CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	N
Application Number(s)	N 21879
Priority or Standard	Priority
Submit Date(s)	4/30/10
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Reviewer Name(s)	Devanand Jillapalli, MD
Review Completion Date	9/25/10
Established Name	Dextromethorphan hydrobromide (DM) and quinidine sulfate (Q)
(Proposed) Trade Name	Zenvia
Therapeutic Class	
Applicant	Avanir Pharmaceuticals
Formulation(s)	Capsule
Dosing Regimen	DM 20 mg/Q 10 mg (b) (4)
Indication(s)	Treatment of pseudobulbar affect
Intended Population(s)	Adult subjects with pseudobulbar affect.

* Starting dose of one capsule of Zenvia 20 (DM 20 mg/Q 10 mg) (b) (4) daily by mouth for 7 days, and thereafter for Q12 hours.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval.

1.2 Risk Benefit Assessment

I discuss the risk benefit assessment in the context of the deficiencies outlined in the Approvable Letter of 10/30/06, and any new issues stemming from the review of data unique to the Complete Response. For each set of deficiencies outlined in the following subheadings, I outline the Applicant's Response and my Conclusion.

Endpoints, Evidence of Effectiveness, and requirements of Fixed-Combination Prescription Drugs for Humans regulations.

In the Approvable Letter, the Agency noted the following concerns regarding endpoints, evidence of effectiveness, and requirements of Fixed-Combination Prescription Drugs for Humans regulations.

We acknowledge that you have submitted the results of two randomized controlled trials that purport to establish substantial evidence of effectiveness of Zenvia in patients with Pseudobulbar Affect (PBA). We agree that Study 106, in patients with Multiple Sclerosis (MS), clearly can be considered one "positive" study contributing to such a finding. However, as you know, this study was not capable by design of establishing the contribution of the individual components of the product, as required by 21CFR300.50 (Fixed-combination prescription drugs for humans).

Study 102, in patients with Amyotrophic Lateral Sclerosis (ALS), was designed to establish the contribution of each component. We also acknowledge that the contrasts between the combination and the individual components reached statistical significance on the protocol specified primary outcome measure, the CNS-LS. However, as you also know, we had repeatedly expressed to you a preference for the designation of laughing and crying episodes as the primary outcome variable. We note that your protocol specified that you would analyze these episodes using Poisson regression.

However, as you acknowledge, the distribution of the episode data did not support the use of the Poisson regression model. Although your protocol did not specify an alternative analysis in this case, you have chosen to analyze the episode data using the NB1 negative binomial model (variance proportional to the mean).

Given the lack of a prespecified alternative to the Poisson model and the fact that there is no single well-established parametric alternative, we performed a Cochran-Mantel-Haenszel (CMH) test with modified ridit scores on the combination-DM comparison; regardless of whether the data for the one outlier patient 08-016 (see below) are included (p=0.13) or excluded (p=0.19), the results do not achieve significance.

We also investigated the NB2 negative binomial model (variance depends on the square of the mean). We believe that the NB2 negative binomial model also provides a reasonable alternative to the Poisson model. This model is less sensitive than the NB1 model in terms of measures of overall model fit to the inclusion of the one outlier in the Dextromethorphan (DM) group (patient 08-016, who had a total of 3010 laughing episodes during the study). In addition, with the NB1 model, the difference between the combination and the DM group increases when this patient's data are excluded, which is counterintuitive. In contrast, with the NB2 model, the difference between these groups decreases when this patient's data are excluded, as is expected. Therefore, we have analyzed the episode data using this latter model.

In this case, the combination-DM comparison is nominally significant (p=0.017) when this patient's data are included, but not if these data are excluded (p=0.34), or if the next worst episode count in the database (398) is imputed (p=0.13). We recognize that this outcome measure is a secondary measure, but, again, we remind you that, on numerous occasions, we strongly suggested that it be deemed the primary outcome. The results we have obtained suggest that the combination may not provide an additional benefit beyond that provided by the DM component itself. You will need to adequately address this concern before we can conclude that the combination policy has been met. It is also worth noting that this finding raises the possibility that a much lower exposure to DM than is achieved with this product might be effective in controlling laughing or crying episodes in these patients (see below).

Applicant's Response: We have accepted the Agency's preference for the designation of laughing and crying episodes as the primary outcome variable. All three phase III controlled studies of pseudobulbar affect (PBA) – Study 102, Study 106 and Study 123, included a pre-specified analysis of laughing and crying PBA episodes. As the Center for Neurologic Studies - Lability Scale (CNS-LS) is expected to be of interest to practitioners, the CNS-LS was retained as an important prespecified secondary endpoint in the pivotal Study 123. Results from Study 123 revealed that both Zenvia 30/10 and Zenvia 20/10 were effective, (b) (4)

In addition, the two Phase III pivotal studies (Study 102 and Study 106) in which a higher dose combination, dextromethorphan (DM) 30 mg/quinidine (Q) 30 mg was administered provide additional evidence of efficacy and establish that the combination product (DM/Q) is more effective than either DM or Q administered alone (a conclusion supported by FDA in a Type C meeting held February 26, 2007). The statistical methods used were appropriate for analyzing the impact of the combination DM/Q product on the reduction of laughing and/or crying episode counts. Results in favor of DM/Q treatment were observed on both the primary outcome measure (CNS-LS) and the secondary outcome measure (episode counts) in Studies 102 and 106.

Evidence from all 3 controlled clinical trials with the combination product of DM/Q in PBA subjects suggests that the CNS-LS is an important assessment tool for PBA for the following reasons: (a) It is a validated, clinically relevant measure for PBA patients, (b) CNS-LS scores have been demonstrated to show a good correlation with PBA episode rates, and (c) CNS-LS scores are reproducible within patients, are less prone to outliers and better approximate a normal distribution, a requirement for valid statistical inference. For these reasons, and based on the fact that episode counts and the CNS-LS were both found to be statistically significant and clinically meaningful in the Study 123 study for the Zenvia 30/10 and Zenvia 20/10 doses, Avanir has included both measures to describe the efficacy of Zenvia in the product label.

Reviewer's Conclusions: A statistically significant effect of DM 30 mg/Q 30 mg (Study 106) and DM 30 mg/Q 10 mg and DM 20 mg/Q 10 mg (Study 123) over placebo, as assessed by laughing and crying episodes, and CNS-LS, have been demonstrated.

In Study 102, as outlined in the Approvable Letter, the Agency acknowledged that the contrasts between the combination and the individual components reached statistical significance on the protocol specified primary outcome measure, the CNS-LS. However, on the secondary measure of episode counts using several models, results of comparison between the combination product and DM alone do not achieve statistical significance whether data for one outlier patient was included or not in one analysis, and nominal significance if the outlier data are included but not if outlier data are excluded in another analysis. The Agency stated in the Approvable Letter that the Applicant "will need to adequately address this concern before we can conclude that the combination policy has been met. It is also worth noting that this finding raises the possibility that a much lower exposure to DM than is achieved with this product might be effective in controlling laughing or crying episodes in these patients."

The Applicant argues that since the contrasts between the combination and the individual components reached statistical significance in favor of the combination on the CNS-LS, and since CNS-LS is an important tool for the assessment of PBA, that Study 102 does demonstrate the combination product (DM/Q) was more effective than either DM or Q administered alone. In the minutes of the post-action meeting between the Agency and the Applicant held on 2/26/07, the Agency stated "we will accept that Zenvia (30 mg Q formulation) has been shown to be more effective than either component." In Study 123, the mean change from baseline in CNS-LS scores across visits range from -6.77 to -8.59 (mean -7.89) for DM 30 mg/Q 10 mg and from -6.27 to -8.89 (mean -7.76) for DM 20 mg/Q 10 mg, which are similar to -7.67 observed for DM 30 mg/Q 30 mg in Study 102 but clearly higher than -5.15 for DM alone and -4.68 for Q alone. In addition, in Study 123, efficacy as assessed by CNS-LS paralleled that assessed by laughing and crying episodes. Furthermore, efficacy in Study 123 was demonstrated using lower exposure of DM (resulting from a lower Q dose), particularly for the DM 20 mg/Q 10 mg dose, than the dose (DM 30 mg/Q 30 mg) used in either Study 102 or Study 106 (see Table 4 and Table 5 in section 4.4.3 of this review).

Overall, the Applicant demonstrated the efficacy of different formulations of DM/Q – a higher Q dose formulation (DM 30 mg/Q 30 mg) in Study 106 and Study 102, and lower Q dose formulations (DM 30 mg/Q 10 mg and DM 20 mg/Q 10 mg) resulting in a lower DM exposure in Study 123. The applicant also met the requirements of 21CFR300.50 (Fixed-combination prescription drugs for humans). Dose selection between DM 30 mg/Q 10 mg and DM 20 mg/Q 10 mg is discussed further below under a separate subheading.

Cardiac Effects of Quinidine, Drug Interactions involving CYP2D6 and CYP3A4 enzymes, Atrial Fibrillation/Atrial Flutter, (b) (4) Polymorphisms

In the Approvable Letter, the Agency noted the following concerns regarding the cardiac effects of Q, drug interactions involving CYP2D6 and CYP3A4 enzymes, atrial fibrillation/atrial flutter, (b) (4) polymorphisms.

Numerous findings in the safety database raise serious concerns about the safety in use of this product.

First, we note that quinidine is well known to be associated with serious ventricular arrhythmias, including torsades de pointes. These arrhythmias can occur at low quinidine doses in susceptible patients (e.g., those with congenital prolonged QT syndrome), but higher quinidine doses can also be associated with serious cardiac events, presumably in a dose related fashion.

In this regard, we note the results of Study 119, your thorough QT study. This study demonstrated that at the daily dose of the combination that you propose, the drug is associated with a maximum mean paired placebo and baseline subtracted QTcF of about 10 msec, with a 95% upper bound one-sided confidence interval of about 15 msec (we presume this increase is directly a result of the quinidine component), and that the prolongation persists throughout the dosing interval. You suggest that this is of little consequence because Agency guidance states that this degree of increase is "inconclusive" regarding its clinical significance. However, we disagree with your conclusion. In our view, quinidine poses a known proarrhythmic risk, and as such this degree of QT interval increase raises serious concerns. In this regard, we also note that, in this study, over 4% of the EKGs in patients who received the recommended dose had QTc intervals that were increased between 30-60 msec above baseline, compared to 0.9% of those EKGs in the placebo arm.

Further, and equally, if not more, disturbing, the maximum mean paired placebo and baseline subtracted QTcF was about 18 msec (upper bound of the 95% CI was 25 msec) at the supratherapeutic dose of the combination, which was only twice that of the recommended dose (at this dose, 7.2% of the EKGs were associated with an increase in QTc of 30-60 msecs). Given that quinidine is metabolized by CYP3A4, and given the availability and use of numerous 3A4 inhibitors, we expect that, in practice, many patients may be exposed to levels of quinidine that were achieved with the supratherapeutic dose used in this study (or higher), and that these levels will be associated with serious cardiovascular consequences. In addition, we have performed PK/PD modeling of quinidine's effect on the QT interval; we have determined that 5% of the population who receives the recommended dose of Zenvia would be expected to experience a prolongation of the QTc interval of about 19 msec.

In addition, quinidine's potent inhibition of CYP2D6 poses additional risks, especially in this vulnerable population. For example, we are aware of a death in the database that appeared likely related to elevated plasma levels of oxycodone, a substrate for both 3A4 and 2D6. The patient was also receiving, in addition to Zenvia, a potent 3A4 inhibitor (clarithromycin). The combination of 3A4 and 2D6 inhibition was likely responsible for the dangerously elevated oxycodone levels in this patient. We also note that at least one other patient in the data base was receiving oxycodone, Zenvia and another potent 3A4 inhibitor (erythromycin). These cases highlight the dangers that are potentially associated with the use of Zenvia, especially when it is used in association with other metabolic inhibitors and CYP2D6 substrates, as would be expected in the relatively sick populations in whom PBA may occur. We are very concerned that labeling statements warning against such use would not be entirely successful in preventing such concomitant drug use.

Finally, quinidine is known to be particularly dangerous in patients who are moving in and out of atrial flutter/fibrillation, due to the risk both of torsades de pointes, and of supraventricular tachychardia from quinidine effects on atrio-ventricular conduction. In this regard, we note at least one case in the database of a patient who entered the trial with a history of atrial flutter who became symptomatic (i.e., experienced palpitations) on treatment. The population in whom PBA is common may include many such patients, and we are concerned that these patients will be particularly vulnerable to serious ventricular arrythmias if treated with Zenvia.

Applicant's Response: To address the FDA concerns regarding QTc prolongation and ventricular arrhythmia with the DM 30 mg/Q 30 mg combination dose, Avanir has developed a lower Q dose formulation, Zenvia 30/10 and Zenvia 20/10. Decreasing the Q dose resulted in lower exposure to Q (Q C_{max} 62 ng/mL for DM 30 mg/Q 10 mg compared to 177 ng/mL for DM 30 mg/Q 30 mg). Based on the results of the clinical thorough QT studies, Q in DM/Q has the potential to prolong the QTc interval but these changes are concentration-related and predictable, and compared to DM/Q at higher Q dose formulations (30 to 60 mg), DM 30 mg/Q 10 mg offers an improved safety margin. On the basis of cardiac safety assessment in clinical studies, the risk

for QT prolongation leading to ventricular tachycardia or torsades de pointes with the lower formulations of Zenvia will be minimized.

On the basis of the results of the interaction study with desipramine, which is primarily metabolized by CYP2D6 (approximately 8-fold increase in exposure when DM/Q was added), co-administration of ZENVIA with drugs that undergo extensive CYP2D6 metabolism may result in altered drug effects, due to accumulation of parent drug. Consequently, we have proposed labeling language to caution physicians about the concomitant administration of Zenvia with drugs that undergo extensive CYP2D6 metabolism and indicate that dose modification of the concomitant medication may be required.

In clinical studies, the incidence of AEs was higher in PBA patients receiving DM/Q with inhibitors of CYP2D6 or CYP3A4, or opiates/opioids. These findings might reflect greater use of concomitant medications by patients with more severe illness or with comorbidities, who are also more likely to report disease-related symptoms as AEs than patients with milder disease and not using concomitant medications. The latter hypothesis is supported by the observation that the incidences of AEs were also increased in PBA patients receiving placebo medication in combination with these concomitant medications in controlled studies. The number of TEAEs in patients receiving other concomitant medications (CYP2D6 and CYP3A4 inducers, CYP2D6 substrates and thiazides) was low. PBA patients receiving drugs known to affect the QT interval and other drugs known to affect ECG did not show increased incidences of cardiac AEs compared to control treatments.

Q is a substrate for CYP3A4, and its plasma concentrations may be increased if administered with other drugs that are CYP3A4 inhibitors such as ketoconazole. However, Q is given in very low doses with Zenvia administration (10 mg/dose), and effective plasma concentrations are well below the antiarrhythmic therapeutic range of 2 to 5 μg/mL; the mean Q concentration in PBA subjects receiving Zenvia treatment is 0.05-0.06 μg/mL. Although CYP3A4 inhibition is unlikely to raise Q concentrations into the antiarrhythmic therapeutic range, or even, 3-fold to the concentrations utilized with the previous DM/Q formulations, the potential interaction should still be taken into consideration when prescribing Zenvia. Caution should be exercised when prescribing strong CYP3A4 inhibitors and we have proposed labeling language to address this concern.

At the dose level in Zenvia, Q has the potential to prolong the QTc interval on the electrocardiogram. Therefore, the prescribing information provides cautionary language about prescribing Zenvia to patients taking drugs known to prolong the QT interval, including Q. Patients with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy were not included in clinical trials of Zenvia, so we have also included cautionary language in the label regarding the use of Zenvia in patients with these conditions. When used for cardiac indications, Q has proarrhythmic risks in addition to torsades de pointes including atrioventricular (AV) conduction block. The prescribing information recommends that Zenvia be contraindicated in patients with complete AV block without implanted pacemakers, or patients who are at high risk of complete AV block.

We have designed elements of REMS to reduce the occurrence of serious drug-drug interactions with Zenvia.

There is no documented evidence in the literature or from Avanir's integrated clinical data that subjects with atrial fibrillation or atrial flutter are at increased risk of arrhythmias when treated with Q.

The percentage of PBA patients who are CYP2D6 poor metabolizers (PMs) is small and is anticipated to parallel that observed in the overall population. PMs do not require the Q component of Zenvia to achieve plasma levels of DM that are comparable to that of extensive metabolizers (EMs) who have taken Zenvia. However, evidence from the Zenvia safety database suggests that there is no difference in the safety profile of Zenvia by CYP2D6 metabolizer status. Laboratory tests are available to determine CYP2D6 phenotype, and we have included a statement to this effect in the Zenvia product labeling to remind physicians of such tests.

Reviewer's Conclusions: The new DM/Q formulations with a lower Q dose (10 mg) results in approximately one-third the exposure of Q in the previous DM/Q formulation with a higher Q dose (30 mg). DM 30 mg/Q 10 mg clearly prolongs QT interval. There is some merit to the Applicant's argument that the degree of QT prolongation is finite and predictable. In the double-blind phase of Study 123, the mean QTcF interval change from baseline to Day 84 was greater in the DM 30 mg/Q 10 mg group (4.8 msec) than in either the DM 20 mg/Q 10 mg (1.0 msec) or the placebo group (1.0 msec), and more subjects had increases from baseline to Day 84 in QTcF of 30–60 msec in the DM 30 mg/Q 10 mg group (11/110; 10%) compared with the DM 20 mg/Q 10 mg (2/107; 1.9%) and placebo groups (4/109; 3.7%). There were no subjects with a change from baseline of $\geq$ 60 msec in QT interval. There were no significant effects on the PR and QRS intervals suggesting that the pro-arrhythmic potential of DM/Q 10 mg on sinus, AV and ventricular conduction is low. Although Q prolongs QTc interval, such an effect appears finite and predictable, and can be mitigated via labeling. See IRT review for labeling recommendations.

Assessments of all the 92 deaths in the safety database for sudden deaths (potentially due to cardiac arrhythmia) by the Adjudication Committee of Cardiologists (see section 7.3.5 of this review) are limited because they are post-hoc analyses. Across the integrated clinical studies, there were no subjects who experienced a cardiac arrhythmia as a serious adverse event (SAE). There were several subjects who discontinued due to treatment-emergent adverse events (TEAE) of cardiac arrhythmia. Many of them had pre-existing risk factors that confounded causality assessment. There appeared to be a temporal relationship between the TEAEs of cardiac arrhythmia and DM/Q in some subjects; however, some of them were on DM/Q formulations with high Q dose, and others continued on in the study without apparent recurrence of the events in question. In the pooled controlled trials, compared to the pooled placebo group, the incidence of subjects experiencing any cardiac arrhythmia was greater in the DM/Q 30 mg group, and comparable in the DM/Q 10 mg group; however, the numbers of subjects experiencing each cardiac arrhythmia was quite small. The occurrence of any cardiac arrhythmia in DM/Q 10 mg doses was very infrequent.

Cardiac arrhythmia can potentially manifest as syncope/pre-syncope and or palpitations. Across the integrated clinical studies, there were few subjects who experienced syncope/ presyncope or palpitations as an SAE or resulted in discontinuation. Many of them had pre-existing risk factors that confounded causality assessment. Most (3/4) of the subjects who experienced SAEs continued on in the study without apparent recurrence of syncope or palpitations. In the double-blind phase of Study 123, compared to placebo group (1/109 = 0.9%), subjects who experienced syncope/presyncope were numerically higher in the DM 30 mg/Q 10 mg (4/110 =3.6%) and comparable in the DM 20 mg/Q 10 mg group (1/107 = 0.9%). The Applicant concludes that there is no documented evidence in the literature (based on an extensive literature review conducted by the Applicant's consultant cardiologist, (b) (6)) or from Avanir's integrated clinical data that subjects with atrial fibrillation or atrial flutter are at increased risk of arrhythmias when treated with Q. A consult with the Cardio-Renal Division for expert assessment of the cardiac risk of DM/Q has not yet been finalized. In addition to the assessment, recommendations on labeling are expected from the consultants.

In clinical studies, the incidences of AEs in subjects receiving DM/Q with inhibitors or substrates of CYP2D6 or CYP3A4, or opiates/opioids, or drugs known to affect QT interval, were similar between DM/Q dose groups and placebo group, or were numerically too small for meaningful between-treatment group comparisons. I agree that the potential for altered drug effects resulting from co-administration of Zenvia with drugs that undergo extensive CYP2D6 metabolism (based on the results of the interaction study with desipramine), and the potential interaction between Zenvia and strong CYP3A4 inhibitors need to be communicated in the label.

Respiratory Failure, Survival in amyotrophic lateral sclerosis (ALS) patients, and Imbalance in Deaths between Treatment Groups in Study 123.

In the Approvable Letter, the Agency noted the following concern regarding respiratory failure and survival in ALS subjects. In addition, there are safety concerns arising from data in Study 123 showing excess deaths in the DM/Q 10 mg dose groups compared to placebo group.

> We note the occurrence of 48 deaths in the open-label experience, many in ALS patients, presumably due to respiratory failure. However, you have not provided evidence that this number of deaths, from this cause, would be expected in this time period in this population. We are concerned that the very high levels of DM produced by Zenvia in this vulnerable population may have contributed to respiratory depression in these patients. We also note the occurrence of a relatively large number of respiratory depression and failure events, categorized as serious adverse events. You will need to address our concern that this product may be associated with respiratory depression and failure in this vulnerable population (we include in this vulnerable population other populations in whom PBA may occur, including patients with stroke and Alzheimer's Disease, groups in whom you have obtained very little clinical experience).

Applicant's Response: The data in the Avanir clinical program indicates that the proportions of deaths at various time points from ALS diagnosis are expected based on the reported literature. The ten fatal outcomes in Study 123 appear to have occurred as result of respiratory complications secondary to the progression of the underlying neurodegenerative disorder, ALS, a finding that is entirely consistent with the medical literature. The lower number of deaths in the

placebo group compared to active treatment can in large part be due to imbalances in the time from diagnosis to randomization among groups. In Study 107, the survival rate was consistent with the expected survival rate for subjects with this disease, and was comparable to data from published studies. On the basis of these analyses, there is no evidence to suggest an increased mortality rate for ALS subjects in Zenvia trials.

Reviewer's Conclusions: I agree with the Applicant that compromised respiratory function as the most frequent cause of the 10 deaths among the ALS subjects in Study 123 is in accordance with expectations in ALS subjects. Although it is true that the mortality rate, on face, is statistically comparable among the treatment groups in the double-blind phase of Study 123 [DM/Q 10 mg group 6/133 = 0.045 (95% CI: 0.02 to 0.09); placebo 1/64 = 0.016 (95% CI: 0.004 to 0.08)], this study is not powered to detect differences in mortality, if any, between study groups. In particular, since respiratory-related deaths and adverse events are very common occurrence in ALS subjects, a drug-related effect on these events may be difficult to detect unless the study is large and appropriately designed to detect a clinically meaningful effect.

Any attempt to explain the mortality rate in the double-blind phase of Study 123 by comparing to the mortality rates in other cohorts is limited because of the inherent shortcomings of such comparison. Importantly, the use of a concurrent placebo control in a clinical trial, as is the case in Study 123, provides the maximum ability to distinguish efficacy and safety effects caused by the study drug from those resulting from the underlying disease or intercurrent illness. The absolute numbers of deaths in the double-blind phase of Study 123 are quite small such that the theoretical occurrence of one additional death in the placebo group (incidence, 2/64 = 0.03) would nearly halve the relative risk of death in any DM/Q 10 dose group from 2.8 (0.045/0.016) to 1.5 (0.045/0.03). The chance of the observed result (6 deaths in DM/Q versus 1 death in placebo) is 0.27 if there is no difference in risk of death between drug and placebo arms.

Nevertheless, concern remains that the imbalances in the deaths between the treatment groups in the double-blind phase of Study 123 are more than a chance finding. DM/Q could potentially alter the rate of progression of ALS or affect the disease in other ways leading to excess deaths in the study drug group compared to placebo group. In this context, deaths may not necessarily occur acutely to study drug exposure (i.e., can occur later during exposure or even after discontinuation) and evidence of respiratory involvement prior to study enrollment in the majority of deaths, by itself, is not reassuring as study drug could further increase the rate of decline in these subjects.

The Respiratory Report (see section 7.3.5 of this review) states that the lower number of deaths in the placebo group compared to active treatment can in large part be due to imbalances in the time from diagnosis to randomization among treatment groups. There are clear imbalances in the median time from diagnosis to randomization between treatment groups at baseline (12 months in DM 30 mg/Q 10 mg group; 9.5 months in DM 20 mg/Q 10 mg group; 6.5 months in placebo group) that could potentially explain the mortality differences between treatment groups, as the duration of disease is an important independent predictor of death in ALS. However, the conclusion that the lower number of deaths in the placebo group compared to active treatment can be due to imbalances in the time from diagnosis to randomization among groups is valid if the time from diagnosis to randomization in the deaths also cluster around the mean/median in

each treatment group. The absolute numbers of ALS deaths in each treatment group are small, and it is difficult to extrapolate the outcome associated with a group mean/median to an individual case within that group.

Bulbar onset is another important independent predictor of mortality in ALS. At randomization in Study 123, the proportion of ALS subjects with bulbar onset is evenly distributed among the treatment groups.

Deaths (most commonly respiratory) and non-fatal respiratory events in ALS are likely a continuum of the spectrum of respiratory dysfunction in ALS subjects. Therefore, it would be important to assess the incidence of non-fatal respiratory-related adverse events in the DM/Q 10 group compared to the placebo group. In the controlled studies of ALS, the incidence of subjects with any non-fatal respiratory-related SAE or TEAEs in the placebo group was comparable to or *higher* than in DM/Q 10 mg groups, weakening the concern that the imbalance in ALS deaths between treatment groups in Study 123 is more than a chance finding.

Overall, the data do not support the conclusion that the imbalance in ALS deaths between treatment groups in Study 123 is more than a chance finding. The imbalance in the number of deaths noted in Study 123 should be included in section 6 of the label.

Aspiration, Nausea, Vomiting and Somnolence

In the Approvable Letter, the Agency noted the following concern regarding aspiration, nausea, vomiting and somnolence.

> We also note a 6% incidence of vomiting in the patients treated with Zenvia in Study 102 compared to no vomiting in the other treatment groups. We further note a 33% incidence of nausea in the Zenvia treated patients in this study, compared to 6-8% in the other treatment groups. These findings are particularly worrisome in vulnerable populations because of the risk of aspiration, especially in those patients with difficulty swallowing, in whom the risk of aspiration is even greater. Further, we believe the risk for aspiration may be especially great in these patients, given the 13% incidence of somnolence in the Zenvia treated patients compared to 3% in the DM patients and 0 in the quinidine-treated patients in Study 102 (we also note a 5% incidence of somnolence compared to 1% in the placebo group in Study 106).

Applicant's Response: In ALS, respiratory disorders and respiratory-related complications are common and respiratory failure has been reported to be the most common cause of death. In 3 controlled clinical studies with DM/Q for the treatment of PBA in subjects with underlying ALS and multiple sclerosis (MS), 2 DM/Q-treated subjects with ALS and 1 placebo subject with ALS reported aspiration/aspiration pneumonia. In all 3 subjects, the respiratory event was reviewed and was determined to be related to the patient's underlying disease and not related to study drug. There was no evidence to suggest that the few cases of aspiration/aspiration pneumonia were associated with DM/Q treatment. With respect to possible risk factors for aspiration/aspiration pneumonia, the incidence of nausea, vomiting and somnolence were low and similar to placebo. An analysis of nausea over time revealed that the incidence of nausea decreased after the first week of therapy. In contrast, the few events of vomiting that occurred

did not show a time-related pattern, which suggests that there is no correlation between events of nausea and vomiting with events of aspiration/aspiration pneumonia. The incidence of nausea, vomiting, and somnolence during the OLE was generally comparable to that or lower than that observed in Zenvia-treated subjects during the DB phase of the study.

Reviewer's Conclusions: Among controlled trials, the number of subjects experiencing aspiration or aspiration pneumonia was numerically too small for meaningful between-treatment group comparisons. Across the integrated clinical trials there were a total of 9 subjects (8 of them with ALS) who experienced aspiration or aspiration pneumonia. Eight of these events were serious, three of which were fatal; the remaining 6 subjects recovered. In each of these subjects, there is no apparent occurrence of nausea, vomiting, dysphagia, somnolence or sedation in close proximity to the occurrence of aspiration or aspiration pneumonia. From the narratives, it is difficult to deduct causality, or exclude either the study drug or intercurrent illnesses as a potential cause of the event in question with any reasonable degree of confidence. However, the odds of developing aspiration or aspiration pneumonia in subjects who experienced any TEAE of nausea, vomiting, dysphagia, somnolence or sedation is 13.5 times that in subjects who did not experience any of these TEAEs, and appears driven mainly by dysphagia. The events of dysphagia, nausea and somnolence occur evenly among treatment groups in ALS subjects in controlled studies. Therefore, overall, the data do not support the conclusion that the events of aspiration or aspiration pneumonia are likely related to the study drug.

Falls and Dizziness

In the Approvable Letter, the Agency noted the following concern regarding falls and dizziness.

> We are also greatly concerned about the risk of falls in these patients. We have re-calculated the incidence of falls in both controlled trials, including those patients whose adverse event was categorized as an injury, but who clearly sustained their injuries as a result of falls. In Study 102, the incidence of falls was 13% in the Zenvia group, 12% in the DM group, and 0 in the quinidine group. A similar re-calculation of the incidence of falls in Study 106 yielded a 5% incidence of falls in the Zenvia group compared to a 3% incidence in the placebo group. The number of falls in Study 106 was too small to serve as a reliable indicator of risk in the MS population; however, Study 102 suggests that Zenvia increases the risk of fall in the ALS population.
>
> Further, we calculated the incidence of an increased risk of falls in both studies, by adding the incidences of events that could reasonably be considered to predispose to falls. In this analysis, we combined various event terms, including disoriented, dizzy, lightheaded, shaky, unstable, etc. (we acknowledge that these calculations presuppose that each event reported occurred in separate individuals; this, of course, may not be true). When these events were combined, the incidence of events in Study 102 that could be considered to predispose to falls was 43% in the Zenvia group, 27% in the DM group, and 5% in the quinidine group. In Study 106, the incidence of these predisposing events was 41% in the Zenvia group, and 23% in the placebo group. Although the specific terms to include in these calculations could be a matter for discussion, we believe grouping appropriate terms is clinically meaningful (an examination of dizziness alone shows a 20% incidence in the Zenvia group, a 15% incidence in the DM group, and a 3% incidence in the quinidine group in Study 102 and a 26% incidence in the Zenvia group and a 9% incidence in the placebo group in Study 106). These numbers are disturbing, given the potential serious consequences of falls in these populations. Please address these concerns.

Applicant's Response: Analyses conducted on the data from the pivotal Study 123 trial strongly suggest that the incidence of falls in PBA subjects is related to the underlying neurological condition of the patient and is not caused by Zenvia use. The combined incidences of falls and injuries that clearly could have been caused by a fall (when falls were not reported) in Zenvia-treated subjects within a primary disease category were either equal to or lower than those observed in placebo subjects. There was no evidence to suggest an association between falls and dizziness. The overall incidence of dizziness was slightly higher in subjects in the Zenvia 30/10 and Zenvia 20/10 dose groups compared to placebo, but ameliorated after the first two weeks of therapy. Based on these results, physicians and patients should inform patients to exercise caution until they know how Zenvia may affect them. To this aim, Zenvia product labeling includes dizziness as a Warning and Precaution and dizziness is included as one of the topics that physicians should discuss with patients for whom they prescribe Zenvia.

Reviewer's Conclusions: Data from the pooled controlled trials suggest an excess of fall or fall-related events in the DM/Q groups compared to placebo, particularly in the MS subjects. However, in the double-blind phase of Study 123, the incidences of falls are comparable between treatment groups. Data do not show a clear pattern for the incidence of falls over time. Five subjects experienced falls as an SAE, some of them with small subdural hematomas. All of these SAEs occurred in the open-label Study 107 many days after exposure to study drug began, and all subjects recovered from the event. The fact that most subjects continued on in the study with no apparent recurrence, on face, appears reassuring, but details are lacking whether these subjects continued to independently ambulate or have become wheelchair-bound. Subject-discontinuations too occurred mostly in the open-label studies. From the narratives, it is difficult to deduct causality, or exclude either the study drug or intercurrent illnesses as a potential cause of the event in question with any reasonable degree of confidence.

Controlled data show a clear dose-related increase in the incidence of dizziness compared to placebo group. Dizziness was most frequently reported within the first two weeks of therapy, leveling off with continued exposure, and did not occur in temporal proximity to the events of falls. All the SAEs of dizziness and most of the discontinuations occurred in open-label studies. All subjects who experienced SAEs and almost all subjects who discontinued recovered. Across the integrated clinical trials, the odds of a fall in subjects who experienced any TEAE of dizziness is only 1.46 times that in subjects who did not experience any TEAE of dizziness.

Overall, the data do not support the conclusion that falls are likely related to the study drug. There is a clear dose-related effect of DM/Q on dizziness. While this dose-related effect of DM/Q on dizziness can seemingly influence falls, data do not support such a conclusion.

Hepatotoxicity

In the Approvable Letter, the Agency noted the following concern regarding hepatotoxicity.

Although we acknowledge that there do not seem to be important systematic laboratory changes induced by treatment with Zenvia, we are particularly concerned about the occurrence of significant hepatic injury in patient 136-9004 who became jaundiced after 2 ½ months of treatment with study drug. This patient had significant elevations in AST, ALT, and bilirubin, with a mild increase in alkaline phosphatase. No viral or chemical cause for these changes was found, and, although this patient was receiving treatment with numerous concomitant medications, none would have been expected to have caused this injury. The pattern of injury seen in this patient is very similar to that seen with other drugs known to result in hepatic failure. For these other drugs, the incidence of hepatic failure in general use is about 10% of the incidence of the finding of hepatic injury in clinical trials (e.g., in this case, the incidence of the finding of hepatic injury is about 1/1000 patients; the incidence of hepatic failure in general use, if this case is drug related, would be expected to be about 1/10,000). We recognize that, typically, such cases of drug-induced serious liver injury occur in the setting of a general, systematic increase in liver function tests, which did not occur here. Nonetheless, this case is troubling, and raises the concern that Zenvia is hepatotoxic. Please address this concern. We note that, if this patient was receiving active drug, it will be critical to closely follow him, to determine if an alternative underlying explanation for these findings emerges (e.g., episodes of alcohol abuse, underlying malignancy, etc.).

Applicant's Response: Zenvia is a novel combination product containing DM and Q, both of which are metabolized primarily by liver enzymes. To date, there is no evidence that DM usage, even at high doses, is associated with liver toxicity. At the recommended maintenance dose of Q for cardiac arrhythmias (200-400 mg 3 to 4 times daily = 600-1600 mg/day), a few cases of hepatotoxicity have been reported. The daily dose of Q (20 mg) in Zenvia is 1-3% of a recommended antiarrhythmic dose of Q. Data obtained from Study 123, a controlled, pivotal, Phase III study in PBA subjects revealed no evidence of hepatotoxicity with Zenvia use. The incidence of hepatobiliary AEs (including elevated liver enzymes) was low and most of the events were mild or moderate in intensity. Many subjects who showed elevated liver enzymes were taking concomitant medication known to increase liver function parameters (Rilutek, Avonex or Copaxone) as a part of the treatment of their underlying condition (ALS or MS). Mean laboratory parameters of ALT, AST, alkaline phosphatase, and GGT were comparable at baseline and showed no treatment-related differences at Day 84. The laboratory shift data from the controlled and uncontrolled PBA studies showed no remarkable trends in subjects exposed to the DM/Q combination. Thus, the evidence from the Avanir clinical program suggests that Zenvia does not cause drug related liver injury.

Reviewer's Conclusions: Across the clinical studies, there was one case of hepatitis (#109-136-004) occurring after 77 days of exposure to DM 45 mg/Q 30 mg. Although gall bladder stone is a potential explanation for this event, a relationship between DM/Q and hepatitis can not be entirely excluded. This subject was not rechallenged; however, recovered and did well thereafter with no recurrence of liver problems. Even assuming the worst case scenario that there was indeed a causal relationship between hepatitis and DM/Q, it appears that this adverse event is not only monitorable but, importantly, reversible. There was one subject (#123-106-724) with ALT elevated $\geq$ 3 times the upper limit of normal and bilirubin elevated $\geq$ 2 times the upper limit of normal in the context of infectious mononucleosis. Liver enzymes returned to normal after about 2-3 weeks. A negative rechallenge with DM/Q (subject went on to complete the study) argues against a relationship with DM/Q, and in favor of infectious mononucleosis as the underlying etiology.

Other than the two subjects noted above, there were no other subjects who died due to, or experienced a non-fatal hepatic-related SAE or abnormal liver function values as an SAE in the integrated clinical studies (Pool 1). In Pool 1, discontinuations due to hepatic AEs (abnormal liver function tests reported as AEs) occurred in 8 subjects. Most of these abnormal elevations of liver function tests occurred early during exposure between Study Day 28 – 50, and importantly, all subjects recovered. Controlled trials showed no excess of hepatic or abnormally elevated liver function tests in the DM/Q groups as compared to the placebo group.

In the integrated clinical studies, there were a two subjects who had ALT or AST values ≥ 10 times the upper limit of normal but without a concomitant ≥ 2-fold the upper limit of normal increase in total bilirubin (see section 7.4.2 of this review). One subject had bilirubin values > 2 times the upper limit of normal but without accompanying elevation of ALT or AST values.

Data in the pooled controlled studies did not show any differences between treatment groups for median change from baseline in liver function parameters. However, in Study 123, subjects in DM /Q 10 mg group who had shifts in ALT, AST and total bilirubin from normal at baseline to abnormally high at End of Study (Day 84) were numerically higher than in the placebo group.

Overall, based on the available data contained in safety database, the potential for DM/Q to cause severe drug induced liver injury is low.

PBA indication – Global versus restricted in ALS and MS subjects only

In the Approvable Letter, the Agency noted the following concern regarding the populations with PBA that need to be adequately studied.

> Further, we note, again, that numerous vulnerable populations (e.g., patients with Alzheimer's disease) have not been adequately studied, and we believe that they will need to be before the drug can be approved.

Applicant's Response: The Applicant refers to the meeting between the Agency and the Applicant on 7/16/07, during which the Agency told the Applicant that "It may be possible for you to gain approval of Zenvia without studying Alzheimer patients, but only for a more limited indication in PBA, as thought to occur mainly in MS, ALS, stroke, and traumatic brain injury. We would consider a global claim for PBA based on a single adequate study in patients with MS and a single adequate study in patients with ALS." The Applicant then summarizes the positive efficacy results of Study 123 in both ALS and MS subjects, and provides a summary table of subjects with PBA in the database by primary diseases: ALS = 46% (439/946), MS = 39% (371/946), stroke = 5% (45/946), traumatic brain injury = 2% (23/946), dementia = 2% (17/946) and other primary diseases with PBA = 5% (51/946). In light of agreements with FDA and the evidence of efficacy and safety demonstrated in controlled clinical studies of PBA, the Applicant is seeking a global claim for the treatment of PBA. The Adverse Reactions and Clinical Studies sections of the proposed product labeling identify the underlying conditions of the PBA subjects who were studied in the Zenvia development program. (b) (4)

(b) (4)

The Applicant believes that these measures sufficiently mitigate the risk and will help to ensure the appropriate use of Zenvia.

Reviewer's Conclusions: The safety experience in PBA subjects with primary diseases other than ALS or MS that the Applicant refers to in the above response was all accrued in the open-label Study 107. There were no controlled studies which enrolled PBA with diseases other than ALS or MS.

The Applicant states that PBA is estimated to occur in 49% of patients with ALS, in 10% of patients with MS, in 11% of patients 1 year after suffering a stroke, and in 11% of patients after a traumatic brain injury. One published review (*Wortzel HS, 2008*) reports that it occurs in 50% of patients with ALS, in 10% of patients with MS, in 5-11% of patients with traumatic brain injury, in 11-34% in patients with post-stroke (most occurring within the first year), and 10-74% in Alzheimer's disease. The accuracy of these estimates is uncertain; however, assuming the most conservative estimates to be reasonably accurate, a global claim for the treatment of PBA will significantly expand the population of subjects with PBA to those with other neurological illnesses other than ALS or MS (see table below).

Table 1: Prevalence of subjects with PBA in various underlying neurological diseases in the US

Disease		Prevalence of disease in US (population: 300 million)	Percentage of subjects with PBA	Number of subjects with PBA in US
Amyotrophic lateral sclerosis		2,400 – 22,140 [a]	49-50%	1,200 - 11,070
Multiple Sclerosis	Northern US	90,000 - 240,000 [b]	10%	9,000 - 24,000
	Southern US	18,000 - 42,000 [b]		1,800 – 4,200
Stroke		750,000[c]	11-34%	82,500 - 255,000
Alzheimer's disease		2,000,000[d]	10-74%	200,000 - 1,480,000
Traumatic brain injury		400,000[e]	5-11%	20,000 - 44, 0000

[a]Prevalence rates of ALS are between 0.80 – 7.38 per 100,000 (Katirji B, 2002; page 418)
[b]The disease has a prevalence of less than 1 per 100,000 in equatorial areas; 6 to 14 per 100,000 in the southern United States and southern Europe; and 30 to 80 per 100,000 in Canada, northern Europe, and the northern United States (Adams and Victor, 2009, chapter 36).
[c]750,000 new or recurrent strokes occur every year in the US (Bradley WG, 2008; page 1165)
[d]In the year 2008, there were estimated to be more than 2 million persons with Alzheimer disease in the United States (Adams and Victor, 2009, chapter 39).
[e]An estimated 500,000 Americans are admitted to hospitals yearly following cerebral trauma; of these, 75,000 to 90,000 die and even larger numbers, most of them young and otherwise healthy, are left permanently disabled (Adams and Victor, 2009, chapter 35). Thus, approximately 400,000 Americans survive cerebral trauma.

There are safety data for a limited number of subjects with PBA and neurological diseases other than ALS or MS accrued in the open-label Study 107. However, subjects with several of these diseases are generally older and often have intercurrent illnesses – cardiac disorders in particular, and without adequate controlled safety data, it would be difficult to distinguish the effects of the study drug from either the intercurrent illnesses or the effects of the underlying disease. Data from the open-label Study 107 (table below) show that, using person-time as the denominator, the incidences of PBA subjects with any TEAE or SAE vary from one underlying neurological illness to another. Although the numbers of subjects with other neurological illnesses enrolled in the open-label Study 107 are small, these data suggest that safety in subjects with PBA in one underlying condition can not necessarily be extrapolated to subjects with PBA in another

neurological condition. Therefore, I recommend the approval of Zenvia for the treatment of PBA in ALS and MS subjects only.

Table 2: Incidences of subjects experiencing any TEAE or SAE using subjects at risk or person-time exposure as denominator, by underlying diseases in open-label Study 107

	ALS		MS		Other		AD		Stroke		TBI	
Subjects at risk (N)	**176**		**223**		**73**		**14**		**45**		**21**	
	n	%	n	%	n	%	n	%	n	%	n	%
Any TEAE	172	97.7	209	93.7	69	94.5	10	71.4	42	93.3	19	90.5
Any SAE	93	52.8	46	20.6	23	31.5	4	28.6	6	13 3	3	14.3
Exposure in person-years (pt-yrs)	**185.3**		**390.4**		**97.1**		**9.0**		**53.4**		**26.5**	
	n	n/pt-yrs	n	n/pt-yrs	n	n/pt-yrs	n	n/pt-yrs	n	n/pt-yrs	n	n/pt-yrs
Any TEAE	172	0.93	209	0.54	69	0.71	10	1.11	42	0.79	19	0.72
Any SAE	93	0.51	46	0.12	23	0.24	4	0.44	6	0 11	3	0.11

ALS= amyotrophic lateral sclerosis; MS = multiple sclerosis; AD = Alzheimer's disease; TBI = traumatic brain injury;
Other = PBA in primary lateral sclerosis, Parkinson's disease, Parkinson's syndrome, corticobasilar degeneration, frontotemperal dementia, bulbar motor neuron disease, bulbar palsy, cerebral palsy, hydrocephalus, movement disorder, progressive bulbar palsy, progressive supranuclear palsy and spinocerebelar ataxia.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; Reviewer's analysis of EX, DM and AE datasets.

Dose Selection

In the Approvable Letter, the Agency noted that lower doses of both Q and DM components of the combination may result in a product that is equally effective and potentially much safer.

We also again note that lower doses of both the quinidine and DM components of the combination may result in a product that is equally effective, and potentially much safer, than the current proposed product (we remind you that the results of the analyses of the laughing/crying episodes at least suggest that [substantially] lower exposures of DM may control these events). We recognize that you have chosen your dose of quinidine based on a finding that this dose converted 8/8 extensive metabolizers of 2D6 (EMs) into poor metabolizers (PMs), as assessed by urinary metabolic ratio. We remind you, however, that a 10 mg dose of quinidine converted 6/7 EMs to PMs. It is clear that the lowest dose of quinidine that will give the desired effect is much to be preferred; this is similarly true for the dose of DM, and further dose finding to identify the lowest effective doses of each component should be undertaken.

Applicant's Response: Avanir designed the Study 123 to evaluate the efficacy, and pharmacokinetics of two lower dose combinations of Zenvia (Zenvia 30/10 and Zenvia 20/10). Study 123 demonstrated that the lower dose formulation (Zenvia 30/10 and Zenvia 20/10) is efficacious in reducing PBA episodes and provides a better overall safety profile than the higher dose formulation of the combination product DM/Q (DM 30 mg/Q 30 mg). There was a suggestion that ZENVIA 30/10 may provide additional benefit for some patients, based upon the earlier time of improvement in the CNS-LS score, slightly higher percentage of patients achieving onset of action, earlier time to a statistically significant difference in the number of episode free days, and a slightly higher clinical response compared with ZENVIA 20/10. (b) (4)

Reviewer's Conclusions: Study 123 results show that the lower Q dose formulations (DM 30 mg/Q 10 mg and DM 20 mg/Q 10 mg) is efficacious in reducing PBA episodes and provides a better overall safety profile than the higher dose Q formulation of the combination product, DM 30 mg/Q 30 mg. The overall efficacy of DM 20 mg/Q 10 mg is either similar to DM 30 mg/Q 10 mg, or marginally *better* in some endpoints/time points, or marginally *worse* in some endpoints/time points (discussed in section 6.1.8 of this review). The availability of two dose formulation without a clear advantage of one over the other in efficacy may potentially lead physicians to prescribe the larger dose in the belief that it may have better efficacy. Such a scenario has potential safety implications. Although the differences between DM 20 mg/Q 10 mg and DM 30 mg/Q 10 mg doses in safety were not consistent (discussed in section 7.5.1 of this review), the preponderance of evidence in the overall safety data suggest that DM 20 mg/Q 10 mg has a better safety profile than DM 30 mg/Q 10 mg. Therefore, I recommend the approval of DM 20 mg/Q 10 mg dose (b) (4)

Risk Management

Under the "Abuse Liability Comments" section of the Approvable Letter, the Agency provided advice regarding educating patients on storage of Zenvia, and that the Applicant provide information on proposed monitoring of databases for abuse and misuse of the product.

(b) (4)
you should educate patients on the safe storage of Zenvia in the home, away from children, adolescents and from anyone for whom the product has not been prescribed.

You should provide information on how you plan to collect, analyze and evaluate the information collected by monitoring various databases for abuse and misuse of the product; (b) (4) (b) (4) and propose interventions if abuse or misuse of the product is determined.

