placebo was determined from an ANCOVA model that included main effects for treatment and center with the baseline value as a covariate.

Subjective Variables for Sleep Maintenance

The sponsor also included the following Subjective Variables: Subjective TST (sTST), subjective WASO (sWASO), LSO, subjective NAASO (sNAASO), and sleep quality. They were assessed using a questionnaire completed in the *morning* about one hour after each PSG recording completion. Of note, drowsiness, ability to function, and total nap time during the day were assessed using an *evening* questionnaire completed on Night 2, Night 16, and Night 30.
Other secondary subjective efficacy variables included the 2-item Clinical Global Impressions (CGI) scale for severity of illness and therapeutic effect completed by a clinician; the 5-item CGI scale pertaining to therapeutic effect completed by the subject; the Insomnia Severity Index (ISI) completed by the subject; and a subjective assessment of average nightly total sleep time over the past 5 days following administration of the study drug at home.

Team meeting discussion concluded that sWASO will be considered as subjective primary variable for sleep maintenance; LSO will be considered as subjective primary variable for sleep initiation.

- **sWASO and sTST**

Table 16 is provided by the sponsor for both sTST and sWASO results.

Table 16. Total Sleep Time and sWASO of SP-0501

Variable Using the Morning Questionnaire	Placebo (N=72)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
sTST (minutes)	n=72	n=75	n=73
Baseline (Mean of Days -5 and -4) (SD)	341.2 (52.20)	330.0 (63.23)	339.3 (61.45)
Day 2 (Visit 4)	n=72	n=75	n=73
Mean (SD)	348.3 (70.03)	361.8 (64.03)	369.0 (78.39)
p-value[1]		p=0.0169	p=0.0256
Day 16 (Visit 5)	n=70	n=69	n=70
Mean (SD)	353.6 (85.25)	361.0 (67.22)	371.5 (72.06)
p-value[1]		p=0.3260	p=0.1611
Day 30 (Visit 6)	n=68	n=69	n=69
Mean (SD)	365.2 (68.23)	360.7 (68.72)	373.0 (75.30)
p-value[1]		p=0.9972	p=0.6831
sWASO (minutes)	n=72	n=75	n=73
Baseline (Mean of Days -5 and -4) (SD)	74.6 (39.74)	80.6 (48.12)	78.2 (43.06)
Day 2 (Visit 4)	n=71	n=75	n=73
Mean (SD)	72.5 (45.91)	55.7 (39.81)	54.9 (44.76)
p-value[1]		p=0.0005	p=0.0007
Day 16 (Visit 5)	n=70	n=69	n=70
Mean (SD)	66.9 (59.65)	59.0 (54.14)	58.4 (49.09)
p-value[1]		p=0.2582	p=0.3357
Day 30 (Visit 6)	n=68	n=69	n=69
Mean (SD)	59.6 (43.21)	63.1 (47.24)	58.2 (53.07)
p-value[1]		p=0.8958	p=0.8020

At neither doses, sWASO improvement was significant on Day 30, though at both doses, sWASO was significantly improved on Day 2. The results of sTST are the same.

- Latency Sleep Onset

  Table 17 presents the result of LSO in SP-0501.

Table 17. Subjective Sleep Variables LSO at Baseline, Day 2, Day 16, and Day 30: Post-hoc ITT Analysis Set

Variable Using the Morning Questionnaire	Placebo (N=72)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
LSO (minutes)[1]	n=72	n=75	n=73
Baseline (Mean of Days -5 and -4) (SD)	54.7 (30.52)	61.4 (39.43)	64.0 (43.45)
Day 2 (Visit 4)	n=72	n=75	n=73
Mean (SD)	56.4 (46.66)	50.3 (36.73)	55.7 (56.96)
p-value[2]		p=0.2296	p=0.0960
Day 16 (Visit 5)	n=70	n=69	n=70
Mean (SD)	55.1 (62.42)	52.9 (35.17)	48.7 (42.35)
p-value[2]		p=0.9838	p=0.2689
Day 30 (Visit 6)	n=68	n=69	n=68
Mean (SD)	44.1 (41.26)	48.9 (34.71)	48.3 (47.40)
p-value[2]		p=0.3567	p=0.8242

No statistically significance is seen with LSO results on any night.

The Agency Statistician Tristan Messie, PhD summarizes his finding and analysis in Table 18.

Dr. Messie concludes the following: Since the Division's recommended approach was to start with the high dose at the latest time and work to the first time, first for oWASO, then for sWASO, LPS, and finally for LSO, if an intermediate test is not significant at 0.05 then no further testing of this sequence of tests should be done in order to control the experiment wise type I error at 0.05.

- Objective WASO was generally significantly reduced at each time for both 6 mg and 3mg as compared to placebo.

- Subjective WASO was not significantly reduced on the first nights (sponsor designated as primary) of Visit 6 and Visit 5 for the 6 mg group vs. placebo. However, if we look at the 2nd night of each visit or the average of nights 1 and 2 then subjective WASO appears to be significantly reduced for the 6 mg group as compared to placebo.

- Objective LPS was only significant at Visit 4 and even that was not consistent over both nights. So, it is not clear that there is an effect on objective LPS beyond the first night of application of the drug. The same was true for the subjective LSO and since it is lower in the testing hierarchy no claims on LSO should be possible.

Table 18. Results for 1st Night, 2nd Night, and Average of Two at Each Visit SP-0501 (OC Analysis Set)

			p-value for comparison with placebo		
Endpoint	Group	Night of Visit	Visit 6 (Night 29,30)	Visit 5 (Night 15,16)	Visit 4 (Night 1,2)
oWASO	6 mg	1st	0.001	0.001	<0.001
		2nd	<0.001	0.001	<0.001
		Avg	<0.001	<0.001	<0.001
	3 mg	1st	0.017	0.003	<0.001
		2nd	0.002	0.001	0.006
		Avg	0.001	<0.001	<0.001
sWASO	6 mg	1st	0.628	0.202	<0.001
		2nd	0.001	0.042	0.009
		Avg	0.020	0.042	<0.001
	3 mg	1st	0.648	0.151	<0.001
		2nd	0.059	0.248	0.257
		Avg	0.343	0.103	0.005
oLPS	6 mg	1st	0.864	0.592	0.001
		2nd	0.322	0.747	0.183
		Avg	0.487	0.841	0.007
	3 mg	1st	0.800	0.227	0.006
		2nd	0.699*	0.157*	0.282
		Avg	0.557*	0.051*	0.010
sLSO	6 mg	1st	0.651*	0.145	0.049
		2nd	0.763	0.452	0.809*
		Avg	0.699*	0.069	0.284
	3 mg	1st	0.237	0.907*	0.126
		2nd	0.518	0.649*	0.820
		Avg	0.334*	0.944*	0.187

*sign of t-statistic favors placebo

In summary, using Dr. Messie's analysis, this study does not support the claim for sleep maintenance or sleep initiation.

5.2 Study 503 – A Phase III, randomized, double blind, placebo-controlled, parallel group, multi-center study to assess the long term efficacy and safety of Doxepin HCl in primary elderly insomnia patients with sleep maintenance difficulties

5.2.1 Method

Study design: Similar to Study 501, the subjects were randomized into three treatment groups in a 1:1:1 ratio, which is placebo (81), but doxepin 1mg (77), doxepin 3mg (82). The doses were fixed. The duration of double blind treatment was up to 85 nights. There were also a total of 7 visits from Screening to Final Study Day or Early Termination but each visit during double blind treatment involved only one night stay. Subjects recorded their usual bedtime in a sleep diary between Visit 1 (Screening) and Visit 2 (Nights -6 and -5, PSG Screening) as instructed, from which each subject's median bedtime was determined according to the 7 consecutive nights before Visit 2.

PSG recordings were conducted as part of the screening and 5 times during double blind treatment period (up to Night 85, see below "Double-blind Treatment").

Subjective efficacy assessments were provided by the subjects through the Interactive Voice Response System (IVRS) from home starting on Day 0 and every 7 days thereafter.

- Initial Screening

Initial screening visit (Visit 1) can be any time between Day -27 to -14. If indicated, a seven-day medication washout was pursued during this period.

- PSG Screening

During Visit 2 (Nights -6 and -5), subjects began a single-blind placebo treatment which could last for one week (Nights -6 to 0), if eligible for subsequent steps of the study, and continued to take single-blind placebo for 5 consecutive nights at home (Nights -4 through 0).

- Baseline

After Visit 3, those who remained eligible for study entry were randomly assigned to one of three treatment groups (placebo, doxepin 1 mg, or doxepin 3 mg).

- Double-blind Treatment

From Visit 4 (double-blind treatment period, which includes Visits 4-6, Nights 1-85), subjects began 85 consecutive nights of treatment. During each scheduled study visit (Visits 3-7, that are Night 1, Night 15, Night 29, Night 57, and Night 85), subjects were given a single dose of study drug with 100 mL of water approximately 30 minutes prior to their median bedtime and participated in two consecutive nights of continuous 8-hour PSG recordings in the sleep center. After completing each study visit, subjects were dispensed double-blind study drug and instructed to self-administer study drug with 100 mL of water 30 minutes before bedtime when dosing at home (Nights 3-14; Nights 16- 28; Nights 30-56, and Nights 58-84). According to the sponsor's

response to biopharmaceutical reviewer, there was no specific instruction on timing of food consumption at home.

- Discontinuation Period

Subjects were discharged from the sleep center on Day 86 (or upon early termination) after completion of all final study-related assessments.

Subjects: A total of 240 male and female subjects, 65 years of age or older were randomized.

- Main selection criteria regarding to baseline insomnia were similar to Study 501:
    1. At least a 3-month history of primary insomnia (as defined in DSM-IV-TR)
    2. Reported experiencing the following:

    1) ≥60 minutes of Wake After Sleep Onset (WASO),
    2) ≥20 minutes of Latency to Sleep Onset (LSO), and
    3) ≤6.5 hours of Total Sleep Time (TST) on at least 4 of 7 consecutive nights prior to PSG Screening.
- Major exclusion criteria included following history and conditions:
    1. Were using any of the following medications that could not be discontinued for the purpose of study entry (with the exception of sleep aids, which may have been discontinued at Visit 1): anxiolytics; antidepressants; anticonvulsants; antipsychotics; appetite suppressants; barbiturates; histamine-1 receptor antagonists except for loratadine, desloratidine and fexofenadine; narcotic analgesics; cytochrome P450 (CYP450) 2D6 inhibitors; sedative-hypnotics (other than study drug) or sleep aids (may be discontinued at Visit 1); systemic corticosteroids; theophylline; respiratory stimulants and decongestants; and other drugs known to inhibit doxepin metabolism.
    2. Had symptoms consistent with the diagnosis of any sleep disorder other than primary insomnia (e.g., sleep apnea, narcolepsy, periodic leg movements, and restless leg syndrome).
    3. Had insomnia associated with circadian rhythm disturbances, such as night or rotating shift work or travel across more than four time zones during the 14 days before Visit 1 or during the study.
    4. Had a self-reported intentional napping more than twice per week.
    5. Had a variation in bedtime of more than 2 hours on 5 of 7 consecutive nights as recorded on the sleep diary (maintained for 7 nights immediately prior to PSG Screening [Visit 2]).

- PSG screening criteria for entering double blind treatment are as follows:
    1. Mean WTDS of ≥ 60 minutes from two PSG screening nights,
    2. Total sleep time (TST) >240 minutes and ≤ 390 minutes on both PSG screening nights.
    3. Latency to persistent sleep (LPS) >10 minutes on both PSG screening nights.
    4. On Night -6, <15 periodic limb movements with arousal per hour of sleep and <15 apnea/hypopneas per hour of sleep.

Concomitant Use of Medications:
As in SP-0501, the sponsor reports that certain medications (see Exclusion Criteria #2) were strictly prohibited from Visit 1 through the Final Study Day:

Caffeine-containing products were prohibited 6 hours before any study visit in the sleep center. Alcohol was prohibited on the day of admission; it was limited to two beverages per day and not within 4 hours of bedtime at home. Fewer than 15 cigarettes or nicotine equivalent was allowed during the study but the usual sleep period.

Protocol deviations: Does not appear to affect efficacy in significant way.

5.2.2 Demographics and Other Disease Characteristics at Baseline

Subject demographic data at baseline are summarized in the following table by the sponsor.

Table 19. Subject Demographics at Baseline: Safety Analysis Set (SP-0503)

Variable/Category	Placebo (N=81)	Doxepin 1 mg (N=77)	Doxepin 3 mg (N=82)	Total (N=240)
Age (years)				
Mean (SD)	71.5 (5.50)	71.3 (5.23)	71.4 (4.88)	71.4 (5.19)
Range	65–93	64–85	65–88	64–93
Sex [n (%)]				
Male	33 (41%)	27 (35%)	25 (30%)	85 (35%)
Female	48 (59%)	50 (65%)	57 (70%)	155 (65%)
Race/Ethnicity [n (%)]				
White	67 (83%)	63 (82%)	63 (77%)	193 (80%)
Black/African American	6 (7%)	5 (6%)	10 (12%)	21 (9%)
Hispanic	4 (5%)	8 (10%)	9 (11%)	21 (9%)
Asian	1 (1%)	1 (1%)	0 (0%)	2 (1%)
Other	3 (4%)	0 (0%)	0 (0%)	3 (1%)
Weight (kg)				
Mean (SD)	78.8 (15.53)	75.5 (16.02)	75.5 (13.23)	76.6 (14.97)
Range	52–118	45–108	50–107	45–118
BMI (kg/m^2)				
Mean (SD)	28.0 (4.77)	27.5 (5.42)	27.1 (4.37)	27.5 (4.85)
Range	20.0–44.1	18.3–41.8	18.8–39.7	18.3–44.1

Concurrent Conditions: The most common cardiovascular history (68%), followed by renal-genitourinary history (61%), musculoskeletal history (60%), ENT history (50%), and among

others. Excluding insomnia as a psychiatric condition, only 2% had concurrent psychiatric diagnosis. Among the renal-genitourinary disorders, it is unclear how many had enlarged prostate or tendency of urinary retention. No concomitant medications taken seemed to have significant hypnotic or sedative effects.

5.2.3 Patient Disposition

All 240 patients randomized received double-blind treatment and 214 (89%) patients completed the study. The most common reasons for dropout were consent withdrawn (mostly in placebo group), adverse events (4% in placebo and doxepin 3mg group, 1% in doxepin 1mg group), and protocol violation (placebo 2%, doxepin 1mg 3% and doxepin 3mg 1%).

5.2.4 Analysis and Results

Statistic Method
The sponsor's main approach is as follows: "Primary analyses, based on the ITT Analysis Set, were performed for all efficacy variables using observed data. The ITT Analysis Set included all randomized subjects who received at least one dose of double-blind study drug. Analysis of covariance (ANCOVA) methods were used to compare the mean WASO values from PSG recordings obtained on Night 1 following administration of placebo, doxepin 1 mg, or doxepin 3 mg. The model included main effects for treatment and center with the baseline WASO value as a covariate. Each pair-wise comparison of doxepin to placebo was performed using a linear contrast. The same methods were used to analyze all other continuous efficacy variables."

"For LPS, latency to REM sleep, latency to Stage 2 sleep, and LSO, data were analyzed using log-transformed values (natural log). Analyses of WASO, LPS, and TST were performed to assess the response to treatment as defined by categorical levels of response. Descriptive statistics were presented for WASO at Night 1 by sex and by race/ethnicity. Scores obtained from the CGI scale for therapeutic effect (completed by both the clinician and the subject) were assessed categorically. Comparison of each doxepin group to placebo was conducted using the Cochran-Mantel-Haenszel chi-square (row mean score) test stratifying by center. The CGI scale for severity of illness and the ISI were analyzed using ANCOVA."

"Subjective efficacy data collected via the IVRS were analyzed using the same methods used to compare the inpatient efficacy variables using an ANCOVA model. Additional analyses on these data were performed with imputed missing baseline values using the overall population baseline mean. Sensitivity analyses with imputed missing data using the last observation carried forward (LOCF) method and the baseline observation carried forward (BOCF) method for the primary (WASO) and key secondary variables (WTDS, WTAS, TST, SE in Hour 8, SE in the last quarter, LPS, and sTST) were performed using the ITT Analysis Set. A sequential step-down procedure was implemented for WASO (Nights 1, 29, and 85), sTST (Day 2), LPS (Night 1), and SE in Hour 8 (Night 1). Comparison of doxepin 3 mg to placebo was conducted first. Comparison of doxepin 1 mg to placebo was made only for those comparisons that resulted in a statistically significant difference between doxepin 3 mg and placebo."

Primary Efficacy Variable was also defined as objective WASO on Night 1 (Night 3) and assessed at the 5% level of significance (two-sided), using a linear contrast within the context of the ANCOVA model to compare the mean WASO for the doxepin 3 mg group to placebo. If order of testing for statistical significance will be as follows:

- WASO at Visit 3
- WASO at Visit 5
- WASO at Visit 7
- sTST at Visit 3
- LPS at Visit 3
- SE in Hour 8 at Visit 3

Objective Variables for Sleep Maintenance

As in Study 501, division meeting discussion concluded that oWASO of the last PSG will be considered as objective primary variable for sleep maintenance and LPS of the last PSG will be considered as objective primary variable for sleep initiation.

The Agency Statistician Tristan Messie, PhD computed the following approaches for objective WASO (see Table 20 on next page).

Doxepin 3mg group shows superior to doxepin 1mg in all analyses; doxepin 1mg group showed marginal efficacy with LOCF approach at the end of the study and without efficacy during prior visits. OC and BOCF show the better efficacy results.

Table 20. Comparison of Results from various Imputation Methods for Missing objective WASO data (SP-0503) by Tristan Messie, Ph.D.

		PLACEBO		1 MG				3 MG			
Pop	Night	N	MEAN (S.D.)	N	MEAN (S.D.)	LS MEAN (S.E.) Difference from placebo	p-value	N	MEAN (S.D.)	LS MEAN (S.E.) Difference from placebo	p-value
OC	Baseline	81	119.5 (37.7)	77	120.1 (35.0)	0.9 (5.4)	0.867	82	117.9 (28.1)	-1.2 (5.3)	0.821
	1	81	108.9 (46.0)	77	91.8 (47.1)	-17.8 (6.3)	0.0053	82	74.5 (37.9)	-33.8 (6.2)	<0.0001
	15	78	107.1 (41.1)	74	100.8 (46.2)	-8.5 (6.5)	0.1945	80	91.0 (46.7)	-17.4 (6.4)	0.0069
	29	75	104.6 (53.5)	74	96.4 (45.3)	-10.8 (6.3)	0.0878	77	84.3 (40.9)	-22.1 (6.3)	0.0005
	57	71	100.8 (42.1)	71	94.0 (38.7)	-8.5 (6.1)	0.1662	75	83.0 (42.5)	-18.3 (6.0)	0.0029
	85	70	109.2 (50.8)	69	97.0 (44.2)	-14.6 (6.8)	0.0330	74	75.7 (37.5)	-33.2 (6.7)	<0.0001
LOCF	15	81	107.5 (42.2)	77	99.9 (46.0)	-8.0 (6.4)	0.209	82	90.2 (46.6)	-16.8 (6.3)	0.008
	29	81	105.0 (53.4)	77	95.7 (45.1)	-10.0 (6.4)	0.121	82	87.5 (45.1)	-16.9 (6.3)	0.008
	57	81	101.4 (42.4)	77	93.1 (39.5)	-8.5 (6.0)	0.155	82	86.1 (46.3)	-14.5 (5.9)	0.015
	85	81	107.4 (50.0)	77	95.0 (44.3)	-13.0 (6.5)	0.046	82	79.7 (42.5)	-26.5 (6.4)	<0.001
BOCF	15	81	109.5 (45.7)	77	101.4 (45.9)	-8.8 (6.3)	0.167	82	91.5 (46.3)	-17.5 (6.2)	0.005
	29	81	107.3 (56.0)	77	97.2 (45.1)	-11.1 (6.1)	0.071	82	86.4 (40.8)	-20.5 (6.0)	0.001
	57	81	105.6 (46.3)	77	95.6 (39.0)	-10.4 (5.8)	0.073	82	85.2 (41.9)	-19.8 (5.7)	0.001
	85	81	112.6 (52.2)	77	97.9 (43.5)	-15.3 (6.3)	0.015	82	78.7 (37.5)	-32.9 (6.2)	<0.001

Similarly, Dr. Messie computed two different analyses for object LPS and summarized in the following table.

Table 21. Objective Latency to Persistent Sleep by Night for OC and ITT-LOCF analyses (SP-0503) by Tristan Messie, PhD

POP-ULATION	TIME	PLACEBO			1 MG				3MG			
		N	MEAN of Log LSO (S.D.)	GEO-METRIC MEAN of LSO	N	MEAN of Log LSO (S.D.)	GEO-METRIC MEAN of LSO	p-value for diff from placebo	N	MEAN of Log LSO (S.D.)	GEO-METRIC MEAN of LSO	p-value for diff from placebo
OC	Night 1	81	3.39 (0.82)	29.7	77	3.42 (0.70)	30.6	0.5733	82	3.14 (0.67)	23.1	0.1079
	Night 15	78	3.43 (0.94)	30.9	74	3.43 (0.78)	30.8	0.8046	80	3.35 (0.84)	28.6	0.8388
	Night 30	75	3.24 (1.00)	25.4	74	3.46 (0.95)	31.7	0.1268	77	3.26 (0.96)	26.0	0.5422
	Night 57	71	3.14 (0.82)	23.2	71	3.28 (0.89)	26.7	0.1870	75	3.32 (0.76)	27.7	0.0522
	Night 85	70	3.10 (1.03)	22.2	69	3.01 (0.92)	20.4	0.6493	74	3.31 (0.81)	27.4	0.0286
LOCF	Night 15	81	3.42 (0.96)	30.6	77	3.42 (0.80)	30.6	0.7847	82	3.35 (0.83)	28.5	0.7795
	Night 30	81	3.26 (1.00)	26.0	77	3.45 (0.96)	31.4	0.1345	82	3.28 (0.96)	26.6	0.4453
	Night 57	81	3.20 (0.84)	24.6	77	3.34 (0.94)	28.1	0.2116	82	3.35 (0.76)	28.4	0.0822
	Night 85	81	3.15 (1.02)	23.4	77	3.06 (0.98)	21.4	0.7092	82	3.34 (0.81)	28.2	0.0386

Results from both approaches showed superiority of doxepin 3mg group on Night 85 but not on Night 1 or any other prior visits. Doxepin 1mg group shows no superiority to placebo during any visit.

Subjective Variables for Sleep Maintenance

The sponsor also included the following Subjective Variables: Subjective TST (sTST), subjective WASO (sWASO), LSO, subjective NAASO (sNAASO), and sleep quality. These variables were assessed using a questionnaire completed in the morning following each PSG recording night. Drowsiness, ability to function, and total nap time during the day were assessed using an evening questionnaire completed prior to PSG recording at Nights -6, -5, 1, 15, 29, 57, and 85.
Division meeting discussion also concluded that sWASO of last PSG will be considered as subjective primary variable for sleep maintenance; LSO will be considered as subjective primary variable for sleep initiation.

Similarly to the approach in Study 0501, Dr. Messie provides the following result from both OC and LOCF approaches.

