

and that the largest, placebo-corrected, time-matched mean QTc change from baseline should be < 5 msec.

I have raised the question whether there are mild QTc increments in QTc at 3 and 12 hours in all subjects treated with high dose 10 mg ZS. If so, the largest mean treatment effect (placebo-corrected) was ~ 5-7 msec (for all 3 QT corrections) at 12 hours. Thus, we still do not know if ZS prolongs QTc and have not been able to exclude a risk of 10 msec.

- My answer to question # 2 is that there are data that raise the suspicion of a different gender effect of high dose 10 mg ZS on QTc prolongation based upon mean results and CIs not associated with statistical significance. The gender analyses raise the question of possibly greater numerical QTc prolongation at 3 hours in males (vs females) and a substantial mean QTc increment (~ 10 msec) at 12 hours only in females. I am not aware of other drug results that show such a gender difference of QTc prolongation occurring at a certain time only in one gender and not in the other gender. It is difficult to know whether these possible gender differences are or are not real. Of note, the gender analyses were based upon approximately half the number of subjects (~ 20) of that (~ 40) analyzed in the full analysis of all subjects.

It is also possible that the apparent gender effects raised are an artifact of multiplicity (i.e. making multiple statistical comparisons such as 3 paired treatment comparisons on 12 occasions; total 36 statistical comparisons).

- In answering question # 3, I note my thoughts about approval and labeling with certain caveats. At this time I think that it is a fair perspective to say that ZS could produce relatively small QTc increments that were not statistically significant but are possible because a margin of 10 msec was not able to be excluded in the "thorough" QTc study. These possible increments by themselves do not necessarily raise serious safety concerns if one would assume that ZS exposure would not exceed that associated with 10 mg daily ZS treatment in a healthy subject (~ fold C_{max} and AUC of that expected in healthy subjects treated with 2.5 mg daily, the recommended dose). However, I have concerns that potentially much higher selegiline exposures could be experienced and these significantly higher exposures could potentially be associated with significant QTc prolongation and thus a risk of Torsades des pointes which can be fatal. My concerns about this risk in the face of markedly increased exposures to selegiline are based upon 3 considerations : 1) a published study showing that patients with hepatic impairment had a mean increased AUC and C_{max} that were 18 fold and 7 fold respectively greater than those of healthy subjects and patients with renal impairment had a mean increased AUC and C_{max} that were 6 fold and 4 fold respectively greater than those of healthy subjects; 2) a publication showing administration of several single doses of oral conventional selegiline was associated with markedly increase exposures (e.g. 22 fold increased AUC and 11 fold increased C_{max} for 10 mg selegiline; the approved daily dose); and 3) I am not convinced that we are confident that markedly increased exposures (AUC and/or C_{max}) are not possible from drug-drug interactions from other drugs altering the metabolism of selegiline by direct inhibitory actions or competitive inhibitory actions on

important CYP enzymes involved in the metabolism of selegiline. I do not necessarily find it reassuring that we are not aware of serious safety risks from these potential interactions in patients who are taking conventional oral selegiline (Eldepryl).

Furthermore, I do not know how we could convey useful information in the label about results from the publication in which markedly increased mean selegiline exposures were observed in patients with hepatic or renal impairment. The authors of this publication did not clearly define renal or hepatic impairment so that we could define it in the label and give useful, practical advice about whom this safety concern might be relevant. Given these uncertainties about the risks of potentially markedly increase selegiline exposure after ZS treatment and the outlined concerns about possible risks for increased QTc/Torsades des pointes (and also increased tyramine sensitivity hypertensive “cheese” reactions), I think that it is necessary that these clinical pharmacology issues/questions be answered prior to approval.

The sponsor could determine if the suspected increased PK exposures of selegiline are real risks. If they are not believed to be real, then I do not necessarily think that additional QTc study must be conducted prior to approval. However, if the risks of many fold (> 4) increased exposure are shown to be realistic, then it would seem necessary for the sponsor to assess QTc effects of higher doses of ZS and clearly establish whether there is or is not a potential for significant QTc prolongation at much higher exposures than that observed with 10 mg ZS in healthy subjects.

Alternatively, the sponsor might conduct an additional study investigating QTc prolongation at higher doses (e.g. 20 and 30 mg daily compared to placebo, moxifloxacin, and 10 mg daily) in the presence of tyramine restriction in an in-patient setting and not wait until the results of PK studies are known.

FDA Clinical Comment in Approvable Letter : Need to Conduct Orthostatic Vital Sign Assessments Timed to Dosing

Clinical Comment : “Given the higher Cmax expected with Zelapar 2.5 mg/day compared to the marketed selegiline formulation, we believe it is important to characterize changes in blood pressure in relation to dosing, ideally capturing results at Tmax. Such data was not collected in the controlled trials, but was collected in Study 101 (PK and tyramine challenge study). Unfortunately, the only analyses of the BP data from Study 101 are based on mean changes; outlier analyses based on pre-defined clinically important changes would be more informative. We ask you to perform such analyses for both resting BP and orthostatic BP. Unfortunately, Study 101 does not have a placebo-control group. Therefore, within the tyramine challenge study requested above we ask that you include a placebo control group and again collect resting and orthostatic BP data in relation to timing of dose.

Valeant Response to Comment : Effect of Selegiline on Resting and Orthostatic Blood Pressure

As part of the Tyramine-Challenge Clinical Pharmacology Study, Valeant did investigate the effect of selegiline (following ZELAPARTM administration) on resting and orthostatic blood pressure during the conduct of the Tyramine-Challenge study (Study RNA-ZEL-B21-102). The results of that study are summarized below.

- There were no changes in orthostatic BP related to timing of dose.
- The change in orthostatic SBP on treatment relative to the pre-randomization baseline was variable and no trends were apparent between treatment groups or within treatment groups with respect to time after dosing.
- The mean change from baseline orthostatic SBP at scheduled time points over the 24-hour post-dose assessment period ranged from -5.7 to 3.2 mmHg for 2.5 mg ZELAPAR TM, from -3.6 to 2.4 mmHg for 5 mg ZELAPARTM, and from -4.5 to 4.4 mmHg for the 10 mg ZELAPARTM dose, with no discernable pattern to the values.

Reviewer Comment

- I agree with the sponsor's response that the study of orthostatic blood pressure responses did not show a clear effect on orthostatic blood pressures indicating orthostatic hypotension related to ZS treatment compared to placebo treatment.
- The sponsor has also analyzed these data for categorical increments blood pressure (SBP \geq 20 mm Hg and/or 10 mm DBP \geq 10 mm hg) in supine, standing and orthostatic positions. There is no real suggestion of ZS-induced categorical increments in blood pressure timed to dosing for ZS relative to placebo. A question of ZS related increments in blood pressure had been raised in the previous 101 study in which ZS was compared to Eldepryl (10 mg QD) but in which there was no placebo group.

QUESTION POSED BY CLINICAL REVIEWER DURING REVIEW ABOUT EFFECT OF RENAL AND HEPATIC IMPAIRMENT ON ZYDIS SELEGILINE PHARMOCOKINETICS

FDA:

Why should there not be a concern now that people with various degrees of hepatic and/or renal impairment who take 2.5 mg daily Zydis selegiline will not experience a markedly increased plasma exposure of selegiline that could be associated with an increased tyramine sensitivity (i.e. possible risk of hypertensive, "cheese" reaction)? We know that conventional selegiline loses its MAO-B selectivity (i.e. exhibits progressively increasing inhibition of MAO-A) as dose/exposure of conventional selegiline increases and that there is increased sensitivity to tyramine. Your data also shows that there is increased sensitivity to tyramine for blood pressure responses with high dose Zydis selegiline.

Sponsor's Response:

The data submitted in this application does establish that ZELAPAR™ (ZYDIS® selegiline), at the clinically recommended dose (2.5 mg daily) has a reasonable safety margin for tyramine-induced increases in blood pressure. As the reviewer notes, there is increased sensitivity to tyramine at a dosage of 10 mg daily of ZELAPAR™, suggesting some loss of MAO-B selectivity at 4-times the recommended dose.

In a recently published study (Anttila et al., 2005) 10 patients with liver disease, 10 patients with renal disease, 10 patients receiving hepatic enzyme inducers, and 10 healthy controls received a single 20 mg oral dose of conventional selegiline (ELDEPRYL®) [2-4 times the usual single dose] and the pharmacokinetics of selegiline and its metabolites were measured for 48 hours after dose administration. Relative to the healthy controls, patients with “chronic liver disease” had a 7-fold increase in mean selegiline C_{max} and an 18-fold increase in mean selegiline AUC. The study also demonstrated a 4-fold and 6-fold increase in mean selegiline C_{max} and AUC, respectively, in 10 patients with “impaired kidney function”. Unfortunately, the degree of hepatic or renal impairment could not be assessed as the limited baseline laboratory results in the impaired groups overlapped the normal range up to 3-4 times the upper limit of normal, and the study participants were not stratified by degree of impairment. Baseline values (means, individual results, or ranges) for serum albumin, serum bilirubin, INR or prothrombin time were not reported for the population with hepatic disease; and the presence or absence of ascites or other signs and symptoms was not mentioned. No values for creatinine clearance or other measures of GFR were reported for the group with renal impairment.

Examination of the individual plasma concentration versus time curves presented in the publication (figure 2) suggests that many of the subjects with liver impairment or renal impairment had plasma concentrations that were very similar to the control subjects. While the results of this study raise concerns that some individuals with hepatic or renal disease had substantial increases in selegiline exposure, others were largely unaffected and the relationship between disease severity and impairment of drug clearance is undefined. There were no reported adverse events in any participant nor any clinically relevant changes observed in post-study laboratory test results.

In light of the data quoted above, one cannot exclude the possibility that renal or hepatic impairment might increase systemic exposure of selegiline to levels outside the safety margin for increased tyramine sensitivity. Since the pharmacokinetics of ZELAPAR™ (ZYDIS® selegiline) and its metabolites have not been evaluated in patients with hepatic or renal insufficiency, it is not presently known to what extent the systemic exposure of selegiline is affected by varying degrees of renal and/or hepatic dysfunction. It should be further noted that selegiline following Zelapar administration is principally absorbed through the buccal route. This results in lower first-pass metabolism and hepatic impairment may have a lesser influence on the systemic selegiline levels. Valeant has agreed with the Agency to conduct pharmacokinetic studies of ZELAPAR™ in hepatic and renal impairment as Phase 4 commitments.

Until the results of definitive studies are available to support recommendations regarding the use and possible dose adjustments of ZELAPAR™, the Sponsor recommends that the following warning be included in the Zelapar package insert and that the package inserts for existing

selegiline formulations should also be modified with this wording: _____

b(4)

Reviewer Comment

- I agree essentially with most of the sponsor's comments on this study. This study raises serious questions about how renal or hepatic impairment may significantly increase exposure both C_{max} and AUC. Of interest, it seems that exposure of only selected patients is substantially increased and that exposure in many seems unaltered.

A major problem with interpreting the significance of this study is the fact, as noted by the sponsor, that the degree of impairment for enrollment in this study is not clearly characterized. Thus, we are not able to assess how these effects might be experienced in patients in whom we typically characterize the degree of impairment according to particular criteria as mild, moderate, or severe. The enrollment criteria did not seem very quantitatively specific. Of interest, the mean serum aminotransferase (AST, ALT) levels of hepatically impaired subjects were increased approximately 2-3 fold of the mean of the controls, and the mean BUN and creatinine of renally impaired subjects were approximately 2.5 fold of mean levels of controls. Impaired subjects in the hepatic group had a diagnosis of liver dysfunction "confirmed histologically" and renally impaired subjects had "stable long-term renal impairment with elevated serum creatinine values." In addition to the curves showing large variability in exposures, the SD for each mean AUC is very large and greater than the mean similarly reflecting the impression from visualizing individual subject exposure.

- From a PK perspective, there are also some study design issues that make me question their relevance to the application under review. The standard dose of conventional, swallowed selegiline is 10 mg daily (5 mg BID). In this study patients were administered a single dose of 20 mg selegiline and data that were collected were not at steady state. Ideally, it would have been potentially more relevant for us to know what is the effect of either impairment on an approved dose (5 mg BID) and at steady state which is reached after several days of multidosing administration. I question whether similar quantitative effects (e.g. 18 and 6 fold increase in AUC exposure and 7 and 4 fold increase in C_{max} in hepatic and renal impairment, respectively) would have been observed if selegiline had been administered as 5 mg BID and assessed at steady state.
- Following my review of this publication, I contacted Charlene Flowers in the Office of Drug Safety (ODS) and requested a specialized search of the Adverse Event Reporting System (AERS) data base, a repository for MedWatch Reports, to identify case reports of various adverse events in patients with underlying renal or hepatic disorder/impairment. Unfortunately, a wild card search of AERS utilizing selected hepatic% and renal% terms in the descriptive event and relevant medical history fields was limited by abbreviated words, misspelled words, or foreign jargon. Ultimately, we were unsuccessful at identifying the

population of interest. When a typically search of AERS with terms indicative of associated renal or hepatic impairment is conducted the results identify patients who experienced renal/hepatic impairment subsequent to the temporal administration of selegiline. Thus, we do not know how frequently patients with adverse events associated with selegiline treatment had associated renal or hepatic impairment without reading and analyzing individual MEDWATCH reports.

- Although there are problems/limitations/shortcoming of this study, I think that it is difficult to ignore the findings in this study. These findings in this publication are contradictory to the impression one would get from the uncontrolled (no unimpaired hepatic or renal control group within the study) study of transdermal selegiline in another NDA. If there really is an increased exposure associated with either impairment (and the renal seems more difficult to accept considering the supposedly low excretion by kidney), then patients could be at a potentially serious risk for adverse reactions, perhaps the most serious being a hypertensive “cheese” reaction from loss of the relative selectivity for MAO-B. I do not think that the sponsor’s cautionary advice for the label is very practical or helpful. I also note that the fact that our Clinical Pharmacology reviewers think that 2 separate studies should be conducted in patients with hepatic and renal impairment leads me to believe that neither can they dismiss the possible implications or significance of this recent publication.

One approach could be to disregard these findings and request that the sponsor conduct phase 4 studies assessing effects of renal and hepatic impairment and not mention anything in the label or perhaps mention something about these findings and craft some type of precautionary statement. This would seem difficult without knowing what to say about specific degree of impairment. One could entertain this argument considering that selegiline has been approved and used for many years and we do not have a clear suggestion of increase risk for adverse events with either impairment. The contradictory results of the transdermal selegiline studies would seem to support this approach along with concerns about the results in the publication itself. An alternative approach could be to contraindicate selegiline use in patients with renal or hepatic impairment but again it would seem difficult to craft language describing how this impairment is defined. Finally, the most conservative approach would be to require that the sponsor conduct both of these studies prior to approval because it is not acceptable to allow this risk for this new formulation.

b(5)

1.1. Reviewer Conclusions

1. ZS at 2.5 mg daily is an effective dose for the sponsor’s desired indication/claim. The sponsor did not adequately study the 1.25 mg daily dose to receive a claim for this dose.
2. **I have concerns about the potential safety of ZS 2.5 mg daily if patients treated with this dose have various conditions (e.g. hepatic impairment, renal impairment, concomitant sex steroid treatment, concomitant treatment with a drug provoking increased exposure via a drug-drug interaction (DDI) with important CYP metabolizing enzymes of ZS) that could markedly increase selegiline exposure. My**

concerns are most pointedly directed at the risk of a hypertensive “cheese” reaction at very high multiple exposure of ZS 2,5 mg , and possible QTc prolongation and corresponding risk of Torsades des pointes (that can be fatal) because the QTc study is “positive” and did not exclude a possible QTc prolongation below 10 msec.

My concerns about this risk in the face of markedly increased exposures to selegiline are based upon 3 considerations : 1) a published study showing that patients with hepatic impairment had a mean increased AUC and Cmax that were 18 fold and 7 fold respectively greater than those of healthy subjects and patients with renal impairment had a mean increased AUC and Cmax that were 6 fold and 4 fold respectively greater than those of healthy subjects; 2) a publication showing administration of several single doses of oral conventional selegiline was associated with markedly increase exposures (e.g. 22 fold increased AUC and 11 fold increased Cmax for 10 mg selegiline; the approved daily dose); and 3) I am not convinced that we are confident that markedly increased exposures (AUC and/or Cmax) are not possible from DDIs from other drugs altering the metabolism of selegiline by direct inhibitory actions or by indirect competitive antagonistic/inhibitory actions on important CYP enzymes involved in the metabolism of selegiline. I do not necessarily find it reassuring that we are not aware of serious safety risks from these potential interactions in patients who are taking conventional oral selegiline (Eldepryl).

Very recently, a more detailed Clinical Pharmacology/Biopharmaceutical review (9/21/05), that addressed the publications stimulating concern about increased selegiline exposure and publications characterizing CYP enzymes in selegiline metabolism was completed. This review noted that the understanding about the CYP enzymes involved in selegiline metabolism is not very clear. Thus, not only do we NOT have a clear understanding of which CYP enzymes play an important, major role in selegiline metabolism, the full complement of which CYP enzymes are involved in selegiline metabolism has not been clearly established. In the absence of this critical information, it is not possible to recognize and understand the potential for various DDIs (e.g. especially by direct CYP enzyme inhibition or indirect antagonistic/competitive CYP enzyme inhibition). This critical information is most relevant to this NDA because markedly increased selegiline exposures can markedly increase safety risks for tyramine-induced hypertensive “cheese” reactions, possibly QTc prolongation/Torsades des pointes, and other dose-related selegiline toxicities. _____

b(5)

These publications do not permit us to describe the risks in the label because of shortcomings/limitations in the way the study was conducted and/or because of insufficient information in the publication. For example, it is not possible to describe what patients with what precise level of hepatic or renal impairment would be at risk. The risks of hepatic and renal impairment are most problematic because these conditions could be relatively common in the rather elderly population treated ZS. Although the likelihood of concomitant oral contraceptive use with ZS seems rather limited and the risk of hormone replacement interactions does not seem that great, the risk of many other potentially important DDIs are essentially unknown/undefined.

My thinking is that these important issues with potentially serious safety issues should be addressed prior to approval of ZS.

1.2. Reviewer Recommendations

Action Recommendation

I consider this application to be approvable because there is an absence of important clinical pharmacology information that impacts significantly on the safety of ZS.

Requirements for Approval

1. The sponsor should conduct a study investigating the effect of hepatic impairment on ZS PK at steady state.
2. The sponsor should conduct a study investigating the effect of renal impairment on ZS PK at steady state.
3. The sponsor should conduct a study investigating the effect of sex steroids (oral contraceptive and hormone replacement therapy) on ZS PK at steady state.
4. The sponsor should address the human metabolism of ZS, identify which CYP enzymes are involved in metabolism and play major, important roles, and provide information on the potential for drug-drug interactions (DDIs) with these metabolizing enzymes whereby such DDIs could potentially result in a many fold increase in selegiline (AUC and/or Cmax).
5. If any of these studies showed a potential for a marked increase in selegiline exposure (> 6 fold for AUC or Cmax), the sponsor should conduct another QTc study to characterize the effect of higher doses of ZS (.e.g. 10, 20, and 30 mg compared to placebo and moxifloxacin-positive control) of healthy subjects studied in an in-patient setting under conditions of tyramine dietary restriction).

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2. BACKGROUND / INTRODUCTION

Background on Conventional Selegiline (Eldepryl ®)

Conventional selegiline is currently approved (1989) in the U.S. as well as in several other countries for the treatment of patients with Parkinson's disease (PD) who are receiving levodopa/L-DOPA (LD) therapy (with or without a peripheral decarboxylase inhibitor) and who are experiencing deterioration in their therapeutic response to LD. Selegiline is thought to exert its therapeutic effect via inhibition of the monoamine oxidase (MAO) B enzyme and the decrease in dopamine metabolism and turnover. Selegiline is marketed in the U.S. as Eldepryl ®, a formulation that is swallowed. Throughout this NDA conventional selegiline may also be referred to as Eldepryl. Although Eldepryl has also been studied to determine if it exerts a neuroprotective effect on dopaminergic neurons of Parkinson's disease patients, convincing evidence has not yet been generated.

ELDEPRYL (selegiline hydrochloride) is a levorotatory acetylenic derivative of phenethylamine. It is also commonly referred to in the clinical and pharmacological literature as 1-deprenyl.

The chemical name for selegiline is: (R)-(-)- N₂,2 -dimethyl- N-2 -propynylphenethylamine hydrochloride. It is a white to near white crystalline powder, freely soluble in water, chloroform, and methanol, and has a molecular weight of 223.75. The structural formula is as follows:

b(4)

One very important safety concern with Eldepryl is the potential to produce hypertensive "cheese" reactions when tyramine-containing products are ingested and Eldepryl has exerted non-selective inhibition of MAO-A. Thus, the main warning in the Eldepryl label is against the use of higher than recommended doses (i.e. 5 mg BID). Severe syndromes with potentially a fatal outcome may also occur from a drug-drug interaction with various drugs such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and meperidine. Severe CNS toxicity associated with hyperpyrexia and death has been reported with the use of TCAs and conventional selegiline. Severe reactions consisting of diaphoresis, flushing, ataxia, tremor, hyperthermia, hypertension/hypotension, seizures, palpitation, dizziness, and/or mental changes

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(e.g. agitation, confusion, and hallucinations potentially progressing to delirium and coma) have been reported with the use of SSRIs and conventional selegiline. The occurrence of stupor muscular rigidity, severe agitation, and hyperthermia has been reported in some patients receiving the combination of meperidine and selegiline. Other main side effects from selegiline consist mainly of exacerbation of side effects produced by LD (e.g. nausea, vomiting, orthostatic hypotension, light headedness, syncope, hallucinations, dyskinesia, headache).

Regulatory History and Clinical Development of Zydis Selegiline

Zydis selegiline (ZS) is a rapidly-dissolving oral dosage formulation of selegiline consisting of an open matrix of water-soluble ~~polymer~~. This formulation dissolves quickly (e.g. beginning within seconds) in saliva on the tongue, releasing selegiline into the saliva, and does not require added water to aid disintegration, dissolution or absorption. Major theoretical advantages of the ZS formulation include : 1) improved patient compliance with the easily administered tablet that rapidly dissolves on the tongue, especially for patients with swallowing difficulties; 2) reduced variability in absorption relative to orally-administered standard tablets, with potentially more predictable clinical effects; and 3) reduced overall exposure to selegiline and metabolites (based on administered dose), and reduced production of potentially active metabolites. b(4)

The original IND (47005) for ZS was submitted to the FDA in 1994 by RP Scherer DDS. When the sponsor discovered and notified FDA that ZS was not bioequivalent to conventional selegiline, it was clear that clinical efficacy data would be required to support the registration of ZS. In 1996 the DNDP informed Scherer that an open-label, randomized, controlled study (Z/SEL/95/008) of parallel groups of low and high ZS and Eldepryl would not be sufficient to support efficacy. Elan Pharmaceuticals took over the clinical development of ZS from Scherer in 1997. DNDP had recommended that the sponsor conduct a single, pivotal, "large" double-blinded, placebo-controlled study of ZS in Parkinson's disease patients but the sponsor planned to conduct two smaller studies (double-blinded, placebo-controlled, parallel group) with identical designs. In February 1999, Elan Pharmaceuticals assumed ownership of ZS from Scherer and completed pivotal studies Z/SEL/97/025, and Z/SEL/97/026, and their extension phase (Z/SEL/97/027). On 11/7/01 Elan Pharmaceuticals had a pre-NDA meeting with DNDP to review mainly issues of format and content. Elan Pharmaceuticals and in addition to other Pre-NDA meetings previously for ZS. At the 11/01 meeting DNDP agreed that one positive, statistically robust study (e.g. study Z/SEL/97/026) could serve as the main basis for approval of ZS.

Early pharmacokinetic studies conducted in healthy volunteers indicated that ZS provided increased plasma concentrations of selegiline, generated a lower fraction of metabolites, and had a much higher relative bioavailability compared with standard oral tablets. Selegiline plasma concentrations were on the order of 5 - 8 times greater than that seen with the standard oral selegiline tables, suggesting a dose range of 1.25 to 2.5 mg was a potentially effective and therapeutically equivalent dose range. Based upon this information, ZS was administered in the

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pivotal trials at 1.25 mg daily initially and subsequently at 2.5 mg daily.

ZS has been approved outside the U.S. ZS was first approved in 1998 in the United Kingdom, was subsequently approved in 9 other countries, and approval is pending in another country. Approval is for adjunctive therapy of Parkinson's disease with LD and for symptomatic relief or to delay the need for LD in early Parkinson's disease.

Pharmacology/Mechanism of Action of Selegiline

Selegiline (phenylisopropyl-N-methylpropylamine hydrochloride) belongs to the class of enzyme-activated irreversible inhibitors, also referred to as "suicide" substrates for monoamine oxidases (MAOs). MAOs are enzymes associated primarily with the outer mitochondrial membrane. MAOs are widely distributed throughout the body and are found in brain and in peripheral tissues such as the gut and heart. MAO catalyzes the deamination of monoamine neurotransmitters or neuromodulators among other substrates and occurs in two main forms, termed MAO-A and MAO-B. In humans, peripheral MAO is predominantly type A, while in the brain MAO is present as both forms; cortical MAO is predominantly type A, while in the striatum the predominant form is type B.

As a substrate selective for MAO-B, selegiline (L-selegiline isomer) acts in a two-step sequence, first binding to the enzyme active site then forming a covalent bond with the flavin moiety after deamination. After creation of the selegiline-enzyme combination, the MAO-B enzyme is permanently inactivated. The net result is a reduction in the ability of MAO-B to oxidize (degrade) amine neurotransmitters and neuromodulators. Restoration of MAO-B function can only be achieved through turnover of the inactivated enzyme and its replacement by synthesis of new enzyme, a process in humans that can take from two weeks up to 30-40 days to complete. When compared to other MAO-B inhibitors such as pargyline or moclobemide, and when given in therapeutically-relevant doses, selegiline displays a relatively high degree of selectivity for MAO-B. As a result, selegiline is expected to show improved tolerability and reduced potential for drug interactions than other, less selective MAO inhibitors.