Applicant's Response: (b) (4) The following should be noted: if a future submission applies to a reformulation of the Zenvia components, dextromethorphan and quinidine, CSS will need to reevaluate all data collected by the Sponsor in order to assess the potential for abuse of the new product." The Agency also provided the following comment in written response to the pre-NDA meeting background package on 11/6/09: (b) (4)

(b) (4)

(b) (4)

Reviewer's Conclusions: The Agency's advice was provided in the context of the abuse/misuse evaluation of DM/Q formulations, and therefore, this section is appropriately addressed by the Controlled Substance Staff review. (b) (4)

1.3 Recommendations for Post-market Risk Management Activities

No recommendations for post-marketing risk management activities.

1.4 Recommendations for Post-market Studies/Clinical Trials

No recommendation for post-marketing studies/clinical trials.

2 Introduction and Regulatory Background

Pseudobulbar affect (PBA), also known in the literature as pathological laughing and crying or involuntary emotional expression disorder, is defined as outbursts of involuntary, uncontrollable, stereotypical episodes of laughing or crying (*Bradley WG, 2008; page 111*). These episodes do not appear to reflect the true underlying emotional state of the patient. These events occur in patients with underlying neurological disorders or injury. The estimated occurrence of PBA in various underlying neurological illnesses is summarized in Table 1. The underlying pathophysiology is poorly understood, however, is believed to involve pathways regulating affect.

PBA appears to be a part of a wider-range syndrome called pseudobulbar syndrome, which is characterized by inability to forcefully close the eyes, open and close the mouth, chew, swallow, phonate, and articulate and of course, by PBA. In this context, not surprisingly, among patients with ALS, PBA occurs more frequently in those with bulbar involvement.

2.1 Product Information

Zenvia is a combination product containing two approved drugs: dextromethorphan hydrobromide USP (DM) and Q sulfate USP (Q). The Applicant uses the term "Zenvia" when referring to the lower Q dose formulations: DM 20 mg/Q 10 mg and DM 30 mg/Q 10 mg; and the term "DM/Q" when referring to other formulations of DM and Q (such as DM 30 mg/Q 30 mg). In this review, I use the term "DM/Q 10 mg" to refer to the combined DM 20 mg/Q 10 mg

and DM 30 mg/Q 10 mg dose groups, "DM/Q 30 mg" to refer to the any DM dose given with Q 30 mg, and "DM/Q" to refer to any DM and Q dose combination.

Zenvia was formerly known as AVP-923 or Neurodex. Zenvia is provided as an immediate release solid oral dosage form (hard gelatin capsule) in (b) (4) DM 20 mg/Q 10 mg, (b) (4) This combination product is not approved in any country.

DM is considered to be the component that is responsible for controlling PBA. However, higher levels of DM appear necessary to produce this effect than can typically be obtained with the widely available over-the-counter antitussive products taken at the labeled doses (30-180 mg/day). This limitation of the oral route is because DM is effectively metabolized by CYP2D6. Therefore, Q, a potent inhibitor of CYP2D6, is also given in combination with DM to competitively inhibit the metabolism of DM such that there are increased plasma levels of DM. Q also increases the duration of action of DM by prolonging its half-life. The mechanism of action of DM in controlling PBA is largely unknown but is postulated to be via the $sigma_1$ and NMDA receptors.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there is no approved treatment for PBA. However, combinations of DM and Q have been used off-label for the treatment of PBA in subjects with ALS (*Miller RG, 2009*). Other treatments for PBA include off-label use of tricyclic antidepressants (amitriptyline), selective serotonin reuptake inhibitors, L-dopa/carbidopa, lithium, mirtazepine (Remeron) and venlafaxine (Effexor).

2.3 Availability of Proposed Active Ingredient in the United States

DM (D-3-methoxy-N-methylmorphinan) has been marketed as an over-the-counter non-opioid antitussive agent in numerous syrups and lozenges, or in combinations with antihistamines and other agents for many years in the United States. DM is the D-isomer of the codeine analog methorphan; however, unlike the L-isomer, it has no analgesic or addictive properties and does not act through opioid receptors. The ***average adult dosage of dextromethorphan hydrobromide is 10 to 30 mg three to six times daily (30-180 mg/day)***. Its half-life is about 11 hours. MAO inhibitor (isocarboxazid, phenelzine, procarbazine, rasagiline, seligiline, tranylcypromine) use is contraindicated within 14 days to avoid the risk of serotonergic syndrome. Although DM has been given a statutory exclusion as a scheduled drug, there have been recent concerns regarding the abuse potential of DM.

Q, a diastereomer of the antimalarial quinine, is marketed as an antiarrhythmic (class IA) and antimalarial drug. Q is drug of choice for new onset (< 1 year) atrial fibrillation/flutter when direct current cardioversion is not desirable, maintenance of sinus rhythm after cardioversion in such patients, and suppression of life-threatening ventricular arrhythmias such as ventricular tachycardias. The dosage range of Q sulfate for adults is from 400 to 4000 mg/day; however,

typical antiarrhythmic doses are 200 to 400 mg 3 to 4 times daily (600-1600 mg/day). The elimination half-life of Q is approximately 6-8 hours in adults. The average therapeutic range is 6 to 15 μmol/L (2 to 5 μg/mL) of plasma. Toxicity is almost certain at concentrations above 25 μmol/L (8 μg/mL).

2.4 Important Safety Issues with Consideration to Related Drugs

Dextromethorphan:

The DM monograph (Martindale) states that hypersensitivity reactions such as a fixed-drug reaction, urticaria, angioedema have been reported. Severe and sometimes fatal reactions have been reported after use of DM in patients receiving MAOIs. The monograph warns about the possibility of interactions with inhibitors of CYP2D6. Excitation, confusion, and respiratory depression may occur after overdosage. DM should not be given to patients at risk of developing respiratory failure.

Quinidine:
The Q label includes a black box warning regarding increased risk of mortality in trials of antiarrhythmic therapy for non-life threatening arrhythmias. Other warnings include proarrhythmic effects, paradoxical increase in ventricular rate in atrial flutter/fibrillation, exacerbated bradycardia in sick sinus syndrome, vagolysis and thrombocytopenia. Precautions include use with caution in patients with heart block, and drug interactions.

Qualaquin (quinine sulfate) was approved under NDA 021799 on 8/12/05. Available as 324 mg capsules, the dosage for uncomplicated malaria in adults is 648 mg every 8 hours (1,944 mg/day) for 7 days. Since Qualaquin was approved on 8/12/05, the Agency had become aware, through a review of Adverse Event Reporting System (AERS) data, of adverse events of serious and life-threatening hematologic reactions, including thrombocytopenia and hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP) associated with the use of Qualaquin. Chronic renal impairment associated with the development of TTP has been reported. Although the approved indication of Qualaquin is for uncomplicated malaria, the Agency noted that the majority of quinine used in the United States is for the prevention or treatment of leg cramps. The Agency considered this information to be "new safety information", and under section 505-1(b) of FDCA, issued a box warning (reproduced below), and a Medication Guide (warning patients of the serious side effects or even death). This is further discussed in 7.4.6 of this review.

WARNING:
QUALAQUIN® use for the treatment or prevention of nocturnal leg cramps may result in serious and life-threatening hematologic reactions, including thrombocytopenia and hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP). Chronic renal impairment associated with the development of TTP has been reported. The risk associated with QUALAQUIN use in the absence of evidence of its effectiveness in the treatment or prevention of nocturnal leg cramps outweighs any potential benefit (see WARNINGS).

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

The clinical development program of Zenvia for the treatment of PBA was conducted under IND 56,954. The original NDA 21879 for DM 30 mg/Q 30 mg (propriety name was Neurodex) for the treatment of PBA was submitted on 1/30/06. After completing the review, an Approvable Letter was issued on 10/30/06. Between the issuance of the Approvable letter and the Complete Response submission on 4/30/10, there were several regulatory interactions with the Applicant. These interactions included the Agency's review and feedback on Study 123 protocol under Special Protocol Agreement. Important areas of agreement, advice, etc are referred to in the relevant sections of this review.

2.6 Other Relevant Background Information

There was no other relevant background information for this NDA.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In conducting the safety of this NDA, I assessed the consistency of the relevant data contained in this NDA by an audit. I reviewed approximately 15% of Case Report Forms that were new to the Complete Response, comparing the information in these CRFs to the corresponding narrative summaries for individual patients, source documents and datasets. Other than a few discrepancies, I did not see any systemic problem between the source data and the transcribed data that has the potential to undermine the integrity of the data.

3.2 Compliance with Good Clinical Practices

The Applicant attested to conducting the clinical trials submitted for review in compliance with the applicable regulations. I did not find evidence of unethical conduct on the part of the Applicant or the study site personnel with the exception of Site 301.

The Applicant conducted Good Clinical Practice (GCP) audits at 9 (17.3%) of the 52 sites in Study 123. Concerns were raised about GCP and protocol compliance at Site 301 (PI: Dr. Soniza Alves Leon; Rio de Janeiro, Brazil) since source data from this site was not always complete or accurate at the time of the subjects' visits. A total of 7 (7/326 = 2.1%) subjects had enrolled at this site; 5 were ALS subjects and 2 MS subjects. The Applicant executed a Correction Action Plan which included re-training of site personnel at this site. However, Site 301 continued to raise concerns regarding data collection and recording. Therefore after all

subjects were completed or discontinued, a second audit – a 100% quality control data review, was performed on data from all enrolled subjects (with the exception of Subject #123-301-504 whose records were not accessible) at this site.

The audits revealed four critical areas of concern at this site.

> The source data was not always contemporaneous, complete or accurate at the time of the subjects' visits, despite repeated instructions to the PI to provide appropriate and timely documentation when documentation gaps were identified during monitoring visits. Every medical chart reviewed contained a significant amount of addenda for each study visit, and in many cases, the addenda were written several months after the corresponding study visit thereby compromising the integrity and reliability of the data.
>
> Several patient diaries contained comments about their state of health during study visits that appeared to be potential adverse events (AEs) (e.g. headache, insomnia, muscle aches, influenza, and fever). In several cases, no source documentation was available to indicate that the PI inquired about the diary entries or assessed the symptoms for possible AEs. These apparent AEs were not captured in the CRF. In other instances, the AEs were captured, but the PI did not assess their severity, relationship to study drug, resolution, etc. Therefore, a concern arose about under-reporting of AEs and/or incomplete data regarding AEs.
>
> Because of the apparent under-reporting of AEs, there is a consequential concern that the concomitant medications that may have been used to treat the symptoms identified in the patient diaries were also not captured in source documentation or the CRF. In many cases, there was no evidence in the patient chart that the PI inquired about the use of any concomitant medications.
>
> Some data discrepancies were found between the source documentation and the CRF. In some cases, the discrepancies were corrected in the source documentation, but data clarification forms were not provided to data management, despite multiple visits to the site by the Applicant to review source documents and query the PI to obtain missing and incomplete data, and to obtain clarifications for discrepant data. Therefore, the database continues to have inaccurate data.

During my audit of the narratives and AE datasets, I found the following discrepancies for one subject (#123/301/501) at this site. The narrative for this subject states that sometime between 4/8/09 and 4/14/09 the patient's diary revealed the events of headache, dry mouth, swallowing difficulty, abundant salivation; additionally, sometime between 4/15/09 and 4/21/09, the patient experienced mental confusion, disorientation and occasional hallucinations, fell and hit his head. However, the events of headache, swallowing difficulty, abundant salivation and fall/head injury were not captured in the AE or ADAE datasets. Since all clinical studies were completed without any cut-off dates for this Complete Response submission, I asked the Applicant for an explanation of why these events were not included in these dataset. In response (dated 6/25/10), the Applicant states that study database was locked on 7/30/09. A 100% quality control data audit was conducted after the database lock (10/27/09 – 10/29/09). Additional information (containing the above reported AEs) on this subject was then obtained which was not recorded in the original CRF due to the database lock but was included in the narrative. In response to my request, the Applicant states that to the best of the Applicant's knowledge, there is no other subject for whom AEs were obtained after the database lock and therefore not included in the AE dataset. Additionally, a statistical efficacy analysis excluding subjects enrolled at Site 301 was also done, and is discussed in section 6.1.10 of this review.

DSI inspections: On 6/17/10, the Division of Neurology Products sent a consult to the Division of Scientific Investigations (DSI) with a request to inspect of any two of the three sites for Study 123 that were tied for the largest number of subjects enrolled (#101, #106 and #121). Site #301 was not included in this request because the Applicant had already performed a 100% data review audit, subject enrollment at this site was fairly evenly distributed among treatment groups, and exclusion of the data from this site did not change the efficacy results. The reason for the request to DSI was because Study 123 is the only controlled study evaluating the safety and efficacy of the proposed two DM/Q 10 mg formulations, underscoring the need to evaluate the integrity of the data prior to approval.

DSI completed the inspection at Site 101 (Dr. Daniel Wynn, Northbrook, IL). At this site 22 subjects were screened, 18 were randomized, and 15 completed the study. No Form 483 was issued. However, minor transcription errors in drug accountability counts and in the number of laughing/crying episodes in a few subjects were noted. In 3 (3 out of 18) subjects, the number of inappropriate laughing/crying episodes was incorrectly recorded on the respective CRF. Subject #101-706 diary for the 7 days prior to Visit 5 showed 3 episodes but was incorrectly recorded as 0. Subject #101-715 diary for the 7 days prior to Visit 4 showed 3 episodes but was incorrectly recorded as 2. Subject #101-719 diary for the 7 days prior to Visit 5 showed 2 episodes but was incorrectly recorded as 0. Reviewer's comments: These minor discrepancies in three subjects, that too at only one visit each, do not materially affects the efficacy conclusions.

DSI also completed inspection at Site 121 (Dr. Erik Pioro, Cleveland, OH). At this site 24 subjects were screened, 22 were randomized, and 20 completed the study. Five subjects at this site reported AEs in the their diaries which were not recorded in the respective case report forms: #121-508 coughed at lot; #121-512 used a nebulizer and got shaky, also had feet swelling and dizziness; #121-514 experienced leg cramps and abdominal pain; #121-515 had swollen feet, nausea, bad stomach cramps and diarrhea; #121-505, a female of childbearing potential, did not receive a pregnancy test during double-blind phase. Reviewer's comments: most of these events occurred frequently in Study 123, and their underreporting by few subjects do not change the safety conclusions.

3.3 Financial Disclosures

With the exception of one investigator, all investigators have no disclosable financial interests related to the Applicant of the covered study – Study 123 in this Complete Response. The Applicant licensed a series of patents owned by the non-profit organization Center for Neurologic Study (CNS) located in San Diego, CA, which will provide market exclusivity for the future sales of Zenvia under NDA 21-879. (b) (6) and is also the principle investigator for clinical research conducted through the non-profit organization.

Site 103 enrolled 5 of the 326 total patients randomized in the study (1.5%). Data from this site is included in the study results. The Applicant states that based on the small percentage of patients randomized, the inclusion or exclusion of the data generated from this site should not have any

significant impact on overall safety and efficacy outcome of the study. Further, (b) (6) did not participate in any other activity (e.g., study design, data management and/or analysis, consultant, advisor, speaker, etc.). Reviewer's comments: I agree with the Applicant.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There were no major chemistry, manufacturing and controls issues to preclude approval.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

There were no major pharmacology/toxicology issues to preclude approval.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action of DM in controlling PBA is largely unknown but is postulated to be via the $sigma_1$ and NMDA receptors.

4.4.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted.

4.4.3 Pharmacokinetics

Table 3 summarizes the PK data of DM, Q and their metabolites.

DM is metabolized predominantly by CYP2D6 to dextrorphan, and to a lesser extent (10%) through N-demethylation by CYP3A4 to 3-methoxymorphinan. Dextrorphan is further metabolized by CYP3A4 to 3-hydroxymorphinan. Approximately 7-10% of Caucasian and 3-8% of blacks lack the capacity to effectively metabolize CYP2D6 substrates and are classified as "poor metabolizers".

Q is metabolized by CYP3A4 to 3-hydroxyquinidine, and to a lesser extent by 2C9 to N-oxidation. Since Q is an inhibitor of CYP2D6, it is given in combination with DM to maximally inhibit CYP2D6. The PK data of Q in different DM/Q formulations across several clinical trials (see table below) shows the C_{max} and AUC are generally dose-proportional.

Table 3: PK data of DM, Q and their metabolites

Parameter	Analyte			
	Dextromethorphan	Dextrorphan	Quinidine	3-Hydroxyquinidine[13†]
C_{max} (ng/mL)	104 (24%)	107 (33%)	160 (19%)	20 (13 – 34)
T_{max} (h)	6 (40%)	33 (60%)	2 (12%)	Approximately 1.5
$t_{½}$ (h)	16.4 (23%)* in EM[12]	Not available	8	9 (38%)

* The $t_{½}$ value is based on the literature.
† Values are adjusted to a 25 mg dose, following a single-dose.
Source: NDA Complete Response 4/30/10; Study 125 study report; page 23

Assessment of dose-linearity for DM using data from pooled PK studies shows that 30 mg, 45 mg and 60 mg DM doses in the presence of Q 30 mg are approximately dose-proportional (Table 4). PK Data from Study 123 (Table 5) show that the exposure for DM 30 mg when given with Q 10 mg is lower than when given with Q 30 mg (Table 4).

Table 4: Mean C_{max} and AUC of different DM doses on Day 8 when given with Q 30 mg in pooled PK studies

Study	DM Dose	C_{max} (ng/ml)	Mean AUC $_{0-12}$ (ng*hr/ml)
99-AVR-101	30 mg	95.5 (21)	1049 (23)
99-AVR-103	45 mg	141.5 (53)	1438 (59)
	60 mg	191.8 (24)	1963 (31)

Source: Dr. Ju-Ping Lai's review.

Table 5: Summary of plasma levels of DM, dextrorphan, and Q, by Visit, double-blind phase of Study 123

	Plasma Levels (ng/mL)	
Visit/Analyte	AVP-923-30 (n = 110)	AVP-923-20 (n = 107)
Visit 3 (Day 29)		
Dextromethorphan		
n	91	76
Mean (SD)	80.42 (42.817)	47.76 (27.554)
Dextrorphan		
N	91	76
Mean (SD)	145.80 (60.449)	86.33 (35.209)
Quinidine		
n	89	75
Mean (SD)	53.48 (30.201)	51.59 (32.980)
Visit 4 (Day 57)		
Dextromethorphan		
n	96	77
Mean (SD)	81.93 (45.726)	53.18 (36.573)
Dextrorphan		
n	96	76
Mean (SD)	145.27 (62.759)	92.75 (37.139)
Quinidine		
n	94	75
Mean (SD)	58.67 (29.579)	58.09 (38.953)

Source: NDA Complete Response 4/30/10; Module 5.3.5.3: Study 123 study report, Table 11-4, page 76

Similarly, for Q, assessment of dose-linearity using data from pooled PK and clinical studies shows that 25 mg, 50 mg and 75 mg Q doses in the presence of DM 30 mg are approximately dose-proportional (Table 6). PK Data for Q from different DM/Q formulations is summarized in Table 7.

Table 6: Mean Cmax and AUC of different Q doses on Day 7 when given with DM 30 mg in Study 100

Quinidine Dose*	C_{max} (µg/ml)	AUC_{last} (µg*hr/ml)
25 mg	0.16 (31)	0.92 (40)
50 mg	0.29 (35)	1.71 (30)
75 mg	0.41 (12)	2.48 (11)

* The amount of Q used Study 100 was calculated on the basis of quinidine sulfate, although the quinidine drug substance contained approximately 13.6% dihydroquinidine. Therefore the 25 mg Q dosage strength is equivalent to approximately 28.8 mg Q.
Source: Dr. Ju-Ping Lai's review.

Table 7: PK data for Q in different DM/Q formulations

	Study 05-AVR-119	Study 07-AVR-123		Study 08-AVR-126	Study 07-AVR-125
PK Parameter (units)	***DM 30 mg/ Q 30 mg***	***Zenvia 20/10***	***Zenvia 30/10***	***Zenvia 30/10***	***Zenvia 30/10***
C_{max} (ng/mL)	177	54	62	59	66
AUC_{0-12} (ng·h/mL)	1320	401	471	527	488

Source: NDA Complete Response 4/30/10; module 1.11.3, Efficacy information amendment, Table 2, page 15

5 Sources of Clinical Data

The primary sources of the clinical data were the clinical trials conducted by the Applicant which are contained in the databases of the Complete Response, the original NDA submission and amendments to the NDA. Several of the amendments to the NDA were in response to requests for additional information and analyses from this reviewer during the review process.

5.1 Tables of Studies/Clinical Trials

The DM/Q combination product development program was conducted under IND 56,954. The development program consisted of a total of 19 clinical studies. Of these 19 studies, 12 were Phase I and the remaining 7 were Phase II/III. There was 1 investigator-sponsored clinical study (CNS-93). In addition, the Applicant conducted 3 population PK meta-analyses of data from several completed clinical studies (Study 117, Study 127 and Study 128). A summary table of clinical studies with design, sample size, dose range and duration is below.

Table 8: Summary of clinical studies

Study No./ Status	Study Type	Design and Subject Population	Age range/ Sex (M%/F%)	Subjects Exposed to DM/Q	DM Daily Dose (mg)	Q Daily Dose (mg)
Applicant-sponsored studies						
99-AVR-100 Completed	Phase 1 PK dose-ranging	Two-part open-label, single-dose DM (Part I) and RD multiple-dose DM30+diff Q doses (Part II) Healthy volunteers	20-86 Part I: (50/50) Part II: (48/52)	39	60	5-150
99-AVR-101 Completed	Phase 1 PK	Single and multiple dose of DM30+Q30 Healthy volunteers	36-74 (50/50)	10	60	50
00-AVR-103 Completed	Phase 1 PK in EM and PM; determine lowest dose of Q to inhibit 2D6	OL, PG (DM 60 and 45), single and multiple dose interaction. Healthy volunteers	DM60: 19-47 (38/62) DM45: 19-60 (21/12)	48	90, 120	60, 90, 120
04-AVR-111 Completed	Phase 1 Food effect on PK	RD, single –dose, 2-way XO Healthy volunteers	19-53 yrs (61/39)	18	30	30
04-AVR-112 Completed	Phase 1 PK Drug interaction with desipramine	Sequential treatment. Impact of DM30/Q30 on steady state PK of desipramine Healthy volunteers	19-42 (64/36)	15	60	60
04-AVR-115 Completed	Phase 1 PK Hepatic impairment	OL, multiple-dose, PG (healthy, mild, mod) Healthy volunteers and patients with mild and moderate hepatic impairment	44-62 (52/48)	21	60	60
04-AVR-116 Completed	Phase 1 PK Renal impairment	PK of DM30/Q30 in Healthy volunteers and patients with mild and moderate renal impairment	44-73 (52/48)	21	60	60
05-AVR-119 Completed	Phase 1 QT study	RD, DB, PC, two doses (DM 30 /Q 30 & DM60/Q60) with moxifloxacin Healthy volunteers (PMs excluded)	19-55 (75/25)	36	60, 120	60, 120
06-AVR-121 Completed	Phase 1 PK Drug interaction with paroxetine	OL, RD, PG (paroxetine X12 days→DM30/Q30; reverse in other arm) Healthy volunteers	19-55 (78/22)	27	60	60
06-AVR-122 Completed	Phase 1 PK Drug interaction with memantine	OL, RD, PG (memantine X11 days→DM30/Q30; reverse in other arm) Healthy volunteers	19-55 (75/25)	51	60	60
07-AVR-125 Completed	Phase 1 PK of different combinations and regimen of DM+Q	RD, DB, PC Healthy volunteers	21-61 (55/24)	79	60, 90, 120	15, 20, 30, 60
08-AVR-126 Completed	Phase 1 QT study	RD, DB, PC, XO, 7 doses of DM 30 /Q 10 or placebo, one dose moxifloxacin Healthy volunteers (EMs only)	19-45 (68/32)	50	30, 60	10, 20

01-AVR-105 Completed	Phase 2 Open-label dose-escalation safety (n=36)	OL treatment with DM30/Q30. Start 1 cap/day, increase weekly to 4 caps/day. Patients with DPN pain	22-78 (53/47)	36	30, 45, 60, 90, 120	30, 45, 60, 90, 120
04-AVR-117* Completed	**Population PK analysis** (Total n=170; HV=53; PBA=117)	PK analysis of DM/Q in Healthy subjects and in PBA patient population	HV=19-69 PBA=25-82	-	-	-
09-AVR-127@ Completed	**Population PK analysis** (Total n=133; HV=109; PBA=24)	Meta-analysis of modeling of the inhibition by Q of the metabolism of DM to dextrorphan; HV and PBA	HV=19-61 PBA=29-65	-	-	-
09-AVR-128# Completed	**Population PK and PD analysis** (Total n=702; HV=56; PBA=616)	Meta-analysis of modeling of the QT changes and occurrence of Adverse Effects. HV and PBA	HV=19-55 PBA=21-82	-	-	-
99-AVR-102 Completed	Phase 3, 28-day, Controlled efficacy and safety (n=140)	RD (1:1:2) , DB, AC, PG (DM30, Q30, DM30/Q30) ALS patients with PBA	33-82 (62/38)	70	60	60
02-AVR-106 Completed	Phase 3, 12-wk, Controlled efficacy and safety (n=150)	RD (1:1) , DB, PC, PG (DM30/Q30, placebo) MS patients with PBA	21-71 (17/83)	76	60	60
02-AVR-107 Completed	Phase 3,open-label, 52 wks (n=553) with option for extension (n=262)	OL treatment with DM30/Q30 Patients with PBA	18-86 (42/58)	553&	60	60
04-AVR-109 Completed	Phase 3, 12-wk, Controlled efficacy and safety (n=379)	RD (1:1:1), DB, PC, PG (DM45/Q30, DM30/Q30, Placebo). Patients with DPN pain	28-86 (62/38)	256	60, 90	60
07-AVR-123-DB Completed	Phase 3, 12-wk, Controlled efficacy and safety (n=326)	RD (1:1:1) , DB, PC, PG (DM30/Q10, DM20/Q10, placebo) ALS (n=197) and MS (n=129) patients with PBA	25-80 (46/54)	217	40, 60	20
07-AVR-123-OLE Completed	Phase 3, open-label extension, 12-wk (n=253)	OL treatment with DM30/Q10 ALS (n=146) and MS (n=107) patients with PBA~	26-80 (54/46)	253	60	20
Investigator-sponsored study						
CNS-93 Completed	Phase 2 Controlled efficacy (4 wks each period with 1 wk washout)	DB, XO , PC single center, two-period; DM30/Q75 versus placebo Patients with PBA^	33-72 (67/33)	12	60	150

ALS = amyotrophic lateral sclerosis; DM = dextromethorphan; MS = multiple sclerosis; PBA = pseudobulbar affect; DPN = diabetic peripheral neuropathy; PK = pharmacokinetics; Q = quinidine; RD = randomized; PC = placebo-controlled; AC = active controlled; XO = crossover; OL = open-label; PG = parallel group; EM = extensive metabolizers; PM = poor metabolizers; HV = healthy volunteers.
All subjects in Study 99-AVR-101 were previously enrolled in Study 99-AVR-100. Study 02-AVR-107 included a total of 99 PBA patients who were previously enrolled in Study 99-AVR-102 or Study 02-AVR-106.
~Optional study extension: will allow subjects who feel as if they are benefiting from treatment to continue treatment past Week 52
^CNS-93 enrolled 8 patients with ALS and 4 patients with other neurological diseases (1 MND, 1 MSA, 1 PLS and 1 unclassified neurological disease)
*Plasma concentrations of DM, DX and Q and urine concentrations of DM and DX from nine clinical studies were combined
@Meta-analysis of Study 07-AVR-123 Study 08-AVR-125and Study 08-AVR-126
#Meta-analysis of Study 99-AVR-102, Study 02-AVR-106, Study 05-AVR-119, Study 07-AVR-123 and Study 08-AVR-126
&553 subjects were enrolled but one subject was never dosed; therefore only 552 subjects were included in the safety population.
Source: NDA Complete Response 4/30/10; module 5.3.5.3.ISS, modified from Table 1, page 18; Module 5.2 Tabular Listing, Table 5.2-1, pages 1-25

The definitive clinical studies that supported the original NDA submission of 1/30/06 were conducted using the DM 30 mg/Q 30 mg combination product. Included in the original NDA were data from and/or reports of 7 Phase I studies, 2 controlled clinical studies (Study 102 and Study 106), 2 open-label clinical studies (Study 107 and Study 105) and the investigator-sponsored clinical study (CNS-93). The thorough QT study (Study 119) was completed in 11/18/05 and the study report submitted along with the 120-day safety report in the first cycle.

In response to the Approvable Letter of 10/30/06, the Applicant conducted Study 123 to provide the primary efficacy and safety data for the new DM 20 mg/Q 10 mg and DM 30 mg/Q 10 mg

dose formulations. The Applicant conducted a new thorough QT study (Study 126) using lower dose of Q (10 mg), and other additional Phase I clinical studies. Thus, in addition to the data submitted in the Original NDA submission, the Complete Response of 4/30/10 includes the data from and the final study reports of Study 123, 1 completed open-label study (Study 107) and 5 clinical studies:

- ***Study 107***: open-label safety study of DM 30 mg/Q 30 mg in subjects with PBA. This study was ongoing at the time of original NDA submission with a data cut-off date of 10/31/05 for the first cycle. It was completed on 6/7/07.
- ***Study 121***: drug interaction study of DM 30 mg/Q 30 mg with paroxetine (study dates: 6/13/06-7/15/06).
- ***Study 122***: drug interaction study of DM 30 mg/Q 30 mg with memantine (study dates: 6/6/06-11/10/06).
- ***Study 125***: PK study with several new dose formulations and dose regimens (study dates: 11/5/07-2/9/08).
- ***Study 126***: cardiac repolarization study with DM 30 mg/Q 10 mg (study dates: 11/14/08-12/24/08)
- ***Study 109***: a diabetic peripheral neuropathic pain study with DM 30 mg/Q 30 mg and DM 45 mg/Q 30 mg (study dates: 6/21/05-2/12/07).

5.2 Review Strategy

I reviewed primarily the data and the information contained in the Complete Response of 4/30/10. However, in order to highlight the differences or similarities between the new data (data in the Complete Response that is new compared to original NDA) and the prior data (original NDA), throughout this review I present data for the higher Q (DM 30 mg/Q 30 mg) dose which is essentially the data from trials supporting the original NDA versus the new data for the lower Q (DM 20 or 30 mg/Q10 mg). Dr. Ronald Farkas was the primary reviewer for the Original NDA of 1/30/06. Where applicable, I used citations from Dr. Farkas' review.

The Applicant submitted the Complete Response and subsequent amendments using the eCTD format, (b) (4). I also reviewed secondary sources of clinical data (i.e., relevant INDs /NDAs, other labels, literature and references) in assessing major concerns for DM/Q as suggested by its pharmacology or with pharmacologically related drugs. When assessing important adverse events, I reviewed both the Applicant's narrative description of individual patients and the associated CRF and medical records that were submitted.

Given the heterogeneous (ALS and MS) group of subjects comprising Pool 3, there is a potential for the study drug to either exacerbate symptoms that are more commonly experienced by ALS or MS subjects, or a potential to cause adverse events that may be somewhat specific to the underlying primary disease. Therefore, in each of the sections of the review, I discuss the safety for the combined study population and for each primary disease population.

Finally, I discuss whether the Applicant adequately addressed all the safety concerns as communicated in the Approvable Letter of 10/30/06, and whether or not the new data contained in the Complete Response of 4/30/10 alter the benefit-risk assessments for the new DM/Q formulations using the lower dose of Q (10 mg) as compared to the prior DM/Q formulations using higher doses of Q (30 mg).

5.3 Discussion of Individual Studies/Clinical Trials

There were ***three controlled efficacy trials of PBA subjects***: Study 102, Study 106 and the double-blind phase of Study 123. Studies 102 and 106 were submitted in support of the original NDA and were reviewed in the first cycle. A higher dose of Q (DM 30 mg/Q 30 mg) was used in both of these studies. In response to the Agency's suggestion (Approvable Letter 10/30/06) that a lower dose of Q be evaluated, the Applicant conducted Study 123 using a lower dose of Q (DM 20 mg/Q 10 mg and DM 30 mg/Q 10 mg).

Study 102: Study 102 was a multicenter (17 centers, all in the US) Phase II/III, double-blind, controlled (no placebo), parallel group study in which 140 subjects with ALS and PBA were randomized (2:1:1) to DM 30 mg/Q 30 mg (n = 70), DM 30 mg alone (n = 33) or Q 30 mg alone (n = 37). Subjects took assigned dose twice a day for 28 days (there was no dose titration). DM and Q were chosen as control groups because they are the components of DM/Q, and to meet the requirements of 21CFR300.50 (Fixed-combination prescription drugs for humans). The study included a Screening Visit and 3 other clinic visits on Days 1, 15 and 29. Day 29 was the last day the subject was on study and could occur anywhere between the mornings of Day 26 – 32. Eligible subjects were male or female subjects aged 18-80 years, with ALS or probable ALS by Word Federation of Neurology (WFN) criteria, with clinical history of PBA, Vital capacity of ≥ 50%, and a CNS-LS score on Day 1 ≥ 13.

Efficacy variables:

- *Primary efficacy variable* was the *CNS-LS score*. For a discussion of the CNS-LS, see section 6.1.1. Assessments were made during clinic visits at Screening, Days 1 (Baseline, before taking the first dose), 15 and 29.
- *Secondary efficacy variables* included counts of laughing/crying episodes, Quality of Life and Quality of Relationships. Subjects at baseline had to have a CNS-LS score of ≥ 13. Subjects recorded daily in a diary the date and time each dose was taken, the number of laughing/crying episodes experienced, and any AEs that had occurred since the last visit. Diaries were collected on Day 15 and at the time of study completion

All efficacy variables involving a change were determined by the baseline score being subtracted from the mean of the non-missing scores on Days 15 and 29. The primary analysis was the ANCOVA on the average of the Day 15 and 29 scores, adjusted for center and baseline CNS-LS score.

Results: ITT population comprised of all randomized subjects who are not "poor metabolizers" of CYP2D6. Subjects randomized to Q had approximately 20% greater incidence of bulbar ALS

(21/34 = 61.8%) compared to DM/Q (29/65 = 44.6%) or DM (14/30 = 46.7%). There were no significant baseline differences in the weekly episodes of laughing/crying between the treatment groups. The contrasts between the combination and the individual components in the modified ITT population reached statistical significance on CNS-LS – the protocol specified primary outcome: DM 30 mg/Q 30 mg versus DM (mean change -7.67 and -5.15, respectively; p = 0.0016); DM 30 mg/Q 30 mg versus Q (mean change -7.67 and -4.68, respectively; p = <0.0001).

The Applicant did not collect the actual baseline episode count. At baseline, each subject estimated historically the number of laughing or crying episodes per week. The following table from Dr. Massie's review (original NDA submission) summarizes the laughing/crying counts at baseline and during on-treatment. One outlier (subject # 08-016) in the DM group experienced a total of 3,010 episodes (average >100 per day), more than 9 times the number of episodes in the next highest count. Statistical results for comparison between DM 30 mg/Q 30 mg versus component group did not reach statistical significance: DM 30 mg/Q 30 mg versus DM, p = 0.017 (outlier included) and 0.343 (outlier excluded); DM 30 mg/Q 30 mg versus Q, p = 0.107.

Table 9: Laughing/crying episodes in Study 102

	Historically Reported Number of Episodes per Week				Number of Episodes Per Week During Treatment			
	N	Mean	Median	Std Dev	N	Mean	Median	Std Dev
Treatment Group AVP-923	70	23.1	13.0	31.2	67	9.4	2.5	20.3
Q	37	20.6	14.0	19.1	37	13.0	6.3	14.1
DM	33	36.0	12.0	63.8	33	34.4	4.8	125.8
DM (excluding outlier)	32	36.0	11.0	64.8	32	12.8	4.7	19.7
DM (impute 398=next worst count overall for outlier)	33	36.0	12.0	63.8	33	15.3	4.8	24.2

Source: Dr. T. Massie's statistical review (8/31/06), Table 9, page 26.

Study 106: Study 106 was a 12-week, multicenter, Phase III, double-blind, placebo-controlled, parallel group study in which 150 subjects with MS and PBA were randomized (1:1) to DM 30 mg/Q 30 mg (n = 76) or placebo (n = 74). There were a total of 22 centers in two countries: 18 centers in US and 4 in Israel. Subjects took assigned dose twice a day for 85 days (there was no dose titration). The study included a Screening Visit and other clinic visits on Days 1, 15, 29, 57 and 85. Eligible subjects included male or female subjects aged 18-68 years, with MS or probable MS (McDonald criteria) and with clinical history of PBA, and a CNS-LS score on Day 1 ≥ 13.

Efficacy variables:

- *Primary efficacy variable* was the *CNS-LS score*. Assessments were made during clinic visits at Screening, Days 1 (Baseline, before taking the first dose), and on Days 15, 29, 57 and 85.
- *Secondary efficacy variables* included counts of laughing/crying episodes, Quality of Life, Quality of Relationships, and Pain Intensity Rating Scale (PIRS, a 5 point Likert scale). Subjects at baseline had to have a CNS-LS score of ≥ 13. Subjects recorded daily

in a diary the date and time each dose was taken, the number of laughing/crying episodes experienced, and any AEs that had occurred since the last visit.

Results: The primary efficacy analysis compared the change in CNS-LS score between DM/Q and placebo groups, where individual change was defined as the difference between the baseline scores (Day 1) and the average of the Day 15, Day 29, Day 57 and Day 85 scores. The comparison between DM 30 mg/Q 30 mg and placebo reached statistical significance on CNS-LS – the protocol specified primary outcome: mean change in CNS-LS score, 7.9 and 4.3, respectively ($p < 0.0001$). Subjects treated with DM/Q experienced approximately half as many episodes of inappropriate laughing, crying, and laughing and crying as subjects receiving placebo (p-value = 0.002). Between-treatment group comparison of Complete Remission, defined as no episodes during treatment, was statistically significant at all time points, favoring DM 30 mg/Q 30 mg.

Study 123-DB: Double-blind phase of Study 123 was a 12-week, multicenter, Phase III, double-blind, placebo-controlled, parallel group study in which 326 subjects with PBA and underlying ALS or MS were randomized (1:1:1) to DM 20 mg/Q 10 mg (n = 107), DM 30 mg/Q 10 mg (n = 110) or placebo (n = 109). This study is further discussed in section 6.1.1 of this review.

There were ***two open-label trials of PBA subjects***: Study 107 and open-label phase of Study 123.

Study 107: Study 107 was a 52-week, multicenter (44 centers: 4 in Israel, 1 in Serbia and remaining in US), open-label study of DM 30 mg/Q 30 mg administered once daily for one week and thereafter twice daily. A total of 553 subjects (aged 18-75 years) with PBA as a result of an underlying neurological disease were enrolled, however, only 552 subjects received at least one dose of study medication. A total of 99 subjects in this open-label study had previously participated in either Study 102 (n = 10) or Study 106 (n = 89); 47 of these 99 subjects did not receive DM 30 mg/Q 30 mg while participating in Study 102 or Study 106 (i.e., were randomized to placebo, DM or Q groups). Thus, there were more than 500 subjects in Study 107 who were naïve to DM 30 mg/Q 30 mg. The underlying neurological conditions of enrolled subjects were: MS (n = 223; 40.4%), ALS including primary lateral sclerosis and bulbar motor neuron disease (n = 193; 35%), subjects with only ALS (n = 176; 31.9%), stroke (n = 45; 8.2%), traumatic brain injury (n = 23; 4.2%), dementia (n = 17; 3.1%) and other neurological conditions (n = 51; 9.2%) which include diverse entities such as spinocerebellar ataxias, cerebral palsy, Parkinson's disease, Huntington's disease, brain aneurysms and AV malformations. Subjects who completed 52-weeks of treatment could continue to receive study medication in an optional extension phase. A total of 296 subjects completed 52 weeks of treatment; of these, 262 subjects entered the extension phase. Study 107 began on 3/3/03, and at the time the Applicant terminated this extension phase (6/7/07), there were 168 subjects who were in this extension phase of the study.

Study 123 open-label phase: Study 123-open-label was a 12-week, multicenter, open-label study of DM 30 mg/Q 10 mg administered twice daily in subjects (PBA resulting from ALS or MS) who completed the 12-week double-blind phase of Study 123. The baseline visit for the

open-label phase of the study occurred at no later than 14 days after Visit 5 (Day 84) of the double-blind phase. After the baseline visit, there were three additional visits (Day 15, 42 and 84). Of the 283 (283/326 = 86.8%) subjects completing the double-blind phase of Study 123, 253 (253/283 = 89.4%) subjects enrolled in the open-label phase of Study 123 (146 ALS subjects and 106 MS subjects). Eighteen (7.1%) withdrew from the study – due to an SAE, AE or exacerbation of the underlying disease. The remaining 235 (235/253 = 92.9%) subjects completed the study.

There were ***two trials of subjects with painful diabetic neuropathy***: Study 105 and Study 109.

Study 105: This is a multicenter (5 centers), Phase II, open-label, dose-escalation study of DM and Q in 36 patients with painful diabetic neuropathy. Subjects were between 18 and 80 years of age, with acceptably controlled diabetes mellitus and a clinical diagnosis of distal symmetrical diabetic neuropathy. Subjects had daily pain associated with their diabetic neuropathy for 3 months before the Screening visit and scored at least moderate (≥ 2) on the Pain Intensity Rating Scale at the visit on Day 1. Subjects who met the inclusion/exclusion criteria underwent a washout period during which all analgesics were discontinued. This was followed by 29 days of treatment with capsules containing 30 mg DM / 30 mg Q, beginning with 1 capsule per day and escalating approximately weekly to a maximum dose of 4 capsules (120 mg DM / 120 mg Q) per day. Subjects who could not tolerate a dose level could return to the previous level, or substitute a capsule containing 30 mg DM / 30 mg Q, or, if unable to tolerate the lowest dose level, discontinued from study.

Study 109: Study 109 was a 13-week, multicenter (47 centers), randomized, double-blind, placebo-controlled and 3-arm, parallel group study. A total of 379 subjects (had to score ≥ 2 on a 5-point Pain Intensity Rating Scale on Day 1) were randomized to 90 mg DM/60 mg Q (N = 131), 60 mg DM/60 mg Q (N = 125), or placebo (N = 125). Study medications were administered orally once a day for 1 week and twice day for the next 12 weeks. Subjects were recruited from a population of subjects with diabetes mellitus (type 1 or 2) with documented glycemic control and established anti-diabetic therapy for at least 3 months before the study, and who had for the previous 3 months daily pain associated with distal symmetric diabetic polyneuropathy. After screening, subjects were discontinued from tricyclic antidepressant drugs for 14 days and from shorter-acting analgesics and anti-epileptic drugs for 7 days.

Subjects returned to the clinic for on-study visits at Days 15, 29, 50, 71, and 92 (the final scheduled visit, during which efficacy and safety assessments were conducted). Efficacy of DM/Q was assessed by scores on the 11-point (0–10) Pain Rating Scale from daily subject diaries (the primary endpoint).

The number of subjects who discontinued was 52 (39.7%) in the 90 mg DM/60 mg Q treatment group, 51 (40.8%) in the 60 mg DM/60 mg Q treatment group, and 34 (27.6%) in the placebo treatment group. For the primary efficacy variable, the Pain Rating Scale, analysis using the protocol-specified primary analysis method demonstrated that patients in the 90 mg DM/60 mg Q treatment group had significantly less pain than patients in the placebo treatment group ($p < 0.0001$).

6 Review of Efficacy

6.1 Indication

6.1.1 Methods

In the Approvable Letter 10/30/06, the Agency recommended that a lower dose of Q be evaluated. The Applicant conducted Study 123 to assess the efficacy and safety of a lower dose of Q (DM 20 mg/Q 10 mg and DM 30 mg/Q 10 mg).

Design of Study 123:
Study 123-DB was a 12-week, multicenter (52 centers), Phase III, double-blind, placebo-controlled, parallel group study in which 326 subjects with PBA and underlying ALS or MS were randomized (1:1:1) by center to DM 20 mg/Q 10 mg (n = 107), DM 30 mg/Q 10 mg (n = 110) or placebo (n = 109). Study medications were administered orally once a day for 1 week and twice day for the next 11 weeks. In addition to assessing efficacy and safety, another objective of this study was to determine the PK parameters of the two different doses of DM/Q 10 mg formulation in a subset (16 ALS subjects and 8 MS subjects) of the study population. The study was conducted in USA (n = 224; 36 sites), Argentina (n = 82; 11 sites) and Brazil (n = 20; 5 sites).

Subjects were screened during the 4 weeks preceding entry into the study. Eligible subjects were given a diary with instruction to record all laughing and/or crying episodes over a 7-day period before entering the study. After randomization, subjects were to enter daily in the diary the time the doses were taken, the daily number of laughing and/or crying episodes, and any adverse events experienced. Subjects with MS were instructed to also record daily the pain they experienced using the Pain Rating Scale (PRS). Subjects were to bring these diaries with them to each clinic visit. After evaluating the subject's ability to comply with these requirements, the investigator determined if a caregiver should complete the study diary and assessments.

Eligible subjects were male or female subjects aged 18-80 years with clinical history and clinically relevant symptoms of PBA, and a diagnosis of ALS (no longer than 30 months from diagnosis) or diagnosis of MS or probable MS (McDonald criteria), a CNS-LS score at baseline (Day 1) $\geq$ 13, resting respiratory rate between 12 and 20 breaths per minute, and a resting diurnal SaO2 $\geq$ 95% measured with pulse oximeter. If a subject experienced an acute exacerbation or an acute episode of the underlying neurological disorder during the study, the subject's participation was immediately terminated. An exacerbation of the underlying neurological disorder was defined as the onset of new neurological symptoms associated with the disorder or worsening of preexisting symptoms associated with the disorder that (1) persisted 48 hours or more, (2) required specific treatment, and (3) was accompanied by objective neurological or behavioral changes observed by the investigator and was not related to PBA symptoms.

Efficacy variables:

- *Primary efficacy endpoint*: *Number of episodes of laughing and/or crying*. The analysis was based on the changes from baseline in episode rates as recorded daily in the subject diary. The Agency had repeatedly expressed a preference for the designation of laughing and crying episodes as the primary outcome variable during the development program. However, the Applicant designated this endpoint as a secondary variable in Study 102 and Study 106.
- *Secondary efficacy variables*:
    - *Mean change in CNS-LS score*: The CNS-LS questionnaire is a 7-item self-report measure with scores for each item ranging from 1 – 5, such that the range of possible total scores is 7 (best) to 35 (worst). Three (1, 3 and 6) of the 7 items assess crying and the remaining four assess laughter. The Applicant chose the cut-off score of 13 as an inclusion criterion because it predicts neurologists' diagnosis of PBA for 82% of participants. During the regulatory interactions with the Applicant, the Agency expressed reservations regarding the use of CNS-LS because it did not have the ability to assess the severity of individual episodes of pathological laughter and crying, item 5 of the scale appeared to assess the tendency to have happy or funny thoughts as opposed to externally visible laughter and crying, and the unclear clinical significance for a given change in the score from baseline. Subjects completed the CNS-LS at the screening visit, at the baseline visit (Day 1) before taking their first dose of medication, and on Days 15, 29, 57, and 84, or at the last study visit. A copy of this questionnaire is reproduced below.

Figure 1: CNS-LS questionnaire

Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Final study report; section 16.1.1 Protocol and protocol amendments, page 66.

    - *Mean change in Neuropsychiatric Inventory (NPI) score*: The NPI is a retrospective (to 1 month) caregiver–informant interview assessing frequency and

severity of 12 neuropsychiatric symptom domains. These 12 domains include delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviors, nighttime behavioral disturbances, and appetite/eating abnormalities. The NPI score is based on the sum of the severity ratings (0 = absent, 1 = mild to 3 = severe). The NPI was completed at the baseline visit (Day 1) and on Day 84 (Visit 5). A copy of this questionnaire is reproduced in section 9 of this review.

- *Mean change in SF-36 Health Survey Medical Outcomes (SF-36) score*: The SF-36 is a short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. Subjects completed the survey at the baseline visit (Day 1) before dosing and on Day 84 (Visit 5).