Table 22. Comparison of Observed Case and ITT-LOCF results for subjective WASO by Night (SP-0503)

		PLACEBO		1 MG				3MG			
	Night	N	MEAN (S.D.)	N	MEAN (S.D.)	LS MEAN (S.E.) Difference from placebo	p-value	N	MEAN (S.D.)	LS MEAN (S.E.) Difference from placebo	p-value
OC	Night 1	78	89.0 (66.0)	74	84.4 (80.6)	-1.9 (10.2)	0.8497	82	62.1 (62.7)	-19.2 (10.0)	0.0561
	Night 15	76	87.8 (61.4)	72	86.7 (61.8)	-1.7 (9.4)	0.8571	78	67.9 (64.7)	-16.7 (9.3)	0.0729
	Night 29	75	92.6 (74.6)	73	73.5 (68.2)	-19.4 (10.0)	0.0531	77	68.0 (49.3)	-21.7 (9.9)	0.0296
	Night 57	69	78.0 (64.2)	70	78.1 (75.9)	3.4 (10.2)	0.7417	74	62.5 (47.9)	-5.9 (10.1)	0.5627
	Night 85	69	88.6 (62.9)	69	57.9 (61.1)	-29.7 (10.1)	0.0037	74	56.7 (64.3)	-24.5 (10.0)	0.0153
LOCF	Night 15	80	88.5 (60.6)	77	84.8 (60.8)	-0.7 (9.2)	0.9360	82	68.2 (63.8)	-14.8 (9.1)	0.1051
	Night 29	81	91.7 (72.8)	77	71.5 (67.2)	-17.1 (9.6)	0.0763	82	69.2 (49.7)	-17.2 (9.5)	0.0705
	Night 57	81	81.4 (71.8)	77	77.1 (74.5)	-0.9 (10.1)	0.9284	82	65.0 (48.5)	-10.4 (10.0)	0.3005
	Night 85	81	86.2 (60.5)	77	59.6 (60.4)	-23.5 (9.4)	0.0128	82	59.4 (63.5)	-21.4 (9.3)	0.0215

Note: A few patients had their first sWASO measurement at night 16 which explains how the sample size for LOCF at night 16 can be greater than for OC at Night 1

Both approaches show that doxepin 3mg group has superiority to placebo during most visits; doxepin 1mg only shows efficacy at the end of the study.

Based on the sponsor's pre-specified testing hierarchy, subjective LPS and sleep efficiency were not tested due to insignificant differences of sTST between doxepin 3mg and placebo on Night 1, the first time point.

In summary, from Dr. Messie's analysis, this study data doesn't appear to support the claim of sleep initiation or sleep maintenance in acute setting as with LOCF missing data management, sWASO didn't show positive result till the end of the study; Even with OC missing data management, sWASO didn't seem to be consistent over time (showed positive results on Night 29, but lost on Night 57, and regain on Night 85). This raises a practical question of its use in clinical setting. My opinion is that this should be regarded as a negative study.

5.3 Study 509 – A Phase III, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Outpatient Study to Assess the Efficacy and Safety of Doxepin HCl in Elderly Patients with Primary Sleep Maintenance Insomnia

5.3.1 Method

Study Design: Patients eligible for the study were randomized to one of two treatment groups in a 1:1 ratio (doxepin 6 mg or placebo) and entered the 4-week double-blind treatment period. The study basically involve the following periods:

- Screening (Visit 1)

Subjects were screened according to selection criteria and if eligible, they were asked to discontinue any cytochrome P450 (CYP450) 2D6 inhibitors, as well as medications taken at bedtime for sleep.

- Placebo Lead-in Period (beginning at Visit 2)

Subjects took single-blind placebo during each evening 1 hour before bed time for one-week. Subjects were instructed to contact an Interactive Voice Response System (IVRS) every morning to respond to subjective sleep assessment questions. The IVRS data were used to confirm study eligibility.

- Double-blind Treatment Period

From the evening of Visit 3 (Baseline), subjects started the 4-week double-blind treatment. subjects were instructed to take study drug each evening as a single oral dose 1 hour prior to bedtime. Additionally, subjects were instructed to contact the IVRS each morning to respond to daily subjective sleep assessment questions. Subjects returned to the study centers for outpatient visits at the end of each week (Weeks 1, 2, and 3) and received dosing instructions and double-blind study drug for one week.

Following the completion of the Double-blind Treatment Period, subjects were evaluated on the Final Study Day (Day 28 or Early Termination [ET]). Safety assessments were conducted throughout the study.

Subjects: A total of 32 of the 34 study centers randomized 255 subjects into the study.

Main inclusion criteria were:

1. Male and female patients, 65 years of age or older
2. With at least a 3-month history of primary insomnia as defined in DSM-IV-TR.
3. Daily IVRS responses recorded during the Placebo Lead-in Period.
4. At least a 3-month history of primary insomnia (as defined in DSM-IV-TR)
5. Reported experiencing the following on at least 4 of 7 consecutive nights for at least 3 months:
   1) ≥60 minutes of subjective Wake After Sleep Onset (WASO),

2) ≥45 minutes of Latency to Sleep Onset (LSO), and
3) ≤6.5 hours of Total Sleep Time (TST).

Subjects were eligible for randomization to double-blind treatment if they met each of the following criteria at Baseline (Visit 3):

- Reported ≥60 minutes of sWASO on at least 4 nights
- Reported ≥30 minutes of LSO on at least 4 nights
- Reported ≤6.5 hours of sTST on at least 4 nights
- Reported a variation in bedtime ≤2 hours

Subject exclusion criteria were:

1. A history of epilepsy or serious head injury
2. Used doxepin for any indication within 30 days prior to screening.
3. Inability to refrain from nicotine product during normal sleep hours
4. A history of alcohol or drug abuse or dependence with a year
5. Current sue of the following medications that can't be discontinued: Antipsychotics, appetite suppressants, systemic corticosteroids, theophylline, respiratory stimulants, or decongestants, anxiolytics, antidepressants, anticonvulsants, histamine-1 receptor antagonists (except loratadine, desloratadine, and fexofenadine), narcotic analgesics, sedative hypnotics (other than study drug), or OTC sleep aids (unless some of these are taken for the indication of sleep like sleep aids)
6. Current use of P450 2D6 inhibitors.
7. Had symptoms consistent with the diagnosis of any sleep disorder other than chronic (primary) insomnia (e.g., sleep apnea, narcolepsy, periodic leg movements, restless leg syndrome, etc.).

Concomitant medications: See exclusion criteria #5 and 6.

5.3.2 Demographics and Other Disease Characters at Baseline

Table 23 summarizes the baseline demographics provided by the sponsor.

Concurrent Conditions:

Renal-genitourinary disorders were the most common concurrent condition (70%), followed by musculoskeletal (67%), cardiovascular (66%), ENT (57%), and gastrointestinal (48%) histories. With insomnia per se as a psychiatric diagnosis, the sponsor didn't separate it from other psychiatric diagnosis. Thus, the psychiatric condition in this study is unclear. Although the sponsor split the diagnosis of alcohol/drug abuse from psychiatric diagnosis, the incidence of abuse disorders is very low (1%). Among the renal-genitourinary disorders, it is unclear how many had enlarged prostate or tendency of urinary retention. No concomitant medications taken seemed to have significant sedative or hypnotic effects.

Table 23. Subject Demographics at Baseline, Safety Set (SP-0509)

Variable	Placebo (N=124)	Doxepin 6 mg (N=130)	Total (N=254)
Age (years)			
Mean (SD)	72.5 (5.85)	72.4 (5.95)	72.5 (5.89)
Median (Range)	71.0 (64–90)	71.5 (64–91)	71.0 (64–91)
Sex [n (%)]			
Male	48 (39%)	42 (32%)	90 (35%)
Female	76 (61%)	88 (68%)	164 (65%)
Race/Ethnicity [n (%)]			
White	108 (87%)	114 (88%)	222 (87%)
Black/African American	7 (6%)	10 (8%)	17 (7%)
Hispanic	5 (4%)	3 (2%)	8 (3%)
Asian	2 (2%)	3 (2%)	5 (2%)
Other	2 (2%)	0 (0%)	2 (1%)
Weight (kg)	n=123	n=130	n=253
Mean (SD)	77.1 (16.69)	77.4 (15.53)	77.2 (16.07)
Median (Range)	78.5 (36–133)	75.8 (46–135)	76.3 (36–135)
Height (cm)	n=124	n=130	n=254
Mean (SD)	166.3 (10.29)	165.4 (8.73)	165.8 (9.51)
Median (Range)	165.1 (142.2–201.0)	165.1 (147.3–190.5)	165.1 (142.2–201.0)
BMI (kg/m^2)	n=123	n=130	n=253
Mean (SD)	27.7 (5.02)	28.2 (4.94)	28.0 (4.97)
Median (Range)	27.1 (18.0–50.3)	27.9 (18.7–43.5)	27.7 (18.0–50.3)

5.3.3 Patient Disposition

Almost all randomized patients (255) received double-blind study drug (254) and were included in the Safety Analysis Set. Overall, 93% (237/254) subjects completed the study.

A total of 18 subjects (7%) dropped out of the study. The most frequent reason for discontinuation in both treatment groups was consent withdrawn (6% in the placebo group and 3% in the doxepin 6 mg group). Among the 17 patients who discontinued after receiving double-blind treatment, two withdrew from the study due to an AE. The subject who withdrew from the doxepin 6 mg group was due to hypoacusis of the left ear and tinnitus.

5.3.4 Analysis and Results

There was no objective efficacy assessment in this study. The sponsor's primary efficacy variable was Subjective Total Sleep Time (sTST) at Week 1. Table 24 summarizes the primary efficacy variable, sTST, at baseline and at Week 1 by treatment group using the ITT Analysis Set.

Table 24. sTST, at baseline and at Week 1 by treatment group using the ITT Analysis Set, provided by the sponsor (SP-0509)

sTST (minutes)	Placebo (N=124)	Doxepin 6 mg (N=130)
Baseline[1]	n=124	n=130
Mean (SD)	293.5 (49.09)	283.1 (49.96)
Median (Range)	300.0 (107.1–385.7)	288.2 (158.6–377.1)
Week 1[1]	n=122	n=129
Mean (SD)	316.7 (56.22)	335.2 (61.20)
Median (Range)	318.9 (156.0–458.6)	336.4 (201.4–475.7)
Difference of LS Mean (Std. Err.)		18.6 (5.39)
95% CI of LS Mean Difference		(18.0, 39.3)
p-value[3]		p<0.0001
Week 2[1]	n=118	n=127
Mean (SD)	328.2 (54.28)	332.3 (64.63)
Median (Range)	334.6 (192.0–492.0)	335.0 (175.7–497.1)
Difference of LS Mean (Std. Err.)		14.2 (5.61)
95% CI of LS Mean Difference		(3.1, 25.2)
p-value[3]		p=0.0121
Week 3[1]	n=114	n=125
Mean (SD)	331.7 (60.87)	341.4 (62.06)
Median (Range)	336.2 (181.4–475.7)	334.3 (216.4–479.3)
Difference of LS Mean (Std. Err.)		18.2 (6.09)
95% CI of LS Mean Difference		(6.2, 30.2)
p-value[3]		p=0.0031
Week 4[1]	n=109	n=122
Mean (SD)	336.4 (64.71)	346.1 (66.44)
Median (Range)	345.0 (153.8–468.3)	341.8 (201.4–496.3)
Difference of LS Mean (Std. Err.)		21.1 (6.63)
95% CI of LS Mean Difference		(8.0, 34.1)
p-value[3]		p=0.0017
Average Across Weeks 1 Through 4[2]	n=108	n=122
Mean (SD)	330.5 (54.92)	338.9 (58.88)
Median (Range)	337.5 (182.1–468.8)	333.5 (226.7–463.7)
Difference of LS Mean (Std. Err.)		18.3 (5.34)
95% CI of LS Mean Difference		(7.8, 28.9)
p-value[3]		p=0.0007

Notes: Values of sTST >12 hours were excluded from the analysis.
[1] Baseline was the mean of the IVRS values reported during the Placebo Lead-in Period. Weeks 1, 2, 3, and 4 were defined as the mean of the IVRS reported values between study visits during the treatment period.
[2] Average across Weeks 1 through 4 was calculated as the average of all non-missing IVRS entries if at least four observations were available at each week.
[3] p-value comparing treatments was determined from an ANCOVA model that included main effects for treatment and center with the baseline value as a covariate.

The mean sTST values were slightly higher in the placebo group (293.5 minutes) than in the doxepin 6 mg group (283.1 minutes) at baseline. There was a statistically significant increase ($p<0.0001$) in the mean sTST value for doxepin 6 mg compared with placebo at Week 1. The LS mean sTST value was 28.6 minutes longer in the doxepin 6 mg group compared with the placebo group. According to Dr. Messie, an additional sensitivity analysis was performed on a subset of the ITT Analysis Set that excluded site 04, which incorrectly instructed subjects to round the IVRS data during the Placebo Lead-in Period to the nearest 15 minutes. Similar results were observed using the PP Analysis Set and sensitivity analyses.

The key secondary efficacy variable was subjective Latency to Sleep Onset (LSO) during Week 1. A summary of LSO at baseline and Week 1 by treatment group using the ITT Analysis Set is provided by Dr. Messie in the following table.

Table 25. Subjective WASO analyses for OC and ITT-LOCF populations by Week

POP	TIME	PLACEBO		6 MG		6 MG VS. PLACEBO	
		N	Mean (S.D.)	N	Mean (S.D.)	Difference LS Mean (S.E.)	p-value
OC	Baseline	125	111.3 (47.1)	130	116.5 (49.1)	5.9 (6.0)	0.3313
	Week 1	122	97.4 (50.2)	129	79.1 (49.0)	-22.2 (4.8)	<0.0001
	Week 2	118	85.1 (50.4)	127	75.9 (47.0)	-12.6 (5.1)	0.0145
	Week 3	114	82.4 (49.7)	125	70.4 (46.8)	-15.8 (4.9)	0.0016
	Week 4	108	78.9 (56.5)	122	66.5 (43.9)	-16.8 (5.5)	0.0026
LOCF	Week 2	122	86.2 (50.3)	129	75.9 (47.0)	-13.8 (5.1)	0.0071
	Week 3	122	85.0 (50.7)	129	71.2 (46.9)	-17.8 (4.9)	0.0004
	Week 4	122	83.7 (56.2)	129	67.8 (43.9)	-19.1 (5.3)	0.0003

At baseline, the LSO values were slightly lower in the placebo group. The geometric LS mean LSO at Week 1 in the doxepin 6 mg group was not statistically significantly different than placebo ($p=0.1547$). Similar results were observed using the PP Analysis Set and sensitivity analyses. Numerical decreases in LSO from baseline were observed throughout the treatment period in the doxepin 6 mg group and the placebo group. There were no statistically

significant differences between the two treatment groups at any noted timepoint using the ITT Analysis Set.

Table 26. Subjective LSO analyses for OC and ITT-LOCF populations by Week

POP	TIME	PLACEBO			6 MG			
		N	Mean (S.D.)	Geometric Mean	N	Mean (S.D.)	Geometric Mean	6 MG vs. placebo p-value
OC	Baseline	125	4.24 (0.46)	69.3	130	4.32 (0.49)	75.3	0.1244
	Week 1	122	4.08 (0.51)	59.1	129	4.08 (0.52)	58.9	0.1547
	Week 2	118	3.96 (0.51)	52.2	127	4.06 (0.61)	58.1	0.4884
	Week 3	114	3.95 (0.56)	52.1	125	3.98 (0.64)	53.4	0.4635
	Week 4	109	3.89 (0.58)	49.0	122	3.94 (0.67)	51.4	0.6629
LOCF	Week 2	122	3.96 (0.53)	52.6	129	4.07 (0.61)	58.6	0.4790
	Week 3	122	3.97 (0.58)	53.2	129	3.99 (0.65)	54.0	0.3596
	Week 4	122	3.93 (0.60)	50.8	129	3.96 (0.68)	52.6	0.5440

Other Endpoints

There was no significant difference between Doxepin 6 mg and placebo on the subjective number of awakenings after sleep onset (NAASO) for any week, e.g., week 1 (p=0.1025), week 4 (p=0.9175). Thus, the sponsor's claim of an effect towards [redacted] (b) (4) has no supportive data from this study.

In summary, this study has positive subjective measure for sleep maintenance but not sleep initiation. However, the lack of objective measure in this study makes it difficult to accept the claim.

5.4 Study 502: A Phase III, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Assess the Efficacy and Safety of Doxepin HCl for the Treatment of Transient Insomnia in Adult Subjects

5.4.1 Method

Subjects were screened for eligibility, including a 7 consecutive day daily sleep diary. They were then randomized into two groups: Placebo and doxepin 6mg in a 1: 1 ratio according to a computer-generated randomization scheme.
On Night 1, in order to phase advance, lights out occurred 3 hours before each subject's individual adjusted median habitual bedtime. Doxepin 6 mg or placebo was given our hour before lights out. Following lights out, continuous 8-hour PSG recordings were started.

On Day 2, approximately one hour after completion of PSG recording, subjects were asked to complete a questionnaire to assess subjective sleep characteristics. Next day hangover/residual effects were assessed using DSST, SCT, and VAS for sleepiness. Subjects were discharged from the sleep center after all study-related assessments were completed.

Subject selection criteria:

Male or female 25 to 55 years of age, inclusive.

- Subjects had a body mass index (BMI) ≥20 kg/m2 and ≤30 kg/m2.
- Subjects had a 3-month history of a normal nightly sleep pattern based on their self-reports of the following information:
    1. Usual lights out time of ≥22:00 and ≤24:00 hours
    2. Usual sleep onset of ≥10 and ≤30 minutes
    3. Usual sTST of ≥7 and ≤9 hours per night
    4. Usual time in bed of ≤9 hours per night
- No habitual daytime napping (napping more than once per week or more than twice in the last week), and no decrease in daytime functioning due to sleep problems
- Subjects had an Epworth Sleepiness Scale score ≤12.
- Subjects had a difference of ≤1.5 hours between their usual weekday and weekend

5.4.2 Demographics and Other Disease Characteristics at Baseline

Table 27. Demographics at Baseline (SP-0502)

Variable	Placebo (N=282)	Doxepin 6 mg (N=283)	Total (N=565)
Age (years)			
Mean (SD)	35.9 (8.13)	35.2 (8.20)	35.5 (8.17)
Range	25–55	25–55	25–55
Sex [n (%)]			
Male	134 (48%)	123 (43%)	257 (45%)
Female	148 (52%)	160 (57%)	308 (55%)
Race/Ethnicity [n (%)]			
White	151 (54%)	133 (47%)	284 (50%)
Black/African American	39 (14%)	45 (16%)	84 (15%)
Hispanic	87 (31%)	93 (33%)	180 (32%)
Native Hawaiian or Other Pacific Islander	0 (0%)	1 (<1%)	1 (<1%)
Asian	2 (1%)	6 (2%)	8 (1%)
Other	3 (1%)	5 (2%)	8 (1%)
Weight (kg)			
Mean (SD)	73.4 (13.27)	73.9 (13.46)	73.7 (13.36)
Range	46–109	50–120	46–120
BMI (kg/m^2)			
Mean (SD)	25.1 (2.90)	25.2 (2.75)	25.2 (2.82)
Range	19.2–32.1	20.0–32.3	19.2–32.3

5.4.3 Patient Disposition

This is a one-night study, all completed the study.

5.4.4 Analysis and Results

The primary efficacy variable, LPS, was measured using PSG recordings. A summary of LPS by treatment group using the ITT analysis set is presented below.

Table 28. LPS on Night 1: ITT Analysis Set

LPS (minutes)	Placebo (N=282)	Doxepin 6 mg (N=283)
Subjects	282	282
Mean (SD)	33.6 (36.87)	20.6 (18.93)
Median (Range)	19.3 (0.0–236.0)	15.0 (0.5–165.0)
LS Mean (Std. Err.)	32.9 (1.83)	20.0 (1.83)
Difference of LS Mean (Std. Err.)		-13.0 (2.44)
95% CI of LS Mean Difference		(-17.8, -8.2)
p-value[1]		p<0.0001

[1] p-value for comparing treatments was determined from an ANOVA model that included main effects for treatment and center.

There was a statistically significant decrease ($p<0.0001$) in the mean LPS for the doxepin 6 mg group compared with the placebo group. The LS mean estimate for LPS was 13.0 minutes shorter for the doxepin 6 mg group compared with the placebo group.

Below is a summary of WASO by treatment group based on the ITT analysis set.

Table 29. WASO on Night 1: ITT Analysis Set WASO (minutes) (SP-0502)

WASO (minutes)	Placebo (N=282)	Doxepin 6 mg (N=283)
Subjects	n=281	n=281
Mean (SD)	77.5 (62.11)	38.4 (31.70)
Median (Range)	60.5 (6.5–364.0)	28.5 (1.0–189.0)
LS Mean (Std. Err.)	79.4 (3.11)	40.4 (3.11)
Difference of LS Mean (Std. Err.)		-39.1 (4.16)
95% CI of LS Mean Difference		(-47.2, -30.9)
p-value[1]		p<0.0001

[1] p-value for comparing treatments was determined from an ANOVA model that included main effects for treatment and center.

There was a statistically significant decrease in the mean WASO for the doxepin 6 mg group compared with the placebo group. The LS mean WASO estimate was 39.1 minutes shorter for the doxepin 6 mg group compared with the placebo group.

5.5 Summary of Efficacy

In summary, a total of 731 subjects exposed to Silenor (excluding placebo) in all 11 trials (Phases 1 – 3); among them, 627 were in Phase II and Phase III studies, and 512 were ≥ 65 years of age.

The exposure to each doxepin HCl dose group in Phase II and III trials is summarized as follows:

Table 30. Dose Exposure to Each Doxepin HCl Dose Group in Six Phase II and III Studies

Phase II-III Trials	**1mg**	**3mg**	**6mg**	**Duration**
SP-0401	66	66	67	2 nights each
SP-0402	74	75	74	2 nights each
Phase II Total	**140**	**141**	**141**	
SP-0501	--	75	73	35 nights
SP-0503	77	82	--	85 nights
SP-0509	--	--	130	28 nights
SP-0502	--	--	283	1 night
Total Phase II+III	**217**	**298**	**627**	

5.5.1 Indications and Primary Endpoints

In each of the insomnia efficacy studies, the primary efficacy measure was a sleep maintenance variable, whereas in the transient insomnia study the primary efficacy measure was a sleep onset variable. The PSG studies used identical efficacy measures and, whenever possible, the same

assessment timepoints. The primary support variables were Wake After Sleep Onset (WASO) and subjective Total Sleep Time (sTST) for sleep maintenance; Latency to Persistent Sleep (LPS) and Latency to Sleep Onset (LSO) for sleep onset; and Sleep Efficiency (SE) in Hour 8 for the (b) (4)

According to the sponsor, for indication of "sleep maintenance," WASO with PSG is the objective assessment for the two long-term PSG studies and the primary efficacy variable. Though sTST is the subjective measure for all efficacy studies per the sponsor, together with some other measures, they are considered as secondary endpoints.

For indication of "sleep onset," objective assessment is LPS in studies #501 (adults) and #502 (geriatrics); subjective assessment is LSO in two Phase 2 and three Phase 3 studies (#401 and #501 for adults; #402 and #503 for geriatrics; plus, #502 in healthy subjects with transient insomnia.).

The sponsor summarizes the variables measured in all these studies in the table below.

Table 31. Primary and Secondary Support Variables Presented in the Summary of Clinical Efficacy for Doxepin

	Sleep Maintenance						Sleep Onset		Prevention of Early Morning Awakenings		
	Objective (PSG)				Subjective		Objective (PSG)	Subjective	Objective (PSG)		
Study	WASO	WTDS	TST	SE	sTST	sWASO	LPS	LSO	SE Hr 8	WTAS	SE Last Qtr
Phase 2 Chronic Insomnia Studies											
0401	X	X[1]	X	X	X	X	X	X	X	X	ND
0402[2]	X	X[1]	X	X	X	X	X	X	X	X	ND
Phase 3 Chronic Insomnia Studies											
0501	X[1]	X	X	X	X	X	X	X	X	X	X
0503[2]	X[1]	X	X	X	X	X	X	X	X	X	X
0509[2]	NA	NA	NA	NA	X[1]	X	NA	X	NA	NA	NA
Phase 3 Transient Insomnia Study											
0502	X	X	X	X	X	X	X[1]	X	X	X	X

[1] Primary efficacy variable for the study.

[2] Study performed in the elderly (≥65 years of age).

Notes: NA=not applicable; ND=not done; WASO=Wake After Sleep Onset; WTDS=Wake Time During Sleep; TST=Total Sleep Time; SE=Sleep Efficiency; sTST=subjective TST; sWASO=subjective WASO; LPS=Latency to Persistent Sleep; LSO=Latency to Sleep Onset; SE Hr 8=SE in Hour 8; WTAS=Wake Time After Sleep; SE Last Qtr=SE in the last quarter of the night. The primary support variables identified for each claim are shaded; the secondary support variables are not shaded.

As discussed in the team meetings, oWASO and sWASO are defined as primary variables for sleep maintenance; and oLPS and sLSO as primary endpoints for sleep initiation/onset. The statistic analysis of these studies was verified and conducted by the Agency Statistician, Tristan Messie, Ph.D. The results of these key objective and subjective variables are summarized by Dr. Messie in his review (Table 32).