Selegiline selectively and irreversibly inhibits monoamine oxidase Type B (MAO-B) and is used in Parkinson's disease patients to decrease the metabolism of dopamine and thereby enhance the effects of levodopa/L-DOPA (LD) and extend its effectiveness. In recent years, a number of other pharmacologic actions have also been identified for selegiline, including modulation of gene expression, modulation of apoptosis, and neuroprotective effects. The relationship of these potential actions of selegiline to its effectiveness in extending the action of LD in patients with Parkinson's disease is unclear.

Rationale for Selegiline Use

As LD has a relatively short half-life, requiring multiple doses during the day, the therapeutic approach to managing ON-OFF fluctuations is to pharmacologically extend the duration of each dose of LD by reducing the metabolism of the end product (dopamine) and its removal from the

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synapse via inhibition of MAO-B activity. This prolongation of dopamine's synaptic residence time essentially "smooths out" the rise and fall of dopaminergic stimulation delivered to the basal ganglia and is thought to reduce the stimulus driving the development of fluctuations in LD response.

Intended Use of Selegiline

LD, often combined with a peripheral decarboxylase inhibitor (PDI) such as carbidopa, is the primary therapy for Parkinson's disease. Patients newly diagnosed typically respond well and are stable on LD therapy for many years. As the disease progresses, however, many patients begin to lose their responsiveness to LD and develop a number of complications, especially motor complications. (e.g. end of dose wearing off, "ON-OFF", dyskinesias). Late complications of LD therapy may include the emergence of dysphagia, autonomic dysfunction, affective symptoms, or motor symptoms such as end-of-dose wearing off, ON-OFF fluctuations, and or dyskinesias.

Patients with ON-OFF fluctuations undergo disabling and unpredictable episodes during which patients normally responding to L-DOPA (the "ON" phase) experience a transient, sudden resurgence of PD symptoms such as freezing, tremor or bradykinesia (the "OFF" phase). The development of ON-OFF fluctuations has been linked to unfavorable changes in dopaminergic receptor function in the basal ganglia, primarily in response to the pulsatile nature of dopaminergic stimulation produced by intermittent dosing with LD. Estimates from the literature indicate nearly half of Parkinson's disease patients may experience motor fluctuations after 4-6 years of LD therapy. These symptoms also have a negative impact on the patient's affective state. Patients experiencing ON-OFF fluctuations are essentially disabled during the OFF periods, and form the target patient population (intended use) for ZS.

Clinical Evidence for Selegiline Effectiveness

Numerous clinical trials have been published demonstrating the effectiveness of selegiline in extending the efficacy of LD therapy in Parkinson's disease patients experiencing deteriorations in clinical benefit. In larger studies, short term therapy is associated with changes in LD response reflecting improved motor coordination, walking, ON-OFF fluctuations, and global improvement. Large, long-term studies appear to provide the best overall evaluation of response to selegiline as adjunctive therapy and, in general, support the efficacy and safety of selegiline, particularly in patients experiencing motor fluctuations. In the positive long-term studies, selegiline exerted an LD sparing effect and delayed progression to predetermined endpoints such as requiring increased LD or a dopamine agonist. Improvements in motor coordination, walking ability and motor fluctuations were also noted as well as improvements in patient disease status and performance on global scales and on various standardized assessment tools such as the Unified Parkinson's Disease Rating Scale (UPDRS) or others. These favorable outcomes for selegiline were consistent with those observed in the published short-term trials. In addition, some studies report improved survival with the addition of selegiline.

However, one large-scale open-label trial involving short-term selegiline monotherapy in early-

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stage Parkinson's disease followed by randomization to long-term therapy with either LD or LD plus selegiline found little benefit from the addition of selegiline and reported an increased mortality in the selegiline groups. The results of this study were reviewed and engendered much commentary, but little support for these discrepant findings. Several studies were subsequently published contradicting the findings, criticizing the open-label study design, re-assignments of patients to treatments, and deficiencies in the actual cause of death information gathered and the claim of increased mortality findings, including some longitudinal studies. Despite the extended evaluation of data from the negative trial, no clear reasons for the observed increase in mortality were identified. Thus, the safety of selegiline monotherapy or selegiline adjunctive therapy with LD in early-stage Parkinson's disease is still open to question. However, based on the weight of the numerous positive, published, short- and long-term trials cited above, the efficacy and safety of adjunct therapy in mid-to-late stage Parkinson's disease, particularly in patients experiencing LD wearing-off or ON-OFF fluctuations, seems clear.

Approvable Letter

On 2/7/03, an approvable letter was issued to the sponsor (Elan) noting 2 main clinical concerns (conduct a tyramine sensitivity study and conduct a QTc study) among several other concerns of other disciplines. During the interim, Elan sold this product to another sponsor (Valeant Pharmaceuticals). There have also been interactions between the division and sponsor to provide advice to the sponsor. Most notably, there was a face to face meeting (5/25/04) with Valeant and the DNDP to discuss the study design for the tyramine sensitivity study and the QTc study. The sponsor did not follow much of the advice of the DNDP and markedly altered its study design for the tyramine sensitivity study. The DNDP had a teleconference with the sponsor to provide additional advice on the tyramine sensitivity study but the sponsor did not inform the DNDP that the tyramine sensitivity study had already been completed. The sponsor submitted (received 12/16/04) a response to the approvable letter by the new sponsor but this application was not filed because of deficiencies (significant deficiencies and problems related to the navigability of the application, no requested re-analysis of oropharyngeal adverse events, and other more minor ones). The sponsor's response was re-submitted and received by the Agency on 3/20/05 and this response is the subject of this review.

3. SPONSOR'S RESPONSE TO CLINICAL COMMENTS IN APPROVABLE LETTER

Some comments listed in the Approvable letter under Clinical section are specifically comments from the Biopharmaceutical/Clinical Pharmacology reviewer(s) or Statistical reviewer(s). I have not included nor commented on these responses in my review because these responses require review/comment by the reviewer of the respective discipline from which the comment originated. This observation explains why "Clinical Comments" and respective sponsor responses are not consecutive.

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Clinical Comment 1: Need to Conduct Tyramine Challenge Study Assessing Pressor Responses

1. a) “We are concerned about the results you have obtained in your tyramine challenge studies, in particular, Study 101. As you know, this study yielded a pressor ratio of 6.8 for Eldepryl, a value considerably greater than that previously obtained for this product. In addition, the percent of patients whose threshold dose of tyramine in the Eldepryl group was 50 mg or less was 59%, also a value at considerable variance with previous data for this product. The corresponding values obtained for your product displayed a confusing pattern, with the Zydis 1.25 mg dose having the greatest response. If these values are accurate, they raise considerable concern about the potential for both your product and marketed selegiline products to produce considerable degrees of MAO-A inhibition and hypertensive crises in patients with unrestricted diets. However, there are a number of factors that make the interpretation of this study difficult, including the absence of both a placebo and a positive control group.”

Valeant Response to Comment 1 a: Contradictory results from tyramine challenge Studies

We acknowledge that the results from the prior tyramine-challenge studies are not in full agreement with that published in the medical literature, at least in part due to the study design and lack of adequate controls. Rather than attempt to explain the differences between these studies, we have conducted a new Phase 1 Clinical Study “A Phase 1 Study in Healthy Subjects to Evaluate the Effect of Steady-State Doses of ZELAPARTM (Zydis® Selegiline HCl) on Blood Pressure Responses to Tyramine” (Protocol RNA-ZEL-B21-102) to address the tyramine-pressor effects of ZELAPAR TM (Zydis®-selegiline) compared to an active control, NARDIL®. The key pharmacodynamic results of that study are summarized and discussed below.

- This study was a robust evaluation of the potential for ZELAPAR TM to interact with tyramine. The results demonstrate that the clinically recommended dose of ZELAPARTM 2.5 mg once daily is similar to placebo with regard to its effect on the tyramine pressor response at steady state.
- The active control drug (NARDIL 30 mg) demonstrated a clear positive effect on tyramine pressor response that was comparable to the published results and this effect was substantially higher than that observed with the clinically recommended 2.5 mg ZELAPAR dose. ZELAPAR, at an intermediate dose of 5 mg and at a supratherapeutic dose of 10 mg daily, was shown to enhance the tyramine pressor effect, but the level of effect observed following the 5 mg dose was clinically and statistically significantly lower than that observed with NARDIL 30 mg.
- At two supra-therapeutic doses of 5 mg and 10 mg daily, there was an enhanced tyramine pressor effect, but the effect observed following the 5 mg dose was clinically and statistically significantly lower than that observed with NARDIL 30 mg.

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A more detailed summary of the results are in ATTACHMENT A-1; the full Clinical Study Report is located in Section 3 of the Response to the Approvable Letter.

Reviewer Comment

- **I will present a more detailed description of this study (“A Phase 1 Study in Healthy Subjects to Evaluate the Effect of Steady-State Doses of ZELAPAR™ (Zydis® Selegiline HCl) on Blood Pressure Responses to Tyramine” - Protocol RNA-ZEL-B-21-102) and its specific results along with comments later in this review.**
- In general, I agree with the sponsor’s above response and comments.
- The data show that the higher doses (5 and 10 mg daily) of ZS showed an increased sensitivity to tyramine relative to increased pressor responses. However, none of the ZS doses (2.5, 5, or 10 mg daily) seemed capable of producing a sustained threshold pressor response (≥ 30 mm increase systolic blood pressure) after challenge with increasing tyramine doses up to 100 mg under fasting conditions more frequently than placebo-treated subjects. In contrast, a substantial percentage of subjects (15 % challenged with 25 mg tyramine and 62 % challenged with 100 mg tyramine) treated with the positive control (phenelzine, non-selective MAO inhibitor) showed sustained threshold pressor responses (2 consecutive ≥ 30 mm increment of systolic blood pressure) after challenge with increasing tyramine doses up to 100 mg under fasting conditions more frequently than placebo-treated subjects (0 %).

A “high” tyramine content oral challenge from food and/or drink is considered to be probably in the range of 40-50 mg tyramine. In addition, administration of a tyramine challenge added to food can be associated with decreased bioavailability of tyramine (including decrease C_{max} , AUC and delayed T_{max}) and decreased pressor responses depending on various conditions. Given that the fasting tyramine study challenge would appear to represent a tyramine challenge under a worst case scenario that could be experienced by eating and/or drinking food or liquid containing 100 mg of readily bioavailable tyramine, I interpret these results as suggesting that none of the daily ZS treatments (2.5, 5, or 10 mg) appear to be associated with a significant risk for a tyramine-induced hypertensive “cheese” reaction. The ZS dose to be approved would be 2.5 mg. The fact that none of the higher doses of ZS (5 and 10 mg daily) appeared to be capable of inducing sustained pressor responses suggests a reasonable margin of safety with respect to a hypertensive risk for patients who might experience a significantly increased pharmacokinetic (PK) exposure (up to an equivalent dose of 10 mg daily) for some reason.

- The sponsor did not conduct a fasting tyramine challenge study as we had recommended (particularly including additional doses at small increments up to 800 mg day and inclusion of a treatment group taking conventional swallowed selegiline 5 mg BID for comparison). Nevertheless, I think that the sponsor’s results are adequate and allow us to address the

question of whether these doses of ZS appear to be associated with a significant risk for a tyramine-induced hypertensive “cheese” reaction. This most recent study suggested that there appears to be an increased frequency for observing “threshold pressor responses” when a single isolated threshold pressor response is used as the criterion for a threshold response rather than requiring 2 consecutive blood pressures to achieve the criterion. In retrospect, I consider that results of the sponsors’ previous “definitive” fasting tyramine challenge study (AN17933-101) were erroneous and suggested that subjects showing tyramine-induced threshold pressor responses likely represented false positive responses.

Clinical Comment : Need to Conduct Orthostatic Vital Sign Assessments Timed to Dosing

Clinical Comment 4: “Given the higher C_{max} expected with Zelapar 2.5 mg/day compared to the marketed selegiline formulation, we believe it is important to characterize changes in blood pressure in relation to dosing, ideally capturing results at T_{max}. Such data was not collected in the controlled trials, but was collected in Study 101 (PK and tyramine challenge study). Unfortunately, the only analyses of the BP data from Study 101 are based on mean changes; outlier analyses based on pre-defined clinically important changes would be more informative. We ask you to perform such analyses for both resting BP and orthostatic BP. Unfortunately, Study 101 does not have a placebo-control group. Therefore, within the tyramine challenge study requested above we ask that you include a placebo control group and again collect resting and orthostatic BP data in relation to timing of dose.

Valeant Response to Comment 4: Effect of Selegiline on Resting and Orthostatic Blood Pressure

As part of the Tyramine-Challenge Clinical Pharmacology Study, Valeant did investigate the effect of selegiline (following ZELAPARTM administration) on resting and orthostatic blood pressure during the conduct of the Tyramine-Challenge study (Study RNA-ZEL-B21-102). The results of that study are summarized below.

- There were no changes in orthostatic BP related to timing of dose.
- The change in orthostatic SBP on treatment relative to the pre-randomization baseline was variable and no trends were apparent between treatment groups or within treatment groups with respect to time after dosing.
- The mean change from baseline orthostatic SBP at scheduled time points over the 24-hour post-dose assessment period ranged from -5.7 to 3.2 mmHg for 2.5 mg ZELAPARTM, from -3.6 to 2.4 mmHg for 5 mg ZELAPARTM, and from -4.5 to 4.4 mmHg for the 10 mg ZELAPARTM dose, with no discernable pattern to the values.

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Reviewer Comment

- I agree with the sponsor's response that the study of orthostatic blood pressure responses did not show a clear effect on orthostatic blood pressures indicating orthostatic hypotension related to ZS treatment compared to placebo treatment.
- The sponsor has also analyzed these data for categorical increments blood pressure (SBP \geq 20 mm Hg and/or 10 mm DBP \geq 10 mm hg) in supine, standing and orthostatic positions. There is no real suggestion of ZS-induced categorical increments in blood pressure timed to dosing for ZS relative to placebo. A question of ZS related increments in blood pressure had been raised in the previous 101 study in which ZS was compared to Eldepryl (10 mg QD) but in which there was no placebo group.

Clinical Comment : Need to Conduct Thorough QTc Study

Clinical Comment 5: "As with blood pressure data above, we believe it is critical to investigate ECG data timed to dosing. This has not been done in any of your studies to date. ECG data (not timed to dosing) was provided initially for one controlled trial, Study 25, and revealed a 7 msec prolongation of QT interval on Zelapar vs. placebo. While not found in the other controlled trial, Study 26, this still raises the possibility of QT prolongation with selegiline. Given the higher Cmax with Zelapar, we ask you to investigate the possibility of QT prolongation further. As with the BP data above, we believe ECG data in relation to dosing can be most efficiently collected within the new tyramine challenge study."

Valeant Response to Comment 5: Effect of Selegiline on QTc Prolongation

Although Elan Pharmaceuticals presented an explanation of the inconsistencies in QTc results from Studies 025 and 026, as summarized in ~~the~~ analysis, submitted in the August 7, 2003 amendment to the NDA, Valeant agreed to conduct a definitive QTc study entitled, "A Negative and Positive Controlled Evaluation in Healthy Male and Female Subjects of the Potential for ZELAPAR (Zydis® selegiline HCl) at Steady-State to Affect ECG Parameters with Special Emphasis on Cardiac Repolarization" (Protocol RNA600301-101), in accordance with discussions with the Division. The results of that definitive study are reported below.

- The mean maximum on-treatment values for all ECG parameters were within the normal range for all treatment groups. No apparent differences between treatment groups were evident for HR, RR, PR, or QRS. The mean maximum changes from baseline achieved in the ZELAPARTM treatment groups for QT parameters was consistent with those observed for placebo, and less than the mean maximum changes from baseline QT and QTc demonstrated in the moxifloxacin group.
- The maximum change from baseline for QTcI was an increase of approximately 18 msec and 17 msec in the 2.5 mg ZELAPARTM and 10 mg ZELAPARTM groups, respectively, compared

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to 17 msec in the placebo group and 23 msec in the moxifloxacin group. The increase in QTcI from baseline elicited by administration of moxifloxacin was significantly different from the change from baseline QTcI in the ZELAPARTM treatment groups or placebo. These results validated the sensitivity of this study to detect small changes in QTc intervals.

- Neither the 2.5 mg ZELAPARTM group nor the 10 mg ZELAPARTM group were significantly different from placebo with respect to on-treatment changes in QTcI, nor was any significant difference detected between the two ZELAPAR treatment groups.

Reviewer Comment

- **I will present a more detailed description of this study (“A Negative and Positive Controlled Evaluation in Healthy Male and Female Subjects of the Potential for ZELAPAR - Zydis® selegiline HCl at Steady-State to Affect ECG Parameters with Special Emphasis on Cardiac Repolarization”)) and its specific results along with comments later in this review.**
- Considering all these results and analyses, critical questions to be answered ultimately are :
 - 1) Does ZS treatment prolong QTc relative to placebo?
 - 2) Is there a gender difference in the magnitude of ZS-related QTc prolongation relative to placebo?
 - 3) If there is a suggestion of a ZS-related QTc prolongation relative to placebo, is there any clinical concern relative to an approval action or labeling based upon the magnitude of the suggested QTc prolongation?
- **Considering all these results and analyses, I still cannot answer question # 1 by noting that ZS does or does not prolong QTc relative to placebo.** Although I agree that this study did not show any statistically significant increments in QTc for ZS relative to placebo, I interpret this “thorough” QTc study as being a “positive” study because it did not exclude a possible increase in QTc below 10 msec. The conservative ANCOVA analysis (using Dunnett’s test) showed that the upper bound of the 95 % CI (one-sided) was ~ 11 msec and the QTc guidance says that the largest time-matched QTc increment of the change from baseline should exclude 10 msec for this upper boundary to be called a “negative” study that exclude this value as a potential risk.

I have raised the question whether there are mild QTc increments in QTc at 3 and 12 hours in all subjects treated with high dose 10 mg ZS. If so, the largest mean treatment effect (placebo-corrected) was ~ 5-7 msec (for all 3 QT corrections) at 12 hours. Thus, we still do not know if ZS prolongs QTc and have not been able to exclude a risk of 10 msec.

- My answer to question # 2 is that there are data that raise the suspicion of a different gender effect of high dose 10 mg ZS on QTc prolongation based upon mean results and CIs not associated with statistical significance. The gender analyses raise the question of possibly greater numerical QTc prolongation at 3 hours in males (vs females) and a substantial mean QTc increment (~ 10 msec) at 12 hours only in females. I am not aware of other drug results that show such a gender difference of QTc prolongation occurring at a certain time only in one gender and not in the other gender. It is difficult to know whether these possible gender differences are or are not real. Of note, the gender analyses were based upon approximately half the number of subjects (~ 20) of that (~ 40) analyzed in the full analysis of all subjects.

It is also possible that the apparent gender effects raised are an artifact of multiplicity (i.e. making multiple statistical comparisons such as 3 paired treatment comparisons on 12 occasions; total 36 statistical comparisons).

- In answering question # 3, I note my thoughts about approval and labeling with certain caveats. At this time I think that it is a fair perspective to say that ZS could produce relatively small QTc increments that were not statistically significant but are possible because a margin of 10 msec was not able to be excluded in the "thorough" QTc study. These possible increments by themselves do not necessarily raise serious safety concerns if one would assume that ZS exposure would not exceed that associated with 10 mg daily ZS treatment in a healthy subject (~ fold Cmax and AUC of that expected in healthy subjects treated with 2.5 mg daily, the recommended dose). However, I have concerns that potentially much higher selegiline exposures could be experienced and these significantly higher exposures could potentially be associated with significant QTc prolongation and thus a risk of Torsades des pointes. My concerns about this risk in the face of markedly increased exposures to selegiline are based upon 3 considerations : 1) a published study showing that patients with hepatic impairment had a mean increased AUC and Cmax that were 18 fold and 7 fold respectively greater than those of healthy subjects and patients with renal impairment had a mean increased AUC and Cmax that were 6 fold and 4 fold respectively greater than those of healthy subjects; 2) a publication showing administration of several single doses of oral conventional selegiline was associated with markedly increase exposures (e.g. 22 fold increased AUC and 11 fold increased Cmax for 10 mg selegiline; the approved daily dose); and 3) I am not convinced that we are confident that markedly increased exposures (AUC and/or Cmax) are not possible from drug-drug interactions from other drugs altering the metabolism of selegiline by direct inhibitory actions or competitive inhibitory on important CYP enzymes involved in the metabolism of selegiline. I do not necessarily find it reassuring that we are not aware of serious safety risks from these potential interactions in patients who are taking conventional oral selegiline (Eldepryl).

Furthermore, I do not know how we could convey useful information in the label about results from the publication in which markedly increased mean selegiline exposures were

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**4. QUESTION POSED BY CLINICAL REVIEWER DURING REVIEW
ABOUT EFFECT OF RENAL AND HEPATIC IMPAIRMENT ON
ZYDIS SELEGILINE PHARMOCOKINETICS**

FDA:

Why should there not be a concern now that people with various degrees of hepatic and/or renal impairment who take 2.5 mg daily Zydis selegiline will not experience a markedly increased plasma exposure of selegiline that could be associated with an increased tyramine sensitivity (i.e. possible risk of hypertensive, "cheese" reaction)? We know that conventional selegiline loses its MAO-B selectivity (i.e. exhibits progressively increasing inhibition of MAO-A) as dose/exposure of conventional selegiline increases and that there is increased sensitivity to tyramine. Your data also shows that there is increased sensitivity to tyramine for blood pressure responses with high dose Zydis selegiline.

Sponsor's Response:

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In response to Dr. Kampala's July 8, 2005 email question regarding the plasma exposure of selegiline in hepatically- and renally- impaired patients, we have prepared the response below. Dr. Kampala's question is presented in **bold**, followed by the Valeant response. A copy of the referenced email and publication has also been attached for ease of review.

The data submitted in this application does establish that ZELAPAR™ (ZYDIS® selegiline), at the clinically recommended dose (2.5 mg daily) has a reasonable safety margin for tyramine-induced increases in blood pressure. As the reviewer notes, there is increased sensitivity to tyramine at a dosage of 10 mg daily of ZELAPAR™, suggesting some loss of MAO-B selectivity at 4-times the recommended dose.

In a recently published study (Anttila et al., 2005) 10 patients with liver disease, 10 patients with renal disease, 10 patients receiving hepatic enzyme inducers, and 10 healthy controls received a single 20 mg oral dose of conventional selegiline (ELDEPRYL®) [2-4 times the usual single dose] and the pharmacokinetics of selegiline and its metabolites were measured for 48 hours after dose administration. Relative to the healthy controls, patients with "chronic liver disease" had a 7-fold increase in mean selegiline C_{max} and an 18-fold increase in mean selegiline AUC. The study also demonstrated a 4-fold and 6-fold increase in mean selegiline C_{max} and AUC, respectively, in 10 patients with "impaired kidney function". Unfortunately, the degree of hepatic or renal impairment could not be assessed as the limited baseline laboratory results in the impaired groups overlapped the normal range up to 3-4 times the upper limit of normal, and the study participants were not stratified by degree of impairment. Baseline values (means, individual results, or ranges) for serum albumin, serum bilirubin, INR or prothrombin time were not reported for the population with hepatic disease; and the presence or absence of ascites or other signs and symptoms was not mentioned. No values for creatinine clearance or other measures of GFR were reported for the group with renal impairment.

Examination of the individual plasma concentration versus time curves presented in the publication (figure 2) suggests that many of the subjects with liver impairment or renal impairment had plasma concentrations that were very similar to the control subjects. While the results of this study raise concerns that some individuals with hepatic or renal disease had substantial increases in selegiline exposure, others were largely unaffected and the relationship between disease severity and impairment of drug clearance is undefined. There were no reported adverse events in any participant nor any clinically relevant changes observed in post-study laboratory test results.

In light of the data quoted above, one cannot exclude the possibility that renal or hepatic impairment might increase systemic exposure of selegiline to levels outside the safety margin for increased tyramine sensitivity. Since the pharmacokinetics of ZELAPAR™ (ZYDIS® selegiline) and its metabolites have not been evaluated in patients with hepatic or renal insufficiency, it is not presently known to what extent the systemic exposure of selegiline is affected by varying

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degrees of renal and/or hepatic dysfunction. It should be further noted that selegiline following Zelapar administration is principally absorbed through the buccal route. This results in lower first-pass metabolism and hepatic impairment may have a lesser influence on the systemic selegiline levels. Valeant has agreed with the Agency to conduct pharmacokinetic studies of ZELAPAR™ in hepatic and renal impairment as Phase 4 commitments.

Until the results of definitive studies are available to support recommendations regarding the use and possible dose adjustments of ZELAPAR™, the Sponsor recommends that the following warning be included in the Zelapar package insert and that the package inserts for existing selegiline formulations should also be modified with this wording:

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Reviewer Comment

- I agree essentially with most of the sponsor's comments on this study. This study raises serious questions about how renal or hepatic impairment may significantly increase exposure both C_{max} and AUC. Of interest, it seems that exposure of only selected patients is substantially increased and that exposure in many seems unaltered.

A major problem with interpreting the significance of this study is the fact, as noted by the sponsor, that the degree of impairment for enrollment in this study is not clearly characterized. Thus, we are not able to assess how these effects might be experienced in patients in whom we typically characterize the degree of impairment according to particular criteria as mild, moderate, or severe. The enrollment criteria did not seem very quantitatively specific. Of interest, the mean serum aminotransferase (AST, ALT) levels of hepatically impaired subjects were increased approximately 2-3 fold of the mean of the controls, and the mean BUN and creatinine of renally impaired subjects were approximately 2.5 fold of mean levels of controls. Impaired subjects in the hepatic group had a diagnosis of liver dysfunction "confirmed histologically" and renally impaired subjects had "stable long-term renal impairment with elevated serum creatinine values." In addition to the curves showing large variability in exposures, the SD for each mean AUC is very large and greater than the mean similarly reflecting the impression from visualizing individual subject exposure.