- *Mean change in Beck Depression Inventory (BDI-II) score*: The BDI-II is a 21-item self-report instrument intended to assess the existence and severity of symptoms of depression as listed in the DSM-IV. Subjects completed the BDI-II at the screening visit, at the baseline visit (Day 1) before taking their first dose of medication, and on Day 84 (Visit 5). A copy of this questionnaire is reproduced in section 9 of this review.

- *Mean change in the Pain Rating Scale (PRS) score in MS subjects*: The PRS required the subjects with MS to rate their pain over the past 12 hours on a scale of 0 to 10 (0 = none, 10 = worst pain ever experienced), by circling the number that best described their pain on average over the past 12 hours. Only MS subjects were asked to complete the PRS in their daily diaries. The diaries were reviewed at all study visits. A copy of this questionnaire is reproduced in section 9 of this review.

- *Caregiver Strain Index (CSI)*: The CSI is a self-administered 12-item questionnaire that measures strain related to care provision. Positive responses to 7 or more items indicate a greater level of strain. Any positive answer may indicate a need for intervention in that area. The CSI was administered to subjects' caregivers at baseline (Visit 1) and on Day 84 (Visit 5) or the end of the study. A copy of this questionnaire is reproduced in section 9 of this review.

Protocol changes (Amendment 1; 6/6/08): The number of MS subjects enrolled were increased from the originally planned 90 to 126.

Study visits:

Figure 2: Schedule of observations and procedures, double-blind phase Study 123

Event	Screening -28 to -1 Days [a]	Baseline, Day 1	Visit 2, Day 15	Visit 3, Day 29	Visit 4, Day 57	Visit 5, Day 84 (End of Study)
Informed consent form signed	X					
Medical history	X					
Physical examination	X					X
Record vital signs	X	X	X	X	X	X
Review of inclusion and exclusion criteria	X	X				
CNS-Lability Scale	X	X	X	X	X	X
Beck Depression Inventory	X	X				X
SF-36 Health Survey		X				X
Neuropsychiatric Inventory [b]		X				X
Caregiver's Strain Index [b]		X				X
Pain Rating Scale [c]	X	X	X	X	X	X
Resting 12-lead ECG with 2-min rhythm strip	X	X	X	X	X	X
Chemistry, hematology, and urinalysis	X			X		X
Urinary pregnancy test (hCG) [d]	X	X		X		X
Resting diurnal and nocturnal oxygen saturation	X		X			X[e]
Review previous and concomitant medication	X	X	X	X	X	X
Dispense study medication		X		X	X	
Dispense diary card	X	X	X	X	X	
Review of adverse events		X	X	X	X	X
Review and collect diary card		X	X	X	X	X
Return unused study medication [f]			X	X	X	X
Blood sample for PK profiling				X[g]	X[g]	
Blood sample for P450 2D6 genotyping		X				

Source: Appendix 16.1.1, Table 1.1.
CNS = Center for Neurologic Studies; ECG = electrocardiogram, hCG= human chorionic gonadotropin; PK = pharmacokinetics.
[a]Subjects returned to the study site within 2 days after completing the 7-day laughing and/or crying diary-recording period for the baseline visit on Day 1.
[b]Completed by the subject's caregiver.
[c]Subjects with multiple sclerosis only.
[d]For women of childbearing potential only.
[e]Only resting diurnal oxygen saturation was measured at this visit.
[f]Subjects returned study medication at Visits 2, 3, 4, and the end-of-study visit, although the protocol shows return at only the end-of-study visit.
[g]A blood specimen was drawn for dextromethorphan, dextrorphan, and quinidine levels.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Study Report, Table 9-1, page 24

Statistical Analysis:
Analysis data sets included the following populations:

- Intent-to-treat population (ITT): included all randomized subjects.
- Efficacy evaluable (EE) population: included all subjects who were protocol adherent, defined as those who completed the Day 84 visit or the end-of-study visit within 48 hours of a discontinuation, and who took at least 80% of their scheduled doses prior to discontinuation of the study medication.

Primary efficacy analysis: A baseline daily episode count was calculated based on a subject's pretreatment entries recorded at the baseline visit. Episode counts were the total number of laughing and/or crying episodes reported and analyzed as a rate expressed as episodes per day. Post-randomization, daily laughing/crying episode counts were recorded in subject daily diaries. Daily episode rates at each visit were determined as averages using all available non-missing counts for the previous 7 days. The primary efficacy analysis was based on the changes from baseline in laughing/crying episode rates recorded in the subject diary and estimated using a longitudinal negative binomial regression model on the daily episode counts. Independent variables in the model included treatment (DM 30 mg/Q 10 mg vs. placebo and DM 20 mg/Q 10

mg vs. placebo), period (before or after treatment), underlying disease diagnosis (ALS vs. MS) and site (with small sites pooled).

There were two sensitivity analyses for the primary endpoint. A nonlongitudinal analysis was performed on the total number of laughing/crying episodes over the entire double-blind phase, similar to the efficacy analysis in the previous cycle. Another sensitivity analysis used a generalized estimating equation model for daily episode rate assuming a negative binomial distribution function and a compound symmetry correlation variance structure.

An additional analysis of the primary outcome compared the mean change in daily episode rates (laughing and crying combined and separately) from baseline to Day 84 for the DM 30 mg/Q 10 mg group vs. placebo and for the DM 20 mg/Q 10 mg group vs. placebo using the Wilcoxon rank-sum test. Similar analyses compared the mean change in daily episode rates from baseline to each visit, overall and by region (U.S./Latin America) and by diagnosis within each region.

Secondary efficacy analyses: Analysis of the secondary efficacy endpoints of mean change in CNS-LS, NPI, SF-36, BDI-II, and PRS score (in MS subjects only) were analyzed as differences between Day 84 and baseline values. Except for the SF-36 reported health transition item, the analysis of these endpoints was performed by multiple regression models that included treatment as the fixed effect, and baseline value, study site, and diagnosis (ALS or MS) as covariates.

6.1.2 Demographics and baseline characteristics

The following table summarizes the demographic and baseline characteristics of the ITT population for double-blind phase of Study 123. Compared to the DM 20 mg/Q 10 mg (second column) and placebo groups, the mean and median age was higher and the proportion of male subjects lower in the DM 30 mg/Q 10 mg group.

Table 10: Summary of demographic and baseline characteristics of the ITT population in Study 123

Characteristic	DB Phase AVP-923-30 (n = 110)	AVP-923-20 (n = 107)	Placebo (n = 109)
Age[a] (years)			
n	110	107	109
Mean (SD)	53.08 (11.016)	50.81 (11.114)	50.27 (11.939)
Median (min, max)	54.5 (29.0, 76.0)	50.0 (28.0, 80.0)	50.0 (25.0, 75.0)
Ethnicity (n)			
Caucasian	80 (72.7%)	80 (74.8%)	83 (76.1%)
Black	6 (5.5%)	2 (1.9%)	4 (3.7%)
Asian	1 (0.9%)	0	1 (0.9%)
Hispanic	21 (19.1%)	21 (19.6%)	21 (19.3%)
Other	2 (1.8%)	4 (3.7%)	0 (0.0)
Sex (n)[b]			
Male	46 (41.8%)	53 (49.5%)	50 (45.9%)
Female	64 (58.2%)	54 (50.5%)	59 (54.1%)
Height (cm)[b]			
n	110	107	109
Mean (SD)	168.35 (9.420)	168.86 (9.546)	169.15 (9.576)
Median (min, max)	169.5 (139.7, 188.0)	168.0 (147.0, 190.5)	167.6 (149.9, 191.0)
Weight (kg)			
n	110	107	109
Mean (SD)	73.25 (14.324)	74.09 (15.921)	76.85 (20.388)
Median (min, max)	73.05 (44.0, 110.7)	72.80 (44.5, 127.1)	73.5 (44.4, 145.1)
Pulse rate (bpm)			
n	110	107	109
Mean (SD)	76.04 (11.031)	76.27 (9.991)	75.04 (9.196)
Median (min,max)	76.0 (50.0, 110.0)	76.00 (60.0, 107.0)	76.0 (45.0, 100.0)
Body temperature (°C)			
n	110	107	109
Mean (SD)	36.44 (0.454)	36.38 (0.457)	36.34 (0.420)
Median (min, max)	36.45 (35.0, 37.3)	36.5 (34.6, 37.4)	36.40 (35.2, 37.3)
Systolic BP (mm Hg)			
n	110	107	109
Mean (SD)	121.98 (12.388)	123.26 (13.564)	122.61 (13.625)
Median (min, max)	120.0 (97.0, 163.0)	121.0 (97.0, 184.0)	120.0 (100.0, 174.0)
Diastolic BP (mm Hg)			
n	110	107	109
Mean (SD)	74.74 (9.682)	76.36 (10.667)	77.04 (9.624)
Median (min, max)	75.0 (49.0, 102.0)	78.00 (57.0, 110.0)	78.0 (57.0, 102.0)

ITT = intent to treat; DB = double blind; SD = standard deviation; min = minimum; max = maximum; bpm = beats per minute; BP = blood pressure.
[a]Age was calculated as the number of full years completed from date of birth until screening date in DB phase.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Final study report, Table 10-2, page 53

Since age, time from diagnosis, bulbar onset and to a lesser extent sex are important factors associated with a higher mortality in the ALS population, I looked at the differences between the treatment groups at baseline with regard to these factors (see table below). In ALS subjects, both the median and mean age are higher in the DM 30 mg/Q 10 mg group than either DM 20 mg/Q 10 mg or placebo groups. Similarly, the proportion of male ALS subjects was higher in the DM 30 mg/Q 10 mg group than in either DM 20 mg/Q 10 mg or placebo groups. The mean and median duration of time from diagnosis of ALS for both DM/Q groups, particularly for the DM 30 mg/Q 10 mg group, were longer than in the placebo group. The median time from diagnosis of ALS in the DM 30 mg/Q 10 mg subjects was nearly twice that of subjects in the placebo group. There were a total of 14 outliers in the distribution of the time from diagnosis of ALS. Eliminating these 14 outliers and recalculating the measures of central tendency yielded a median of 10 months in the DM 30 mg/Q 10 mg group, 8 months in the DM 20 mg/Q 10 mg group and 6 months in the placebo group (data not included in the table below). The proportion of ALS subjects with bulbar onset was evenly distributed among the treatment groups at randomization.

Table 11: Age, sex distribution and time from diagnosis in ALS and MS subjects at baseline (Study 123)

			DM 20/Q 10	DM 30/Q 10	Any DM/Q10	Placebo
AGE (years)	ALS	Mean	54.4	57.9	56.1	54.5
		Std Dev	11.2	9.52	10.5	11.1
		Median	55	59	58	55.5
		Min	28	33	28	25
		Max	80	76	80	75
	MS	Mean	44.6	46.2	45 5	44.3
		Std Dev	7.91	9.26	8.64	10.5
		Median	46	46	46	44
		Min	29	29	29	26
		Max	62	66	66	75
Time from Diagnosis (months)	ALS	Mean	15.9	21.2	18.5	12.7
		Std Dev	23.3	30	26.8	18.1
		Median	9.5	12	11	6.5
		Min	0	0	0	0
		Max	159	152	159	103
	MS	Mean	126	137	132	128
		Std Dev	92.7	105	98 9	90.5
		Median	115	118	118	114
		Min	5	2	2	20
		Max	325	483	483	517
SEX	ALS	Male	39/68 (57.3%)	41/65 (63.1%)	80/133 (60.2%)	36/64 (56.2%)
		Female	29/68 (42.7%)	24/65 (36.9%)	53/133 (39.8%)	28/64 (43.8%)
	MS	Male	14/39 (35.9%)	5/45 (11.1%)	19/84 (22.6%)	14/45 (31.1%)
		Female	25/39 (64.1%)	40/45 (88.9%)	65/84 (79.4%)	31/45 (68.9%)
Type of onset	ALS only	Bulbar	30/68 (44.1%)	29/65 (44.6%)	59/133 (44.4%)	29/64 (45.3%)
		Spinal	38/68 (55.9%)	36/65 (55.4%)	74/133 (55.6%)	35/64 (54.7%)

Source: NDA Complete Response 4/30/10; Reviewer's analysis of DM, EX and ALSTYPE datasets (DMEX; STUDYID Study 123; Tabulate, EXTRT/ARM; AGE, DXDUR, SEX, ONSTYPE; PRIMDIS)

The following tables provide summary statistics for the sum total of all laughing and crying episode counts and episode rate by treatment group at baseline. The treatment groups are reasonably balanced with respect to the median number of total episode counts per subject. Since this simple sum of episodes does not adjust for the fact that the sum will tend to be lower when a subject has fewer days of episodes than a subject who has them for all 7 days, the episode rate was used.

Table 12: Total Sum of Laughing and Crying Episodes at baseline by treatment (Study 123)

Statistic	DM 30 mg/Q 10 mg	DM 20 mg/Q 10 mg	Placebo
Total sum of laughing and crying episodes			
Mean	31.71	53.09	30.58
Median	19	21.5	18
S.D.	66.44	111.37	53.12
Range	0, 671	1, 714	0, 483
Episode rate			
Mean	4.6	6.7	4.44
Median	2.93	3.07	2.46
S.D.	9.48	12.9	7.64
Range	0, 95.9	0.143, 78.9	0, 69

Source: Dr. Tristan Massie, the statistical reviewer, provided tables in response to my request for these data (email dated 8/16/10). The above table is a modified version of the provided tables.

Since ALS subjects in the DM/Q dose groups have a longer time from diagnosis than placebo subjects, I asked Dr. Tristan Massie, the statistical reviewer, to perform analysis to see whether subjects with longer disease duration have more events, and whether there was a greater treatment effect in those with more baseline events than in those with fewer. The data from his analyses (negative binomial analyses of these data, similar to the primary analysis) do not support the expectation that subjects with longer disease duration have more events. Nor does it appear that there was a greater treatment effect in those with more baseline events than in those with fewer (data not included in this review).

6.1.3 Subject Disposition

A total of 332 subjects were screened; six of these subjects were screening failures. The remaining 326 subjects were randomized to DM 20 mg/Q 10 mg (n = 107), DM 30 mg/Q 10 mg (n = 110) and placebo (n = 109). The following table summarizes the subject disposition in the double-blind phase of 123. The number of subjects in DM 20 mg/Q 10 mg group who withdrew from the study was over 2-fold the number who withdrew from DM 30 mg/Q 10 mg group. The majority of this imbalance in the dropout rate between these DM/Q treatment groups is due to AEs, lost to follow-up, protocol violation and other reasons. The imbalance in the dropout rate between the two DM/Q groups was more pronounced in the ALS subjects (15/68 = 22.1% in DM 20 mg/Q 10 mg group, 6/65 = 9.2% in DM 30 mg/Q 10 mg group, and 9/64 = 14.1% in placebo group) than in the MS subjects (4/39 = 10.3% in DM 20 mg/Q 10 mg group and 3/45 = 6.7% in DM 30 mg/Q 10 mg group). In the ALS subjects, the proportion of subjects who withdrew due to lost to follow-up, AEs, SAEs, protocol violation and other reasons was greater in the DM 20 mg/Q 10 mg group compared to DM 30 mg/Q 10 mg group. Protocol violations occurred in two subjects with ALS (Beck Depression Inventory score > 20 in both subjects) and one subject with MS (randomization without biochemistry laboratory results). Withdrawal due to 'other' category occurred in two ALS subjects in DM 20 mg/Q 10 mg group (one ALS subject who did not meet inclusion criteria of Beck Depression Inventory score <19, and the other could not keep appointments due to ALS progression), two ALS subjects in placebo group (lack of efficacy and exacerbation of ALS), and one MS subject on placebo who could not take medications and keep study visits due to recent surgery with complications.

Table 13: Summary of subject disposition in double-blind phase of Study 123

Subject Category	**DM20/Q10 (n = 107)**	**DM30/Q10 (n = 110)**	**Any DM/Q10 (N = 217)**	**Placebo (n = 109)**
Subjects randomized	107 (100)	110 (100)	217 (100)	109 (100)
Subjects with ALS	68 (63.6)	65 (59.1)	133 (61.3)	64 (58.7)
Subjects with MS	39 (36.4)	45 (40.9)	84 (38.7)	45 (41.3)
Subjects in the United States	72 (67.3)	77 (70.0)	149 (68.7)	75 (68.8)
Subjects in Latin America	35 (32.7)	33 (30.0)	68 (31.3)	34 (31.2)
Subjects dosed	107 (100)	110 (100)	217 (100)	109 (100)
Subjects completing study	88 (82.2)	101 (91.8)	189 (87.1)	94 (86.2)
Subjects who withdrew	19 (17.8)	9 (8.2)	28 (12.9)	15 (13.8)
Reason for withdrawal				
Lost to follow-up	3 (2.8)	1 (0.9)	4 (1.8)	2 (1.8)
Exacerbation of MS	0 (0.0)	1 (0.9)	1 (0.5)	1 (0.9)
Adverse event	5 (4.7)	1 (0.9)	6 (2.8)	0 (0.0)

Serious adverse event	3 (2.8)	2 (1.8)	5 (2.3)	1 (0.9)
Medication refusal due to AE	2 (1.9)	2 (1.8)	4 (1.8)	0 (0.0)
Withdrew consent	2 (1.9)	2 (1.8)	4 (1.8)	7 (6.4)
Protocol violation	2 (1.9)	0 (0.0)	2 (0.9)	1 (0.9)
Other	2 (1.9)	0 (0.0)	2 (0.9)	3 (2.8)

ALS = amyotrophic lateral sclerosis; MS = multiple sclerosis; AE = adverse event.
Note: Percentages are based on the number of subjects randomized in each treatment group
Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Final study report, Table 10-1, page 51

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy analysis was based on the changes from baseline in laughing/crying episode rates recorded in the subject diary and estimated using a longitudinal negative binomial regression model. Independent variables included in this model were: treatment (DM 30 mg/Q 10 mg versus placebo and DM 20 mg/Q 10 mg versus placebo), period (before or after treatment), underlying disease diagnosis (ALS versus MS) and site (with small sites pooled). No imputation was done for missing data.

The following table summarizes the efficacy analysis of the primary endpoint in the ITT population. Estimates are the change in average episode rate from baseline for the placebo group, and the additional change from baseline (or *treatment effect*) observed in the DM 30 mg/Q 10 mg or DM 20 mg/Q 10 mg group relative to placebo. Results are presented on a *log-scale* and then as an *estimate of percentage change* (Exp). Thus, for each DM/Q dose group comparison with placebo group in the following table, for example, the first line "Treatment (DM30/Q10 vs placebo)" estimate -0.6326 represents the change from baseline *treatment effect* in *log-scale*, and the next line "Exp (Treatment (DM30/Q10 vs Placebo))" estimate 0.5312 represents the *percentage change*, i.e., 53.12% as many episodes as subjects receiving placebo.

In the overall ITT population, subjects treated with either DM 30 mg/Q 10 mg or DM 20 mg/Q 10 mg experienced approximately half (53.12% and 51.03%, respectively) as many episodes of inappropriate laughing/crying as subjects receiving placebo; the differences between the DM/Q groups and placebo were statistically significant ($p < 0.0001$). Similar results using the ITT population by ALS diagnosis were obtained ($p < 0.0001$ for DM 30 mg/Q 10 mg and DM 20 mg/Q 10 mg groups). In MS subjects, the results showed a significant effect due to DM 30 mg/Q 10 mg when compared with placebo ($p = 0.041$), however, was not statistically significant due to DM 20 mg/Q 10 mg when compared with placebo ($p = 0.811$). It appears that MS subjects taking DM 20 mg/Q 10 mg dose experienced 101% [Exp (Treatment (DM20/Q10 vs Placebo)) = 1.0146] as many episodes as subjects receiving placebo, suggesting that efficacy may be better in the placebo subjects. I asked Dr. Massie, the statistical reviewer, to explore this further. Dr. Massie believes that this result suggesting that DM 20 mg/Q 10 mg was numerically worse than placebo in MS subjects is a failing of the longitudinal negative binomial model. This might be because there were a higher proportion of zero daily counts than the negative binomial model can accommodate. To further support his conclusions, Dr. Massie points to analyses using other models (including a model that accounts for high proportion of zero values) which suggest that the efficacy for the DM 20 mg/Q 10 mg dose in MS subjects is at least in the right direction if not nominally significant.

Table 14: Primary endpoint (primary analysis using longitudinal negative binomial model): Study 123 – ITT population (all subjects, ALS subjects and MS subjects)

Parameter	Estimate	Standard Error	95% Confidence Interval	P-value
All subjects				
Treatment (DM30/Q10 vs Placebo) Exp (Treatment (DM30/Q10 vs Placebo))	-0.6326 0.5312	0.0372 0.0197	(-0.7054, -0.5597) (0.4939, 0.5714)	<0.0001
Treatment (DM20/Q10 vs Placebo) Exp (Treatment (DM20/Q10 vs Placebo))	-0.6727 0.5103	0.0360 0.0184	(-0.7433, -0.6021) (0.4755, 0.5477)	<0.0001
ALS subjects				
Treatment (DM30/Q10 vs Placebo) Exp (Treatment (DM30/Q10 vs Placebo))	-0.9830 0.3742	0.0483 NA	(-1.0777, -0.8883) (0.3404, 0.4113)	<0.0001
Treatment (DM20/Q10 vs Placebo) Exp (Treatment (DM20/Q10 vs Placebo))	-1.0390 0.3538	0.0452 NA	(-1.1277, -0.9504) (0.3238, 0.3866)	<0.0001
MS subjects				
Treatment (DM30/Q10 vs Placebo) Exp (Treatment (DM30/Q10 vs Placebo))	-0.1183 0.8885	0.0579 NA	(-0.2318, -0.0047) (0.7931, 0.9953)	0.041
Treatment (DM20/Q10 vs Placebo) Exp (Treatment (DM20/Q10 vs Placebo))	0.0145 1.0146	0.0608 NA	(-0.1046, 0.1337) (0.9007, 1.1430)	0.811

Note: EXP = exponentiating the original estimate to provide an estimate of percentage change
Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Final study report, Tables 9.1.1, 9.1.1A, 9.1.1M, 9.2.1

Primary efficacy endpoint results in the Efficacy Evaluable (EE; see section 6.1.1 of this review for definition) population using the longitudinal model were similar to the results in the ITT population, showing average episodes in the DM/Q 10 mg groups that were approximately half of that in the placebo group (55.55% for DM 30 mg/Q 10; 52.34% for DM 20 mg/Q 10 mg), and statistically significant when compared to the placebo group.

In a variation of the primary analysis model, site categories (US versus Latin America) were used instead of individual sites with small sites pooled. Results in the overall ITT population, or ALS or MS subsets of the ITT population, showed that subjects treated with DM 30 mg/Q 10 mg or DM 20 mg/Q 10 mg experienced approximately a 40% reduction in the number of laughing/crying episodes as compared to subjects taking placebo (tables not included in review); for each of the DM/Q groups, the number of episodes was significantly lower than in the placebo group ($p < 0.0001$).

Nonlongitudinal analysis was performed (sensitivity analysis) on the laughing/crying episodes over the entire double-blind phase (see table below), similar to the efficacy analysis in the previous review cycle. Nonlongitudinal analyses of laughing and crying episodes over the double-blind phase showed a statistical significance for DM 30 mg/Q 10 mg and DM 20 mg/Q 10 mg (compared to placebo) for all subjects ($p < 0.0001$ for both treatment groups), for the ALS subgroup ($p < 0.0001$ and $p = 0.049$, respectively) but did not achieve statistical significance within the MS subgroup ($p = 0.209$ and $p = 0.316$, respectively).

Table 15: Primary endpoint sensitivity analysis using non-longitudinal negative binomial model): Total episode rate in Study 123 – ITT population (All subjects, ALS subjects and MS subjects)

Laughing and Crying episodes	Combined N=312	ALS Only N=186	MS Only N=126

Parameter	Estimate	Standard Error	p-value	Estimate	Standard Error	p-value	Estimate	Standard Error	p-value
Treatment (DM**30**/Q10 vs Placebo)	-0.5442	0.1156	<0.0001	-0.7255	0.1500	<0.0001	-0.2148	0.1710	0.209
Exp (DM**30**/Q10 vs Placebo)	0.5803	NA		0.4841	NA		0.8067	NA	
Treatment (DM**20**/Q10 vs Placebo)	-0.2180	0.1048	0.037	-0.2475	0.1256	0.049	-0.1846	0.1841	0.316
Exp (DM**20**/Q10 vs Placebo)	0.8041	NA		0.7808	NA		0.8314	NA	

Note: EXP = exponentiating the original estimate to provide an estimate of percentage change
Note: Episode rates are reported as total number of episodes from Day 1 to end of study, adjusted by days with non-missing counts. Rates are expressed as average episodes per day over the double-blind period.
Note: p-values are computed using negative binomial regression (constant dispersion) for the total number of episodes over the double-blind period, with baseline episode rate, and pooled study site included as covariates. Diagnosis is included as a covariate in the analysis of the combined population.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Final study report, Tables 9.3AM

Nonlongitudinal analyses in the ITT population was done for the combined laughing and crying episodes, crying episodes only, and laughing episodes only (see table below). Results showed that the effect of DM 30 mg/Q 10 mg or DM 20 mg/Q 10 mg was statistically significant when compared with placebo for combined laughing and crying episodes, and crying episodes only, but were not statistically significant for laughing episodes only. However, the laughing episode rates in the DM/Q treatment groups were lower compared to the placebo group.

Table 16: Primary endpoint (sensitivity analysis using non-longitudinal negative binomial model): Episode rates in Study 123 – ITT population

	DM 30 mg/Q 10 mg	DM 20 mg/Q 10 mg	Placebo
Laughing episodes only			
N	107	98	106
Mean (Std Dev)	0.47 (0.84)	1.84 (7.22)	1.05 (2.32)
Median	0.08	0.09	0.20
Min, Max	0.00, 4.32	0.00 55.75	0.00, 18.61
p-value	0.139	0.266	
Crying episodes only			
N	107	100	107
Mean (Std Dev)	0.49 (0.88)	0.68 (1.95)	1.07 (1.57)
Median	0.11	0.18	0.46
Min, Max	0.00, 5.51	0.00, 18.21	0.00, 8.60
p-value	<0.0001	0.003	
Laughing + Crying episodes			
N	107	100	107
Mean (Std Dev)	0.94 (1.39)	2.49 (7.94)	2.08 (3.04)
Median	0.30	0.37	0.86
Min, Max	0.00, 9.83	0.00, 57.89	0.00, 18.75
p-value	<0.0001	0.037	

Note: Episode rates are reported as total number of episodes from Day 1 to end of study, adjusted by days with nonmissing counts. Rates are expressed as average episodes per day over the double-blind period.
P-values are computed using negative binomial regression (constant dispersion), with baseline episode rate, pooled study site, and clinical diagnosis included as a covariate.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Final study report, Tables 9.3

An additional analysis of the primary endpoint compared the mean change in daily episode rates from baseline to Day 84 (see tables below) between treatment groups. In the overall study subjects and the ALS subset of the ITT population, decreases from baseline to Day 84 in laughing and crying episodes, and crying only episodes were statistically significant for both DM/Q groups compared to the placebo group; however, laughing episodes were not statistically significant between either DM/Q treatment group and placebo group. In the MS subjects, numerical decreases from baseline to Day 84 in laughing, crying, and laughing and crying episodes were present in all treatment groups; however, the differences between the DM/Q treatment groups and the placebo group were not statistically significant.

Table 17: Primary endpoint: Mean change from baseline to Day 84 in the laughing or crying or laughing/crying episode rates in Study 123 – ITT population (***All subjects***)

Visit		**DM 30 mg/Q 10 mg (n = 110)**	**DM 20 mg/Q 10 mg (n = 107)**	**Placebo (n = 109)**
Laughing episodes only				
Baseline[a]	n	107	103	106
	Mean (SD)	1.70 (3.391)	4.05 (11.781)	2.50 (7.347)
Visit 5 (Day 84)	n	92	82	91
	Mean (SD)	0.37 (0.811)	2.01 (13.382)	0.86 (1.757)
Change from baseline to Visit 5	n	92	82	89
	Mean (SD)	-1.45 (3.447)	-1.28 (6.048)	-1.88 (6.642)
	p-value[b]	0.2276	0.2208	
Crying episodes only				
Baseline[a]	n	106	106	107
	Mean (SD)	3.01 (6.688)	2.82 (4.158)	1.99 (1.982)
Visit 5 (Day 84)	n	93	82	94
	Mean (SD)	0.39 (0.945)	0.48 (1.502)	0.83 (1.258)
Change from baseline to Visit 5	n	92	82	92
	Mean (SD)	-2.70 (6.975)	-2.60 (3.513)	-1.10 (1.601)
	p-value[b]	0.0038	0.0005	
Laughing + Crying episodes				
Baseline[a]	n	108	106	107
	Mean (SD)	4.65 (9.478)	6.76 (12.887)	4.45 (7.642)
Visit 5 (Day 84)	n	93	82	94
	Mean (SD)	0.76 (1.506)	2.49 (13.572)	1.63 (2.285)
Change from baseline to Visit 5	n	93	82	92
	Mean (SD)	-4.11 (9.984)	-3.88 (7.866)	-2.94 (6.838)
	p-value[b]	0.0099	0.0048	

[a]Baseline episode rate was determined from the subject pretreatment diary entries.
[b]p-value for Wilcoxon rank-sum test comparing active treatment to placebo.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Final study report, Tables 11-1 and 11-3, pages 61 and 63

Table 18: Primary endpoint: Mean change from baseline to Day 84 in the laughing or crying or laughing/crying episode rates in Study 123 – ITT population (***ALS subjects***)

	ALS (N = 197)		
Visit Statistics	AVP-923-30 (N = 65)	AVP-923-20 (N = 68)	Placebo (N = 64)
Laughing			
Change From Baseline To Day 84			
N	52	48	51
Mean (Std Dev)	-2.08 (4.386)	-1.68 (7.830)	-2.57 (8.605)
95% C.I.	(-3.298, -0.856)	(-3.950, 0.598)	(-4.986, -0.146)
Min, Max	-30.1 , 0.3	-23.9 , 41.9	-55.7 , 4.0
Median	-1.01	-0.85	-0.46
P-value [2]	0.0898	0.1214	
Crying			
Change From Baseline To Day 84			
N	52	48	53
Mean (Std Dev)	-3.00 (9.131)	-3.17 (4.353)	-0.84 (1.548)
95% C.I.	(-5.544, -0.460)	(-4.429, -1.901)	(-1.269, -0.416)
Min, Max	-65.4 , 0.9	-20.1 , 0.6	-6.4 , 2.3
Median	-1.14	-1.64	-0.43
P-value [2]	0.0102	0.0002	
Laughing/Crying			
Change From Baseline To Day 84			
N	52	48	53
Mean (Std Dev)	-5.07 (13.125)	-4.84 (10.089)	-3.32 (8.711)
95% C.I.	(-8.725, -1.417)	(-7.771, -1.912)	(-5.724, -0.922)
Min, Max	-95.6 , 0.9	-35.9 , 41.9	-56.9 , 3.9
Median	-2.64	-2.57	-1.02
P-value [2]	0.0057	0.0029	

[2] P-value for Wilcoxon rank-sum test comparing active treatment to placebo.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Final study report, Tables 11.1.2

Table 19: Primary endpoint: Mean change from baseline to Day 84 in the laughing or crying or laughing/crying episode rates in Study 123 – ITT population (***MS subjects***)

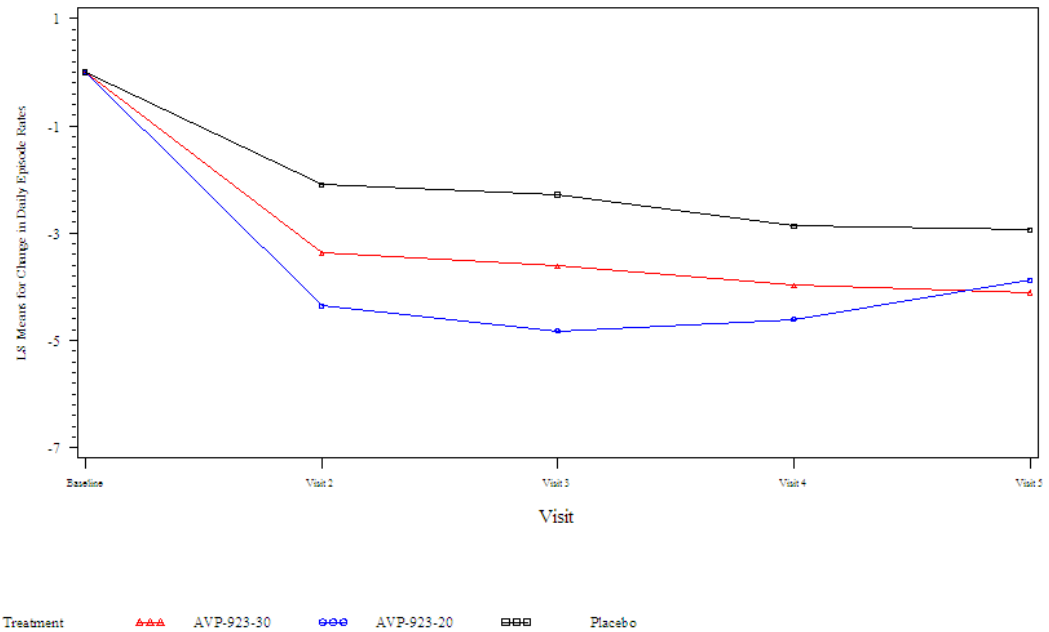
	MS (N = 129)		
Visit Statistics	AVP-923-30 (N = 45)	AVP-923-20 (N = 39)	Placebo (N = 45)
Laughing			
Change From Baseline To Day 84			
N	40	34	38
Mean (Std Dev)	-0.64 (1.168)	-0.72 (1.385)	-0.96 (1.830)
95% C.I.	(-1.009, -0.262)	(-1.202, -0.235)	(-1.563, -0.359)
Min, Max	-3.4 , 2.4	-6.4 , 1.0	-8.6 , 0.7
Median	-0.07	-0.21	-0.14
P-value [2]	0.8868	0.9592	

Change From Baseline To Day 84			
N	40	34	39
Mean (Std Dev)	-2.31 (2.057)	-1.80 (1.477)	-1.46 (1.623)
95% C.I.	(-2.970, -1.654)	(-2.316, -1.286)	(-1.984, -0.932)
Min, Max	-7.7 , 0.0	-6.6 , -0.1	-5.6 , 1.9
Median	-1.99	-1.57	-1.14
P-value [2]	0.1334	0.4585	
Change From Baseline To Day 84			
N	41	34	39
Mean (Std Dev)	-2.89 (2.629)	-2.52 (1.908)	-2.42 (2.764)
95% C.I.	(-3.719, -2.059)	(-3.185, -1.854)	(-3.313, -1.521)
Min, Max	-9.5 , 1.0	-6.9 , -0.1	-11.7 , 2.0
Median	-2.71	-2.31	-1.29
P-value [2]	0.5998	0.6343	

[2] P-value for Wilcoxon rank-sum test comparing active treatment to placebo.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Final study report, Tables 11.1.2

A plot of change from baseline in laughing and crying episode rates over time (Figure below) shows the treatment difference between the DM/Q groups and placebo is maintained starting at Visit 2 (Day 15) till the end of the study. The treatment difference (compared to placebo) for DM 20 mg/Q 10 mg appears larger than for DM 30 mg/Q 10 mg between Visit 2 (Day 15) and Visit 4 (Day 57), but not at the end of the study (Day 84).

Figure 3: Change in laughing and crying episode rates over time by treatment group (ITT Population)



Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Final study report, Figure 11-1

6.1.5 Analysis of Secondary Endpoints(s)

Mean change in CNS-LS total score: The CNS-LS was a secondary endpoint in Study 123 (it was the primary endpoint in Study 102 and Study 106). The changes from baseline at each Visit by treatment groups and diagnosis are summarized in the following tables. In the overall subject population, with the exception of DM 20 mg/Q 10 mg at Visit 2 (Day 15), decreases from baseline were statistically significant between both DM/Q groups and placebo at all time points. In ALS subjects, changes from baseline were statistically significant between both DM/Q groups and placebo at all time points. In MS subjects, there were greater decreases in scores in the DM/Q groups compared with the placebo group at all time points; however, these differences were not statistically significant at almost all the time points.

Table 20: Mean change in CNS-LS total score (ITT population)

	DB Phase		
Parameter[a]	**AVP-923-30 (n = 110)**	**AVP-923-20 (n = 107)**	**Placebo (n = 109)**
Change from baseline to Visit 2			
n	107	97	106
Mean (SD)	-6.77 (5.239)	-6.27 (5.552)	-4.58 (4.982)
p-value[b,c]	0.0010	0.1252	
Change from baseline to Visit 3			
n	105	93	102
Mean (SD)	-8.03 (5.591)	-7.62 (5.421)	-5.70 (5.034)
p-value[b,c]	0.0003	0.0510	
Change from baseline to Visit 4			
n	103	89	98
Mean (SD)	-8.59 (5.745)	-8.89 (5.501)	-5.66 (5.038)
p-value[b,c]	<0.001	<0.001	
Change from baseline to Visit 5			
n	103	96	101
Mean (SD)	-8.17 (6.104)	-8.24 (6.126)	-5.72 (5.280)
p-value[b,c]	0.0002	0.0113	

[a]Visit 2 = Day 15, Visit 3 = Day 29, Visit 4 = 57, and Visit 5 = Day 84. Change from baseline was computed as post-baseline minus baseline.
[b]p-value was based on contrast comparing active treatment with placebo.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Final study report, Table 11-3, page 67

Table 21: Analysis of CNS-LS by diagnosis (ITT population)

	ALS (N=197)			MS (N=129)		
Statistics	AVP-923-30 (N = 65)	AVP-923-20 (N = 68)	Placebo (N = 64)	AVP-923-30 (N = 45)	AVP-923-20 (N = 39)	Placebo (N = 45)
Baseline						
N	65	68	62	45	39	45
Mean (Std Dev)	19.26 (4.708)	21.13 (5.269)	19.82 (4.622)	20.58 (5.216)	20.85 (4.626)	20.04 (4.738)
95% C.I.	(18.095, 20.428)	(19.857, 22.408)	(18.649, 20.996)	(19.011, 22.145)	(19.347, 22.346)	(18.621, 21.468)
Min, Max	8.0 , 32.0	13.0 , 33.0	13.0 , 32.0	13.0 , 34.0	13.0 , 31.0	11.0 , 31.0
Median	19.00	20.50	19.00	20.00	21.00	19.00

Change from Baseline to Day 15						
N	63	60	62	44	37	44
Mean (Std Dev)	-6.60 (4.864)	-6.80 (5.278)	-4.23 (4.792)	-7.00 (5.783)	-5.41 (5.942)	-5.07 (5.254)
95% C.I.	(-7.828, -5.378)	(-8.163, -5.437)	(-5.443, -3.009)	(-8.758, -5.242)	(-7.386, -3.424)	(-6.665, -3.471)
Min, Max	-21.0 , 4.0	-21.0 , 3.0	-17.0 , 5.0	-22.0 , 1.0	-23.0 , 4.0	-23.0 , 0.0
Median	-6.00	-6.00	-3.50	-6.00	-5.00	-3.50
P-value [1]	0.0004	0.0123		0.0693	0.9538	
Change from Baseline to Day 29						
N	62	57	60	43	36	42
Mean (Std Dev)	-7.81 (4.922)	-8.35 (5.041)	-4.97 (4.683)	-8.35 (6.484)	-6.47 (5.863)	-6.74 (5.383)
95% C.I.	(-9.056, -6.557)	(-9.688, -7.013)	(-6.176, -3.757)	(-10.344, -6.353)	(-8.456, -4.489)	(-8.416, -5.061)
Min, Max	-22.0 , 1.0	-21.0 , 3.0	-16.0 , 4.0	-25.0 , 1.0	-22.0 , 3.0	-19.0 , 2.0
Median	-7.00	-8.00	-4.00	-7.00	-5.50	-5.00
P-value [1]	<.0001	0.0003		0.1403	0.6477	
Change from Baseline to Day 57						
N	61	55	58	42	34	40
Mean (Std Dev)	-8.20 (4.819)	-8.98 (5.626)	-4.98 (4.996)	-9.17 (6.896)	-8.74 (5.373)	-6.65 (4.995)
95% C.I.	(-9.431, -6.962)	(-10.503, -7.461)	(-6.297, -3.669)	(-11.316, -7.018)	(-10.610, -6.861)	(-8.248, -5.052)
Min, Max	-22.0 , 2.0	-24.0 , 3.0	-18.0 , 7.0	-26.0 , 2.0	-23.0 , 0.0	-18.0 , 4.0
Median	-8.00	-8.00	-5.00	-8.00	-8.00	-6.00
P-value [1]	<.0001	<.0001		0.0233	0.1231	
Change from Baseline to Day 84						
N	61	58	57	42	38	44
Mean (Std Dev)	-7.75 (5.588)	-8.40 (6.266)	-4.98 (4.438)	-8.79 (6.809)	-8.00 (5.982)	-6.68 (6.126)
95% C.I.	(-9.185, -6.323)	(-10.044, -6.749)	(-6.160, -3.805)	(-10.908, -6.664)	(-9.966, -6.034)	(-8.544, -4.819)
Min, Max	-25.0 , 3.0	-23.0 , 6.0	-16.0 , 6.0	-26.0 , 1.0	-23.0 , 5.0	-22.0 , 6.0
Median	-7.00	-8.50	-5.00	-7.50	-8.00	-6.00
P-value [1]	0.0001	0.0018		0.1424	0.4713	

[1] p-value for treatment effect (active vs. placebo) within diagnosis in multiple regression model with baseline as covariate and site (US/non-US) and treatment as factors.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Final study report, Table 21.2

6.1.6 Other Endpoints

Number of episode-free days: In the overall subject population, with the exception of DM 20 mg/Q 10 mg at Visit 2 (Day 15), the differences between the mean number of days free from episodes of laughing or crying between both DM/Q groups and placebo were statistically significant favoring the DM/Q groups at all time points (see table below).

Table 22: Number of episode-free days (ITT population)

Statistics	AVP-923-30 (N = 110)	AVP-923-20 (N = 107)	Placebo (N = 109)
Visit 2 (Day 15)			
N	88	76	75
Mean (Std Dev)	8.8 (4.28)	8.1 (4.82)	7.1 (4.01)
95% C.I.	(7.86, 9.67)	(7.04, 9.25)	(6.18, 8.03)
Min, Max	1.0, 17.0	1.0, 20.0	1.0, 17.0
Median	10.0	8.0	7.0
P-value [1]	0.0123	0.1528	
Visit 3 (Day 29)			
N	89	81	80
Mean (Std Dev)	9.5 (4.76)	9.8 (4.41)	7.7 (4.06)
95% C.I.	(8.46, 10.46)	(8.85, 10.80)	(6.76, 8.57)
Min, Max	1.0, 21.0	1.0, 21.0	1.0, 15.0
Median	11.0	11.0	8.0
P-value [1]	0.0094	0.0015	
Visit 4 (Day 57)			
N	92	76	80
Mean (Std Dev)	20.8 (9.28)	21.5 (8.67)	16.9 (9.77)
95% C.I.	(18.91, 22.75)	(19.52, 23.48)	(14.69, 19.04)
Min, Max	1.0, 43.0	1.0, 33.0	1.0, 36.0
Median	24.0	25.5	18.0
P-value [1]	0.0071	0.0021	
Visit 5 (Day 84)			
N	86	72	79
Mean (Std Dev)	20.6 (7.92)	21.6 (6.68)	16.6 (9.41)
95% C.I.	(18.87, 22.27)	(20.06, 23.19)	(14.46, 18.68)
Min, Max	1.0, 31.0	2.0, 30.0	1.0, 28.0
Median	24.0	24.0	20.0
P-value [1]	0.0035	0.0002	

Note: Number of episode-free days since previous visit, where number of episode-free days = (number of days since last visit) - (number of days with at least one laughing/crying episode).
[1] P-value is based on two-sample t-test for comparing active treatment to placebo.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Final study report, Table 19

Percentage of subjects showing remission and clinical response: Remission was defined as no episodes reported during the last 14 days of study participation. Clinical response was defined as a 40% decrease in episode rate compared to the baseline episode rate. The analysis of subjects with clinical response and remission at Day 84 is summarized in the following table, and cumulative responder analysis displayed in the following figure. The differences in percentages of subjects with remission between both DM/Q groups and placebo group were statistically significant favoring the DM/Q groups. The differences in percentages of subjects who met the criteria for clinical response were statistically significant between the DM 30 mg/Q 10 mg and placebo, but not between DM 20 mg/Q 10 mg and placebo groups.

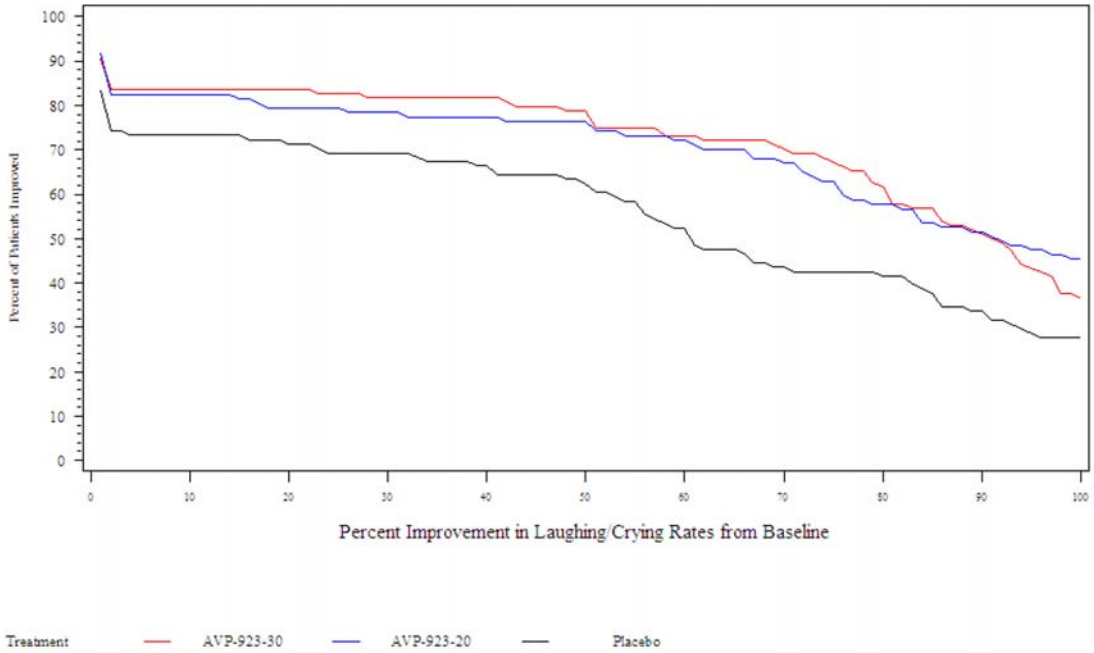
Table 23: Clinical response and remission at Day 84 (ITT population)

	AVP-923-30 (N = 110) n (%)	AVP-923-20 (N = 107) n (%)	Placebo (N = 109) n (%)
Remission [1] at Day 84			
Yes	45 (40.9%)	43 (40.2%)	22 (20.2%)
No	65 (59.1%)	64 (59.8%)	87 (79.8%)
P-value[3]	0.0009	0.0014	
Clinical Response [2] at Day 84			
Yes	85 (77.3%)	75 (70.1%)	67 (61.5%)
No	25 (22.7%)	32 (29.9%)	42 (38.5%)
P-value[3]	0.0112	0.1817	

[1] Remission means no episodes during the last 14 days of study participation.
[2] Clinical response means 40% decrease in episode rate (compared to baseline episode rate).
[3] P-value based on chi-square test comparing active treatment to placebo.

Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Final study report, Table 20.1

Figure 4: Laughing/crying episodes – Cumulative responder analysis by treatment group (ITT population)



Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Final study report, Figure 11-3

6.1.7 Subpopulations

Efficacy in the ALS and MS subpopulations has been discussed in the above sections.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

(b) (4)

(b) (4)

The differences between the DM 30 mg/Q 10 mg and DM 20 mg/Q 10 mg are 53.12% and 51.03%, respectively, for the primary endpoint; -4.11 and -3.88, respectively, for the mean change in the number of laughing and crying episodes; 74.8% and 73.7%, respectively for Time to onset of action (defined as the time in which a subject achieved a 30% decrease from baseline in the episode count); and 8.8 days and 8.1 days, respectively, for the mean number of episode free days at day 15. Significant differences in CNS-LS scores between the DM 30 mg/Q 10 mg and placebo were observed at all study visits whereas significant differences between the DM 20 mg/Q 10 mg and placebo were observed at Days 57 and 84 only.

However, other efficacy data suggest that DM 20 mg/Q 10 mg is better than DM 30 mg/Q 10 mg. Compared to placebo, the treatment difference for DM 20 mg/Q 10 mg is larger than for DM 30 mg/Q 10 mg between Visit 2 (Day 15) and Visit 4 (Day 57), but not at the end of the study (Figure 3). Although the mean number of episode free days at Day 15 is higher in the DM 30 mg/Q 10 mg group (8.8 days versus 8.1 days), at the end of the study the mean number of episode free days is higher in the DM 20 mg/Q 10 mg (21.6 days) compared to DM 30 mg/Q 10 mg group (20.6 days). Mean changes from baseline in CNS-LS total score in DM 30 mg/Q 10 mg group were numerically *less* than in the DM 20 mg/Q 10 mg group at Day 57 (-8.59 and -8.89, respectively) and at Day 84 (-8.17 and -8.24, respectively).

Thus, the overall efficacy of DM 20 mg/Q 10 mg is either similar to DM 30 mg/Q 10 mg, or marginally *better* in some endpoints/time points, or marginally *worse* in some endpoints/time points. The availability of two dose formulation without a clear advantage of one over the other in efficacy may potentially lead physicians to prescribe the larger dose in the belief that it may have better efficacy. Such a scenario has potential safety implications that are discussed in section 7.5.1 of this review.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The double-blind phase of Study 123 was for 12 weeks in duration. Persistence of efficacy over these 12 weeks has been discussed in the above sections.

6.1.10 Additional Efficacy Issues/Analyses

Data from Site 301: As discussed in section 3 of this review, the Applicant reports conducting 100% quality control data review at Site 301 (Principal Investigator: Dr. Soniza Alves Leon, Rio de Janeiro, Brazil), uncovering systemic deficiencies in compliance with FDA GCP regulations and ICH GCP guidelines. A total of 7 (7/326 = 2.1%) subjects (5 with ALS and 2 with MS) had enrolled at this Site. Therefore, the Applicant performed a statistical efficacy analysis excluding the subjects enrolled at Site 301. With *data from Site 301 omitted*, the primary analysis of the primary endpoint using longitudinal negative binomial model showed that in the overall ITT population, subjects treated with either DM 30 mg/Q 10 mg or DM 20 mg/Q 10 mg experienced

52.36% and 50.55%, respectively, reduction of episodes of inappropriate laughing/crying as subjects receiving placebo (with *all sites included* the data was 53.12% and 51.03% reductions, respectively); the differences between the DM/Q groups and placebo were statistically significant ($p < 0.0001$). Nonlongitudinal analysis was also done with data from Site 301 omitted. Nonlongitudinal analyses of laughing and crying episodes showed statistical significance for DM 30 mg/Q 10 mg and DM 20 mg/Q 10 mg (compared to placebo) for all subjects ($p < 0.0001$ and $p = 0.030$, respectively), essentially unchanged from when the data from Site 301 was included ($p < 0.0001$ and $p = 0.037$, respectively).

Applicant's efficacy conclusions: In the ITT population, results of the longitudinal negative binomial model show that subjects treated with DM 30 mg/Q 10 mg or DM 20 mg/Q 10 mg experienced approximately half as many episodes as subjects receiving placebo ($p < 0.0001$). The results of the nonlongitudinal analysis in the overall ITT population and ALS subset were similar to that in the longitudinal primary analysis; subjects with MS showed either a significant effect due to or a trend in favor of DM 30 mg/Q 10 mg or DM 20 mg/Q 10 mg when compared with placebo. The between-treatment group differences in the decrease from baseline in CNS-LS total scores were statistically significant for the DM 30 mg/Q 10 mg at all time points, and for DM 20 mg/Q 10 mg at Days 57 and 84, but not at Days 15 and 29. Overall, while it is difficult to reach a definitive conclusion, it appears that there may be an incremental benefit of the DM 30 mg/Q 10 mg formulation over DM 20 mg/Q 10 mg.

Reviewer's comments: I agree that in Study 123, efficacy has been demonstrated for DM 30 mg/Q 10 mg and DM 20 mg/Q 10 mg doses in the overall study population and in ALS subjects, with efficacy in the MS subgroup either nominally significant or trending in the right direction. As discussed in the above section 6.1.8 of this review, the overall efficacy of DM 20 mg/Q 10 mg is either similar to DM 30 mg/Q 10 mg, or marginally *better* in some endpoints/time points, or marginally *worse* in some endpoints/time points. The availability of two dose formulation without a clear advantage of one over the other in efficacy may potentially lead physicians to prescribe the larger dose in the belief that it may have better efficacy. Such a scenario has potential safety implications that are discussed in section 7.5.1 of this review

7 Review of Safety

7.1 Methods

The safety analysis population consisted of all randomized subjects exposed to at least one dose of study treatment.

Safety in the clinical trials was assessed by collection of adverse events, clinical assessment of subjects including vital signs, and testing including clinical laboratory parameters and electrocardiogram (ECG). O_2 saturation assessments were performed in Study 123. Pooling of studies is discussed further below in this section.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The DM/Q combination product development program was conducted under IND 56,954. The Applicant conducted a total of 19 clinical studies, 12 of which were Phase I which enrolled healthy volunteers and subjects with hepatic or renal impairment. There was one additional investigator-sponsored clinical study. A summary of the clinical trials in the development program is found in Table 8. A brief discussion of which clinical studies were submitted in the original NDA and which additional studies are new to the Complete Response is found in section 5.1 of this review.

The Applicant provided a fully updated Integrated Summary of Safety (ISS) in the Complete Response. The ISS seeks to focus on the safety of the two new dose formulations using lower Q dose (10 mg), and integrates the data from the clinical studies using higher doses of DM and/or Q to highlight the differences in safety between the higher and lower doses of the components of the combination product. The ISS also includes an evaluation of the relationship between safety parameters and concomitant medications of special interest including those that interact with DM and Q drug metabolizing enzymes, CYP2D6 and CYP3A4, and those that are known to increase the risk of QT prolongation and could potentially interact with Q. Compared to the original NDA submission, the number of subjects exposed to the DM/Q in current ISS are higher and the duration of exposure are longer (up to 3 years).

Long-term safety data for the PBA population was from two long-term open-label studies: Study 107 and the open-label phase in Study 123. These two studies are described in section 5.3 of this review.

7.1.2 Categorization of Adverse Events

The ISS safety data comprised of all treatment-emergent adverse events, serious adverse events including deaths, AEs leading to withdrawal, clinical laboratory (chemistry, hematology, and urinalysis), electrocardiograms, vital signs and O_2 saturation assessments. Since physical examination abnormalities that were recorded post-baseline were reported as AEs, no separate analysis of physical examination results was done. The Applicant designated several events as special-interest adverse events; these are discussed in section 7.3.5 of this review.

The Applicant defined an adverse event (AE) as any untoward medical occurrence or unintended change from the subject's baseline (pre-treatment) condition, including intercurrent illness, that occurs during the course of a clinical trial after treatment has started, whether considered related to treatment or not. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Clinical AEs were described by diagnosis and not by symptoms when possible (e.g., cold, seasonal allergies, etc., instead of "runny nose."). I reviewed the Applicant's definition of an SAE; this definition is consistent with 21CFR312.32(a).

In all the controlled and uncontrolled trials of subjects with PBA, subjects received a diary in which they recorded any AEs that had occurred since the last visit. On the Visit days, subjects were questioned regarding any AEs that might have occurred since their previous visit with non-leading questions. AEs were also recorded when reported spontaneously by the subject. At each study visit, for each AE, the following were recorded in the CRF: verbatim description, date of onset, whether or not the event started before the first dose of the investigational product, intensity, whether or not serious, outcome, relationship to study drug and action taken with respect to investigational product.

The following definition was used to designate an AE as a treatment-emergent: All AEs that begin on or after the date of first dose of a study, and on or before the *earlier* of (1) 30 days after the last dose or (2) the date of the final follow-up visit. Since the date of the final follow-up visit was different for different studies, treatment emergence of AEs was determined for each study separately. For subjects who enrolled in a second study (e.g., open-label studies), continuing AEs that began in the first study and continued into the second study was not be counted as a TEAE for the second study, unless the AE changed in frequency or severity. Any AE that began on or after the first dose date of the second study was considered a TEAE in the second study.

Adverse events from the integrated studies (Pool 1; see further below in this section) were recoded to MedDRA version 10.1. AEs were then classified by system organ class and preferred term. The adverse event dataset (AE) for the integrated studies (Pool 1) contained 5,625 reported verbatim terms that were coded into 1,170 preferred terms and 25 body system terms. I reviewed approximately 15% of verbatim terms at random to assess the appropriateness of the coding of the verbatim terms into preferred terms for the AE dataset. There were a few instances of inappropriate coding. For example, 'jaw tight and quivering' was coded as 'paresthesia'. Verbatim term 'jerking of eyes (eye muscle spasm)' was coded to 'ciliary muscle spasm'; ciliary muscles are responsible for pupillary constriction, not movement of the eyes. Coding for other terms did not reflect the potential significance of the verbatim term. For example, 'Rt, parietal contusion' was simply coded as 'contusion' masking a potential head injury. 'Lower calf warm to touch' was coded as 'feeling hot', not quite reflecting the potential for a warm lower calf to be a manifestation of more serious deep vein thrombosis. One subject (#102-011-012) reported '(fall) bruised back' while on DM30 only in Study 102 which was coded to 'contusion', but was not also coded to 'fall'. I also reviewed all the preferred terms and their mapping to body systems, and what preferred terms were contained in a given body system. There were few discrepancies. For example, 'diplopia', 'ophthalmoplegia' and 'oscillopsia' were coded to 'eye disorders'; however, many important causes of these conditions result from central nervous disorders. I audited the narratives which were provided for SAEs and AE leading to withdrawal to see if the AEs described in the narrative were captured in the CRFs, and whether they were appropriately coded to preferred terms. Despite the above noted few discrepancies, overall, the coding of the verbatim terms to preferred terms was appropriate and should allow for reasonably accurate assessment of TEAEs.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

All clinical studies were grouped into 5 pools for safety analyses. Within each pool, descriptive analysis between treatment groups was performed on all AEs (including all deaths and other SAEs) and general safety data.

Pool 1: A total of 1,679 unique subjects (healthy volunteers, patients with PBA and patients with diabetic peripheral neuropathy) from 11 studies were combined to form Pool 1; of these, 1,396 were exposed to any DM/Q combination, 316 to placebo and the remaining to DM or Q only. The following are the 11 studies that were pooled: Study 100, Study 101, Study 102, Study 103, Study 105, Study 106, Study 107, Study 109, double-blind phase of Study 123, Study 125 and open-label phase of Study 123. Eight short-term Phase I PK and drug-drug interaction studies were excluded because the data from these studies were derived from special studies or special population. A total of 240 subjects were in these 8 excluded studies (216 healthy volunteers, 12 with hepatic impairment, and 12 with renal impairment). The Agency accepted this proposed pooling of studies during the Type C meeting of 11/18/09.

Pool 2: A total of 1,069 subjects with PBA from 5 Phase III ***controlled and uncontrolled*** studies were combined to form Pool 2. These controlled studies in PBA subjects were: Study 102, Study 106, double-blind phase of Study 123, open-label Study 107 and the open-label phase of Study 123.

Pool 3: A total of 616 unique subjects with PBA from 3 Phase III ***controlled studies*** were combined to form Pool 3. These three controlled studies in PBA subjects were: Study 102, Study 106 and double-blind phase of Study 123.

Pool 4: There were 887 subjects (623 subjects were not previously enrolled in any Applicant-sponsored study) with PBA who had "long-term exposure" to a DM/Q combination; these subjects were combined to form Pool 4. "Long-term exposure" was defined as at least 90 days of total exposure to DM/Q totaled over all studies in which the subject previously participated before enrolling in Study 107 or the open-label phase of Study 123. Results are included for 75 patients who received DM 20 mg/Q 10 mg during the double-blind phase and DM 30 mg/Q 10 mg in the OLE phase for a total exposure ≥90 days (no patients received DM 20 mg/Q 10 mg for ≥90 days since the only dose given in the OLE phase was DM 30 mg/Q 10 mg). Pool 4 also includes 7 patients who received placebo during the DB phase and DM 30 mg/Q 10 mg in the OLE phase for a total exposure ≥90 days.

Pool 5: A total of 415 subjects with painful diabetic peripheral neuropathy from one Phase II (Study 105) and one Phase III (Study 109) studies were combined to form Pool 5. The Applicant refers to this population as "Other Safety Patients (OSP)" in the ISS.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Across the development program consisting of 19 clinical studies (all completed), there were 1, 919 unique subjects who were enrolled (randomized to various arms) in the clinical studies: 1,069 were subjects with PBA, 411 healthy volunteers, 415 subjects with diabetic peripheral neuropathy and 24 subjects in "special population" category (hepatic and renal impairment). The following tables summarize the study drug exposure by treatment for all subjects in the entire development program and by each major primary disease (ALS and MS). As specified in the ISS Statistical Analysis Plan, the following convention was used to display the exposure data. Within a column of the following tables, each subject is counted only one time, and the subject's duration of exposure is summed across the studies in which that subject was exposed to the indicated dose levels or treatments. For example, if a subject took 20 mg DM/10 mg Q for 75 days in double-blind phase of Study 123 and 30 mg DM/10 mg Q for 75 days in the open-label phase of Study 123, that subject would be summarized as having 75 days of exposure in the 20 mg DM/10 mg Q treatment category, 75 days of exposure in the 30 mg DM/10 mg Q treatment category, and 150 days of exposure in the "All doses with 10 mg Q" treatment category.

Subjects who enrolled in multiple studies may have received more than one treatment. Safety data that were collected on or after the date of first dose in the initial study and prior to the date of first dose in the second study was attributed to the first-study treatment. Data collected on or after the day of first dose in the second study was attributed to the second-study treatment. If the same treatment was received during consecutive studies, all safety data collected on or after the first dose date in the first study was handled together.

From the following tables, a total of 364 subjects (all had PBA) were exposed to (b) (4) DM 20 mg/Q 10 mg or DM 30 mg/Q 10 mg for a combined person-time exposure of 103.7 person-years; with the exception of one subject, all of these subjects were exposed to any DM/Q10 mg dose for less than 180 days. In comparison, 1,034 subjects were exposed to any DM/Q30 mg dose for a combined person-time exposure of 833.7 person-years; 392 of these subjects had exposure ≥ 0.5 year (180 days), 294 subjects had exposure ≥ 1 year, and 159 subjects had exposure ≥ 2 years. Although the numbers of subjects exposed to the (b) (4) doses are small and the duration of exposures relatively short, there is substantially greater and longer duration of exposure at higher doses of Q (DM/Q30 mg) which provide informative data about the safety of the (b) (4) clinically useful doses. Thus, the combined safety exposure data for any DM/Q combination are consistent with the ICH recommendation.

Table 24: Study drug exposure by treatment across the entire development program

	AVP-923							
Duration of Dosing	20 mg DM/ 10 mg Q (N=107)	30 mg DM/ 10 mg Q (N=333)	All doses with 10 mg Q (N=364)	All doses with 30 mg Q (N=1034)	All AVP-923 (N=1500)	Placebo (N=369)	DM 30 mg [1] (N=149)	Q 30 mg (N=37)
N	107	333	364	1034	1500	367	149	37
Mean (days)	74.8	89.7	104.0	294.5	229.4	63.7	8.1	27.6
Median (days)	84.0	85.0	88.5	92.0	92.0	84.0	1.0	29.0
SD (days)	22.94	56.46	64.14	394.27	343.40	34.68	11.18	4.76
Min, Max (days)	1, 96	1, 178	1, 184	1, 1612	1, 1612	1, 124	1, 33	5, 32
Total Exposure (days)	8007	29858	37865	304491	344149	23378	1212	1023
N	107	333	364	1034	1500	367	149	37
Mean (years)	0.20	0.25	0.28	0.81	0.63	0.17	0.02	0.08
Median (years)	0.23	0.23	0.24	0.25	0.25	0.23	0.00	0.08
SD (years)	0.063	0.155	0.176	1.079	0.940	0.095	0.031	0.013
Min, Max (years)	0.0, 0.3	0.0, 0.5	0.0, 0.5	0.0, 4.4	0.0, 4.4	0.0, 0.3	0.0, 0.1	0.0, 0.1
Total Exposure (years)	21.9	81.7	103.7	833.7	942.2	64.0	3.3	2.8
>=0.5 years	0	0	1 (0.3%)	392 (37.9%)	393 (26.2%)	0	0	0
>=1.0 years	0	0	0	294 (28.4%)	294 (19.6%)	0	0	0
>=1.5 years	0	0	0	212 (20.5%)	212 (14.1%)	0	0	0
>=2.0 years	0	0	0	159 (15.4%)	159 (10.6%)	0	0	0
>=2.5 years	0	0	0	117 (11.3%)	117 (7.8%)	0	0	0
>=3.0 years	0	0	0	80 (7.7%)	80 (5.3%)	0	0	0
>=3.5 years	0	0	0	41 (4.0%)	41 (2.7%)	0	0	0
>=4.0 years	0	0	0	11 (1.1%)	11 (0.7%)	0	0	0

Note: Figures across a row may not add up as a given subject for example may have taken DM 20 mg/Q 10 mg in the Study 123-DB and then DM 30 mg/Q 10 mg in Study 123-OLE but is counted only once under All DM/Q10 mg.; 0.5 year = 180 days.
Source: NDA Complete Response 4/30/10; 1.11.3 Efficacy amendment (6/25/10) in response to my request for additional data; Table 999.3.3, page 1/1.

Table 25: Study drug exposure over all clinical studies by treatment and primary disease (ALS and MS)

	20 mg DM / 10 mg Q	30 mg DM /10 mg Q	All DM / 10 mg Q	All DM / 30 mg Q	All DM/Q doses	Placebo	DM 30 mg#	Q 30 mg
All subjects in development program								
N	107	333*	364	1034^	1500	367	149	37
Total Exposure (years)	21.9	81.7	103.7	833.7	942.2	64.0	3.3	2.8
>=0.5 years	0	1 (0.3%)	1 (0.3%)	392 (37.9%)	393 (26.2%)	0	0	0
>=1.0 years	0	0	0	294 (28.4%)	294 (19.6%)	0	0	0
ALS subjects with PBA								
n	68	158*	181	258^	439	64	33	37
Total Exposure (years)	13.7	47.0	60.7	217.0	277.6	14.2	2.5	2.8
>=0.5 years (n)	0	0	1 (0.6%)	126 (48.8%)	127 (28.9%)	0	0	0
>=1.0 years (n)	0	0	0	79 (30.6%)	79 (18.0%)	0	0	0
MS subjects with PBA								
n	39	111*	119	252^	371	119	0	0
Total Exposure (years)	8.2	33.9	42.1	405.0	447.1	23.9	NA	NA
>=0.5 years (n)	0	0	0	177 (70.2%)	177 (47.7%)	0	0	0
>=1.0 years (n)	0	0	0	148 (58.7%)	148 (39.9%)	0	0	0

DM = Dextromethorphan; Q = Quinidine Sulfate; NOS = not otherwise specified; NA = Not Applicable.
#Some healthy volunteers in study 103 received doses of 45 mg DM or 60 mg DM; all others received 30 mg DM.
*Of the 333 subjects who received DM 30 mg/Q 10 mg dose, 158 were ALS subjects, 111 were MS subjects, and 64 were healthy volunteers participating in Study 126 QT study (n=50) and PK Study 125 (n=14).
^ Of the 1,034 subjects who received DM 30 mg/Q30 mg dose, 258 were ALS subjects, 252 were MS subjects, and 524 were PBA subjects with other primary diseases, healthy volunteers participating in PK studies.
Note: Figures across a row may not add up as a given subject for example may have taken DM 20 mg/Q 10 mg in the Study 123-DB and then DM 30 mg/Q 10 mg in Study 123-OLE but is counted only once under All DM/Q10 mg.
Source: NDA Complete Response 4/30/10; 1.11.3 Efficacy amendment (6/25/10) in response to my request for additional data; adapted from Tables 999.3.1-3, page 1-8/8.

Pool 3 combines the three controlled studies of subjects with PBA (Study 102, Study 106 and Study 123). The following table summarizes the study drug exposure for Pool 3 and for each of the underlying diseases (ALS and MS). In Study 102, there was no concurrent placebo group and was for only 28 days in duration compared to 12 weeks for the remaining two controlled studies. Pooling of these studies will therefore result in an imbalance in the exposure between the treatment groups. To account for this imbalance, I used person-time exposures to calculate exposure-adjusted incidence rates in the relevant sections of this review.

Table 26: Subject exposures by treatment group in Pool 3.

	20 mg DM / 10 mg Q	30 mg DM /10 mg Q	All DM / 10 mg Q	30 mg DM / 30 mg Q	All DM/Q doses	Placebo	DM 30 mg[#]	Q 30 mg
POOL 3								
All subjects								
N	107	110	217	146	363	183	33	37
Total Exposure (years)	21.92	24.43	46.35	19.34	65.69	38.08	2.50	2.80
ALS subjects								
N	68	65	133	70	203	64	33	37
Total Exposure (years)	13.69	14.41	28.11	4.71	32.82	14.17	2.50	2.80
MS subjects								
N	39	45	84	76	160	119	0	0
Total Exposure (years)	8.23	10.02	18.25	14.63	32.88	23.90	NA	Na
Study 123-double-blind								
All Subjects								
N	107	110	217		217	109		
Total Exposure (years)	21.92	24.43	46.35		46.35	23.73		
ALS subjects								
N	68	65	133		133	64		
Total Exposure (years)	13.69	14.41	28.11		28.11	14.17		
MS subjects								
N	39	45	84		84	45		
Total Exposure (years)	8.23	10.02	18.25		18.25	9.56		
Study 106								
MS subjects (No ALS)								
N				76	76	74		
Total Exposure (years)				14.63	14.63	14.34		
Study 102								
ALS subjects (No MS)								
N				70	70		33	37
Total Exposure (years)				4.71	4.71		2.50	2.80

Source: NDA Complete Response 4/30/10; Module 5.3.5.3; ISS, modified from Tables 4.1.3 and 4.2.2, and Reviewer's analysis of DM and EX datasets (EX+PRIMDIS from DM) with deletion of duplicate entry for subject 102-015-003 who was listed for both ALS and O under PRIMDIS.

I also summarize in the following table the extent of exposure in the pooled open-label studies of PBA subjects (Study 107 and open-label phase of Study 123). The median exposure for ALS subjects to DM 30 mg/Q 10 mg was 85 days compared to 301 days of exposure to DM 30 mg/Q 30 mg. Similarly, MS subjects had a median exposure of 84 days to DM 30 mg/Q 10 mg compared to 588 days to DM 30 mg/Q 30 mg. To account for this imbalance, I used person-time exposures to calculate open-label exposure-adjusted incidence rates between DM 30 mg/Q 10 mg and DM 30 mg/Q 30 mg dose groups in the relevant sections of this review.

Table 27: Study drug exposure by treatment in the open-label studies of PBA subjects (Study 107 and Study open-label phase of Study 123)

	20 mg DM / 10 mg Q	30 mg DM /10 mg Q	All DM / 10 mg Q	All DM / 30 mg Q	All DM/Q doses	Placebo	DM 30 mg[#]	Q 30 mg
All subjects								
N	0	253	253	552	805	0	0	0
Total Exposure (years)	NA	56.5	56.5	761.7	818.2	NA	NA	NA
>=0.5 years	0	0	0	391 (70.8%)	391 (48.6%)	0	0	0
>=1.0 years	0	0	0	291 (52.7%)	291 (36.1%)	0	0	0
>=3.0 years	0	0	0	76 (13.8%)	76 (9.4%)	0	0	0
ALS subjects								
N	NA	146	146	176*	322	NA	NA	NA
Total Exposure (years)		32.6	32.6	185.3	217.9			
MS subjects								
N	NA	107	107	223*	330	NA	NA	NA
Total Exposure (years)		23.9	23.9	390.4	414.3			

DM = Dextromethorphan; Q = Quinidine Sulfate; NOS = not otherwise specified; NA = Not Applicable.
#Some healthy volunteers in study 103 received doses of 45 mg DM or 60 mg DM; all others received 30 mg DM.
*176 subjects had ALS; however, there were 17 subjects with other motor neuron diseases, resulting in a total of 193 subjects with ALS and other motor neuron diseases in Study 107. Total number of ALS subjects and MS subjects do not add up to 552 because Study 107 enrolled other subjects with diverse neurological disorders with PBA.
Source: NDA Complete Response 4/30/10; 1.11.3 Efficacy amendment (6/25/10) in response to my request for additional data; adapted from Tables 999.3.4, page 1/8; and reviewer's analysis of EX and DM dataset (DMEX.S107+123OL; Tabulate, EXDUR as analysis variable; variables PRIMDIS and PDCAT); 0.5 yr = 182.625 days; 1 yr = 365.25 days.

7.2.2 Explorations for Dose Response

In the original NDA, the Applicant conducted definitive trials using DM 30 mg/Q 30 mg formulation. In the Approvable Letter, the Agency recommended 10 mg of Q in the formulation, and to identify the lowest doses that are effective and safe. In response the Applicant developed two new formulations using the lower Q dose (DM 30 mg/Q 10 mg and DM 20 mg/Q 10 mg) which were used in Study 123. Throughout this review, the safety of both these two doses is explored and discussed.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was done.

7.2.4 Routine Clinical Testing

Routine clinical testing the large Phase III clinical trials included collection of adverse events, vital signs, laboratory and ECG assessments.

7.2.5 Metabolic, Clearance, and Interaction Workup

The Applicant conducted several clinical studies to evaluate drug-drug interaction. These studies are discussed in section 7.5.5 of this review.

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

The Applicant identified several important adverse events that are known to occur with the use of DM or Q. Important events like hypersensitivity reactions and seizures in DM, and thrombocytopenia in Q, were identified as events of critical significance. These are discussed in section 7.3.4 of this review. The Applicant assessed the cardiac effects of Q and important drug-drug interactions. These are discussed in section 7.3.5 and 7.5.5 of this review.

7.3 Major Safety Results

7.3.1 Deaths

In the original NDA submission, there was one death in a Phase I study, one death in the controlled trials and 48 deaths in the then ongoing open-label study (Study 107). The safety database from the controlled trials were very small: 70 ALS subjects exposed to DM 30 mg/Q 30 mg for 4 weeks, 76 MS subjects exposed to DM 30 mg/Q 30 mg for 12 weeks, and 74 placebo subjects.

The open-label Study 107 enrolled 463 subjects with PBA (as of the cut-off date of 10/31/05 in the original NDA) who were treated with DM 30 mg/Q 30 mg BID for an initial 52-week period followed by an option for completers to enroll in an additional Extension Phase. A total of 191 subjects (41.3%) enrolled had MS, 156 (33.7%) had ALS, and the remaining 116 subjects had PBA with diverse neurological disorders. There were 48 deaths reported as of the cut off-date in the original NDA: 40 in the ALS subjects, 4 in MS subjects and the remaining 4 deaths (1 each) in primary lateral sclerosis, progressive bulbar palsy, spinocerebellar ataxia and progressive supranuclear palsy. The majority of the cause of death in ALS subjects was due to respiratory failure (24 deaths), other respiratory-related causes (pneumonia) or cardiac/cardio-respiratory arrest. The deaths in MS subjects were due to acute myelomonocytic leukemia, myocardial infarction and non-accidental overdose. Dr. Farkas highlighted several deaths from this open-label study that appear to underscore the potential for drug-drug interactions to adversely affect the safety profile of DM/Q.

Overall deaths in the development program presented in the Complete Response: There were a total of 92 deaths in the entire safety database. These deaths are summarized in the following table. The majority (83/92 = 90.2%) of these deaths occurred in open-label studies (Study 107, Study 123 open-label phase, and Study 105), and most (75/92 = 81.5%) of the deaths

were in ALS subjects. The 10 deaths in the double-blind and open-label phases of Study 123, 1 death in Study 105 and 31 of the 79 deaths in Study 107 are new to the Complete Response.

Table 28: Summary of deaths across the development program

Study Number	Dose	Primary Disease	Number of Deaths	Duration of Exposure (days)	Adverse Event / Cause of Death (study day)
07-AVR-123[a] Double-blind and Open-label phases	DM 30 mg/ Q 10 mg	PBA (ALS)	6[a]	57 to 169	4 Respiratory Failure (41-95); Dyspnea (96); Pneumonia (113)
	DM 20 mg/ Q 10 mg	PBA (ALS)	3	84	Respiratory Failure (84)
				23	Disease Progression (41)
				84	Oxygen Saturation Decreased (85)[b]; Respiratory Depression (85, 89)
	Placebo	PBA (ALS)	1	8	Disease Progression (40)
99-AVR-100 Phase I PK	DM 30 mg/ Q 75 mg	Healthy volunteer[c]	1	4	Myocardial infarction (6 days after last dose of study drug)
99-AVR-102 Controlled	DM 30 mg/ Q 30 mg	PBA (ALS)	1	28[d]	Respiratory failure (30)
01-AVR-105 Open-label	DM 30 mg/ Q 30 mg	DPN	1	29	Arrhythmia (33) Myocardial Infarction (33)
02-AVR-107 Open-label	DM 30 mg/ Q 30 mg	PBA (ALS) 64 PBA (Other[e]) 15	79	11 to 1393	53 Respiratory Failure; 26 other
Total			92		

[a] Deaths are shown for both phases of the study, DB and OLE. For the DM 30 mg/Q 10 mg dose, there were 3 deaths in the double-blind phase and 3 additional deaths in the open-label extension.
[b] Death of ALS patient #123-301-501 was reviewed by the Mortality Endpoint Adjudication Committee, which concluded that it was probably due to progression of the underlying disease, i.e. unlikely to be treatment-related.
[c] Not included in the integrated dataset; this death was previously presented in the original NDA submission of 1/30/06.
[d] For the subjects with missing last dose dates in the database, the last dose date from the safety narrative was used.
[e] Other: Parkinson's, primary lateral sclerosis, progressive bulbar palsy, progressive supranuclean palsy, spinocerebelar ataxia.
DM = dextromethorphan; Q = quinidine; PBA = pseudobulbar affect; ALS = amyotrophic lateral sclerosis; DPN = painful diabetic peripheral neuropathy.
Source: NDA Complete Response 4/30/10; module 5.3.5.3.ISS, modified from Table 15, page 54.

Deaths in Study double-blind phase of Study 123: A total of 326 subjects participated in the 12-week Study 123; of these subjects, 197 (60.4%) subjects had ALS and the remaining 129 (39.6%) had MS. There were a total of 7 deaths during the double-blind phase of Study 123, and 3 additional deaths during the open-label phase of Study 123. All the deaths were in ALS subjects; no deaths were reported in MS subjects. The following table summarizes the demographics, exposures and fatal AEs experienced by the 7 subjects who died in the double-blind phase of Study 123.

Table 29: Summary of the demographic, exposure and fatal AEs experienced by the 7 subjects who died in double-blind phase of Study 123.

Treatment group	Subject #	Sex	Metabo-lizer category	Age at ALS diagnosis (yrs)	Time from Diagnosis to randomiz-ation (months)	Preferred terms	Time from Diagnosis to event (months)	Total duration of exposure (days)	Study day of AE start (days)	Day of AE start[#] from last dose (days)

Treatment group	Subject #	Sex	Metabo-lizer category	Age at ALS diagnosis (yrs)	Time from Diagnosis to randomiz-ation (months)	Preferred terms	Time from Diagnosis to event (months)	Total duration of exposure (days)	Study day of AE start (days)	Day of AE start# from last dose (days)
DM 20/Q 10	133-501	F	Slow	53.6	17	Respiratory failure	19.8	84	(b) (6)	
	135-501	M	Extensive	41.8	3	Disease progression	4.4	23		
	301-501	M	Extensive	45.8	26	Oxygen saturation decreased	28.8	84		
						Respiratory depression*	28.8	84		
DM 30/Q 10	126-501	M	Extensive	66.5	6	Increased bronchial secretion	8.8	84		
						Respiratory failure	9.2	84		
	135-508	M	Extensive	64.8	2	Respiratory failure	4.8	57#		
	301-504	F	Extensive	56.0	24	Pneumonia	27.8	84		
Placebo	135-511	M	Extensive	59.6	5	Disease progression	6.3	8^		

*There were two reported AEs of 'respiratory depression' in this subject: one was reported to start on study day 85 and another on study day 89; both AEs were reported to have ended on study day 89 – the day of death.
^Exposure of 8 days is from the narrative; the total duration per EX dataset is 40 days.
#Table 4 (page 26) of the Respiratory Report (Module 5.3.5.3) has a column for "Days off study drug at the time of ***death***". Data from this column for subjects flagged # are: (b) (6) days (subject 301-501); (b) (6) days (subject 135-508); (b) (6) days (subject 301-504); for other subjects, the day of AE onset is the day of death. In addition, the exposure for subject 135-508 from this report is 82.
Source: NDA Complete Response 4/30/10; Reviewer's analysis of DM, EX and AE datasets: DMEXAE .Pool3.AETRTEM .ALS.S123.Deaths.Summary in common AEs folder, Subset Fatal AEs USUBJID 1; DMEXAE.Pool3.AETRTEM .ALS.S123.Deaths.Summary in common AEs folder). Tabulate: ARM, USUBJID, SEX, Age at DX, DXDUR, AEDECOD, AESTDY, DUREXPO and AESLDDY).

There appears to be approximately a 3-fold higher risk of death in subjects exposed to any DM/Q10 dose as compared to the placebo subjects (see table below); however, the absolute numbers of deaths in the various treatment groups are small. From the above table (Table 29), 3 deaths occurred (b) (6) days after the last dose of study medication. In one subject (#123-301-504) in particular the fatal event of pneumonia began 30 days after the last dose and died (b) (6) days after the last dose. Assuming that these three deaths occurring after relatively longer interval after study discontinuation is less likely to be drug related, the incidence of deaths in the ALS subjects exposed to any DM/Q 10 mg dose is 0.03 compared to 0 in the placebo group (Table 30). The imbalance in deaths is further discussed in section 7.3.5 of this review.

Table 30: Deaths in the double-blind phase of Study 123 by treatment groups, for the overall population and ALS subjects

	All subjects				ALS subjects			
	DM20 /Q10	DM30/ Q10	Any DM /Q10	Placebo	DM 20 /Q 10	DM 30 /Q 10	Any DM /Q10	Placebo
N	107	110	217	109	68	65	133	64
All Deaths, n	3	3	6	1	3	3	6	1
Incidence, n/N [95% CI*]	0.028 [0.01 to 0.08]	0.027 [0.01 to 0.08]	0.028 [0.01 to 0.06]	0.009 [0.002 to 0.05]	0.044 [0.02 to 0.12]	0.046 [0.02 to 0.13]	0.045 [0.02 to 0.09]	0.016 [0.004 to 0.08]
Revised deaths#, n	3	1	4	0	3	1	4	0
Incidence, n/N [95% CI*]	0.028 [0.01 to 0.08]	0.009 [0.002 to 0.05]	0.018 [0.007 to 0.05]	0 [0 to ∞]	0.044 [0.02 to 0.12]	0.015 [0.003 to 0.08]	0.03 [0.01 to 0.07]	[0 to ∞]

DM = dextromethorphan; Q = quinidine; CI = confidence intervals
#exclusion of deaths that occurred 27-33 days after the last dose of study medication.
*asymptotic confidence intervals may not be accurate because the events are very few.
Source: NDA Complete Response 4/30/10; Reviewer's analysis of DM and AE dataset.

The narratives for the 10 deaths in Study 123 are below.

Subject 133-501 (**respiratory failure**): 55-year old Caucasian female diagnosed with ALS on 12/19/06 was randomized to DM 20 mg/Q 10 mg dose group in Study 123. Study drug was first administered on 6/12/08 and the last dose was on 9/3/08 (84 days). Her past medical history included essential hypertension, migraine headaches, painful right frozen shoulder, alcohol use approximately twice a month and seasonal allergies; PEG was placed on 6/2/08 (prior to randomization) due to "rapid progression of ALS" (swallowing difficulties?) and choking episodes (she had declined an even earlier recommendation for PEG placement). Concomitant medications included paroxetine, riluzole, lisinopril, ibuprofen PRN and diphenhydramine PRN. On (b) (6) the investigator was notified that the patient was too ill to complete the end of study visit scheduled for the next day. On (b) (6) she was admitted to a hospital to treat possible ileus; her respirations were of normal effort and breath sounds were clear. Laboratory tests were remarkable for a low sodium level (117; ref range: 136-145) at admission. By that evening she deteriorated and "Do Not Resuscitate" orders were instituted. She died few hours later. The hospital diagnosis was dehydration and cardiac arrest. An autopsy done (b) (6) concluded that it was likely that the subject died due to complications secondary to ALS. The investigator assessed the event as most likely related to pre-existing disease (progression of ALS) and not related with study medication and the Applicant agrees. Reviewer's comments: PEG placement prior to randomization suggests that the underlying ALS was at an advanced stage even before randomization. However, an adverse effect of the study drug on the overall course of the disease or the rate of the disease progression can not be excluded.

Subject 135-501 (**disease progression**): 42-year old Caucasian male diagnosed with ALS on 3/18/08 was randomized to DM 20 mg/Q 10 mg dose group in Study 123. Study drug was first administered on 5/20/08 and the last dose on 6/12/08 (per CRF), for a total of 23 days. Past medical history was significant for hypertension, testicular cancer (S/P right inguinal orchiectomy in 10/07; no further details), left nephrectomy (kidney donor) and PEG placement on (b) (6) for nutritional support. Concomitant medications included oxycodone elixir prn, baclofen, ramipril, tizanidine Bayer aspirin and Restoril. Study medication was terminated prematurely on 6/12/08 due to health state decline and "end stage ALS". He was seen on 6/17/08 for study close out assessment. He received hospice care and died at home on (b) (6) No relevant diagnostic or laboratory tests were done. No records or death certificate are reportedly available. An autopsy was not performed. Per the accompanying notes in the Serious Adverse Event Report Form of the CRF, the Principal Investigator considered the relationship of death due to study medication as unlikely with alternative causality of rapid progression of ALS with "symptoms begin in 10/2009 (sic)". Reviewer's comments: The duration of ALS from diagnosis to randomization of only 2.1 months and death occurring only (b) (6) days post randomization, suggests that there was quite a rapid progression of disease. PEG placement prior to randomization indicates that the underlying ALS was at an advanced stage even before randomization. It is unknown if other explanatory factors such as long delay from ALS symptoms onset (date is not clear) to diagnosis or bulbar onset were present.

Subject 301-501 (**respiratory depression**): 48-year Hispanic male diagnosed with ALS in Jan 2007 was randomized to DM 20 mg/Q 10 mg dose group in Study 123. Symptoms began sometime in 2006 with distal amyotrophy and fasciculations, dysphagia and dysphonia but no prior episodes of choking or aspiration. Exposure to the study drug began on 2/18/09 and the date of the last dose was on 5/9/09 (reportedly forgot to take study medication between 5/9/09 and 5/12/09), for a total of 81 days. He had a history of smoking 5 cigarettes per day since age 15 and discontinued smoking in Sep 2008. Concomitant medication was riluzole. On 3/18/09 (Day 29) he reported change in breathing pattern (referred to as difficulty breathing), however, his resting O_2 saturation at this visit was 98%. Final study visit was on 5/13/09. The follow-up information dated 9/25/09 states that sometime between 4/15/09 and 4/21/09, he experienced mental confusion, disorientation, occasional hallucinations, and "fell and hit his head".

The narrative states that at the last visit (5/13/09), the subject was lucid, oriented in time and space, with intermittent apnea but was not cyanotic, but oxygen saturation low (83%); these events from this visit were

coded as 'oxygen saturation decreased' and 'respiratory depression'. The subject apparently did not have dyspnea or any kind of complaint, and did not receive any specific treatment for this finding. Several days after the last dose, on (b) (6), the subject was found dead in sleep. No autopsy was performed. The cause of death was thought to be respiratory depression. The investigator felt that the death was possibly related to either ALS or the study medication. The Applicant concluded that ALS by itself can evolve with bulbar symptoms and contribute to low saturation of oxygen, and that there is not enough information to consider the reported event as related to the study medication. Reviewer's comments: A causal relationship to the study medication, particularly affecting the rate of disease progression, can not be excluded.

Subject 126-501 (**respiratory failure**): 67-year old Caucasian male diagnosed with ALS on 1/18/08 was randomized to DM 30 mg/Q 10 mg dose group in Study 123. Study drug was first administered on 8/13/08 and the last dose was on 11/3/08 (83 days). ALS symptoms began in June 2007. His past medical history included hypertension, hypercholesterolemia, seasonal allergies and non-specific ST abnormality on ECG. PEG was placed on (b) (6) (prior to randomization) due to dysphagia. He began to use BiPAP beginning in July 2008 (prior to randomization). Concomitant medications included simvastatin, amlodipine and atorvastatin, Robinul (glycopyrrolate), Vitamin C, Vitamin E, Beta Carotene and naproxen PRN. At Screening, the subject's resting diurnal oxygen saturation was 92% and 94%, (two measurements) which were a deviation from inclusion criteria of ≥ 95%; he experienced a transient (10 seconds) event of desaturation with oxygen saturation drop of 4%. Subject was enrolled after obtaining approval from the Applicant's medical monitor. He reported two falls on 8/19/08 and 8/31/08, with the outcome reported as 'recovered'. He was unable to attend the final study visit on 11/4/08 (Day 83) because he required almost continuous suctioning of secretions. He died due to respiratory failure on (b) (6) days after the last dose). The Applicant reports that the death certificate is not available. The investigator assessed the event as most likely related to pre-existing disease (progression of ALS) and not related with study medication and the Applicant agrees. Reviewer's comments: Subject clearly had advanced disease and respiratory involvement prior to randomization as evidenced by BiPAP, PEG placement and transient oxygen desaturation. However, an adverse effect of the study medication on the rate of disease progression can not be excluded.

Subject 135-508 (**respiratory failure**): 65-year old male diagnosed with ALS on 7/7/08 was randomized to DM 30 mg/Q 10 mg dose group in Study 123. Study drug was first administered on 9/9/08 and the last dose administered was on 11/4/08 (56 days). Past medical history was significant for asthma, reflux, muscle cramps, dysphagia (1/15/08), aphasia and respiratory congestion. Relevant concomitant medications included pantoprazole, Avalax for sinus congestion, Advair 100/50 for asthma, Flonase inhalation spray, riluzole. On (b) (6) the site was notified by the family that the subject experienced fatal respiratory failure at home on (b) (6). The site was unable to obtain any additional information as the subject's family did not return any phone calls. The investigator concluded that the event of fatal respiratory failure was unrelated to the study medication and most likely related progression of ALS. The Applicant agrees with the investigator. Reviewer's comments: The duration of ALS from diagnosis to randomization of only 2.1 months and death occurring (b) (6) days post randomization (b) (6) days of treatment with study drug), suggests that there was quite a rapid progression of disease. It is unknown if other explanatory factors such as long delay from ALS symptoms onset (onset date is unknown) to diagnosis or bulbar onset were present. An adverse effect of the study drug on the rate of the disease progression can not be excluded.

Subject 301-504 (**pneumonia**): 58-year old Hispanic female diagnosed with ALS in March 07 was randomized to DM 30 mg/Q 10 mg dose group in Study 123. Dosing began on 3/2/09 and was discontinued on 5/24/09 (84 days; study completion). Past medical and surgical history was not provided. Concomitant medication was riluzole. Post randomization, following 58 days of exposure to DM 30 mg/Q 10 mg, she experienced dysphonia and dysphagia "without previous episodes of respiratory disorders or aspiration episodes". On (b) (6) days after study completion) the subject was admitted to the hospital for the treatment of pneumonia by bronchoaspiration. She was treated with metamizole (NSAID), heparin SQ, omeprazole and IV antibiotics. On (b) (6), the subject suffered cardiopulmonary arrest. She responded to resuscitative measures and was intubated. However, on (b) (6), after blood transfusion for anemia, she had a cardiopulmonary arrest. Resuscitation measures were futile. The death certificate listed

respiratory insufficiency, pulmonary sepsis and ALS progression as the causes of death. No autopsy was performed. The investigator assessed the event as not related with study medication and the Applicant agrees. Reviewer's comments: The event of 'pneumonia' occurred (b) (6) days and death (b) (6) days after the study medication was discontinued. On face, this relatively long interval between the last dose of study medication and onset of event may not suggest a causal relationship between the study drug and the adverse event. Whether or not ALS was at an advanced stage at randomization is unknown.

Subject 135-511 (**disease progression**): 60-year Caucasian male diagnosed with ALS in October 2008 was randomized to **placebo** group in Study 123. Symptoms began three years earlier. Exposure to the study drug began on 3/11/09 and date of the last dose was 3/19/09; per the narrative, the study medication was discontinued 8 days after initiation by the subject, by choice. He had a past medical history significant for left subdural hematoma, hypertension, hyperlipidemia, BiPAP starting in 10/08, dysphagia since an unknown date in 2007, hypoxia since 3/4/09 and PEG tube placement in (b) (6) Concomitant medication was Zocor (simvastatin), Flomax (morniflumate), omeprazole, riluzole, and oxygen per inhalation continuously since 3/4/09. On (b) (6) he was hospitalized for progressive shortness of breath for one week. He continued to decline, and was discharged home two days later with hospice care. He died on (b) (6) at home.

Subject #121-508 (**respiratory failure**): 60-year old Caucasian male diagnosed with ALS in Jan 08 was enrolled in the ***open-label extension of Study 123***. DM 30 mg/Q 10 mg was first administered on 8/19/08 and the last dose on 2/18/09. Past medical history included alcohol use (two beers per week), asthma, hypertension, dysphagia and choking, PEG placement on (b) (4) increased phlegm and mild orthopnea. Concomitant medications included lisinopril, riluzole, vitamin C, vitamin E, selenium, creatine (dose not specified), alpha lipoic acid, colloidal silver (compounded), super B complex, aspirin (enteric coated), albuterol inhalation and Wal-Tussin (guaifenesin). Between 1/3/09 and 2/18/09, he was treated with antibiotics and bronchodilators for worsening chest congestion, and was on BiPAP. During the Visit 4, he was unable to lie down to have ECG, and was prescribed amitriptyline 25 mg QD (for treatment of PBA). The subject's spouse notified the site that the subject had expired on (b) (4) due to worsening chest congestion. No autopsy was done and death certificate was not available. The investigator concluded that the event of fatal chest congestion was unrelated to the study medication and Applicant agrees with the investigator.

Subject #201-509 (**respiratory failure and disease progression**): 69-year old Caucasian male diagnosed with ALS on 7/1/08 was enrolled in the ***open-label extension of Study 123***. DM 30 mg/Q 10 mg was first administered on 12/19/08 and the last dose on 1/11/09. Past medical history included hypertension, swallowing difficulties since Sep 07. Concomitant medication included riluzole, losartan, alprazolam and Centrum (minerals and vitamins). On (b) (4) the patient experienced respiratory insufficiency due to worsening of ALS and was hospitalized. Oxygen saturation was on 87% and carbon dioxide partial pressure was 49% (hypercapnia). Pneumonia and hypoxemia were treated with antibiotics and O_2 supplementation. On (b) (4) he experienced cardiac arrest and died. No autopsy was performed. The investigator concluded that the fatal events were not related to the study medication and most likely related to ALS progression. The Applicant agrees with the investigator.