Upon further exploration, Dr. Messie concluded that the results of sTST are similar to sWASO in this program. The inconsistent results of subjective measure from these studies underline the importance of having both subject and objective measures from the same study. In my opinion, it is inappropriate to use positive results from studies with only subjective measure to substitute negative results of subjective measure in studies where both objective and subjective measures were investigated. Likewise, although Phase 2 studies show clear efficacy on the only night studied, it is inappropriate to pool their results to substitute the Night 1 negative results of longer term studies. Therefore, the studies presented do not demonstrate convincible efficacies for the sponsor's claims of sleep initiation, maintenance, or (b) (4)

Table 32. Summary of Key Analysis p-values by Study

Study		Dose	P-Values as Compared to Placebo				
	Endpoint	Group	Night 85	Night 57	Night 29	Night 15	Night 1
401 (Phase 2 Crossover)	WASO	6					<0.0001
	LPS	6					0.0397
402 (Phase 2 Crossover/ Elderly)	WASO	6					<0.0001
	LPS	6					0.1063
501 (Adults)	**WASO**	**6**			**0.0007**	**0.0011**	**<0.0001**
		3			**0.0173**	**0.0025**	**<0.0001**
	sWASO	**6**			0.6282	0.2016	**0.0004**
		3			0.6483	0.1512	**0.0003**
	LPS	6			0.8643	0.5921	0.0009
		3			0.7995*	0.2271*	0.0058
	sLSO	6			0.6511*	0.1451	0.0492
		3			0.2365*	0.9071*	0.1259
502 (Transient Insomnia)	WASO	6					<.0001
	sWASO	6					0.0063
	LPS	6					<0.0001
	LSO	6					<0.0001
503 (Elderly)	**WASO**	**3**	**<.0001**	**0.0029**	**0.0005**	**0.0069**	**<0.0001**
		1	**0.0330**	0.1662	0.0878	0.1945	0.0053
	sWASO	**3**	**0.0153**	0.5627	**0.0296**	0.0729	0.0561
		1	**0.0037**	0.7417	0.0531	0.8571	0.8497
	LPS	3	0.0286*	0.0522*	0.5422*	0.8388	0.1079
		1	0.6493	0.1870*	0.1268*	0.8046	0.5733*
	sLSO	3	0.8479	0.9931	0.6544*	0.916	0.0860
		1	0.2826	0.9631*	0.1798*	0.3567*	0.2304*
509 (Elderly/ Subjective Only)	**sWASO**	**6**		**0.0026 (Week 4)**	**0.0016 (Week 3)**	**0.0145 (Week 2)**	**<0.0001 (Week 1)**
	sLSO	6		0.6629 (Week 4)	0.4635 (Week 3)	0.4884* (Week 2)	0.1547 (Week 1)

5.5.2 Analysis of Clinical Information Relevant to Dosing Recommendations

Using the defined endpoints, oWASO and sWASO, neither the adult study nor the geriatric study shows efficacy.

Study SP-0501 only showed efficacy for the first night and no consistent subjective measure remains effective afterwards.

With regard to geriatric study, doxepin 1mg didn't show positive results till the end of the study; doxepin 3mg did show some positive results before the end of the study - with OC missing data

management, the efficacy didn't seem to be consistent over time (showed positive results on Night 29, but lost on Night 57, and regain on Night 85). Yet, this result is not clinically practical and I do not recommend either dosages.

Unfortunately, the study that included doxepin 6mg per day didn't have objective measure and there is no safety data for this dosage for 3 months. Thus, I will not recommend this, either.

5.5.3 Discussion of Persistence of Efficacy and/or Tolerance Effects

The efficacy in SP-0501 and SP-0503 as partly measured by oWASO is positive throughout the study. But the other part of efficacy measure in these studies, sWASO, didn't show positive result after the first night (SP-0501) or till at least one month or later (SP-0503), depending on the statistic method; with OC missing data management, the efficacy that showed at the end of one month (Night 29) still lost towards the end of second month (Night 57), and only reappeared again at the end of the study (Night 85).

There is no specific measure for tolerance in these studies. However, judging from subjective measures that weren't positive after Night 1 in the three longer time studies, tolerance effect can't be totally ruled out.

5.5.4 Additional Efficacy Issues/Analyses

(b) (4)

2. Demographic Analysis of Efficacy

From Dr. Messie's review, there is no statistically differential effect of treatment depending on age, gender or race in these two studies.

3. Treatment Effect by Site

Similarly, there was no treatment effect by site in either study – for details, please see statistic review by Dr. Messie.

6 Review of Safety

6.1 Methods

6.1.1 Clinical Studies Used to Evaluate Safety

All studies in the clinical program are used to evaluate death, serious adverse events, and dropouts.

The sponsor used MedDRA as coding dictionary.

6.1.2 Pooling Data across Studies to Estimate and Compare Incidence

The common adverse events are reviewed based on data from four Phase 3, double-blind studies, separating the two age groups (adult and geriatric) studied. Due to the different length of studies and population, these data are not pooled for common adverse events or labs.

6.2 Adequacy of Safety Assessment

6.2.1 Overall Exposure at Each Doses/Durations

The overall exposure at each doses for overall duration are adequate. The following table summarizes number of subjects in different dose groups for various durations in this clinical program, provided by the sponsor.

Table 33. Overall Dose Exposure of Various Treatment Groups of All Phase 1-3 Studies

Number of Days	Placebo (N=699)	Doxepin 1 mg (N=232)	Doxepin 3 mg (N=313)	Doxepin 6 mg (N=730)	All Doxepin [a] (N=966)
1–14 days	434 (62.1%)	158 (68.1%)	164 (52.4%)	534 (73.2%)	547 (56.6%)
15–35 days	186 (26.6%)	1 (0.4%)	69 (22.0%)	195 (26.7%)	265 (27.4%)
36–60 days	7 (1.0%)	3 (1.3%)	5 (1.6%)	1 (0.1%)	9 (0.9%)
61–91 days	72 (10.3%)	70 (30.2%)	75 (24.0%)	0	145 (15.0%)

Notes: For the Phase 1 and Phase 2 studies, the number of days of exposure is equal to the number of doses of doxepin or placebo the subject received. For the Phase 3 studies, the number of days of exposure is calculated as (the date of last dose of double-blind study drug – date of first dose of double-blind study drug + 1) and, due to noncompliance, may include days on which the subject did not take study drug.
[a] Includes all subjects who received any dose of doxepin 1 mg, 3 mg, or 6 mg in any study.

Total exposure of unique subjects in all doxepin groups is 964 subjects. A total of 720 subjects have an average of 29.7 days of exposure to doxepin 1 mg, 3 mg, or 6 mg in Phase 3 All Studies Safety Analysis Set. Total subject-day exposure for all Phase 3 studies is 21,394 and overall drug exposure is 22,445 subject-days.

6.2.2 Routine Clinical Testing

Routine clinical testing appears to be adequate, but timing for ECG and Laboratory Tests of Phase 3 controlled studies as well as studies for drug-drug interactions were not within the time frame of Tmax. Therefore, there was no adequate safety data for ECG and laboratory tests. Urinalysis data are not integrated which makes it hard to conclude.

6.2.3 Metabolic, Clearance, and Interaction Workup

Metabolic and clearance workup is adequate. However, the design for rebound insomnia was not designed properly; it is hard to draw conclusions from it. The sponsor also conducted two drug-drug interaction studies and they are adequate for PK and PD evaluation but since the drug combination treatment was only one day in both studies, it is not so adequate to draw safety conclusions from them.

6.2.4 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The sponsor summarized AEs commonly seen with sedative/hypnotic class of drugs or psychotherapeutic doses of doxepin in the following five categories: Central Nervous System, Psychiatric, General Category (cluster term of Accidental Injury), Cardiovascular Category, and the Potential Anticholinergic Category. QT interval and other key ECG parameters are reported in subsection of ECG changes. The evaluation appears sufficient, except the timing of ECG performed was inappropriate.

6.3 Safety Results

6.3.1 Deaths

There was no death in the clinical program.

6.3.2 Nonfatal Serious Adverse Events

A total of seven subjects had SAE. None of them was in the highest dose tested (that is 6mg). One was in placebo group (injury). The sponsor summarizes all these events in the following table:

Table 34. Serious Adverse Events in All Studies (provided by the sponsor)

Preferred Term	Placebo (N=699)	Doxepin 1 mg (N=232)	Doxepin 3 mg (N=313)	Doxepin 6 mg (N=730)	All Doxepin (N=966)
Subjects with at Least One SAE	1 (0.1%)	3 (1.3%)	3 (1.0%)	0	6 (0.6%)
Cerebrovascular Accident	0	1 (0.4%)	0	0	1 (0.1%)
Chest Pain [a]	0	0	1 (0.3%)	0	1 (0.1%)
Fall [b]	0	0	1 (0.3%)	0	1 (0.1%)
Gastroenteritis	0	0	1 (0.3%)	0	1 (0.1%)
Hypertension [a]	0	0	1 (0.3%)	0	1 (0.1%)
Injury	1 (0.1%)	0	0	0	0
Lung Adenocarcinoma Stage I [b]	0	0	1 (0.3%)	0	1 (0.1%)
Non-cardiac Chest Pain	0	1 (0.4%)	0	0	1 (0.1%)
Pneumonia	0	1 (0.4%)	0	0	1 (0.1%)

Note: Subjects reporting multiple TEAEs within an SOC or PT are only counted once within that SOC or PT. [a] The chest pain (two episodes) and hypertension SAEs were experienced by the same subject (Subject 0501/06/3223).
[b] The fall and lung adenocarcinoma SAEs were experienced by the same subject (Subject 0503/78/7188).

None of these events is considered to be associated with the study drug but three of them led to discontinuation of the study (see next subsection also). Below are summaries of SAE cases of doxepin groups:

1) Cerebrovascular accident
Subject 0503/26/7166 is an 82-year-old Caucasian female in doxepin 1 mg group. In addition to primary insomnia, her medical history included hypertension since 1995, hypercholesterolemia since 1970, ankle swelling, angina, and left radical mastectomy for breast cancer in 1971. Concomitant medication hydrochlorothiazide/triamterene, multivitamin, ibuprofen, naproxen, and guaifenesin/ dextromethorphan hydrobromide.

After she received double-blind study drug for 31 days, ((b) (6) , she awoke with dysarthria, left facial droop, left-sided heaviness and clumsiness, and impaired gait the following day. The symptoms were persistent and nonprogressive. Two days later, she was seen by her primary care physician and referred to the ER. On admission, her vital signs were within normal limits. She was alert and oriented but had left facial weakness and sensory loss, mild left pronator drift, left hamstring weakness, mild ataxia on the left, and gait impairment. Admission laboratory values were within normal limits with the exception of low-density lipoproteins 238, total cholesterol 323, and triglycerides 149 (normal reference ranges unavailable). An ECG revealed sinus tachycardia (heart rate of 100 bpm) and left axis deviation; otherwise it was normal. Computerized tomography (CT) of the brain revealed infarcts of the posterior limb of the right internal capsule and right occipital lobe. An echocardiogram showed greater than 55% ejection fraction and normal left ventricular function with mild left ventricular hypertrophy. The diastolic function class showed a relaxation abnormality (grade 1)

corresponding to E/A reversal. There was mild aortic, mitral, pulmonary, and tricuspid regurgitation but no hemodynamically significant stenosis on Carotid ultrasound. She was started on ezetimibe and hospitalized due to a right brain cerebrovascular accident. Four days later, she was discharged home on ezetimibe and clopidogrel bisulfate. Though she was stable, the event resolved with sequelae and *withdrew* from the study.

Reviewer's comment: Considering patient's age and medical history, it is hard to attribute this event to the study drug.

2) Chest pain and hypertension
Subject #0501/06/3223 is a 59 year-old African American female enrolled in the doxepin 3 mg group. She has a history of hypertension, exertional dyspnea, dizziness, syncope, right-sided weakness, depression, and lupus. During initial Screening, she was found having blood pressure 151/77 mmHg, mild elevations of BUN (29 mg/dL; reference range 6-21 mg/dL) and creatinine (1.3 mg/dL; reference range 0.7-1.2 mg/dL). Her ECG revealed normal sinus rhythm, a heart rate of 54 bpm, and nonspecific T wave abnormality. During the single-blind Placebo Lead-in Period (i.e., prior to randomization), she had uncontrolled hypertension, with blood pressure measurements of 160-190/81-108 mmHg (Night -13 to Day -4). She also had two episodes of chest pain with T-wave inversions on ECG 8 days after she was withdrawn from the study due to uncontrolled hypertension, and abnormal stress test 25 days after the last dose of double-blind study drug. She was admitted to the hospital on both occasions and was discharged to home one to two days later.

Concomitant medications taken within 30 days of the initial SAEs included metoprolol 100 mg BID, lisinopril 40 mg QD, amiloride/hydrochlorothiazide 25 mg QD, potassium chloride 8 mEq QD, and aspirin 325 mg QD.

Reviewer's comment: The patient had high systolic blood pressure at baseline which got worse during the placebo lead-in period. Her chest pain is reportedly over a week after her withdrawal from the study. Considering her demographic background, medical history, and the timing of hypertension and chest pain, these events are probably not related to the study drug.
3) Fall and adenocarcinoma
Subject #0503/78/7188 is a 73-year-old Caucasian female in the doxepin 3 mg group. Her medical history includes primary insomnia, open reduction internal fixation of left medial malleolus fracture, thyroid cyst, reticulum cell sarcoma Stage II and lymphoma (1959) in remission after radiation therapy, and tobacco smoking (30 packs/year; quit 20 years ago). Her concomitant medications included estropipate, Co-Q10, fish oil, selenium, B-complex, glucosamine with chondroitin, vitamin E, and vitamin C.

On Day 24 of the study, she reported fall from stairway while carrying heavy luggage during her vacation. It resulted in a mild left posterior parietal scalp hematoma, moderate left ankle sprain, severe left elbow fracture, impacted fracture of the left wrist, confirmed by X-rays conducted in the ER. She was treated with meperidine HCl 25 mg intravenously (IV) and promethazine HCl 25

mg IV for pain and surgery next day. Although the subject did not experience dizziness or loss of consciousness prior to the fall, she *withdrew* from the study due to the SAE of fall.

Additionally, a chest x-ray in ER revealed a vague 1 cm nodular density projecting over the right second rib. Upon discharge from the hospital two days later, she was in stable condition. But transthoracic needle biopsy of the right upper lung revealed Stage 1A lung adenocarcinoma about two months later, 60 days after administration of the last dose of study drug. She eventually had right upper lobectomy and mediastinal lymphadenectomy in subsequent months.

Reviewer's comment: Given patient's age and circumstance, it is hard to attribute the incident of fall to the study drug. Adenocarcinoma is unlikely the outcome of a study of 3 months and considering her smoking history.

4) "Non-cardiac chest pain"
Subject 0402/03/279 is a 70-year-old Caucasian male randomized to take study drug in the following order: Doxepin 1 mg, 3 mg, 6 mg and placebo. In addition to primary sleep maintenance insomnia, he also had significant coronary artery disease (balloon angioplasty with stent placement in 1990), hypertension, hyperlipidemia, and sinus bradycardia. His concomitant medications at the time of the event were simvastatin, folic acid, omega-3I, atenolol, vitamin B6 and B12, lisinopril, and aspirin.

After he received two doses of doxepin 1 mg, with the last dose administered on November (b) (6) Night 2 of Treatment Period 1), he developed substernal chest pain, reportedly lasted approximately 15 minutes and resolved with rest, shortly after he walked across the street and walked back. He was admitted to the hospital for further evaluation but discharged next day without requiring treatment as his cardiac isoenzymes, electrocardiograms and a stress echocardiogram were all normal.

Reviewer's comment: Though his clinical presentation mimics cardiac chest pain, esp. his baseline medical condition indicated that he could be at high risk of cardiac event. However, work-up was negative and he was discharged with no reported complications. Thus, the diagnosis of non-cardiac chest pain was probably correct.

5) Pneumonia
Subject 0503/32/7307, a 74-year-old Caucasian female in the doxepin 1 mg group. In addition to primary insomnia, she had history of hypertension, rheumatoid arthritis, osteoporosis, chronic constipation, left knee replacement, and hysterectomy. Concomitant medications included glucosamine, folic acid, vitamin C, losartan potassium, sulindac, fish oil, garlic, infliximab, and Robitussin.

She was started on double-blind study drug on (b) (6) On Day 36 (b) (6) she developed symptoms of dry cough with intermittent fever and unsteady gait, shortness of breath, occasional headaches, decreased appetite, and weakness. Four days later, she was hospitalized for pneumonia. She also had unsteady gait and had fallen the day before the hospitalization.

Her vital signs were normal except for a body temperature of 101.8 °F and oxygen saturation of 93% to 95% on room air. Lab results showed a WBC count of 13.1 × 10^9/L with neutrophils 81%, and platelets 288 × 10^9/L. Chest x-ray showed a right lower lobe infiltrate consistent with community-acquired pneumonia. A CT scan of the chest performed on the second day of hospitalization revealed severe infiltrates in the lower and middle lobes of the right lung that had air space character, and a small right pleural effusion. She was started on levalbuterol tartrate and ipratropium bromide inhalers, as well as ceftriaxone sodium, azithromycin, and enoxaparin for prophylaxis of deep vein thrombosis. She appeared to improve and was discharged home with levofloxacin after four days of hospitalization. After resuming the study drug for two days subsequently, she was found taking treatment for rheumatoid arthritis and discontinued for protocol violation. One day afterward, she was again hospitalized for worsening symptoms of pneumonia with relevant vital signs and lab results. She eventually improved with treatment of piperacillin/tazobactam and vancomycin and was discharged home shortly afterwards. Her discharge medications included fluconazole, benzonatate, and hydrocodone bitartrate with homatropine methylbromide. Pneumonia resolved in (b) (6).

Reviewer's comment: Pneumonia is common in elderly patients. It is probably not related to the study drug use.

6) Gastroenteritis
Subject 0503/07/7532 is a 74-year-old Hispanic female in the doxepin 3 mg group. Her medical history included primary insomnia, bilateral tinnitus, varicose veins, hypercholesterolemia, osteoarthritis, hypothyroidism, hiatal hernia, heartburn, penicillin and aspirin drug allergies, edema, irritable bowel syndrome, previous hyperthyroidism, gastric polyps, internal fixation right tibial fracture, cholecystectomy, appendectomy, and 3 cesarean sections. Concomitant medications included esomeptrazole magnesium, levothyroxine sodium, furosemide, acetaminophen, and trimethobenzamide.

The subject received double-blind study drug from (b) (6) through (b) (6) (Day 32). On Day 32, the subject developed gastroenteritis with episodes of vomiting, diarrhea, dizziness, and headaches. Her symptoms worsened despite treatment of trimethobenzamide. On Three days later, she was hospitalized due to severe symptoms of gastroenteritis. An x-ray of the abdomen revealed abnormal small bowel gas pattern showing moderate distention of multiple small bowel segments in the mid abdomen and left lower quadrant. CT scan of the abdomen and pelvis revealed diffuse fatty infiltration of the liver parenchyma as well as abnormal appearance of the small bowel, which suggested mild to moderate dilatation and seemed to involve the proximal to mid small bowel.

After treated with a combination of metronidazole, metoclopramide HCl, pantoprazole sodium, and chlordiazepoxide/methscopolamine, she was discharged in stable condition. The gastroenteritis resolved on September 06, 2006. The subject *withdrew* from the study due to the SAE of gastroenteritis. She also experienced a TEAE of headache on Day 7.

Reviewer's comment: Gastroenteritis is common. Given his history, it is unlikely to be drug-related.

6.3.3 Dropouts and/or Discontinuations

A total of 19 subjects dropped out of the study program. Among them, 15 subjects discontinued due to adverse events during study drug treatment; four of them were considered as SAEs (see previous subsection: Cerebrovascular accident, uncontrolled hypertension, gastroenteritis, and fall).

The table below summarizes the dropouts from various treatment groups.

Table 34. AEs that Led to Premature Discontinuation from Studies
(All Subjects Safety Analysis Set, provided by the sponsor)

System Organ Class Preferred Term	Placebo (N=699)	Doxepin HCl 1 mg (N=232)	Doxepin HCl 3 mg (N=313)	Doxepin HCl 6 mg (N=730)	All Doxepin (N=966)
Cerebrovascular Accident	0	1 (0.4%)	0	0	1 (0.1%)
Somnolence	0	0	0	1 (0.1%)	1 (0.1%)
Paraesthesia	1 (0.1%)	0	0	0	0
Anxiety	0	0	0	2 (0.3%)	2 (0.2%)
Uncontrolled hypertension	0	0	1 (0.3%)	0	1 (0.1%)
Worsen Sinus Bradycardia	0	0	0	1 (0.1%)	1 (0.1%)
Gastroenteritis	0	0	1 (0.3%)	0	1 (0.1%)
Herpes Zoster	0	0	0	1 (0.1%)	1 (0.1%)
Hypoacusis	0	0	0	1 (0.1%)	1 (0.1%)
Tinnitus	1 (0.1%)	0	0	0	0
Abdominal Pain Upper	0	0	1 (0.3%)	0	1 (0.1%)
Fall	0	0	1 (0.3%)	0	1 (0.1%)
Ankle Fracture	1 (0.1%)	0	0	0	0
Back Pain	1 (0.1%)	0	0	0	0

According what described in SAE, the case of uncontrolled hypertension actually started during the Lead-in placebo period. The case of sinus bradycardia was a 71 year-old Caucasian male with history of ongoing sinus bradycardia, ST elevation, hypertension, hypercholesterolemia, high blood glucose, and creatinine elevation. He was enrolled in a double-blind, four-way cross over study and the onset of exacerbation started 14 hours prior to the first administration of double blind treatment (doxepin 6mg). His heart rate went from 54 to 48 bpm on the day after dosing. There

was no other AE described. It resolved without treatment three days after the onset. –*Thus, it is probably not related to the study drug in my opinion.*

Among other four patients who are not listed in above table, two were listed by the sponsor as non-treatment emergent (discontinued due to AEs prior to receiving double-blind study drug): One of the patients who had hypertension in placebo group of SP-0501 and another had tinnitus in doxepin 3 mg group of SP-0501. An additional patient from doxepin 1 mg group of SP-0503 was shown on the CRF AE page as a permanent discontinuation of study drug due to the AE (pneumonia as SAE) but the sponsor stated it as due to a protocol violation. Lastly, there was a subject dropped out from SP-0507 (an open label, cross-over study) due to development of dental caries and its treatment of pain medications. He was on Sinequan 50mg.

6.3.4 Other Significant Adverse Events

Syncope: Two young healthy subjects experienced syncope in Phase 1 drug-drug interaction studies and another had vasovagal syncope. Two were on doxepin 6mg with Cimetidine or Sertraline and both happened between 7 to 15 minutes after blood drawn that was scheduled after dosing. One resolved after one minute. The third subject was in study 507 and was on Sinequan 50mg. She experienced syncope at the time blood was drawn. Patient continued the study and didn't have more reaction afterwards.

Though these events resolved without consequences, there was no vital sign or ECG information during or immediately after syncope.

6.3.5 Common Adverse Events

Adverse event coding in datasets is generally appropriate except for vascular disorder and hypertension. The sponsor provided table for overall AE incidences in all safety analysis set that mixed trials of different designs. There is no table for adverse events that are ≥ 1%.

Table 36 lists drug-related adverse events, using the criteria of 5% or more and at least twice in a treatment group than placebo, in overall Phase 3 studies submitted by the sponsor. It shows that incidences of Infections & Infestations became much lower once the events are broken down to upper respiratory tract infection and gastroenteritis.

Table 36. Common Drug Related Adverse Events

System Organ Class Preferred Term	Placebo (N=699)	Doxepin 1 mg (N=232)	Doxepin 3 mg (N=313)	Doxepin 6 mg (N=730)	All Doxepin1 (N=966)
Nervous System Disorders: Total	49 (7.0%)	12 (5.2%)	23 (7.3%)	55 (7.5%)	89 (9.2%)
Somnolence	12 (1.7%)	6 (2.6%)	11 (3.5%)	16 (2.2%)	32 (3.3%)
Infections and Infestations: Total	22 (3.1%)	16 (6.9%)	17 (5.4%)	13 (1.8%)	46 (4.8%)

6.3.5.1 Adult Studies:

There is only one short term (about one month) study for adult patients (18-64 years old): SP-0501, comparing placebo, 3mg and 6mg doxepin treatment. The sponsor summarizes the common adverse events in the table below.