- From a PK perspective, there are also some study design issues that make me question their relevance to the application under review. The standard dose of conventional, swallowed selegiline is 10 mg daily (5 mg BID). In this study patients were administered a single dose of 20 mg selegiline and samples that were collected were not at steady state. Ideally, it would have been potentially more relevant for us to know what is the effect of either impairment on an approved dose (5 mg BID) and at steady state which is reached after several days of multidosing administration. I question whether similar quantitative effects (e.g. 18 and 6 fold

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increase in AUC exposure and 7 and 4 fold increase in Cmax in hepatic and renal impairment, respectively) would have been observed if selegiline had been administered as 5 mg BID and assessed at steady state.

- I am not aware that the sponsor (Somerset Pharmaceuticals) of conventional selegiline had conducted a study assessing the effect of renal or hepatic impairment on swallowed selegiline (i.e. Eldepryl). This same sponsor, however, has conducted 2 small studies in renally (N = 4 subjects/ group including mild, moderate and severe impairment groups) and hepatically impaired (N = 1 mild and 7 moderate impairment according to Child-Pugh classification) subjects after administration of transdermal selegiline. Results of these studies were reviewed in NDAs 21336 and 21708 for transdermal selegiline (single dose administration of 20 mg patch) by Dr. Iftexhar Mahmood (2/28/02). a major flaw or drawback associated with each study was the lack of a control group with normal renal and hepatic function for comparison with the impaired subjects. The sponsor interpreted results relative to historical control data. Cmax and AUC were similar across the 3 renal groups. Selegiline Cmax and AUC was approximately one third of that observed in the historical control group. In the renal impairment study, Dr. Mahmood concluded that it appears "that the pharmacokinetics of selegiline among patients with different degrees of renal impairment (mild, moderate and severe) are not different, no dosage adjustment of selegiline is required in patients with renal impairment. In the hepatic impairment study, Dr. Mahmood concluded that "it is difficult to draw any conclusion about the impact of hepatic impairment on the pharmacokinetics of selegiline mainly due to small sample size used in this study. Based upon the results of the study dosage adjustment of selegiline may not be required in patients with hepatic impairment, however, caution should be employed in this patient population when selegiline is given."

It is also important to note that I surveyed Cmax and AUC in other single dose transdermal selegiline PK studies of 20 mg (or a similar dose such as 15 or 22.5 mg with dose adjustment to estimate the equivalent Cmax and AUC for the 20 mg dose). My survey of across study results comparisons suggest that the historical control data used by Somerset could possibly be an overestimate (?up to 2 fold) of what control group might have shown if included in the renal and hepatic impairment studies. There appears to be some considerable variation of Cmax and AUC across studies. However, even if there was an effect, it would tend to seem relatively small and not nearly as great as that suggested in the recent publication of oral, conventional selegiline (Eldepryl).

I think that it is difficult to draw strict conclusions from these studies in regard to the potential relevance to ZS particularly because of : 1) the absence of internal control groups; 2) the study design involving a single dosing administration of a transdermal patch of selegiline that would provide a lower Cmax but higher AUC than ZS 2.5 mg and which would not show effects at steady state; and 3) the question of whether the magnitude of an effect of hepatic or renal impairment might be substantially different in the face of relative low selegiline exposures expected with Eldepryl (5 mg BID) or ZS 2.5 mg compared with many fold higher exposures associated with 20 mg transdermal selegiline. Despite these

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results with transdermal differences, I am not certain whether these limited results are applicable to what might be expected with ZS because it is a different product administered by a different route (although both formulations bypass “first hepatic pass effects”) and the AUC exposure with transdermal selegiline is much higher than that with ZS.

- Following my review of this publication, I contacted Charlene Flowers in the Office of Drug Safety (ODS) and requested a specialized search of the Adverse Event Reporting System (AERS) data base, a repository for MedWatch Reports, to identify case reports of various adverse events in patients with underlying renal or hepatic disorder/impairment. Unfortunately, a wild card search of AERS utilizing selected hepatic% and renal% terms in the descriptive event and relevant medical history fields was limited by abbreviated words, misspelled words, or foreign jargon. Ultimately, we were unsuccessful at identifying the population of interest. When a typically search of AERS with terms indicative of associated renal or hepatic impairment is conducted the results identify patients who experienced renal/hepatic impairment subsequent to the temporal administration of selegiline. Thus, we do not know how frequently patients with adverse events associated with selegiline treatment had associated renal or hepatic impairment without reading and analyzing individual MEDWATCH reports.
- Although there are problems/limitations/shortcoming of this study, I think that it is difficult to ignore the findings in this study. These findings in this publication are contradictory to the impression one would get from the transdermal study. If there really is an increased exposure associated with either impairment (and the renal seems more difficult to accept considering the supposedly low excretion by kidney), then patients could be at a potentially serious risk for adverse reactions, perhaps the most serious being a hypertensive “cheese” reaction from loss of the relative selectivity for MAO-B. I do not think that the sponsor’s cautionary advice for the label is very helpful. I also note that the fact that our Clinical Pharmacology reviewers think that 2 separate studies should be conducted in patients with hepatic and renal impairment leads me to believe that neither can they dismiss the possible implications or significance of this recent publication.

One approach could be to disregard these findings and request that the sponsor conduct phase 4 studies assessing effects of renal and hepatic impairment and not mention anything in the label or perhaps mention something about these findings and craft some type of precautionary statement. This would seem difficult without know what to say about specific impairment. One could entertain this argument considering that selegiline has been approved and used for many years and we do not have a clear suggestion of increase risk for adverse events with either impairment. The contradictory results of the transdermal selegiline studies would seem to support this approach along with concerns about the results in the publication itself. An alternative approach could be to contraindicate selegiline use in patients with renal or hepatic impairment but again it would seem difficult to craft language describing how this impairment is defined. Finally, the most conservative approach would be to require that the sponsor conduct both of these studies prior to approval because it is not acceptable to allow

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this risk for this new formulation. If this was the action, then it would seem that

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5. DESCRIPTION OF QTC STUDY AND RESULTS AND REVIEWER COMMENTS

Sponsor's Description of QTC Study

Title : "A Negative and Positive Controlled Evaluation in Healthy Male and Female Subjects of the Potential for Zelapar® (Zydis® selegiline HCl) at Steady- State to Affect ECG Parameters with Special Emphasis on Cardiac Repolarization"

Objective :

Primary : Determine the electrocardiographic effects of selegiline delivered as a ZYDIS formulation (ZELAPAR)

Secondary :

- Investigate the correlation of any observed effects of selegiline on ECG parameters to plasma concentrations of selegiline
- Evaluate the safety and tolerability of ZELAPAR

Design :

This was a randomized double-blind (for ZELAPAR), placebo-controlled, parallel group, multiple-dose study designed to define the ECG effects of ZELAPAR in healthy volunteer subjects at steady-state for selegiline compared to baseline, placebo, and a positive control (moxifloxacin). A total of 160 subjects were planned for randomization to 1 of 4 study treatments, with 40 subjects per treatment group. Each treatment group was balanced with respect to gender and consisted of 20 men and 20 women.

Following an initial screening period (Day -21 to -1), qualified subjects were randomized in a 1:1:1:1 ratio to one of the four treatment groups briefly described in Table 1 below. A more detailed description of the study treatments and method of administration is provided in Table 2. Subjects randomized to Group 1 or Group 2 received a clinical or suprathapeutic dose of ZELAPAR, respectively, once daily for 10 days. Subjects in Group 3 received placebo once daily for 10 days. The active and placebo treatments were blinded using a double-dummy dosing procedure. Subjects randomized to Group 4 served as a positive control group and received 9 daily doses of placebo followed by a single dose of open-label moxifloxacin on the tenth day.

Study Treatments

Table 1 Description of Study Treatments

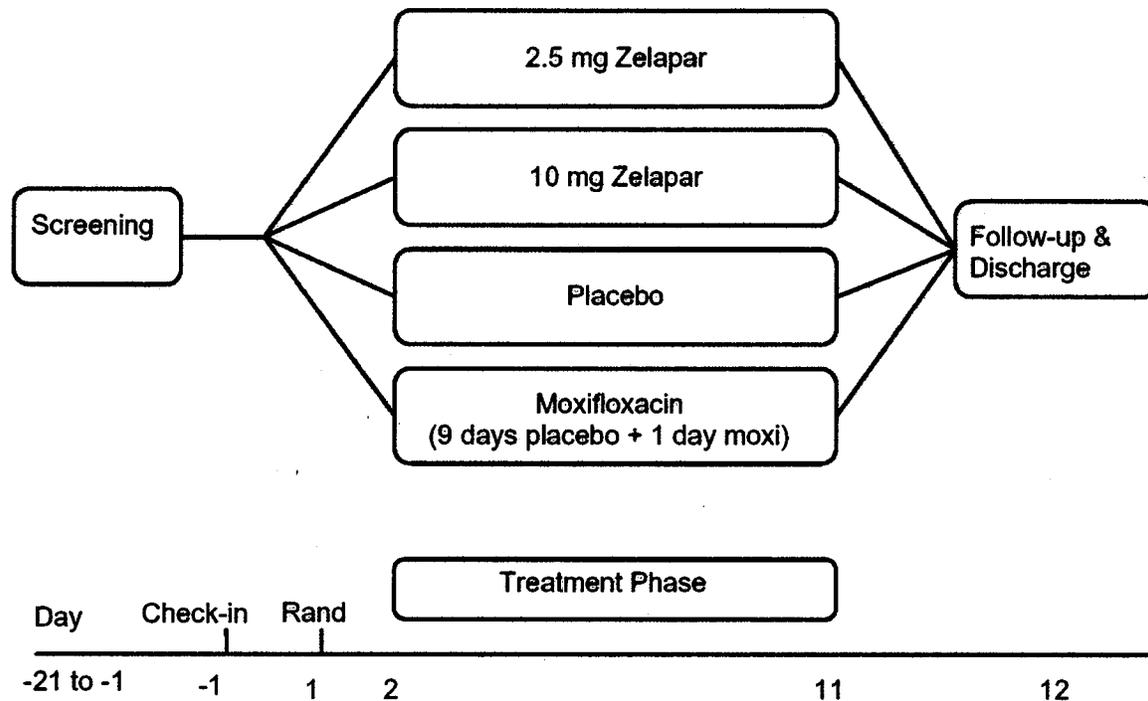
Dose Group	N Total/Male/Female	Treatment
1	40/20/20	ZELAPAR 2.5 mg Two 1.25 mg ZYDIS selegiline HCl tablets and six ZELAPAR placebo tablets QD po X 10 days
2	40/20/20	ZELAPAR 10.0 mg Eight 1.25 mg ZYDIS selegiline HCl tablets QD po X 10 days
3	40/20/20	Placebo Eight ZELAPAR placebo tablets QD po X 10 days
4	40/20/20	Moxifloxacin 400 mg Eight ZELAPAR placebo tablets QD po X 9 days One 400 mg moxifloxacin tablet po on Day 11 (10 th dosing day)

All qualified subjects checked in to the clinic on Day -1. A baseline continuous 24-hour digital ECG assessment was performed on Day 1. Study medication was administered for 10 days from Day 2 through Day 11. Subjects were released from the clinic and readmitted on Day 10. On Day 11, when selegiline was anticipated to have achieved steady state in plasma, ECG assessments were repeated and blood samples were obtained immediately before dosing and at specified time points after dosing for the determination of plasma concentrations of selegiline. Subjects were discharged from the clinic on Day 12 following completion of the 24-hour continuous ECG recording and all required study release procedures.

Routine safety assessments, including vital signs, clinical laboratory tests, safety ECGs, and review of AEs, were conducted at scheduled points throughout the study. The ECG parameters, including HR, QRS, PR, and QT, were determined from the digitally stored 12-lead continuous ECG recordings (H-12) by a central laboratory blinded to treatment and recording time. Corrected QT (QTc) was derived using two standard formulae (Bazett's and Fridericia's), and a correction factor individualized for each subject. A schematic of the overall study design is provided in Figure 1.

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Figure 1 Schematic of Study Design



Both positive and negative control groups are essential to define the ECG effects of selegiline delivered via the ZYDIS formulation in light of the large degree of spontaneous inter- and intrasubject variability in QT interval duration. Use of a placebo served as a negative control for the potential ECG effects of an active treatment. Comparison of ZELAPAR to moxifloxacin (positive control) demonstrated whether the study had the sensitivity to detect small changes in QT intervals. Moxifloxacin has been shown to increase QTc duration by 5-10 msec following oral or intravenous administration.

Restrictions

1. Subjects were to abstain from consuming alcoholic beverages for at least 48 hours prior to entering the clinic until discharge from the study.
2. Caffeine intake was restricted to no more than 3 cups of coffee, tea, or 12-ounce can of caffeine-containing soda. Subjects were not to consume any caffeine from midnight prior to initiation of the 24-hour continuous digital ECG recording until completion of the ECG assessment.
3. Subjects were to refrain from strenuous physical activities during participation in the study.

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4. Subjects were not allowed to take any medications (Rx or OTC) during the course of the study, with the exception of oral contraceptives unless approved by the investigator in consultation with the sponsor.

Subjects were required to fast for 12 hours after 7:00 pm on the evening prior to the clinical laboratory tests conducted during the screening period (Days -21 to -1) and again after 7:00 pm on the evening of Day 11. Subjects received a low fat meal on Day 11. Subjects maintained a consistent schedule of non-strenuous activity. Subjects were at rest in a supine position for 10-15 minutes around each ECG assessment time point.

Removal of Subjects from Therapy or Assessment

Subjects were advised that their participation in the study was voluntary and that they were free to leave without negative repercussions from the investigator or institution.

Subjects who discontinued were not replaced.

Treatments Administered

Study medication was administered in the morning before breakfast. With the exception of the moxifloxacin tablet administered to subjects in Group 4 on Day 11, the study medication was taken without liquid and subjects refrained from ingesting food or liquid for 5 minutes before and after taking the medication. Subjects receiving moxifloxacin were allowed a sufficient amount of water to swallow the tablet.

Blinding

This was a double-blind study with respect to ZELAPAR and placebo tablets. The ZELAPAR study medication was provided in a double-dummy manner so that all subjects in the ZELAPAR or placebo groups received eight tablets daily. Subjects in the moxifloxacin group received eight placebo tablets daily for the first 9 dosing days in a blinded manner. Open label moxifloxacin was administered as one 400 mg tablet to these subjects on the 10th treatment day (Study Day 11).

Prior and Concomitant Treatments

Subjects were instructed not to take any medications except oral contraceptives during the study unless absolutely necessary. Any prescription or OTC medications (including vitamins and herbal supplements) were considered concomitant medications and documented on the CRF. The information collected on prior and concomitant medications included indication, start and stop dates, dose, frequency, and route of administration.

Table 2 Schedule of Study Assessments and Procedures

Procedure	Screening Day -21 to -1	Day -1	Day 1	Days 2-9	Day 10	Day 11	Day 12
Informed Consent	X						
Medical history	X						
Eligibility review	X						
Physical examination	X						X
Vital signs	X	X			X	X	X
ECG-H12 (24-hour)			X			X	
Safety ECG (standard) ^a	X	X		X ^b	X		X
Clinical laboratory tests ^c	X						X
HIV, hepatitis B,C	X						
Urine alcohol & drug screen	X	X			X		
Serum pregnancy test	X	X					X
Check-in		X			X		
Overnight stay		X	X		X	X	
Randomization			X				
Administer study drug				X	X	X ^d	
Blood Samples for Plasma Concentration						X ^e	
AE assessment			X	X	X	X	X
Concomitant Medication Review		X	X	X	X	X	X
Discharge							X

^a Safety ECGs performed 2 hours after dosing on treatment days

^b Day 5 only

^c Blood and urine samples obtained after a 12-hour fast beginning at 7:00 pm the previous evening

^d Group 4 received placebo tablets on Days 2 to 10 and a single 400 mg dose of moxifloxacin on Day 11

^e Pre-dose (0), 0.25, 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose

Subjects meeting all of the following criteria were considered for admission to the study :

1. Healthy men or women of any race, at least 18 years old or of legal age of consent (whichever is greater), and less than 45 years old at the time of screening.
2. BMI score between 18.5 – 30 kg/m² (inclusive) and weight . 50 kg.
3. In good general health with no history of significant disease (as determined by the investigator in consultation with the sponsor) based on the medical history, physical examination, clinical laboratory evaluations, and 12-lead ECG.

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Key Exclusion Criteria :

Subjects meeting any of the following criteria were not included in the study :

1. Systolic blood pressure (BP) <100 or >140 mmHg, diastolic BP <60 or >95 mmHg, pulse rate <50 or >100 bpm at screening, unless a repeat test within 15 minutes later showed values within these ranges
2. History of undiagnosed chest pain or vascular malformation, including intracranial aneurysm (with the exception of minor skin vascular malformations);
3. PR interval >240 msec, QRS duration >110 msec, or QTc >450 msec, any clinically significant ECG morphological changes;
4. Use of any concomitant medications other than oral contraceptives.
6. Any disease or condition that might affect drug absorption, metabolism or excretion or compromise the cardiovascular, hematological, renal, hepatic, pulmonary, endocrine, central nervous, or gastrointestinal systems (unless deemed not clinically significant by the investigator and the sponsor);
7. History of alcoholism or drug addiction, use of any recreational drugs within 3 months prior to receiving study medication, or positive screen for substances of abuse prestudy.
8. Past or present chronic use of systemic medications, use of any drug therapy (including herbal preparations, e.g. St. John's Wort) known to induce or inhibit drug metabolism within 30 days prior to dosing; or use of any medications (prescription or over-the-counter, including antacids, multivitamins, nutritional supplements, and herbal preparations), within 14 days prior to dosing, unless approved by the sponsor.
9. History of smoking more than 10 cigarettes a day.
10. Previous receipt of an investigational drug or product or participation in a drug study within a period of 30 days prior to receiving study medication; for investigational drugs with a $t_{1/2}$ greater than 15 days, this proscription was extended to 60 days, or five-times the $t_{1/2}$, whichever was longer;

Digital 24-Hour ECG Assessment Methodology

Digital 12-lead ECG data were digitally obtained using a ~~digital~~ digital H-12 ECG continuous recorder. The ECG data were collected continuously every 10-15 seconds for all 12 leads simultaneously for a 24-hour period on Day 1 (baseline) and on Day 11, which coincided with the 10th and last dose of study medication. Each 10-15 second recording was separated by

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an interval of approximately one minute. Subjects assumed a supine or semisupine position for 10-15 minutes prior to each ECG assessment time point in order to stabilize their resting heart rate. The ECG data for each subject were recorded on a 40 MB compact flash memory card along with the subject's unique identification number and demographic information.

The analysis system generated three discrete 4-second data packets each separated by an interval of approximately 1 minute corresponding to each of the 12 daily time points specified by the protocol. The ECG assessments were performed at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18, and 23.5 hours post-dose on Day 1 and Day 11 (since no study medication was administered on Day 1, the ECG assessment points corresponded to the Day 11 post-dose time points according to the clock). Both ECG assessment days provided a total of 36 baseline (Day 1) and 36 on-treatment (Day 11) measurements per subject. If the ECG data packet recorded at a given time point was of poor quality or showed artifacts, another 4-second data packet suitable for analysis was captured as close as possible to the specified time point.

The digital ECG packets were sent to a central laboratory. _____
_____ for a treatment-blinded high-resolution measurement of the cardiac intervals and morphological assessment by a central cardiologist blinded to the study treatment. The digital ECG data were transferred into the central ECG laboratory's validated data management system, _____. Interval duration measurements were initially performed by trained analysts using a proprietary validated electronic caliper system applied on a computer screen. A cardiologist subsequently verified the interval durations and performed the morphology analysis with particular attention given to note any abnormal T-U wave complex indicative of an effect on cardiac repolarization.

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Manual on-screen measurements of the RR, PR, QRS, and QT interval durations were performed on the Lead II recordings in each data packet. QTcF and QTcB were derived as follows :

Three (3) RR mean RR Interval reported
Three (3) PR mean PR Interval reported
Three (3) QRS mean QRS Width reported
Three (3) QT mean QT Interval is reported

The following calculations were made from the interval measurements :

QTc correction by the Bazett's formula : $QTcB = QT/(RR)^{1/2}$
Mean QTcB = (QTcB1 + QTcB2 + QTcB3)/3

QTc correction using Fridericia's formula : $QTcF = QT/(RR)^{1/3}$

Three (3) Heart Rate measurements:

HR1 = 60 / RR1

HR2 = 60 / RR2

HR3 = 60 / RR3

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Mean HR $=(\text{HR1} + \text{HR2} + \text{HR3})/3$

Each fiducial point (onset of QRS, offset of T wave, etc.) was electronically marked and the original ECG waveform and such annotations were separately saved in an XML formatted file available for independent review.

Safety Assessments

Routine safety assessments, including a physical examination, measurement of vital signs, clinical laboratory tests, safety ECGs, and review of AEs and concomitant medications, were conducted at scheduled points throughout the study.

Laboratory Assessments

Clinical laboratory tests (hematology, serum chemistry, and urinalysis) were performed at screening and at the end of the study. Samples were obtained for the following standard tests after a 12-hour fast beginning at 7:00 pm the previous evening:

Hematology: hematocrit, hemoglobin, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and platelet count.

Serum Chemistry: albumin, alkaline phosphatase, BUN, creatinine, glucose, total cholesterol, triglycerides, potassium, CPK, GGT, ALT, AST, sodium, chloride, total bilirubin, total protein, uric acid, calcium, phosphorus, LDH, bicarbonate

Urinalysis: pH, specific gravity, glucose, ketones, leukocytes, occult blood, protein

Hepatitis B and C, and HIV: (performed at screening only)

Pregnancy Test: Serum β -HCG was performed on all female subjects of childbearing potential at Screening, Day -1, and Day 12 prior to discharge

Drugs of Abuse: urine alcohol and barbiturates cocaine metabolites, opiates, benzodiazepines, and cannabinoids (performed at screening and on Day -1 and Day 10 of the study)

Safety ECGs

Standard 12-lead digital ECGs were recorded at screening, Day -1, Day 5 and Day 10 about 2 hours after dosing and on Day 12. The parameters obtained from the safety ECGs, including QRS, PR, QT, and QTc were available for immediate review by the investigator for the purposes of safety assessment and determining subject eligibility for the study. The data from the safety ECGs were not included in the formal analysis of the ECGs obtained from the continuous H-12 recordings; however, the safety ECGs were also analyzed by the central laboratory.

Vital Signs

Vital signs included oral body temperature, respiration rate, sitting blood pressure (5 minutes) and pulse rate. Vital sign measurements were obtained at screening, check-in (Day -1), after dosing on Day 10 and Day 11, and at the end-of-study (Day 12).

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Adverse Events

A standard definition of an Adverse Event (AE) was used and all AEs were followed until resolution or completion of the study.

Drug Concentration Measurements

Serial blood samples were obtained for the determination of selegiline plasma concentrations at specified times over an 8-hour period commencing immediately prior to dosing on Day 11. The timing of the blood sample collection was designed to measure the peak plasma concentration profile of selegiline to determine if any effect on the ECG parameters was related to the plasma levels of selegiline. Blood samples were obtained for selegiline analysis from all subjects, including those in the open-label moxifloxacin treatment group. Blood samples were not analyzed for moxifloxacin. The time points for blood sample collection were:

Pre-dose (0), 0.25, 0.5, 1, 2, 3, 4, 6, and 8 hours post dose

Plasma concentrations of selegiline were analyzed at _____
_____ using validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay method _____. Samples from all subjects, including those in the placebo group and the open-label moxifloxacin treatment were analyzed. The method was validated for selegiline over the range _____, pg/mL ($r = 0.9978$), with a LOQ of 50.00 pg/mL. All results were reported as free base (pg/mL). Copies of the method validation report and the bioanalytical report are provided in Appendix 16.1.10.

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Statistical Methods Planned and Determination of Sample Size

Statistical and Analytical Plans

A Statistical Analysis Plan (SAP) was developed by the CRO in collaboration with the sponsor for the analysis of subject demographics, ECG assessments, safety evaluations, and selegiline plasma concentrations.

The SAS® statistical software package, Version 8.2, was used to provide all statistical analyses. Continuous variables were summarized by treatment using the following descriptive statistics: N, mean, standard deviation, median, minimum, and maximum. Categorical variables were tabulated by treatment using the number and percentage of subjects by category.

Subject Data Sets to be Analyzed

Intent-to Treat

The Intent-to-Treat (ITT) population included all subjects who received at least one dose of study drug and had at least one post-dosing evaluation. The ECG analyses were performed on the ITT population.

Safety

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The safety population included all subjects with available data who had at least one dose of study medication.

ECG Analyses

The ECG intervals were analyzed to describe central tendency and outlier effects for heart rate and PR, QRS, QT, and QTc (QTc-I, QTc-F, QTc-B) intervals. Any new ECG morphological changes were identified. "New" ECG changes were defined as those "not present on any baseline ECG but present on any on treatment ECG." Baseline was defined as the mean of all of the values of ECG measurements taken on Day 1.

The primary QT to QTcI correction formula was derived for each subject using the 36 baseline ECGs (3 ECGs at each of 12 time points) taken on Day 1. The QT-RR relationship was iterated to determine an individual correction exponent for each individual. The resulting exponent provided for a formula to fit a correlation line for all RR and QT points approximating a zero slope. This is considered the most accurate method for the correction of QT to QTc and was the primary endpoint of the trial.