Subject #201-511 (**dyspnea**): 81-year old Indo-American male diagnosed with ALS in July 08 was enrolled in the ***open-label extension of Study 123***. DM 30 mg/Q 10 mg was first administered on 5/14/09 and the last dose on 8/12/09. Past history included hypertension and prostatectomy due to adenoma in 2000. Concomitant medications included memantine, enalapril, vitamin E and vitamin B. On 8/5/09 he experienced flu-like syndrome and dyspnea; he was started treatment with ciprofloxacin. On (b) (4) days after the last dose of study drug) subject was admitted to the hospital secondary to dyspnea, lung and plural infection and bronchoaspiration. He was treated with antibiotics and bronchodilators. On (b) (4) the patient had a cardiorespiratory arrest and died. No autopsy was performed. The cause of death was considered as disease progression. The investigator concluded that the event of dyspnea was not related to study medication and most likely related to a pre-existing disease. The Applicant agrees with the investigator.

Deaths in ALS subjects, other deaths of special interest, the Applicant's conclusions regarding deaths and reviewer's comments and conclusions are discussed in section 7.3.5 (Submission specific primary safety concerns) of this review.

7.3.2 Serious Adverse Events

In the original NDA submission, there were four SAEs in Study 102 of ALS subjects with PBA; all four were respiratory-related (aspiration, dysphagia and respiratory failure in DM 30 mg/Q 30 mg arm, and pneumonia in the Q arm). In the 12-week Study 106 of MS subjects with PBA, there were two SAEs (optic neuritis and dysfunctional vaginal bleeding) in the DM 30 mg/Q 30 mg arm and four SAEs in placebo group. Dr. Farkas raised concerns that potentially there may be an increased risk of these SAEs from DM/Q since all the SAEs in ALS subjects were all respiratory-related.

SAEs (including fatal):
The following table summarizes the number of subjects who experienced at least one SAE by treatment groups across the pooled controlled studies (Pool 3) of subjects with PBA (Study 102, Study 106 and double-blind phase of Study 123). The overall incidence of subjects, driven primarily by the subset of subjects with ALS, who experienced at least one SAE in the DM 30 mg/Q 30 mg dose group, is more than two-fold *lower* when compared to either pooled placebo or any DM /Q 10 mg dose groups. However, a number of differences in the design and DM/Q dose among the controlled studies, and in particular, the relatively smaller and shorter ALS subject-exposures to DM 30 mg/Q 30 mg in Study 102, limit direct comparison between pooled treatment groups.

Table 31: Subjects with at least one SAE (including fatal) by treatment groups and by underlying disease (Pool 3)

	DM 20/Q 10 n/N (%)	DM 30/Q 10 n/N (%)	DM 30/Q 30 n/N (%)	Any DM/Q n/N (%)	Placebo n/N (%)	DM 30/Q 0 n/N (%)	DM 0/Q 30 n/N (%)
All subjects	9/107 (8.4)	8/110 (7.3)	5/146 (3.4)	22/363 (6.0%)	14/183 (7.7)*	0/33	1/37 (2.7)
ALS	9/68 (13.2)	7/65 (10.8)	3/70 (4.3)	19/203 (9.4%)	8/64 (12.5)	0/33	1/37 (2.7)
MS	0/39 (0)	1/45 (2.2)	2/76 (2.6)	3/160 (1.9%)	6/119 (5.0)*	NA	NA

*MS subjects randomized to placebo were pooled from Study 106 and Study 123. The incidence of MS subjects with at least one SAE in the placebo group was 4/74 (5.4%) in Study 106 and 2/45 (4.4%) in Study 123.
Note: There were no subjects who experienced SAEs in the DM alone arm of Study 102.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; reviewer's analysis of DM and AE datasets; subset (Pool 3 and AESER); Tables, Summary (USUBJID, PRIMDIS, EXDOSTXT); Tabulate.

Unlike Study 102 and Study 106 in which a higher dose of Q (30 mg) was used, a lower dose of Q (10 mg) was used Study 123. Data from this placebo-controlled Study 123 is new to the Complete Response. There were 27 (27/326 = 8.3%) subjects in the double-blind phase of Study 123 who experienced SAEs *including* fatal SAEs. These subjects are summarized in the following table. As can be seen from the table below, with the exception of fatal events (which were discussed in the previous section), the proportion of subjects who experienced any *non-fatal* SAE in the placebo group appear to be comparable to or numerically higher than that in any dose DM/Q treatment groups in the overall study population or the ALS or MS subgroups.

Table 32: Overall incidence of all SAEs and non-fatal SAEs in the double-blind phase of Study 123.

	DM 20/Q 10 n/N (%)	DM 30/Q 10 n/N (%)	Any DM/Q10 dose n/N (%)	Placebo n/N (%)
SAEs including deaths				
All subjects	9/107 (8.4)	8/110 (7.3)	17/217 (7.8)	10/109 (9.2)
ALS	9/68 (13.2)	7/65 (10.8)	16/133 (12.0)	8/64 (12.5)[#]
MS	0/39 (0)	1/45 (2.2)	1/84 (1.2)	2/45 (4.4)
Fatal SAEs				
All subjects	3/68 (4.4)	3/65 (4.6)	6/133 (4.5)	1/64 (1.6)
ALS	3/68 (4.4)	3/65 (4.6)	6/133 (4.5)	1/64 (1.6)[#]
MS	0/39	0/45	0/84	0/45
Non-fatal SAEs				
All subjects	6/107 (8.8)	5/110 (7.7)	11/217 (8.3)	10/109 (15.6)
ALS	6/68 (8.8)	4 /65 (6.2)	10/133 (7.5)	8/109 (12.5)[#]
MS	0/39	1/45 (1.5)	1/84 (0.8)	2/45 (3.1)

ALS= amyotrophic lateral sclerosis; MS = multiple sclerosis
[#]A given subject may have experienced both non-fatal and fatal SAEs. Subject 135-511 (placebo) experienced 'respiratory insufficiency' from which subject recovered and subsequently experienced 'progression of ALS' which was fatal.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; reviewer's analysis of DM and AE datasets; subset (Pool 3 and AESER); Tables, Summary (USUBJID, PRIMDIS, EXDOSTXT); Tabulate.

I discuss further the deaths and the non-fatal respiratory-related SAEs in subjects with ALS in section 7.3.5 (Submission specific primary safety concerns).

The following table lists all the individual *non-fatal* SAEs experienced by subjects in the double-blind phase of Study 123. Only one subject experienced any given SAE; there were no non-fatal SAEs that were experienced by ≥ 2 or more subjects.

Table 33: Incidence of individual non-fatal SAEs among ALS and MS subjects in Study 123 during the double-blind phase.

ALS subjects with PBA	**D20/Q10**		**D30/Q10**		**Any DM/Q**		**Placebo**	
	N = 68		N = 65		N = 133		N = 64	
	n	%	n	%	n	%	n	%
ALS subjects with any one SAE	6	8.8	4	6.2	10	7.5	8	12.5
Respiratory failure	0	0	1	1.5	1	0.8	0	0
Pulmonary embolism	1	1.5	1	1.5	2	1.5	0	0.0
Dysphagia	0	0	1	1.5	1	0.8	2	3.1
Dyspnoea	0	0	1	1.5	1	0.8	1	1.6
Acute respiratory distress syndrome	0	0	1	1.5	1	0.8	0	0
Postoperative respiratory distress	0	0	1	1.5	1	0.8	0	0
Syncope	0	0	1	1.5	1	0.8	0	0
Abdominal pain	1	1.5	0	0	1	0.8	0	0
Catheter related infection	1	1.5	0	0	1	0.8	0	0
Constipation	1	1.5	0	0	1	0.8	0	0
Dehydration	1	1.5	0	0	1	0.8	0	0
Infection	1	1.5	0	0	1	0.8	0	0
Inguinal hernia	1	1.5	0	0	1	0.8	0	0
Muscle spasms	1	1.5	0	0	1	0.8	0	0
Muscle spasticity	1	1.5	0	0	1	0.8	0	0
Overdose	1	1.5	0	0	1	0.8	0	0
Suicide attempt	1	1.5	0	0	1	0.8	0	0
Cellulitis	0	0	0	0	0	0	1	1.6

Cholecystitis acute	0	0	0	0	0	0	1	1.6
Cholelithiasis	0	0	0	0	0	0	1	1.6
Complication of device insertion	0	0	0	0	0	0	1	1.6
Deep vein thrombosis	0	0	0	0	0	0	1	1.6
Feeding tube complication	0	0	0	0	0	0	1	1.6
Pneumonia aspiration	0	0	0	0	0	0	1	1.6
Transient ischaemic attack	0	0	0	0	0	0	1	1.6
MS subjects with PBA	**N = 39**		**N = 45**		**N = 84**		**N = 45**	
	n	%	n	%	n	%	n	%
MS subjects with any SAE	0	0	1	2.2	1	1.2	2	4.4
Anxiety	0	0	1	2.2	1	1.2	0	0
Multiple sclerosis	0	0	1	2.2	1	1.2	0	0
Breast cancer	0	0	0	0	0	0	1	2.2
Deep vein thrombosis	0	0	0	0	0	0	1	2.2
Urosepsis	0	0	0	0	0	0	1	2.2

Source: NDA Complete Response 4/30/10; Reviewer's analysis of AE and DM dataset; Study 123; subset (Pool 3, PRIMDIS, AESER).

I discuss the narratives of subjects who experienced non-fatal SAEs in the following paragraphs.

Subject 129-508 ('**acute respiratory distress' and 'postoperative respiratory distress'**): 74-year old Caucasian female, diagnosed with ALS on 3/15/07, was randomized to DM 30 mg/Q 10 mg dose group in Study 123. ALS symptoms began in Feb 03 (sic) with right leg weakness. Study drug was first administered on 10/24/08 and the last dose prior to event was on (b) (4) Her past medical history included urinary incontinence, hypothyroidism, hypercholesterolemia, dysphagia, dysarthria, spastic quadriparesis. Relevant concomitant medications included levothyroxine, rabeprazole, ezetimibe, Premarin (conjugated estrogens), tolterodine tartrate. On (b) (4), she underwent elective surgery to repair vaginal vault prolapse, mid-urethral sling and intraoperative cystoscopy. The procedure was uncomplicated with minimal blood loss. She was extubated immediately following the procedure, but after transfer to her room a few hours later, she experienced stridor and mild tachycardia, red rash across her chest, face and right arm. Emergent treatment included racemic epinephrine and Benadryl IV. After transient improvement, she had another episode of stridor with dropping O_2 saturation values, therefore was intubated. She gradually improved, was extubated, and eventually discharged on (b) (4). She resumed study medication on 11/19/08 and did not have recurrence of these events. The investigator concluded that the event of acute respiratory distress was unlikely related to the study medication with an alternative causality as possible reaction to post-operative medications and/or increased spasticity after recovery from anesthesia. The Applicant agrees with the investigator.

Subject 135-510 (**pulmonary embolism**): 59-year old black male, diagnosed with ALS on 9/17/07, was randomized to DM 30 mg/Q 10 mg dose group in Study 123. ALS symptoms started on 10/06. Study drug was first administered on 2/6/09 and the last dose prior to event was on (b) (4) Past medical history included borderline hypertension, hyperlipidemia, weight loss, back pain, a recent history of falls. Relevant concomitant medications included riluzole, Lotrel (amlodipine/ benazepril), Baclofen, multivitamins and dietary supplements. By Study day (b) (4) subject was under the care of the hospice, with morphine 5 mg q4 prn. About 4 days after the last dose (b) (4), subject was hospitalized for syncope, and was diagnosed to have bilateral pulmonary emboli. Anticoagulation was started and subject discharged to home hospice three days later. The investigator concluded that the event of bilateral pulmonary emboli was unlikely related to the study medication, with the alternative causality of known complication of ALS. The Applicant agrees with the investigator.

Subject 147-501 (**dysphagia, dyspnoea and respiratory failure**): 63-year Caucasian female, diagnosed with ALS on 9/07, was randomized to DM 30 mg/Q 10 mg dose group in Study 123. Study drug was first

administered on 1/2/09 and the last dose prior to event was on 1/9/09 (8 days). Past medical history included gastroesophageal reflux disease and previous cigarette smoking (quantity and length of time not specified). Subject had been wheelchair dependent and had not ambulated since approximately 6/08. Relevant concomitant medications included riluzole, Naproxen, acetaminophen, Qualaquin (quinine) 324 mg qhs (started on 12/1/08 for leg cramps), omeprazole, loratadine, baclofen 5 mg QID and dalteparin, fexofenadine (Allegra), pseudoephedrine. On (b) (4) she was evaluated in the Emergency Department (ED) for increased weakness and shortness of breath. Baseline oximetry on 12/16/08 showed a transient drop in O_2 saturation values. ED notes reported "she has not felt well since starting a new study medication for her ALS and has had intermittent shortness of breath since starting the medication" (study medication that was started just the day before). Her O_2 saturation values were 89 to 90% without supplemental oxygen. BiPAP (which she had been using since 8/08) settings were modified resulting in resolution of respiratory insufficiency. Subject also had increased difficulty chewing and swallowing over several months. She remained hospitalized for an elective PEG placement on (b) (4) and was discharged on (b) (4) She resumed DM 30 mg/Q 10 mg and completed the study. The investigatory concluded that dysphagia and dyspnea were not related to study medication and most likely related to ALS progression. The Applicant agrees with the investigator. Reviewer's comments: Her presenting respiratory symptoms started just the day after DM 30 mg/Q 10 mg began. BiPAP use and wheelchair dependency prior to randomization suggest advanced ALS and respiratory decline at randomization. While there appears to be a temporal relationship between the onset of these events and study medication, these events resolved and did not recur on rechallenge. She went on to complete the double-blind phase of the study with 84 days of total exposure. She had been taking Qualaquin (quinine) 324 mg for over a month prior to randomization, and the relationship between Qualquin /DM/Q and her presenting symptoms is uncertain.

Subject 302-503 (**syncope**): 67-year old Caucasian male, diagnosed with ALS in 11/07 (unspecified day), was randomized to DM 30 mg/Q 10 mg dose group in Study 123. Study drug was first administered on 3/26/09 and the last dose prior to event was on 5/30/09. Past medical history included benign prostatic hyperplasia and GERD. Relevant concomitant medications included omeprazole and vitamin supplementation. On (b) (4) he began taking tamsulosin (an alpha blocker) 0.4 mg for benign prostatic hyperplasia. On the same day, he experienced syncope and was admitted to the hospital. BP was 80/50 mmHg. IV fluids were administered and he was discharged the next day. Study medication was resumed the next day, or (b) (4) The investigator concluded that the event of syncope was unlikely related to the study medication, and directly related to tamsulosin (postural hypotension/syncope is included under Warnings and Precautions). The Applicant agrees with the investigator.

Subject 117-510 (**muscle spasticity**): 48-year old Caucasian male, diagnosed with ALS (CRF states that he had primary lateral sclerosis) on an unspecified date, was randomized to DM 20 mg/Q 10 mg dose group in Study 123. Study drug was first administered on 9/30/08 and the last dose prior to event was on 10/2/08. Past medical history included depression, increased salivation, shortness of breath, BiPAP use, pain, insomnia, cocaine methadone and amphetamine use, dysarthria, dysphagia, spasticity (per CRF, treated since 2004 requiring baclofen pump) and fatigue. Relevant concomitant medications included riluzole, Tylenol with codeine prn, Xanax prn, oral baclofen 5 mg po qd, and baclofen pump 338 micrograms (mcg) at bedtime. On 10/2/08 (study day 3), he experienced ***worsening spasticity*** and stopped the study drug. Study drug was resumed again on 10/4/08 but the spasticity worsened and the subject contacted the site to notify them of this occurrence. The subject was then discontinued from study drug on 10/8/08 after receiving the morning dose, and he reported that by midnight the same day he was felt significantly better. The investigator considered that the event of worsening spasticity was probably related to the study medication. The Applicant agrees with the investigator. Reviewer's comments: The temporal relationship between worsening of spasticity and study medication, and more importantly, positive rechallenge, suggests that the causality of this event with the study drug is more than likely.

Subject 118-505 (**intractable muscle spasms**): 59-year old Caucasian female, diagnosed with ALS on 7/10/08, was randomized to DM 20 mg/Q 10 mg dose group in Study 123. The initial symptom appears to be bulbar (accidental swallowing of dental paste) in 7/08. Medical and surgical history included osteoporosis, Grave's disease, BiPAP (1/09), muscle spasms (since 1/09) and PEG placement (b) (4) due to dysphagia). Concomitant medications included ibandronate (for osteoporosis sodium), baclofen 10 mg

TID, aspirin, Synthroid and riluzole, all administered via PEG tube. Study drug was first administered on 2/27/09. On (b) (4) (*during Screening*), she experienced pulmonary, upper respiratory bronchospasm, and was admitted in a hospital. Cardiac enzymes (troponin) were mildly elevated but a cardiac work-up was negative for myocardial injury. She recovered from the events and was discharged from the hospital on (b) (4). On (b) (4) following administration of the study drug (study day 1), she experienced ***acute intractable muscle spasms*** within "1 hour + 10 minutes after initial dose of study drug" for which she was hospitalized on that day. The narrative provides a lot of detail about 'bronchospasm' and 'cardiac enzymes increased' that occurred prior to the first dose of study medication, but is silent on 'muscle spasms'. Physician notes indicate that 'spasticity' was first reported on 1/22/09, and on 2/16/09 (prior to randomization), subject's husband reported 'pain from cramps was severe'. Hospital notes from (b) (4) states that "… presents with muscle spasms. Pt was in (illegible) on per her baseline, tried a 'trial drug' for ALS + developed severe muscle cramping. Pt admitted for further care." The physician writing this note concludes: "Neuro – ALS has muscle spasms. Likely may been due to trial medication. However spasms are seen in ALS. Will continue with current regimen Neurontin + Baclofen". The AE and EX datasets indicate that study medication was given only for one day, and that these events resolved by 3/1/09. Study medication was discontinued and she was withdrawn from the study. In the narrative, the investigator draws conclusions about 'bronchospasm' and 'cardiac enzymes increased' – both of which occur prior to randomization, but not on 'muscle spasms'. The narrative does not provide the Applicant's conclusions about 'muscle spasms'. Reviewer's comments: The temporal relationship between acute intractable muscle spasms and study medication suggests that the causality of this event with the study drug is likely.

Subject 121-501 (**abdominal pain, dehydration, infection around PEG tube, worsening of constipation**): 44-year old Caucasian male, diagnosed with ALS on 5/25/07, was randomized to DM 20 mg/Q 10 mg dose group in Study 123. Study drug was first administered on 3/21/08 and the last dose prior to event was on 4/9/08 (Day 20). Past medical history included constipation, dysphagia, cough due to thick saliva, loss of balance, gait dysfunction, falls, loss of ambulation, and allergy to multiple medications. Relevant concomitant medications included Rilutek, baclofen, tizanidine, ibuprofen, omeprazole PRN, vitamins and dietary supplements, lithium 300 mg BID and Dulcolax (bisacodyl) suppository PRN. On (b) (4) he experienced dehydration leading to constipation and was admitted to the hospital the same day. The narrative states that he had dysphagia which limited the fluid intake and resulted in dehydration which contributed to the patient developing constipation. He was given IV fluids and soap enema, resulting in resolution of these events, and was discharged two days later, on (b) (4). Study medication was resumed. Elective PEG tube placement surgery was done on (b) (4). On (b) (4) he experienced an infection around his PEG tube and was admitted to the hospital; he recovered following treatment with antibiotics. He had another hospitalization on (b) (6) for worsening constipation. The total duration of exposure to study drug was 84 days. The investigator considered these events as probably related to the underlying disease. The Applicant agrees with the investigator.

Subject 121-502 (**drug overdose and suicide attempt**): 37-year old Caucasian male, diagnosed with ALS on 10/25/07, was randomized to DM 20 mg/Q 10 mg dose group in Study 123. Study drug was first administered on 4/14/08 and the last dose was on 7/6/08 (study completion; total exposure 84 days). Past medical and surgical history included cigarette smoking, occasional alcohol use, history of falls, gait instability, PBA, situational depression secondary to diagnosis of ALS (since 10/07), and intermittent panic attacks. Relevant concomitant medications included Qualaquin (quinine) 324 mg QHS (since 12/18/07), tizanidine, Darvocet N-100, Vicodin 5/500, riluzole, lithium 300 mg BID (since 3/20/08), multivitamins and dietary supplements. On (b) (6) days after study completion), it was reported that the subject had an argument with his significant other, left home, checked into a hotel, and later was found semi-conscious on the floor of his hotel room. In the emergency room, he admitted that he wanted to commit suicide because of his terminal ALS diagnosis. He took unknown doses of lithium, quinine, Zanaflex and Vicodin. He was noted to be very depressed and crying. He recovered and was discharged 7 days later, on (b) (6). The investigator concluded that the event of drug overdose-suicide attempt was unrelated to the study medication, with an alternative causality due to the underlying disease. The Applicant concluded that event was unrelated to the study medication. Reviewer's comments: relationship between this SAE and study medication is uncertain.

Subject 121-505 (**pulmonary embolism**): 38-year old black female, diagnosed with ALS on 2/06, was randomized to DM 20 mg/Q 10 mg dose group in Study 123. Study drug was first administered on 7/11/08. Past medical history was significant for opiate abuse, positive anti-cardiolipin screen, headache, frequent falls, gait disturbance (use of cane and walker). Relevant concomitant medications included baclofen, tizanidine and lorazepam. On (b) (6) she woke up with severe mid-chest pain. Work-up in the hospital included a VQ scan which showed a moderate probability of pulmonary thromboembolism. An ultrasonogram of the lower limbs did not reveal a DVT. She was started on anticoagulation. At this admission, elevated liver function tests were also noted, with further serial evaluation (see table below). Hepatitis panel was negative. An abdominal US of the right upper quadrant on (b) (6) showed cholelithiasis and non-visualization of the pancreas and left lobe of the liver. A biliary (HIDA) scan was negative for cystic duct or common duct obstruction and there was no evidence of acute cholecystitis. MRI of the abdomen showed multiple stones within the gallbladder, without gallbladder wall thickening or pericholecystic fluid. There was no evidence of biliary ductal dilatation. There was a filling defect within the distal common bile duct, which could represent a small stone.

	(b) (6)			
Total bilirubin mg/dL	1.2	1.1	NA	NA
Conj bilirubin mg/dL		0.8	NA	NA
ALT U/L	573	369	357	489
AST U/L	1129	260	335	496
Alk phos U/L	136	195	207	183

She was discharged on (b) (6). Study drug was resumed and she completed the study (total exposure of 83 days). The investigator concluded that this event was most likely related to leg weakness from ALS predisposing subject to blood clot formation. The Applicant agrees with the investigator. Reviewer's comments: The cause of abnormal liver function tests is uncertain. Gallstones are a potential cause but the incomplete liver function tests profile is not consistent with a biliary outflow obstruction. Importantly, she resumed the study drug and completed the study without any apparent liver abnormality, arguing against a relationship between DM/Q and liver function abnormality.

Subject 116-503 (inguinal hernia repair): 69-year old Caucasian male, randomized to DM 20 mg/Q 10 mg dose group in the double-blind phase of Study 123, underwent inguinal herniorraphy.

A total of 8 subjects randomized to the ***placebo group*** during the double-blind phase of Study 123 experienced the following SAEs: cellulitis, cholecystitis acute, cholelithiasis, complication of device insertion and feeding tube complication, deep vein thrombosis, dysphagia, dyspnoea, pneumonia aspiration and transient ischemic attack.

SAEs in open-label studies of PBA subjects:

Across the pooled open-label studies of subjects with PBA (Study 107 and Study 123 open-label extension), there were 195 (195/805 = 24.2%) subjects who reported at least one SAE (including deaths). A total of 14 (14/253 = 5.5%) subjects reported at least one SAE during participation in the 12-week open-label extension of Study 123. In the open-label Study 107 (52 weeks with option for additional treatment beyond 52 weeks), 181 (181/552 = 32.8%) subjects experienced at least one SAE. During the original NDA review, as of the data cut-off date for the then ongoing open-label Study 107, there were 117 subjects who experienced at least one SAE; Dr. Farkas reviewed these SAEs and detected no drug-related SAEs while acknowledging that the power of this uncontrolled data to detect drug-related SAEs is weak given the high expected rate of SAEs in this type of patient population. Since the original NDA submission, Study 107 has been completed and there were additional reports of SAEs in the interval. The narratives for selected SAEs of interest are included in the relevant sections of this review.

The following table summarizes the incidence of common SAEs across these open-label studies. The higher incidence of subjects with SAEs in Study 107 reflects the long exposures achieved (761.7 person years) compared to the shorter exposures in open-label phase of Study 123 (56.5 person-years). Thus, the overall relative risk for subjects who experienced any SAE in the DM/Q 30 mg group relative to the DM/Q 10 mg group decreases from 6.0 (32.8/5.5) to 1.0 [(181/761.7 = 0.24)/(14/56.5 = 0.25)] when the person-time is used as the denominator instead of persons at risk.

Table 34: Incidence of common (≥ 3% in the pooled open-label group) SAEs in open-label studies of PBA subjects

Serious adverse event	Study 107 D30/Q30 N=552		Study 123-OLE D20/Q10 N=253		Combined Open-label studies Any DM/Q N=805	
	n	%	n	%	n	%
Any SAE	181	32.8	14	5.5	195	24.2
Respiratory failure	54	9.8	2	0.8	56	7.0
Dysphagia	27	4 9	1	0.4	28	3.5
Multiple sclerosis	18	3 3	0	0.0	18	2.2
Pneumonia	12	2 2	0	0.0	12	1.5
Chest pain	8	1.4	0	0.0	8	1.0
Urinary tract infection	7	1.3	0	0.0	7	0.9
Cerebrovascular accident	6	1.1	0	0.0	6	0.7
Fall	6	1.1	0	0.0	6	0.7
Dyspnoea	5	0.9	1	0.4	6	0.7
Cardiac arrest	4	0.7	0	0.0	4	0.5
Deep vein thrombosis	4	0.7	0	0.0	4	0.5
Muscle spasticity	4	0.7	0	0.0	4	0.5
Pneumonia aspiration	4	0.7	0	0.0	4	0.5
Respiratory arrest	4	0.7	0	0.0	4	0.5
Skin laceration	4	0.7	0	0.0	4	0.5
Weight decreased	4	0.7	0	0.0	4	0.5
Acute respiratory failure	3	0.5	0	0.0	3	0.4
Amyotrophic lateral sclerosis	3	0.5	0	0.0	3	0.4
Bronchitis	3	0 5	0	0.0	3	0.4
Catheter site infection	3	0.5	0	0.0	3	0.4
Cellulitis	3	0.5	0	0.0	3	0.4
Death	3	0.5	0	0.0	3	0.4
Hip fracture	3	0.5	0	0.0	3	0.4
Lobar pneumonia	3	0.5	0	0.0	3	0.4
Vomiting	3	0.5	0	0.0	3	0.4
Respiratory disorder	2	0.4	1	0.4	3	0.4

Source: NDA Complete Response 4/30/10; Reviewer's analysis of AE and DM dataset.

As pointed earlier, subjects who were enrolled in Study 107 all had PBA but had different underlying neurological disorders. The following table lists the common SAEs experienced by the underlying neurological disorder. As can be seen, subjects with ALS had the highest incidence of any SAE, likely reflecting the progressive nature of the underlying disease over a relatively short time frame. Certain SAEs occur as expected with relatively higher frequency in

a given underlying neurological condition but not in others. For example, respiratory-related SAEs are more common in ALS, and cerebrovascular accident occurs more frequently in the elderly subjects with dementia. Given the absence of a concurrent placebo control, it would be difficult to differentiate the effects of the drug from those of the underlying disorder or concurrent illnesses.

Table 35: Incidence of common SAEs by underlying neurological disorder in Study 107

SAE	ALS N=176		MS N=223		Other N=73		AD N=14		Stroke N=45		TBI N=21	
	n	%	n	%	n	%	n	%	n	%	n	%
Any SAE	98	55.7	46	20.6	23	31.5	5	35.7	6	13.3	3	14.3
Respiratory failure	52	29.5	0	0	2	2.7	0	0	0	0	0	0
Dysphagia	25	14.2	0	0	2	2.7	0	0	0	0	0	0
Multiple sclerosis	0	0	18	8.1	0	0	0	0	0	0	0	0
Pneumonia	9	5.1	0	0	3	4.1	0	0	0	0	0	0
Chest pain	4	2.3	2	0.9	2	2.7	0	0	0	0	0	0
Urinary tract infection	0	0	5	2.2	2	2.7	0	0	0	0	0	0
Cerebrovascular accident	1	0.6	1	0.4	0	0	2	14.3	2	4.4	0	0
Fall	3	1.7	0	0	1	1.4	1	7.1	0	0	1	4.8
Dyspnoea	4	2.3	0	0	1	1.4	0	0	0	0	0	0
Skin laceration	3	1.7	1	0.4	0	0	0	0	0	0	0	0
Weight decreased	4	2.3	0	0	0	0	0	0	0	0	0	0
Cardiac arrest	3	1.7	0	0	0	0	1	7.1	0	0	0	0
Pneumonia aspiration	3	1.7	1	0.4	0	0	0	0	0	0	0	0
Deep vein thrombosis	0	0	2	0.9	2	2.7	0	0	0	0	0	0
Respiratory arrest	4	2.3	0	0	0	0	0	0	0	0	0	0

ALS= amyotrophic lateral sclerosis; MS = multiple sclerosis; AD = Alzheimer's disease; TBI = traumatic brain injury;
Other = PBA in primary lateral sclerosis, Parkinson's disease, Parkinson's syndrome, corticobasilar degeneration, frontotemperal dementia, bulbar motor neuron disease, bulbar palsy, cerebral palsy, hydrocephalus, movement disorder, progressive bulbar palsy, progressive supranuclear palsy and spinocerebelar ataxia.
Source: NDA Complete Response 4/30/10; Reviewer's analysis of AE and DM dataset.

7.3.3 Dropouts and/or Discontinuations

The following table summarizes the overall number of subjects who discontinued due to a TEAE by treatment groups across the pooled controlled studies (Pool 3) of subjects with PBA (Study 102, Study 106 and double-blind phase of Study 123). Overall, a total of 60 (60/616 = 11%) subjects withdrew due to AE from all the three controlled studies of PBA. Compared to the incidence in the pooled placebo subjects, the incidence of subjects who experienced at least one TEAE leading to discontinuation in the DM 30 mg/Q 30 mg dose group was more than two-fold *higher* than in all subjects and in the subset of MS subjects, and almost four-fold *higher* in the subset of ALS subjects. In contrast, compared to the placebo group, the incidence was either numerically comparable or higher in the DM 20 mg/Q 10 mg dose group, and lower in the DM 30 mg/Q 10 mg dose group.

Table 36: Overall incidence of subjects with at least one TEAE leading to discontinuation by treatment and by primary disease in controlled studies of PBA (Pool 3)

	DM 20/Q 10 n/N (%)	DM 30/Q 10 n/N (%)	DM 30/Q 30 n/N (%)	Any DM/Q n/N (%)	Placebo n/N (%)	DM 30/Q 0 n/N (%)	DM 0/Q 30 n/N (%)
All subjects	9/107 (8.4)	5/110 (4.5)^	28/146 (19.2)	42/363 (11.6%)	13/183 (7.1)*	2/33 (6.1)	3/37 (8.1)
ALS	5/68 (7.4)	3/65 (4.6)	17/70 (24.3)	25/203 (12.3)	4/64 (6.3)	2/33 (6.1)	3/37 (8.1)
MS	4/39 (10.3)	2/45 (4.4)^	11/76 (14.5)	17/160 (10.6)	9/119 (7.6)*	NA	NA

Note: SAEs leading to discontinuation: 2 ALS subjects in DM 20 /Q 10 group (muscle spasticity and muscle spasms); 1 MS subject in DM 30/Q 10 group (anxiety and multiple sclerosis); 1 ALS subject in DM 30/Q 10 group (respiratory failure); and 2 ALS subjects in placebo group (deep vein thrombosis and dyspnea).
*MS subjects randomized to placebo were pooled from Study 106 and Study 123. The incidence of MS subjects with at least one TEAE leading to discontinuation in the placebo group was 7/74 (9.5%) in Study 106 and 1/45 (2.2%) in Study 123. The incidence of all subjects discontinuing who were randomized to placebo in Study 123 was 5/109 (4.6%): 4/64 (6.3%) were ALS subjects and 1/45 (2.2%) were MS subjects.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS, adapted from Tables 22.1.3 and 22.2.2; reviewer's analysis of AE dataset (subset AE: Pool 3 Y, AEACN discontinued; Tabulate), and DMEXAE dataset (subset Pool 3 Y for each dataset and join; AEACN discontinued; Tabulate).

In the MS subjects (Study 106) and in the ALS subjects (Study 102), most of the discontinuations were due to Nervous system, Musculoskeletal and Connective Tissue, and Gastrointestinal disorders; the individual AEs which led to the highest number of dropouts were fatigue, nausea, diarrhoea, asthenia, headache and muscle spasticity. These events were reviewed by Dr. Farkas as part of the original NDA review.

Incidence of TEAE leading to discontinuation for the most common body system disorders by treatment groups in ALS and MS subjects in the pooled controlled trials of PBA (Pool 3) are provided in the following tables. Among ALS subjects, compared to the incidence in the pooled placebo subjects, the incidence of subject-discontinuations in the DM 30 mg/Q *30* mg dose group was nearly four-fold higher. In the MS subjects too, the incidence of the TEAEs leading to discontinuation is higher in the DM/Q 30 mg group than in the placebo or DM/Q 10 mg groups. In both these DM/Q groups (Q 10 or 30 mg), there is an excess of TEAEs that led to discontinuations in the Nervous system, Musculoskeletal and Connective Tissue, and Gastrointestinal disorders, compared to the placebo group. There were two cardio-vascular-related AEs (not included in the following tables) leading to withdrawal (atrial flutter and bradycardia) in the DM 30 mg/Q 30 mg group compared to none in the control groups; these are discussed in section 7.3.5 of this review. As discussed in section 7.3.2 of this review, a number of differences in the design, DM/Q dose and enrolled population in the component studies of Pool 3 limit direct comparison between pooled treatment groups. This is particularly true in controlled studies of ALS subjects because no concurrent placebo group was used in Study 102 which was also shorter in duration than Study 123.

Table 37: Incidence of TEAE leading to discontinuation for the most common body system disorders by treatment groups in ALS subjects in Pool 3.

	AVP-923							
System Organ Class/ Preferred Term	20 mg DM/ 10 mg Q (N=68)	30 mg DM/ 10 mg Q (N=65)	All doses with 10 mg Q (N=133)	All doses with 30 mg Q (N=70)	All AVP-923 (N=203)	Placebo (N=64)	DM 30 mg (N=33)	Q 30 mg (N=37)
Any Adverse Event	5 (7.4%)	3 (4.6%)	8 (6.0%)	17 (24.3%)	25 (12.3%)	4 (6.3%)	2 (6.1%)	3 (8.1%)
NERVOUS SYSTEM DISORDERS	2 (2.9%)	1 (1.5%)	3 (2.3%)	11 (15.7%)	14 (6.9%)	0	2 (6.1%)	0
BALANCE DISORDER	0	0	0	1 (1.4%)	1 (0.5%)	0	0	0
DIZZINESS	0	0	0	1 (1.4%)	1 (0.5%)	0	2 (6.1%)	0
DYSARTHRIA	0	0	0	2 (2.9%)	2 (1.0%)	0	0	0
HEADACHE	0	0	0	4 (5.7%)	4 (2.0%)	0	0	0
LETHARGY	0	1 (1.5%)	1 (0.8%)	0	1 (0.5%)	0	0	0

MUSCLE SPASTICITY	2 (2.9%)	0	2 (1.5%)	2 (2.9%)	4 (2.0%)	0	0	0
SEDATION	0	0	0	2 (2.9%)	2 (1.0%)	0	0	0
SOMNOLENCE	0	0	0	2 (2.9%)	2 (1.0%)	0	1 (3.0%)	0
TREMOR	0	0	0	1 (1.4%)	1 (0.5%)	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (2.9%)	0	2 (1.5%)	5 (7.1%)	7 (3.4%)	0	1 (3.0%)	1 (2.7%)
JOINT STIFFNESS	0	0	0	1 (1.4%)	1 (0.5%)	0	0	0
MUSCLE SPASMS	2 (2.9%)	0	2 (1.5%)	1 (1.4%)	3 (1.5%)	0	0	1 (2.7%)
MUSCLE TIGHTNESS	0	0	0	1 (1.4%)	1 (0.5%)	0	0	0
MUSCULAR WEAKNESS	0	0	0	0	0	0	1 (3.0%)	0
MUSCULOSKELETAL STIFFNESS	0	0	0	3 (4.3%)	3 (1.5%)	0	0	0
PAIN IN EXTREMITY	0	0	0	1 (1.4%)	1 (0.5%)	0	0	0
GASTROINTESTINAL DISORDERS	1 (1.5%)	0	1 (0.8%)	5 (7.1%)	6 (3.0%)	0	1 (3.0%)	0
ABDOMINAL PAIN	1 (1.5%)	0	1 (0.8%)	0	1 (0.5%)	0	0	0
DIARRHOEA	0	0	0	3 (4.3%)	3 (1.5%)	0	1 (3.0%)	0
NAUSEA	0	0	0	4 (5.7%)	4 (2.0%)	0	1 (3.0%)	0
TONGUE DISORDER	0	0	0	1 (1.4%)	1 (0.5%)	0	0	0
VOMITING	0	0	0	1 (1.4%)	1 (0.5%)	0	0	0

Treatment categories are not mutually exclusive. Thus, patients may contribute to events in more than one treatment category. In each AE group or preferred term, a patient is counted only once within each treatment category, ie, only first occurrences are tabulated within each treatment category. Multiple events may have been reported as leading to a single patient discontinuation.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS, adapted from Tables 22.1.3 and 22.2.2.

Table 38: Incidence of TEAEs leading to discontinuation for the most common body system disorders by treatment groups in MS subjects in Pool 3.

	AVP-923							
System Organ Class/ Preferred Term	20 mg DM/ 10 mg Q (N=39)	30 mg DM/ 10 mg Q (N=45)	All doses with 10 mg Q (N=84)	All doses with 30 mg Q (N=76)	All AVP-923 (N=160)	Placebo (N=119)	DM 30 mg (N=0)	Q 30 mg (N=0)
Any Adverse Event	4 (10.3%)	2 (4.4%)	6 (7.1%)	11 (14.5%)	17 (10.6%)	9 (7.6%)	0	0
NERVOUS SYSTEM DISORDERS	3 (7.7%)	1 (2.2%)	4 (4.8%)	4 (5.3%)	8 (5.0%)	1 (0.8%)	0	0
DISTURBANCE IN ATTENTION	0	0	0	1 (1.3%)	1 (0.6%)	0	0	0
DIZZINESS	1 (2.6%)	0	1 (1.2%)	2 (2.6%)	3 (1.9%)	0	0	0
DYSGEUSIA	1 (2.6%)	0	1 (1.2%)	0	1 (0.6%)	0	0	0
MULTIPLE SCLEROSIS	0	1 (2.2%)	1 (1.2%)	0	1 (0.6%)	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	0	3 (3.9%)	3 (1.9%)	2 (1.7%)	0	0
MUSCLE SPASMS	0	0	0	2 (2.6%)	2 (1.3%)	1 (0.8%)	0	0
MUSCULAR WEAKNESS	0	0	0	1 (1.3%)	1 (0.6%)	0	0	0
PAIN IN EXTREMITY	0	0	0	0	0	1 (0.8%)	0	0
GASTROINTESTINAL DISORDERS	0	1 (2.2%)	1 (1.2%)	3 (3.9%)	4 (2.5%)	1 (0.8%)	0	0
ABDOMINAL PAIN LOWER	0	0	0	0	0	1 (0.8%)	0	0
DIARRHOEA	0	1 (2.2%)	1 (1.2%)	1 (1.3%)	2 (1.3%)	0	0	0
DRY MOUTH	0	0	0	1 (1.3%)	1 (0.6%)	0	0	0
DYSPEPSIA	0	0	0	0	0	1 (0.8%)	0	0
NAUSEA	0	0	0	2 (2.6%)	2 (1.3%)	1 (0.8%)	0	0

Treatment categories are not mutually exclusive. Thus, patients may contribute to events in more than one treatment category. In each AE group or preferred term, a patient is counted only once within each treatment category, ie, only first occurrences are tabulated within each treatment category. Multiple events may have been reported as leading to a single patient discontinuation.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS, adapted from Tables 22.1.3 and 22.2.2.

Double-blind phase of Study 123

Data from this placebo-controlled Study 123 is unique to the Complete Response. There were 20 (20/326 = 6.1%) subjects in the double-blind phase of Study 123 who experienced TEAEs leading to discontinuation. These subjects are summarized in the following table. Subjects who discontinued due to a TEAE in DM 20/Q 10 mg dose group were numerically higher than in either the DM 30 mg/Q 10 mg or placebo group, in both the overall subjects and in the ALS subjects. In the MS population, subjects discontinuing due to a TEAE in any DM/Q 10 mg group were numerically higher than in the placebo subjects, and almost five-fold higher in the

DM 20 mg/Q 10 mg group than in the placebo arm; however, the numbers of these discontinuations and the numbers of enrolled MS subjects are small.

Table 39: Overall incidence of subject discontinuations in Study 123

	DM 20/Q 10 n/N (%)	DM 30/Q 10 n/N (%)	Any DM /Q 10 n/N (%)	Placebo n/N (%)
All subjects	9/107 (8.4)	5/110 (4.5)	14/217 (6.5)	5/109 (4.6%)
ALS	5/68 (7.4)	3/65 (4.6)	8/133 (6.0)	4/64 (6.3)
MS	4/39 (10.3)	2/45 (4.4)	6/84 (7.1)	1/45 (2.2%)

Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS, adapted from Tables 22.1.3 and 22.2.2; reviewer's analysis of AE dataset (subset AE: Pool 3 Y, AEACN discontinued; Tabulate), and DMEXAE dataset (subset Pool 3 Y for each dataset and join; AEACN discontinued; Tabulate)

When both ALS and MS subjects who discontinued were pooled together, only one preferred term (muscle spasticity) was experienced by 3 subjects in any treatment arm (3 in the DM 20 mg/Q 10 mg dose group, 0 in DM 30 mg/Q 10 mg dose group and 1 in placebo group). The following table summarizes the incidence of TEAEs leading to discontinuations by the underlying primary disease in the double-blind phase of Study 123. In ALS subjects, among the TEAEs which led to discontinuation in 2 subjects in any treatment arm, two subjects each experienced muscle spasticity and muscle spasms in DM 20 mg/Q 10 mg dose group, none in DM 30 mg/Q 10 mg dose group, and 2 subject experienced dyspnea in the placebo group. In the MS subjects, the excess of discontinuations in the DM 20 mg/Q 10 mg were driven mainly by Nervous system disorders but all the preferred terms in this body system were experienced by only one subject in any dose group.

Table 40: Incidence of discontinuations due to TEAEs in Study 123 in subjects with ALS and MS (experienced by ≥ 2 subjects in any body systems or preferred term).

ALS SUBJECTS			
BODY SYSTEM (experienced by ≥ 2 subjects) Preferred Term (experienced by ≥ 2 subjects)	**DM 20 mg/ Q 10 mg (N = 68) n (%)**	**DM 30 mg/ Q 10 mg (N = 65) n (%)**	**Placebo (N = 64) n (%)**
Number of discontinuations due to TEAEs	5 (7.4)	3 (4.6)	4 (6.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (2.9)	0	1 (1.6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (2.9)	0	0
Muscle spasms	2 (2.9)	0	0
NERVOUS SYSTEM DISORDERS	2 (2.9)	1 (1.5)	0
Muscle spasticity	2 (2.9)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	2 (3.2)
Dyspnoea	0	0	2 (3.2)
MS SUBJECTS			
BODY SYSTEM (experienced by ≥ 2 subjects) Preferred Term (experienced by ≥ 2 subjects)	**DM 20 mg/ Q 10 mg (N = 39) n (%)**	**DM 30 mg/ Q 10 mg (N = 45) n (%)**	**Placebo (N = 45) n (%)**
Number of discontinuations due to AEs	4 (10.3)	2 (4.4)	1 (2.2)
NERVOUS SYSTEM DISORDERS	3 (7.7)	1 (2.2)	1 (2.2)

ALS subjects, any DM/Q 10 dose group: All preferred terms leading to discontinuations: muscle spasticity (SAE for subject# 117-510), muscle spasms (SAE for subject# 118-505), abdominal pain, decreased appetite, chest pain, electrocardiogram T wave inversion, fatigue, insomnia, lethargy and tinnitus.
ALS subjects, placebo group: All preferred terms leading to discontinuations: dyspnoea (SAE for subject# 118-503), impulsive behavior and deep vein thrombosis (SAE).

MS subjects, any DM/Q 10 dose group: All preferred terms leading to discontinuations: muscle spasticity, asthenia, atrioventricular block first degree, anger, anxiety (SAE for subject# 139-703), dizziness, dysgeusia, fall, multiple sclerosis (SAE for subject# 139-703), diarrhoea, paraparesis, parosmia, QRS axis abnormal and sinus bradycardia
MS subjects, placebo group: All preferred terms leading to discontinuations: muscle spasticity and muscle spasms
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS, adapted from Tables 31 and 32, pages 82-84; reviewer's analysis of AE dataset (subset AE: Pool 3 Y, AEACN discontinued; Tabulate), and DMEXAE dataset (subset Pool 3 Y for each dataset and join; AEACN discontinued; Tabulate)

The following table summarizes the demographic and other important characteristics of subjects discontinuing due to TEAEs. In the ALS subset, subjects discontinuing from the DM 20 mg/Q 10 mg treatment group, compared to the remaining two treatment arms, were quite young, mostly males, with a much *longer* duration of PBA symptoms, and these discontinuations occurred quite early after exposure began. In the MS population, subjects discontinuing from the DM 20 mg/Q 10 mg treatment group, compared to the remaining two treatment arms, were older, with a much *shorter* duration of PBA symptoms, and longer duration of time from diagnosis.