Using the same criteria for drug-related adverse events, somnolence and overall infections seem to be the only ones meet the criteria. Others are not necessarily drug-related. Overall GI reaction (nausea and vomiting) also meet the criteria for drug-relatedness in doxepin 6mg group (6, 8% vs. 3, 4% of placebo group) during the discontinuation phase. In the response to our 74-day letter, the sponsor reports that this is a 52 year-old Caucasian female.

Table 37. TEAEs Experienced by Greater than or Equal to 2 Percent of Subjects in any Treatment Group of SP-501 (Double-blind Treatment Period-Emergent)

MedDRA System Organ Class/ Preferred Term	Placebo (N=73) n (%)	Doxepin 3 mg (N=75) n (%)	Doxepin 6 mg (N=73) n (%)
Subject with any Double-blind Treatment Period-emergent AE	16 (22%)	23 (31%)	20 (27%)
Nervous System Disorders	8 (11%)	9 (12%)	9 (12%)
Somnolence	3 (4%)	7 (9%)	4 (5%)
Sedation	0 (0%)	0 (0%)	2 (3%)
Headache	6 (8%)	4 (5%)	0 (0%)
Infections and Infestations	1 (1%)	5 (7%)	6 (8%)
Upper respiratory tract infection	1 (1%)	2 (3%)	1 (1%)
Tooth infection	0 (0%)	2 (3%)	0 (0%)
Gastrointestinal Disorders	2 (3%)	3 (4%)	2 (3%)
Nausea	0 (0%)	3 (4%)	1 (1%)
Injury, Poisoning & Procedural Complications	0 (0%)	2 (3%)	2 (3%)
Post procedural complication	0 (0%)	2 (3%)	1 (1%)
Psychiatric Disorders[1]	1 (1%)	1 (1%)	2 (3%)
Skin and Subcutaneous Tissue Disorders	3 (4%)	0 (0%)	2 (3%)
Dermatitis contact	2 (3%)	0 (0%)	1 (1%)

[1]Psychiatric disorder included abnormal dreams, nightmare, anxiety, and depression.

6.3.5.2 Geriatric Studies

There is only one short term (about one month) study in geriatric patients: SP-0509, comparing placebo and doxepin 6mg treatment. The table below summarizes the common adverse events prepared by the sponsor.

Table 38. TEAEs Experienced by Greater than or Equal to 2 Percent of Subjects in any Treatment Group of SP-509 (Safety Analysis Set)

MedDRA System Organ Class/ Preferred Term	Placebo (N=124)		Doxepin 6 mg (N=130)	
	n	(%)	n	(%)
Subject with any TEAE	34	(27%)	40	(31%)
Nervous System Disorders	10	(8%)	19	(15%)
Somnolence	4	(3%)	7	(5%)
Sedation	0	(0%)	5	(4%)
Dizziness	0	(0%)	3	(2%)
Headache	5	(4%)	0	(0%)
Gastrointestinal Disorders	7	(6%)	8	(6%)
Dry Mouth	1	(1%)	3	(2%)
Diarrhoea	3	(2%)	1	(1%)
Infections and Infestations	8	(6%)	6	(5%)
Upper Respiratory Tract Infection	1	(1%)	2	(2%)
General Disorders and Administration Site Conditions	5	(4%)	4	(3%)
Oedema Peripheral	2	(2%)	0	(0%)
Psychiatric Disorders[1]	0	(0%)	2	(2%)
Skin and Subcutaneous Tissue Disorders	3	(2%)	2	(2%)
Pruritis	2	(2%)	0	(0%)
Injury, Poisoning, and Procedural Complications	4	(3%)	0	(0%)
Fall	2	(2%)	0	(0%)
Laceration	2	(2%)	0	(0%)

[1]Psychiatric disorder included nightmares and anxiety.

None of these events meet the criteria of drug-related common adverse events but sedation is close to the criteria (4% vs 0 in placebo). As mentioned in previous subsection, if sedation and somnolence are combined, the incidences in doxepin treatment group are clearly over 5% and more than doubled than those in placebo group. Psychiatric disorders and dizziness also only appeared in doxepin group.
There is also one long term (about 3 months) study in geriatric patients: SP-0503. The common adverse events are presented by the sponsor in the table below.

Table 39. TEAEs Experienced by Greater than or Equal to 2 Percent of Subjects in Any Treatment Group SP-503 (Safety Analysis Set)

MedDRA System Organ Class/ Preferred Term	Placebo (N=81)	Doxepin 1 mg (N=77)	Doxepin 3 mg (N=82)
Subject with any TEAE	42 (52%)	31 (40%)	31 (38%)
Infections and Infestations	11 (14%)	12 (16%)	11 (13%)
Gastroenteritis	0 (0%)	0 (0%)	3 (4%)
Nasopharyngitis	1 (1%)	1 (1%)	2 (2%)
Bronchitis	2 (2%)	1 (1%)	1 (1%)
Upper respiratory tract infection	1 (1%)	2 (3%)	1 (1%)
Sinusitis	1 (1%)	3 (4%)	0 (0%)
Urinary tract infection	2 (2%)	2 (3%)	0 (0%)
Nervous System Disorders	16 (20%)	6 (8%)	9 (11%)
Headache	11 (14%)	2 (3%)	5 (6%)
Dizziness	2 (2%)	0 (0%)	2 (2%)
Somnolence	4 (5%)	4 (5%)	2 (2%)
Gastrointestinal Disorders	10 (12%)	4 (5%)	5 (6%)
Dry mouth	2 (2%)	1 (1%)	2 (2%)
Stomach discomfort	0 (0%)	0 (0%)	2 (2%)
Diarrhoea	2 (2%)	2 (3%)	0 (0%)
Nausea	2 (2%)	0 (0%)	0 (0%)
Vascular Disorders	0 (0%)	2 (3%)	5 (6%)
Hypertension	0 (0%)	1 (1%)	3 (4%)
Injury, Poisoning and Procedural Complications	5 (6%)	1 (1%)	4 (5%)
Fall	0 (0%)	0 (0%)	2 (2%)
Joint sprain	1 (1%)	0 (0%)	2 (2%)
Respiratory, Thoracic and Mediastinal Disorders	5 (6%)	2 (3%)	4 (5%)
Pharyngolaryngeal pain	2 (2%)	0 (0%)	0 (0%)
Psychiatric Disorders[1]	1 (1%)	1 (1%)	2 (2%)
Musculoskeletal and Connective Tissue Disorders	3 (4%)	1 (1%)	2 (2%)
Back pain	1 (1%)	0 (0%)	2 (2%)

[1]Psychiatric disorder included abnormal dreams (3mg), elevated mood (3mg), libido decreased (3mg), adjustment disorder (1mg), and disorientation (placebo).

Only overall vascular disorders appear to be drug-related, esp. at doxepin 3mg dose level (6% vs 0 in placebo group); among them, one patient who was coded as blood pressure inadequately controlled at 3mg

dose level should also be included in hypertension (that is 4 and 5% instead of 3 and 4%). Other two events in this category are hot flush at 1mg level and hematoma at 3mg level, each consists of 1 event.

However, in the response to our 74-day letter, the sponsor didn't count this hypertension as more than 5 %. The only event they believe that is 5% is nausea in the adult study SP-0501.

6.3.6 Laboratory Findings

Lab tests (clinical chemistry, hematology, and urinalysis) were conducted at Baseline and Last Study Day – about 2.5 days after the last dosing (Day 38 upon completion) in SP-0501, the next day morning after the last dosing (Day 86 upon study completion) in SP-0503 and (Day 28 upon completion) in SP-509. Thus, they were close to or within Tmax time frame (if nonfed, doxepin 3 hours, nordoxepin 8 hours) for SP-0503 and SP-0509, but not for SP-0501. The following tables illustrate mean changes of clinical laboratory test results from baseline to endpoint in key clinical studies.

6.3.6.1 Clinical Chemistry Tests

Mean changes of clinical chemistry tests are summarized in Tables 40-45 that were submitted by the sponsor on Nov. 25, 2008 upon our request.

Table 40a. Mean Changes in Clinical Chemistry Tests from Baseline to Endpoint (SP501)

Parameter	Timepoint	Analysis	Placebo (N=73)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
Magnesium mg/dL	Baseline	Mean (SD)	2.0 (0.2)	2.0 (0.1)	2.0 (0.2)
	Final [1]	Mean (SD)	2.0 (0.2)	2.0 (0.2)	2.0 (0.2)
		Change (SD)	-0.0 (0.2)	-0.0 (0.2)	-0.0 (0.2)
Phosphorus (inorganic) mg/dL	Baseline	Mean (SD)	3.6 (0.5)	3.6 (0.5)	3.5 (0.5)
	Final [1]	Mean (SD)	3.7 (0.5)	3.7 (0.5)	3.7 (0.6)
		Change (SD)	0.1 (0.6)	0.1 (0.6)	0.1 (0.6)
Potassium mEq/L	Baseline	Mean (SD)	4.1 (0.4)	4.1 (0.4)	4.2 (0.3)
	Final [1]	Mean (SD)	4.2 (0.8)	4.1 (0.4)	4.1 (0.4)
		Change (SD)	0.1 (0.8)	0.0 (0.4)	-0.1 (0.4)
Protein, Total g/dL	Baseline	Mean (SD)	7.4 (0.4)	7.3 (0.4)	7.3 (0.5)
	Final [1]	Mean (SD)	7.1 (0.5)	7.1 (0.4)	7.1 (0.5)
		Change (SD)	-0.3 (0.4)	-0.2 (0.4)	-0.2 (0.4)
Sodium mEq/L	Baseline	Mean (SD)	139.9 (2.5)	139.9 (2.3)	140.0 (2.6)
	Final [1]	Mean (SD)	139.7 (2.5)	140.3 (2.3)	140.1 (2.0)
		Change (SD)	-0.1 (3.0)	0.5 (2.5)	0.1 (2.7)
Uric Acid mg/dL	Baseline	Mean (SD)	5.0 (1.5)	5.0 (1.3)	5.1 (1.4)
	Final [1]	Mean (SD)	4.9 (1.4)	5.1 (1.2)	5.0 (1.3)
		Change (SD)	-0.1 (0.8)	0.0 (0.7)	-0.0 (0.8)

[1] Day 38 or Early Termination. The earliest non-missing value after the stop of double-blind treatment is used.

Table 40b Changes in Clinical Chemistry Tests from Baseline to Endpoint in SP-501 (Continued)

Parameter	Timepoint	Analysis	Placebo (N=73)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
Albumin g/dL	Baseline	Mean (SD)	4.5 (0.3)	4.5 (0.2)	4.5 (0.2)
	Final [1]	Mean (SD)	4.3 (0.3)	4.3 (0.3)	4.3 (0.3)
		Change (SD)	-0.2 (0.3)	-0.2 (0.2)	-0.2 (0.3)
Alkaline phosphatase U/L	Baseline	Mean (SD)	67.8 (19.8)	70.4 (21.3)	74.4 (19.3)
	Final [1]	Mean (SD)	65.4 (20.0)	68.6 (18.5)	73.2 (21.0)
		Change (SD)	-1.5 (6.5)	-1.8 (8.9)	-1.6 (9.9)
ALT U/L	Baseline	Mean (SD)	24.2 (13.2)	27.1 (15.4)	24.9 (12.6)
	Final [1]	Mean (SD)	23.8 (12.6)	24.7 (13.2)	27.6 (21.3)
		Change (SD)	-0.3 (11.3)	-2.4 (11.5)	2.5 (15.3)
AST U/L	Baseline	Mean (SD)	23.2 (7.6)	23.1 (5.5)	22.4 (5.1)
	Final [1]	Mean (SD)	22.4 (7.6)	22.0 (6.1)	24.6 (18.5)
		Change (SD)	-0.8 (8.3)	-1.1 (5.6)	2.0 (17.0)
Bicarbonate mEq/L	Baseline	Mean (SD)	26.2 (2.6)	26.2 (2.4)	25.7 (2.1)
	Final [1]	Mean (SD)	26.0 (2.7)	26.4 (2.5)	25.9 (2.2)
		Change (SD)	-0.2 (3.2)	0.2 (2.8)	0.1 (2.8)
Bilirubin Total mg/dL	Baseline	Mean (SD)	0.5 (0.2)	0.5 (0.3)	0.5 (0.3)
	Final [1]	Mean (SD)	0.5 (0.2)	0.5 (0.3)	0.5 (0.2)
		Change (SD)	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)
BUN mg/dL	Baseline	Mean (SD)	13.2 (4.1)	13.3 (3.7)	12.8 (3.4)
	Final [1]	Mean (SD)	13.5 (4.2)	13.5 (3.0)	13.2 (3.6)
		Change (SD)	0.3 (3.8)	0.1 (3.0)	0.5 (3.1)
Chloride mEq/L	Baseline	Mean (SD)	102.8 (2.9)	102.7 (1.9)	103.2 (2.2)
	Final [1]	Mean (SD)	103.4 (2.4)	103.5 (2.2)	103.4 (2.3)
		Change (SD)	0.5 (3.1)	0.8 (2.4)	0.1 (2.5)
Creatinine mg/dL	Baseline	Mean (SD)	1.0 (0.2)	1.0 (0.1)	1.0 (0.2)
	Final [1]	Mean (SD)	1.1 (0.2)	1.0 (0.2)	1.0 (0.1)
		Change (SD)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)
GGT U/L	Baseline	Mean (SD)	22.2 (18.2)	22.3 (13.3)	22.8 (14.5)
	Final [1]	Mean (SD)	21.4 (14.4)	21.2 (13.1)	21.1 (13.4)
		Change (SD)	0.1 (10.3)	-1.0 (6.5)	-1.7 (8.1)
Glucose mg/dL	Baseline	Mean (SD)	89.8 (13.1)	91.2 (13.9)	92.3 (11.6)
	Final [1]	Mean (SD)	93.3 (19.1)	96.5 (19.1)	96.8 (22.9)
		Change (SD)	3.1 (14.0)	5.3 (17.3)	4.4 (17.9)

In SP-501, there were very mild increase of serum glucose in doxepin treatment groups comparing with placebo but not seem to be dose related. The numbers do not appear to be clinically

significant. Only ALT and AST had noticeable small increases in doxepin 6mg compared to placebo at endpoint; however, these changes are neither statistically nor clinically significant. There was no associated change in total bilirubin.

Table 41a. Mean Changes in Clinical Chemistry Tests from Baseline to Endpoint in SP-503
(submitted by the sponsor on Nov. 25, 2008 upon our request)

Parameter	Timepoint	Analysis	Placebo (N=81)	Doxepin 1 mg (N=77)	Doxepin 3 mg (N=82)
Albumin g/dL	Baseline	Mean (SD)	4.3 (0.3)	4.4 (0.3)	4.4 (0.2)
	Final [1]	Mean (SD)	4.2 (0.3)	4.3 (0.3)	4.2 (0.2)
		Change (SD)	-0.1 (0.2)	-0.1 (0.2)	-0.1 (0.2)
Alkaline phosphatase U/L	Baseline	Mean (SD)	75.6 (18.1)	71.9 (20.3)	73.0 (19.6)
	Final [1]	Mean (SD)	75.9 (21.2)	74.3 (25.1)	71.4 (18.4)
		Change (SD)	0.8 (11.4)	2.2 (15.1)	-1.6 (9.3)
ALT U/L	Baseline	Mean (SD)	23.3 (8.8)	24.4 (8.5)	24.2 (9.8)
	Final [1]	Mean (SD)	22.6 (8.9)	22.7 (8.9)	24.6 (11.7)
		Change (SD)	-0.3 (7.2)	-1.7 (7.2)	0.3 (8.2)
AST U/L	Baseline	Mean (SD)	23.4 (5.2)	25.6 (6.7)	23.9 (6.2)
	Final [1]	Mean (SD)	22.8 (5.7)	24.7 (6.4)	24.2 (6.3)
		Change (SD)	-0.5 (4.7)	-0.7 (5.4)	0.3 (5.2)
Bicarbonate mEq/L	Baseline	Mean (SD)	26.1 (2.6)	26.5 (2.3)	26.6 (2.4)
	Final [1]	Mean (SD)	26.1 (2.6)	26.8 (3.0)	26.8 (2.7)
		Change (SD)	0.1 (2.8)	0.3 (2.9)	0.2 (3.1)
Bilirubin Total mg/dL	Baseline	Mean (SD)	0.5 (0.2)	0.5 (0.2)	0.5 (0.2)
	Final [1]	Mean (SD)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)
		Change (SD)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)
BUN mg/dL	Baseline	Mean (SD)	17.4 (4.5)	16.8 (6.4)	16.7 (4.1)
	Final [1]	Mean (SD)	16.8 (4.4)	16.1 (4.7)	16.9 (5.0)
		Change (SD)	-0.7 (4.2)	-0.8 (4.3)	0.2 (4.2)
Chloride mEq/L	Baseline	Mean (SD)	103.1 (2.6)	102.5 (2.7)	102.4 (2.5)
	Final [1]	Mean (SD)	103.8 (2.7)	103.4 (2.4)	103.6 (2.5)
		Change (SD)	0.7 (2.6)	0.8 (2.3)	1.2 (2.6)
Creatinine mg/dL	Baseline	Mean (SD)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)
	Final [1]	Mean (SD)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)
		Change (SD)	0.0 (0.1)	-0.0 (0.1)	0.0 (0.1)
GGT U/L	Baseline	Mean (SD)	24.7 (21.6)	23.7 (20.6)	28.1 (24.9)
	Final [1]	Mean (SD)	28.9 (40.4)	23.7 (22.9)	25.4 (21.2)
		Change (SD)	4.2 (30.2)	0.1 (17.5)	-2.7 (13.0)
Glucose mg/dL	Baseline	Mean (SD)	96.8 (16.2)	95.8 (15.8)	97.2 (20.7)
	Final [1]	Mean (SD)	112.8 (34.2)	107.6 (29.0)	103.0 (22.9)
		Change (SD)	16.0 (32.8)	11.7 (26.9)	5.8 (27.7)

Table 41b. Mean Changes in Clinical Chemistry Tests from Baseline to Endpoint in SP-503 (Continued)

Parameter	Timepoint	Analysis	Placebo (N=81)	Doxepin 1 mg (N=77)	Doxepin 3 mg (N=82)
Magnesium mg/dL	Baseline	Mean (SD)	2.0 (0.2)	2.0 (0.2)	2.0 (0.2)
	Final [1]	Mean (SD)	2.0 (0.2)	2.0 (0.2)	2.0 (0.2)
		Change (SD)	-0.0 (0.2)	0.0 (0.2)	-0.0 (0.2)
Phosphorus (inorganic) mg/dL	Baseline	Mean (SD)	3.6 (0.5)	3.6 (0.5)	3.7 (0.5)
	Final [1]	Mean (SD)	3.5 (0.5)	3.5 (0.5)	3.5 (0.4)
		Change (SD)	-0.1 (0.6)	-0.1 (0.5)	-0.2 (0.5)
Potassium mEq/L	Baseline	Mean (SD)	4.4 (0.5)	4.4 (0.5)	4.3 (0.5)
	Final [1]	Mean (SD)	4.3 (0.5)	4.2 (0.5)	4.2 (0.5)
		Change (SD)	-0.1 (0.5)	-0.2 (0.5)	-0.2 (0.5)
Protein, Total g/dL	Baseline	Mean (SD)	7.1 (0.4)	7.1 (0.4)	7.1 (0.4)
	Final [1]	Mean (SD)	6.9 (0.4)	7.0 (0.4)	7.0 (0.4)
		Change (SD)	-0.1 (0.4)	-0.1 (0.3)	-0.1 (0.3)
Sodium mEq/L	Baseline	Mean (SD)	140.7 (2.4)	140.4 (2.4)	140.5 (2.4)
	Final [1]	Mean (SD)	141.0 (2.6)	140.7 (1.9)	141.1 (2.2)
		Change (SD)	0.3 (2.9)	0.3 (2.6)	0.6 (2.4)
Uric Acid mg/dL	Baseline	Mean (SD)	5.6 (1.4)	5.5 (1.3)	5.3 (1.5)
	Final [1]	Mean (SD)	5.7 (1.4)	5.6 (1.3)	5.6 (1.4)
		Change (SD)	0.2 (0.8)	0.1 (0.7)	0.3 (0.9)

[1] Day 86 or Early Termination. If multiple laboratory assessments are obtained after the last dose of double-blind study drug, the earliest non-missing value is used.

In SP-503, both doxepin dose groups showed less increase of blood glucose compared to placebo. There was minimal increase of ALT, AST, BUN, sodium, and uric acid in doxepin 6mg group, compared to placebo – they are neither statistically nor clinically significant.

Table 42a. Mean Changes in Clinical Chemistry Tests from Baseline to Endpoint in SP-509
(submitted by the sponsor on Nov. 25, 2008 upon our request)

Parameter	Timepoint	Analysis	Placebo (N=124)	Doxepin 6 mg (N=130)
Albumin g/dL	Baseline	Mean (SD)	4.3 (0.2)	4.4 (0.2)
	Final [1]	Mean (SD)	4.3 (0.2)	4.3 (0.3)
		Change (SD)	-0.1 (0.2)	-0.1 (0.2)
Alkaline phosphatase U/L	Baseline	Mean (SD)	74.9 (19.1)	73.5 (17.2)
	Final [1]	Mean (SD)	75.0 (19.9)	73.5 (17.6)
		Change (SD)	0.0 (7.7)	-0.0 (8.4)
ALT U/L	Baseline	Mean (SD)	23.9 (8.5)	24.5 (9.6)
	Final [1]	Mean (SD)	23.0 (8.7)	23.7 (9.8)
		Change (SD)	-1.0 (5.6)	-0.8 (7.2)
AST U/L	Baseline	Mean (SD)	23.9 (6.1)	23.9 (5.8)
	Final [1]	Mean (SD)	23.4 (6.9)	23.4 (6.1)
		Change (SD)	-0.6 (4.1)	-0.5 (4.7)
Bicarbonate mEq/L	Baseline	Mean (SD)	26.7 (2.9)	26.6 (2.5)
	Final [1]	Mean (SD)	26.7 (2.7)	26.7 (2.8)
		Change (SD)	-0.0 (2.7)	0.1 (2.6)
Bilirubin Total mg/dL	Baseline	Mean (SD)	0.6 (0.3)	0.5 (0.3)
	Final [1]	Mean (SD)	0.6 (0.3)	0.5 (0.3)
		Change (SD)	0.0 (0.2)	-0.0 (0.2)
BUN mg/dL	Baseline	Mean (SD)	17.2 (5.3)	18.7 (6.5)
	Final [1]	Mean (SD)	17.6 (5.0)	18.4 (6.3)
		Change (SD)	0.4 (3.7)	-0.3 (4.5)
Chloride mEq/L	Baseline	Mean (SD)	102.5 (2.6)	102.4 (2.5)
	Final [1]	Mean (SD)	103.1 (2.7)	102.7 (3.0)
		Change (SD)	0.6 (2.2)	0.4 (2.3)
Creatinine mg/dL	Baseline	Mean (SD)	1.1 (0.2)	1.1 (0.2)
	Final [1]	Mean (SD)	1.1 (0.2)	1.1 (0.2)
		Change (SD)	0.0 (0.1)	-0.0 (0.1)
GGT U/L	Baseline	Mean (SD)	21.9 (13.3)	23.8 (16.4)
	Final [1]	Mean (SD)	20.7 (11.8)	23.4 (15.1)
		Change (SD)	-1.0 (9.8)	-0.5 (7.8)
Glucose mg/dL	Baseline	Mean (SD)	98.9 (19.1)	97.1 (17.2)
	Final [1]	Mean (SD)	107.5 (31.0)	104.9 (29.3)
		Change (SD)	8.9 (27.5)	7.7 (27.2)

Table 42b. Mean Changes in Clinical Chemistry Tests from Baseline to Endpoint in SP-509 (Continued)

Parameter	Timepoint	Analysis	Placebo (N=124)	Doxepin 6 mg (N=130)
Magnesium mg/dL	Baseline	Mean (SD)	2.0 (0.2)	2.1 (0.2)
	Final [1]	Mean (SD)	2.1 (0.2)	2.0 (0.2)
		Change (SD)	0.0 (0.2)	-0.0 (0.2)
Phosphorus (inorganic) mg/dL	Baseline	Mean (SD)	3.6 (0.5)	3.6 (0.5)
	Final [1]	Mean (SD)	3.4 (0.5)	3.5 (0.5)
		Change (SD)	-0.1 (0.5)	-0.1 (0.6)
Potassium mEq/L	Baseline	Mean (SD)	4.4 (0.4)	4.4 (0.5)
	Final [1]	Mean (SD)	4.3 (0.5)	4.3 (0.5)
		Change (SD)	-0.1 (0.5)	-0.1 (0.5)
Protein, Total g/dL	Baseline	Mean (SD)	7.1 (0.4)	7.1 (0.4)
	Final [1]	Mean (SD)	7.0 (0.4)	7.0 (0.4)
		Change (SD)	-0.1 (0.3)	-0.1 (0.3)
Sodium mEq/L	Baseline	Mean (SD)	140.2 (2.5)	140.3 (2.7)
	Final [1]	Mean (SD)	140.3 (2.4)	140.1 (2.6)
		Change (SD)	0.1 (2.4)	-0.2 (2.2)
Uric Acid mg/dL	Baseline	Mean (SD)	5.3 (1.5)	5.6 (1.6)
	Final [1]	Mean (SD)	5.4 (1.5)	5.6 (1.5)
		Change (SD)	0.1 (0.7)	0.0 (0.7)

[1] Day 28 (Week 4) or Early Termination. If multiple laboratory assessments are obtained after the last dose of double-blind study drug, the earliest non-missing value is used.