The QTcI was calculated by selecting the exponent of the standard QTc formula (i.e., $QTcI = QT / (RR)^{\text{exponent}}$) which, when plotting RR against QTcI gave the slope closest to zero. Only baseline ECGs were used in the calculation of the exponent. An examination of the slopes was performed for subjects with an exponent value of less than 0.15. If the value of the slope at 0.20 in these subjects was not significantly different than zero, 0.20 was assigned to these subjects. For all subjects with exponents > 0.15 , the actual calculated exponent was used. This subject-specific exponent was then used for the calculation of all QTcI.

QT intervals were also corrected using standard formulae:

Bazett's formula: $QTcB = QT / (RR)^{1/2}$

Fridericia's formula: $QTcF = QT / (RR)^{1/3}$

QT intervals corrected using Bazett's or Fridericia's formulae were considered secondary endpoints.

Central tendency and outlier analyses were performed for each ECG interval.

Central Tendency Analysis

Descriptive statistics (e.g., frequency, percent, mean, standard deviation (SD), coefficient of variation [CV%], median, maximum, and minimum) and confidence intervals were used to summarize the ECG variables and the corresponding changes from baseline to Day 11 (multiple dose steady-state day) for each treatment group. Ninety-five percent confidence intervals for differences between the treatment and placebo groups were presented.

Change from mean of all baseline ECGs to the mean of all on-treatment ECG values for a

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given subject was presented for each of the following ECG intervals :
HR, PR, QRS, QT, QTc (I, F, B)

The mean time-averaged change from baseline was determined for all ECGs taken at steady-state.

In addition, a secondary time-matched analysis for central tendency only for QTc I, F and B was done. This analysis compared each Day 1 time point (e.g. 8 am) with each corresponding time point (eg, 8 am) at steady state on Day 1. Mean change from baseline with its 95% confidence intervals was computed for each time point.

For all analyses, the QTc value at each time point was determined by taking the mean of the triplicate QTc measurements sampled at each time point.

Change from baseline at each time point was first calculated for each subject by taking the QTc value at each post-dose time point on Day 11 and subtracting the QTc value at each corresponding baseline time point (time-matched change). In this way, each subject had 12 change from baseline QTc results on Day 11 (one at each time point) and the results at each time point were then summarized for all subjects within a treatment group to derive the descriptive statistics.

Descriptive statistics were also produced for the time-averaged change from baseline QTc to the on-treatment value on Day 11. These data were calculated for each subject by taking the mean of all twelve values of Day 11 QTc and subtracting the mean of all twelve values of baseline QTc. In this way, each subject had one change from baseline QTc to the mean on treatment value on Day 11. .

The change from mean baseline QTc to the maximum on-treatment observation was determined for each subject by taking the single maximum QTc value on Day 11 (the average of the 3 ECGs taken at a given time point was used as that time point's single best point estimate of the ECG interval value) and subtracting the time-averaged baseline value for that subject. In this way, each subject had one change from mean baseline QTc to the maximum on-treatment observation. This result was then used to summarize the results and produce descriptive statistics for each treatment group.

Pair-wise between-treatment comparisons of the change from baseline in QTc were performed using an analysis of covariance (ANCOVA) that incorporated treatment, gender, and time into the model. All twelve values of baseline QTc and all twelve values of Day 11 QTc for each subject were included in this analysis. Treatment-by-gender interaction was dropped from the model since it was not significant at the $p \leq 0.1$ level.

Outlier Analyses

All outliers were summarized for each treatment group on the basis of incidence rates. The

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outlier summary tables include counts of subjects. Therefore, if a subject experienced more than one episode of a particular outlier event, the subject was counted only once for that event.

Outlier analyses were performed using the following categorical classifications :

- For QT parameters: from mean baseline to the determination of those subjects who attained QT values > 500 msec when not present at baseline (new onset).
- For QTc: from mean baseline to the determination of those subjects who attained QTc values > 500 msec when not present at baseline (new onset)
- For QTc: from mean baseline to the determination of those subjects who attained QTc values > 480 msec when not present at baseline (new onset)
- QTc increase from baseline of <30 msec, .30 to .60 msec and >60 msec.
- The percentage of subjects in each treatment group that had a new abnormal U wave.
- PR change from baseline: 25% increase when PR > 200 msec
- QRS change from baseline: 25% increase when QRS > 100 msec
- HR changes reflecting a 25% decrease from baseline to a HR < 50 bpm or a 25% increase from baseline reflecting a HR > 100 bpm

Morphological Analyses

New onset (presented as percentage of subjects meeting the new criteria) :

Second degree heart block, third degree heart block, complete right bundle branch block, complete left bundle branch block, ST segment change (elevation and depression separately), T wave abnormalities (negative T waves only), and myocardial infarction pattern.

Subgroup Analyses

The ECG data analyses were performed for all subjects and then separately for males and females.

Secondary Statistical ECG Analyses

Least Square Means (LS Means) for each ECG parameter were calculated based on an ANCOVA model – change from baseline (mean of all triple ECG means on Day 1) including treatment, gender, treatment-by-gender interaction, and baseline value in the model. If a

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statistically significant treatment-by-gender interaction was detected, results would be presented by gender, and the magnitude, direction and potential sources of the interaction would be explored. An adjustment was done based on all pairwise comparisons using the Tukey-Kramer Adjustment for Multiple Comparisons.

All data collected were presented in data listings. Unused data or extra measurements (such as unscheduled or repeat assessments), were not included in the formal ECG analysis tables, but were included in subject listings. Data from subjects excluded from an analysis population were included in the data listings, but not in the summaries. Demographic characteristics (gender, race, age, BMI, height, and weight) were summarized by treatment.

Demographic and Baseline Characteristics

Demographic and safety summary statistics were generated for all subjects in the Safety Population. Individual subject demographics and baseline characteristics (medical history, vital signs, standard 12-lead ECG at screening, serum pregnancy test, tests for hepatitis B surface antigen, hepatitis C antibody, or HIV antibody, urine drug screen and ethanol test) were presented in subject listings. Demographic characteristics (gender, race, age, height, and weight) were summarized by treatment.

Summary of Safety Data

All subjects who received at least one dose of study medication were included in the evaluation of safety.

Vital signs and clinical laboratory test results were summarized by treatment using descriptive statistics and changes from baseline values.

The frequency of AEs, SAEs, treatment-emergent, and treatment-related AEs, as well as AEs by maximum severity, were summarized using MedDRA® 6.0 by system organ class, preferred term, and treatment. The number and percent of subjects who experienced at least one adverse event were also summarized.

Selegiline Plasma Concentration Analyses

For plasma concentrations of selegiline, individual subject concentrations as a function of time were presented in data listings. Below quantitation limit (BQL) concentrations were treated as zero for descriptive statistics. Mean concentrations that were BQL were presented as BQL, and the SD and CV% were reported as not applicable (NA).

Graphical presentations of the relationships between each of the QTc parameters (i.e., QTcI, QTcF, and QTcB) versus plasma concentrations were presented using both the actual QTc parameter and a change from baseline. Overall subject plots were presented using the maximum change in the QTc parameter versus the maximum plasma concentrations (i.e. C_{max}) for Day 11 and the maximum change in the QTc parameter versus the plasma concentration at that time. Individual subject graphical presentations (i.e., maximum QTc change from baseline and maximum QTc value versus the plasma concentration) were also

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presented.

Regression analysis plots were generated for both ZELAPAR dose groups, using individual subject data for plasma concentrations of selegiline and QTc (I, B, F) interval duration and change from baseline.

Determination of Sample Size

The sample size chosen for this study was based on precedents set by similar ECG safety studies and was also based on formal power calculations as defined in the protocol. The null hypothesis assumed that there is no relationship in the QTc change from baseline vs. plasma levels of selegiline. Moxifloxacin was used as a positive control to determine “assay sensitivity” in that the study could detect a small positive change (5-10 msec) in QTc duration from baseline. Changes on treatments (ZELAPAR and moxifloxacin) were all placebo corrected using the concomitant placebo group mean change from baseline. The sample size of 40 per group for the 4 treatment groups or a total of 160 subjects was planned.

The sample size was calculated using the following assumptions:

- The average QTcF change from baseline is estimated as -1.00 msec for placebo and 5 msec for ZELAPAR; SD = 7.9.
- The Type I error rate α of 5%.
- The Type II error rate β of 20% (80% power).
- A two-sided test of H_0 : no treatment difference.
- A 1:1 randomization of each ZELAPAR dose to placebo.

Result: a sample size of about 40 subjects per treatment group would be required.

Changes in the Conduct of the Study or Planned Analyses

The original protocol (14 May, 2004) was amended on 3 June and on 29 June 2004.

Amendment No.1 (3 June 2004) provided for increasing the number of subjects in each dose group from 20 to 40, for a total planned enrollment of 160 subjects. Two additional blood samples were added at 0.5 and 4 hours after dosing on Day 11 to allow for more definitive characterization of plasma concentrations of selegiline over time. These changes were made as a result of discussions between the sponsor and the Agency. A total of 36 subjects completed the study prior to implementation of the additional sampling time points, corresponding to 10 (of a total 44) in the 2.5 mg ZELAPAR group and 9 (of a total 45) in the 10 mg ZELAPAR group.

Amendment No.2 (29 June 2004) corrected a number of administrative and typographical errors in the original protocol. The amendment clarified that recording of adverse events and review of concomitant medications was to be performed on all study days.

Sponsor's Description of Study Results

STUDY SUBJECTS

Disposition of Subjects

A total of 177 subjects were enrolled, with 44, 45, 44, and 44 subjects randomized to the 2.5 mg ZELAPAR, 10 mg ZELAPAR, placebo and moxifloxacin groups, respectively. All of the 177 randomized subjects received at least one dose of study medication. Of these, 165 completed the study. Subject disposition is summarized in Table 3.

Table 3 Disposition of Subjects

Subject Disposition	Zelapar 2.5 mg N (%)	Zelapar 10 mg N (%)	Placebo N (%)	Moxifloxacin N (%)	Overall N (%)
No. Enrolled	44	45	44	44	177
No. Randomized	44 (100%)	45 (100%)	44 (100%)	44 (100%)	177 (100%)
No. Treated	44 (100%)	45 (100%)	44 (100%)	44 (100%)	177 (100%)
No. Completed	40 (90.9%)	44 (97.8%)	41 (93.2%)	40 (90.9%)	165 (93.2%)
No. Discontinued	4 (9.1%)	1 (2.2%)	3 (6.8%)	4 (9.1%)	12 (6.8%)
adverse events	1 (2.3%)	0	0	1 (2.3%)	2 (1.1%)
withdrew consent	0	1 (2.2%)	1 (2.3%)	2 (4.5%)	4 (2.3%)
lost to follow-up	3 (6.8%)	0	1 (2.3%)	1 (2.3%)	5 (2.8%)
non-compliance	0	0	1 (2.3%)	0	1 (0.6%)

Data Source: Table 15.2: Appendix 16.2, Listing 1

Two subjects discontinued the study as a result of AEs. Subject No. 013 (2.5 mg ZELAPAR) discontinued on Day 5 after experiencing an abnormal ECG, chest discomfort, and hypertension, which resulted in hospitalization and was deemed serious. Subject No. 031 (moxifloxacin) discontinued on Day 9 as a result of a rash after having received 8 daily doses of study medication (placebo).

Protocol Deviations

A total of 28 subjects had at least one protocol violation; of these, 9 were in the 2.5 mg Zelapar group, 7 in the 10 mg Zelapar group, 6 in the placebo group, and 6 were in the moxifloxacin group. The following types of protocol deviations were noted and are presented by treatment group in Table 4 :

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Table 4 Protocol Deviations by Treatment Group

Deviation	ZELAPAR 2.5 mg N (%)	ZELAPAR 10 mg N (%)	Placebo N (%)	Moxifloxacin N (%)	Overall N (%)
No. Enrolled	44	45	44	44	177
Total Deviations ^a	9 (20%)	7 (16%)	6 (14%)	6 (14%)	28 (16%)
Inc/Exc ^b	4 (9%)	3 (7%)	1 (2%)	3 (7%)	11 (6%)
PK sampling time	1 (2%)	2 (4%)	0	0	3 (2%)
Missed dose	0	2 (4%)	4 (9%)	1 (2%)	7 (4%)
Dose outside 4h window	3 (7%)	0	1 (2%)	3 (7%)	7 (4%)
Prohibited medication	1 (2%)	0	0	0	1 (0.6%)

^a The sum of specific deviations may not equal the total since a subject may have had more than one protocol deviation

^b All eligibility deviations were limited to BMI ≥ 30 kg/m²

A total of 11 subjects exceeded the maximum limit for BMI (30.0 kg/mm²). None of these subjects had a BMI > 31.0 kg/mm² and they met all the other eligibility criteria for the study. The deviations from scheduled blood sampling time points were not considered to significantly affect the analysis of selegiline plasma levels at steady-state, nor were the deviations from the dosing regimen specified in the protocol expected to confound the interpretation of ECG and safety results or the relationship of any ECG effects to plasma levels of selegiline. One subject used an implanted subdermal hormonal contraceptive which was not allowed under the protocol. No remarkable differences were noted among the treatment groups with regard to the number or nature of protocol deviations.

SPONSOR'S DESCRIPTION OF RESULTS : EVALUATION OF ECG PARAMETERS

Data Sets Analyzed

The ECG analyses were performed on the intent-to-treat population, which comprised all subjects who received at least one dose of study drug and had at least one post-dose ECG evaluation on Day 11. A total of 165 subjects were included in the ITT analysis population; 40, 44, 41, and 40 subjects in the 2.5 mg ZELAPAR, 10.0 mg ZELAPAR, placebo, and moxifloxacin treatment groups, respectively.

Demographic and Other Baseline Characteristics

Demographic and baseline characteristics are summarized in Table 5.

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Table 5 Summary of Demographic and Baseline Characteristics

Demographic Characteristic	Zelapar 2.5 mg (N = 44)	Zelapar 10 mg (N = 45)	Placebo (N = 44)	Moxifloxacin (N = 44)
Age (years)				
Mean [SD]	32.6 [7.64]	31.9 [7.48]	29.1 [7.00]	30.3 [7.84]
Median	34.0	31.0	29.0	29.5
(Min - Max)	(18 - 44)	(19 - 45)	(18 - 44)	(18 - 45)
Gender				
Female (%)	22 (50.0%)	23 (51.1%)	22 (50.0%)	22 (50.0%)
Male (%)	22 (50.0%)	22 (48.9%)	22 (50.0%)	22 (50.0%)
Race				
Hispanic (%)	27 (61.4%)	28 (62.2%)	31 (70.5%)	25 (56.8%)
Black (%)	11 (25.0%)	11 (24.4%)	10 (22.7%)	10 (22.7%)
Caucasian (%)	6 (13.6%)	6 (13.3%)	3 (6.8%)	9 (20.5%)
BMI (Kg/m²)				
Mean [SD]	25.3 [2.92]	25.3 [2.84]	24.1 [2.78]	25.6 [3.05]
Median	25.3	24.4	24.0	25.8
(Min - Max)	(20 - 31)	(21 - 31)	(20 - 31)	(20 - 31)
SD = Standard Deviation				
BMI = Body mass index				
Data Source: Table 15.1				

The distribution of subjects among the treatment groups was relatively similar for mean age, BMI, weight and height, and race.

Medical history abnormalities and physical examination observations obtained at screening (Visit 1). No clinically important abnormalities were noted at the baseline examinations and none of the observations represented a violation of study eligibility criteria.

Measurements of Treatment Compliance

No formal analysis of treatment compliance was conducted.

Plasma Concentration Results

Blood samples were obtained from all subjects over an 8-hour period on the tenth dosing day (Day 11) for the determination of plasma selegiline levels. Plasma levels of moxifloxacin were not analyzed. The following sampling time points were used to provide a plasma concentration-time profile adequate to identify the peak concentration of selegiline. 0 (pre-dose), and at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 hours

While samples were obtained and analyzed in a blinded manner for all subjects, results were summarized only for subjects who received ZELAPAR. Mean plasma concentrations of selegiline at steady-state on Day 11 are summarized by treatment and time in Table 6 and illustrated in Figure 2.

Table 6 Summary of Mean (SD) Plasma Concentration of Selegiline by treatment and Time at Steady-State on Study Day 11

Time (hours) ^a	2.5 mg ZELAPAR N completed = 40			10 mg ZELAPAR N completed = 44		
	n	Mean pg/mL	(SD)	n	Mean pg/mL	(SD)
0 (pre-dose)	40	6.79	(21.143)	43	185.29	(125.724)
0.25	40	984.44	(523.523)	44	3768.1	(2128.72)
0.5	30	1096.8	(542.309)	35	5440.2	(2671.13)
1	40	899.35	(589.102)	44	5289.3	(2361.07)
2	40	456.20	(350.143)	44	3161.2	(1503.89)
3	40	264.06	(211.444)	44	1880.9	(927.959)
4	30	175.28	(146.511)	34	1272.6	(626.925)
6	40	84.96	(81.145)	44	668.52	(308.887)
8	40	57.35	(63.282)	44	494.70	(239.063)

^a The 0.5 and 4 hour sampling timepoints were added under Protocol Amendment No.1 after 2 cohorts (32 subjects) had completed the Day 11 procedures.

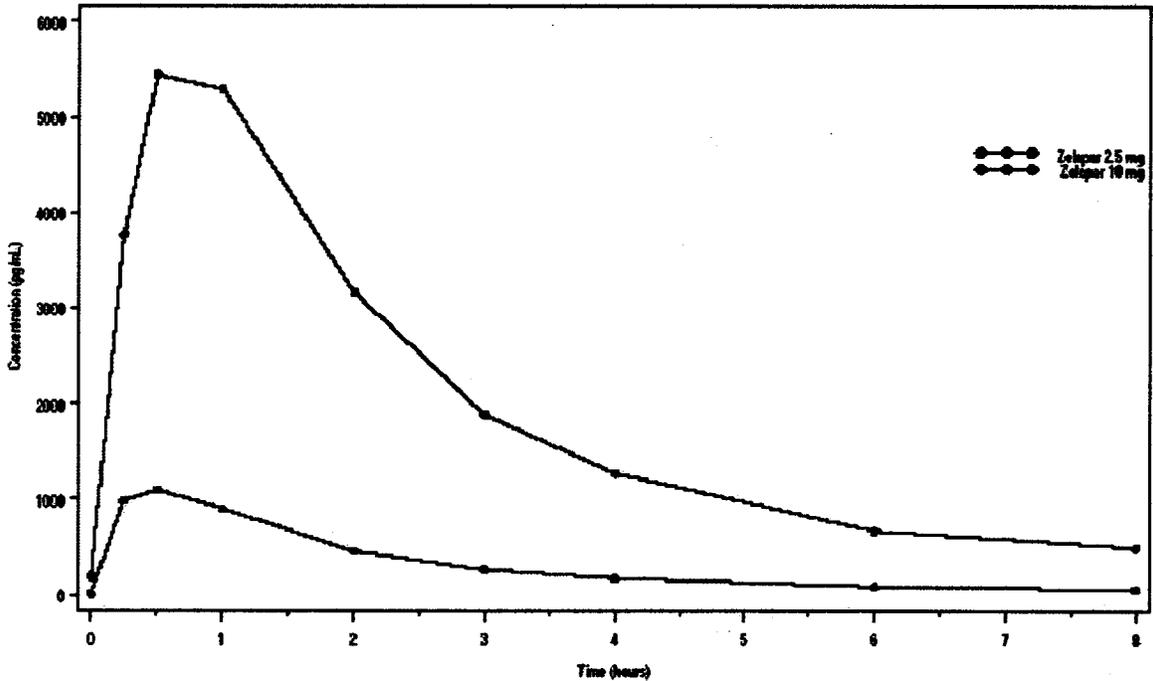
SD = Standard Deviation

Data Source: Table 15.3

Over the 8-hour collection period, mean plasma levels of selegiline ranged from 6.8 to 1097 pg/mL in the 2.5 mg ZELAPAR group and from 185.3 to 5440 pg/mL in the 10 mg ZELAPAR group. Peak mean plasma concentrations of selegiline were attained at 30 minutes after dosing in both ZELAPAR treatment groups. These results are consistent with the plasma levels attained in previous studies with the 2.5 mg and 10 mg doses of ZELAPAR.

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Figure 2 Mean plasma Concentration of Selegiline at Steady-State on Study Day 11 by Treatment



Data Source: Appendix 16.2, Figure 2

Electrocardiographic Interval Results

The analysis and interpretation of the ECG interval results were performed by _____

_____ The following presentation and summary of the ECG results are derived from _____ report.

Baseline ECG

The four treatment groups were well matched with regard to mean baseline ECG interval assessments (Table 7).

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Table 7 Mean Baseline ECG Parameters by Treatment

Parameter (SD)	2.5 mg Zelapar N=44	10 mg Zelapar N=45	Placebo N=44	Moxifloxacin N=44
Heart Rate (bpm)	68.03 (9.449)	67.31 (7.472)	65.97 (6.521)	66.52 (7.150)
RR (msec)	916.51 (118.545)	922.56 (107.253)	942.61 (98.570)	934.77 (102.604)
PR (msec)	154.08 (17.574)	152.23 (17.383)	150.29 (14.877)	148.79 (17.173)
QRS (msec)	86.12 (6.067)	88.20 (5.738)	86.92 (6.214)	86.44 (4.911)
QT (msec)	387.66 (26.579)	382.05 (24.926)	387.44 (19.334)	390.15 (20.430)
QTcI (msec)	402.23 (21.934)	394.28 (21.397)	397.24 (16.936)	401.20 (16.206)
QTcB (msec)	407.86 (18.572)	400.56 (20.125)	402.09 (17.593)	406.57 (16.814)
QTcF (msec)	400.58 (17.560)	393.93 (19.231)	396.75 (15.692)	400.62 (15.007)

SD = Standard Deviation

Data Source: Table 15.5; Appendix 16.2, Listing 25

Central Tendency

Descriptive statistics for the mean QTc values (QTcB, QTcF, and QTcI) at baseline and Day 11, as well as changes from baseline are summarized by treatment for each time point in Table 15.4.2 (not presented). The mean (SD) change from baseline QTcI is presented in Table 8 and depicted graphically by treatment in Figure 3.

Table 8 Mean (SD) QTcI Change from Baseline at Each Time Point on Day 11

Time Point (h)	2.5 mg Zelapar	10 mg Zelapar	Placebo	Moxifloxacin
Mean QTcI (SD) msec				
0.25	-3.68 (12.738)	-0.86 (13.417)	-1.36 (13.641)	-6.67 (13.847)
0.5	-9.05 (15.888)	-3.95 (16.472)	-4.68 (15.730)	-1.32 (15.509)
1	-11.45 (12.798)	-7.09 (13.743)	-4.20 (16.689)	2.19 (14.754)
2	-5.15 (15.994)	-4.65 (13.355)	-1.71 (12.966)	5.79 (16.114)
3	-3.28 (16.752)	-1.42 (15.684)	-4.63 (15.022)	7.85 (16.103)
4	2.34 (17.339)	-1.35 (17.246)	-0.61 (17.221)	4.85 (16.107)
5	0.64 (12.824)	2.78 (11.042)	1.56 (14.219)	6.41 (10.931)
6	-6.05 (12.674)	-2.72 (12.969)	-0.59 (17.320)	0.39 (20.516)
8	-2.87 (14.343)	-3.67 (12.964)	-1.15 (13.941)	2.61 (14.963)
12	0.18 (14.616)	1.73 (16.785)	-3.13 (10.020)	4.59 (15.209)
18	5.93 (10.751)	3.04 (15.066)	2.83 (12.706)	7.24 (18.185)
23.5	-1.95 (15.070)	-4.38 (12.907)	-4.56 (15.615)	0.01 (17.687)

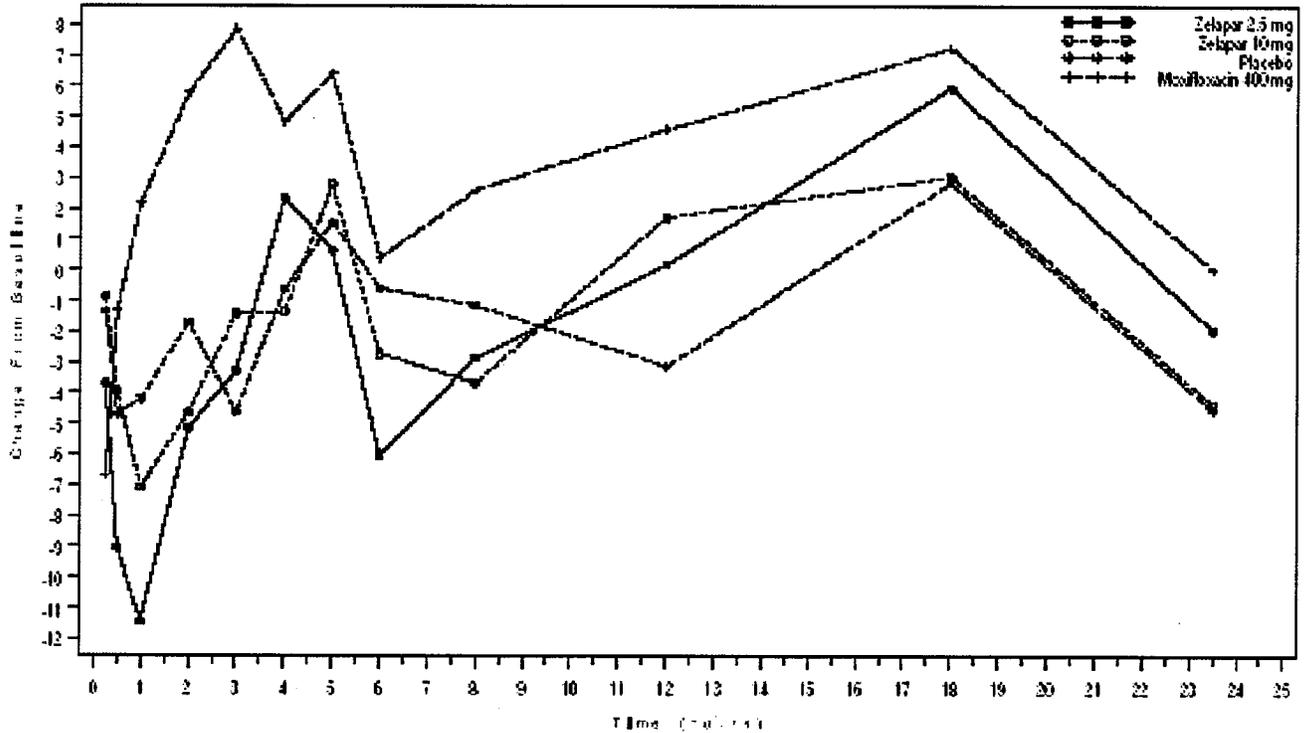
SD = Standard Deviation

Data Source: Table 15.4.2; Appendix 16.2, Listing 25

The overall profile of the mean change from baseline QTcI over time in the ZELAPAR treatment appeared similar to that observed in the placebo group. As expected, the moxifloxacin treatment group demonstrated an approximately 8 msec increase in the length of the QTcI interval over baseline at 3 hours after dosing. The similarity of the QTcI profile between the ZELAPAR and placebo groups is very evident from the plot of the mean change from baseline at each time point (Figure 3). All four treatment groups showed an increase in the mean QTcI interval length at 18 hours post-dosing of approximately the same magnitude. This observation reflects the well documented circadian variation in QT that is manifested by an increase in QT during sleep in the early hours of the morning.