Table 41: Demographic and baseline characteristics of subjects discontinuing due to TEAEs by primary disease in Study 123

Primary disease			DM 20/Q 10	DM 30/Q 10	Placebo
ALS subjects	Age (years)	Median	35	58	60
		Mean	38.9	56.3	61
	Sex	Female	1	0	2
		Male	8	3	3
	Time from diagnosis of ALS (months)	Median	19	26	5
		Mean	24.4	64.7	5.2
	Duration of PBA symptoms (months)	Median	11	2	5
		Mean	8.44	21.7	3.6
	AE start relative to Study Day (days)	Median	2	15	28
		Mean	7.11	38.7	31.6
	Duration of exposure (days)	Median	9	19	40
		Mean	12.9	37.7	59.4
	Outcome	Not Recovered	2	2	0
		Recovered	7	0	4
		Recovered w/ Sequelae	0	0	1
		Unknown	0	1	0
MS subjects	Age (years)	Median	50	37	30
		Mean	52.8	38.8	30
	Sex	Female	7	4	2
		Male	3	0	0
	Time from diagnosis of ALS (months)	Median	257	91	110
		Mean	196	138	110
	Duration of PBA symptoms (months)	Median	11	76	47
		Mean	10	57	47
	AE start relative to Study Day (days)	Median	5	20	8
		Mean	13.6	32.5	8
	Duration of exposure (days)	Median	27	20	15
		Mean	19.3	39	15
	Outcome	Not Recovered	6	0	0
		Recovered	4	4	2

Source: NDA Complete Response 4/30/10; module 5.3.5.3; reviewer's analysis of AE dataset (subset AE: Pool 3 Y, AETRTEM Y, AEACN discontinued; Tabulate), and DMEXAE dataset (subset Pool 3 Y for each dataset and join; AEACN discontinued; Tabulate)

Discontinuations in open-label studies of PBA subjects

The following tables summarize the incidence of subjects discontinuing due to TEAE in the long-term exposure in PBA subjects (Pool 4). For both the underlying primary diseases, the incidence of subjects discontinuing due to a TEAE in any DM/Q30 mg dose group is many-fold

higher than in any DM/Q10 mg dose group, but this is confounded by the differential exposures between these dosage groups. In the ALS subjects, the person-time for DM/Q 30 mg group (N = 147) was 207.8 person-years compared to 45.5 person-years for DM/Q 10 mg dose group (N = 103). The overall relative risk for ALS subjects who discontinued due to any TEAE in the DM/Q 30 mg group relative to the DM/Q 10 mg group decreases from 6.8 (39.5/5.8) to 2.2 [(58/207.8 = 0.28)/(6/45.5 = 0.13)] when the person-time is used as the denominator instead of persons at risk. The relative risk for ALS subjects who discontinued due to any Respiratory, thoracic and mediastinal disorders (driven by respiratory failure) in the DM/Q 30 mg group decreases from 15.1 (29.3/1.9) to 4.7 [(43/207.8 = 0.21)/(2/45.5 = 0.04)] when the person-time is used as the denominator, but nevertheless, has a four-fold higher risk than in the DM/Q 10 mg group. Otherwise, the risk for most events leading to discontinuations in the DM/Q 30 mg group is either marginally elevated or is comparable to that in the DM/Q 10 mg group when adjusted for exposure time in both disease subsets.

Table 42: Incidence of TEAE leading to discontinuation by treatment in ALS subjects in the long-term open-label exposure in PBA subjects (incidence ≥ 2% in body system disorder for all doses with 30 mg Q).

	AVP-923				
System Organ Class/ Preferred Term	20 mg DM/ 10 mg Q (N=45)	30 mg DM/ 10 mg Q (N=103)	All doses with 10 mg Q (N=103)	All doses with 30 mg Q (N=147)	All AVP-923 (N=250)
Any Adverse Event	0	6 (5.8%)	6 (5.8%)	58 (39.5%)	64 (25.6%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	2 (1.9%)	2 (1.9%)	43 (29.3%)	45 (18.0%)
ACUTE RESPIRATORY FAILURE	0	0	0	1 (0.7%)	1 (0.4%)
DYSPNOEA	0	0	0	1 (0.7%)	1 (0.4%)
EPISTAXIS	0	0	0	1 (0.7%)	1 (0.4%)
PNEUMONIA ASPIRATION	0	0	0	2 (1.4%)	2 (0.8%)
RESPIRATORY ARREST	0	0	0	3 (2.0%)	3 (1.2%)
RESPIRATORY DISORDER	0	1 (1.0%)	1 (1.0%)	1 (0.7%)	2 (0.8%)
RESPIRATORY FAILURE	0	1 (1.0%)	1 (1.0%)	36 (24.5%)	37 (14.8%)
NERVOUS SYSTEM DISORDERS	0	0	0	4 (2.7%)	4 (1.6%)
AMYOTROPHIC LATERAL SCLEROSIS	0	0	0	1 (0.7%)	1 (0.4%)
CEREBROVASCULAR ACCIDENT	0	0	0	1 (0.7%)	1 (0.4%)
HEADACHE	0	0	0	1 (0.7%)	1 (0.4%)
MUSCLE SPASTICITY	0	0	0	1 (0.7%)	1 (0.4%)
INFECTIONS AND INFESTATIONS	0	0	0	6 (4.1%)	6 (2.4%)
PNEUMONIA	0	0	0	4 (2.7%)	4 (1.6%)
UPPER RESPIRATORY TRACT INFECTION	0	0	0	2 (1.4%)	2 (0.8%)
CARDIAC DISORDERS	0	0	0	4 (2.7%)	4 (1.6%)
CARDIAC ARREST	0	0	0	3 (2.0%)	3 (1.2%)
CARDIO-RESPIRATORY ARREST	0	0	0	1 (0.7%)	1 (0.4%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	2 (1.9%)	2 (1.9%)	6 (4.1%)	8 (3.2%)
ASTHENIA	0	0	0	1 (0.7%)	1 (0.4%)
CHEST PAIN	0	0	0	1 (0.7%)	1 (0.4%)
DEATH	0	0	0	2 (1.4%)	2 (0.8%)
DISEASE PROGRESSION	0	1 (1.0%)	1 (1.0%)	0	1 (0.4%)
FATIGUE	0	0	0	1 (0.7%)	1 (0.4%)

INFECTIONS AND INFESTATIONS	0	0	0	6 (4.1%)	6 (2.4%)
PNEUMONIA	0	0	0	4 (2.7%)	4 (1.6%)
UPPER RESPIRATORY TRACT INFECTION	0	0	0	2 (1.4%)	2 (0.8%)

Treatment categories are not mutually exclusive. Thus, patients may contribute to events in more than one treatment category.
Note: Percentages are calculated as the number of patients in the indicated population and treatment category who experienced an event divided by the number of patients in the population and treatment category.
Note: In each AE group or preferred term, a patient is counted only once within each treatment category, ie, only first occurrences are tabulated within each treatment category and primary disease.
Note: Multiple events may have been reported as leading to a single patient discontinuation
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS, Table 22.2.3.

Table 43: Incidence of TEAE leading to discontinuation by treatment in MS subjects in the long-term open-label exposure in PBA subjects (incidence ≥ 2% in body system disorder for all doses with 30 mg Q).

	AVP-923				
System Organ Class/ Preferred Term	20 mg DM/ 10 mg Q (N=30)	30 mg DM/ 10 mg Q (N=73)	All doses with 10 mg Q (N=73)	All doses with 30 mg Q (N=192)	All AVP-923 (N=265)
Any Adverse Event	0	1 (1.4%)	1 (1.4%)	24 (12.5%)	25 (9.4%)
PSYCHIATRIC DISORDERS	0	0	0	5 (2.6%)	5 (1.9%)
ANORGASMIA	0	0	0	1 (0.5%)	1 (0.4%)
ANXIETY	0	0	0	1 (0.5%)	1 (0.4%)
DEPRESSION	0	0	0	1 (0.5%)	1 (0.4%)
LIBIDO DECREASED	0	0	0	1 (0.5%)	1 (0.4%)
OBSESSIVE-COMPULSIVE DISORDER	0	0	0	1 (0.5%)	1 (0.4%)
SUICIDAL IDEATION	0	0	0	1 (0.5%)	1 (0.4%)
NERVOUS SYSTEM DISORDERS	0	1 (1.4%)	1 (1.4%)	6 (3.1%)	7 (2.6%)
CEREBROVASCULAR ACCIDENT	0	0	0	1 (0.5%)	1 (0.4%)
MIGRAINE	0	0	0	1 (0.5%)	1 (0.4%)
MULTIPLE SCLEROSIS	0	0	0	2 (1.0%)	2 (0.8%)
OPTIC NEURITIS	0	1 (1.4%)	1 (1.4%)	0	1 (0.4%)
TREMOR	0	0	0	1 (0.5%)	1 (0.4%)
TRIGEMINAL NEURALGIA	0	0	0	1 (0.5%)	1 (0.4%)

Treatment categories are not mutually exclusive. Thus, patients may contribute to events in more than one treatment category.
Note: Percentages are calculated as the number of patients in the indicated population and treatment category who experienced an event divided by the number of patients in the population and treatment category.
Note: In each AE group or preferred term, a patient is counted only once within each treatment category, ie, only first occurrences are tabulated within each treatment category and primary disease.
Note: Multiple events may have been reported as leading to a single patient discontinuation
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS, Table 22.2.3.

The narratives for many TEAEs leading to withdrawal of special interest are included in the relevant sections of this review.

7.3.4 Significant Adverse Events

The Applicant short-listed a set of adverse events to help identify a potential event of critical significance.

Across the integrated clinical trials, there were no cases of angioedema, anaphylaxis, anaphylactoid reaction, aplastic anemia, bone marrow depression, disseminated intravascular coagulation, hemolytic anemia, hepatic failure, liver necrosis, liver transplantation, myocardial fibrosis, myocarditis, pancytopenia, pulmonary fibrosis, rhabdomylosis, Stevens Johnson's syndrome, torsades de pointes or ventricuar fibrillation.

Although typically rare, respiratory failure was quite common occurrence in ALS subjects. These events are reviewed in the next section, 7.3.5, of this review. There were, however, several subjects who experienced an AE of potential critical significance. These subjects are briefly discussed below.

Acute renal failure: There were two subjects who experienced acute renal failure. Subject #107-048-021 experienced acute renal failure with IV acyclovir which resolved; this narrative is provided in section 7.4.2 Laboratory findings section of this review. The other subject (#109-133-009) was on placebo.

Pancreatitis: Subject #107-016-004 was a 62-year old female with ALS who experienced gallstone pancreatitis while on DM 30 mg/Q 30 mg. She recovered.

Toxic epidermal necrolysis (epidermal necrosis): Subject #107-028-003 was a 34-year old female with MS who developed skin necrosis on Day 229 of DM 30 mg/Q 30 mg. She recovered in 30 days. The investigator considered it as moderate in severity and was not considered serious. She remained in the study, continued dosing with DM 30 mg/Q 30 mg for a total of 563 days. A narrative is not provided. Reviewer's comments: Skin necrosis was one of the terms to identify potential cases of toxic epidermal necrolysis. From the limited information available, this case does not appear to be toxic epidermal necrolysis. It is not clear if the skin necrosis is associated with Avonex injections.

Thrombocytopenia: Subject #107-034-052 (old ID: 34-3452) is a 73-year old male with ALS, who previously experienced SAEs of aspiration pneumonia, right hip fracture secondary to falling on ice, respiratory insufficiency while on DM 30 mg/Q 30 mg. On Day (b) (6), he was hospitalized for treatment of pneumonia and was treated with IV antibiotics. During hospitalization, his platelet count dropped from 150,000 to 101,000/μL, considered secondary to heparin-associated antibodies. This event of thrombocytopenia was not considered serious. This event of critical significance is further discussed in section 7.4.6 of this review.

Convulsions: There were several subjects who experienced convulsions, almost all of them while participating in the open-label Study 107. Many of them had prior history of convulsions or had predisposing risk factors such as traumatic brain injury.

Suicide completed, attempted and ideation: Three subjects experienced completed suicide, two experienced SAEs of attempted suicide and hospitalization for ideation. These narratives are provided below. In addition, there were three other subjects (two with MS and one with traumatic brain injury) who experienced non-serious suicidal ideation.

Subject #107-025-008 (Old ID: 25-2508) is a 67 year old male with ALS who on Day (b) (6) of DM 30 mg/Q 30 mg was found dead in his home of apparent exposure to large amounts of carbon monoxide poisoning. The coroner ruled it as a suicide. The investigator concluded that the suicide was not related to the study drug. Reviewer's comments: No further details regarding predisposing factors are in the narrative.

Subject #107-044-007 (Old ID: 44-4407) is a 57 year old male with spinocerebellar ataxia who on Day (b) (6) of DM 30 mg/Q 30 mg was found dead in his home by hanging himself. He had a recent onset of reactive depression to primary neurological disease.

Subject #106-003-002 was a 43-year old female MS patient who was enrolled in Study 107 with an ongoing depressive disorder. On Day (b) (6) of DM 30 mg/Q 30 mg, she was found dead in her home. Autopsy results found very high oxycodone blood level 0.69 mg/L (690 µg/mL). The coroner suspected that this subject died of an intentional overdose of oxycodone, consistent with the plasma levels of oxycodone found at autopsy. Narrative with more detail is included in section 7.5.5 of this review.

Subject # 123-121-502 is a 37-year old male with ALS who attempted suicide, and was considered as an SAE. Narrative is provided in section 7.3.2 of this review.

Subject #107-027-001 is a 33-year old male with history of traumatic brain injury who Day (b) (6) of DM 30 mg/Q 30 mg experienced an SAE of panic attack and suicidal ideation and was hospitalized. He was again hospitalized for worsening suicidal ideation. The investigator concludes that these events were not related to the study medication but rather to the pre-existing traumatic head injury and anxiety.

7.3.5 Submission Specific Primary Safety Concerns

There were several specific safety concerns that were identified by the Applicant or the Agency during the review of the original data. The Applicant analyzed these events of special interest individually, and also assessed several AEs after grouping them to ensure that they were not undercounted during coding. For example, for 'falls', the Applicant grouped all adverse events of actual falls (fall, falling, fell), grouped events related to falls (injury, fracture, laceration, contusion), and analyzed AEs that could possibly lead to falls (dizziness, sedation, somnolence, ataxia, balance). I reviewed the preferred terms that were grouped together for appropriateness of inclusion. I also searched the verbatim terms and preferred terms using text strings to identify adverse events that should have been included but were omitted.

ALS Deaths and Respiratory-related AEs:
The Complete Response submission contains an "Epidemiological and clinical assessment of fatal and other serious respiratory events for Zenvia" (Respiratory Report) prepared by (b) (6) . This Respiratory Report represents Dr. (b) (6) review of all the deaths in Study 123, reflecting his/her clinical expertise as a pulmonologist with the clinic for the management of patients with neuromuscular diseases consisting of predominantly ALS patients, and compares the data from Study 123 with the data from the 6-year clinical database of patients with ALS followed at the (b) (6) clinic.

This Report summarizes survival data from several population-based studies or large clinical series. The median duration of survival from diagnosis varied from 16 – 30.6 months in these

publications. These studies identified several factors that appear to be independent predictors of survival or death. In particular, bulbar onset was consistently associated with a shorter duration of survival than individuals with spinal onset. Other factors that are predictive of poor prognosis include advanced age, shorter onset-diagnosis interval, and duration of disease. Studies of mortality indicate that respiratory failure was the most frequent cause of death in ALS subjects, ranging from 77 - 82%.

Dr. (b) (6) reviewed all the deaths in the Study 123 but did not review any of the deaths in other Phase III clinical studies of PBA. There were 7 deaths – all ALS subjects, during the double-blind phase: 6 (6/217 = 2.8%) in the DM/Q 10 groups compared to 1 (1/109 = 0.9%) in the placebo group; and 3 additional deaths during the open-label phase. Dr. (b) (6) concludes that none of the deaths were proximal to initiation of therapy or associated with acute administration of the drug for the following reasons. Among the 6 patients who died in the active treatment groups, drug exposure was 24 days for one patient and 81-83 days for the others. Only two of these deaths occurred while patients were still on treatment, occurring more than 80 days after treatment initiation. The other 4 deaths occurred between 8 and 47 days after terminating study drug. The treatment duration for the single death in the placebo group was 7 days with death occurring 32 days after discontinuation of therapy (Reviewer's comments: death actually occurred 48 days after discontinuation).

Dr. (b) (6) reviewed data from the narratives and case summaries for evidences of respiratory involvement prior to study enrollment such as recommendations for or use of non-invasive ventilatory support, polycythemia, choking episodes, hypoxemia, etc. Dr. (b) (6) concludes that there is convincing evidence of clinically significant pre-existing diaphragm impairment or alternative causes of death in 7 of the 10 deaths. In the remaining 3 deaths, that there was indirect evidence for respiratory involvement in 2 subjects (pre-existing diaphragmatic impairment likely in subject #123-301-501 with tetraparesis, flu-like symptoms 2 weeks prior to death followed by the development of new onset dyspnea; pneumonia due to aspiration in subject #123-201-511). In the remaining subject (#123-135-508) there was little information available to confidently determine whether a pre-existing respiratory dysfunction was present and contributed to the death.

The Respiratory Report then presents actual mortality rates in Study 123, and the expected rates compared with an ALS cohort in a database maintained by the (b) (6) on a longitudinal sample of 313 patients who have been followed from diagnosis. The median survival in this (b) (6) cohort was 25 months from diagnosis of ALS. ALS survival in Study 123 was 94.9% (187/197 enrolled ALS patients), with all 10 deaths occurring within 900 days since diagnosis. In contrast, the survival data from the (b) (6) show that 57% of ALS subjects had died by 900 days after diagnosis. Comparing the survival rates from Study 123 and the (b) (6) database results in a hazard ratio 10.4 (95% CI 5.5 to 19.7). Several factors that can explain this difference in survival were explored. These factors include selection of ALS subjects in Study 123 with $\leq$ 30 months from diagnosis, $SaO_2 \geq 95\%$, loss of follow-up data on completion of study, differences between the mean ages of ALS subjects in Study 123 and the (b) (6) cohort. Survival in the (b) (6) cohort after excluding 57 deaths that occurred within 295 days of diagnosis (median time from diagnosis to randomization in Study 123) was compared to the survival in Study 123, resulting a lower hazard ratio of 7.1% (95% CI 3.7 to 13.3). When the

survival of patients in the (b) (6) cohort were stratified by age ≤ 62 years old versus > 62 years old (62 years being the median age in the database), there was a significant difference between these age-dependent cohorts, with a hazard ratio of 2.1 (95% CI 1.6 to 2.7) favoring the younger cohort. The ALS subjects in Study 123 were younger (mean age at randomization 55.6 years) than in the (b) (6) cohort (61 years at the time of referral).

Dr. (b) (6) states that although there was no statistical difference in survival among the treatment groups in Study 123, the apparent greater survival that was observed among patients randomized to placebo could potentially be accounted for by the fact that the median time from diagnosis of ALS to randomization was higher in the active treatment groups (386 days in DM 20 mg/Q 10 mg; 208 days in DM 30 mg/Q 10 mg) relative to placebo (161 days). The median time from diagnosis of ALS to death was 519 days in DM 20 mg/Q 10 mg, 291 days in DM 30 mg/Q 10 mg, and 200 days in the placebo group. The cumulative survival in the (b) (6) cohort at each of the above median time from diagnosis to death were estimated (63% at 519 days, 81% at 291 days and 91% at 200 days), and then the expected deaths for each of the dose groups in Study 123 were calculated:

- For the 64 patients assigned to placebo there would have been 6 deaths expected at 200 days (actual: 1 death)
- For the 68 patients receiving Zenvia 20/10 there would have been 26 deaths expected at 519 days from diagnosis (actual: 4 deaths)
- For the 65 patients receiving Zenvia 30/10 there would have been 12 deaths expected at 291 days (actual: 5 deaths)

The Respiratory Report also evaluated the incidence of nonfatal adverse respiratory-related events (respiratory failure, respiratory depression, dyspnea, dysphagia, choking, pneumonia, nausea, vomiting and pulmonary embolism) in the double-blind phase of Study 123, and states that the incidence was low and generally comparable among the three treatment groups. This Report also states that the O_2 saturation data (see section 7.4.3 of this review) suggest that changes from baseline did not show any clinically meaningful differences in any of the treatment groups.

Applicant's and Dr. (b) (6) conclusions: The Respiratory Report states that the causes of the 10 deaths among the ALS subjects in Study 123 are in accordance with expectations in an ALS population, i.e. compromised respiratory function. Overall, the proportion of deaths in Study 123 was several fold lower compared to other studies including the (b) (6) cohort, and this may be partially explained by several evaluable factors including age and selection of ALS subjects in Study 123 with ≤ 30 months from diagnosis. The mortality rate was statistically comparable among the three treatment groups, suggesting that these deaths resulted as a natural course of disease compounded by other co-morbidities rather than being treatment-related. The lower number of deaths in the placebo group compared to active treatment can in large part be due to imbalances in the time from diagnosis to randomization among groups. The low incidence of non-fatal respiratory AEs was also comparable across treatment groups, further supporting a relationship to disease rather than treatment. Taken together, these results provide evidence that treatment with Zenvia at either of the two doses used in Study 123 did not augment the respiratory effects that are generally associated with ALS. There is currently nothing in the

published literature suggesting any signals for respiratory events with either of these drugs used individually or in combination.

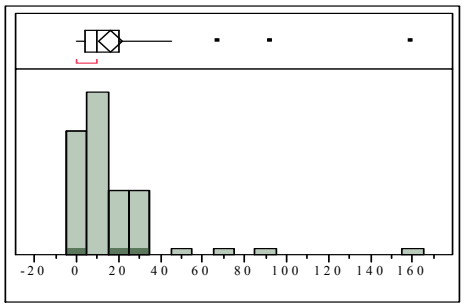
Reviewer's comments and conclusions: I agree with Dr. (b) (6) that compromised respiratory function as the most frequent cause of the 10 deaths among the ALS subjects in Study 123 is in accordance with expectations in ALS population. Although it is true that the mortality rate is statistically comparable among the three treatment groups in the double-blind phase of Study 123 (Table 30), this study is not powered to detect differences in mortality, if any, between study groups. In particular, since respiratory-related deaths and adverse events are very common occurrence in ALS subjects, a drug-related effect on these events may be difficult to detect unless the study is large and appropriately designed to detect a clinically meaningful effect.

Any attempt to explain the mortality rate in the double-blind phase of Study 123 by comparing to the mortality rates in other cohorts is limited because of the inherent shortcomings of such comparison. Importantly, the use of a concurrent placebo control in a clinical trial, as is the case in Study 123, provides the maximum ability to distinguish efficacy and safety effects caused by the study drug from those resulting from the underlying disease or intercurrent illness. In this regard, the relative risk for death in ALS subjects in any DM/Q 10 mg dose group (incidence, 6/133 = 0.045) in the double-blind phase of Study 123 is nearly 3-fold (2.8) relative to the placebo group (incidence, 1/64 = 0.016). There was one subject (#123-301-504) in whom death occurred 48 days after the last dose of study drug. Assuming that this death occurring after relatively long interval after the last dose is less likely to be drug-related and eliminating this subject, the relative risk for death in any DM/Q 10 mg dose group (incidence, 5/133 = 0.038) reduces to 2.3 relative to the risk in the placebo group. Admittedly, the absolute numbers of deaths in the double-blind phase of Study 123 are quite small such that a theoretical occurrence of one additional death in the placebo group (incidence, 2/64 = 0.03) would nearly halve the relative risk of death in any DM/Q 10 dose group to 1.5. Dr. Massie, the statistical reviewer, calculated the chance of the observed result (6 deaths in DM/Q versus 1 death in placebo) to be 0.27 if there is no difference in risk of death between drug and placebo arms.

Nevertheless, concern remains that the imbalances in the deaths between the treatment groups in the double-blind phase of Study 123 are more than a chance finding. DM/Q could potentially alter the rate of progression of ALS or affect the disease in other ways leading to excess deaths in the study drug group compared to placebo group. In this context, deaths may not necessarily occur acutely to study drug exposure (i.e., can occur later during exposure or even after discontinuation) and evidence of respiratory involvement prior to study enrollment in the majority of deaths, by itself, is not reassuring as study drug could further increase the rate of decline in these subjects. Study 123, by design, was not capable of evaluating for these potential effects of the study drug. Potentially, a very large, randomized, placebo-controlled study with stratification of subjects by important independent predictors of death in ALS, with lead-in and follow-up study periods of sufficient duration, and serial standardized collection of important variables such as vital capacity and ALSFRS-R score, time to recommendation/use of non-invasive ventilatory support, etc, might be helpful. Even then, as pointed above, since respiratory-related deaths and adverse events are very common occurrence in ALS subjects, a drug-related effect on these events may be difficult to detect in clinical trials.

The Respiratory Report states that the lower number of deaths in the placebo group compared to active treatment can in large part be due to imbalances in the time from diagnosis to randomization among treatment groups. There are clear imbalances in the time from diagnosis to randomization between treatment groups at baseline (Table 11) that could potentially explain the mortality differences between treatment groups, as the duration of disease is an important independent predictor of death in ALS. However, the conclusion that the lower number of deaths in the placebo group compared to active treatment groups can be due to imbalances in the time from diagnosis to randomization among groups is valid if the time from diagnosis to randomization in the deaths also cluster around the mean/median in each treatment group. The following distributions of the time from diagnosis to randomization for each treatment group (ALS subset) illustrate the location of ALS deaths (highlighted) within each group. The absolute numbers of ALS deaths in each treatment group are small, and it is difficult to extrapolate the outcome associated with a group mean/median to an individual case within that group.

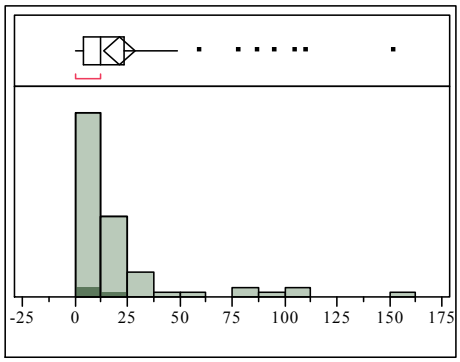
Figure 5: Distribution of time from diagnosis at randomization for ALS subjects in DM 20 mg/Q 10 mg group in Study 123 (values for the 3 highlighted deaths are: 3, 17 and 26 months).



100.0%	maximum	159.00
99.5%		159.00
97.5%		110.42
90.0%		29.10
75.0%	quartile	20.50
50.0%	median	9.50
25.0%	quartile	4.00
10.0%		1.00
2.5%		0.00
0.5%		0.00
0.0%	minimum	0.00

Source: NDA Complete Response 4/30/10; module 5.3.5.3.ISS; reviewer's analysis of AE and DM datasets: Analyze, distribution (DXDUR and ARM).

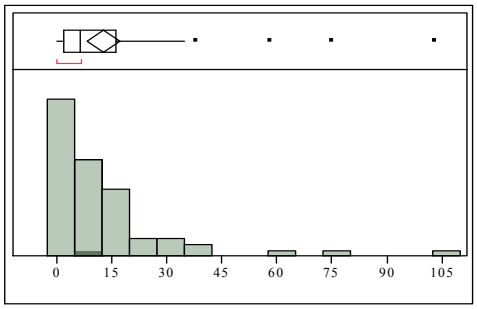
Figure 6: Distribution of time from diagnosis at randomization for ALS subjects in DM 30 mg/Q 10 mg group in Study 123 (values for the 3 highlighted deaths are: 2, 6 and 24 months)



100.0%	maximum	152.00
99 5%		152.00
97 5%		124.70
90.0%		66.60
75.0%	quartile	23.50
50.0%	median	12.00
25.0%	quartile	4.00
10.0%		1.00
2.5%		0.00
0.5%		0.00
0.0%	minimum	0.00

Source: NDA Complete Response 4/30/10; module 5.3.5.3.ISS; reviewer's analysis of AE and DM datasets: Analyze, distribution (DXDUR and ARM).

Figure 7: Distribution of time from diagnosis at randomization for ALS subjects in the placebo group in Study 123 (value for the 1 highlighted death is 5 months)



100.0%	maximum	103.00
99.5%		103.00
97.5%		85.50
90.0%		33.50
75.0%	quartile	16.00
50.0%	median	6.50
25.0%	quartile	2.00
10.0%		0.50
2.5%		0.00
0.5%		0.00
0.0%	minimum	0.00

Source: NDA Complete Response 4/30/10; module 5.3.5.3.ISS; reviewer's analysis of AE and DM datasets: Analyze, distribution (DXDUR and ARM).

Bulbar onset is another important independent predictor of mortality in ALS. At randomization in Study 123, the proportion of ALS subjects with bulbar onset is evenly distributed among the treatment groups (Table 11). The distribution of the 7 deaths during the double-blind phase by the type of ALS onset and treatment do not suggest any particular pattern for concern (see table below).

Table 44: Distribution of deaths by the onset type and treatment during the double-blind phase of Study 123

Type of onset	DM 20/Q 10 N = 68	DM 30/Q 10 N = 65	Any DM/Q 10 N = 133	Placebo N = 64
Bulbar	0/30 (0)	2/29 (6.9%)	2/59 (3.4%)	1/29 (3.4%)
Spinal	3/38 (7.9%)	1/36 (2.8%)	4/74 (5.4%)	0/35 (0)

Source: NDA Complete Response 4/30/10; module 5.3.5.3.ISS; reviewer's analysis of AE and ALSTYPE datasets

The median age for ALS subjects in DM 20 mg/Q 10 mg group was 55 years (25% and 75% quartile were 47.25 and 61, respectively) but the three deaths were younger (41.8, 45.8 and 53.6 years); median age in the DM 30 mg/Q 10 mg group was 59 (25% and 75% quartile were 51 and 64, respectively) with the ages of the three deaths in this group, 56, 64.8 and 66.5; and in the placebo group, the median age was 55.5 (25% and 75% quartile were 47.25 and 63, respectively) with the age of the single death in this group, 59.6 years.

Deaths (most commonly respiratory) and non-fatal respiratory events in ALS are likely a continuum of the spectrum of respiratory dysfunction in ALS subjects. Therefore, it would be important to assess the incidence of non-fatal respiratory-related adverse events in the DM/Q 10 group compared to the placebo group. The following table summarizes the non-fatal respiratory-related SAEs in ALS subjects in the controlled studies (Study 102 and Study 123). The incidence of subjects with a non-fatal respiratory-related SAE in the placebo group was higher than in either DM/Q 10 mg groups. There were only three subjects who discontinued due to a respiratory-related AE: one subject in the Q 30 mg only group (dyspnea) and 3 in the placebo group (dyspnea and deep vein thrombosis). In the double-blind phase of Study 123, in order to increase the likelihood of detecting a drug-related effect, I included only those non-fatal respiratory-related TEAEs experienced by ≥ 2 subjects (Table 46). The incidence of subjects experiencing any respiratory-related TEAEs in the placebo group was comparable to or higher

than in either DM/Q 10 mg dose group, weakening the concern that the imbalance in ALS deaths between treatment groups in Study 123 is more than a chance finding.

Table 45: Subjects with non-fatal respiratory-related SAEs by treatment group in controlled studies of ALS (Study 102 and Study 123)

	DM 20/ Q10 N=68		**DM 30/ Q10 N=65**		**Any DM/ Q10 N=133**		**DM 30/ Q 30 N=70**		**Any DM/ Q (10 or 30) N=203**		**Placebo N=64**		**Q30 N=37**	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any SAE	9	13.2	7	10.8	16	12.0	3	4.3	19	9.4	8	12.5	1	2.7
Any non-fatal respiratory related SAE*	2	2.9	3	4.6	5	3.8	2	2.9	7	3.4	5[#]	7.8	1	2.7

NOTE: There were no subjects with SAEs in DM30 only arm in Study 102
[#]A given subject may have experienced both non-fatal and fatal SAEs. For example, subject 135-511 (placebo) experienced 'respiratory insufficiency' from which subject recovered and subsequently experienced 'progression of ALS' which was fatal.
All respiratory-related preferred terms associated with non-fatal outcome*: dyspnea, bronchospasm, pulmonary embolism, respiratory failure (#147-501; there was one other subject #135-511 who earlier recovered from an SAE of respiratory failure who later died of 'disease progression'), acute respiratory distress syndrome, postoperative respiratory distress, pneumonia aspiration, pneumonia, aspiration, ***dysphagia and deep vein thrombosis.*
Source: NDA Complete Response 4/30/10; Reviewer's analysis of AE and DM dataset; subset (Pool 3, PRIMDIS, AESER, ARM).

Table 46: Incidence of non-fatal respiratory-related TEAEs, each TEAE experienced by ≥ 2 subjects, in the double-blind phase of Study 123

	DM 20/10 N=68		**DM 30/Q10 N=65**		**Placebo N=64**	
	n	%	n	%	n	%
Any TEAE	56	82.4	59	90.8	54	84.4
Any non-fatal respiratory related TEAE*	3	4.4	4	6.2	4	6.3

**All respiratory-related preferred terms associated with non-fatal outcome (*experienced ≥ 2 subjects): cough, deep vein thrombosis, dysphagia, dyspnoea, pulmonary embolism and respiratory failure.
Source: NDA Complete Response 4/30/10; Reviewer's analysis of AE and DM dataset; subset (Pool 3, PRIMDIS, AEDECOD, ARM).

Overall, the data do not support the conclusion that the imbalance in ALS deaths between treatment groups in Study 123 is more than a chance finding. The imbalance in the number of deaths noted in Study 123 should be included in section 6 of the label.

Deaths and other adverse events potentially due to unrecognized cardiac arrhythmias, and cardiovascular AEs:

Sudden death can occur as a result of cardiac arrhythmias associated with QT interval prolongation (torsades de pointes) or other non-cardiac mechanisms. In order to further explore cardiac arrhythmias as a potential cause for deaths, the Applicant convened an Adjudication Committee of Cardiologists to screen the 92 deaths that occurred in the development program in order to identify those that might have been due to cardiovascular causes. The Committee was asked to identify events of sudden death, where, arrhythmia might have been involved. Cause-specific mortality was first attributed to a general pathophysiological category: cardiovascular, respiratory, or other. A determination was then made as to whether the cardiovascular deaths

were sudden and/or unexpected. Potential relationship to DM/Q treatment was assessed. Seven of the 92 deaths were considered sudden (4 subjects coded as 'cardiac arrest', 2 subjects coded as 'death' and 1 subject coded as 'cardiorespiratory'). After a review of all deaths, the Committee considered only one (#107-030-001) of these cases to be a cardiovascular-related death since arrhythmia could not be excluded (narrative provided below); however, there was no evidence of QTc interval prolongation after dosing with DM/Q in this subject. With the exception of one subject (#107-052-002; narrative provided below), none of these seven deaths considered as sudden had prolonged QTc intervals. The Applicant concludes that none of these events appear to represent unrecognized QTc interval prolongation or cardiac arrhythmia.

> Subject #107-030-001 (original ID 30-3001) is a 64-year old Caucasian female with ALS who was enrolled in the open-label Study 107. Concomitant medications included sertaline, riluzole, atenolol, irbesartan and Premarin. DM 30 mg/Q 30 mg was started on 4/11/03 and discontinued on (b) (6) day of death, after (b) (6) days of treatment. She began to have coughing spells at 11 AM of 1/8/04 and was transported to the hospital. At the hospital, her husband was informed that she had died from cardiac arrest at 12:30 PM on the same day, of unknown cause. The coroner determined that the cause of death was hypertensive cardiovascular disease. Further details are lacking in the brief narrative.
>
> Subject #107-052-002 (original ID 52-5202) is a 74-year-old male with Alzheimer's Disease, coronary disease, hypertension and hypothyroidism, was enrolled in the open-label Study 107. Concomitant medications were not provided. Prolonged QTcF interval (increase of 39 msec compared with baseline values) was noted on Day 29 of DM 30 mg/Q 30 mg. On Day (b) (6), he was found unresponsive with O_2 saturation of 79.8% on room air; comfort measures were initiated and he died later that day. No autopsy was done. The investigator indicated that the death was most likely progression of Alzheimer's disease, and not related to the study drug. Since he did not die until Day (b) (6), the Applicant considers that it is unlikely that the sudden death was related to QTc interval prolongation. Reviewer's comments: ECG dataset contains no other ECG data for this subject.

AEs of cardiac arrhythmia: The Applicant conducted an analysis of all AEs of cardiac arrhythmias in the clinical trials. In Pool 3, the incidences of subjects with any cardiac arrhythmia in the DM/Q 10 mg dose group were similar to the placebo group but numerically lower than in the DM/Q 30 mg dose group (see table below). In the double-blind phase of Study 123, there were 2 (1.8%) subjects with any arrhythmia in the DM 30 mg/Q 10 mg group, and 1 (0.9%) each in the DM 20 mg/Q 10 mg and placebo group.

Table 47: Incidence of arrhythmia in controlled studies of PBA (Pool 3)

	DM 20 mg/ Q 10 mg N = 107 n (%)	DM 30 mg/ Q 10 mg N = 110 n (%)	All doses with Q 10 mg N = 217 n (%)	All doses with Q 30 mg N = 146 n (%)	All doses of DM/Q N = 363 n (%)	Placebo N = 183 n (%)
Any arrhythmia	1 (0.9)	2 (1.8)	3 (1.4)	5 (3.4)	8 (2.2)	3 (1.6)
Atrial flutter	0	0	0	1 (0.7)	1 (0.3)	0
Atrial fibrillation	0	0	0	0	0	0
Atrioventricular block first degree	1* (0.9)	1 (0.9)	2 (0.9)	0	2 (0.6)	0
Bradycardia NOS (< 60 bpm)	0	0	0	1 (0.7)	1 (0.3)	1 (0.5)
Bundle branch block, left	0	0	0	1 (0.7)	1 (0.3)	0
Sinus bradycardia	1* (0.9)	0	1 (0.5)	1 (0.7)	2 (0.6)	0
Sinus tachycardia	0	0	0	0	0	1 (0.5)
Tachycardia	0	1 (0.9)	1 (0.5)	0	1 (0.3)	0

Supraventricular tachycardia	0	0	0	1 (0.7)	1 (0.3)	0
Ventricular extrasystoles	0	0	0	0	0	1 (0.5)

* Same subject (#126-701) in Study 123
Source: NDA Complete Response 4/30/10; module 5.3.5.3.ISS; Cardiac safety report, Table 9, page 42

Across all the integrated clinical trials (Pool 1), there was one death in a subject due to myocardial infarction with arrhythmia not ruled out; otherwise, no arrhythmia was reported as an SAE. Six subject-discontinuations were attributed to cardiac arrhythmias. The narratives for these subjects are provided in the relevant sub-sections in the following paragraphs.

Bradycardia: Since Q suppresses sinus node activity, subjects taking Q, particularly those with sinus node dysfunction, can have bradycardia as an adverse effect. Bradycardia is a contraindication to treatment with Q at antiarrhythmic doses and an adverse effect of Q overdose, and symptomatic bradycardia is given as a reason to discontinue the administration of Q.

In the pooled controlled trials of PBA (Pool 3), there were a total of 4 subjects who experienced an event of either bradycardia or sinus bradycardia (Table 47). Three subjects were in the DM/Q groups and 1 subject in the placebo group. In the integrated studies (Pool 1), bradycardia or sinus bradycardia was not reported as an SAE in any subject. Across Pool 1, there were four subjects who discontinued due to bradycardia alone or along with other events. The narratives are provided below.

> Subject #106-011-000 (old ID: 1100) is a 68 year-old Caucasian male with MS who was enrolled in Study 106. Medical history included glaucoma, constipation and spasticity but no cardiovascular disease. ECG report comment at screening was "abnormal, not clinically significant— anteroseptal infarct." On Day (b) of DM 30 mg/Q 30 mg he experienced ***bradycardia*** (verbatim term "bradycardia"; self-reported heart rate of 48 beats per min), nausea, weakness, dizziness, and hypertonia; he recovered on the same day. Heart rate recorded in the CRF on Day 3 was 72 beats per min. He discontinued study medication because of these AEs. ECG heart rate on Day 3 was 60 beats per min (baseline, 64 beats per min). The investigator indicated that this subject's bradycardia, nausea, weakness, dizziness, and hypertonia had a possible relationship to study drug. Reviewer's comments: While the pre-existing anteroseptal infarct on ECG is potentially confounding, a temporal relationship between the study drug and the event can not be excluded.
>
> Subject #106-002-002 (old ID: 02-0202) is a 47 year-old MS subject who was enrolled in Study 107. Medical history included hypothyroidism. She had earlier experienced a fall after missing a landing on an unfamiliar staircase and fracturing her left tibia and fibula. She discontinued DM 30 mg/Q 30 mg on Day (b) (6) in Study 107 due to ***bradycardia*** (she was on placebo in the double-blind Study 106); the outcome is reported as not recovered. ECG heart rate on Day (b) (6) was 43 beats per min (baseline was 54 beats per min at randomization; and 51 beats per min prior to start of open-label phase); ECG findings was "marked sinus bradycardia". At the early termination visit, 21 days later, ECG heart rate was 48 beats per min. Reviewer's comments: Subject appears to have a bradycardia at baseline ranging from 51 – 54 (on placebo during Study 106).
>
> Subject #123-126-701 is a 50 year-old female subject with MS who was enrolled in Study 123. Medical history included left anterior hemiblock. Concomitant medications included ranitidine, estradiol, aspirin, gabapentin, and multivitamins. On Day 29 of DM 20 mg/Q 10 mg treatment, her ECG was read as abnormal: ***sinus bradycardia***, ***first degree AV block***, resulting in discontinuation due to these AEs. The outcome is reported as not recovered. The investigator considered the event of first degree atrioventricular block to be possibly related to the study drug and the event of sinus bradycardia not related to the study

drug. Reviewer's comments: Pre-existing left anterior hemiblock is confounding; however, a causal relationship with the study drug and these AEs can not be excluded.

Subject #106-002-007 was a 47-year old Caucasian female with MS who was enrolled in Study 107. On Day 115 of DM 30 mg/Q 30 mg treatment (85 days in Study 106 and 30 days in Study 107), she experienced ***bradycardia*** resulting in discontinuation. On Day 115, ECG heart rate was 59 beats per min (baseline was 52 beats per min at randomization; and 59 beats per min prior to start of open-label phase); ECG findings was "abnormal, not clinically significant". A narrative is not available for this subject; however, from the datasets (EG and AE), it appears that this subject continued in Study 107 for a total exposure of 1,242 days (ECG heart rate remained between 55 – 61 during the rest of the study). Reviewer's comments: Subject had a bradycardia at baseline of 52 beats per min. Importantly, she continued on in the study for a total of 1,242 days without apparent recurrence of clinical significance.

Cardiac conduction abnormalities: At antiarrhythmic doses, Q has the potential to decrease cardiac conduction including depression of AV conduction, presumably due to the inhibition of Q inhibition of cardiac sodium channels.

In the pooled controlled trials of PBA (Pool 3), there were a total of 2 subjects (one each in DM 20 mg/Q 10 mg and DM 30 mg/Q 10 mg groups) who experienced an event of first degree AV block and 1 subject in the DM 30 mg/Q 30 mg group with bundle branch block (Table 47). In the integrated studies (Pool 1), conduction block (atrioventricular or bundle branch) was not reported as an SAE in any subject. Across Pool 1, there were two subjects who discontinued due to cardiac conduction block; these subjects are summarized below.

Subject #123-126-701: Narrative provided above under bradycardia.

Subject #109-102-009 is a 75 year-old Caucasian male subject with painful diabetic neuropathy was enrolled in Study 109. Medical history included first-degree atrioventricular block, peripheral edema, hyperlipidaemia, obesity, colon cancer and hypertension. Concomitant medications at the time of the events included simvastatin, enalapril, glyburide, chromium picolinate 200 mcg daily, and insulin. At screening, the subject was noted to have first-degree atrioventricular block and prolonged PR interval that were considered abnormal and clinically significant. After receiving the first dose of DM 60 mg/Q 60 mg, on his ECG, there was progression to ***second-degree atrioventricular block***. The study drug was discontinued. The second-degree atrioventricular block resolved. The Investigator considered the PR prolongation and second-degree atrioventricular to have possible relationships to study drug. Reviewer's comments: There is pre-existing left first degree AV block; however, there appears to be a temporal relationship between the *high dose of Q* (60 mg) and the progression to second-degree AV block.

In addition to the above two subjects who discontinued, there were 11 subjects in all the integrated clinical studies (Pool 1) who experienced cardiac conduction abnormalities (bundle branch block, AV block first or second degree) as TEAEs:

- two MS subjects on DM 30 mg/Q 30 mg (Days 30 and 1,184);
- two ALS subjects, 1 each on DM 30 mg/Q 30 mg (Day 27) and on DM 30 mg/Q 10 mg (Day 1);
- six subjects with painful diabetic peripheral neuropathy (1 subject on DM 60 mg/Q 60 mg at Day 30; 1 subject on DM 45 mg/Q 30 mg at Day 92; 1 subject on DM 30 mg/Q 30 mg at Day 92; and 3 subjects on placebo at Days 1, 1 and 92);
- one subject with parkinsonian syndrome on DM 30 mg/Q 30 mg at Day 356.

Tachycardia and supraventricular tachycardia: Increases in ventricular heart rates can occur with Q in patients with atrial fibrillation/flutter, in patients with normally innervated hearts via an anti-vagal action.

In the pooled controlled trials of PBA (Pool 3), there were a total of 2 subjects (one each in DM 30 mg/Q 10 mg group and DM 30 mg/Q 30 mg group) who experienced either tachycardia or supraventricular tachycardia, compared to none in the placebo group (Table 47). In the integrated studies (Pool 1), these AEs were not reported as an SAE in any subject. Across Pool 1, there were three subjects who discontinued due to tachycardia; these subjects are summarized below.

> Subject #109-147-004 (old ID: 147-9004) is a 47 year-old female subject with painful diabetic neuropathy who was enrolled in Study 109. Medical history included GERD, hyperlipidaemia, depression, and hypertension. Concomitant medications at the time of the event included insulin, Avandia, Diovan, Zocor, and Nexium. On Day 2 of DM 90 mg/Q 60 mg the subject experienced diarrhea, hypertension exacerbation, nausea, and tachycardia. The study drug was discontinued, the events resolved, and the subject discontinued participation in the study due to the adverse events. The Investigator considered these events to have a possible relationship to study drug. Reviewer's comments: A temporal relationship between tachycardia and *high dose* of DM/Q (90 mg/60 mg) is likely present.
>
> Subject #109-147-006 (old ID: 147-9006) is a 68 year-old male subject with painful diabetic neuropathy who was enrolled in Study 109. Medical history included cholecystitis and hypertension. Concomitant medications at the time of the event included metformin, Benicar, bumetanide and glipizide. On Day 8 of DM 90 mg/Q 60 mg the subject experienced hypotension and tachycardia. The study drug was discontinued; the same day, both events resolved. The Investigator considered these events to have a possible relationship to study drug. Reviewer's comments: A temporal relationship between these events and *high dose* of DM/Q (90 mg/60 mg) is likely present.
>
> Subject #125-000-012 (original ID 12) is a 24-year old healthy female volunteer who was enrolled in Study 125 – a single center, randomized, double-blind, placebo-controlled, parallel-group, multiple dose PK evaluation of various oral dose combinations of DM and Q administered to healthy subjects. She experienced the following AEs after receiving Treatment A (45 mg DM/30 mg Q BID for 2 days) before the study medication was discontinued on Day 3: chills approximately 2 hours post dose on Day 1, followed by diarrhea 45 minutes later. On Day 3, she experienced mydriasis, dizziness, dry mouth, palpitations, skin warm, hyperhidrosis and tachycardia approximately 4 hours after the last dose on Day 2. All AEs resolved without treatment. All AEs were deemed possibly related to the study drug with the exception of diarrhea, which was deemed remotely related. The subject was withdrawn from the study on Day 3. Reviewer's comments: There does appear to be a temporal relationship of the study drug to tachycardia and palpitations.

In addition to the above three subjects who discontinued, there were 4 subjects in the integrated clinical studies (Pool 1) who experienced tachycardia, supraventricular tachycardia or supraventricular extrasystoles as TEAEs:

- three ALS subjects, 2 on DM 30 mg/Q 30 mg (Day 25 and 165) and 1 on DM 30 mg/Q 10 mg (Day 25);
- one subject with painful diabetic peripheral neuropathy on DM 30 mg/Q 30 mg (Day 11)

Atrial flutter/fibrillation // Ventricular tachycardia/fibrillation: In the Approvable Letter, the Agency expressed concern that Q is known to be particularly dangerous in patients who are

moving in and out of atrial flutter/fibrillation, due to the risk both of torsades de pointes, and of supraventricular tachycardia from Q effects on AV conduction.

The Applicant's consultant cardiologist, Dr. (b) (6), conducted an extensive review of the literature to evaluate the effects of Q in subjects who are moving in and of atrial fibrillations/flutter. Dr. (b) (6) summarizes the findings and conclusions in a report: Use of Zenvia in patients with paroxysmal atrial fibrillation or flutter. Dr. (b) (6) and the Applicant conclude that there is no clear documentation for this concern in the literature.