Compared to placebo, there is no noticeable change in doxepin group from the submitted data above in SP-509. Serum glucose in doxepin group had less increase than that in placebo.

Overall, there were no clinical or statistically significant changes in clinical chemistry of the three pivotal studies.

Outlier Analysis:

Outliers of clinical laboratory tests of these studies are summarized in Tables 43 - 45.

Table 43. Summary of Outlier Values for Serum Chemistry: Safety Analysis Set (SP-0501)

Parameter/Criteria	Time point	Placebo (N=73)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
AST (U/L)	Baseline	0/ 73 (0 %)	0/ 75 (0 %)	0/ 73 (0 %)
> 3 x ULN	Final*	0/ 70 (0 %)	0/ 75 (0 %)	1/ 71 (1 %)
ALT (U/L)	Baseline	0/ 73 (0 %)	0/ 75 (0 %)	0/ 73 (0 %)
> 3 x ULN	Final*	0/ 70 (0 %)	0/ 75 (0 %)	1/ 71 (1 %)

*Day 38 or Early Termination. If multiple laboratory assessments are obtained after the last dose of double-blind study drug, the earliest non-missing value is used

Based on information of subject ID, there was one outlier of both AST and ALT in doxepin 6mg group. There was no outlier in bilirubin total (≥ 2.0 mg/dL) or ALK (≥ 3 x ULN).

Table 44. Summary of Outlier Values for Serum Chemistry: Safety Analysis Set (SP-0503)

Parameter/Criteria	Time point	Placebo (N=81)	Doxepin 1 mg (N=77)	Doxepin 3 mg (N=82)
BUN (mg/dL)	Baseline	2/ 81 (2 %)	3/ 77 (4 %)	0/ 82 (0 %)
> 30 mg/dL	Final*	0/ 78 (0 %)	1/ 75 (1 %)	2/ 82 (2 %)
Creatinine (mg/dL)	Baseline	0/ 81 (0 %)	1/ 77 (1 %)	0/ 82 (0 %)
> 2.0 mg/dL	Final*	0/ 78 (0 %)	1/ 75 (1 %)	0/ 82 (0 %)
Uric Acid (mg/dL)	Baseline	2/ 81 (2 %)	1/ 77 (1 %)	1/ 82 (1 %)
> 10.5 mg/dL (males); > 8.5 mg/dL (females)	Final*	1/ 78 (1 %)	1/ 75 (1 %)	2/ 82 (2 %)

*Day 86 or Early Termination. If multiple laboratory assessments are obtained after the last dose of double-blind study drug, the earliest non-missing value is used.

There was no outlier for liver function tests. According to subject ID numbers, the outlier with both BUN and creatinine elevations in doxepin 1 mg group was an outlier at baseline as well. Similarly, the outlier with elevated uric acid in that group also had a higher value at baseline, so is one of two outliers in doxepin 3mg group.

Table 45. Summary of Outlier Values for Serum Chemistry: Safety Analysis Set (SP-0509)

Parameter/Criteria	Time point	Placebo (N=124)	Doxepin 6 mg (N=130)
BUN (mg/dL)	Baseline	4/124 (3 %)	9/130 (7 %)
> 30 mg/dL	Final*	3/122 (2 %)	6/129 (5 %)
Creatinine (mg/dL)	Baseline	1/124 (1 %)	1/130 (1 %)
> 2.0 mg/dL	Final*	1/122 (1 %)	1/129 (1 %)
Uric Acid (mg/dL)	Baseline	1/124 (1 %)	4/130 (3 %)
> 10.5 mg/dL (males); > 8.5 mg/dL (females)	Final*	1/122 (1 %)	2/129 (2 %)

*Day 28 (Week 4) or Early Termination. If multiple laboratory assessments are obtained after the last dose of double-blind study drug, the earliest non-missing value is used.

Per information on subject ID's, the outliers of uric acid at final had high baseline values; two of them in doxepin 6mg group didn't remain to be outliers. Rates of outliers of creatinine elevation were the same in two treatment groups; apparently, only one of the six outliers with high BUN in doxepin 6mg at final didn't have high value at baseline; similarly, only one of the three in placebo group had newly increased BUN.

In summary, these outlier data of clinical chemistry tests of three studies are probably not clinically significant.

6.3.6.2 Hematology:

Below are tables (Tables 46 – 48) of mean changes of hematology test results from baseline to endpoint of key studies:

Table 46a. Mean Change of Hematology from Baseline to Endpoint in SP-501
(Submitted by the sponsor on Nov. 25, 2008, upon our request)

Parameter	Timepoint	Analysis	Placebo (N=73)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
Basophils (Abs) ×10^9/L	Baseline	Mean (SD)	0.03 (0.03)	0.03 (0.03)	0.03 (0.02)
	Final [1]	Mean (SD)	0.03 (0.03)	0.03 (0.03)	0.03 (0.03)
		Change (SD)	-0.00 (0.03)	-0.00 (0.03)	0.00 (0.03)
Basophils (Diff) %	Baseline	Mean (SD)	0.55 (0.38)	0.54 (0.42)	0.52 (0.35)
	Final [1]	Mean (SD)	0.55 (0.37)	0.50 (0.40)	0.51 (0.42)
		Change (SD)	-0.01 (0.42)	-0.05 (0.47)	0.02 (0.53)
Eosinophils (Abs) ×10^9/L	Baseline	Mean (SD)	0.13 (0.10)	0.14 (0.10)	0.15 (0.12)
	Final [1]	Mean (SD)	0.17 (0.13)	0.16 (0.10)	0.18 (0.22)
		Change (SD)	0.04 (0.08)	0.02 (0.07)	0.03 (0.20)
Eosinophils (Diff) %	Baseline	Mean (SD)	2.13 (1.83)	2.33 (1.50)	2.26 (1.43)
	Final [1]	Mean (SD)	3.01 (2.91)	2.70 (1.77)	2.84 (3.44)
		Change (SD)	0.91 (1.58)	0.45 (1.30)	0.57 (3.10)
Erythrocytes ×10^12/L	Baseline	Mean (SD)	4.64 (0.45)	4.57 (0.39)	4.67 (0.39)
	Final [1]	Mean (SD)	4.65 (0.46)	4.63 (0.40)	4.69 (0.45)
		Change (SD)	0.00 (0.21)	0.05 (0.23)	0.01 (0.25)
Hematocrit %	Baseline	Mean (SD)	41.7 (3.9)	41.1 (3.8)	41.5 (3.4)
	Final [1]	Mean (SD)	41.8 (4.0)	41.5 (4.0)	41.5 (3.9)
		Change (SD)	-0.0 (2.0)	0.4 (2.4)	-0.2 (2.4)

Table 46b. Mean Change of Hematology from Baseline to Endpoint in SP-501
(Continued)

Hemoglobin g/dL	Baseline	Mean (SD)	14.0 (1.5)	13.8 (1.4)	14.0 (1.3)
	Final [1]	Mean (SD)	14.1 (1.4)	14.0 (1.4)	14.0 (1.4)
		Change (SD)	0.0 (0.7)	0.1 (0.7)	-0.0 (0.8)
Leukocytes ×10^9/L	Baseline	Mean (SD)	6.3 (1.9)	6.3 (2.0)	6.6 (2.0)
	Final [1]	Mean (SD)	5.9 (1.7)	6.1 (1.9)	6.1 (1.7)
		Change (SD)	-0.3 (1.2)	-0.3 (1.2)	-0.5 (1.4)
Lymphocytes (Abs) ×10^9/L	Baseline	Mean (SD)	1.89 (0.58)	1.95 (0.55)	2.00 (0.63)
	Final [1]	Mean (SD)	2.01 (0.60)	2.19 (0.68)	2.06 (0.64)
		Change (SD)	0.13 (0.44)	0.21 (0.43)	0.08 (0.53)
Lymphocytes (Diff) %	Baseline	Mean (SD)	30.68 (6.92)	31.88 (7.60)	31.52 (9.52)
	Final [1]	Mean (SD)	35.28 (9.21)	35.82 (9.53)	34.01 (8.80)
		Change (SD)	4.41 (7.40)	4.44 (7.90)	2.87 (6.77)
Monocytes (Abs) ×10^9/L	Baseline	Mean (SD)	0.44 (0.18)	0.42 (0.15)	0.44 (0.15)
	Final [1]	Mean (SD)	0.43 (0.16)	0.41 (0.13)	0.43 (0.14)
		Change (SD)	-0.01 (0.16)	-0.02 (0.13)	-0.01 (0.15)

Table 46c. Mean Change of Hematology from Baseline to Endpoint in SP-501
(Continued)

Parameter	Timepoint	Analysis	Placebo (N=73)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
Monocytes (Diff) %	Baseline	Mean (SD)	7.08 (2.40)	6.89 (2.10)	6.84 (2.01)
	Final [1]	Mean (SD)	7.55 (2.48)	6.80 (2.06)	7.23 (2.29)
		Change (SD)	0.38 (2.85)	-0.01 (1.91)	0.37 (2.21)
Neutrophils (Abs) ×10^9/L	Baseline	Mean (SD)	3.79 (1.43)	3.81 (1.66)	3.98 (1.66)
	Final [1]	Mean (SD)	3.22 (1.33)	3.48 (1.39)	3.46 (1.23)
		Change (SD)	-0.49 (1.04)	-0.46 (1.17)	-0.59 (1.23)
Neutrophils (Diff) %	Baseline	Mean (SD)	59.56 (7.65)	58.36 (8.34)	58.87 (10.34)
	Final [1]	Mean (SD)	53.61 (10.49)	54.18 (10.26)	55.40 (9.57)
		Change (SD)	-5.68 (9.30)	-4.83 (9.26)	-3.84 (7.89)
Platelet count ×10^9/L	Baseline	Mean (SD)	272.5 (61.8)	283.2 (66.5)	275.4 (60.6)
	Final [1]	Mean (SD)	274.8 (70.9)	288.1 (70.4)	267.4 (57.2)
		Change (SD)	3.6 (31.3)	4.2 (35.5)	-6.6 (27.6)

[1] Day 38 or Early Termination. The earliest non-missing value after the stop of double-blind treatment is used.

In Study 501, both leukocytes and platelet account decrease slightly and seem to be dose related for platelets; but neither is statistically significant. All other parameters seem to be stable through the study.

In Study 503, there are slightly more decrease of leukocytes and neutrophils (both differential and absolute), and appear to be dose-related; however, they don't seem to be statistically significant. There are no other apparent relevant changes. (See Tables 47a-47b)

Table 47a. Mean Change of Hematology from Baseline to Endpoint in SP-503
(Submitted by the sponsor on Nov. 25, 2008, upon our request)

Parameter	Timepoint	Analysis	Placebo (N=81)	Doxepin 1 mg (N=77)	Doxepin 3 mg (N=82)
Monocytes (Diff) %	Baseline	Mean (SD)	8.27 (2.62)	8.60 (2.42)	7.60 (1.99)
	Final [1]	Mean (SD)	8.41 (2.79)	8.64 (2.53)	7.62 (2.41)
		Change (SD)	0.19 (1.70)	-0.14 (1.98)	0.10 (2.07)
Neutrophils (Abs) ×10^9/L	Baseline	Mean (SD)	3.98 (1.22)	3.93 (1.32)	4.34 (1.57)
	Final [1]	Mean (SD)	3.79 (1.72)	3.41 (1.17)	3.79 (1.64)
		Change (SD)	-0.17 (1.46)	-0.49 (1.11)	-0.58 (1.76)
Neutrophils (Diff) %	Baseline	Mean (SD)	60.52 (8.06)	60.02 (8.87)	61.93 (8.51)
	Final [1]	Mean (SD)	57.94 (9.48)	56.48 (8.41)	56.45 (9.78)
		Change (SD)	-2.44 (8.20)	-3.22 (8.80)	-5.59 (9.90)
Platelet count ×10^9/L	Baseline	Mean (SD)	256.3 (61.0)	264.7 (63.0)	264.7 (53.4)
	Final [1]	Mean (SD)	244.0 (63.0)	263.1 (63.7)	258.1 (51.0)
		Change (SD)	-10.7 (25.7)	-3.2 (44.1)	-6.4 (38.7)

[1] Day 86 or Early Termination. If multiple laboratory assessments are obtained after the last dose of double-blind study drug, the earliest non-missing value is used.

(To be continued on next page)

Table 47b. Mean Change of Hematology from Baseline to Endpoint in SP-503

Parameter	Timepoint	Analysis	Placebo (N=81)	Doxepin 1 mg (N=77)	Doxepin 3 mg (N=82)
Basophils (Abs) ×10^9/L	Baseline	Mean (SD)	0.03 (0.02)	0.03 (0.02)	0.04 (0.03)
	Final [1]	Mean (SD)	0.03 (0.03)	0.03 (0.02)	0.04 (0.03)
		Change (SD)	-0.00 (0.03)	-0.00 (0.03)	-0.00 (0.03)
Basophils (Diff) %	Baseline	Mean (SD)	0.54 (0.38)	0.52 (0.42)	0.57 (0.36)
	Final [1]	Mean (SD)	0.54 (0.35)	0.49 (0.25)	0.58 (0.38)
		Change (SD)	-0.01 (0.45)	-0.04 (0.49)	0.01 (0.49)
Eosinophils (Abs) ×10^9/L	Baseline	Mean (SD)	0.17 (0.08)	0.19 (0.14)	0.16 (0.11)
	Final [1]	Mean (SD)	0.20 (0.11)	0.22 (0.14)	0.23 (0.19)
		Change (SD)	0.04 (0.07)	0.03 (0.12)	0.06 (0.13)
Eosinophils (Diff) %	Baseline	Mean (SD)	2.61 (1.41)	2.98 (2.30)	2.39 (1.50)
	Final [1]	Mean (SD)	3.35 (1.90)	3.66 (2.32)	3.47 (2.37)
		Change (SD)	0.78 (1.28)	0.64 (1.96)	1.07 (1.73)
Erythrocytes ×10^12/L	Baseline	Mean (SD)	4.53 (0.45)	4.60 (0.40)	4.59 (0.42)
	Final [1]	Mean (SD)	4.52 (0.43)	4.61 (0.38)	4.58 (0.43)
		Change (SD)	-0.01 (0.25)	0.01 (0.27)	-0.00 (0.25)
Hematocrit %	Baseline	Mean (SD)	41.3 (3.8)	41.5 (3.5)	41.6 (3.5)
	Final [1]	Mean (SD)	41.3 (3.7)	41.6 (3.0)	41.6 (3.8)
		Change (SD)	-0.0 (2.2)	0.0 (2.1)	0.1 (2.2)
Hemoglobin g/dL	Baseline	Mean (SD)	14.0 (1.3)	14.1 (1.2)	14.1 (1.2)
	Final [1]	Mean (SD)	14.0 (1.3)	14.1 (1.1)	14.1 (1.3)
		Change (SD)	-0.0 (0.7)	-0.0 (0.7)	-0.0 (0.7)
Leukocytes ×10^9/L	Baseline	Mean (SD)	6.5 (1.4)	6.4 (1.7)	6.9 (1.9)
	Final [1]	Mean (SD)	6.4 (2.0)	5.9 (1.5)	6.5 (2.0)
		Change (SD)	-0.1 (1.6)	-0.5 (1.2)	-0.4 (1.8)
Lymphocytes (Abs) ×10^9/L	Baseline	Mean (SD)	1.79 (0.47)	1.75 (0.57)	1.85 (0.58)
	Final [1]	Mean (SD)	1.84 (0.57)	1.78 (0.54)	2.03 (0.63)
		Change (SD)	0.04 (0.35)	0.04 (0.36)	0.17 (0.55)
Lymphocytes (Diff) %	Baseline	Mean (SD)	28.07 (6.88)	27.88 (7.90)	27.51 (7.52)
	Final [1]	Mean (SD)	29.76 (8.04)	30.73 (8.14)	31.88 (9.50)
		Change (SD)	1.49 (6.92)	2.76 (7.15)	4.41 (8.56)
Monocytes (Abs) ×10^9/L	Baseline	Mean (SD)	0.53 (0.19)	0.55 (0.20)	0.52 (0.19)
	Final [1]	Mean (SD)	0.53 (0.22)	0.50 (0.16)	0.49 (0.21)
		Change (SD)	0.01 (0.15)	-0.06 (0.14)	-0.03 (0.17)

Table 48a. Mean Change of Hematology from Baseline to Endpoint in SP-509
(Submitted by the sponsor on Nov. 25, 2008, upon our request)

Parameter	Timepoint	Analysis	Placebo (N=124)	Doxepin 6 mg (N=130)
Basophils (Abs) ×10^9/L	Baseline	Mean (SD)	0.03 (0.02)	0.04 (0.03)
	Final [1]	Mean (SD)	0.03 (0.02)	0.03 (0.02)
		Change (SD)	0.00 (0.03)	0.00 (0.04)
Basophils (Diff) %	Baseline	Mean (SD)	0.50 (0.32)	0.56 (0.39)
	Final [1]	Mean (SD)	0.47 (0.33)	0.53 (0.34)
		Change (SD)	-0.03 (0.42)	-0.02 (0.52)
Eosinophils (Abs) ×10^9/L	Baseline	Mean (SD)	0.16 (0.13)	0.19 (0.15)
	Final [1]	Mean (SD)	0.17 (0.17)	0.22 (0.17)
		Change (SD)	0.01 (0.09)	0.03 (0.12)
Eosinophils (Diff) %	Baseline	Mean (SD)	2.44 (1.77)	2.85 (2.07)
	Final [1]	Mean (SD)	2.73 (2.26)	3.50 (2.64)
		Change (SD)	0.29 (1.35)	0.64 (1.89)
Erythrocytes ×10^12/L	Baseline	Mean (SD)	4.61 (0.41)	4.56 (0.40)
	Final [1]	Mean (SD)	4.53 (0.44)	4.49 (0.41)
		Change (SD)	-0.08 (0.23)	-0.07 (0.18)
Hematocrit %	Baseline	Mean (SD)	41.9 (3.4)	41.4 (3.4)
	Final [1]	Mean (SD)	41.2 (3.8)	40.6 (3.5)
		Change (SD)	-0.7 (2.1)	-0.7 (1.7)
Hemoglobin g/dL	Baseline	Mean (SD)	14.2 (1.2)	14.0 (1.2)
	Final [1]	Mean (SD)	14.0 (1.3)	13.7 (1.2)
		Change (SD)	-0.2 (0.7)	-0.2 (0.6)
Leukocytes ×10^9/L	Baseline	Mean (SD)	6.8 (1.6)	6.8 (1.7)
	Final [1]	Mean (SD)	6.5 (1.6)	6.4 (1.6)
		Change (SD)	-0.3 (1.1)	-0.4 (1.2)
Lymphocytes (Abs) ×10^9/L	Baseline	Mean (SD)	1.84 (0.67)	1.84 (0.53)
	Final [1]	Mean (SD)	1.81 (0.74)	1.78 (0.57)
		Change (SD)	-0.04 (0.37)	-0.05 (0.37)
Lymphocytes (Diff) %	Baseline	Mean (SD)	27.56 (8.04)	27.70 (7.64)
	Final [1]	Mean (SD)	28.15 (7.70)	28.50 (8.26)
		Change (SD)	0.56 (6.09)	0.86 (5.41)
Monocytes (Abs) ×10^9/L	Baseline	Mean (SD)	0.50 (0.15)	0.53 (0.17)
	Final [1]	Mean (SD)	0.49 (0.15)	0.51 (0.17)
		Change (SD)	-0.01 (0.13)	-0.02 (0.14)

Table 48b. Mean Change of Hematology from Baseline to Endpoint in SP-509

Parameter	Timepoint	Analysis	Placebo (N=124)	Doxepin 6 mg (N=130)
Monocytes (Diff) %	Baseline	Mean (SD)	7.50 (2.16)	7.89 (2.08)
	Final [1]	Mean (SD)	7.69 (2.11)	8.10 (2.48)
		Change (SD)	0.19 (1.83)	0.21 (2.00)
Neutrophils (Abs) ×10^9/L	Baseline	Mean (SD)	4.23 (1.30)	4.22 (1.44)
	Final [1]	Mean (SD)	3.95 (1.20)	3.87 (1.35)
		Change (SD)	-0.28 (1.07)	-0.36 (1.10)
Neutrophils (Diff) %	Baseline	Mean (SD)	62.00 (8.38)	61.00 (8.38)
	Final [1]	Mean (SD)	60.96 (7.93)	59.37 (9.01)
		Change (SD)	-1.01 (7.47)	-1.69 (6.95)
Platelet count ×10^9/L	Baseline	Mean (SD)	261.2 (61.9)	269.8 (77.8)
	Final [1]	Mean (SD)	256.4 (58.3)	265.1 (75.6)
		Change (SD)	-4.8 (29.5)	-5.9 (32.4)

[1] Day 28 (Week 4) or Early Termination. If multiple laboratory assessments are obtained after the last dose of double-blind study drug, the earliest non-missing value is used.

There appears to be slight more decrease in neutrophils, both differential and absolute, in doxepin group than placebo; yet the decrement is not statistically significant. Lymphocytes and eosinophils (absolute and differential) had some increase in doxepin group compared to placebo: Change of eosinophils differential seems to be statistically significant but with unclear clinical significance and change in absolute value is not statistically significant. Minor changes in lymphocyte and platelet counts are not significant, either.

Overall, no statistically significant changes in hematology test results though there seem to be a trend of decrement of neutrophils in doxepin groups than placebo, so is platelets but not in all studies. The trend of increment of eosinophils in one of these studies was not statistically significant, either.