The between treatment comparison of the mean change from baseline for QTcF and QTcB over time (data not presented here) was generally similar to that observed for QTcI.

Figure 3 Mean Change from Baseline QTcI by Time and Treatment



Data Source: Appendix 16.2, Figure 7

A summary of the change from mean baseline ECG parameters (HR, RR, PR, QRS, QT,

QTcB, QTcF, and QTcI) to the mean maximum on-treatment observations was calculated and included in the submission. A partial presentation of these results is reproduced here in .

Table 9 Summary of ECG Parameters – Mean Change from Baseline to Mean Maximum On-Treatment Value on Day 11 by Treatment

Parameter (SD)	2.5 mg Zelapar N=40	10 mg Zelapar N=44	Placebo N=41	Moxifloxacin N=40
Heart Rate (bpm)				
Max on-treatment	86.79 (12.959)	89.64 (11.824)	85.19 (10.861)	88.76 (11.849)
Change	18.93 (8.686)	22.28 (9.046)	18.99 (11.577)	21.72 (10.215)
RR (msec)				
Max on-treatment	1043.77 (136.512)	1051.30 (131.182)	1046.22 (116.456)	1021.37 (123.301)
Change	125.15 (82.346)	129.06 (72.591)	106.94 (123.110)	93.91 (75.540)
PR (msec)				
Max on-treatment	163.60 (17.893)	162.47 (20.434)	159.47 (16.863)	157.19 (17.294)
Change	9.17 (8.019)	9.90 (8.309)	8.94 (7.681)	8.92 (7.058)
QRS (msec)				
Max on-treatment	92.53 (5.826)	93.23 (6.450)	93.54 (6.124)	91.34 (5.087)
Change	6.37 (3.799)	5.10 (4.041)	6.05 (4.014)	5.23 (4.386)
QT (msec)				
Max on-treatment	415.36 (27.325)	408.05 (27.113)	411.40 (23.135)	419.78 (20.483)
Change	27.79 (20.338)	27.19 (16.942)	24.55 (20.075)	29.79 (16.701)
QTcI (msec)				
Max on-treatment	419.93 (24.063)	410.43 (21.441)	414.35 (19.160)	425.19 (16.574)
Change	17.77 (11.491)	17.35 (9.141)	17.19 (10.389)	23.01 (10.654)
QTcB (msec)				
Max on-treatment	428.58 (21.933)	422.11 (19.694)	423.46 (19.192)	436.07 (16.103)
Change	21.20 (10.219)	22.68 (10.500)	21.30 (13.827)	28.11 (10.003)
QTcF (msec)				
Max on-treatment	417.47 (20.128)	409.95 (19.441)	413.41 (19.052)	424.58 (15.910)
Change	17.24 (11.760)	17.18 (9.073)	16.81 (11.361)	23.11 (11.117)

Data Source: Table 15.5; Appendix 16.2, Listing 25

The mean maximum on-treatment values for all ECG parameters were within the normal range for all treatment groups. No apparent differences between treatment groups were evident for HR, RR, PR, or QRS. The mean maximum changes from baseline achieved in the ZELAPAR treatment groups for QT parameters was consistent with those observed for placebo, and less than the mean maximum changes from baseline QT and QTc demonstrated in the moxifloxacin group. The maximum mean change from baseline for QTcI was an increase of approximately 18 msec and 17 msec in the 2.5 mg ZELAPAR and 10 mg ZELAPAR groups, respectively, compared to 17 msec in the placebo group and 23 msec in the moxifloxacin group.

Analysis of QTc Effect Between-Treatments

Pair-wise between-treatment comparisons of the change from baseline in QTc interval length

were performed using an analysis of covariance (ANCOVA) that incorporated treatment, gender, and time into the model. Treatment-by-gender interaction was dropped from the model since it was not significant at the p.0.1 level. The results of the between-treatment analyses are summarized for QTcI, QTcF, and QTcB were calculated and provided and results for QTcI are shown in Table 10.

Table 10 Summary of Analysis (ANCOVA) of the Between-Treatment Comparisons of Change from Baseline QTcI at Day 11

Treatment Comparison		Change from Baseline QTcI (msec)		Difference (95% CI)	p-value ^a
		LS Mean (SE)			
Treatment 1	Treatment 2	Treatment 1	Treatment 2		
Zelapar 2.5 mg	Zelapar 10 mg	-2.54 (1.32)	-1.93 (1.26)	-0.61 (-4.22, 2.99)	0.7385
Zelapar 2.5 mg	Moxifloxacin	-2.54 (1.32)	2.85 (1.32)	-5.39 (-9.03, -1.75)	0.0037 ^b
Zelapar 2.5 mg	Placebo	-2.54 (1.32)	-1.89 (1.29)	-0.66 (-4.29, 2.97)	0.7218
Zelapar 10 mg	Moxifloxacin	-1.93 (1.26)	2.85 (1.32)	-4.78 (-8.38, -1.17)	0.0095 ^b
Zelapar 10 mg	Placebo	-1.93 (1.26)	-1.89 (1.29)	-0.04 (-3.58, 3.49)	0.9802
Moxifloxacin	Placebo	2.85 (1.32)	-1.89 (1.29)	4.73 (1.10, 8.36)	0.0106 ^b

^a The p-value was calculated using an analysis of covariance (ANCOVA) model with treatment as the main effect and baseline QTc, time and gender as the covariates. Treatment by gender interaction was not significant at the <0.10 level and was consequently dropped from the model

^b statistically significant at p < 0.05

LS = least squares

SE = standard error

Data Source: Table 15.16

The increase in QTcI from baseline elicited by administration of moxifloxacin was significantly different from the change from baseline QTcI in the ZELAPAR treatment groups or placebo. These results validated the sensitivity of this study to detect small changes in QTc intervals. Neither the 2.5 mg ZELAPAR group nor the 10 mg ZELAPAR group were significantly different from placebo with respect to on-treatment changes in QTcI, nor was any significant difference detected between the two ZELAPAR treatment groups. The between-treatment analyses of the change in QTcB and QTcF from baseline yielded the same results as the between-treatment analysis of change in QTcI. For both QT correction methods, the moxifloxacin treatment group demonstrated a significant difference in the change from baseline as compared to either of the ZELAPAR doses or placebo, and no significant differences were detected between ZELAPAR and placebo for either dose, nor were any differences seen between the two ZELAPAR doses.

Outlier Analysis

Table 11 summarizes the number and percentage of subjects meeting or exceeding the categorical criteria for new-onset (not present at baseline) ECG outliers as set forth in the FDA/HPB guidance for the clinical evaluation of QTc prolongation and proarrhythmic potential.

Table 11 Summary of New-Onset ECG Interval Categorical Outliers on Day 11 by Treatment

Parameter	2.5 mg Zelapar N=40 (%)	10 mg Zelapar N=44 (%)	Placebo N=41 (%)	Moxifloxacin N=40 (%)
Heart Rate				
Bradycardia <i>a</i>	0	0	1 (2.4%)	1 (2.5%)
Tachycardia <i>b</i>	3 (7.5%)	9 (20.5%)	2 (4.9%)	7 (17.5%)
PR <i>c</i>	0	0	0	0
QRS <i>d</i>	0	0	0	0
QTcX >500 msec <i>e</i>				
QT	0	0	0	0
QTcl	0	0	0	0
QTcF	0	0	0	0
QTcB	0	0	0	0
QTcX >480 msec <i>f</i>				
QT	0	0	0	0
QTcl	1 (2.5%)	0	0	0
QTcF	0	0	0	0
QTcB	0	0	0	0
QT change from baseline (msec)				
<30	25 (62.5%)	25 (56.8%)	23 (56.1%)	20 (50.0%)
≥30 to ≤60	12 (30.0%)	18 (40.9%)	17 (41.5%)	18 (45.0%)
>60	3 (7.5%)	1 (2.3%)	1 (2.4%)	2 (5.0%)
QTcl change from baseline(msec)				
<30	36 (90.0%)	40 (90.9%)	36 (87.8%)	30 (75.0%)
≥30 to ≤60	4 (10.0%)	4 (9.1%)	5 (12.2%)	10 (25.0%)
>60	0	0	0	0
QTcF change from baseline(msec)				
<30	35 (87.5%)	40 (90.9%)	35 (85.4%)	29 (72.5%)
≥30 to ≤60	5 (12.5%)	4 (9.1%)	6 (14.6%)	11 (27.5%)
>60	0	0	0	0
QTcB change from baseline(msec)				
<30	34 (85.0%)	32 (72.7%)	31 (75.6%)	24 (60.0%)
≥30 to ≤60	6 (15.0%)	12 (27.3%)	10 (24.4%)	16 (40.0%)
>60	0	0	0	0

a on-treatment value <50 bpm and representing a 25% decrease from baseline
b on-treatment value >100 bpm and representing a 25% increase from baseline
c on-treatment value >200 msec and representing a 25% increase from baseline
d on-treatment value >100 msec and representing a 25% increase from baseline
e baseline ≤ 500 msec and on-treatment >500 msec
f baseline ≤ 480 msec and on-treatment >480 msec

Data Source: Table 15.4.1; Appendix 16.2, Listing 25

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No subjects who received ZELAPAR were identified as bradycardic outliers, but one subject in each of the placebo and moxifloxacin groups experienced a new onset HR of < 50 bpm that represented a decrease of 25% or more from baseline. More tachycardic outliers were identified in the ZELAPAR and moxifloxacin groups than in the placebo group; 3 subjects (7.5%) in the 2.5 mg ZELAPAR group, 9 subjects (20.5%) in the 10 mg ZELAPAR group, 2 subjects (4.9%) in the placebo group, and 7 subjects (17.5%) in the moxifloxacin group demonstrated new-onset HR >100 bpm on Day 11 that represented a 25% or greater increase over baseline values. The central tendency analysis of heart rate (HR) did not show any treatment-related differences in mean heart rate, and considerable inter- and intrasubject variability in heart rate existed in this study; therefore, no clear signal of any effect of ZELAPAR on HR was apparent.

No subjects met the criteria for PR or QRS outliers.

No subjects exhibited a new-onset absolute QT or QTc value > 500 msec. Only one subject in the 2.5 mg ZELAPAR group was identified as having a new-onset QT or QTc value > 480 msec. Subject No.069 had a maximum QTcI interval measurement of 494 msec 3 hours after dosing on Day 11. She had one baseline QTcI measurement > 480 msec (482 msec at 5 hours); however, the Day 11 observation is considered an outlier since the mean for all 12 baseline QTcI measurements was < 480 msec.

The number of subjects in either ZELAPAR dose group that showed changes from baseline QTc of 30 to 60 msec or >60 msec was similar to that seen in the placebo group. The number of subjects that exhibited a 30-60 msec change from baseline QTc was higher in the moxifloxacin treatment group compared to the ZELAPAR or placebo groups, consistent with the recognized ability of moxifloxacin to prolong QTc and accounting for intersubject variability in sensitivity to its effects. No subjects in any treatment group exhibited an increase in QTc that was >60 msec relative to baseline.

Conduction Abnormalities and Waveform Morphology

New-onset conduction and ECG morphology abnormalities are summarized by treatment in Table 12. A small number of subjects exhibited new-onset conduction abnormalities; however, these observations were seen across all treatments, including placebo.

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Table 12 New-Onset Abnormalities and Waveform Morphology

Parameter	2.5 mg Zelapar N=40 (%)	10 mg Zelapar N=44 (%)	Placebo N=41 (%)	Moxifloxacin N=40 (%)
Conduction				
First Degree AV Block	0	0	1 (2.4%)	0
Incomplete RBBB	0	1 (2.3%)	0	0
Intraventricular Conduction Defect	0	2 (4.5%)	1 (2.4%)	2 (5.0%)
Left Anterior Hemiblock	1 (2.5%)	0	0	1 (2.5%)
Prolonged QTc	1 (2.5%)	0	1 (2.4%)	2 (5.0%)
RBBB	1 (2.5%)	0	0	0
ST Segment				
Depressed	1 (2.5%)	2 (4.5%)	0	0
T Wave				
Biphasic	0	1 (2.3%)	3 (7.3%)	0
Flat	11 (27.5%)	8 (18.2%)	8 (19.5%)	9 (22.5%)
Inverted	2 (5.0%)	1 (2.3%)	2 (4.9%)	4 (10.0%)

AV = atrioventricular

RBBB = right bundle branch block

Data Source: Table 15.11: Appendix 16.2. Listing 24

One subject in the 2.5 mg ZELAPAR group and two subjects in the 10 mg ZELAPAR group showed a new-onset ST segment depression, which was not seen in the placebo or moxifloxacin treatment groups. This observation was not considered clinically significant by the reviewing cardiologist.

A similar number of subjects with flat T waves were seen across all four treatments. T wave inversions were noted in 2 subjects (5%) in the 2.5 mg ZELAPAR group, 1 subject (2.3%) in the 10 mg ZELAPAR group, 2 subjects (5%) in the placebo group, and 4 subjects (10%) in the moxifloxacin group. These results were not subjected to statistical analyses; therefore, it is not possible to discern whether the higher number of T wave inversion in the moxifloxacin group represents a genuine difference. The reviewing cardiologist noted the difference in his summary report, but remarked that it was probably of no consequence.

Gender Analysis

No gender differences were demonstrated for any of the ECG results.

Correlation of QTc to Selegiline Plasma Concentration

A regression analysis was performed to correlate change in QTc from baseline to the plasma concentrations of selegiline at steady-state on Day 11. The results of the regression analysis for QTcI are presented in Table 13.

Table 13 Regression Analysis of Change from baseline QTcI vs Selegiline Concentration on Day 11 by Zydis Selegiline (Zelapar) Treatment

Treatment	Y-Intercept (msec)	Intercept p-Value	Slope	Slope p-Value	r ²
Zelapar 2.5 mg	-5.4751	<0.0001	0.0005	0.7304	0.0004
Zelapar 10 mg	-4.0844	<0.0001	0.0004	0.1469	0.0034
All Zelapar ^a	-5.0068	<0.0001	0.0006	0.0144	0.0097

^a 2.5 mg and 10 mg groups combined

Data Source: Table 15.14

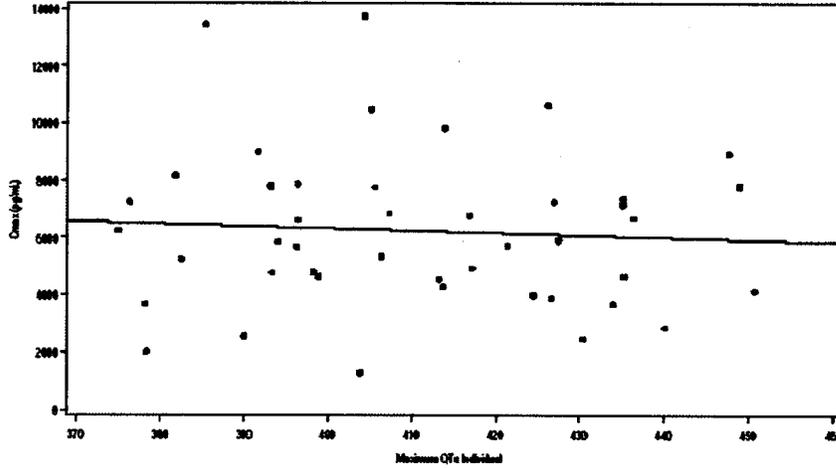
The slope of the QTcI-selegiline concentration relationship regression line was essentially zero for both the 2.5 mg ZELAPAR dose (0.0005) and the 10 mg ZELAPAR dose (0.0004), as well as for both ZELAPAR dose groups combined (0.0006), indicating a lack of any correlation between plasma levels of selegiline and response in QTcI.

The regression analyses of the relationship between QTcB and QTcF and plasma selegiline concentrations were consistent with the results obtained for QTcI.

The relationship between the maximum QTcI and the maximum plasma concentration of selegiline achieved at steady-state is displayed graphically in Figure 4 for the 10 mg ZELAPAR group. A time-matched plot of the maximum QTcI on Day 11 and the selegiline plasma concentration corresponding to that QTcI maximum is plotted in Figure 5 for the 10 mg ZELAPAR group. These analyses explore the maximum potential effect of selegiline on QTc.

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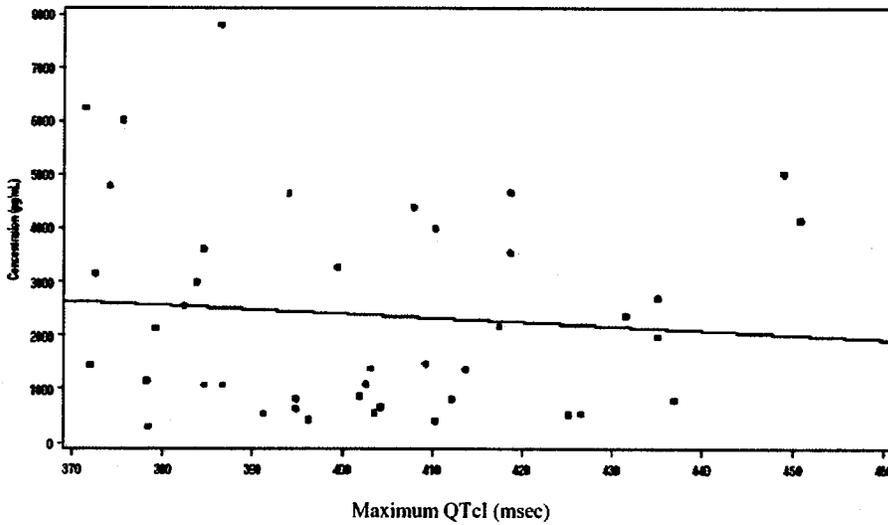
Figure 4 Maximal QTcI on Day 11 versus Maximal Selegiline Plasma Concentration on Day 11 (10 mg Zydis selegiline)



Data Source: Appendix 16.2, Figure 5

No trend toward prolongation of QTcI as a function of peak selegiline plasma concentrations could be distinguished (Figure 4). Similarly, there was no trend observed when maximal QTcI effect was examined as a function of the corresponding selegiline concentration at the time of maximal QTcI effect (Figure 5).

Figure 5 Plot of Regression Analysis of Maximal QTcI vs Selegiline Plasma Concentration at the Maximal QTcI Point on Day 11 (10 mg Zydis Selegiline)



Data Source: Appendix 16.2, Figure 6

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Plotting maximum QTcB and QTcF intervals versus maximum plasma selegiline concentrations yielded similar results to those obtained in the analysis of maximum QTcI and selegiline concentration. Thus, there is no defined relationship nor even any trend associated with maximal QTcI effect and selegiline concentration.

Statistical/Analytical Issues

Adjustments for Covariates

Treatment by gender interaction was not significant at the < 0.10 level and was consequently dropped from the model for the ANCOVA analysis of QTc change from baseline.

Handling of Missing Data

No rules for imputing values for missing data were applicable to this study.

Multiple Comparisons/Multiplicity

The Tukey-Kramer method was applied to adjust for multiple comparisons.

Use of an Analysis Subset of Subjects

All analyses of ECG data were performed on the ITT population.

Examination of Subgroups

The ECG analyses were performed on the overall ITT population and separately by gender. No statistical comparison of any differences between males and females was performed.

Safety Experience

The sponsor presented the safety experience in this study. The sponsor's conclusions were that, overall, ZELAPAR was well tolerated by the subjects in this study and the results of the AE, clinical laboratory tests, and safety ECG monitoring were consistent with the established safety profile of selegiline. However, I have not presented nor discussed these data because there were no significant nor noteworthy findings that changed my assessment of the safety profile of ZS based upon all the other data already known and reviewed.

Sponsor's Conclusions

ECG Analysis Conclusions

This study design included a placebo and an active control. The positive control, orally administered moxifloxacin (400 mg tablet), elicited a mean increase in QTcI of 7.8 msec three hours after dosing, indicating that the assay was sufficiently sensitive to detect any effect of the test study drug on cardiac repolarization. The results for moxifloxacin demonstrated an effect that was significantly different from placebo and consistent with the literature and approved prescribing information for AVELOX (moxifloxacin 400 mg tablet). In contrast, following clinical

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or suprathreshold doses of ZELAPAR (ZYDIS selegiline), the analysis of ECG intervals at steady-state did not produce any signal of an effect on heart rate, QTc prolongation or any other conduction or ECG morphology abnormalities and was not different from placebo. The lack of any potential for QTc prolongation was thoroughly defined by examination of absolute change from baseline, gender subgroup analysis, and correlation of QTc effect to maximum and time-matched plasma levels of selegiline.

In conclusion, this definitive ECG trial showed that ZELAPAR, at a therapeutic dose of 2.5 mg/day or even at a suprathreshold dose of 10 mg/day, does not affect ECG intervals and in particular, has no effect on cardiac repolarization as measured by QTc interval duration.

Reviewer Comments

- In general, I agree with much of the sponsor's description of results/analyses of the "thorough" QTc study. Based upon results from this new study including data from all subjects (males and females) ZS treatment (2.5 or 10 mg daily) did not appear to show any clear, statistically significant effect on electrocardiographic parameters, particularly with regard to QTc prolongation (using individual, Fridericia, and Bazett corrections) compared to placebo treatment in the time-matched comparisons of QTc change from baseline. Neither did the overall mean QTc change from baseline (Table 10) nor the maximal QTc change from baseline (Table 9) for either ZS dose suggest QTc prolongation relative to placebo. The positive control (moxifloxacin) used to demonstrate assay sensitivity did show assay sensitivity by various analyses and the moxifloxacin prolonged QTc compared to placebo and each ZS dose. In addition, the analyses of frequency of outliers (Table 11) for various thresholds suggesting QTc prolongation showed that there was a greater frequency of these outliers associated with moxifloxacin treatment than with placebo or either ZS treatment, which were usually similar in their frequencies.
- Table 14 shows the mean treatment effect (ZS-placebo) of each QT correction change from baseline over the 24 hour period for all subjects. These analyses (submitted during review) are based upon a more conservative ANCOVA analysis model (including treatment and gender) with correction for multiple (i.e. 3) paired treatment comparisons by Dunnett's test. This table also shows the 95 % confidence intervals (2-sided) and the respective p values that have been adjusted for multiplicity of paired treatment comparisons. I think that the most interesting observation from reviewing results in this table is that there may be a ZS dose-dependent mild increment in mean treatment effect of QTc change from baseline at 3 and 12 hours. Results were generally similar irrespective of which QT correction was used. The 2.5 mg ZS dose shows no clear increment at + 3 hours and a slight increment (~ 2-3 msec) at + 12 hours. In contrast, the 10 mg ZS dose shows approximately a 3-4 msec increment at + 3 hours and a 5-7 msec increment at + 12 hours. The 2 largest increments in treatment effect of QTc for moxifloxacin also occurred at 3 (~ 12 msec) and 12 hours (~ 8 msec).