Across all the integrated clinical studies (Pool 1), there were 7 subjects for whom atrial fibrillation (n=6) or flutter (n=1) was recorded as *medical history*. While none of these subjects experienced supraventricular tachycardia, torsades de points, atrial fibrillation or flutter while on DM/Q treatment, two of these subjects experienced a cardiovascular non-arrhythmic SAE; the narratives for these patients are summarized below.

> Subject #107-052-002 was a 74-year old male with a history of Alzheimer's disease, acute coronary disease, hypertension, hypothyroidism, and atrial fibrillation enrolled in Study 107. On Day (b) (6) of DM 30 mg/Q 30 mg treatment, he suffered ***cardiorespiratory arrest***. He was found in the nursing home where he resided, unresponsive to verbal and tactile stimuli. His respiratory rate was 45 per minute, his heart rate was 105 bpm, and the oxygen saturation was 80% on room air. Resuscitation was not done as he had a living will and a 'Do Not Resuscitate' order. He expired about 11 hours after being found unresponsive. The investigator assessed the event as not related to the study drug, and as related to the progression of Alzheimer's disease. Reviewer's comments: relationship between the event and study drug is uncertain.
>
> Subject #109-134-013 with a medical history of atrial fibrillation was enrolled in Study 109, and was discontinued from the study due to the SAE of DVT. Subject was receiving *placebo*.

In the integrated clinical trials pool (Pool 1), there were a total of 5 subjects who *experienced* atrial fibrillation (n=4) or flutter (n=1). None of these subjects experienced these events as an SAE. One (#102-005-001) of these subjects discontinued as a result of atrial flutter; brief narrative for this subject is included below. All these 5 subjects were in the DM 30 mg/Q 30 mg dose; none were taking any DM /Q 10 mg doses. All were aged > 61 years (61, 63, 67, 68 and 72 years). Two subjects had ALS as the underlying primary disease, two had painful diabetic neuropathy and one subject had history of viral meningoencephalitis. None of these patients had atrial fibrillation or atrial flutter in their recorded medical histories. Hypertension, bradycardia, hyperlipidemia and stroke were the co-morbidities in most of these subjects. Atrial fibrillation or flutter occurred on Days 3 (see narrative below for #102-005-001), 10, 55, 92 and 1211.

> Subject #102-005-001 (Old ID: 0501) is a 68-year old Caucasian male with bulbar onset ALS who was enrolled in Study 102. Medical history included right MCA stroke secondary to carotid artery dissection and intermittent psoriasis. No concomitant medications were recorded. On Day 2 of DM 30 mg/Q 30 mg, he developed fatigue and insomnia, and ***atrial flutter*** (verbatim: "increased awareness of atrial flutter") on Day 3, and weight decreased and gait abnormal on Day 4. The subject discontinued study medication because of these AEs after receiving a total of 6 doses of DM 30 mg/Q 30 mg. He recovered from his fatigue, insomnia, weight decreased, and gait abnormal on Day 6, but his atrial flutter was ongoing at the time of his final assessment. The investigator indicated that this subject's atrial flutter, fatigue, insomnia, and gait abnormal had a possible relationship to study drug. Reviewer's comments: There appears to be a temporal relationship between the study drug and atrial flutter.

Syncope, presyncope and palpitations

The Applicant also considered syncope and palpitations are potentially representing unrecognized cardiac arrhythmias. Across all the integrated clinical studies including open-label studies (Pool 1), 17 subjects (1.2%) were identified with syncope, and 24 subjects (1.7%) were identified with palpitations. In the pooled controlled studies of PBA (Pool 3), the incidence of syncope and presyncope was 5 (2.3%) in subjects exposed to DM any dose/Q 10 mg, 1 (0.7%) in subjects exposed to DM any dose/Q 30 mg, and 2 (1.1%) in the placebo group. In the double-blind phase of Study 123, the incidence of subjects with presyncope/syncope in the DM 30 mg/Q 10 mg group is numerically higher than either the DM 20 mg/Q 10 mg or placebo groups (see table below).

Table 48: Incidence of subjects with palpitations, presyncope or syncope in the double-blind phase of Study 123.

Preferred term	DM 20/Q 10 N=107 n (%)	DM 30/Q 10 N=110 n (%)	Placebo N=109 n (%)
Palpitations	1 (0.9)	0 (0)	0 (0)
Presyncope/Syncope	1 (0.9)	4 (3.6)	1 (0.9)

One MS subject each in the DM 20 mg/Q 10 mg and placebo experienced syncope; all other subjects experiencing these events were ALS subjects.
Source: NDA Complete Response 4/30/10; reviewer's analysis of the AE dataset: subset Pool 3 Y and Study 123 Y.

Syncope was reported as an SAE in three subjects, and two subjects discontinued due to syncope or syncope vasovagal. These subjects are summarized below.

Subject #107-003-318 (original ID 03-0318) is a 67-year old Caucasian female with MS who was enrolled in the open-label Study 107 on 4/23/04. Medical history included MS, hypertension, hyponatremia, diabetes and ministrokes. On Day (b) (6) of DM 30 mg/Q 30 mg, she was taken to the ER due to nausea, vomiting, diarrhea and brief loss of consciousness. Work-up showed hyponatremia (129 mmol/L) and was otherwise negative. She was discharge 2 days later. The study drug was continued without interruption and the investigator determined that the event of syncope was not related to study drug.

Subject #123-302-503 (narrative included in section 7.3.2 of this review): syncope was attributed to tamulosin due to the temporal relationship of the event to the start of tamulosin. Subject went on to complete the open-label study on DM 30 mg/Q 10 mg.

Subject #109-122-9004 is a 68-year old Caucasian male who was enrolled in Study 109. Medical history included hypertension, pernicious anaemia, myeloproliferative disorder, left external carotid artery occlusion, lightheadedness, blood clots, and pulmonary embolism. Concomitant medications at the time of the event included warfarin, pioglitazone, lisinopril, ferrous sulfate 325 mg daily, and Centrum Silver. On Day (b) after starting DM 90 mg/Q 60 mg, he presented to the hospital after experiencing 4 severe episodes of vertigo within 1 to 2 hours, lightheadedness, a spinning sensation, and syncope. ECG showed a 0.5 mm elevation in ST segment, and therefore, he underwent cardiac catheterization that revealed significant coronary artery disease (CAD). Stents were placed in the diagonal branch and left anterior descending arteries, and was given meclizine for the vertigo and lightheadedness. He was discharged from the hospital after (b) days. The last dose of study drug was on Day (b), the same day that he was hospitalized. He discontinued participation in the study due to the coronary artery disease and syncope. The Investigator considered the coronary artery disease and syncope to be unrelated to study drug. Reviewer's comments: causality of syncope confounded by prior history of lightheadedness and anemia.

Subject #107-018-009 (original ID 1809) is a 46-year old Caucasian male with ALS who was enrolled in the open-label Study 107. Medical history included ALS, toes numb/tingling and osteoarthritis. Concomitant medications included riluzole and minocycline for ALS, ibuprofen, bisacodyl,

dexbrompheniramine, pseudoephedrine, and nutritional supplements. Subject developed syncope on study Day 61 (DM 30 mg/Q 30 mg) and discontinued study medication because of this AE. He reportedly recovered from his syncope on Day 81 without treatment. The investigator indicated that this subject's syncope was unlikely to be related to study medication.

Subject #109-106-007 (original ID 106-9007) is a 60-year old Caucasian male who was enrolled in the open-label Study 109. Medical history included diabetic peripheral neuropathy with pain, hypocholesterolaemia, osteoarthritis, squamous cell carcinoma, hypertension, and intermittent claudication. Concomitant medications at the time of the events included metformin, glipizide, Lotrel and Zocor. On Day 1 after receiving DM 45 mg/Q 30 mg, the subject experienced dizziness, nausea, and syncope vasovagal. The study drug was discontinued. The Investigator considered syncope vasovagal to have a possible relationship to study drug. Reviewer's comments: There does appear to be a temporal relationship of the study drug to syncope.

Palpitations were reported as an SAE in one subject, and resulted in discontinuations in four subjects. These subjects are briefly summarized below.

Subject #107-036-004 (original ID 36-3604) is a 57-year old Caucasian female with ALS who was enrolled in the open-label Study 107. On Day (b) (6) of DM 30 mg/Q 30 mg, she experienced serious events of palpitations and chest pain. Cardiac work up was negative. She was admitted to a telemetry unit for further observation. The next morning symptoms resolved, and she signed out of the hospital against medical advice. All tests and telemetry were negative. The subjects later told the Study Coordinator that she probably "smoked too many cigarettes and had too much coffee". No etiology was determined and no further episodes were reported. Study medication was continued without interruption. The investigator determined that the event of palpitations and chest pain was not related to study drug.

Subject #107-005-011 (original ID 511) is a 26-year old Caucasian female with MS who was enrolled in the open-label Study 107. Medical history included thyroid cyst and Hashimoto's disease, elevated rheumatoid factor and depression. Concomitant medications included copaxone, baclofen, clonazepam, levothyroxine, cetirizine, ranitidine and nutritional supplementation. On Day 7 of DM 30 mg/Q 30 mg, she experienced severe heart rate increased (verbatim, "heart racing"), and she discontinued study medication because of this AE. Her heart rate was 60 beats/minute at screening, 76 beats/minute on Day 1, and 60 beats/minute on Day 35 (end of study visit). She recovered from this AE on Day 10 without treatment. The investigator indicated that this subject's heart rate increased had a highly probable relationship to study medication. Reviewer's comments: The presence of Hashimoto's thyroid disease is confounding; however, a temporal relationship of the study drug to palpitations can not be excluded.

Subject #107-006-020 (original ID 1620) is a 38-year old Caucasian female who was enrolled in the open-label Study 107. Medical history included stroke with residual left-sided weakness, spinal cord injury, intermittent bilateral swelling and numbness of the lower extremities, neurogenic bladder and urinary incontinence, primarily wheelchair bound, psychogenic seizure-like events and heart murmur. Concomitant medications included alprazolam, carisoprodol, morphine sulfate for chronic pain, and ibuprofen. She developed nausea and heart rate increased (verbatim: "heart racing") on Day 1 of DM 30 mg/Q 30 mg, and diarrhoea and agitation on Day 2. She received diazepam for agitation. She discontinued study medication because of these AEs. At screening her pulse was 54 beats/minute; no vital signs data are available after the screening visit, as she did not return for follow-up visit. She recovered from her heart rate increased on Day 6 without treatment. The investigator indicated that this subject's diarrhoea, nausea, and heart rate increased had a possible relationship to study medication. Reviewer's comments: There does appear to be a temporal relationship of the study drug to palpitations.

Subject #107-028-005 (original ID 2805) is a 51-year old Caucasian female with MS who was enrolled in the open-label Study 107. Medical history included anxiety, urinary incontinence, dizziness, scleroderma, Raynaud's syndrome and anemia. Concomitant medications included Librax for abdominal cramps, copaxone, carisoprodol, tizanidine, alprazolam, clonazepam, erythromycin (CYP3A4 inhibitor) and

promethazine for sclerodema. She developed palpitations, dry mouth, retching, and taste disturbance ("metal taste in mouth"), after receiving the first dose of DM 30 mg/Q 30 mg. She discontinued study medication because of these AEs and recovered without treatment on the same day. The investigator indicated that this subject's palpitations, dry mouth, retching, and taste disturbance had a probable relationship to study medication. Reviewer's comments: There does appear to be a temporal relationship of the study drug to palpitations, particularly in the context of concomitant use of DM 30 mg/Q 30 mg and erythromycin.

Subject #125-000-012 (original ID 12): Narrative provided under tachycardia.

Applicant's conclusions: The Applicant concludes that the incidence of cardiac arrhythmia, syncope/presyncope or palpitations with DM/Q is extremely low in subjects with PBA. There is no documented evidence in the literature or from the integrated clinical data that subjects with atrial fibrillation or atrial flutter are at increased risk of arrhythmias when treated with Q.

Reviewer's comments: Assessments of all the 92 deaths in the safety database for sudden deaths (potentially due to cardiac arrhythmia) by the Adjudication Committee of Cardiologists are limited because it is a post-hoc analysis. The Committee first assigned a cause-specific mortality to each death (cardiovascular, respiratory, or other), and then a determination was made as to whether the cardiovascular deaths were sudden and/or unexpected. A potential limitation of this approach is that a death may not necessarily be solely due to respiratory or cardiac cause. It is not clear if the Committee considered the possibility that deaths could have been sudden in the respiratory category as well.

Across the integrated clinical studies, there were no subjects who experienced a cardiac arrhythmia as an SAE. There were several subjects who discontinued due to TEAEs of cardiac arrhythmia. Many of them had pre-existing risk factors that confounded causality assessment. There appeared to be a temporal relationship between the TEAEs of cardiac arrhythmia and DM/Q in some subjects; however, some of them were on DM/Q formulations with high Q dose, and others continued on in the study without apparent recurrence of the events in question. In the pooled controlled trials, compared to the pooled placebo group, the incidence of subjects experiencing any cardiac arrhythmia was greater in the DM/Q 30 mg group and comparable in the DM/Q 10 mg group; however, the numbers of subjects experiencing each cardiac arrhythmia was quite small. The occurrence of cardiac arrhythmia in DM/Q 10 mg doses was very infrequent.

Across the integrated clinical studies, there were few subjects who experienced syncope/presyncope or palpitations as an SAE or resulted in discontinuation. Many of them had pre-existing risk factors that confounded causality assessment. Most (3/4) of the subjects who experienced SAEs continued on in the study without apparent recurrence of syncope or palpitations. In the double-blind phase of Study 123, compared to placebo group (1/109 = 0.9%), subjects who experienced syncope/presyncope were numerically higher in the DM 30 mg/Q 10 mg (4/110 =3.6%) and comparable in the DM 20 mg/Q 10 mg group (1/107 = 0.9%).

A consult with the Cardio-Renal Division for expert assessment of the cardiac risk of DM/Q has not yet been finalized.

Falls and Dizziness:

In the Approvable Letter, the Agency expression concern about the risk of falls and dizziness.

Falls: The Applicant's strategy for the analyses of falls was outlined at the beginning of this section. After excluding subjects flagged for actual falls that the Applicant identified in Pool 3, I searched for additional subjects who experienced falls using text string containing 'fall' or 'fell'. I identified one additional subject (#102-011-012) in Study 102 who experienced a verbatim term of '(fall) bruised back'; this subject had ALS and was on DM 30 mg only arm. The following tables summarize the incidences of subjects with any fall, 'falls with one or more possible predisposing events', 'falls with one or more injuries', and 'injuries without falls' across the controlled trials of PBA (Pool 3) in the ALS subjects and MS subjects.

In the ALS subjects, the incidence of subjects with any fall, or 'falls with one or more injuries' in the placebo group is higher than or comparable to that in the DM/Q 10 or DM/Q 30 mg groups. In subjects with a 'fall with one or more possible predisposing events', the incidence in the DM 30 mg/Q 10 mg group is numerically higher than that in the placebo group, and appears driven mainly by the between treatment group imbalances for dizziness/vertigo, and sedation/somnolence events. Subjects who sustained injuries without any falls were all in the DM/Q groups without any subject in the placebo group; however, the absolute numbers in each group were small. In the double-blind phase of Study 123, the incidence of subjects with falls is comparable between treatment groups: 14.7% (10/68) in DM 20 mg/Q 10 mg group, 27.7% (18/65) in the DM 30 mg/Q 10 mg group, and 28.1% (18/64) in the placebo group. In the double-blind phase of Study 123, the incidence of fall-related AEs were also comparable between treatment groups.

Table 49: Incidence of treatment-emergent falls, and falls-related categories by treatment in ALS subjects in Pool 3.

	AVP-923							
System Organ Class/ Preferred Term	20 mg DM/ 10 mg Q (N=68)	30 mg DM/ 10 mg Q (N=65)	All doses with 10 mg Q (N=133)	All doses with 30 mg Q (N=70)	All AVP-923 (N=203)	Placebo (N=64)	DM 30 mg (N=33)	Q 30 mg (N=37)
Any Fall	10 (14.7%)	18 (27.7%)	28 (21.1%)	9 (12.9%)	37 (18.2%)	17 (26.6%)	3 (9.1%)	0
Fall with one or more possible predisposing events	5 (7.4%)	9 (13.8%)	14 (10.5%)	4 (5.7%)	18 (8.9%)	7 (10.9%)	1 (3.0%)	0
Any Ataxia/Gait/Balance Event	0	2 (3.1%)	2 (1.5%)	1 (1.4%)	3 (1.5%)	3 (4.7%)	1 (3.0%)	0
Any Cardiovascular/Cardiovascular-Related Event	1 (1.5%)	2 (3.1%)	3 (2.3%)	0	3 (1.5%)	3 (4.7%)	1 (3.0%)	0
Any Dizziness/Vertigo Event	2 (2.9%)	4 (6.2%)	6 (4.5%)	2 (2.9%)	8 (3.9%)	1 (1.6%)	1 (3.0%)	0
Any Sedation/Somnolence Event	4 (5.9%)	3 (4.6%)	7 (5.3%)	1 (1.4%)	8 (3.9%)	1 (1.6%)	0	0
Fall with one or more injuries [1]	2 (2.9%)	4 (6.2%)	6 (4.5%)	4 (5.7%)	10 (4.9%)	7 (10.9%)	0	0
CONTUSION	0	0	0	0	0	3 (4.7%)	0	0
EXCORIATION	1 (1.5%)	0	1 (0.8%)	0	1 (0.5%)	3 (4.7%)	0	0
FOOT FRACTURE	1 (1.5%)	1 (1.5%)	2 (1.5%)	0	2 (1.0%)	0	0	0
HAND FRACTURE	0	0	0	1 (1.4%)	1 (0.5%)	0	0	0
HEAD INJURY	0	2 (3.1%)	2 (1.5%)	0	2 (1.0%)	1 (1.6%)	0	0
JOINT INJURY	1 (1.5%)	0	1 (0.8%)	1 (1.4%)	2 (1.0%)	0	0	0
JOINT SPRAIN	0	0	0	0	0	1 (1.6%)	0	0
RIB FRACTURE	0	0	0	1 (1.4%)	1 (0.5%)	1 (1.6%)	0	0
SKELETAL INJURY	0	1 (1.5%)	1 (0.8%)	0	1 (0.5%)	1 (1.6%)	0	0
SKIN LACERATION	0	0	0	1 (1.4%)	1 (0.5%)	1 (1.6%)	0	0

Injuries without any fall	2 (2.9%)	4 (6.2%)	6 (4.5%)	2 (2.9%)	8 (3.9%)	0	4 (12.1%)	1 (2.7%)
CONTUSION	0	1 (1.5%)	1 (0.8%)	1 (1.4%)	2 (1.0%)	0	2 (6.1%)	0
EXCORIATION	1 (1.5%)	0	1 (0.8%)	1 (1.4%)	2 (1.0%)	0	0	0
HAND FRACTURE	1 (1.5%)	0	1 (0.8%)	0	1 (0.5%)	0	0	0
HEAD INJURY	0	1 (1.5%)	1 (0.8%)	0	1 (0.5%)	0	0	0
INJURY	0	0	0	0	0	0	1 (3.0%)	0
JOINT DISLOCATION	0	1 (1.5%)	1 (0.8%)	0	1 (0.5%)	0	0	0
JOINT SPRAIN	0	0	0	0	0	0	1 (3.0%)	0
MOUTH INJURY	0	0	0	0	0	0	1 (3.0%)	0
RADIUS FRACTURE	0	0	0	0	0	0	0	1 (2.7%)
SKIN LACERATION	0	2 (3.1%)	2 (1.5%)	0	2 (1.0%)	0	0	0

Note: In the DM 30 mg category, there was one additional fall resulting in a total of 4 (12.1%)
Note: Treatment categories are not mutually exclusive. Thus, patients may contribute to events in more than one treatment category.
Note: In each AE group or preferred term, a patient is counted only once within each treatment category, ie, only first occurrences are tabulated within each treatment category and primary disease.
[1] Injuries are considered to be fall-related if the injury started within 5 days after the fall.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS, Table 17.1.3

In the MS subjects (Pool 3), the incidence of subjects with any fall, or 'falls with one or more predisposing events', and 'falls with one or more injuries' in the DM/Q groups was higher than in the placebo group. The incidence of subjects with any fall in either DM/Q 10 mg groups is over two-fold higher than in the pooled placebo subjects in Pool 3. In contrast, in the double-blind phase of Study 123, the incidence of subjects with fall is comparable between treatment groups: 10.3% (4/39) in DM 20 mg/Q 10 mg group, 8.9% (4/45) in the DM 30 mg/Q 10 mg group, and 8.9% (4/45) in the placebo group.

Table 50: Incidence of treatment-emergent falls, and falls-related categories by treatment in MS subjects in Pool 3.

	AVP-923							
System Organ Class/ Preferred Term	20 mg DM/ 10 mg Q (N=39)	30 mg DM/ 10 mg Q (N=45)	All doses with 10 mg Q (N=84)	All doses with 30 mg Q (N=76)	All AVP-923 (N=160)	Placebo (N=119)	DM 30 mg (N=0)	Q 30 mg (N=0)
Any Fall	4 (10.3%)	4 (8.9%)	8 (9.5%)	4 (5.3%)	12 (7.5%)	5 (4.2%)	0	0
Fall with one or more possible predisposing events	2 (5.1%)	2 (4.4%)	4 (4.8%)	1 (1.3%)	5 (3.1%)	2 (1.7%)	0	0
Any Ataxia/Gait/Balance Event	0	0	0	0	0	0	0	0
Any Cardiovascular/Cardiovascular-Related Event	1 (2.6%)	0	1 (1.2%)	1 (1.3%)	2 (1.3%)	0	0	0
Any Dizziness/Vertigo Event	1 (2.6%)	1 (2.2%)	2 (2.4%)	1 (1.3%)	3 (1.9%)	1 (0.8%)	0	0
Any Sedation/Somnolence Event	1 (2.6%)	1 (2.2%)	2 (2.4%)	0	2 (1.3%)	1 (0.8%)	0	0
Fall with one or more injuries [1]	2 (5.1%)	1 (2.2%)	3 (3.6%)	0	3 (1.9%)	0	0	0
CONTUSION	1 (2.6%)	1 (2.2%)	2 (2.4%)	0	2 (1.3%)	0	0	0
HAND FRACTURE	1 (2.6%)	0	1 (1.2%)	0	1 (0.6%)	0	0	0
JOINT INJURY	1 (2.6%)	0	1 (1.2%)	0	1 (0.6%)	0	0	0
Injuries without any fall	3 (7.7%)	1 (2.2%)	4 (4.8%)	7 (9.2%)	11 (6.9%)	9 (7.6%)	0	0
CONTUSION	0	0	0	2 (2.6%)	2 (1.3%)	3 (2.5%)	0	0
EXCORIATION	1 (2.6%)	0	1 (1.2%)	0	1 (0.6%)	1 (0.8%)	0	0
FOOT FRACTURE	0	0	0	1 (1.3%)	1 (0.6%)	2 (1.7%)	0	0
INJURY	0	0	0	1 (1.3%)	1 (0.6%)	0	0	0
JOINT INJURY	0	0	0	0	0	1 (0.8%)	0	0
JOINT SPRAIN	1 (2.6%)	0	1 (1.2%)	1 (1.3%)	2 (1.3%)	0	0	0

Note: Treatment categories are not mutually exclusive. Thus, patients may contribute to events in more than one treatment category.
Note: In each AE group or preferred term, a patient is counted only once within each treatment category, ie, only first occurrences are tabulated within each treatment category and primary disease.
[1] Injuries are considered to be fall-related if the injury started within 5 days after the fall.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS, Table 17.1.3

Falls were plotted as a function of time (not included in this review) and showed no clear relationship between the incidence and time.

Across all the integrated clinical studies, there were 5 subjects – all in the open-label Study 107, who experienced falls as an SAE. Three were subjects with ALS, 1 with traumatic brain injury and 1 with progressive supranuclear palsy and fronto-temporal dementia. None were fatal, and all recovered from the event. The narratives for these SAEs are provided below.

> Subject #107-024-002 was a 48-year old Caucasian male with ALS enrolled in Study 107. Concomitant medication was caredilol. On Day (b) (6) of DM 30 mg/Q 30 mg, while leaning forward, he lost his balance and fell sustaining a scalp laceration. In the ER, a CT brain showed a small (4.3 mm) hematoma in the subdural space. After a 24-hour observation, he was discharged. He continued in the study taking the study medication for a total of 1432 days.
>
> Subject #107-024-013 was a 72-year old Caucasian male with progressive supranuclear palsy and fronto-temporal dementia enrolled in Study 107. Seven days after study drug discontinuation (reason not in the narrative), he fell while walking. While being evaluated in the ER, he had another fall from the stretcher to the floor. CT brain showed a small subdural hematoma along the falx on the left. After a neurosurgical consultation, he was managed conservatively and was discharged after 5 days. He fully recovered.
>
> Subject #107-025-022 was a 39-year old Caucasian male with ALS and having difficulty with ambulation enrolled in Study 107. On Day (b) (6) of DM 30 mg/Q 30 mg, he fell and struck his head while walking in his home. He sustained scalp laceration. After an overnight observation, he was discharged home. He fully recovered. He continued in the study taking the study medication for a total of 323 days.
>
> Subject #107-034-052 was a 73-year old Caucasian male with ALS enrolled in Study 107. On Day (b) (6) of DM 30 mg/Q 30 mg, he fell on ice in the parking lot and sustained right hip fracture. He underwent surgical repair the next day. Post operative course was complicated by mental status changes and difficulty breathing. CT head and chest were negative. He improved and was discharged after (b) (6) days. He fully recovered. He continued in the study taking the study medication for a total of 451 days.
>
> Subject #107-042-002 was a 74-year old Caucasian male with traumatic brain injury enrolled in Study 107. On Day (b) (6) of DM 30 mg/Q 30 mg, he had a fall resulting in back pain. MRI showed compression fracture of L-2 vertebra. Next day he underwent kyphoplasty of L-2 vertebra without complications. He fully recovered. He continued in the study taking the study medication for a total of 415 days.

A total of 6 subjects discontinued due to a fall; none were serious. These subjects are summarized in the following table. In the majority of subjects, falls occurred quite early after exposure to study drug began suggesting possible temporal relationship between the study drug and falls.

Table 51: Summary of subjects experiencing falls leading to discontinuation in Pool 1

STUDYID	USUBJID	AGE	Diagnosis	Treatment	Study day of fall leading to discontinuation	Outcome
Study 107	106-034-001	48	MS	DM 30/Q 30	12	Recovered
	107-002-002	46	MS	DM 30/Q 30	7	Not Recovered
	107-024-001	40	ALS	DM 30/Q 30	6	Recovered
Study 109	109-134-005	68	DN	Placebo	2	Recovered
Study 123 double-blind	123-139-703	37	MS	DM 30/Q 10	20	Recovered
Study 123 open-label	123-105-506	71	ALS	DM 30/Q 10	8	Recovered

Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS: Reviewer's analysis of AEDM dataset (Pool 1 Y, AE_Fall Y, AECNN Y); STUDYID, USUBJID, AGE, PRIMDIS, AESTDY, AEOUT and DUREXPO; Tabulate

Dizziness: Among the ALS subjects in the pooled controlled studies of PBA, the incidence of dizziness was 14.3% (19/133) in any DM/Q 10 mg group, 20% (14/70) in any DM/Q 30 mg group, and 6.3% (4/64) in the placebo group. In the MS subjects, the incidence of dizziness was 13.1% (11/84) in any DM/Q 10 mg group, 26.3% (20/76) in any DM/Q 30 mg group, and 6.7% (8/119) in the placebo group.

In Study 123, the Applicant pooled several preferred terms associated with dizziness coding them as dizziness (see foot note of Table 52 for a listing). The following table summarizes the incidence of dizziness in the double-blind phase of Study 123. In all subjects, ALS and MS subjects, there is a clear dose-related increase in the incidence of dizziness compared to placebo group. In the MS subjects, in particular, there is an 8-fold excess of dizziness in the DM 30 mg/Q 10 mg group compared to the placebo group.

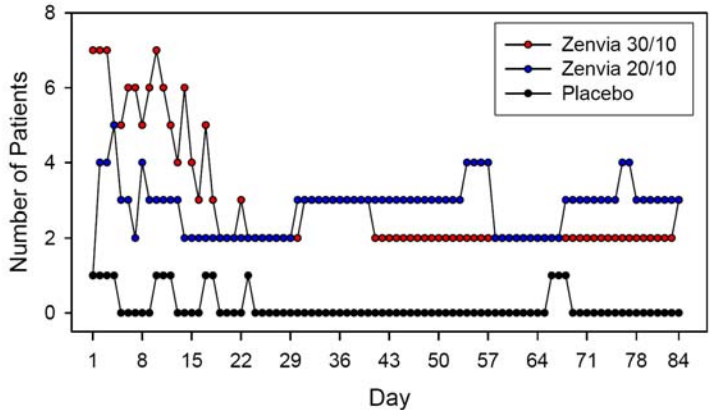
Table 52: Incidence of dizziness in the double-blind phase of Study 123

Dizziness* event	**Zenvia 30/10 (N=110)**	**Zenvia 20/10 (N=107)**	**Placebo (N=109)**
All Subjects	20/110 (18%)	11/107 (10%)	6/109 (6%)
ALS	12/65 (18.5%)	8/68 (11.8%)	5/64 (7.8%)
MS	8/45 (17.8%)	3/39 (7.7%)	1/45 (2.2%)

*Preferred event terms associated with dizziness that were coded as dizziness: dizzy, dizziness, light-headed, light-headedness, intermittent chronic dizzy/dizziness worsening, intermittent dizziness, intermittent light-headedness, intermittent nocturnal dizziness, feeling dizzy, and feeling dizzy occasionally.
Source: NDA Complete Response 4/30/10; module 1.11.3 Efficacy information amendment; modified Table 23, page 60. Reviewer's analysis of DM dataset

Dizziness as a function of time by treatment group (see figure below) showed that dizziness was most frequently reported within the first two weeks of therapy and leveled off with continued exposure. When the function of dizziness by time is compared with the function of falls by time, there does not appear to be a temporal relationship between dizziness and falls (data reviewed but not included in the review).

Figure 8: Dizziness as a function of time by treatment group



Source: NDA Complete Response 4/30/10; module 1.11.3 Efficacy information amendment; Figure 5, page 60.

On face, dizziness appears to be an important risk factor for falls. Across the integrated clinical studies, I calculated the odds of a fall in subjects with and without a TEAE of dizziness (see table below). As can be seen, the odds of a fall in subjects who experienced any TEAE of dizziness is only 1.46 times that in subjects who did not experience any TEAE of dizziness.

Table 53: 2X2 contingency table for subjects with TEAE of dizziness and TEAE of fall, in Pool 1

		TEAE of dizziness	
		Yes	No
TEAE of fall*	Yes	60	138
	No	286	961
	Total	346	1099
	Odds	0.210	0.143
	OR	1.46	

**includes subject #102-011-012 who experienced a verbatim event of "(fall) bruised back" but was not coded to fall
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS: Reviewer's analysis of AEDM dataset (Pool 1 Y).

Across the integrated clinical studies, there were three subjects – all in the open-label Study 107 who experienced dizziness as an SAE. All were ALS subjects. None were fatal, and all recovered.

Subject #107-028-004 was a 45-year old Caucasian male with ALS enrolled in Study 107. On Day (b) (6) of DM 30 mg/Q 30 mg, he bean to experience dizziness. Evaluation in the ER was negative. He improved with meclizine and was diagnosed with labyrinthitis. He continued in the study taking the study medication for a total of 1201 days.

Subject #107-036-004 was a 57-year old Caucasian female with ALS enrolled in Study 107. She had prior history of vertigo prior to start of study medication. On Day (b) (6) of DM 30 mg/Q 30 mg, she complained of dizziness and a "twitching sensation in her head when she turned to the right". After a negative evaluation in the hospital, she was diagnosed to have benign positional vertigo and discharged on meclizine. She continued in the study taking the study medication for a total of 1055 days.

Subject #107-036-006 was a 47-year old Caucasian female with ALS enrolled in Study 107. On Day (b) (6) of DM 30 mg/Q 30 mg, she was hospitalized for evaluation of nausea, vomiting and dizziness. Evaluation in the ER was negative. She was treated for an inner ear problem and discharged the next day. She fully recovered. She continued in the study taking the study medication for a total of 130 days.

In all the integrated clinical studies, there were 35 subjects who discontinued due to dizziness. The majority (16/35 = 45.7%) of subjects discontinued from open-label Study 107; 7 subjects from the controlled study of diabetic subjects with neuropathy; the remaining discontinued from the controlled studies (3 from Study 102, 2 from Study 106 and 1 from Study 123). The underlying diagnosis was ALS (n=7), MS (n=8), diabetic painful neuropathy (n=7), healthy volunteers (n=6) and the remaining with other neurological conditions. In the PK studies and Study 109, high DM/Q doses were used (DM 60/Q45, DM 60/Q30, DM 45/Q60, DM 45/Q30, and DM45/Q30). Majority of discontinuations occurred soon after exposure began (75% discontinued by Day 5). With the exception of 3 subjects, all subjects were noted to have recovered.

Applicant's conclusion regarding falls and dizziness: Analyses conducted on the data from the pivotal Study 123 trial strongly suggest that the incidence of falls in PBA subjects is related to the underlying neurological condition of the patient and is not caused by Zenvia use. There was no evidence to suggest an association between falls and dizziness. The overall incidence of dizziness was slightly higher in subjects in the Zenvia 30/10 and Zenvia 20/10 dose groups compared to placebo, but ameliorated after the first two weeks of therapy. Based on these results, physicians should inform patients to exercise caution until they know how Zenvia may affect them. To this aim, Zenvia product labeling includes dizziness as a Warning and Precaution and dizziness is included as one of the topics that physicians should discuss with patients for whom they prescribe Zenvia.

Reviewer's comments and conclusion regarding falls and dizziness: Data from the pooled controlled trials suggest an excess of fall or fall-related events in the DM/Q groups compared to placebo, particularly in the MS subjects. However, in the double-blind phase of Study 123, the incidences of falls are comparable between treatment groups. Data do not show a clear pattern for the incidence of falls over time. Five subjects experienced falls as an SAE, some of them with small subdural hematomas. All of these SAEs occurred in the open-label Study 107 many days after exposure to study drug began, and all subjects recovered from the event. The fact that most subjects continued on in the study with no apparent recurrence, on face, appears reassuring, but details are lacking whether these subjects continued to independently ambulate or have become wheelchair-bound. Subject-discontinuations too occurred mostly in the open-label studies. From the narratives, it is difficult to deduct causality, or exclude either the study drug or intercurrent illnesses as a potential cause of the event in question with any reasonable degree of confidence.

Controlled data show a clear dose-related increase in the incidence of dizziness compared to placebo group. Dizziness was most frequently reported within the first two weeks of therapy, leveling off with continued exposure, and did not occur in temporal proximity to the events of falls. All the SAEs of dizziness and most of the discontinuations occurred in open-label studies. All subjects who experienced SAEs and almost all subjects who discontinued recovered. Across the integrated clinical trials, the odds of a fall in subjects who experienced any TEAE of dizziness is only 1.46 times that in subjects who did not experience any TEAE of dizziness.

Overall, the data do not support the conclusion that falls are likely related to the study drug. There is a clear dose-related effect of DM/Q on dizziness. While this dose-related effect of DM/Q on dizziness can seemingly influence falls, data do not support such a conclusion.

Aspiration, Nausea, Vomiting and Sedation

In the Approvable Letter, the Agency stated its concern regarding aspiration, nausea, vomiting and sedation.

The incidence of nausea, vomiting, somnolence, sedation, dysphagia, aspiration, pneumonia, aspiration/ bronchoaspiration in Pool 3 is summarized in the following table. In both ALS and

MS subjects, compared to the placebo group, the incidence of nausea is higher in the DM/Q 30 mg group and comparable in the DM/Q 10 mg group. Vomiting showed a dose-related increase in incidence compared to placebo group in the ALS subjects but was comparable between treatment groups in the MS subjects. The incidence of MS subjects with somnolence in the DM/Q 10 mg groups was several-fold higher than in the placebo group. Dysphagia (which I included because it appears to be an important risk factor in the development of aspiration) is evenly distributed between DM/Q 10 mg and placebo groups in ALS subjects; in MS subjects, there were two subjects in the DM/Q 10 mg group versus none in the placebo group. Aspiration, pneumonia aspiration / brochoaspiration occurred only in 3 subjects – 1 each in the DM/Q 10 mg group, DM/Q 30 group and placebo group.

Table 54: Incidence of nausea, vomiting, somnolence and aspiration/pneumonia by treatment and primary disease in controlled trials of PBA (Pool 3)

		Any DM/Q 10	Any DM/Q 30	Placebo	DM only	Q only
ALS	N	133	70	64	33	37
	Nausea	15 (11.3%)	23 (32.9%)	7 (10.9%)	2 (6.1%)	3 (8.1%)
	Vomiting	6 (4.5%)	4 (5.7%)	1 (1.6%)	0	0
	Somnolence	11 (8.3%)	10 (14.3%)	6 (9.4%)	1 (3.0%)	0
	Sedation	1 (0.8%)	3 (4.3%)	0	0	0
	Aspiration	0	1 (1.4%)	0	0	0
	Dysphagia	9/133 (6.8%)	1/70 (1.4%)	4/64 (6.3%)	0	1/37 (2.7%)
	Pneumonia aspiration*	1 (0.8%)	0	1 (1.6%)	0	0
MS	N	84	76	160		
	Nausea	6 (7.1%)	13 (17.1%)	12 (10.1%)	NA	NA
	Vomiting	3 (3.6%)	3 (3.9%)	6 (5.0%)	NA	NA
	Somnolence	7 (8.3%)	4 (5.3%)	3 (2.5%)	NA	NA
	Dysphagia	2/84 (2.4%)	0	0	NA	NA

*Bronchaspiration pneumonia (#123-301-504)
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS: Table 10.2.2

In the double-blind phase of Study 123, the incidence of nausea was fairly evenly distributed among the treatment groups in the ALS subjects; however, appeared to have an excess of events in the DM 30 mg/Q 10 mg group in MS subjects. With the exception of more events of vomiting in the DM 20 mg/Q 10 mg group of ALS subjects, the numbers of subjects experiencing vomiting in each treatment group were small. Subjects experiencing somnolence and dysphagia were evenly balanced among the treatment groups.

Table 55: Incidence of nausea, vomiting, somnolence, sedation and dysphagia by treatment in the double-blind phase of Study 123

	DM 30 mg/Q 10 mg (N=110)		DM 20 mg/Q 10 mg (N=107)		Placebo (N=109)	
	ALS	MS	ALS	MS	ALS	MS
Adverse Event	n=65	n=45	n=68	n=39	n=64	n=45
Nausea	8 (7%)	6 (6%)	8 (7%)	0	7 (6%)	3 (3%)
Vomiting	1 (1%)	3 (3%)	5 (5%)	0	1 (1%)	0
Somnolence	7 (6%)	4 (4%)	5 (5%)	4 (4%)	7 (6%)	3 (3%)
Sedation	0	0	1 (1%)	0	0	0
Dysphagia	4 (6.2%)	1 (2.2%)	5 (7.7%)	1 (2.3%)	4 (6.3%)	0

Source: NDA Complete Response 4/30/10; module 1.11.3 Efficacy information amendment; Table 17, page 52; reviewer's analysis of AE and DM datasets.

Analysis of nausea by time showed a higher occurrence within the first week, leveling off thereafter over time. There was no change in the frequency of vomiting over time.

Across the integrated clinical studies, there were a total of 9 subjects who experienced aspiration (n=1), aspiration pneumonia (n=7) and pneumonia by bronchoaspiration (n=1); these subjects are summarized in the following table. Eight (8/9) subjects had ALS. Eight of these events were serious, three of which (#107-026-016, #107-034-051 and #123-301-504) were fatal; the remaining 6 subjects recovered. Five (5/9) subjects experienced these events while participating in the open-label Study 107. In one subject (#107-024-008), this event led to discontinuation. Four subjects experienced this event within 41 days of study drug exposure (14, 31, 34 and 41); narratives for these subjects (and those with fatal outcomes) are provided below.

Table 56: Subjects experiencing aspiration or aspiration pneumonia in Pool 1

Study ID	Subject ID	Diagnosis	Age	Sex	Treatment	Study day of event	Serious	Outcome	Total duration of exposure
Study 107	107-024-008	ALS	60	M	DM 30/Q 30	(b) (6)	Y	Recovered w/ Sequelae	342
	107-026-016	ALS	61	M	DM 30/Q 30		Y	Fatal	457
	107-029-001	MS	49	F	DM 30/Q 30		Y	Recovered	1029
	107-034-051	ALS	73	M	DM 30/Q 30		Y	Fatal	205
	107-034-052	ALS	73	M	DM 30/Q 30		Y	Recovered	451
Study 109	109-133-026	DN	57	M	DM 30/Q 30		N	Recovered	32
Study 123	123-135-502	ALS	56	M	Placebo		Y	Recovered	30
	123-301-504*	ALS	58	F	DM 30/Q 10		Y	Fatal	84
Study 102	102-001-009#	ALS	62	M	DM 30/Q 30		Y	Recovered	13

*pneumonia by bronchoaspiration; #aspiration; all others pneumonia aspiration
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS: Reviewer's analysis of AEDM dataset (Pool 1 Y, AE_Fall Y, AECNN Y); STUDYID, USUBJID, AGE, PRIMDIS, AESTDY, AEOUT and DUREXPO; Tabulate

Subject #123-301-504: 58-year old Hispanic female diagnosed with ALS was randomized to DM 30 mg/Q 10 mg dose group in Study 123. In the AE dataset, dysphagia was reported on Day 59 which was ongoing; there were no reported AEs of nausea, vomiting, somnolence or sedation. After completing the double-blind phase of the study (84 days), about (b) (6) days after the last dose of study medication, she was admitted to the hospital for the treatment of ***pneumonia by bronchoaspiration***. About (b) (6) days later, she died. A detailed narrative is provided in section 7.3.1 – Deaths of this review.

Subject #107-026-016: 62-year old Caucasian male with ALS was enrolled in the open-label Study 107. Medical history included dysphagia, hypertension and hyperlipidemia. PEG was placed about 7 months after enrollment in the study. In the AE dataset, there are no reported AEs of nausea, vomiting, dysphagia, somnolence or sedation. On Day (b) (6) of DM 30 mg/Q 30 mg, he was hospitalized with a diagnosis of ***aspiration pneumonia*** and respiratory distress. Despite treatment, his respiratory status worsened throughout the hospital stay and he died about (b) days later.

Subject #107-034-051: 73-year old male with ALS was enrolled in open-label Study 107. Medical history included diabetes and peptic ulcer disease. On Day (b) (6) of DM 30 mg/Q 30 mg, he was hospitalized for the treatment of ***aspiration pneumonia***. He had earlier eaten pureed meat suggesting that he had prior difficulties with swallowing. The next day he suffered a cardiac arrest, was successfully resuscitated, but was left with hypoxic encephalopathy. His respiratory function and overall status markedly worsened over the next few days. (b) (6) days later, his family directed that all life support measures end and to begin comfort measures. He died (b) (6) days after admission. In the AE dataset, there were no reports of nausea, vomiting, sedation or somnolence.

Subject 102-001-009: 62-year old male diagnosed with ALS was randomized to DM 30 mg/Q 30 mg dose group in Study 102. Past medical history included hypertension and prostate cancer. Concomitant medications included baclofen, gabapentin, riluzole, and topiramate. He took DM 30 mg/Q 30 mg for 2 days, and then discontinued due to headaches. In the AE dataset, he reported nausea on Day 3 which resolved 3 days later; he did not report vomiting, dysphagia, sedation or somnolence. He restarted study medication and took it for another 8 days before discontinued the study medication at his own request because he thought it was of no benefit to him. On the following day (Day (b) (6)), he was admitted to hospital complaining of choking, difficulty clearing his airway, and fever (low grade - 99ºF). A diagnosis of ***aspiration*** and an upper respiratory infection was made. He was treated with antibiotics, responded well, and discharged (b) days later. The investigator judged the event of aspiration to be secondary to disease progression and not related to the study medication.

Subject #109-133-026: 57-year old Caucasian male diagnosed with painful diabetic neuropathy was randomized to DM 30 mg/Q 10 mg dose group in Study 109. On Day 34 (2 days after study discontinuations), he experienced ***aspiration pneumonia***, from which he recovered in 3 days. Since this event was not serious and did not result in discontinuation, a narrative was not provided. Going through the AE dataset, this subject reported somnolence on Day 1 (reported resolved next day) and nausea on Days 1 and 8 (reported resolved the same day) but did not report vomiting, dysphagia or sedation. On Day (b) (6), he experienced myocardial infarction and discontinued study participation. The investigator judged aspiration pneumonia and myocardial infarction to be unrelated to the study medication.

Subject # 123-135-502: 56-year old male with ALS was randomized to ***placebo*** in Study 123. PEG was placed prior to randomization. On Day (b) (6) he was hospitalized for the treatment of ***aspiration pneumonia***, and recovered. In the AE dataset, nausea was reported on Day 12 (reported to have resolved the same day), but there were no reports of vomiting, sedation or somnolence.

In the remaining three subjects (#107-024-008, 107-029-001 and 107-034-052) – all in the open-label Study 107, an examination of the AE dataset did not reveal events of somnolence, sedation or vomiting around the time of the event of aspiration pneumonia.

On face, nausea, vomiting, dysphagia, sedation and somnolence appear to be risk factors in the development of aspiration or aspiration pneumonia. Across the integrated clinical trials, I calculated the odds of developing aspiration or aspiration pneumonia in subjects with and without TEAE of nausea, vomiting, dysphagia, somnolence or sedation (see table below). The odds of developing aspiration or aspiration pneumonia in subjects who experienced any TEAE of nausea, vomiting, dysphagia, somnolence or sedation is 13.5 times that in subjects who did not experience any of these TEAEs.

Table 57: 2X2 contingency table for subjects with any TEAE of nausea, vomiting, dysphagia, somnolence or sedation, and any TEAE of aspiration or aspiration pneumonia, in Pool 1

		Any TEAE of nausea, vomiting, dysphagia, somnolence or sedation	
		Yes	No
Any TEAE of aspiration or aspiration pneumonia*	Yes	8	1
	No	541	895
	Total	549	896
	Odds	0.0148	0.0011

OR	13.5

**pneumonia by bronchoaspiration (#123-301-504)
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS: Reviewer's analysis of AEDM dataset (Pool 1 Y).

I explored further the association between events of nausea, vomiting, dysphagia, somnolence or sedation and the occurrence of aspiration or aspiration pneumonia (see table below). Subjects who reported a TEAE of dysphagia had the highest odds of developing aspiration or aspiration pneumonia.

Table 58: Odds of developing aspiration or aspiration pneumonia among subjects experiencing any TEAE of nausea, vomiting, dysphagia, somnolence or sedation, in Pool 1.

	Aspiration or aspiration pneumonia		
Preferred term	**NO**	**YES**	**Odds**
Dysphagia	84	4	4/84 = 0.048
Nausea	330	4	4/330 = 0.012
Sedation	8	0	0/8 = 0
Somnolence	180	3	3/180 = 0.017
Vomiting	96	0	0/96 = 0

NOTE: the total number of subjects developing aspiration or aspiration pneumonia is more than 8 because each preferred term is not mutually exclusive; a given subject may have experienced one or more events.
*pneumonia by bronchoaspiration (#123-301-504)
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS: Reviewer's analysis of AEDM dataset (Pool 1 Y).

Applicant's conclusions: There was no evidence to suggest that the few cases of aspiration/ aspiration pneumonia were associated with Zenvia or DM/Q treatment. With respect to possible risk factors for aspiration/aspiration pneumonia, the incidence of nausea, vomiting and somnolence were low and similar to placebo. There is no correlation between events of nausea and vomiting with events of aspiration/aspiration pneumonia.