Outlier Analysis:

The following table illustrates outliers of hematologic parameters in SP-0501:

Table 49. Outliers of Hematologic Parameters in SP-0501

Parameter/Criteria	Time point	Placebo (N=73)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
Hematocrit (%)	Baseline	0/ 73 (0 %)	1/ 75 (1 %)	0/ 73 (0 %)
≤ 37% (males);	Final [1]	0/ 69 (0 %)	1/ 74 (1 %)	2/ 70 (3 %)
≤ 32% (females)				
Hemoglobin (g/dL)	Baseline	0/ 73 (0 %)	1/ 75 (1 %)	0/ 73 (0 %)
≤ 11.5 g/dL (males);	Final [1]	0/ 69 (0 %)	0/ 74 (0 %)	0/ 70 (0 %)
≤ 9.5 g/dL (females)				
Leukocytes (x10^9/L)	Baseline	0/ 73 (0 %)	3/ 75 (4 %)	0/ 73 (0 %)
≤ 2.8 x 10^9/L	Final [1]	0/ 69 (0 %)	3/ 73 (4 %)	2/ 70 (3 %)
Leukocytes (x10^9/L)	Baseline	0/ 73 (0 %)	0/ 75 (0 %)	0/ 73 (0 %)
> 16 x 10^9/L	Final [1]	0/ 69 (0 %)	0/ 73 (0 %)	0/ 70 (0 %)
Neutrophils (x10^9/L)	Baseline	0/ 73 (0 %)	1/ 74 (1 %)	2/ 73 (3 %)
≤ 1.4 x 10^9/L	Final [1]	4/ 68 (6 %)	3/ 69 (4 %)	2/ 67 (3 %)
Neutrophils (%) ≤ 15%	Baseline	0/ 73 (0 %)	0/ 74 (0 %)	0/ 73 (0 %)
	Final [1]	0/ 68 (0 %)	1/ 69 (1 %)	0/ 67 (0 %)
Eosinophils (%) > 10%	Baseline	1/ 73 (1 %)	0/ 74 (0 %)	0/ 73 (0 %)
	Final [1]	2/ 68 (3 %)	0/ 69 (0 %)	1/ 67 (1 %)

Among the three outliers of hematocrit change, one in doxepin 3mg group (it wasn't the same subject who had the baseline abnormality) and 2 in the 6mg group; none in placebo. Among the five outliers of decreased leukocytes, three were new cases: 1 in 3mg group and 2 in 6mg group; none in placebo. However, with regard to decreased neutrophils, four new outliers were in placebo group while two new cases in each of the doxepin groups. Eosinophil increase resulted in one case of new outlier in placebo and one in doxepin 6mg group. There was no outlier of platelet count changes.

In SP-0503, using the same criteria, there was one outlier of hematocrit decrease at the end of the study in doxepin 3mg and one new case in placebo group. No outlier of leukocyte change or platelet change is seen. Yet, increase of eosinophils is seen in four subjects of doxepin treatment groups: 1 in 3mg group and 3 in 1 mg group.

Likewise, outliers of hematocrit decrease and eosinophil increase are seen in SP-0509 but more outliers are seen in placebo group than doxepin 6mg group (3:1 for hematocrit; 2:1 for eosinophils). Since this study is much shorter than SP-0503, it could be due to the duration differences.

6.3.6.3 Urinalysis:

The results for urinalysis were not integrated. The sponsor only emphasized urine glucose that increased in similar number of patients in both placebo and doxepin groups in all three studies. Upon examining the listings, there were a few patients from both groups who had hemoglobin in the urine but overall significance is unclear.

6.3.7 Vital Signs

In all three studies, vital signs were measured at baseline, during each visit and at the end of study. The sponsor's analysis of vital signs only used observed data and in Study 0503, change of blood pressured from baseline to endpoint was not conducted. Request to the sponsor was made on Nov. 19, 2008 and the sponsor resubmitted analyses with the following data. Since measures were conducted both pre-dosing and post-dosing, the analyses were requested for both sets. Mean changes (and standard deviation) of vital signs from baseline to endpoint are presented by each controlled longer term study (1-3 months) and analysis of outliers is presented after mean change analysis.

SP-0501: The following tables illustrate changes of systolic blood pressure, diastolic blood pressure from baseline to endpoint. Although there appears to be statistical significant increase of systolic blood pressure at 3mg dose during last two visits, they don't seem to be clinically meaningful to me. (See below.)

Pre-dose: **Table 50. Change from Baseline in Systolic Blood Pressure: *Pre*-Dose Parameters (SP-0501)**

Vital Sign	Timepoint	Analysis (mmHg)	Placebo	Doxepin 3 mg	Doxepin 6 mg
Systolic Blood Pressure	Baseline (Visit 3)[1]	Mean (SD)	117.7 (10.96)	120.0 (13.74)	118.1 (10.12)
	Visit 4, Night 1[2]	Mean (SD)	117.6 (12.20)	120.2 (12.87)	118.5 (10.90)
		Change (SD)	-0.1 (8.88)	0.2 (9.50)	0.4 (8.72)
		p-value	0.9372	0.8558	0.6834
	Visit 4, Night 2	Mean (SD)	117.7 (12.86)	119.7 (12.80)	119.2 (13.10)
		Change (SD)	0.0 (9.23)	-0.2 (9.23)	1.1 (10.17)
		p-value	0.9899	0.8409	0.3692
	Visit 5, Night 15	Mean (SD)	117.6 (14.84)	122.1 (14.40)	120.1 (12.92)
		Change (SD)	-0.1 (12.04)	2.0 (10.27)	2.0 (10.21)
		p-value	0.9296	0.1114	0.1056
	Visit 5, Night 16	Mean (SD)	115.6 (12.78)	120.2 (11.21)	118.3 (13.30)
		Change (SD)	-2.1 (8.76)	1.1 (9.50)	0.1 (10.73)
		p-value	0.0504	0.3201	0.9596
	Visit 6, Night 29	Mean (SD)	117.9 (12.22)	121.5 (12.43)	118.1 (12.25)
		Change (SD)	0.0 (10.65)	**2.5 (9.04)**	-0.1 (10.23)
		p-value	0.9955	**0.0259**	0.9206
	Visit 6, Night 30	Mean (SD)	116.5 (12.64)	120.4 (12.53)	119.4 (12.58)
		Change (SD)	-1.4 (11.01)	1.5 (10.30)	1.1 (10.36)
		p-value	0.3002	0.2307	0.3739
	Visit 7[3], Night 36	Mean (SD)	116.5 (12.41)	121.5 (13.14)	118.3 (11.38)
		Change (SD)	-1.3 (9.51)	**2.8 (9.17)**	0.2 (10.27)
		p-value	0.2516	**0.0144**	0.8646
	Visit 7[3], Night 37 /Endpoint	Mean (SD)	119.4 (12.02)	123.0 (12.72)	118.8 (11.02)
		Change (SD)	1.7 (11.38)	**2.9 (10.43)**	0.7 (10.29)
		p-value	0.2061	**0.0197**	0.5449

1. Baseline is the average of pre-dose values obtained at Visit 3 (Night -6 and Night -5).
2. Visit 4, Night 1 vital signs were obtained prior to the first dose of study drug.
3. Visit 7 occurred during the placebo-run-out period.

There were no clinically meaningful significant differences in mean changes of diastolic blood pressure, heart rate, and respiratory rate under *pre*-dose conditions during SP-0501.

Post-dose: The mean change of systolic blood pressure from baseline was statistically significant at endpoint (Visit 7) on *post*-dose days; but again, it was only 3-4mmg change and probably not clinically significant. (See table below.)

Table 51. Change from Baseline in Systolic Blood Pressure: Post-Dose Parameters (SP-0501)

Vital Sign	Time point	Analysis (mmHg)	Placebo (N=73)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
Systolic Blood Pressure	Baseline (Visit 3)[1]	Mean (SD)	114.46 (11.25)	118.36 (12.93)	115.44 (9.16)
	Visit 4, Day 2	Mean (SD)	113.87 (11.02)	117.73 (12.65)	115.37 (10.28)
		Change (SD)	-0.59 (7.88)	-0.64 (10.03)	-0.08 (8.40)
		p-value	0.5289	0.5876	0.9383
	Visit 4, Day 3	Mean (SD)	114.72 (12.24)	117.27 (14.46)	115.97 (11.23)
		Change (SD)	0.25 (9.24)	-1.09 (8.92)	0.53 (9.59)
		p-value	0.8178	0.2948	0.6441
	Visit 5, Day 16	Mean (SD)	114.52 (10.90)	117.91 (15.27)	115.86 (11.31)
		Change (SD)	0.06 (10.20)	-0.46 (8.21)	0.42 (8.18)
		p-value	0.9630	0.6317	0.6698
	Visit 5, Day 17	Mean (SD)	115.41 (12.47)	118.08 (15.10)	114.38 (11.52)
		Change (SD)	0.94 (10.21)	-0.28 (8.79)	-1.06 (9.05)
		p-value	0.4385	0.7819	0.3256
	Visit 6, Day 30	Mean (SD)	115.28 (12.40)	120.39 (14.71)	116.23 (11.45)
		Change (SD)	0.82 (11.11)	2.03 (9.62)	0.78 (9.50)
		p-value	0.5376	0.0740	0.4905
	Visit 6, Day 31	Mean (SD)	115.38 (11.41)	119.92 (14.34)	115.86 (11.44)
		Change (SD)	0.92 (8.97)	1.55 (8.78)	0.42 (10.45)
		p-value	0.3930	0.1320	0.7386
	Visit 7[2], Day 37	Mean (SD)	115.28 (11.81)	120.27 (15.16)	116.18 (12.35)
		Change (SD)	0.82 (8.84)	1.91 (7.63)	0.74 (11.43)
		p-value	0.4389	**0.0351**	0.5873
	Visit 7[2], Day 38 /Endpoint	Mean (SD)	114.00 (11.90)	121.38 (14.67)	117.24 (11.24)
		Change (SD)	-0.46 (9.37)	3.01 (9.62)	1.80 (9.64)
		p-value	0.6771	**0.0087**	0.1212

Note: Missing values were imputed using the LOCF method, using only post-dose values.
1. Baseline is the average of post-dose values obtained at Visit 3 (Day -5 and Day -4).
2. Visit 7 occurred during the placebo-run-out period.

There was no significant difference in mean changes of diastolic blood pressure or heart rate from baseline to endpoint on post-dose days. Though p-value of mean change in respiratory rate was 0.0077 for doxepin 3mg group, it is not meaningful clinically as the change was about 1/min only.

6.3.7.1 SP-0503:

Pre-dose: In 1mg dose group, there was a statistically significant drop of systolic blood pressure at Visit 6 (p=0.0042, from 129 mmHg to 125 mmHg) but not at Visit 7/endpoint (p=0.1024) and probably with little clinical significance. There were no significant changes in diastolic blood pressure or heart rate; A seemingly significant change in respiratory rate in 3mg dose group at Visit 5 (p=0.0168) only reflects the change of less than 1/min and thus not clinically meaningful.

Post-dose: No statistically significant changes seen in mean values of systolic blood pressure and respiratory rate; At dose 3mg/day, there was a drop of diastolic blood pressure (p=0.0068) but only about 2mmHg and the effect disappears at Visit 7/Endpoint. Similarly, a drop of heart rate at the beginning of the trial (Visit 3) in 3mg dose group (p=0.0447), it was a 2 beats/min difference and no significant changes seen in later stage of the trial or another dose group.

6.3.7.2 SP-0509:

The sponsor didn't specify the dose condition (pre- or post- dose) of vital signs analyses of this study and only provided one set of analyses. Given data provided, there was no significant change in mean value of systolic blood pressure, heart rate, and respiratory rate; but statistically significant change is seen in mean diastolic blood pressure in 6mg dose group (p=0.0311) at Visit 7/Endpoint. The actual change involved was 1.7 mmHg increments.

Overall, the magnitude of mean changes in vital signs doesn't seem to be clinically meaningful. In addition, the variations are larger than the mean changes in most cases. Some are not necessarily consistent with time progress.

Outliers Analysis:

Based on preset Vital Sign parameters, Tables 52a-d summarize the number of outliers in Studies 501 submitted by the sponsor upon our request. Note: The reference table 1.6.10 of M.5.3.5.3 referred by the sponsor as listing of overall outliers of vital signs shows only three elderly subjects in one page and all from Study 509 without change from baseline indicated all only appear to have low value of blood pressure or heart rate. Request of subject ID or clarification was made on Jan. 30, 2009. The sponsor submits the following for low systolic blood pressure without explanation of the difference of numbers of outliers for Visit 6 (the four digit numbers in the following series tables represent the subject ID.). (The second line on the title of Table 52c is the original title for the table provided by the sponsor.)

Table 52a. Outliers and Subject ID's Submitted by the Sponsor on Jan. 31, 2009

Table 21. Number of Subjects with Outlier Vital Sign Values: Low Systolic Blood Pressure (SP-0501)

Visit	Placebo (N=73)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
Baseline (Visit 4, Night 1)[1]	0	1 {3031}	1 {3036}
Visit 4 (Day 2 through Day 3)[2]	1 {3035}	0	1{3032}
Visit 5 (Night 15 through Day 17)[2]	1 {3035}	0	2 {3289, 3032}
Visit 6 (Night 29 through Day 31)[2]	2 {3182, 3319}	1 {3061}	2 {3032, 3093}
Visit 7 (Night 36 through Day 38)[2, 3]	0	0	1 {3032}

Note: Baseline is defined to be the last assessment of vital signs obtained prior to administration of the first dose of double-blind study drug.

1. Outlier criteria is SBP≤90 mmHg
2. Outlier criteria is SBP≤90 mmHg and a decrease from baseline ≥20 mmHg
3. Visit 7 occurred during the placebo-run-out period.

Nevertheless, the end result is that there was one outlier who had low systolic blood pressure at the end of the study in doxepin 6mg group. Overall, more outliers of low systolic blood pressure were in doxepin 6mg than those in two other treatment groups.

There was no significant difference in low diastolic blood pressure between placebo and doxepin 3mg group and none in doxepin 6mg group. The two tables below show outliers of high blood pressure during Study SP-0501:

Table 52b Number of Subjects with Outlier Vital Sign Values-High Systolic Blood Pressure

Visit	Placebo (N=73)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
Baseline (Visit 4, Night 1)[1]	0	0	0
Visit 4 (Day 2 through Day 3)[2]	0	1 {3223}	0
Visit 5 (Night 15 through Day 17)[2]	0	1 {3223}	0
Visit 6 (Night 29 through Day 31)[2]	0	0	0
Visit 7 (Night 36 through Day 38)[2, 3]	0	0	0

1. Outlier criteria is SBP≥180 mmHg
2. Outlier criteria is SBP≥180 mmHg and an increase from baseline ≥20 mmHg
3. Visit 7 occurred during the placebo-run-out period.

Table 52c. Number of Subjects with Outlier Vital Sign Values: High Diastolic Blood Pressure (SP-0501)

Visit	Placebo (N=73)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
Baseline (Visit 4, Night 1)[1]	0	0	0
Visit 4 (Day 2 through Day 3)[2]	0	0	0
Visit 5 (Night 15 through Day 17)[2]	1 {3046}	0	0
Visit 6 (Night 29 through Day 31)[2]	1 {3046}	0	0
Visit 7 (Night 36 through Day 38)[2, 3]	0	1 {3109}	0

1. Outlier criteria is DBP≥105 mmHg
2. Outlier criteria is DBP≥105 mmHg and an increase from baseline ≥15 mmHg
3. Visit 7 occurred during the placebo-run-out period.

Both high systolic and diastolic blood pressure, one of each, were found in doxepin 3mg group but there was one outlier of high diastolic blood pressure in placebo group also and none in doxepin 6mg group. Interestingly, outliers with low systolic blood pressure was found more in doxepin 6mg group compared to 3mg group or placebo. One subject in 3mg group became an outlier of higher heart rate (HR ≥110 bpm and an increase from baseline ≥15 bpm) at the end of the study but none in other groups. The next table illustrates the outliers of low heart rate in each treatment group of SP-0501 and it appears no significant differences between placebo and doxepin groups.

Table 52d. Number of Subjects with Outlier Vital Sign Values: Low Heart Rate (SP-0501)

Visit	Placebo (N=73)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
Baseline (Visit 4, Night 1)[1]	1 {3219}	0	2 {3213, 3121}
Visit 4 (Day 2 through Day 3)[2]	1 {3196}	1 {3223}	1 {3116}
Visit 5 (Night 15 through Day 17)[2]	0	1 {3014}	1 {3160}
Visit 6 (Night 29 through Day 31)[2]	0	0	0
Visit 7 (Night 36 through Day 38)[2, 3]	2 {3196, 3319}	1 {3223}	0

Note: Baseline is defined to be the last assessment of vital signs obtained prior to administration of the first dose of double-blind study drug.

1. Outlier criteria is HR≤50 bpm
2. Outlier criteria is HR≤50 bpm and a decrease from baseline ≥15 bpm
3. Visit 7 occurred during the placebo-run-out period.

In Study 503, there were no outliers of low systolic blood pressure in doxepin groups but three outliers of high systolic blood pressure, two outliers of high diastolic blood pressure and three

outliers of low diastolic blood pressure at the end of the study in doxepin groups. Outliers of high diastolic blood pressure seem to be the same as placebo; however, those in doxepin group appeared late in the trial while the ones in placebo appeared early in the study. Likewise, outliers high systolic blood pressure appeared late in the study while the ones in placebo group appeared early in the study. There is no outlier at the end of the study in placebo group. (See the three tables below re-submitted by the sponsor.)

Table 53a Number of Subjects with Outlier Vital Sign Values -High Systolic Blood Pressure

Visit	Placebo (N=81)	Doxepin 1 mg (N=77)	Doxepin 3 mg (N=82)
Baseline (Visit 3, Night 1) [1]	1 {7212}	0	0
Visit 3 (Day 2) [2]	1 {7228}	0	0
Visit 4 (Night 15, Day 16) [2]	0	1 {7346}	0
Visit 5 (Night 29, Day 30) [2]	0	0	0
Visit 6 (Night 57, Day 58) [2]	0	0	0
Visit 7 (Night 85, Day 86) [2]	0	1 {7044}	2 {7056, 7345}

Note: Baseline is defined to be the last assessment of vital signs obtained prior to administration of the first dose of double-blind study drug.

1. Outlier criteria is SBP≥180 mmHg
2. Outlier criteria is SBP≥180 mmHg and an increase from baseline ≥20 mmHg

Table 53b Number of Subjects with Outlier Vital Sign Values-High Diastolic Blood Pressure

Visit	Placebo (N=81)	Doxepin 1 mg (N=77)	Doxepin 3 mg (N=82)
Baseline (Visit 3, Night 1) [1]	0	0	0
Visit 3 (Day 2) [2]	2 {7228, 7286}	0	0
Visit 4 (Night 15, Day 16) [2]	0	0	0
Visit 5 (Night 29, Day 30) [2]	0	0	1 {7174}
Visit 6 (Night 57, Day 58) [2]	0	0	0
Visit 7 (Night 85, Day 86) [2]	0	0	1 {7350}

Note: Baseline is defined to be the last assessment of vital signs obtained prior to administration of the first dose of double-blind study drug.

1. Outlier criteria is DBP≥105 mmHg
2. Outlier criteria is DBP≥105 mmHg and an increase from baseline ≥15 mmHg

Table 53c shows more outliers of low diastolic blood pressure in doxepin groups as well.

Table 53 c. Number of Subjects with Outlier Vital Sign Values -Low Diastolic Blood Pressure

Visit	Placebo (N=81)	Doxepin 1 mg (N=77)	Doxepin 3 mg (N=82)
Baseline (Visit 3, Night 1) [1]	0	0	0
Visit 3 (Day 2) [2]	0	0	0
Visit 4 (Night 15, Day 16) [2]	0	0	0
Visit 5 (Night 29, Day 30) [2]	1 {7019}	0	0
Visit 6 (Night 57, Day 58) [2]	0	1 {7021}	0
Visit 7 (Night 85, Day 86) [2]	0	1 {7141}	1 {7079}

Note: Baseline is defined to be the last assessment of vital signs obtained prior to administration of the first dose of double-blind study drug.

1. Outlier criteria is DBP≤50 mmHg
2. Outlier criteria is DBP≤50 mmHg and a decrease from baseline ≥15 mmHg

There was one outlier of low heart rate from each doxepin group at the end of the study (Visit 7) or towards the end (Visit 6), while none at Visit 7 in placebo and two at Visit 6. There was no outlier of high heart rate.

Using the above same criteria, in Study 509, there was no outlier of blood pressure (systolic and diastolic) after baseline comparing the two treatment groups, unlike SP-0503 in which more outliers of high blood pressure were seen at the end of the study. There were no differences of outliers of hear rate changes after baseline in two treatment group, either.

6.3.8 Electrocardiograms (ECGs)

The ECGs were conducted and then interpreted in the central ECG lab by a cardiologist according to the analysis plan of the protocol. Since ECG was performed at different timing of each study, they were close to but not within Tmax time frame (if nonfed, doxepin Tmax=3hr, nordoxepin Tmax=8 hours) for SP-0503 and SP-0509 but not for SP-0501 (see below for details). The mean changes from Baseline to Final Study Day with standard deviations were presented but not analysis of 95% confidence interval. As in subsection of Vital Signs, outlier analysis is presented after the mean changes.

SP-0501: ECG was performed during the Initial Screening (baseline) and during the morning of the Final Study Day (Day 38), approximately 2.5 days after administration of the last dose of double-blind study drug on Night 35, or upon early termination.

Table 54. ECG Parameters – Change from Baseline to Final Study Day: Safety Analysis Set (SP-0501)

ECG Parameter	Placebo (N=73)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
Heart Rate (beats/minute)	n=70	n=75	n=71
Baseline	64.4 (9.39)	66.1 (10.27)	64.4 (10.07)
Final Study Day	63.6 (8.84)	66.2 (9.11)	66.1 (9.75)
Change from baseline	-0.7 (8.89)	0.1 (8.87)	1.5 (9.01)
PR Interval (ms)	n=70	n=75	n=71
Baseline	158.1 (22.76)	157.4 (21.21)	157.9 (22.67)
Final Study Day	162.0 (24.78)	158.7 (20.52)	160.8 (24.67)
Change from baseline	3.7 (12.73)	1.3 (11.56)	2.8 (14.49)
QRS Interval (ms)	n=70	n=75	n=71
Baseline	89.2 (8.52)	89.1 (10.98)	88.8 (9.79)
Final Study Day	89.7 (9.16)	89.3 (9.86)	90.5 (9.79)
Change from baseline	0.5 (7.88)	0.2 (6.62)	1.7 (7.87)
QT Interval (ms)	n=70	n=75	n=71
Baseline	387.2 (28.01)	395.3 (34.68)	391.6 (26.64)
Final Study Day	390.3 (34.12)	398.2 (29.65)	392.6 (31.21)
Change from baseline	2.4 (23.37)	3.0 (23.81)	2.0 (22.72)
QTcF Interval (ms)	n=70	n=75	n=71
Baseline	394.6 (21.93)	405.8 (22.71)	398.9 (20.54)
Final Study Day	395.9 (24.37)	409.7 (19.88)	403.5 (24.73)
Change from baseline	0.9 (16.24)	3.9 (18.27)	5.1 (17.66)
QTcB Interval (ms)	n=70	n=75	n=71
Baseline	398.2 (24.92)	411.2 (22.89)	402.6 (23.87)
Final Study Day	398.6 (24.86)	415.4 (20.83)	409.0 (27.00)
Change from baseline	0.1 (20.19)	4.2 (21.66)	6.6 (21.29)

Data presented are mean (SD).

QRS increased in doxepin 6mg group but not in 3mg group. QTcB was increased in each doxepin treatment group, and appear to be related with increasing doses which is consistent with the existing knowledge on doxepin and related products. Though QTcB increases were within 10ms, the standard deviations are large and somewhat worrisome. Heart rate had minimal change and doesn't seem to be clinically significant overall.

SP-0503: The 12-lead ECGs were conducted during Initial Screening (baseline) and during the morning of the Final Study Day (Day 86/ET), approximately 9 hours postdose, and subsequently read by a cardiologist at a central laboratory in a blinded manner after an initial safety review by an Investigator, as described in the protocol ECG Analysis Plan.

Table 55. ECG Parameters – Change from Baseline to Final Study Day: Safety Analysis Set (SP-0503)

ECG Parameter	Placebo (N=81)	Doxepin 1 mg (N=77)	Doxepin 3 mg (N=82)
Heart Rate (beats/minute)	n=79 1.4 (9.95)	n=76 1.3 (9.25)	n=81 -0.5 (9.53)
PR Interval (ms)	n=77 0.8 (13.79)	n=76 3.7 (12.43)	n=81 4.8 (16.51)
QRS Interval (ms)	n=79 -1.3 (10.16)	n=76 0.2 (8.39)	n=81 0.6 (8.36)
QT Interval (ms)	n=79 -1.5 (23.87)	n=76 3.4 (28.47)	n=81 7.4 (24.06)
QTcF Interval (ms)	n=79 1.4 (17.73)	n=76 4.9 (24.19)	n=81 6.3 (16.94)
QTcB Interval (ms)	n=79 3.0 (22.43)	n=76 6.0 (26.65)	n=81 5.8 (21.25)

Data presented are mean (SD).

In elderly, no increase of heart rate is seen but PR, QRS, and QT intervals are all increased and the increment of PR and QRS seem to be related to increased doses in general, except for QTcB that its changes are similar in both doxepin dose groups.