The sponsor had conducted gender analyses and noted that "No gender differences were demonstrated for any of the ECG results." However, I asked the sponsor to submit additional

Table 14 Treatment Effect (ZS-Placebo) of QTc Change from Baseline at Each Timepoint for All Subjects (ANCOVA Analysis with Multiplicity for Paired Treatment Comparisons Controlled by Dunnett Test)

Dose	Time (hrs)	QTcB			QTcF			QTcI		
		LS Mean Δ change from base-line Rx difference (msecs)	95 % Confidence Interval (CI)	p value	LS Mean Δ change from base-line Rx difference (msecs)	95 % Confidence Interval (CI)	p value	LS Mean Δ change from base-line Rx difference (msecs)	95 % Confidence Interval (CI)	p value
ZS 2.5 mg/d	0.25	-2.6	-10.9,5.7	0.8032	-2.3	-9.5,4.9	0.7931	-2.4	-9.4,4.7	0.7711
	0.5	-4.2	-14.2,5.7	0.6165	-2.6	-11.0,5.7	0.7946	-4.4	-12.9,4.1	0.4698
	1	-6.3	-15.8,3.2	0.2775	-5.5	-13.5,2.5	0.2459	-7.3	-15.2,0.6	0.0782
	2	-2.5	-11.2,6.1	0.8314	-1.3	-9.5,6.9	0.9656	-3.2	-11.1,4.7	0.6536
	3	-0.1	-9.5,9.3	1.000	1.3	-7.3,10.0	0.9691	1.4	-7.2,10.0	0.9647
	4	4.7	-6.1,15.5	0.6049	5.4	-3.8,14.5	0.3729	2.9	-9.4,8.4	0.9983
	5	3.8	-4.2,11.7	0.5468	0.3	-6.0,6.6	0.9992	-0.9	-7.3,5.4	0.9732
	6	-1.7	-12.4,9.1	0.9687	-3.3	-12.1,5.6	0.7139	-5.5	-14.2,3.3	0.3196
	8	-3.6	-12.7,5.5	0.6667	-1.5	-9.0,6.0	0.9303	-1.7	-9.3,5.8	0.9039
	12	2.1	-6.1,10.3	0.8718	2.2	-5.2,9.6	0.8185	3.1	-4.4,10.6	0.6325
	18	1.1	-7.2,9.5	0.9781	2.2	-5.7,10.1	0.8471	3.1	-4.6,10.8	0.6615
	23.5	1.5	-8.1,11.0	0.9694	2.3	-6.2,10.8	0.8625	2.6	-5.8,10.9	0.8028
ZS 10 mg/d	0.25	-1.4	-9.5,6.7	0.9545	0.3	-6.8,7.3	0.9966	0.5	-6.4,7.4	0.9959
	0.5	2.4	-7.3,12.1	0.8860	2.1	-6.0,10.3	0.8696	0.6	-7.7,8.9	0.9956
	1	0.7	-8.4,9.7	0.2775	-2.3	-9.9,5.3	0.8214	-3.0	-10.5,4.6	0.6765
	2	-2.8	-11.1,5.5	0.7643	-1.8	-9.7,6.1	0.9074	-2.8	-10.4, 4.8	0.7083
	3	3.6	-5.5,12.6	0.6730	3.5	-4.9,11.9	0.6275	3.2	-2.11,5.5	0.6955
	4	0.4	-10.1, 10.9	0.9993	2.9	-6.0,11.8	0.7769	-0.5	-9.4,8.4	0.9983
	5	7.3	-0.4,15.0	0.5468	3.5	-2.7,9.6	0.3987	1.5	-4.7,7.7	0.8935
	6	1.6	-8.8,12.0	0.9693	0.2	-8.8,8.5	0.9999	-2.1	-10.5,6.4	0.8888
	8	-1.4	-10.3, 7.5	0.9658	-1.8	-9.1,5.5	0.8919	-2.5	-9.8,4.8	0.7557
	12	6.8	-1.3,14.9	0.1173	4.7	-2.6,12.0	0.2870	4.9	-2.6,12.3	0.2809
	18	-1.9	-10.0,6.2	0.9041	0.5	-7.2,8.1	0.9978	0.3	-7.2,7.8	0.9994
	23.5	-1.3	-10.6,8.0	0.9754	0.6	-7.7,8.8	0.9971	0.2	-7.9,8.2	0.9999

Data source : Sponsor's Tables 6.1, 6.2, and 6.3 from 9/7/05 submission.

information of analyses already conducted and to conduct additional analyses because some results suggested a possible gender difference. Table 15 and Table 16 show results of similar analyses shown in Table 14 for male and female subjects (~ 20 subjects/ gender/treatment). The most relevant observation found in Table 15 for males is that there was a modest increment (~ 4-5 msec) for the high dose ZS at + 3 hours and no clear increment at + 12 hours nor any increment at 3 or 12 hours for 2.5 mg ZS. Results in females (Table 16) showed a slight increment (~ 2 msec) at + 3 hours and a larger, modest increment (6-8 msec) at + 12 hours for 2.5 mg ZS and a slight increment (~ 1-3 msec) at + 3 hours and more marked increment (~ 9-11 msec) at + 12 hours for 10 mg ZS.

Although the p values are not statistically significant for ZS treatment for all subjects (Table 14), the upper bound of the 95 % confidence interval (CI) (2- sided) is ≥ 10 msec for high dose ZS mean treatment effect at 3 and 12 hours. Gender analyses (Table 15, Table 16) also show similar findings for 10 mg ZS at 3 and 12 hours. I make these observations in view of the recently published E14 ICH Harmonised Tripartite Guideline (The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs; 5/12/05) for evaluating QTc prolongation during drug development and providing advice on conducting a "thorough" QTc study and on analyzing and interpreting results from such a study. Of significance relevance to this study, this guidance notes : "Based on similar considerations, a negative 'thorough QT/QTc study' is one which the upper bound of the 95 % one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval excludes 10 ms." **Alternatively, a "positive" would be one in which the upper bound of the 95 % one-sided CI for the largest time-matched mean effect of the drug on the QTc interval does not exclude 10 msec.** It is also relevant to note that a "positive" study does not necessarily "imply that the drug is proarrhythmic."

It is also pertinent to note that the upper bound of the 95 % CI(one-sided) is equivalent to the upper bound of the 90 % CI (2-sided). Thus, I calculated the upper bound of the 95 % CI (one-sided) for particular results using the formulae :

$$\text{upper bound 95 \% CI (2-sided)} - \text{mean} / 1.96 = \text{SE}$$

$$\text{mean} + 1.645 (\text{SE}) = \text{upper bound 90 \% CI (2 sided)} = \text{upper bound 95 \% CI (one-sided)}$$

Table 17 shows mean treatment effect (active drug – placebo) for QTcI change from baseline for each ZS dose and moxifloxacin at 3 and 12 hours for all subjects and for males and females separately according to two ANCOVA statistical analyses (one adjusted p values for multiple paired treatment comparison by Dunnett's test and the other did not but used the Bonferroni adjustment to show the critical alpha required for the multiple paired treatment comparisons), CIs, and p values. Considering these analyses, I think that the most important results to focus on are those at + 3 and + 12 hours for ZS 10 mg initially for all subjects, and then for males and females. The largest time-matched treatment difference occurs at 12 hours and shows a mean increment of ~ 5 msec with a 95 % one-sided CI that exceeds 10 msec (i.e. 11.1 and 10.1 for the different analyses). **Based upon the newly released guidance, these results would be**

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Table 15 Treatment Effect (ZS-Placebo) of QTc Change from Baseline at Each Timepoint for Males (Multiplicity Controlled by Dunnett Test)

Dose	Time (hrs)	QTcB			QTcF			QTcI		
		LS Mean Δ change from base-line Rx difference (msecs)	95 % Con-fidence Inter-val (CI)	p value	LS Mean Δ change from base-line Rx difference (msecs)	95 % Con-fidence Inter-val (CI)	p value	LS Mean Δ change from base-line Rx difference (msecs)	95 % Con-fidence Inter-val (CI)	p value
ZS 2.5 mg/d	0.25	-7.6	-20.3,5.0	0.3416	-6.5	-16.2, 3.2	0.2604	-6.3	-16.1,3.5	0.2882
	0.5	-4.0	-19.6, 11.6	0.8693	-2.4	-15.1, 10.2	0.9396	-3.6	-16.5,9.3	0.8455
	1	-2.2	-15.5, 11.2	0.9635	-3.1	-14.7, 8.4	0.8552	-4.8	-16.6, 7.0	0.6440
	2	-3.1	-16.1,9.9	0.8925	-2.1	-11.8,7.5	0.9170	-3.5	-13.6,6.6	0.7439
	3	-2.2	-16.2, 11.8	0.9649	0.4	-11.7, 12.4	0.9998	0.4	-11.7, 12.5	0.9995
	4	-1.1	-17.4, 15.3	0.9974	-1.4	-12.9, 10.2	0.9848	-1.0	-12.5, 10.6	0.9947
	5	1.7	-10.3, 13.7	0.9754	0.8	-8.2,9.9	0.9931	-0.5	-9.6,8.5	0.9981
	6	-1.5	-16.9, 14.0	0.9922	-2.1	-13.4,9.3	0.9468	-6.0	-17.4,5.4	0.4513
	8	-8.3	-23.3,6.6	0.4047	-3.4	-14.0,7.2	0.7852	-3.7	-14.5,7.1	0.7482
	12	-4.1	-15.9, 7.7	0.7411	-1.6	-11.6,8.4	0.9622	-1.3	-12.0,9.5	0.9844
	18	1.3	-9.0,11.6	0.9808	1.9	-7.4,11.1	0.9304	2.9	-6.2,12.0	0.7867
23.5	2.6	-10.8, 16.0	0.9393	5.3	-6.4,17.0	0.5686	7.2	-4.2,18.6	0.3041	
ZS 10 mg/d	0.25	-1.9	-14.1, 10.3	0.9679	1.1	-8.3,10.4	0.9861	0.6	-8.8,10.0	0.9977
	0.5	-1.2	-16.2, 13.9	0.9954	-0.6	-12.8, 11.7	0.9990	-2.4	-14.8, 10.1	0.9408
	1	7.4	-5.3,20.2	0.3679	2.6	-8.4,13.6	0.9007	0.7	-10.5, 11.8	0.9980
	2	-3.2	-15.8,9.5	0.8790	-2.4	-11.9,7.1	0.8756	-3.0	-12.8,6.9	0.8103
	3	4.2	-9.0,17.5	0.7881	5.2	-6.2,16.6	0.5576	5.0	-6.5,16.4	0.6026
	4	-2.5	-18.0, 13.0	0.9633	-1.8	-12.8,9.1	0.9604	-4.0	-15.0,6.9	0.7100
	5	7.6	-3.9, 19.0	0.2695	4.3	-4.3,12.9	0.4902	2.0	-6.6, 10.6	0.9003
	6	2.5	-12.2, 17.2	0.9557	1.2	-9.6,12.0	0.9878	-1.4	-12.3,9.4	0.9792
	8	-1.9	-6.2, 12.5	0.9805	-0.2	-10.4, 10.1	1.000	-1.2	-11.6,9.3	0.9872
	12	2.9	-8.6,14.4	0.8800	0.7	-9.1,10.5	0.9965	-0.5	-10.9, 10.0	0.9992
	18	-1.7	-11.5,8.1	0.9549	2.0	-6.8,10.8	0.9061	0.5	-8.1,9.2	0.9978
23.5	-0.6	-13.5, 12.4	0.9992	3.3	-8.0,14.6	0.8230	4.0	-6.9,15.0	0.7057	

Data source : Sponsor's Tables 6.1, 6.2, and 6.3 from 9/7/05 submission.

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Table 16 Treatment Effect (ZS-Placebo) of QTc Change from Baseline at Each Timepoint for Females (Multiplicity Controlled by Dunnett Test)

Dose	Time (hrs)	QTcB			QTcF			QTcI		
		LS Mean Δ change from base-line Rx difference	95 % Con-fidence Inter-val (CI)	p value	LS Mean Δ change from base-line Rx difference	95 % Con-fidence Inter-val (CI)	p value	LS Mean Δ change from base-line Rx difference	95 % Con-fidence Inter-val (CI)	p value
ZS 2.5 mg/d	0.25	2.1	-9.0,13.2	0.9435	1.6	-9.1,12.3	0.9705	1.3	-9.1,11.7	0.9814
	0.5	-4.5	-17.5,8.5	0.7462	-2.9	-14.2,8.5	0.8780	-5.2	-16.8,6.4	0.5711
	1	-10.3	-23.8,3.3	0.1789	-7.8	-18.9,3.4	0.2357	-9.7	-20.7,1.3	0.0951
	2	-2.0	-14.1, 10.1	0.9627	-0.7	-14.0, 12.7	0.9627	-3.1	-15.6,9.5	0.8883
	3	1.8	-11.3, 14.8	0.9773	2.2	-10.6, 14.9	0.9576	2.2	-10.4, 14.8	0.9547
	4	10.1	-4.6,24.7	0.2445	11.6	-2.5,25.8	0.1317	6.4	-7.8,20.6	0.5715
	5	5.7	-5.2,16.6	0.4594	-0.2	-9.4,8.9	0.9998	-1.3	-10.6,8.0	0.9746
	6	-1.8	-17.2, 13.5	0.9842	-4.4	-18.4, 10.0	0.7905	-4.9	-18.4,8.6	0.7158
	8	1.0	-10.1, 12.0	0.9935	0.3	-10.6, 11.1	0.9999	0.2	-10.6, 10.9	1.000
	12	8.2	-2.8,19.2	0.1837	6.1	-4.6, 16.8	0.3886	7.5	-2.9,18.0	0.2096
	18	1.0	-12.3, 14.3	0.9963	2.5	-10.3, 15.2	0.9384	3.3	-9.3,15.9	0.8685
	23.5	0.4	-13.7, 14.5	0.9997	-0.5	-13.1, 12.1	0.9993	-1.6	-14.1, 10.8	0.9788
ZS 10 mg/d	0.25	-1.0	-12.0, 10.0	0.9921	-0.6	-11.2, 10.0	0.9980	0.4	-9.9,10.7	0.9994
	0.5	6.0	-6.9,18.8	4.8	4.8	-6.4, 16.1	0.6034	3.7	-7.7, 15.1	0.7770
	1	-6.2	-19.2,6.8	0.5320	-7.2	17.9,3.5	0.2607	-6.6	-17.1,3.9	0.3129
	2	-2.5	-13.9,9.0	0.9182	-1.3	-13.9, 11.3	0.9893	-2.8	-14.6,9.1	0.9007
	3	2.8	-10.0, 15.7	0.9131	1.8	-10.7, 14.4	0.9728	1.4	-11.1 13.8	0.9869
	4	3.2	-11.5, 17.8	0.9184	7.6	-6.6,21.7	0.4391	3.0	-11.2, 17.2	0.9250
	5	7.0	-3.8,17.8	0.2899	2.6	-6.4,11.7	0.8312	1.0	-8.2,10.2	0.9874
	6	0.5	-14.7, 15.6	0.9997	-1.6	-15.4, 12.2	0.9854	-2.8	-16.2, 10.5	0.9210
	8	-1.0	-12.0,9.9	0.9920	-3.5	-14.2,7.3	0.7764	-3.9	-14.6,6.7	0.7051
	12	10.8	-0.2,21.8	0.0556	8.8	-1.9,19.5	0.1299	10.2	-0.3,20.7	0.0584
	18	-2.1	-15.2, 11.1	0.9648	-1.0	-13.6, 11.6	0.9947	0.1	-12.4, 12.6	1.000
	23.5	-2.0	-15.8, 11.8	0.9723	-2.0	-14.3, 10.3	0.9602	-3.5	-15.6, 8.6	0.8325

Data source : Sponsor's Tables 6.1, 6.2, and 6.3 from 9/7/05 submission.

Table 17 Mean Treatment Effect (Active drug – Placebo) of QTcI Change from Baseline for Different Statistical Analyses

Pop-ulation	Rx	Time (hrs)	ANCOVA Analysis (p value adjustment by Dunnett Test for multiple paired Rx comparisons)				ANCOVA Analysis (unadjusted p value for multiple paired Rx comparisons)			
			LS Mean QTcI Δ From baseline Rx Effect (msecs)	95 % CIs (2 sided)	Upper Bound 95 % CI one-sided	P value	LS Mean QTcI Δ From baseline Rx Effect (msecs)	95 % CIs (2 sided)	Upper Bound 95 % CI one-sided	P value Not adjusted
ALL Subjects	ZS 2.5	+ 3	1.4	-7.2, 10.0	8.6	0.9647	1.4	-5.8,8.6	7.4	0.7044
		+ 12	3.1	-4.4, 10.6	9.4	0.6325	3.1	-3.1,9.4	8.4	0.3259
	ZS 10	+ 3	3.2	-5.2, 11.5	10.2	0.6955	3.2	-3.8, 10.1	9.0	0.3685
		+ 12	4.9	-2.6, 12.3	11.1	0.2809	4.9	-1.3, 11.1	10.1	0.1226
	Moxi	+ 3	12.6	4.0,21.1	19.7	0.0019	12.6	5.4,19.7	18.6	0.0006*
		+ 12	7.5	-0.1, 15.1	13.9	0.0534	7.5	1.2,13.9	12.9	0.0204
Males	ZS 2.5	+ 3	0.4	-11.7, 12.5	10.6	0.9995	0.4	-9.6, 10.5	8.9	0.9312
		+ 12	-1.3	-12.0, 9.5	7.8	0.9844	-1.3	-10.2, 7.7	6.3	0.7775
	ZS 10	+ 3	5.0	-6.5, 16.6	14.7	0.6026	5.0	-4.6, 14.5	13.0	0.9312
		+ 12	-0.5	-10.9, 10.0	8.3	0.9922	-0.5	-9.2,8.3	6.9	0.9175
	Moxi	+ 3	11.6	-0.7, 23.9	21.9	0.0698	11.6	1.4,21.8	20.2	0.0268
		+ 12	-1.0	-11.9, 9.9	8.1	0.9918	-1.0	-10.1, 8.0	6.6	0.8214
Females	ZS 2.5	+ 3	2.2	-10.4, 14.8	12.8	0.9547	2.2	-8.3, 12.6	10.9	0.6798
		+ 12	7.5	-2.9, 18.0	16.3	0.2096	7.5	-1.2, 16.2	14.8	0.0892
	ZS 10	+ 3	1.4	-11.1, 13.8	11.8	0.9869	1.4	-9.0, 11.7	10.0	0.7897
		+ 12	10.2	-0.3, 20.7	19.0	0.0584	10.2	1.5,18.9	17.5	0.0226
	Moxi	+ 3	13.3	1.0,25.6	23.6	0.0309	13.3	3.1,23.5	21.9	0.0115*
		+ 12	15.7	5.1,26.3	24.6	0.0019	15.7	6.9,24.5	23.1	0.0007*

* Significant by Bonferroni correction for multiple (3) treatment comparisons yields significance level of 0.05/3 = 0.0167 (applied to unadjusted p values)

Data source : Sponsor's Tables 6.1, 6.2, and 6.3 from 8/4/05 and 9/7/05 submissions.

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interpreted as a “positive” QTc study in which a treatment effect of 10 msec was not excluded. The guidance also seems to allude to that fact that the assessment of the upper bound CI should be interpreted in the present of a mean treatment effect for QTc change from baseline of around 5 msec or greater. Although the guidance does clearly give a priority to either of these criteria applied for interpreting the study as positive or negative, I understand that evolving discussions within the Agency have suggested that the application of the upper bound CI is the most important consideration in excluding a possible QTc change of < 10 msec to label a study as “negative.”

Dr. Norm Stockbridge (Acting Director of CDER’s Division of Cardio-Renal Drug Products), who has seen results from this study, concurred that results indicated that this is a “positive” QTc study. The lower treatment effect at 3 hours also showed an upper bound CI of ≥ 10 msec (i.e. 10.2) for the more conservative analysis. Of additional interest, the upper bound of the 95 % one-sided CI for the 3 hour results for males is also ≥ 10 msec (14.7 and 13.0) associated with a modest increment of 5 msec. In contrast, results of females showed that the largest mean increment (10.2 msec) was considerable at + 12 hours and had a much larger upper bound CI (~ 20 msec). Although both males and females showed the largest time-matched QTcI increment with an upper bound CI ≥ 10 msec, results by gender showed a different time course for response suggesting that the QTcI increment occurred early in males but much later in females. If this possible QTc increment is real, it appears to be dose-dependent and depending on which population is assessed, it is greater at 10 mg ZS or only observed with this high dose. Although none of these results technically show statistically significant treatment effects, the high dose results in females at 12 hours are borderline statistically significant (i.e. 0.0556 and 0.0584) by both analyses and the lower bound of the 95 % 2-sided confidence interval just barely includes zero. It is also relevant to note that the possible QTc prolongation treatment effects are always less than those of moxifloxacin that were largest not only at 2 and 3 hours as expected but also at + 12 hours, a significant increment not previously recognized at that late time after administration of moxifloxacin. **The sponsor did not note any of these possible ZS-related QTc increments that I have noted. Neither did the sponsor interpret results of this study in light of the ICH QTc guidance and by applying CIs.**

There are several puzzling aspects about these ZS results. Overall, these results show a fair degree of variability over time with all CIs including zero and lower bounds of the CI that are frequently modestly negative. However, when I view all these results, I have developed the impression that if there may be mild QTc prolongation with ZS treatment, that it may occur at 3 and 12 hours. I have developed this impression based upon my assessment of a similar magnitude QTc increment across all 3 corrections (QTcI, QTcB, QTcF) and of finding the high dose results as showing greater positive increments or at least a similar increment as observed at the low dose. Of great interest, this possible QTc prolongation appears to show a significant gender difference in that there is larger treatment effect for QTc increment in males (vs females) at 3 hours and a substantial mean increment is evident at 12 hours only in females. I am not aware of other drug results that show such a gender difference of QTc prolongation occurring at a certain time only in one gender and not in the other gender.

There is no easy explanation for the times at which these possible increments were observed. Mean C_{max}/T_{max} for plasma selegiline (parent drug) occurs near 1 hour. Thus, it seems difficult to associate a possible QTc increment directly with selegiline. If real, the ZS-related QTc increment that is delayed relative to plasma selegiline C_{max}/T_{max} would suggest that it could be due to a metabolite and/or a delayed pharmacodynamic effect from selegiline and/or a metabolite. Mean C_{max}/T_{max} for major metabolites (desmethylselegiline, L-amphetamine, L-methamphetamine) of selegiline occurs between 1 -3 hours, with the most delayed C_{max}/T_{max} at 3 hours reflecting L-amphetamine generation. Although a mild QTc increment at 3 hours could be related to amphetamine, there is no apparent explanation for the QTc increment occurring mainly in females at 12 hours. There is no apparent gender difference in PK for plasma selegiline comparing C_{max} and AUC. However, I am not aware of information that would reflect on possible gender differences for the generation of metabolites of selegiline nor on their similarity or difference in kinetic relationships. It is also noteworthy that the possible QTc increment related to high dose ZS occurring at 3 hours was seemingly "isolated" (i.e. not also apparent at 2 and 4 hours) for all subjects and for males. However, positive increments are shown for all 3 QT corrections between 3-5 hours for high dose ZS in females. It is not possible to say whether the apparent increment at 12 hours was isolated because the prior QTc was four hours earlier (+ 8 hours) and the next QTc was much later (i.e. 6 hours later at +18 hours).

Considering the recently released QTc guidance, it appears that this study is "positive" in that the study was not able to exclude a possible ZS treatment effect QTc increment of 10 msec and the largest, placebo-corrected, time-matched mean QTc change from baseline was not < 5 msec (but was ~ 5-7 msec depending on QT correction) . There were no statistically significant QTc differences related to ZS treatment of all subjects according to various analyses and safety endpoints. However, in assessing whether this drug has the potential to affect cardiac repolarization and prolong QTc, the possible treatment effect of the QTc increment change from baseline related to high dose ZS treatment (10 mg/d) was associated with an upper bound 95 % one-sided CI that is of a magnitude that suggests that there may be potential for some concern. To put this possible QTc increment into perspective, it is noteworthy that this possible QTc increment from high dose ZS treatment is less than the definite QTc prolongation known to result from moxifloxacin treatment. However, this potential safety concern with ZS treatment could be significantly exacerbated if treatment with an apparently "safe" dose of ZS (i.e. 2.5 mg) could be associated with a marked increase in exposure significantly above exposures occurring in healthy subjects treated with 10 mg ZS. In our particular situation for dealing with ZS risks, there are suggestions from publications that marked increments in conventional selegiline exposure may be observed in hepatic impairment (up to 18 fold increment), in renal impairment (up to 6 fold increment), and with sex steroid treatment (up to 20 fold). Furthermore, we do not know the potential for other drug-drug interactions through metabolizing CYP enzyme interactions that could possibly result in markedly increased exposure to selegiline because this information is lacking. Thus, possible QTc prolongation has been raised

related to ZS treatment and the possible magnitude of such QTc prolongation does not provide reassurance that there may not be significant risks associated with ZS treatment (2.5 mg) This concern is particularly directed toward patients who would be treated with this dose and who could experience conditions that markedly increased exposure much above exposure expected from administering 10 mg daily ZS to healthy subjects.

- Moxifloxacin showed treatment effect QTc increments (≥ 3 msec relative to placebo) for change from baseline for all subjects at all of the QTc collection times with the exception of 0.25 and 6 hours (Table 8). As expected, the largest moxifloxacin-induced increments occurred between 1 and 3 hours and the maximal increment was ~ 12 msec at 3 hours. However, the second largest treatment effect QTcI increment (~ 8 msec) for all subjects surprisingly occurred at + 12 hours and this substantial mean increment was borderline statistically significant with 2 different ANCOVA model analyses ($p = 0.0534$ with Dunnett's test correcting for multiplicity; $p = 0.0204$ with required alpha of 0.0167 for Bonferroni correction) (Table 17). and the upper bound of the 95 % one-side CI was ~ 25 msec. It is also interesting to note this 12 hour moxifloxacin associated QTcI increment occurred only in females and that the mean QTcI treatment effect increment for females at 12 hours was slightly higher than that observed at 3 hours.
- I was not able to find any publications about QTc prolongation and/or Torsades des pointes associated with selegiline or its metabolites (desmethylselegiline, L-amphetamine, or L-methamphetamine. However, I did find one publication (Drake et al., S Afr Med J., 86:180-1 1996) describing the QT prolongation after ingestion of Ecstasy (3,4-methylenedioxymethamphetamine - MDMA).
- The sponsor had noted that a subgroup analysis according to gender did not show any significant differences. However, I had asked the sponsor to present some results of these gender analyses. After reviewing these results (Figure 6, Figure 7), a question was raised whether females might show some ZS-induced QTc prolongation at 12 hours after treatment compared to placebo treatment. Interestingly, all 3 QT corrections (individual, Fridericia, and Bazett corrections) in females showed a similar pattern in which there was a mild dose-dependent mean treatment difference (mean active treatment result – mean placebo result) increase in QTc prolongation (\sim mean 6 - 8 msec for 2.5 mg ZS and \sim mean 9 - 11 msec for 10 mg ZS; treatment difference relative to placebo by LS means) associated with ZS treatment compared to placebo only at 12 hours but this possible QTc prolongation was less than that produced by moxifloxacin (\sim mean 15- 18 msec; treatment difference relative to placebo by LS means) at 12 hours.

In general, the QTcI, QTcF, and QTcB showed similar results. I have focused my analyses on results using the QTcI which is considered perhaps the best correction. At 12 hours, the mean (least squares) change from baseline QTc treatment difference (active drug – placebo) for females was 7.5 (95 % confidence interval-CI, -1.2, + 16.2; $p = 0.0892$), 10.2 (95 % CI, +1.5, +18.9; $p = 0.0226$), and 15.7 (95 % CI, + 6.9, + 24.5; $p = 0.0007$) msec for ZS (2.5

mg), ZS (10 mg), and moxifloxacin, respectively. These p values are unadjusted. When the Bonferroni adjustment is applied for the 3 treatment comparisons, a p value at a “significant” level is considered to $0.05/3 = 0.0167$. Thus, technically, the only “significant” treatment difference meeting the Bonferroni threshold value was for moxifloxacin that was also associated with positive 95 % confidence intervals. This effect is also reflected in the 95 % CI that is positive at the lower and upper bound for moxifloxacin. Although the upper bound for each ZS treatment was relatively large (2.5 mg, +16.2; 10 mg, +18.9), the lower bound of the CI was negative and thus included zero for the low dose ZS but was positive (1.5) and excluded zero for the high dose ZS.. It is also relevant to note that the Bonferroni correction relates to the multiplicity involved with 3 treatment comparisons (ZS 2.5 mg vs placebo, ZS 10 mg vs placebo, moxifloxacin vs placebo). Application of Dunnett’s test to adjust for multiplicity showed somewhat similar but not identical results (ZS 2.5 mg, CI, -2.9, +19.0, $p = 0.2096$); ZS 10 mg, CI, -0.3, + 20.7, $p = 0.0584$) for p values and 95 % CIs as had the Bonferroni adjustment. **However, no overall adjustment for multiplicity has been made for the multiple comparisons made for 3 paired active treatment comparisons (vs placebo) at the 12 timepoints (i.e. 36 overall comparisons).**

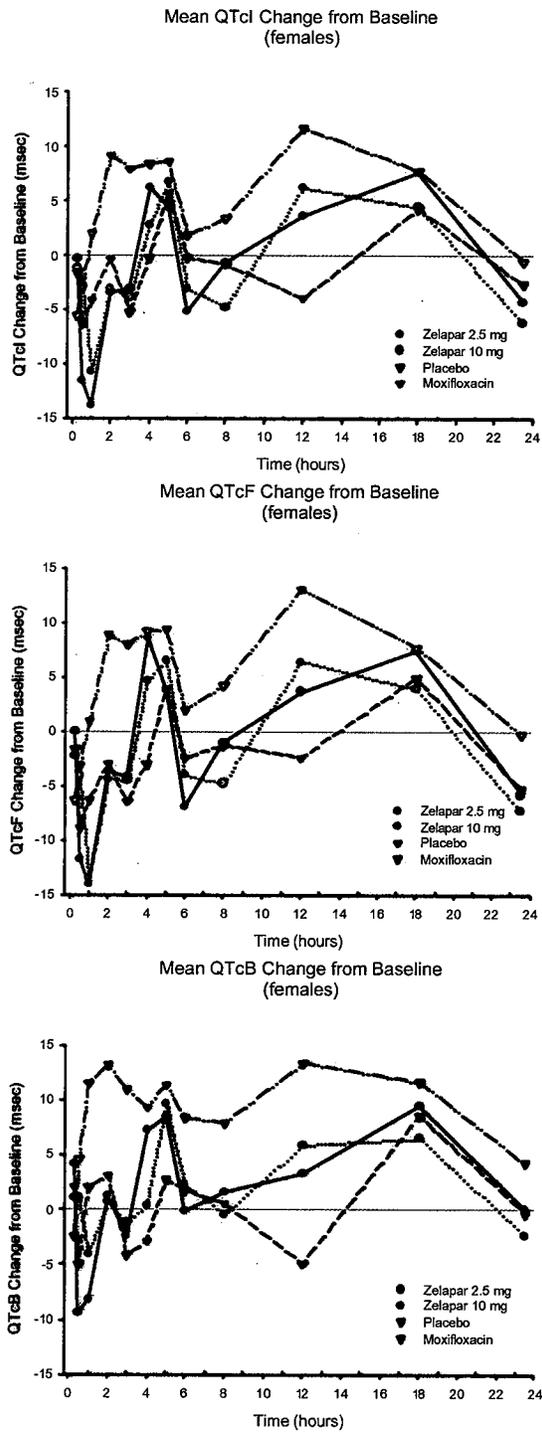
Dr. Andre Jackson, the Clinical Pharmacology/Biopharmaceutical reviewer conducted gender analyses of the PK data collected in the QTc study and in the tyramine challenge study. Results in the QTc study showed that Cmax and AUC (Table 18) were similar for females and males. Similar analyses (2.5, 5 and 10 mg groups; data not presented) of PK results derived from the tyramine challenge study also showed that there was no apparent gender difference in PK of the parent drug for these parameters and that there appeared to be dose-proportionality at steady state for both Cmax and AUC. A comparison across studies for the same ZS doses showed higher absolute values for both Cmax and AUC in the tyramine study that collected PK samples over 24 hours (vs PK collection over 8 hours in the QTc study). There were no analyses permitting an assessment of gender differences in PK of metabolites of ZS.

Table 18 Comparison of PK Parameters According to Gender in the QTc Study

DOSE=2.5 MG						
PARAMETER	GENDER				GENDER	
	MALE				FEMALE	
	N	MEAN	STD	N	MEAN	STD
AREA-TAU	19	2440.84	1757.5	21	2033.54	1358.86
CMAX	19	1309.33	624.3456	21	1167.79	580.369

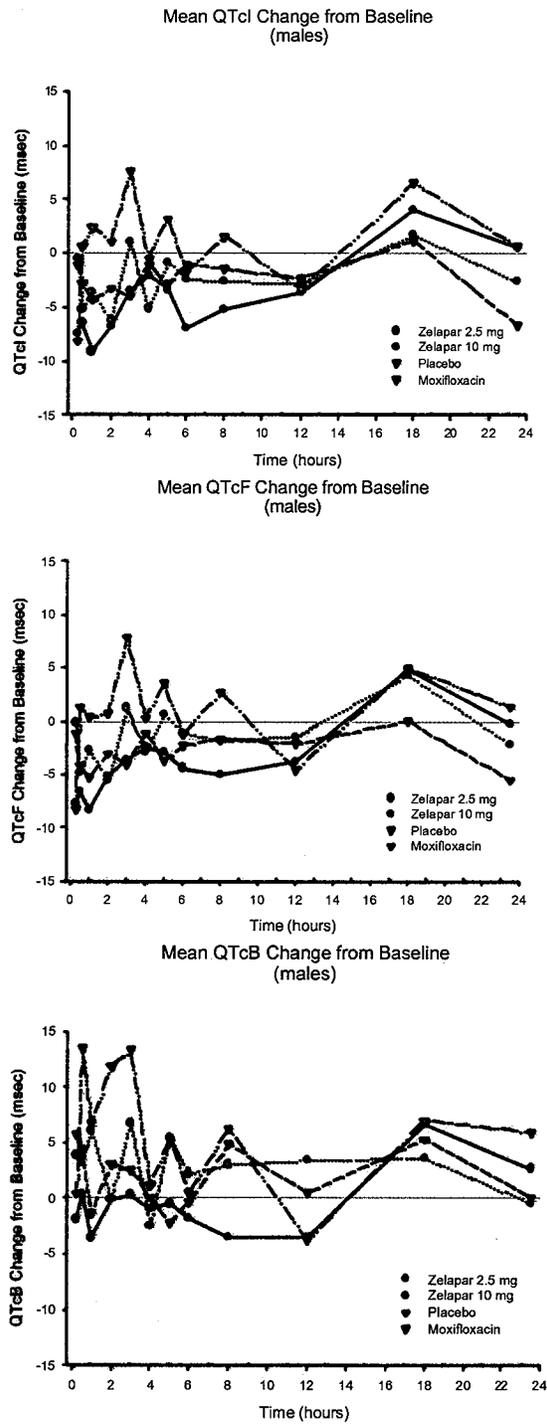
DOSE=10 MG						
PARAMETER	GENDER				GENDER	
	MALE				FEMALE	
	N	MEAN	STD	N	MEAN	STD
AREA-TAU	22	13422	5156.74	22	14716.13	7253.69
CMAX	22	5792.69	1922.57	22	6692.57	3344.73

Figure 6 Mean QTc (I, F, B) Change from Baseline (females)



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Figure 7 Mean QTc (I, F, B) Change from Baseline (males)



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It is also relevant to note that when the sponsor deleted the treatment by gender parameter from its statistical model because the p value was not < 0.1 , this consideration included a treatment effect by gender for all the data and at the timepoints. I suspect that an isolated gender difference at only 12 hours would not have been detected.

In attempting to assess the significance of the apparent or suspected ZS effect on QTc in females, I note that the mean QTc changes from baseline relationships at 12 hours were always similar for all 3 QT corrections (QTcI, QTcB, QTcF) for all treatment groups. To provide a quantitative perspective, the mean QTcI change from baseline was 3.3, 5.9, and 13.2 msec for ZS 2.5 mg, ZS 10 mg, and moxifloxacin, respectively, and -4.9 msec for placebo. If real, the small but greater change in 10 vs 2.5 mg ZS might be consistent with a shallow dose-response, but these changes were clearly less than that of moxifloxacin. Although one could argue that the fact that the constancy of these quantitative relationships regardless of which QT correction was applied suggests that they are real, one could also argue that this might not be so unexpected for a drug that does not substantially alter heart rate (as appears to be the case for ZS). On the other hand, comparisons of different QT corrections for change from baseline data at other timepoints do not always show the same relative relationships at each timepoint, perhaps because the effect may be related to not only the change in heart rate but also to the absolute magnitude of the heart rate at that timepoint when QTcB and QTcF is applied.

The mean maximal QTc change from average QTc baseline for moxifloxacin treatment was statistically significant (unadjusted $p \leq 0.0059$ for all QT corrections; $p \leq 0.0167$ required for statistically significant difference by Bonferroni adjustment) compared to placebo for all subjects. When gender subgroup analysis was performed for moxifloxacin, all QTcs for each gender "trended" toward significance ($p \leq 0.1283$). However, these analyses did not show that there was any statistically significant difference (using Bonferroni threshold $p \leq 0.0167$) for males or females for any QTc with the exception of QTcB for females ($p = 0.0038$). In contrast, there was not even a hint of a statistically significant difference for either ZS treatment (vs placebo) for males, females or all subjects using any of the QT corrections in the assessment of mean maximal QTc change from baseline.

Gender subgroup analysis of outliers suggested a ZS-induced dose-dependent increased incidence of tachycardia ($> 25\%$ increment and value > 100) in females based upon an incidence of 14% and 32% in the 2.5 and 10 mg groups respectively vs 0% for placebo. Although the incidence for this tachycardia was increased in the 10 mg group (9%) compared to the 2.5 mg group (0%), this incidence was similar to that of placebo (10%) suggesting in fact no treatment effect in males. In addition, the outlier analysis of all subjects showed an increased incidence of tachycardia for high dose ZS (21%) vs low dose ZS (8%) vs placebo (5%), but this effect seemed to be primarily driven by the effect in females. Despite these outlier changes, the analysis of central tendency of all subjects did not suggest a significant increase in pulse/heart rate from baseline after treatment for 11 days. The mean change for the high dose ZS was only ~ 3 BPM greater than the similar mean change (~ 19) for low dose ZS or placebo. **Of additional interest, there was no suggestion of an**

increased incidence of QTc outliers (increment 30 – 60 msec, > 60 msec, new onset QTc > 480 msec) for either ZS dose (vs placebo) for females, males, or all subjects with the exception of 32 % incidence of QTcB increment (30 – 60 msec) for the high dose ZS (vs 19 % for low dose ZS and placebo) .

Gender regression analyses were also submitted for change from time-averaged baseline QTc vs plasma selegiline at each timepoint. Of significant interest, a statistically significant p value (< 0.05) for the regression line was observed for all ZS treatment slope analyses (2.5 mg, 10 mg, both doses) for QTcI or QTcF **in males** (Table 19) but there were no statistically significant results for QTcB (p ≥ 0.2113). In contrast, similar corresponding analyses **in females** did not suggest any statistically significant results (p values ranged from 0.1589 – 0.9060). Similar analyses including **all subjects** showed statistically significant (p < 0.05) p values for slope only for analyses of both ZS doses for QTcI (p = 0.0144, slope = 0.0006; Table 13) and QTcF (p value = 0.0089, slope = 0.0006). In the final study report, the sponsor did not comment on the statistically significant p value for all ZS doses for all subjects but noted that the slope for the regression line of this concentration-effect relationship analysis was “essentially zero.” Neither did the sponsor comment on the observations derived from the gender analyses for regression presented earlier.

Table 19 Regression Analyses : Change from Time-Averaged Baseline QTc (msec) vs Plasma Selegiline (pg/ml) at Each Timepoint in MALES

Treatment	Response Var. (QT Correction)	Intercept	Intercept p-value	Slope	Slope p-value	R-square	Adj R-Sq
Zelapar 2.5 mg	QTc Bazett	-4.1274	0.0128	0.0026	0.2113	0.0112	0.0041
Zelapar 10 mg	QTc Bazett	2.2908	0.1636	-0.0004	0.3924	0.0045	-0.0016
Zelapar (All)	QTc Bazett	-1.2635	0.2268	0.0004	0.3454	0.0029	-0.0004
Zelapar 2.5 mg	QTc Fridericia	-8.5498	<.0001	0.0040	0.0136	0.0430	0.0361
Zelapar 10 mg	QTc Fridericia	-5.3445	0.0002	0.0009	0.0307	0.0287	0.0226
Zelapar (All)	QTc Fridericia	-6.6094	<.0001	0.0012	0.0002	0.0438	0.0406
Zelapar 2.5 mg	QTc Individual	-9.0201	<.0001	0.0041	0.0157	0.0413	0.0344
Zelapar 10 mg	QTc Individual	-6.6210	<.0001	0.0011	0.0102	0.0402	0.0343
Zelapar (All)	QTc Individual	-7.3766	<.0001	0.0013	0.0001	0.0482	0.0450

The clinical significance of the statistically significant p values (p < 0.05) suggesting a relationship between QTc and plasma selegiline concentration for both ZS doses combined for all subjects and for males subjects seems quite puzzling. I note that this is puzzling particularly when one recalls that the analyses of QTc change from baseline at each timepoint for all subjects and for males subjects does not seem to suggest any significant QTc prolongation compared to placebo. The gender subgroup analyses had initially raised the question of QTc prolongation in females but surprisingly these regression analyses of QTc change relative to plasma selegiline concentration did not suggest any positive relationship in females.

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When gender subgroup regression analyses were conducted for time-averaged QTc change from baseline vs mean plasma selegiline, the only statistically significant ($p < 0.05$) slope results that were observed were for the 2.5 mg ZS dose for QTcB and QTcF in males. Similar analyses of all subjects revealed a statistically significant slope only for QTcB for 2.5 mg ZS.

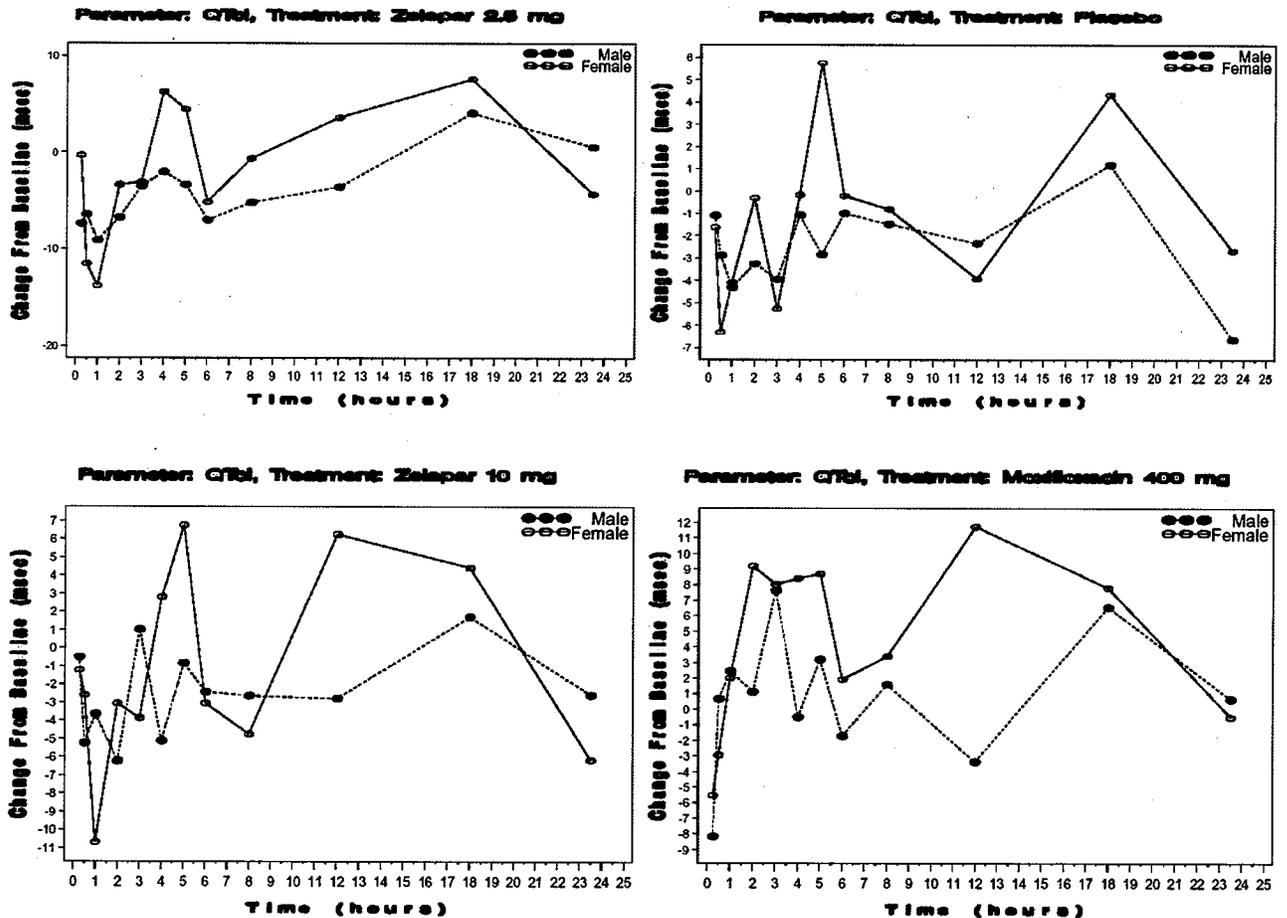
Additional gender regression analyses were also submitted relative to time-averaged QTc change from baseline vs Cmax. Statistically significant p values ($p < 0.05$) for slope were observed for 2.5 mg ZS for all 3 QT corrections and for both ZS doses for QTcB and QTcF (QTcI $p = 0.0632$). There were no statistically significant p values for slope analyses for females for any QT correction or for all subjects with the exception of QTcB for 2.5 mg ZS.

Upon request, the sponsor provided graphs showing the scatterplots used for these regression analyses. All QTc changes from baseline were plotted relative to plasma selegiline concentrations at times (0.25, 0.5, 1, 2, 3, 4, 6, 8 hrs) when both information was collected, and a regression line was determined considering all data plotted. If there was a "perfect" correlation with a slope of + 1.0 based upon the relationship of a certain linear change of ZS concentration relative to an equivalent linear change in QTc, then an increase in selegiline of 1000 pg/ml (1 ng/ml) would be accompanied by ~ a 11 msec QTc increment. Despite the fact that there appeared to be statistically significant slope, the fact that the slopes were so shallow would not suggest a considerable increment in QTc even if selegiline were markedly increased much above levels experienced in this study. For example, based upon a slope of 0.0006 (the "statistically significant" slope for both doses of ZS in all subjects), a markedly increased plasma selegiline (~ 40 ng/ml) about 20 fold that of the mean Cmax for 2.5 mg ZS would be expected to increase QTc by a very minimal amount (e.g. < 1 msec). Thus, I cannot see any significant concern about this statistically significant correlation that would translate into QTc increment associated with any clinical significance. Furthermore, it is not clear that it is appropriate and the optimal way to analyze a relationship between QTc change and selegiline levels by merely computing a regression line amongst all the data points. It may be desirable to compute a regression line for each subject and then analyze all these individual regression lines statistically or to use a different statistical model for analysis.

Figure 8 shows QTcI change from baseline results for males vs females for all 4 treatment groups as per my requested analysis to assess possible gender effects on each treatment. Overall when one views the male vs female mean data for each treatment over the 24 hour period, I would suggest that there is no definite nor clear apparent gender difference for the placebo, and both ZS treatments. In contrast, the panel for moxifloxacin shows that mean female results

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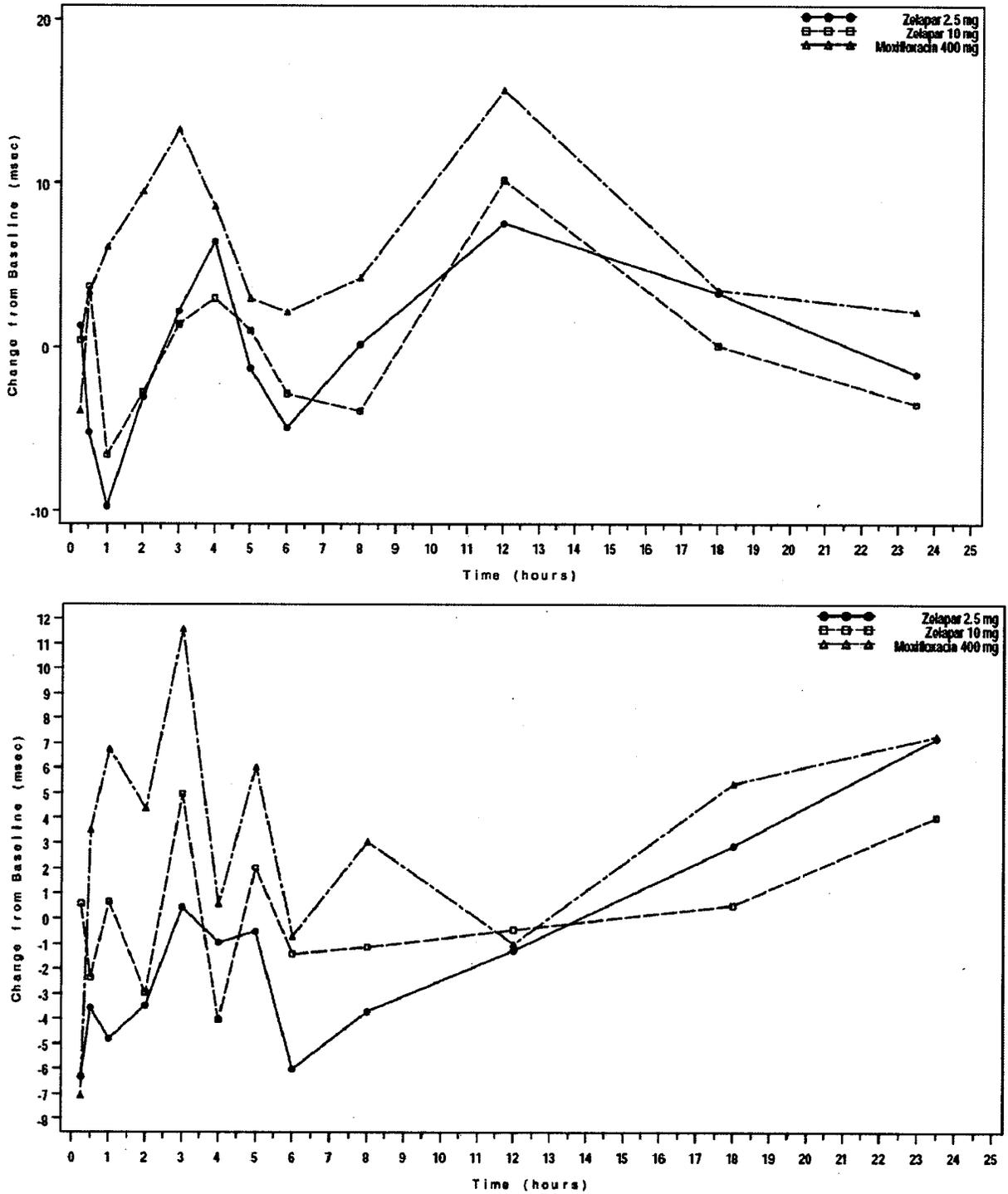
Figure 8 Comparison of Effects of Each Treatment on QTcI Change from Baseline (Time-Matched) Between Females and Males



seem to be consistently higher than mean male results for most of the timepoints, particularly from 2 – 18 hours post-dosing. However, when each timepoint was separately assessed statistically for a treatment difference by gender, the only timepoint associated with a “significant” difference was the 12 hour timepoint for moxifloxacin (p value for all 3 QT corrections was < 0.0038 according to Bonferroni adjustment). This analysis suggested a difference only for moxifloxacin with female data suggesting an apparent QTc increment but male data not showing any increment.

The sponsor also “corrected” all individual subjects results by the mean placebo result at each timepoint and recalculated the data to show the mean QTc change from baseline placebo-corrected, treatment effect. Figure 9 depicts the mean placebo-corrected changes for each treatment for females and males. The most striking observation in this figure is the suggestion of a greater change (i.e. increment) in females vs males for moxifloxacin. When

Figure 9 Change from Baseline (Time-Matched) for Treatment Effect (Treatment result - placebo result; placebo corrected) for QTcI (Upper panel : females; Lower panel : males)



these data were subjected to statistical analyses comparing female vs male results at each timepoint for each treatment, the main finding worthy of comment was that all 3 QT corrected changes from baseline were statistically “significant” for moxifloxacin at 12 hours (Bonferroni adjusted p value ≤ 0.0022). In contrast, the p values for QTcI for ZS 2.5 mg and 10 mg groups were 0.1878 and 0.0645, respectively and did not suggest any significant treatment effect.