SP 509: The sponsor reports that ECGs were obtained at screening (Visit 1; baseline) and the Final Study Day (Day 28/ET), the next morning after the last dosing.

Unlike in SP-0503, there is no increase seen in PR and QRS; heart rate and QTcB increase mildly. Rather all they seem to be decreased compared to baseline. However, the decreases of QRS, QTcB and QTcF in doxepin group are all less than those in placebo. Again, the large standard deviation is worrisome.

The inconsistent changes of ECG parameters in the two elderly studies could be related to the different duration of these trials.

Table 56. ECG Parameters: Change from Baseline to the Final Study Day: Safety Analysis Set (SP-0509)

ECG Parameter	Placebo (N=124)	Doxepin 6 mg (N=130)
Heart Rate (beats/min)	n=122	n=130
Mean (SD)	1.4 (7.06)	3.4 (10.10)
PR Interval (ms)	n=121	n=129
Mean (SD)	-0.2 (16.32)	-3.9 (29.38)
QRS Interval (ms)	n=122	n=130
Mean (SD)	-1.6 (9.55)	-0.4 (10.02)
QT Interval (ms)	n=122	n=130
Mean (SD)	-9.0 (21.28)	-8.8 (26.93)
QTcF Interval (ms)	n=122	n=130
Mean (SD)	-6.7 (18.06)	-2.5 (19.50)
QTcB Interval (ms)	n=122	n=130
Mean (SD)	-5.5 (20.82)	0.9 (22.27)

Outliers Analysis:

Based on preset QT parameters, the tables below summarize the number of outliers in Studies 501, 503, and 509 submitted by the sponsor upon our request in Nov. 2008.

Table 57 shows QTcF and QTcB Changes from Baseline to Final Study Day in SP-0501.

None had QTcF over 480ms or QTc increase more than 60ms from baseline. Among the four outliers of QTcB over 450ms, one outlier reached 480ms or above. With regard to QTcF, although it appears a slightly higher number of outliers in doxepin 3mg group, only one was a new case without baseline abnormality. Most of outliers at final were new cases without being the baseline outliers. The number of outliers in doxepin groups almost doubled the placebo group.

Table 57. QTcF and QTcB Changes from Baseline to Final Study Day: Safety Analysis Set (SP-0501)

Parameter	Placebo (N=73) n=70	Doxepin 3 mg (N=75) n=75	Doxepin 6 mg (N=73) n=71
QTcF Interval, n (%)			
Baseline (Screening)			
>450 ms	0 (0%)	4 (5%)	1 (1%)
>480 ms	0 (0%)	0 (0%)	0 (0%)
>500 ms	0 (0%)	0 (0%)	0 (0%)
Final Study Day			
>450 ms	2 (3%)	3 (4%)	2 (3%)
>480 ms	0 (0%)	0 (0%)	0 (0%)
>500 ms	0 (0%)	0 (0%)	0 (0%)
QTcF Increase From Baseline			
Increase >30 ms	3 (4%)	5 (7%)	5 (7%)
Increase >60 ms	0 (0%)	0 (0%)	0 (0%)
QTcB Interval, n (%)			
Baseline (Screening)			
>450 ms	1 (1%)	3 (4%)	3 (4%)
>480 ms	0 (0%)	0 (0%)	0 (0%)
>500 ms	0 (0%)	0 (0%)	0 (0%)
Final Study Day			
>450 ms	0 (0%)	4 (5%)	4 (6%)
>480 ms	0 (0%)	0 (0%)	1 (1%)
>500 ms	0 (0%)	0 (0%)	0 (0%)
QTcB Increase From Baseline			
Increase >30 ms	5 (7%)	10 (13%)	9 (13%)
Increase >60 ms	0 (0%)	0 (0%)	0 (0%)

Table 58 shows QTcF and QTcB Changes from Baseline to Final Study Day in SP-0503.

In elderly trial, no one outlier had QTc beyond 500ms, but outliers of QTc (QTcB and QTcF) ≥ 450ms in both doxepin groups clearly outnumbered the placebo, so did the number of outliers of QTcB and QTcF increase of more than 30ms in doxepin groups.

Unlike adult study, two geriatric patients had QTcF increase to over 480ms in doxepin 1mg group: One had worsening prolongation (from 450ms at baseline) and one of them was a new case without baseline QTcF prolongation. QTcB analysis reveals similar result, but there is also a new case in doxepin 3mg group. With either analysis, there was no outlier in placebo group that had QTc increment of over 480ms.

Table 58. QTcF and QTcB Changes from Baseline to Final Study Day: Safety Analysis Set (SP-0503)

Parameter	Placebo (N=81)	Doxepin 1 mg (N=77)	Doxepin 3 mg (N=82)
QTcF Interval, n (%)			
Baseline (Screening)	n=81	n=77	n=82
>450 ms	5 (6%)	3 (4%)	6 (7%)
>480 ms	0 (0%)	0 (0%)	0 (0%)
>500 ms	0 (0%)	0 (0%)	0 (0%)
Final Study Day	n=79	n=76	n=81
>450 ms	4 (5%)	9 (12%)	12 (15%)
>480 ms	0 (0%)	2 (3%)	0 (0%)
>500 ms	0 (0%)	0 (0%)	0 (0%)
QTcF Increase From Baseline	n=79	n=76	n=81
Increase >30 ms	5 (6%)	7 (9%)	7 (9%)
Increase >60 ms	1 (1%)	1 (1%)	0 (0%)
QTcB Interval, n (%)			
Baseline (Screening)	n=81	n=77	n=82
>450 ms	10 (12%)	10 (13%)	13 (16%)
>480 ms	1 (1%)	0 (0%)	1 (1%)
>500 ms	0 (0 %)	0 (0%)	0 (0%)
Final Study Day	n=79	n=76	n=81
>450 ms	9 (11%)	13 (17%)	17 (21%)
>480 ms	0 (0%)	2 (3%)	2 (2%)
>500 ms	0 (0%)	0 (0%)	0 (0%)
QTcB Increase From Baseline	n=79	n=76	n=81
Increase >30 ms	7 (9%)	9 (12%)	11 (14%)
Increase >60 ms	1 (1%)	1 (1%)	1 (1%)

Table 59 shows QTcF and QTcB Changes from Baseline to Final Study Day in SP-0509.

In this shorter term geriatric study, no significant difference is seen in number of outliers with QTcB or QTcF of more than 450ms or their increment of more than 30ms regardless the ones who had baseline QT prolongation included or not. No outlier who had QT increment of more than 60ms. The outlier whose QTcB reached to more than 500ms in doxepin group had QTcB of over 450ms at baseline – it shows worsening of prolongation; The outliers with QTcB of more than

480ms in this group also showed worsening as their baseline QTcB was between 450-480ms, so is the case of the outlier with QTcB of over 480ms in doxepin group.

Table 59. QTcF and QTcB Changes from Baseline to Final Study Day: Safety Analysis Set (SP-0509)

Parameter	Placebo (N=124)	Doxepin 6 mg (N=130)
QTcF Interval, n (%)		
Baseline (Screening Period)	n=124	n=130
>450 ms	8 (6%)	11 (8%)
>480 ms	0 (0%)	1 (1%)
>500 ms	0 (0%)	0 (0%)
Final Study Day	n=122	n=130
>450 ms	8 (7%)	9 (7%)
>480 ms	0 (0%)	1 (1%)
>500 ms	0 (0%)	0 (0%)
QTcF Increase From Baseline	n=122	n=130
Increase >30 ms	2 (2%)	3 (2%)
Increase >60 ms	0 (0%)	0 (0%)
QTcB Interval, n (%)		
Baseline (Screening Period)	n=124	n=130
>450 ms	16 (13%)	14 (11%)
>480 ms	4 (3%)	3 (2%)
>500 ms	1 (1%)	1 (1%)
Final Study Day	n=122	n=130
>450 ms	18 (15%)	14 (11%)
>480 ms	1 (1%)	3 (2%)
>500 ms	0 (0%)	1 (1%)
QTcB Increase From Baseline	n=122	n=130
Increase >30 ms	6 (5%)	9 (7%)
Increase >60 ms	0 (0%)	0 (0%)

In summary, the outlier analysis of QTcB and QTcF further confirms the risk of QT prolongation and tendency of its worsening. They appear to be more evident in geriatric patients and may not be strictly dose related, and not all who had baseline prolongations persisted.

6.3.9 Next-Day Residual Effect

The potential next-day effects are mainly measured with psychomotor function and/or alertness using the DSST (digital symbol substitution test), SCT (symbol copying test), and VAS for sleepiness (visual analog scale for sleepiness) according to the agreement with FDA at the EOP2 meeting.

DSST is a performance test that requires sustained concentration, short-term memory, selective recognition, rapid responding, and fine motor control. Subjects were shown a set of symbols with corresponding single digit numbers. In the test, subjects are presented with "blank" boxes with corresponding digits. Subjects were asked to make as many symbol-for-digit substitutions as possible within a 90-second period. The number of correct substitutions in 90 seconds is recorded.

SCT is an assessment of the motor speed component of the DSST. The same symbols were used as the DSST. However, subjects are simply asked to copy them. The score is the number of symbols correctly copied within a 90-second period.

VAS for Sleepiness measures subjective feeling of sleepiness – On a 100 mm horizontal line, with which the right extreme is labeled "very sleepy" (100 mm) and the left extreme is labeled "very alert" (0 mm), subjects are instructed to consider the line for the VAS a continuum with their own recollected personal extremes on either end and to draw a vertical line at a point that best approximated their current level of sleepiness/alertness. Measurements were made per the study reference guidelines on VAS scoring. The study center measured the distance (mm) from the far left hand pre-printed vertical line labeled "very alert" to the subject's response line (i.e., the intersection of the vertical line with the horizontal scale). This score was recorded in the space provided on the VAS for sleepiness worksheet.

Among these three, DSST is more objective and requires more active thinking process and complexed psychomotor activity. There was no next-day driving test conducted.

In SP-0501, the DSST, SCT, and VAS for sleepiness assessments were completed in the evening (pre-dose) of the first night and in the morning approximately 60 minutes after completion of each nightly PSG assessments at PSG Screening (Visit 2), Baseline (Visit 3), the Double-blind Treatment Period (Visits 4, 5, and 6), the Discontinuation Period (Visit 7), and on the Final Study Day (Day 38) or upon early termination. Except for Visit 2 assessments were for practice only, all other results were entered into the database. The differences were calculated between the scores obtained in the evening of the first night (pre-dose) and the average of the scores obtained in the morning of both days post-dose during double-blind treatment as well as during the Discontinuation Period. The table below shows the mean change from Night 1 (pre-dose) to the average of Days 2 and 3 (post-dose).

Table 60. DSST, SCT, and VAS Scores – Mean Change from Night 1 (Pre-dose) to the Average of Days 2 and 3 (Post-dose): Safety Analysis Set (SP-0501)

Test	Placebo (N=73)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
Digit Symbol Substitution Test			
Predose mean (SD)	65.3 (13.02)	64.1 (11.86)	66.3 (13.96)
Mean change[1] (SD)	-3.2 (10.22)	-4.1 (7.12)	-6.1 (9.87)
p-value[2]		p=0.3954	p=0.0524
Symbol Copying Test			
Predose mean (SD)	121.1 (24.02)	117.8 (26.48)	125.1 (25.23)
Mean change[1] (SD)	-1.9 (17.56)	-2.4 (23.85)	-7.3 (17.66)
p-value[2]		p=0.6168	p=0.1621
Visual Analog Scale for Sleepiness			
Predose mean (SD)	41.4 (26.43)	42.7 (23.00)	51.1 (27.72)
Mean change[1] (SD)	-0.7 (22.25)	-0.9 (23.35)	-5.9 (28.78)
p-value[2]		p=0.9380	p=0.8791

[1] Change is the difference between the score obtained on the evening of Night 1 (predose) and the average of the scores obtained on Days 2 and 3 (postdose).

[2] p-value for testing each doxepin dose versus placebo was determined from an ANCOVA model with terms for treatment and center and the Night 1 value as a covariate using Dunnett's test.

In this analysis, there was no statistically significant score change from pre-dose in either doxepin dose group compared to placebo; however, the scores of DSST and SCT are lower in doxepin 6mg group than the 3mg group – mostly consistent through each visit, and sleepiness is more evident.

As in SP-0501, the differences between the values obtained pre-dose and the following morning (post-dose) during double-blind treatment were calculated in SP-0503. They were completed pre-dose at each PSG visit, and during the mornings of PSG Screening (Visit 2) [practice only], the Treatment Period (Visits 3 through 7), and the Final Study Day (Day 91/ET). Summary statistics of these scores are presented by visit and treatment group in the table below.

Table 61. DSST, SCT, and VAS Scores – Mean Changes from Night 1 (Pre-dose) to Average of Days 1 and 2 (Post-dose) by Treatment Group: Safety Analysis Set (SP-0503)

Test	Placebo (N=81)	Doxepin 1 mg (N=77)	Doxepin 3 mg (N=82)
Digit Symbol Substitution Test			
Predose mean (SD)	48.1 (13.06)	50.5 (15.13)	46.4 (11.98)
Mean change (SD)	-0.1 (10.11)	-1.3 (8.28)	0.1 (7.21)
p-value[1]		p=0.7131	p=0.9567
Symbol Copying Test			
Predose mean (SD)	93.8 (22.03)	96.0 (28.44)	90.0 (21.22)
Mean change (SD)	-0.4 (14.31)	-1.1 (14.48)	-0.9 (10.13)
p-value[1]		p=0.9842	p=0.5669
Visual Analog Scale for Sleepiness			
Predose mean (SD)	44.1 (24.64)	37.7 (22.83)	38.6 (24.02)
Mean change (SD)	-3.3 (23.92)	3.0 (23.15)	-0.1 (25.89)
p-value[1]		p=0.3864	p=0.8256

[1] p-value for testing each doxepin dose versus placebo was determined from an ANCOVA model with terms for treatment and center and the Night 1 value as a covariate using a linear contrast.

The pre-dose means from Night 1 for the DSST, SCT, and VAS scores were similar across the treatment groups. There was no statistically significant score changes from baseline to next-two-day comparing doxepin 1mg and 3 mg groups. There appears no significant difference between doxepin 1 mg and 3 mg groups.

Next-day residual effect was not examined in SP-0509. There is no analysis based on the next-one-day effect which I personally think would be more accurate.

6.3.10 Special Search

6.3.10.1 Complex Sleep Behaviors and Parasomnias

The sponsor reports that there were no complex sleep behaviors in any subjects in this clinical program. However, a few subjects reported parasomnias, such as nightmares, sleep paralysis, and enuresis, excluding sleep walking. The table below summarizes these events in each treatment group.

Table 62. Parasomnia TEAEs: By PT
(All Subjects Safety Analysis Set, provided by the sponsor**)**

Preferred Term	Placebo (N=699)	Doxepin 1 mg (N=232)	Doxepin 3 mg (N=313)	Doxepin 6 mg (N=730)	All Doxepin (N=966)
Parasomnia: Total	3 (0.4%)	0	4 (1.3%)	2 (0.3%)	6 (0.6%)
Sleepwalking	0	0	0	0	0
Abnormal Dreams	1 (0.1%)	0	2 (0.6%)	1 (0.1%)	3 (0.3%)
Nightmare	1 (0.1%)	0	0	1 (0.1%)	1 (0.1%)
Sleep Paralysis	1 (0.1%)	0	1 (0.3%)	0	1 (0.1%)
Enuresis	0	0	1 (0.3%)	0	1 (0.1%)

Overall doxepin group had more subjects (6, 0.6%) than placebo group (3, 0.4%). The preferred term "abnormal dream" refers to "vivid dream" (2) or "increased dreams" (2) in different study reports.

6.3.10.2 Suicidality

The sponsor reports (in M2.7.4.7. Appendix 4) that potential suicidal events in the Silenor clinical development program were categorized according to the Columbia Classification Algorithm of Suicide Assessment (C-CASA). The sponsor also stated that the search criteria used was promulgated by the Agency in a briefing package for the Psychopharmacologic Drugs Advisory Committee of November 16, 2006 to search the treatment emergent adverse events within the All Subjects Safety Analysis Set, including both preferred terms and verbatim terms (see below for search criteria used and reported).

Criteria Used to Search Adverse Event Database for Potential Suicide Events are as follows:

Preferred terms searched: COMPLETED SUICIDE, INTENTIONAL SELF-INJURY, SELF-INJURIOUS BEHAVIOUR, SELF-INJURIOUS IDEATION, SUICIDAL IDEATION, SUICIDE ATTEMPT, POISONING DELIBERATE, INTENTIONAL OVERDOSE, MULTIPLE DRUG OVERDOSE INTENTIONAL, OVERDOSE, PRESCRIBED OVERDOSE

Text strings searched within preferred terms, verbatim terms, and comment fields: ACCIDENT, ATTEMPT, BURN, CUT, DROWN, GAS, GUN, HANG, HUNG, IMMOLAT, INJUR, JUMP, MONOXIDE, MUTILAT, OVERDOS, SELF DAMAG, SELF HARM, SELF INFLICT, SELF INJUR, SHOOT, SLASH, SUIC, POISON, ASPHYXIATION, SUFFOCATION, FIREARM
Events excluded after search: UNCONTROLLED HYPERTENSION SECONDARY TO CHANGE IN MED DOSAGE, HEARTBURN, HANGOVER, GASTROENTERITIS,

GASTRITIS, ACUTE BRONCHITIS, ACUTE SINUSITUS, GASTROOESOPHAGEAL REFLUX, BRONCHITIS ACUTE, BURNING BOTH EYES, and POISON IVY RASH
The sponsor reports that nine subjects were identified with TEAEs warranting review of all information in the AE CRFs for potential suicidality (see table below): Four subjects were in the Placebo group, two subjects in the doxepin 1 mg group, one subject in the doxepin 3 mg group, and two subjects in the doxepin 6 mg group. None was identified as indication of suicidality. Thus, there is no treatment emergent suicidality case based on this search in this clinical program.

Table 63. Number of Subjects Who Experienced a TEAE Potentially Representing Suicidality: By SOC, PT, and Verbatim Term (All Subjects Safety Analysis Set)

SOC Preferred Term Verbatim Term (qualifying text string)	Placebo (N=699)	Doxepin 1 mg (N=232)	Doxepin 3 mg (N=313)	Doxepin 6 mg (N=730)	All Doxepin (N=966)
Injury, Poisoning and Procedural Complication					
Injury[a] Multiple Trauma due to Motor Vehicle Accident in which Patient was a Passenger (accident)	1	0	0	0	0
Pneumothorax Traumatic[a] Traumatic Pneumothorax Secondary to Motor Vehicle Accident (accident)	1	0	0	0	0
Rib Fracture[a] Fractured Ribs Secondary to Motor Vehicle Accident (accident)	1	0	0	0	0
Traumatic Haematoma[a] Liver Hematoma Secondary to Motor Vehicle Accident (accident)	1	0	0	0	0
Fall Accidental Fall Due to Tripping (accident)	1	0	0	0	0
Laceration Left Elbow Cut Secondary to Fall (cut)	1	0	0	0	0
Laceration Cut on Right Hand (cut)	1	0	0	0	0
Back Injury Pulled Lower Back Muscle (injur)	0	1	0	1	2
Skin Laceration Cut/Scratch Left Forearm (cut)	0	0	1	0	1
Nervous System Disorders					
Cerebrovascular Accident Right Brain Cerebrovascular Accident (accident)	0	1	0	0	1
Gastrointestinal Disorders					
Abdominal Pain Upper Chest Pain (Epigastric) (gas)	0	0	0	1	1

6.3.10.3 Other Psychiatric Adverse Events

The sponsor reports that there was a slightly higher incidence of TEAEs in the Anxiety/Panic cluster in the doxepin 6 mg group than in the Placebo group. Two subjects prematurely discontinued participation due to a TEAE (anxiety) within this cluster. The sponsor states that "no events of panic were reported." But only one subject reported depression (doxepin 6 mg) and one subject reported euphoria/feeling of well being (PT: elevated mood; doxepin 3 mg).

6.3.10.4 Somnolence and Sedation

In SP-0501, the sponsor included verbatim terms of somnolence, drowsiness, sleepiness, and grogginess for incidence of treatment-emergent somnolence and sedation. A total of 16 subjects were found having experienced an event coded with one of these terms: Three subjects (5%) in the placebo group, seven subjects (9%) in the doxepin 3 mg group, and six subjects (8%) in the doxepin 6 mg group. Thus, it is clearly drug-related and common, but not necessarily dose-related. Time line of these incidences is unclear.

The sponsor reports that most of the events coded to somnolence or sedation were mild or moderate in intensity but none were serious. However, one subject in the doxepin 6 mg group, S#06-3178, withdrew from the study due to severe somnolence (see Dropouts). The sponsor states, "No accidental injuries or automobile accidents were reported."

In SP-0509, using the same verbatim terms of these events, the sponsor reports the incidence of somnolence was 5% in doxepin group and 3% in placebo group; the incidence of sedation was 4% with doxepin 6 mg but (0%) with placebo. Together, somnolence and sedate are 8% in doxepin group vs. 3% in placebo.

As in SP-0501, the sponsor reports that most AEs were assessed as mild or moderate in intensity and no severe events of sedation; however, one subject experienced severe somnolence: Subject 74-5071, a 73-year-old White female in the doxepin 6 mg group, experienced somnolence assessed by the Investigator as severe and probably related to study drug. The event resolved approximately three days after study completion. The subject did not report any other treatment emergent adverse events during the study. Overall, the sponsor reports no accidental injuries or automobile accidents in any doxepin-treated patient.

In Study 0503, the sponsor reports that incidence of somnolence was 5% in both placebo and doxepin 1mg group but only 2% in doxepin 3mg group with the same verbatim search. Incidence of sedation was 1% in doxepin 3 mg group but none in placebo group. Thus, it seems they are neither dose-related, nor drug-related in this long term study. Again, all of these events were reportedly mild or moderate in intensity; none were serious.

6.3.10.5 Weight Gain

The tables below illustrate the mean weight change from baseline to the Final Study Day (as defined in each study protocol) or upon early termination in each of the three controlled studies, as well as outliers per weight classification.

Table 64. Mean Weight and Number of Subjects with Weight Change Greater than or Equal to 7 Percent from Baseline: Safety Analysis Set (SP-0501)

Weight	Placebo (N=73)	Doxepin 3 mg (N=75)	Doxepin 6 mg (N=73)
Weight (kg)	n=67	n=74	n=70
Baseline mean (SD)	74.4 (13.93)	77.5 (14.54)	77.8 (15.35)
Change from Baseline (SD)	-0.3 (2.46)	0.3 (2.21)	-0.0 (2.19)
Weight Classification[1] n (%)			
≥7% Increase	1 (1%)	0 (0%)	0 (0%)
≥7% Decrease	1 (1%)	1 (1%)	1 (1%)

[1] Predefined PCS change in weight.

Table 65. Mean Weight and Number of Subjects with Weight Change Greater than or Equal to 7 Percent from Baseline: Safety Analysis Set (SP-0503)

Weight	Placebo (N=81) n=73	Doxepin 1 mg (N=77) n=75	Doxepin 3 mg (N=82) n=76
Weight (kg)			
Baseline mean (SD)	78.8 (15.53)	75.5 (16.02)	75.5 (13.23)
Change from Baseline (SD)	-0.3 (2.29)	-0.5 (2.12)	-0.1 (1.99)
Weight Classification[1]			
≥7% Increase	1 (1%)	1 (1%)	1 (1%)
≥7% Decrease	3 (4%)	2 (3%)	1 (1%)

[1] Predefined PCS change in weight

Table 66. Mean Weight and Number of Subjects with Weight Change Greater than or Equal to 7 Percent from Baseline: Safety Analysis Set (SP-0509)

Weight	Placebo (N=124)	Doxepin 6 mg (N=130)
Weight (kg)	n=121	n=130
Mean Baseline (SD)	77.1 (16.69)	77.4 (15.53)
Change from Baseline (SD)	0.3 (1.57)	0.4 (1.58)
Weight Classification[1,2] n (%)	n=121	n=130
≥7% Increase	1 (1%)	1 (1%)
≥7% Decrease	0 (0%)	0 (0%)

[1] Predefined PCS change in weight.
[2] Percentages are based on the number of non-missing observations.

From the data provided by the sponsor, there was no/minimal mean weight change in all three controlled studies, in adults and elderly. Comparing each treatment group, there was little difference in numbers of outliers as defined according to weight classification.

6.3.10.6 Anaphylaxis and Angioedema

There was no treatment emergent angioedema or anaphylaxis reaction reported. A special search of preferred terms for related symptoms by the sponsor revealed little evidence of such possible cases.

6.3.10.7 Glucose Metabolism

Comparing placebo and doxepin groups, there were no clinically meaningful mean changes from baseline seen in the three relatively longer term controlled studies submitted. Two subjects in doxepin 3mg group had treatment emergent serum glucose increase and none in placebo (0 vs 0.6%). The percentage of subjects that exhibited shifts in glucose from normal to high was nearly identical in the Placebo (21.9%) and All Doxepin (22.0%) groups. However, given the known concern of glucose metabolism dysregulation in related compounds such as tricyclics and Sinequan, the impact of Silenor on glucose homeostasis cannot be totally ruled out, esp. in real life long term use.

6.3.10.8 Cardiovascular Concerns

The safety concerns for cardiovascular system will be summarized from the following aspects:

1) Cardiovascular events: There were three syncope cases in Phase 1 studies. Though they appear to be related to venipunctures, there were no clear ECG or vitals presented in the case summaries. However, subjects recovered without sequalea. There was no syncope in Phase 3 studies. Two of the SAE events related to cerebrovascular incident and

uncontrolled hypertension don't seem to be drug-related (see SAE subsection). Another case of bradycardia among dropouts also happened to be in the placebo lead-in phase. In common adverse events, vascular disorders appear to be drug-related in SP 503 only, esp. at doxepin 3mg dose level (6% vs 0 in placebo group); among them, one patient who was coded as blood pressure inadequately controlled at 3mg dose level should also be included in hypertension (that is 4 and 5% instead of 3 and 4%). (Note that the previously mentioned case of uncontrolled hypertension was in SP 501.) Other two events in this category are hot flush at 1mg level and hematoma at 3mg level, each consists of 1 event in SP 503.

2) Vital Signs: As detailed analysis has been presented in subsection 6.3.7, I will just re-emphasize changes noticed here (for those without changes, see 6.3.7):

Mean Changes

- In SP 501, endpoint systolic blood pressure was statistically significant compared to baseline pre- and post-doses, but they don't seem to be clinically significant.
- In SP 503, in 1mg dose group, *Pre*-dose, there was a statistically significant drop of systolic blood pressure at Visit 6 (p=0.0042, from 129 mmHg to 125 mmHg) but not at Visit 7/endpoint (p=0.1024). At dose 3mg/day, there was a drop of diastolic blood pressure (p=0.0068) but only about 2mmHg and the effect disappears at Visit 7/Endpoint. Similarly, a drop of heart rate at the beginning of the trial (Visit 3) in 3mg dose group (p=0.0447), it was a 2 beats/min difference and no significant changes seen in later stage of the trial or another dose group. The changes probably carry little clinical significance from such analysis.
- In SP 509, statistically significant change is seen in mean diastolic blood pressure in 6mg dose group (p=0.0311) at Visit 7/Endpoint. The actual change involved was 1.7 mmHg increments which is probably not clinically meaningful.

Outliers

- There was one outlier who had low systolic blood pressure at the end of the study in doxepin 6mg group. Overall, more outliers of low systolic blood pressure were in doxepin 6mg than those in two other treatment groups in SP 501.
- Outlier analysis in elderly studies confirms that heart rate and blood pressure change, either high or low, appear mostly towards end of Study 503 while no such phenomenon in SP 509. This is consistent with findings in common adverse events.

3) ECG data: The ECG testing was performed at times after Tmax in all three Phase 3 studies and the two drug-drug interaction studies, from possibly 1-3 hour to 4 days. Thus, the results can't be used to evaluate cardiac safety appropriately.

Conclusion: Although mechanism wise, it doesn't seem to fit the pattern, hypertension happens to be one of the common treatment emergent adverse events in the 3-month long elderly study. This is of particular concern as it didn't seem to be an issue in the short term (1month) study in the similar population and there is no long term (e.g. 6-month or 12-month studies) safety data to address this concern. The data to evaluate the safety of ECG parameters is insufficient and the risk

of QTc and PR interval prolongation can't be determined in both adult and elderly patients. A TQT study is needed for cardiac safety evaluation should the sponsor still chose to do more studies with this compound.

6.4 Other Safety Explorations

6.4.1 Dose Dependency for Adverse Events

One of the two common adverse events - nausea - happened in doxepin 6mg group. Another common adverse event – hypertension – was more in doxepin 3mg group than in 1 mg group. When lumping studies all together, somnolence also seem to be dose related but not other events.

6.4.2 Time Dependency for Adverse Events

Hypertension cases were seen in the longer term (3-month) geriatric study (SP-0503) only, not in the one-month study of similar population. Outlier analysis of high blood pressure (both systolic and diastolic) show that four cases happened at the end of the 3-month study (final study visit), one at the end of one month, and one on Day 15.

6.4.3 Drug-Demographic Interactions

Instead of conducting demographic analysis for safety for each Phase 3 study separately, the sponsor conducted demographic analysis of all studies that include studies with different designs and durations which is inappropriate in my opinion. In their response to our 74-day letter for defining common adverse events and demographic analysis, the sponsor reports that the only event that meets the criteria was nausea in SP-0501 and the patient was a 52 year-old Caucasian female. Again, they didn't consider hypertension cases as many as at least 5% (see Common Adverse Events of SP-0503). Over all, ethnic group analysis is regarded as too skewed (categories of ethnicities other than Caucasian were too small) to draw meaningful conclusions.

However, with regard to age, since Studies SP-0503 and SP-0509 are geriatric studies, the data of both reflect the geriatric population of 65 years or older. Study 0501 is the only adult study and its data reflect adults of 18-65 years of age. Please see subsections 6.3.5.1 and 6.3.5.2 for details.

6.4.4 Drug-Disease Interactions (liver, renal, etc)

There is no new data for drug-disease interactions in the submission. Doxepin used as an antidepressant is known for necessary caution for liver diseases and reduced dosage is recommended. Since small amount of doxepin and nordoxepin are also eliminated in the urine, caution with renal impairment is needed.

6.4.5 Drug-Drug Interactions

The sponsor conducted SP-0505 for drug-drug interaction with cimetidine and SP-0506 for doxepin interaction with sertraline. Detailed information was reviewed by the Agency Biopharmaceuticals Science Reviewer, Ju-Ping Lai, PhD. Below are a summary of the designs of these two studies and review of safety other than death and SAE since they were reviewed for the whole clinical development group in section 6.3.

6.4.5.1 Doxepin and Cimetidine

Study SP-0505 is a Phase 1, single-center, fixed sequence, open-label drug interaction study conducted with 24 healthy, adult male and female subjects. The primary objective was to evaluate and compare the PK profile of doxepin when administered alone and in combination with cimetidine to healthy subjects. A secondary objective was to assess the safety and tolerability of doxepin when administered alone and in combination with cimetidine to healthy subjects.

The treatment sequence includes two Treatment Periods of a total of 10 days:

- Treatment Period 1
  Day 1: Doxepin 6 mg (a.m.)
- Treatment Period 2
  Day 8: Cimetidine 300 mg (a.m.)
  Cimetidine 300 mg (p.m.)
  Day 9: Doxepin 6 mg + cimetidine 300 mg (a.m.)
  Cimetidine 300 mg (p.m.)
  Day 10: Cimetidine 300 mg (a.m.)

Following coadministration of doxepin 6 mg with cimetidine 300 mg, blood samples were collected through 96 hours post dose (for doxepin and nordoxepin plasma concentrations) and through 24 hours post dose (for cimetidine plasma concentrations).

Doxepin plasma concentrations were higher with cimetidine coadministration (approximately a two-fold mean increase in maximum plasma concentration Cmax and AUC0-∞).

The sponsor reports two dropouts, neither due to AE. Completion rate was 91.7% (22/24). One subject who fainted (syncope after feeling mild nausea and dizziness) was on doxepin 6mg on Day 1; the episode lasted for about 1 minute and nausea and dizziness resolved within 10 min. Subject recovered without treatment and completed the study. There were much fewer side effects while subjects on doxepin 6mg + cimetidine 300mg than on doxepin 6mg alone; no adverse event was more than doxepin alone and no new type of AE was reported. There was no vital signs increase but mild decrease with the combination except pulse rate at 2 hours post-dose (see table below); the changes presented here are not clinically meaningful.

Table 67. Summary of Descriptive Statistics for Vital Signs

Scheduled Time	Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)		Pulse Rate (bpm)	
	Treatment A N=24	Treatment B N=22	Treatment A N=24	Treatment B N=22	Treatment A N=24	Treatment B N=22
Predose (0 hour)	113.2±12.7	107.0±12.0	71.6±8.2	66.1±6.8	65.3±6.4	65.1±9.7
2 hours postdose	101.5±14.5	99.3±9.1	62.3±10.0	60.0±8.5	63.5±8.6	66.2±10.3
24 hours postdose	109.6±11.7	103.8±10.8	68.0±9.8	67.1±6.8	62.8±8.7	62.0±8.8

Treatment A=doxepin 6 mg; Treatment B=doxepin 6 mg + cimetidine 300 mg.

ECG was conducted on Day 13, four days after the combined dosing. The sponsor states that no subject experienced a QT interval >450 ms or reported any AEs for any ECG finding. Mean change of ECG parameters are provided by the sponsor in Table 68.

The RR, PR, QRS, and QT intervals and its corrections all seem to be increased at the end of the study compared to the Screening stage with this drug combination. The mean PR change is 9.1 ± 20.6ms QTcB change is 9.4 ± 3.2ms. Although this study was not designed to evaluate safety, the standard deviations of these parameters are large as seen those in the controlled trials. Additionally, ECG was conducted four days later; thus, it is to assess its true clinical value.

Table 68. Summary of Key Electrocardiogram Parameters

Parameter (Unit)	Screening N=24	Final Study Day N=24
Heart rate (bpm)	70.8±11.2 (43–94)	70.4±10.7 (52–90)
PR interval (ms)	145.6±16.9 (110–196)	154.5±37.5 (116–310)
QRS (ms)	86.0±7.9 (70-102)	87.5±7.7 (72-110)
QT interval (ms)	376.8±25.1 (342–416)	385.9±22.9 (334–428)
QTcF (ms)	395.9±19.3 (355–428)	405.2±21.6 (359–455)
QTcB (ms)	406.6±24.0 (339–451)	416.0±27.2 (350–469)

Data presented are mean ± SD (range).

Like wise, the final clinical laboratory tests were conducted on Day 13. The sponsor reports no AE reported for laboratory abnormalities or any individually clinically significant laboratory abnormalities. One subject who had mild elevation of LFTs (ALT increased from 43 u/L to 75 u/L, ref. 30-65 u/L) at the end of the study and no total bilirubin or ALK elevation.

Most subjects had mildly decreased hematocrit at the end of the study compared to Screening. A few had more obvious decrease but still within normal range (M: 37-49%, F:36-46%); among the four subjects who had it decreased below 37 u/L, one went from 38.4 u/L down to 33.9 u/L and one decreased from 40.3 down to 36.2. The same is true for hemoglobin though only two below normal range. The same two subjects dropped from 12.9 down to 11.1 u/L and 14.1 to 12.5 g/dL (ref. F:12.-16g/dL, M: 14-18g/dL). Though no subject exhibited an abnormal absolute differential count, a few patients' WBC and neutrophils seem to decrease rapidly for the 10-day period: One subject's WBC (ref. 4.8-10.8 $x10^9$/L) decreased from 6.4 to 4.3$x10^9$/L and the neutrophils (1.8-8.0 $x10^9$/L) from 4.3 to 2.1$x10^9$/L; another's WBC changed from 10.8 to 7.1$x10^9$/L with neutrophils changing from 8.0 to 3.5$x10^9$/L. A third patient's WBC count went from 11.4 to 7.5 $x10^9$/L and neutrophils from 7.5 to 4.4 $x10^9$/L. One subject had eosinophils 0.3 $x10^9$/L (ref. 0-0.5 $x10^9$/L) at baseline which increased to double (0.6 $x10^9$/L) after 10 days. There were a few subjects had nonspecific lymphocyte and monocyte increases that are fairly insignificant. Platelet and the rest of the hematologic parameters had insignificant and minimal changes.

Since this is a one-day drug combination study, it is hard to conclude that these laboratory changes are the results of the combined treatment.

6.4.5.2 Doxepin and Sertraline

SP-0506 is a Phase 1, single-center, single-blind, double-dummy, fixed sequence, drug interaction study of doxepin and sertraline in 24 healthy subjects. The primary objective was to characterize the PK and pharmacodynamic (PD) profile of doxepin when administered alone and when coadministered with sertraline to healthy subjects. A secondary objective was to assess the safety and tolerability of doxepin when administered alone and when coadministered with sertraline to healthy subjects.

The treatment sequence for this study is presented below:

- Treatment Period 1
  Day 1: Doxepin 6 mg + sertraline placebo
  Days 8–13: Sertraline 50 mg + doxepin placebo
- Treatment Period 2
  Day 14: Sertraline 50 mg + doxepin placebo
  Day 15: Doxepin 6 mg + sertraline 50 mg

On Day 14, blood samples were collected for the PK evaluation of steady state sertraline and pharmacodynamic assessments of sedation (DSST, SCT, and VAS for sleepiness) were performed through 24 hours post dose. On Day 15, blood samples were collected for PK analysis through 96-

hours post-dose (for doxepin and nordoxepin) and through 24-hours post-dose (for sertraline). Pharmacodynamic assessments were performed through 24 hours post-dose.

Higher exposure was observed following coadministration of doxepin with sertraline (approximately a 1.3-fold increase in mean doxepin Cmax). The largest effect on mean DSST, SCT, and VAS for sleepiness scores occurred at or near the estimated doxepin median time to reach Tmax. The sponsor reports that mean DSST, SCT, and VAS scores returned to approximately baseline at 6–8 hours post dose following administration of doxepin with or without sertraline (see Biopharmacological Science Review conducted by the Agency reviewer, Ju-Ping Lai, PhD for details).

All subjects completed the study. Except for upper abdominal pain, the combination didn't have more adverse events than doxepin alone (+sertraline placebo) or sertraline alone (+doxepin placebo). In fact most TEAEs were reported following administration of doxepin 6 mg alone.

The sponsor reports that vital signs were measured predose and 2, 4, 8, 12, 24, 48, 72, and 96 hours postdose (following administration of Treatment A and Treatment C) and predose and 2, 4, 8, 12, and 24 hours postdose (following Day 14 administration of Treatment B). The final laboratory tests were done on Day 19, four days after the combined dosing. The sponsor states no changes in lab or vital signs reported as AEs. However, systolic and diastolic blood pressures were mildly elevated with the combination treatment at post-dose 2, 4, and 8 hours as presented in Table 69.

Table 69. Summary of Descriptive Statistics for Vital Signs

	Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)		Pulse Rate (bpm)	
Scheduled Time	Treatment A N=24	Treatment C N=24	Treatment A N=24	Treatment C N=24	Treatment A N=24	Treatment C N=24
Predose (0 hour)	112.5±11.7	108.1±9.3	69.2±8.6	65.6±6.7	67.0±8.0	63.4±7.2
2 hours postdose	110.5±10.7	113.3±10.0	66.4±6.2	68.8±6.1	61.2±6.3	64.4±9.4
4 hours postdose	107.9±13.3	111.4±13.0	64.5±8.1	67.2±6.7	63.5±8.6	64.4±9.6
8 hours postdose	108.3±11.1	112.1±12.7	62.3±6.3	65.0±5.7	68.1±8.3	67.5±8.2

Data presented are mean ± SD.
Treatment A=doxepin 6 mg; Treatment C=doxepin 6 mg with sertraline 50 mg.

ECG was conducted on Day 19, four days after the combined dosing. The means of ECG parameters are mildly increased at the end of the study but mostly within normal range. Yet, as in other studies, the standard deviations are large. Prolonged PR interval was seen in one subject (No. 0004) on the Final Study Day: His PR interval was increased from 188 milliseconds (ms) to 300ms at the end-of-study. Otherwise, as in the study with cimetidine, the sponsor reports no subject with a QT of more than 450 ms and no subject's QTcB increased over 30 ms. Mean changes (and standard deviation) of ECG parameters from screening to end of study are summarized in the following table.

Table 70. Mean Changes of ECG Parameters from Screening to End of Study (SP-0506)

ECG Parameters	Screening (n=24)	End of Study (n=24)	Change
	Mean (SD)	Mean (SD)	Mean (SD)
HR (bpm)	68.4 (8.6)	66.1 (8.8)	-2.3 (8.9)
RR (ms)	890.3 (107.8)	923.8 (125.3)	33.5 (118.7)
PR (ms)	145.2 (18.6)	156.2 (34.5)	10.3 (25.0)
QRS (ms)	90.3 (8.0)	91.3 (8.3)	1.0 (4.1)
QT (ms)	375.6 (22.2)	389.4 (23.0)	13.8 (20.8)
QTcB (ms)	399.1 (15.2)	406.8 (20.7)	7.7 (19.9)

Likewise, the final lab tests were conducted on Day 19. The sponsor reports no AEs reported for laboratory abnormalities and no individual laboratory abnormalities observed were considered clinically significant. A few subjects' hematocrit and WBC decreased fairly significantly considering the two week study period though they were still within normal ranges: Hematocrit from 41.3 to 38.6%, 46.2 to 43.3%, 35.4 to 32.6%, and 41.8 to 36.9%% over the two-week period. One subject's WBC decreased from 9 to $6.3x10^9$/L and the neutrophils decreased from 6.3 to $3.1x10^9$/L at the end of the study but most subjects' WBC counts were stable. More subjects had mild platelet decrease than not but they are all still within normal limits.

In clinical chemistry, two subjects had mildly increased ALT, AST and total bilirubin at baseline but returned to normal at the end of the study; another's baseline ALT was 69 and remained at 66 at the end. No other clinically meaningful lab changes seen.

In summary, both drug interaction studies had only one-day drug combination treatment and aren't specifically designed for laboratory values of safety. The changes seen in the study can be random variations. More importantly, the final ECG and laboratory tests were performed four days after the combined dosing which doesn't reflect the impact of the study drug combination on ECG parameters accurately. Moreover, confounding factor from sertraline or cimetidine alone can't be ruled out here as there is no data when subjects were on them without doxepin. Thus, the clinical significance of changes seen in these studies is not entirely clear here and worrisome to some extent.

6.5 Additional Safety Explorations

6.5.1 Rebound, Withdrawal, Drug Abuse Potential, and Overdose

Rebound and Withdrawal:

Rebound insomnia was only examined with WASO in SP-0501. In the Study Report of SP-0503 the sponsor states, "Following discontinuation of study drug, no subject reported experiencing symptoms suggestive of drug withdrawal syndrome, cholinergic rebound, or worsening insomnia." None was mentioned in SP-0509.

Following completion of 35 consecutive nights of double-blind treatment of SP-0501, rebound insomnia was examined during the 2-day Discontinuation Period (placebo dosing) from two perspectives: 1) PSG recording and 2) evaluation of withdrawal symptoms using Tyrer's Symptom Checklist (formally known as the Benzodiazepine Withdrawal Symptom Questionnaire) scores obtained within 1 hour of the end of PSG recording (i.e., lights on).

With sleep data obtained at Baseline (defined as the worst night of Night -6 and Night -5 for WASO, LPS, and TST), subjects were classified as having rebound insomnia if the change from baseline in:

1. WASO increased by ≥ 35 minutes,
2. LPS increased by ≥ 20 minutes, or
3. TST decreased by ≥ 30 minutes

However, the study didn't incorporate randomization of the patients to continue or stop the study drug. Therefore, without appropriate comparison, the study by design can't provide meaning data (placebo group is not considered as appropriate comparison here.) and the details of analyses will not be presented here.

Overdose: Doses of >6 mg are defined as "excessive" is defined as "critical" with respect to the dose for insomnia. The consensus guideline of American Association of Poison Control Centers regarding the management of tricyclic antidepressant poisoning (Woolf et al., 2006) recommends that emergency medical evaluation is warranted for ingestion of more than 5 mg/kg (>350 mg for a 70 kg person) of doxepin, which is over 50-fold greater than the proposed highest dose of 6mg/day. The sponsor reports no overdose in the whole clinical program.

In the event of an overdose, all should receive a baseline 12-lead ECG and be placed on a cardiac monitor. Initial management includes gastric lavage and administration of activated charcoal to reduce absorption. Certain antiarrhythmic drugs (Class 1a, 1c, and 3) should be avoided so that they will not further prolong depolarization and QT interval. Other antiarrhythmics such as lidocaine and phenytoin can benefit for the treatment of ventricular arrhythmias associated with tricyclic compound overdose. Benzodiazepines can be used to treat seizures and additional

supportive treatment needs to be provided. The experience from inpatient management of tricyclic compound overdose is that a widened QRS interval (>0.16 second) is a poor prognostic sign.

Abuse Potential: It was addressed with the Agency during the pre-NDA meeting of May, 2006 and the Agency responded in the Meeting Minutes that CSS concurs with the sponsor's conclusions that Silenor tablets should not be scheduled and that further testing regarding abuse liability potential for this NDA is unnecessary.

6.6 Additional Submissions

Numerous submissions have come in since the original NDA but clinical submissions mainly included information in the response to the 74-day letter on May 1, 2008, the suicidality position statement in July, 2008, drafted labeling as well as information on clinical labs, vital signs, and ECG that were submitted to our requests for more appropriate analysis. These materials are incorporated in the review.

The sponsor's 120-day Safety Update letter states that there was no new study initiated and the cut off date was April 30, 2008.

7 Postmarketing Experience

There is no postmarketing experience for Silenor per se because it has not been approved anywhere in the world. The compound doxepin HCl has been prescribed as an antidepressant since its approval almost 40 years ago but at a much higher dosage (75-150mg). Despite side effects as listed in the labeling, it has been widely used for many years till more availability of SSRIs.

8 Ethics and Good Clinical Practices

8.1 Submission Quality and Integrity

Analyses of vital signs, outliers and demographics for safety were not appropriate for review. It took some efforts to get the data needed that unfortunately costs more time in review.

Rebound insomnia analysis is also inappropriate.

In addition, it would be helpful if the main text indicate what was in the appendix, esp. for important information such as classification of possible suicidality cases and analysis.

8.2 Financial Disclosures

A major issue came up when (b) (6) was indicated as owning 2000 shares of stock in Somaxon. DSI inspection reveals that in the past, (b) (6) was given an application for stock

purchase as an appreciation for helping Somaxon in a clinical trial so that (b) (6) could obtain $2000 worth of shares rather than 200 shares worth $2.50 each. (b) (6) told DSI inspector that he never signed the application to obtain stock ownership and does not own any shares associated with Somaxon.

8.3 Compliance with Good Clinical Practices

DSI report for three study sites shows they were acceptable. (Please see DSI review for details.)

9 Appendices

9.1 Literature Review/References

The sponsor submitted Summary of Clinical Literature with special attention on various aspects of known possible adverse effects from antidepressants and tricyclics and Sinequan, including cardiovascular safety, weight gain and glucose homeostatsis, sexual dysfunction, SIADH, blood dyscrasias, respiratory depression, suicidality issue, overdose, allergic reactions, and interaction with alcohol, etc. Debatable potential carcinogenic effect was mentioned as well. It also included sleep behavior disorders, safety issues in elderly as well as risks in pregnancy and lactation. Like other antidepressants, doxepin has been shown to be excreted in breast milk and adverse effects have been observed in the breast fed infants of mothers taking doxepin. The safety for doxepin in pregnant women has not been demonstrated.

There appear to be no new adverse events from the list of literature reference provided. However, the sponsor did not provide the responsible person(s) for the search, the database searched, the period covered (most seem to be from 1980s and 2000s), and there is no warrant of the quality of data.

9.2 Labeling Review

Labeling was completed by the team. Though I recommend a nonapproval action, draft was sent to the sponsor as scheduled.

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

/s/

June Cai
2/14/2009 05:29:10 PM
MEDICAL OFFICER

Ronald Farkas
2/14/2009 09:31:13 PM
MEDICAL OFFICER
Please also see CDTL review, in which some safety and efficacy conclusions differ.