- Considering all these results and analyses, critical questions to be answered ultimately are :

1) Does ZS treatment prolong QTc relative to placebo?

2) Is there a gender difference in the magnitude of ZS-related QTc prolongation relative to placebo?

3) If there is a suggestion of a ZS-related QTc prolongation relative to placebo, is there any clinical concern relative to an approval action or labeling based upon the magnitude of the suggested QTc prolongation?

- **Considering all these results and analyses, I still cannot answer question # 1 by noting that ZS does or does not prolong QTc relative to placebo.** Although I agree that this study did not show any statistically significant increments in QTc for ZS relative to placebo, I interpret this “thorough” QTc study as being a “positive” study because it did not exclude a possible increase in QTc below 10 msec. The conservative ANCOVA analysis (using Dunnett’s test) showed that the upper bound of the 95 % CI (one-sided) was ~ 11 secs and the QTc guidance says that the largest time-matched QTc increment of the change from baseline should exclude 10 msec for this upper boundary to be called a “negative” study that exclude this value as a potential risk.

I have raised the question whether there are mild QTc increments in QTc at 3 and 12 hours in all subjects treated with high dose 10 mg ZS. If so, the largest mean treatment effect (placebo-corrected) was ~ 5-7 msec (for all 3 QT corrections) at 12 hours. Thus, we still do not know if ZS prolongs QTc and have not been able to exclude a risk of 10 msec.

- My answer to question # 2 is that there are data that raise the suspicion of a different gender effect of high dose 10 mg ZS on QTc prolongation based upon mean results and CIs not associated with statistical significance. The gender analyses raise the question of possibly greater numerical QTc prolongation at 3 hours in males (vs females) and a substantial mean QTc increment (~ 10 msec) at 12 hours only in females. I am not aware of other drug results that show such a gender difference of QTc prolongation occurring at a certain time only in one gender and not in the other gender. It is difficult to know whether these possible gender differences are or are not real. Of note, the gender analyses were based upon approximately half the number of subjects (~ 20) of that (~ 40) analyzed in the full analysis of all subjects.

It is also possible that the apparent gender effects raised are an artifact of multiplicity (i.e. making multiple statistical comparisons such as 3 paired treatment comparisons on 12 occasions; total 36 statistical comparisons).

- In answering question # 3, I note my thoughts about approval and labeling with certain caveats. At this time I think that it is a fair perspective to say that ZS could produce relatively small QTc increments that were not statistically significant but are possible because a margin of 10 msec was not able to be excluded in the “thorough” QTc study. These possible increments by themselves do not necessarily raise serious safety concerns if one would assume that ZS exposure would not exceed that associated with 10 mg daily ZS treatment in a healthy subject (~ fold Cmax and AUC of that expected in healthy subjects treated with 2.5 mg daily, the recommended dose). However, I have concerns that potentially much higher selegiline exposures could be experienced and these significantly higher exposures could potentially be associated with significant QTc prolongation and thus a risk of Torsades des pointes. My concerns about this risk in the face of markedly increased exposures to selegiline are based upon 3 considerations : 1) a published study showing that patients with hepatic impairment had a mean increased AUC and Cmax that were 18 fold and 7 fold respectively greater than those of healthy subjects and patients with renal impairment had a mean increased AUC and Cmax that were 6 fold and 4 fold respectively greater than those of healthy subjects; 2) a publication showing administration of several single doses of oral conventional selegiline was associated with markedly increase exposures (e.g. 22 fold increased AUC and 11 fold increased Cmax for 10 mg selegiline; the approved daily dose); and 3) I am not convinced that we are confident that markedly increased exposures (AUC and/or Cmax) are not possible from drug-drug interactions from other drugs altering the metabolism of selegiline by direct inhibitory actions or competitive inhibitory on important CYP enzymes involved in the metabolism of selegiline. I do not necessarily find it reassuring that we are not aware of serious safety risks from these potential interactions in patients who are taking conventional oral selegiline (Eldepryl).

Furthermore, I do not know how we could convey useful information in the label about results from the publication in which markedly increased mean selegiline exposures were observed in patients with hepatic or renal impairment. The authors of this publication did not clearly define renal or hepatic impairment so that we could define it in the label and give useful, practical advice about whom this safety concern might be relevant. Given these uncertainties about the risks of potentially markedly increase selegiline exposure after ZS treatment and the outlined concerns about possible risks for increased QTc/Torsades des pointes (and also increased tyramine sensitivity hypertensive “cheese” reactions), I think that it is necessary that these clinical pharmacology issues/questions be answered prior to approval.

The sponsor could determine if the suspected increased PK exposures of selegiline are real risks. If they are not believed to be real, then I do not necessarily think that additional

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QTc study must be conducted prior to approval. However, if the risks of many fold (> 4) increased exposure are shown to be realistic, then it would seem necessary for the sponsor to assess QTc effects of higher doses of ZS and clearly establish whether there is or is not a potential for significant QTc prolongation at much higher exposures than that observed with 10 mg ZS in healthy subjects.

Alternatively, the sponsor could conduct additional study of QTc prolongation at higher doses (e.g. 20 and 30 mg daily compared to placebo, moxifloxacin, and 10 mg daily) in the presence of tyramine restriction in an in-patient setting and not wait until the results of PK studies are known.

6. DESCRIPTION OF TYRAMINE SENSITIVITY STUDY AND RESULTS AND REVIEWER COMMENTS

Sponsor's Description of Tyramine Sensitivity Study

Title : "A Phase 1 Study in Healthy Subjects to Evaluate the Effect of Steady-State Doses of ZELAPAR™ (Zydis® Selegiline HCl) on Blood Pressure Responses to Tyramine (Protocol RNA-ZEL-B-21-102)"

Objectives :

Primary : Evaluate the effect of ZELAPAR on potential blood pressure elevations induced by tyramine and to determine if ZELAPAR induces orthostatic hypotension. The primary outcome measures were systolic blood pressure (SBP) and diastolic blood pressure (DBP), both supine and standing for 2 minutes, and the change in SBP and DBP after standing for 2 minutes.

Secondary : Assess whether the observed effects on tyramine-induced blood pressure elevations were correlated with peak plasma concentrations of selegiline (C_{max}) or other pharmacokinetic parameters and to evaluate the safety and tolerability of ZELAPAR tablets.

Design :

This study was a multiple-dose, randomized, double-blind, double-dummy, placebo- and positive-controlled, parallel-group study in healthy 'older' adult subjects (≥ 40 years old). The treatments evaluated were 2.5 mg, 5 mg, or 10 mg ZELAPAR, placebo (negative control), and NARDIL (phenelzine sulfate) as the positive control. A total of 80 subjects (16 per treatment group) were planned for enrollment and eligible subjects were randomized to one of the five study treatments with the objective that at least 60 subjects would complete the study. The treatment groups were balanced with respect to gender and consisted of 8 men and 8 women. There were no replacements for subjects that discontinued. Subjects were confined to the clinical

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facility from baseline through completion of the steady-state tyramine assessment for a total duration of up to 24 days including 16 days of treatment with study medication.

The primary pharmacodynamic variables were:

- Peak SBP response (Emax) following administration of the highest dose of tyramine. The Emax was determined as the highest change from the mean of three pre-dose SBP values
- The lowest dose of tyramine that produces a ≥ 30 mmHg increase in SBP over the mean pre-dose value (threshold dose)

The primary safety variables were :

- The change from baseline in orthostatic blood pressure (SBP and DBP) at steady-state
- The proportion of subjects exhibiting orthostatic hypotension at steady-state

The effect of selegiline (ZELAPAR) on tyramine-induced blood pressure elevations was determined by comparing the tyramine pressor response after 10 days of dosing with randomized study drug to the tyramine pressor response observed at baseline, prior to administration of study drug. The positive control was NARDIL (phenelzine sulfate), a well characterized MAO inhibitor with demonstrated ability to potentiate the pressor effects of tyramine and other sympathomimetic substances. NARDIL tablets (15 mg) were obtained from commercial sources and overencapsulated to allow for blinding. Placebo medication matched to the ZELAPAR tablets and NARDIL capsules served as the negative control.

Treatments Administered

Subjects who qualified for the study, based on having exhibited a minimum BP response to tyramine (3 consecutive SBP measurements ≥ 15 mmHg higher than predose values) were randomized to receive one of the five study treatments described in Table 20.

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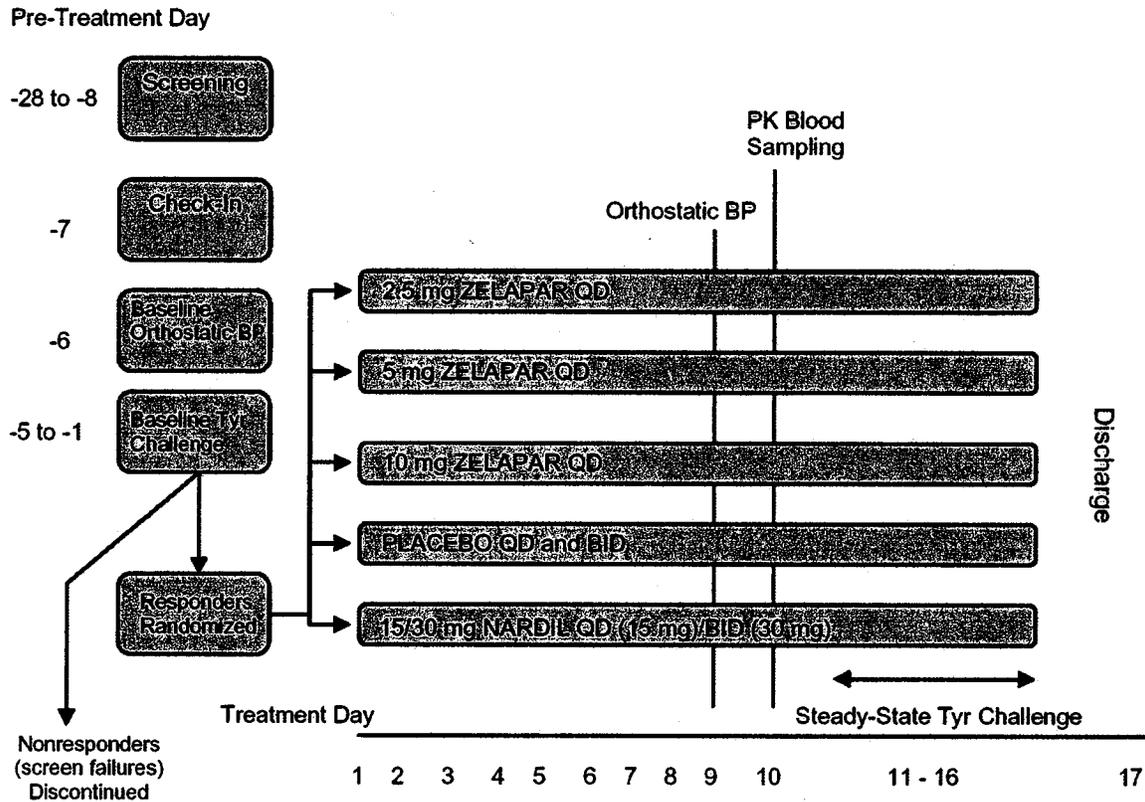
Table 20 Description of Study Treatments

Dose Group	Treatment	Study Days	Dosage
1	ZELAPAR 2.5 mg	1-16	AM Two 1.25 mg ZELAPAR tablets Six ZELAPAR placebo tablets One NARDIL placebo capsule PM One NARDIL placebo capsule
2	ZELAPAR 5 mg	1-16	AM Four 1.25 mg ZELAPAR tablets Four ZELAPAR placebo tablets One NARDIL placebo capsule PM One NARDIL placebo capsule
3	ZELAPAR 10 mg	1-16	AM Eight 1.25 mg ZELAPAR tablets One NARDIL placebo capsule PM One NARDIL placebo capsule
4	Placebo	1-16	AM Eight ZELAPAR placebo tablets One NARDIL placebo capsule PM One NARDIL placebo capsule
5	NARDIL® 15 mg QD	1-3	AM Eight ZELAPAR placebo tablets One 15 mg NARDIL capsule PM One NARDIL placebo capsule
	NARDIL® 15 mg BID (30 mg)	4-16	AM Eight ZELAPAR placebo tablets One 15 mg NARDIL capsule PM One 15 mg NARDIL capsule

A daily schedule of the study assessments and procedures is presented in Table 21. A schematic of the overall study design is provided in Figure 10.

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Figure 10 Study Design Schematic



Qualified subjects checked into the clinic on Day -7. Blood pressure measurements were obtained at scheduled time points over a 24-hour period on Day -6 to establish a baseline for the assessment of orthostatic hypotension at steady-state (Day 9).

A tyramine challenge was conducted prior to administration of study drug and again at selegiline steady-state after 10 days of dosing with double-blind randomized treatment. Tyramine was administered once daily in a series of ascending doses during the baseline period (25, 50, 100, 200, and 400 mg on consecutive days) and again after reaching selegiline steady-state (12.5, 25, 50, 100, 200, and 400 mg on consecutive days). On the days that a dose of tyramine was given, SBP, DBP, and heart rate were measured 3 times at 10-minute intervals prior to dose administration. The mean of these three values represented the predose baseline value. Following the administration of tyramine, heart rate (HR) and BP were measured at 10-minute intervals for the next 2 hours and at 15-minute intervals for the next hour (for a total of 3 hours of monitoring following each tyramine challenge).

Any subject exhibiting a significant hypertensive response to tyramine (SBP \geq 180 mmHg and/or DBP \geq 115 mmHg) during the baseline or steady-state tyramine challenge was not advanced to

the next higher dose of tyramine. Dose escalation could also be stopped for a given subject at the discretion of the investigator prior to reaching a hypertensive response based on the subject's symptoms and level of discomfort. Subjects exhibiting an increase of ≥ 15 mmHg in SBP over pre-dose measurements for three consecutive measurements (taken 10 minutes apart) at baseline were considered to be responders and were randomized to receive study medication. Any subjects that did not exhibit a minimum increase in systolic blood pressure of ≥ 15 mmHg in response to any dose of tyramine at baseline were considered non-responders and were removed from the study as screen failures prior to randomization. Subjects were considered to have completed the study once they reached a threshold response of ≥ 30 mm Hg increase in SBP over pre-dose values during the steady state tyramine challenge or if they received all 6 doses of tyramine at steady-state without achieving the threshold SBP response.

Routine safety assessments, including vital signs, clinical laboratory tests, safety ECGs, and review of AEs and concomitant medications, were conducted at scheduled points (Table 21) throughout the study.

Discussion of Study Design, Including Choice of Control Groups

This study was essentially a drug-interaction study using a pharmacodynamic endpoint to determine whether administration of ZELAPAR (buccally-administered selegiline) at doses of 2.5, 5, or 10 mg daily enhanced the pressor response to orally administered tyramine. The trial included both active and placebo control groups. NARDIL (phenelzine sulfate, 30 mg daily), a potent nonselective MAOI, was used as a positive control to validate the ability to detect changes in the threshold pressor response to tyramine and to serve as an approved comparator drug for ZELAPAR. The placebo served as a negative control for estimating variability in the pressor response and for the assessment of orthostatic hypotension induced by selegiline.

Standard pharmacokinetic and pharmacodynamic drug interaction studies are typically conducted in healthy adult subjects 18 years of age or older. A study population of healthy "older" adults (40 to 70 years) was selected for the tyramine interaction study subject of this report in order to better reflect the intended clinical population of PD patients. It is currently an expected element of the clinical development and safety evaluation of an investigational MAOI to quantify its effect on the tyramine pressor response using a conventional tyramine challenge test. The principle of the tyramine challenge test employed in these studies has been to define the lowest, threshold dose of tyramine necessary to produce a predefined pressor response (commonly an increase in SBP ≥ 30 mmHg above a pre-dose value). The tyramine threshold dose is determined by giving increasing doses of tyramine at intervals until the predefined increase in blood pressure is attained. A second tyramine challenge is performed following administration of the MAOI of interest. The on treatment tyramine challenge usually starts with a lower dose of tyramine than that used to initiate the baseline challenge, but again the doses of tyramine are escalated until the threshold dose is reached. The TPR thus obtained is a measure of treatment-related changes in tyramine sensitivity, and is defined as follows :

TPR (TSF) = Pre-treatment tyramine threshold dose/Post-treatment tyramine threshold dose

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The higher the TPR, the greater the inhibitory effect of the investigational MAOI, and consequently, the tyramine vasopressor response. The comparison of TPRs between treatment groups was traditionally a two-step process involving the calculation of the ratio of the test drug TPR to the control drug TPR or "ratio of ratios."

The conventional TPR method offers a means to evaluate the relative effects of MAOIs on the tyramine pressor response; however, it lacks sensitivity with respect to quantifying differences between the pre-treatment and post-treatment pressor responses at a given dose of tyramine. Since only the lower bound of the threshold pressor response is defined (e.g. ≥ 30 mmHg), the TPR method cannot discriminate the degree of effect within and between tyramine doses along a continuous dose-response curve. For example, a threshold dose of 200 mg tyramine might be demonstrated both in the presence and absence of a particular test drug, yet the difference between the pressor response attained post-treatment (e.g. 45 mmHg) and that observed pre-treatment (e.g. 30 mmHg) may be numerically and clinically significant. This limitation of the TPR method may conceal meaningful differences in the dose response between treatments.

In order to improve the sensitivity of the tyramine challenge assay, the present study employed traditional concepts of pharmacodynamics to evaluate shifts in dose-response :

- a) comparison of the responses at a fixed dosage level; and,
- b) comparison of the doses required to produce a fixed level of response.

Both approaches to quantifying changes in dose-response require one variable, either dose of tyramine or threshold pressor response, to remain constant.

Two primary pharmacodynamic analyses and one primary safety analysis (effect of ZELAPAR on orthostatic blood pressure changes) were performed. The first primary pharmacodynamic analysis was conducted to determine whether an interaction exists between ZELAPAR and tyramine and to determine whether such an effect could be detected for the active control (NARDIL). This analysis compared the effect of each ZELAPAR dose and NARDIL to placebo using the greatest increase in SPB from baseline (E_{max}) at the highest dose of tyramine at steady state. This method was selected for the first primary analysis because: a) it does not require any significant assumptions concerning the dose-response curves; and b) it is expected to have more sensitivity than the traditional "ratio" analysis approach. The study was powered for this analysis. If a ZELAPAR dose was shown to have a significantly greater effect on SBP- E_{max} than placebo, the result would establish the presence of a tyramine interaction at that dosage level. If NARDIL was shown to have a significantly greater effect on SBP- E_{max} than placebo the result would characterize the relative potency of the two MAOIs.

The second primary pharmacodynamic analysis was conducted to estimate the similarity or difference between the effect of ZELAPAR and the effect of NARDIL. This analysis examined the difference in log-tyramine dose required to produce a threshold-response (SPB increase

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≥ 30 mmHg) in the presence of ZELAPAR and the log-tyramine dose required to produce a threshold-response in the presence of NARDIL. This analysis was intended to approximate a relative potency determination at doses of ZELAPAR shown to be different from placebo. Steady-state plasma concentrations of selegiline were determined over a 24-hour period after study drug administration to correlate the maximum tyramine challenge pressor response to peak plasma levels of selegiline.

Selection of Study Population

Subjects were selected from the healthy older (40 to 70 years of age) adult population in the local area of the clinical research facilities.

Key Inclusion Criteria :

Subjects meeting all of the following criteria were considered for admission to the study.

1. Healthy men or women of any race and 40 to 70 years of age (inclusive) at the time of screening
2. Subjects with a BMI between 18.5 and 30.0 kg/m² (inclusive) and weight of at least 50 kg
3. Subjects who were in good general health with no history of significant diseases (as determined by the investigator in consultation with the sponsor) based on the medical history, physical examination, clinical laboratory evaluations (hematology, clinical chemistry, urinalysis), 12-lead ECG, and a normal exercise stress ECG
4. Female subjects of non-childbearing potential, or if sexually active, must have been using or have agreed to use an acceptable method of contraception (which must have included a barrier method if using a hormonal contraceptive). Only nonlactating females were eligible.

Key Exclusion Criteria :

Subjects meeting any of the following criteria were not eligible for the study.

1. Subjects with a systolic blood pressure (SBP) <100 or >140 mmHg; diastolic blood pressure (DBP) <60 or >85 mmHg; pulse rate <50 or >100 bpm at screening or before the first dose of tyramine, unless a repeat test within 15 minutes later showed values within these ranges
2. Subjects with a history of undiagnosed chest pain or vascular malformation, including intracranial aneurysm (with the exception of minor skin vascular malformations)
3. Subjects with any disease or condition that might affect drug absorption, metabolism or excretion or compromise the cardiovascular, hematological, renal, hepatic, pulmonary, endocrine, central nervous, or gastrointestinal systems (unless deemed not clinically significant by the investigator and the sponsor)

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4. Subjects with a history of alcoholism or drug addiction, use of any recreational drugs within 3 months prior to receiving study medication, or positive screen for substances of abuse pre-study
5. Subjects who did not have a systolic blood pressure response of ≥ 15 mm Hg for three consecutive measures (taken 10 minutes apart) during the baseline tyramine challenge portion of the study (defined as a non-responders)
6. Subjects with a past or present chronic use of systemic medications, use of a drug therapy (including herbal preparations, eg, St. John's Wort) known to induce or inhibit drug metabolism within 30 days prior to dosing; or use of any medications (prescription or over-the-counter, including antacids, multivitamins, nutritional supplements, and herbal preparations), within 14 days prior to dosing, unless approved by the sponsor
7. Subjects with a history of smoking more than 10 cigarettes daily (by history only)
8. Subjects who previously received an investigational drug or product or participated in a drug study within a period of 30 days prior to receiving study medication; for investigational drugs with a $t_{1/2}$ greater than 15 days, this proscription was extended to 60 days, or five-times the $t_{1/2}$, whichever is longer

Restrictions

1. Subjects were required to abstain from consuming alcoholic beverages for at least 48 hours prior to entering the clinic on Day -7 until the completion of the study.
2. Subjects were required to abstain from caffeine starting at midnight prior to initiation of each series of tyramine challenge tests through the completion of the tyramine challenge. Otherwise, caffeine intake was restricted to no more than 3 cups of coffee, tea, or 12-ounce can of soda.
3. Subjects were required to fast for at least 8 hours prior to administration of tyramine (no food after midnight preceding each tyramine challenge test).
4. Subjects abstained from consuming tyramine-containing food for at least 5 days prior to the first tyramine dose through completion of the study.
5. Subjects were to refrain from strenuous physical activities during participation in the study. Light exercise, such as walking, was permitted.
6. Subjects were not allowed to take any medications (Rx or OTC) during the course of the study except oral contraceptives, unless approved by the investigator in consultation with the sponsor.

Removal of Subjects from Therapy or Assessment

Subjects were advised that their participation in the study was voluntary and that they were free to leave without negative repercussions from the investigator or institution.

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Subjects that discontinued were not replaced.

Identity of Investigational Products

The placebo tablets matched the ZELAPAR 1.25 mg tablets in appearance and taste. NARDIL (phenelzine sulfate) tablets were overencapsulated to appear similar to a placebo capsule.

Method of Assigning Subjects to Treatment Groups

Qualified subjects were randomized in a 1:1:1:1:1 ratio in blocks of 10 to one of the five treatment groups according to a randomization schedule provided by the biostatistics Department of the CRO (SFBC New Drug Services).

Selection of Doses in the Study

The three doses of ZELAPAR chosen for this study were selected on the basis of the pharmacokinetic (PK) profile and safety in healthy subjects. The lower dose of ZELAPAR (2.5 mg/d for up to 16 days) was anticipated to yield the plasma concentrations of selegiline achieved at steady state with the therapeutic clinical dose and regimen. The higher doses (5 mg/d and 10 mg/d) were selected in consultation with the FDA (May 25, 2004) to provide a 2-fold and 4-fold multiple of the therapeutic dose for the evaluation of any dose response. NARDIL was selected as the positive control based on its pharmacologic activity, commercial availability, and safety profile relative to other MAOIs. The 30 mg/day dose of NARDIL has been shown to elicit a 4- to 5-fold increase in pressor sensitivity to tyramine.

Tyramine is the standard probe to test for inhibition of MAO-A. Studies reported in literature have employed doses of tyramine ranging up to 800 mg and higher. A maximum dose of 400 mg tyramine was selected for the tyramine challenge in this study primarily out of concern for the safety of subjects in the older adult study population. Unlike most previous studies, the study population was enriched for responders during the baseline tyramine challenge and it was therefore expected that most subjects would demonstrate a pressor response at a tyramine dose \leq 400 mg.

FDA (DNBP) had recommended that the sponsor use tyramine doses ranging from 25 mg up to 800 mg at baseline/pre-treatment and from 12.5 mg up to 800 mg post-treatment using 100 mg increments at doses between 100 and 800 mg. This approach had been recommended not only to characterize a dose-response curve based upon a wide range of doses but also to be able to determine the TPR/TSF for most if not all subjects. DNBP had also recommended that the sponsor include a selegiline treatment group (5 mg BID) for comparing results/responses of ZS with an FDA approved MAO-B inhibitor on the market.

Selection and Timing of Dose for Each Subject

Qualified subjects were randomized to one of the five treatment groups detailed in Table 2. Study medication was administered once in the morning and again 12 hours later for up to 16 days.

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The morning dose of ZELAPAR (or ZELAPAR placebo) was administered without liquid and subjects did not ingest food for 5 minutes before or 5 minutes after taking the medication. The morning NARDIL (or NARDIL placebo) dose was taken with water approximately 5 minutes after administration of the last ZELAPAR/placebo tablet. NARDIL or matching placebo was dosed BID, with the second dose occurring 12 hours after the morning dose. Subjects in the NARDIL group received 15 mg NARDIL on study Days 1-3 and 30 mg (15 mg BID) on study Days 4-16.

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