Reviewer's conclusions: Among controlled trials, the number of subjects experiencing aspiration or aspiration pneumonia was numerically too small for meaningful between-treatment group comparisons. Across the integrated clinical trials there were a total of 9 subjects (8 of them with ALS) who experienced aspiration or aspiration pneumonia. Eight of these events were serious, three of which were fatal; the remaining 6 subjects recovered. In each of these subjects, there is no apparent occurrence of nausea, vomiting, dysphagia, somnolence or sedation in close proximity to the occurrence of aspiration or aspiration pneumonia. From the narratives, it is difficult to deduct causality, or exclude either the study drug or intercurrent illnesses as a potential cause of the event in question with any reasonable degree of confidence. However, the odds of developing aspiration or aspiration pneumonia in subjects who experienced any TEAE of nausea, vomiting, dysphagia, somnolence or sedation is 13.5 times that in subjects who did not experience any of these TEAEs, and appears driven mainly by dysphagia. The events of dysphagia, nausea and somnolence occur evenly among treatment groups in ALS subjects in controlled studies. Therefore, overall, the data do not support the conclusion that the events of aspiration or aspiration pneumonia are likely related to the study drug.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Categorization of AEs and appropriateness of coding is discussed in section 7.1.2 of this review.

In the paragraphs below, I review the treatment-emergent common adverse events in the pooled controlled clinical studies (Pool 3) and those occurring during the long term open-label studies (Pool 4). Pool 3 includes Study 102, Study 106 and double-blind phase of Study 123. During the original NDA review cycle, Dr. Farkas raised concerns regarding the excess occurrences of nausea, vomiting, falls and dizziness in the DM/Q treatment groups.

The incidence of TEAE ≥ 5% (for any DM/Q treatment group) across all the controlled clinical trials of PBA is summarized in the following table by treatment groups. The incidence of subjects with any TEAE appears comparable between the placebo group and DM/Q dose groups. The preferred terms, for which the incidences in the DM/Q 10 mg and or DM/Q 30 mg groups were at least 2-fold greater than that in the pooled placebo group were: nausea, dizziness, asthenia, somnolence, dysphagia, dry mouth, urinary tract infection and musculoskeletal stiffness. Among these preferred terms, dry mouth, nausea, musculoskeletal stiffness, dizziness and somnolence appear dose-related. The incidence of nausea and musculoskeletal stiffness in the any DM/Q 30 mg dose group is more than two-fold the incidence in the any DM/Q 10 mg group. I review nausea, vomiting, somnolence, sedation, falls and dizziness in section 7.3.5 of this review. The incidences of nausea, dizziness, somnolence, and fatigue in PBA subjects exposed to DM 30 mg/Q 30 mg in Study 102 were higher than in the DM alone group, potentially due to the increased plasma concentrations of DM in subjects who received the DM/Q combination.

Table 59: Incidence of common (≥ 5% for DM/Q) TEAE by treatment group in the controlled studies (Pool 3).

System Organ Class/ Preferred Term	Number of subjects (%)							
	DM 20 mg/ Q 10 mg N=107	DM 30 mg/ Q 10 mg N=110	All doses with Q 10 mg N=217	All doses with Q 30 mg N=146	All DM/Q doses N=363	Placebo N=183	DM 30 mg alone N=33	Q 30 mg alone N=37
Subjects with any adverse event	84 (78.5%)	91 (82.7%)	175 (80.6%)	124 (84.9%)	299 (82.4%)	153 (83.6%)	23 (69.7%)	24 (64.9%)
Gastrointestinal Disorders								
Constipation	6 (5.6)	7 (6.4)	13 (6.0)	8 (5.5)	21 (5.8)	14 (7.7)	2 (6.1)	0
Diarrhea	14 (13.1)	11 (10.0)	25 (11.5)	18 (12.3)	43 (11.8)	14 (7.7)	9 (27.3)	4 (10.8)
Dry mouth	2 (1.9)	7 (6.4)	9 (4.1)	8 (5.5)	17 (4.7)	1 (0.5)	1 (3.0)	1 (2.7)
Dysphagia	6 (5.6)	5 (4.5)	11 (5.1)	1 (0.7)	12 (3.3)	4 (2.2)	0	1 (2.7)
Nausea	7 (6.5)	14 (12.7)	21 (9.7)	36 (24.7)	57 (15.7)	19 (10.4)	2 (6.1)	3 (8.1)
General Disorders and Administration Site Conditions								
Asthenia	5 (4.7)	2 (1.8)	7 (3.2)	11 (7.5)	18 (5.0)	4 (2.2)	0	4 (10.8)
Fatigue	11 (10.3)	9 (8.2)	20 (9.2)	28 (19.2)	48 (13.2)	25 (13.7)	3 (9.1)	5 (13.5)
Infections and Infestations								
Nasopharyngitis	6 (5.6)	7 (6.4)	13 (6.0)	4 (2.7)	17 (4.7)	13 (7.1)	3 (9.1)	1 (2.7)
Upper Respiratory Tract Infection	2 (1.9)	3 (2.7)	5 (2.3)	8 (5.5)	13 (3.6)	8 (4.4)	1 (3.0)	2 (5.4)
Urinary Tract Infection	4 (3.7)	8 (7.3)	12 (5.5)	3 (2.1)	15 (4.1)	5 (2.7)	0	0
Injury, Poisoning and Procedural Complications								
Fall	14 (13.1)	22 (20.0)	36 (16.6)	13 (8.9)	49 (13.5)	22 (12.0)	3 (9.1)	0
Musculoskeletal and Connective Tissue Disorders								
Muscle Spasms	3 (2.8)	6 (5.5)	9 (4.1)	11 (7.5)	20 (5.5)	15 (8.2)	3 (9.1)	1 (2.7)
Muscular Weakness	5 (4.7)	6 (5.5)	11 (5.1)	7 (4.8)	18 (5.0)	7 (3.8)	1 (3.0)	1 (2.7)
Musculoskeletal Stiffness	2 (1.9)	3 (2.7)	5 (2.3)	9 (6.2)	14 (3.9)	2 (1.1)	1 (3.0)	1 (2.7)
Nervous System Disorders								
Dizziness	11 (10.3)	19 (17.3)	30 (13.8)	34 (23.3)	64 (17.6)	12 (6.6)	5 (15.2)	1 (2.7)
Headache	15 (14.0)	15 (13.6)	30 (13.8)	23 (15.8)	53 (14.6)	39 (21.3)	4 (12.1)	4 (10.8)
Somnolence	8 (7.5)	10 (9.1)	18 (8.3)	14 (9.6)	32 (8.8)	9 (4.9)	1 (3.0)	0

Sources: Table 6.1.3, Table 8.5.1
DM = dextromethorphan hydrobromide USP; Q = quinidine sulfate USP.
AEs for this table were selected by preferred terms reported in ≥5% of patients in any DM/Q treatment group.

Source: NDA Complete Response 4/30/10; module 5.3.5.3.ISS, Table 45, page 144-145.

Since the PBA population in Pool 3 is heterogeneous, the incidence of TEAE ≥ 5% (for any DM/Q treatment group) in each of the subset populations (ALS and MS) in the controlled clinical trials of PBA is summarized by treatment groups in the following tables. In the ALS subjects, the incidence appears comparable between the placebo group and DM/Q dose groups. The incidence of MS subjects with any adverse event in the any DM /Q 10 mg group (71.4%) was numerically less than the pooled placebo group (83.2%) or in the DM/Q 30 mg group. The preferred terms, for which the incidences in the DM/Q 10 mg and or DM/Q 30 mg groups were at least 2-fold greater than that in the pooled placebo group were: nausea, fatigue and dizziness (all dose-related) in the ALS subjects; and dry mouth (dose-related), asthenia, fall, dizziness (dose-related) and somnolence in the MS subjects. When the incidence is compared between the any DM/Q 30 mg dose group and the any DM/Q 10 mg group, there is more than two-fold excess of incidence in the any DM/Q 30 mg dose group for the following terms: nausea in the ALS subjects; and, dry mouth, asthenia and dizziness in the MS subjects. However, falls and somnolence were numerically higher in the any DM/Q 10 mg dose group compared to the DM/Q 30 mg dose group.

Table 60: Incidence of common TEAE (≥ 5%) by treatment in ALS subjects in controlled trials of PBA (Pool 3).

	AVP-923							
System Organ Class/ Preferred Term	20 mg DM/ 10 mg Q (N=68)	30 mg DM/ 10 mg Q (N=65)	All doses with 10 mg Q (N=133)	All doses with 30 mg Q (N=70)	All AVP-923 (N=203)	Placebo (N=64)	DM 30 mg (N=33)	Q 30 mg (N=37)
Any Adverse Event	56 (82.4%)	59 (90.8%)	115 (86.5%)	62 (88.6%)	177 (87.2%)	54 (84.4%)	23 (69.7%)	24 (64.9%)
GASTROINTESTINAL DISORDERS								
CONSTIPATION	6 (8.8%)	6 (9.2%)	12 (9.0%)	5 (7.1%)	17 (8.4%)	8 (12.5%)	2 (6.1%)	0
DIARRHOEA	12 (17.6%)	6 (9.2%)	18 (13.5%)	11 (15.7%)	29 (14.3%)	6 (9.4%)	9 (27.3%)	4 (10.8%)
NAUSEA	7 (10.3%)	8 (12.3%)	15 (11.3%)	23 (32.9%)	38 (18.7%)	7 (10.9%)	2 (6.1%)	3 (8.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS								
FATIGUE	7 (10.3%)	9 (13.8%)	16 (12.0%)	14 (20.0%)	30 (14.8%)	5 (7.8%)	3 (9.1%)	5 (13.5%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS								
FALL	10 (14.7%)	18 (27.7%)	28 (21.1%)	9 (12.9%)	37 (18.2%)	17 (26.6%)	3 (9.1%)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS								
MUSCLE SPASMS	3 (4.4%)	5 (7.7%)	8 (6.0%)	6 (8.6%)	14 (6.9%)	8 (12.5%)	3 (9.1%)	1 (2.7%)
MUSCULAR WEAKNESS	5 (7.4%)	5 (7.7%)	10 (7.5%)	2 (2.9%)	12 (5.9%)	3 (4.7%)	1 (3.0%)	1 (2.7%)
NERVOUS SYSTEM DISORDERS								
DIZZINESS	8 (11.8%)	11 (16.9%)	19 (14.3%)	14 (20.0%)	33 (16.3%)	4 (6.3%)	5 (15.2%)	1 (2.7%)
HEADACHE	7 (10.3%)	10 (15.4%)	17 (12.8%)	11 (15.7%)	28 (13.8%)	12 (18.8%)	4 (12.1%)	4 (10.8%)
SOMNOLENCE	5 (7.4%)	6 (9.2%)	11 (8.3%)	10 (14.3%)	21 (10.3%)	6 (9.4%)	1 (3.0%)	0

Note: Treatment categories are not mutually exclusive. Thus, patients may contribute to events in more than one treatment category.
Note: Percentages are calculated as the number of patients in the indicated population and treatment category who experienced an event divided by the number of patients in the population and treatment category.
Note: In each AE group or preferred term, a patient is counted only once within each treatment category, ie, only first occurrences are tabulated within each treatment category and primary disease.
Note: DM = Dextromethorphan Hydrobromide USP; Q = Quinidine Sulfate USP. NOS = not otherwise specified.

Source: NDA Complete Response 4/30/10; module 5.3.5.3.ISS, Table 8.6.2.

Table 61: Incidence of common TEAE (≥ 5%) by treatment in MS subjects in controlled trials of PBA (Pool 3).

	AVP-923							
System Organ Class/ Preferred Term	20 mg DM/ 10 mg Q (N=39)	30 mg DM/ 10 mg Q (N=45)	All doses with 10 mg Q (N=84)	All doses with 30 mg Q (N=76)	All AVP-923 (N=160)	Placebo (N=119)	DM 30 mg (N=0)	Q 30 mg (N=0)
Any Adverse Event	28 (71.8%)	32 (71.1%)	60 (71.4%)	62 (81.6%)	122 (76.3%)	99 (83.2%)	0	0
GASTROINTESTINAL DISORDERS								
ABDOMINAL PAIN UPPER	2 (5.1%)	2 (4.4%)	4 (4.8%)	4 (5.3%)	8 (5.0%)	4 (3.4%)	0	0
DIARRHOEA	2 (5.1%)	5 (11.1%)	7 (8.3%)	7 (9.2%)	14 (8.8%)	8 (6.7%)	0	0
DRY MOUTH	1 (2.6%)	1 (2.2%)	2 (2.4%)	6 (7.9%)	8 (5.0%)	1 (0.8%)	0	0
NAUSEA	0	6 (13.3%)	6 (7.1%)	13 (17.1%)	19 (11.9%)	12 (10.1%)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS								
ASTHENIA	2 (5.1%)	0	2 (2.4%)	6 (7.9%)	8 (5.0%)	2 (1.7%)	0	0
FATIGUE	4 (10.3%)	0	4 (4.8%)	14 (18.4%)	18 (11.3%)	20 (16.8%)	0	0
INFECTIONS AND INFESTATIONS								
NASOPHARYNGITIS	1 (2.6%)	5 (11.1%)	6 (7.1%)	3 (3.9%)	9 (5.6%)	8 (6.7%)	0	0
UPPER RESPIRATORY TRACT INFECTION	1 (2.6%)	2 (4.4%)	3 (3.6%)	5 (6.6%)	8 (5.0%)	7 (5.9%)	0	0
URINARY TRACT INFECTION	3 (7.7%)	2 (4.4%)	5 (6.0%)	3 (3.9%)	8 (5.0%)	4 (3.4%)	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS								
FALL	4 (10.3%)	4 (8.9%)	8 (9.5%)	4 (5.3%)	12 (7.5%)	5 (4.2%)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS								
ARTHRALGIA	2 (5.1%)	1 (2.2%)	3 (3.6%)	5 (6.6%)	8 (5.0%)	9 (7.6%)	0	0
BACK PAIN	3 (7.7%)	0	3 (3.6%)	5 (6.6%)	8 (5.0%)	6 (5.0%)	0	0
NERVOUS SYSTEM DISORDERS								
DIZZINESS	3 (7.7%)	8 (17.8%)	11 (13.1%)	20 (26.3%)	31 (19.4%)	8 (6.7%)	0	0
HEADACHE	8 (20.5%)	5 (11.1%)	13 (15.5%)	12 (15.8%)	25 (15.6%)	27 (22.7%)	0	0
SOMNOLENCE	3 (7.7%)	4 (8.9%)	7 (8.3%)	4 (5.3%)	11 (6.9%)	3 (2.5%)	0	0

Note: Treatment categories are not mutually exclusive. Thus, patients may contribute to events in more than one treatment category.
Note: Percentages are calculated as the number of patients in the indicated population and treatment category who experienced an event divided by the number of patients in the population and treatment category.
Note: In each AE group or preferred term, a patient is counted only once within each treatment category, ie, only first occurrences are tabulated within each treatment category and primary disease.
Note: DM = Dextromethorphan Hydrobromide USP; Q = Quinidine Sulfate USP. NOS = not otherwise specified.

Source: NDA Complete Response 4/30/10; module 5.3.5.3.ISS, Table 8.6.2.

The incidence of TEAE ≥ 5% (for any DM/Q treatment group) in the double-blind phase of Study 123 is summarized in the following table by treatment groups. The incidence of subjects with any adverse event in the DM 20 mg/Q 10 mg group (78.5%) is numerically less than the placebo group (83.6%) or the DM 30 mg/Q 10 mg group (82.7%). The preferred terms, for which the incidences in the DM 20 mg/Q 10 mg and or DM 30 mg/Q 10 mg groups were at least 2-fold greater than that in the placebo group were: dizziness, diarrhea, dry mouth, vomiting, urinary tract infection, asthenia, peripheral edema and cough. Among these preferred terms, dizziness, dry mouth and urinary tract infection appear to be dose-related. The incidence of dry mouth and urinary tract infection in the DM 30 mg/Q 10 mg dose group is more than two-fold the incidence in the DM 20 mg/Q 10 mg group. As stated earlier, I review nausea, vomiting, somnolence, sedation, falls and dizziness, and respiratory related events in section 7.3.5 of this review

Table 62: Incidence of common TEAE by body system and treatment in double-blind phase of Study 123 (≥ 5% of subjects treated with either dose of DM/Q)

Body System	DM 20 mg/ Q 10 mg (N=107) n (%)	DM 30 mg/ Q 10 mg (N=110) n (%)	Placebo (N=109) n (%)
Patients with TEAEs	84 (78.5)	91 (82.7)	90 (82.6)
Nervous system disorders			
Headache	15 (14.0)	15 (13.6)	17 (15.6)
Dizziness	11 (10.3)	19 (17.3)	5 (4.6)
Somnolence	8 (7.5)	10 (9.1)	9 (8.3)
Gastrointestinal disorders			
Nausea	7 (6.5)	14 (12.7)	10 (9.2)
Diarrhea	14 (13.1)	11 (10.0)	7 (6.4)
Constipation	6 (5.6)	7 (6.4)	8 (7.3)
Dry mouth	2 (1.9)	7 (6.4)	0 (0)
Dysphagia	6 (5.6)	5 (4.5)	4 (3.7)
Stomach discomfort	0	5 (4.5)	3 (2.8)
Vomiting	5 (4.7)	4 (3.6)	1 (0.9)
Infections and infestations			
Nasopharyngitis	6 (5.6)	7 (6.4)	7 (6.4)
Urinary tract infection	4 (3.7)	8 (7.3)	1 (0.9)
Injury, poisoning and procedural complications			
Fall	14 (13.1)	22 (20.0)	20 (18.3)
Musculoskeletal and connective tissue disorders			
Muscle spasms	3 (2.8)	6 (5.5)	9 (8.3)
Muscular weakness	5 (4.7)	6 (5.5)	4 (3.7)
General disorders and administration site conditions			
Asthenia	5 (4.7)	2 (1.8)	2 (1.8)
Fatigue	11 (10.3)	9 (8.2)	10 (9.2)
Peripheral edema	5 (4.7)	0	1 (0.9)
Respiratory, thoracic and mediastinal disorders	21 (19.6)	22 (20.0)	11 (10.1)
Cough	5 (4.7)	4 (3.6)	2 (1.8)

Note: Table includes incidences of TEAEs that would be rounded up to 5% when expressed without decimal places, i.e. all TEAEs with incidence ≥4.5% in either DM/Q treatment group
DM = dextromethorphan hydrobromide USP; Q = quinidine sulfate USP.

Source: NDA Complete Response 4/30/10; module 5.3.5.3.ISS, Table 44, page 142.

The incidence of TEAE ≥ 5% (for any DM/Q 10 mg treatment group) in each of the subset populations (ALS and MS) in the double-blind phase of Study 123 is summarized by treatment groups in the table below. The incidence of ALS subjects with any adverse event in the DM 30 mg/Q 10 mg group (90.8%) was numerically higher than either the DM 20 mg/Q 10 mg or the placebo groups. The preferred terms, for which the incidences in the DM 20 mg/Q 10 mg and or DM 30 mg/Q 10 mg groups were at least 2-fold greater than that in the placebo group are: dizziness, urinary tract infection, dry mouth, insomnia, salivary hypersecretion, stomach discomfort, influenza and vomiting; with the exception of influenza and vomiting; all are dose-related.

Table 63: Incidence of common TEAE by treatment for ALS subjects in double-blind phase of Study 123 (≥ 5% of subjects treated with either dose of DM/Q)

	DM 20 /Q 10 N = 68			DM 30/Q 10 N = 65			Any DM/Q 10 N = 133			Placebo N = 64	
	n	%	RR	n	%	RR	n	%	RR	n	%
Subjects with any TEAE	56	82.4	1.0	59	90.8	1.1	115	86.5	1.0	54	84.4
Fall	10	14.7	0.6	18	27.7	1.0	28	21 1	0.8	17	26.6
Dizziness	8	11.8	1.9	11	16.9	2.7	19	14.3	2 3	4	6.3
Headache	7	10.3	1	10	15.4	0.8	17	12.8	1	12	18.8
Fatigue	7	10.3	1.3	9	13.8	1.8	16	12.0	2	5	7.8
Nausea	7	10.3	0.9	8	12.3	1.1	15	11.3	1.0	7	10.9
Diarrhoea	12	17.6	1.9	6	9.2	1.0	18	13 5	1.4	6	9.4
Constipation	6	8.8	0.7	6	9.2	0.7	12	9.0	0.7	8	12.5
Somnolence	5	7.4	0.8	6	9.2	1.0	11	8.3	0.9	6	9.4
Urinary tract infection	1	1.5	0.9	6	9.2	5.9	7	5.3	3.4	1	1.6
Dry mouth	1	1.5	∞	6	9.2	∞	7	5.3	∞	0	0
Muscular weakness	5	7.4	1.6	5	7.7	1.6	10	7.5	1.6	3	4.7
Muscle spasms	3	4.4	0.4	5	7.7	0.6	8	6.0	0.5	8	12.5
Dysphagia	5	7.4	1.2	4	6.2	1.0	9	6.8	1.1	4	6.3
Insomnia	3	4.4	1.4	4	6.2	2.0	7	5.3	1.7	2	3.1
Back pain	2	2 9	0.5	4	6.2	1.0	6	4.5	0.7	4	6.3
Salivary hypersecretion	1	1.5	0.5	4	6.2	2.0	5	3.8	1 2	2	3.1
Stomach discomfort	0	0	0	4	6.2	3.9	4	3.0	1 9	1	1.6
Nasopharyngitis	5	7.4	0.9	2	3.1	0.4	7	5.3	0.7	5	7.8
Cough	4	5.9	1.9	2	3.1	1.0	6	4.5	1.4	2	3.1
Influenza	4	5.9	3.8	2	3.1	2.0	6	4.5	2 9	1	1.6
Vomiting	5	7.4	4.7	1	1.5	1.0	6	4.5	2 9	1	1.6

RR = relative risk (incidence of DM/Q divided by incidence of placebo)
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS: Reviewer's analysis of AE, DM and EX dataset (subset Pool 3 Y and AETRTEM Y for each dataset and join); Tabulate).

In the MS subjects, the incidence of subjects with any adverse event in the placebo group was higher than either DM/Q dose group (see Table below). The incidence of subjects experiencing dizziness or nasopharyngitis in the DM/Q groups was more than two-fold that of the incidence in placebo; dizziness was dose-related. Although there were several other preferred terms for

which the incidence in any DM/Q dose group was ≥ 2-fold greater than placebo, the absolute number of subjects experiencing an AE in any of the treatment group was small.

Table 64: Incidence of common TEAE by treatment for MS subjects in double-blind phase of Study 123 (≥ 5% of subjects treated with either dose of DM/Q)

	DM 20 /Q 10 N = 39			DM 30/Q 10 N = 45			Any DM/Q10 N = 84			Placebo N = 45	
	n	%	RR	n	%	RR	n	%	RR	n	%
Subjects with any TEAE	28	71.8	0.9	32	71.1	0.9	60	71.4	0.9	36	80.0
Headache	8	20.5	1.8	5	11.1	1.0	13	15.5	1.4	5	11.1
Fall	4	10.3	1.5	4	8.9	1.3	8	9.5	1.4	3	6.7
Fatigue	4	10	1	0	0.0	0.0	4	4.8	0.4	5	11.1
Dizziness	3	7.7	3.5	8	17.8	8.0	11	13.1	5.9	1	2.2
Somnolence	3	7.7	1.2	4	8.9	1.3	7	8.3	1.3	3	6.7
Urinary tract infection	3	7.7	∞	2	4.4	∞	5	6.0	∞	0	0
Back pain	3	8	∞	0	0.0	∞	3	3.6	∞	0	0
Diarrhoea	2	5 1	2.3	5	11.1	5.0	7	8.3	3.8	1	2.2
Abdominal pain upper	2	5.1	2.3	2	4.4	2.0	4	4.8	2.1	1	2.2
Arthralgia	2	5 1	2.3	1	2.2	1.0	3	3.6	1.6	1	2.2
Sinus congestion	2	5.1	2.3	1	2.2	1.0	3	3.6	1.6	1	2.2
GGT increased	2	5.1	∞	1	2.2	∞	3	3.6	∞	0	0
ALT increased	2	5.1	∞	1	2.2	∞	3	3.6	∞	0	0
Sinusitis	2	5.1	∞	1	2.2	∞	3	3.6	∞	0	0
Musculoskeletal stiffness	2	5.1	∞	1	2.2	∞	3	3.6	∞	0	0
AST increased	2	5.1	∞	1	2.2	∞	3	3.6	∞	0	0
Asthenia	2	5	∞	0	0.0	∞	2	2.4	∞	0	0
Oral herpes	2	5	∞	0	0.0	∞	2	2.4	∞	0	0
Nasopharyngitis	1	2.6	0.6	5	11.1	2.5	6	7 1	1.6	2	4.4
Nausea	0	0.0	0.0	6	13.3	2.0	6	7.1	1.1	3	6.7
Pain in extremity	0	0.0	0.0	3	6.7	0.6	3	3.6	0.3	5	11.1
Vomiting	0	0.0	∞	3	6.7	∞	3	3.6	∞	0	0.0

RR = relative risk (incidence of DM/Q divided by incidence of placebo); GGT = Gamma-glutamyltransferase; ALT = alanine aminotransferase AST = aspartate aminotransferase
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS: Reviewer's analysis of AE, DM and EX dataset (subset Pool 3 Y and AETRTEM Y for each dataset and join); Tabulate).

Common TEAEs in long-term open-label studies:

The following Tables summarize the incidence of common TEAEs in the long-term exposure in PBA subjects (Pool 4). For both the underlying primary diseases, the incidence of subjects with a TEAE in the DM/Q30 dose group is many-fold higher than the DM/Q10 mg dose group, but this is confounded by the differential total exposure time between these dosage groups. In the ALS subjects, the person-time for DM/Q 30 mg group (N = 147) was 207.8 person-years compared to 45.5 person-years for DM/Q 10 mg dose group (N = 103). Thus, the relative risk of a TEAE in the DM/Q 30 mg dose group compared to the DM/Q10 mg dose group in ALS subjects is lower by a factor of 0.31 [(45.5/207.8 = 0.22)/(103/147 = 0.70)] when the exposure is adjusted for time. The relative risk for 'respiratory failure' in the DM/Q 30 mg dose group compared to DM/Q 10 mg dose group reduces from 9.8 (28.6/2.9) to 3.1 [(42/207.8 =

0.2)/(3/45.5 = 0.07)]. Otherwise, the risk for most events is fairly comparable between these two DM/Q dose groups or marginally elevated in the DM 30 mg/Q 30 mg group.

Similarly in the MS subjects, the person-time for DM /Q 30 mg group (N = 192) was 397.9 person-years compared to 32.9 person-years for DM/Q 10 mg dose group (N = 73). The relative risk of a TEAE in the DM/Q 30 mg dose group compared to the DM/Q10 mg dose group in MS subjects is lower by a factor of 0.22 when the exposure is adjusted for time. The risk for terms 'multiple sclerosis' and 'musculoskeletal pain' appear to remain elevated in the DM/Q 30 dose group despite accounting for the differential total time exposure. Otherwise, the risk for most events in the DM/Q 30 mg group is either marginally elevated or is comparable to that in the DM/Q 10 mg group.

Table 65: Incidence of common TEAEs (≥ 5%) by treatment in ALS subjects in the long-term open-label exposure in PBA subjects (only reviewer-selected body systems reproduced for brevity)

	AVP-923			
System Organ Class/ Preferred Term	20 mg DM/ 10 mg Q (N=45)	30 mg DM/ 10 mg Q (N=103)	All doses with 10 mg Q (N=103)	All doses with 30 mg Q (N=147)
Any Adverse Event	36 (80.0%)	86 (83.5%)	91 (88.3%)	145 (98.6%)
GASTROINTESTINAL DISORDERS				
ABDOMINAL PAIN UPPER	1 (2.2%)	2 (1.9%)	3 (2.9%)	11 (7.5%)
CONSTIPATION	4 (8.9%)	10 (9.7%)	13 (12.6%)	36 (24.5%)
DIARRHOEA	10 (22.2%)	6 (5.8%)	15 (14.6%)	35 (23.8%)
DRY MOUTH	0	7 (6.8%)	7 (6.8%)	15 (10.2%)
DYSPHAGIA	3 (6.7%)	10 (9.7%)	12 (11.7%)	49 (33.3%)
NAUSEA	4 (8.9%)	12 (11.7%)	15 (14.6%)	43 (29.3%)
SALIVARY HYPERSECRETION	1 (2.2%)	7 (6.8%)	8 (7.8%)	27 (18.4%)
STOMACH DISCOMFORT	0	5 (4.9%)	5 (4.9%)	16 (10.9%)
VOMITING	4 (8.9%)	2 (1.9%)	6 (5.8%)	9 (6.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
ASTHENIA	1 (2.2%)	2 (1.9%)	3 (2.9%)	19 (12.9%)
FATIGUE	5 (11.1%)	11 (10.7%)	16 (15.5%)	26 (17.7%)
GAIT DISTURBANCE	0	2 (1.9%)	2 (1.9%)	11 (7.5%)
OEDEMA PERIPHERAL	3 (6.7%)	4 (3.9%)	6 (5.8%)	26 (17.7%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
ARTHRALGIA	3 (6.7%)	7 (6.8%)	10 (9.7%)	13 (8.8%)
BACK PAIN	2 (4.4%)	9 (8.7%)	11 (10.7%)	20 (13.6%)
MUSCLE SPASMS	1 (2.2%)	6 (5.8%)	7 (6.8%)	19 (12.9%)
MUSCULAR WEAKNESS	4 (8.9%)	6 (5.8%)	9 (8.7%)	35 (23.8%)
MUSCULOSKELETAL PAIN	0	4 (3.9%)	4 (3.9%)	14 (9.5%)
MUSCULOSKELETAL STIFFNESS	0	3 (2.9%)	3 (2.9%)	17 (11.6%)
PAIN IN EXTREMITY	2 (4.4%)	5 (4.9%)	7 (6.8%)	17 (11.6%)
NERVOUS SYSTEM DISORDERS				
DIZZINESS	5 (11.1%)	12 (11.7%)	16 (15.5%)	31 (21.1%)
DYSARTHRIA	3 (6.7%)	3 (2.9%)	4 (3.9%)	13 (8.8%)
HEADACHE	6 (13.3%)	13 (12.6%)	17 (16.5%)	38 (25.9%)
MUSCLE SPASTICITY	1 (2.2%)	4 (3.9%)	5 (4.9%)	20 (13.6%)
PSYCHIATRIC DISORDERS				
ANXIETY	1 (2.2%)	0	1 (1.0%)	18 (12.2%)
DEPRESSION	0	2 (1.9%)	2 (1.9%)	15 (10.2%)
INSOMNIA	2 (4.4%)	6 (5.8%)	8 (7.8%)	23 (15.6%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
CHOKING	1 (2.2%)	6 (5.8%)	7 (6.8%)	12 (8.2%)
COUGH	3 (6.7%)	8 (7.8%)	11 (10.7%)	32 (21.8%)
DYSPNOEA	2 (4.4%)	8 (7.8%)	10 (9.7%)	28 (19.0%)
NASAL CONGESTION	1 (2.2%)	2 (1.9%)	3 (2.9%)	15 (10.2%)
PHARYNGOLARYNGEAL PAIN	1 (2.2%)	4 (3.9%)	5 (4.9%)	15 (10.2%)
RESPIRATORY FAILURE	0	3 (2.9%)	3 (2.9%)	42 (28.6%)

Treatment categories are not mutually exclusive. Thus, patients may contribute to events in more than one treatment category.

Note: Percentages are calculated as the number of patients in the indicated population and treatment category who experienced an event divided by the number of patients in the population and treatment category.
Note: In each AE group or preferred term, a patient is counted only once within each treatment category, ie, only first occurrences are tabulated within each treatment category and primary disease.
Note: Multiple events may have been reported as leading to a single patient discontinuation
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS, Table 22.2.3.

Table 66: Incidence of common TEAEs (≥ 5%) by treatment in MS subjects in the long-term open-label exposure in PBA subjects (only reviewer-selected body systems reproduced for brevity)

	AVP-923			
System Organ Class/ Preferred Term	20 mg DM/ 10 mg Q (N=30)	30 mg DM/ 10 mg Q (N=73)	All doses with 10 mg Q (N=73)	All doses with 30 mg Q (N=192)
Any Adverse Event	21 (70.0%)	50 (68.5%)	56 (76.7%)	184 (95.8%)
GASTROINTESTINAL DISORDERS				
ABDOMINAL PAIN UPPER	2 (6.7%)	2 (2.7%)	4 (5.5%)	15 (7.8%)
CONSTIPATION	0	2 (2.7%)	2 (2.7%)	21 (10.9%)
DIARRHOEA	2 (6.7%)	7 (9.6%)	8 (11.0%)	43 (22.4%)
DRY MOUTH	1 (3.3%)	1 (1.4%)	2 (2.7%)	13 (6.8%)
DYSPEPSIA	0	0	0	16 (8.3%)
NAUSEA	0	7 (9.6%)	7 (9.6%)	53 (27.6%)
STOMACH DISCOMFORT	0	1 (1.4%)	1 (1.4%)	16 (8.3%)
VOMITING	0	4 (5.5%)	4 (5.5%)	28 (14.6%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
ASTHENIA	1 (3.3%)	0	1 (1.4%)	21 (10.9%)
CHEST PAIN	0	0	0	17 (8.9%)
FATIGUE	4 (13.3%)	4 (5.5%)	8 (11.0%)	66 (34.4%)
GAIT DISTURBANCE	0	2 (2.7%)	2 (2.7%)	19 (9.9%)
OEDEMA PERIPHERAL	1 (3.3%)	2 (2.7%)	3 (4.1%)	21 (10.9%)
PAIN	0	2 (2.7%)	2 (2.7%)	18 (9.4%)
PYREXIA	1 (3.3%)	2 (2.7%)	3 (4.1%)	28 (14.6%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
ARTHRALGIA	2 (6.7%)	4 (5.5%)	5 (6.8%)	32 (16.7%)
BACK PAIN	3 (10.0%)	4 (5.5%)	6 (8.2%)	36 (18.8%)
MUSCLE SPASMS	0	2 (2.7%)	2 (2.7%)	27 (14.1%)
MUSCULAR WEAKNESS	0	2 (2.7%)	2 (2.7%)	33 (17.2%)
MUSCULOSKELETAL CHEST PAIN	0	0	0	14 (7.3%)
MUSCULOSKELETAL PAIN	0	1 (1.4%)	1 (1.4%)	28 (14.6%)
MUSCULOSKELETAL STIFFNESS	2 (6.7%)	1 (1.4%)	3 (4.1%)	17 (8.9%)
NECK PAIN	0	1 (1.4%)	1 (1.4%)	19 (9.9%)
PAIN IN EXTREMITY	0	5 (6.8%)	5 (6.8%)	44 (22.9%)
NERVOUS SYSTEM DISORDERS				
BALANCE DISORDER	1 (3.3%)	2 (2.7%)	3 (4.1%)	15 (7.8%)
DIZZINESS	1 (3.3%)	10 (13.7%)	10 (13.7%)	61 (31.8%)
HEADACHE	6 (20.0%)	10 (13.7%)	13 (17.8%)	68 (35.4%)
HYPOAESTHESIA	1 (3.3%)	2 (2.7%)	3 (4.1%)	38 (19.8%)
MULTIPLE SCLEROSIS	0	0	0	47 (24.5%)
MUSCLE SPASTICITY	0	1 (1.4%)	1 (1.4%)	22 (11.5%)
PARAESTHESIA	0	3 (4.1%)	3 (4.1%)	29 (15.1%)
SINUS HEADACHE	0	2 (2.7%)	2 (2.7%)	14 (7.3%)
SOMNOLENCE	2 (6.7%)	5 (6.8%)	6 (8.2%)	10 (5.2%)
TREMOR	1 (3.3%)	0	1 (1.4%)	16 (8.3%)

Treatment categories are not mutually exclusive. Thus, patients may contribute to events in more than one treatment category.
Note: Percentages are calculated as the number of patients in the indicated population and treatment category who experienced an event divided by the number of patients in the population and treatment category.
Note: In each AE group or preferred term, a patient is counted only once within each treatment category, ie, only first occurrences are tabulated within each treatment category and primary disease.
Note: Multiple events may have been reported as leading to a single patient discontinuation
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS, Table 22.2.3.

7.4.2 Laboratory Findings

Clinical hematology and clinical chemistry tests and urinalysis were measured in clinical studies at protocol-defined visits within each trial. Chemistry, hematology tests and urinalysis performed (see Table below) were all similar in the three controlled trials and two open-label studies of PBA with a few exceptions. For example, carbon dioxide (bicarbonate) was part of the chemistry panel in Study 102, Study 106 and Study 107, however, was not assessed in Study 123.

Table 67: Chemistry, hematology and urinalysis tests in controlled trials.

Blood Chemistry	
Alanine aminotransferase (ALT)	γ-Glutamyltransferase (GGT)
Albumin	Glucose (random)
Alkaline phosphatase	Lactate dehydrogenase (LDH)
Aspartate aminotransferase (AST)	Phosphorus
Blood urea nitrogen (BUN)	Potassium
Calcium	Sodium
Chloride	Total bilirubin
Cholesterol (total)	Total protein
Creatine kinase (CK)	Triglycerides
Creatinine	Uric acid
Hematology	
Hematocrit	Red blood cells (RBCs)
Hemoglobin	Total white blood cells (WBCs) and differential
Platelets	
Urinalysis	
Blood	Protein
Glucose	RBCs
Ketones	Specific gravity
pH	WBCs
Pregnancy testing[a]	
Urinary human chorionic gonadotropin (hCG)	

[a]Performed only for women of childbearing potential at screening, baseline and on Days 29 and 84 for the double-blind phase and at baseline and on Days 42 and 84 for the open-label extension phase.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Final study report; Table 9-5, page 39

I reviewed the measures of central tendency for change from baseline over time for laboratory parameters in the pooled controlled trials of PBA (Pool 3). The median change from baseline in the laboratory parameters were fairly similar between treatment groups (data for reviewer-selected laboratory parameters of interest only included in the table below). Since, DM/Q 10 mg doses in PBA subjects were used only in Study 123, laboratory changes for these groups are best discussed in the context of the concurrent placebo arm for Study 123, which is discussed below.

Table 68: Mean and median changes in selected laboratory parameters by treatment in PBA subjects (Pool 3)

	AVP-923							
Parameter and Assessment	20 mg DM/ 10 mg Q (N=107)	30 mg DM/ 10 mg Q (N=110)	All doses with 10 mg Q (N=217)	All doses with 30 mg Q (N=146)	All AVP-923 (N=363)	Placebo (N=183)	DM 30 mg (N=33)	Q 30 mg (N=37)
ALT								

Final Visit Change from Baseline								
N	84	97	181	98	279	131	29	34
Mean	-0.8	-2.3	-1.6	-0.1	-1.1	-0.7	-0.9	-1.0
SD	10.46	13.45	12.15	19.78	15.25	12.20	18.01	11.14
Median	-1.0	-1.0	-1.0	-1.0	-1.0	0.0	0.0	-1.0
Minimum, Maximum	-38, 33	-60, 28	-60, 33	-78, 119	-78, 119	-70, 60	-70, 34	-28, 30

AST

Final Visit Change from Baseline								
N	84	96	180	98	278	130	29	34
Mean	-0.4	-0.8	-0.6	-0.8	-0.7	-0.8	0.5	-1.7
SD	6.21	8.16	7.30	10.38	8.49	7.14	7.72	7.44
Median	-1.0	-1.0	-1.0	-0.5	-1.0	-1.0	0.0	-1.0
Minimum, Maximum	-18, 31	-26, 23	-26, 31	-50, 50	-50, 50	-26, 26	-14, 19	-25, 13

Alkaline Phosphatase

Final Visit Change from Baseline								
N	86	100	186	98	284	135	29	34
Mean	-0.4	-1.0	-0.7	3.5	0.7	-2.6	-0.6	-0.6
SD	11.89	12.10	11.98	22.45	16.44	11.93	27.53	13.69
Median	-1.0	0.0	-1.0	4.0	0.0	-2.0	6.0	0.5
Minimum, Maximum	-61, 25	-31, 39	-61, 39	-87, 163	-87, 163	-52, 61	-131, 21	-37, 39

GGT

Final Visit Change from Baseline								
N	86	100	186	98	284	135	29	34
Mean	-0.9	-1.3	-1.1	3.0	0.3	-1.6	-11.8	-3.6
SD	20.90	16.45	18.59	26.87	21.84	17.29	59.11	13.05
Median	-1.5	1.0	-0.5	0.0	0.0	0.0	0.0	-1.0
Minimum, Maximum	-152, 63	-55, 66	-152, 66	-73, 195	-152, 195	-117, 40	-308, 20	-49, 14

Total Bilirubin

Final Visit Change from Baseline								
N	84	97	181	98	279	132	29	34
Mean	0.07	-0.58	-0.28	-0.08	-0.21	-0.38	-1.53	0.35
SD	3.414	2.605	3.017	3.969	3.376	2.908	5.117	3.567
Median	0.00	0.00	0.00	-0.43	0.00	0.00	-1.71	1.71
Minimum, Maximum	-12.0, 14.0	-9.0, 7.0	-12.0, 14.0	-8.6, 25.7	-12.0, 25.7	-13.0, 7.0	-18.8, 6.8	-13.7, 5.1

Bicarbonate

Final Visit Change from Baseline								
N	0	0	0	98	98	42	29	34
Mean	NA	NA	NA	-0.10	-0.10	0.13	0.48	-0.44
SD	NA	NA	NA	2.616	2.616	3.754	3.334	3.164
Median	NA	NA	NA	0.00	0.00	-0.40	1.00	-0.50
Minimum, Maximum	NA	NA	NA	-7.0, 7.0	-7.0, 7.0	-9.0, 9.2	-7.0, 7.0	-5.0, 6.0

CK

Final Visit Change from Baseline								
N	84	97	181	98	279	132	29	34
Mean	8.0	5.2	6.5	-11.8	0.1	-10.4	-3.6	-13.3
SD	88.92	73.72	80.91	67.60	76.88	66.02	131.79	118.80
Median	4.5	1.0	2.0	-4.0	0.0	-0.5	-10.0	6.0
Minimum, Maximum	-233, 440	-252, 300	-252, 440	-217, 194	-252, 440	-283, 282	-410, 335	-450, 269

Potassium

Final Visit Change from Baseline								
N	86	100	186	98	284	134	29	34
Mean	0.08	0.04	0.06	-0.03	0.03	0.02	0.00	-0.05
SD	0.390	0.426	0.409	0.412	0.411	0.383	0.354	0.306
Median	0.10	0.10	0.10	0.00	0.10	0.00	0.00	0.00
Minimum, Maximum	-1.2, 1.1	-1.5, 1.1	-1.5, 1.1	-2.0, 1.1	-2.0, 1.1	-1.3, 0.9	-1.1, 0.5	-0.8, 0.5

Note: Treatment categories are not mutually exclusive. Thus, patients may contribute to more than one treatment category.
Note: DM = Dextromethorphan Hydrobromide USP; Q = Quinidine Sulfate USP. NOS = not otherwise specified. NA = Not Available.
Note: The early termination (ET) visit includes measurements collected on the last on-treatment date where labs were collected for non-completers.
Note: The final visit includes the last on-treatment measurements for completers.
Note: The End of Study includes the last on-treatment measurements for all completers and non-completers.

Range of median values at baseline: ALT 21-25; AST 22-26; Alk phosphate 66-74; GGT 22-29; Total bilirubin 7.00-10.26; Bicarbonate 21-28; CK 80.0-164; Potassium 4.10-4.30.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS; Table 42.1.3

Data from Study 123 is unique to the Complete Response. In the table below, I include data for selected laboratory tests of interest from Study 123. I reviewed all the laboratory data from Study 123, and find that the median changes from baseline in the laboratory parameters including liver function tests, creatine and urea over time were fairly similar between treatment groups.

Table 69: Mean and median changes in selected laboratory parameters by treatment in the double-blind phase of Study 123

Lab Test Visit	AVP-923-30 (N = 110)	AVP-923-20 (N = 107)	Placebo (N = 109)	Overall (N = 326)
ALT (SGPT) (U/L)				
Change from Baseline to Day 84				
N	90	86	90	266
Mean (Std Dev)	-5.2 (36.05)	-1.0 (10.48)	-0.2 (10.48)	-2.1 (22.66)
95% C.I.	(-12.73, 2.37)	(-3.26, 1.23)	(-2.38, 2.01)	(-4.88, 0.59)
Min, Max	-320.0, 28.0	-38.0, 33.0	-29.0, 60.0	-320.0, 60.0
Median	-1.5	-1.0	-1.0	-1.0
AST (SGOT) (U/L)				
Change from Baseline to Day 84				
N	88	84	88	260
Mean (Std Dev)	-1.6 (15.07)	-0.4 (6.27)	-0.2 (6.80)	-0.8 (10.24)
95% C.I.	(-4.84, 1.55)	(-1.80, 0.92)	(-1.67, 1.21)	(-2.03, 0.47)
Min, Max	-119.0, 23.0	-18.0, 31.0	-20.0, 26.0	-119.0, 31.0
Median	0.0	-0.5	-1.0	-0.5
Alkaline Phosphatase (U/L)				
Change from Baseline to Day 84				
N	96	90	96	282
Mean (Std Dev)	-1.0 (12.15)	0.2 (11.56)	-1.9 (12.78)	-0.9 (12.18)
95% C.I.	(-3.49, 1.43)	(-2.18, 2.67)	(-4.45, 0.72)	(-2.34, 0.52)
Min, Max	-31.0, 39.0	-61.0, 25.0	-52.0, 61.0	-61.0, 61.0
Median	0.0	-0.5	-2.0	-1.0
GGT (U/L)				
Change from Baseline to Day 84				
N	96	90	96	282
Mean (Std Dev)	-2.7 (15.81)	-0.6 (20.65)	-1.2 (17.64)	-1.5 (18.04)
95% C.I.	(-5.93, 0.48)	(-4.89, 3.76)	(-4.78, 2.37)	(-3.63, 0.60)
Min, Max	-55.0, 66.0	-152.0, 63.0	-117.0, 40.0	-152.0, 66.0
Median	0.5	-1.0	0.0	0.0
Total Bilirubin (umol/L)				
Change from Baseline to Day 84				
N	90	86	91	267
Mean (Std Dev)	-0.6 (2.63)	0.3 (3.76)	-0.2 (2.97)	-0.2 (3.16)
95% C.I.	(-1.18, -0.07)	(-0.50, 1.11)	(-0.77, 0.47)	(-0.55, 0.21)
Min, Max	-9.0, 7.0	-12.0, 15.0	-13.0, 7.0	-13.0, 15.0
Median	0.0	0.0	0.0	0.0
Cholesterol (High Performance) (mmol/L)				
Change from Baseline to Day 84				
N	96	90	96	282
Mean (Std Dev)	0.0 (0.77)	0.1 (0.61)	-0.1 (0.64)	0.0 (0.68)
95% C.I.	(-0.13, 0.18)	(-0.06, 0.20)	(-0.20, 0.06)	(-0.07, 0.09)
Min, Max	-1.6, 2.6	-1.5, 1.7	-2.6, 1.3	-2.6, 2.6
Median	-0.0	0.1	-0.1	0.0
Triglycerides (GPO) (mmol/L)				
Change from Baseline to Day 84				
N	96	90	96	282
Mean (Std Dev)	0.0 (0.77)	-0.1 (0.73)	-0.1 (0.62)	-0.1 (0.71)
95% C.I.	(-0.12, 0.19)	(-0.28, 0.03)	(-0.20, 0.05)	(-0.14, 0.03)
Min, Max	-2.5, 3.0	-2.4, 2.5	-2.9, 1.5	-2.9, 3.0
Median	0.1	-0.1	-0.1	-0.0
Creatine Kinase (U/L)				
Change from Baseline to Day 84				
N	90	86	91	267
Mean (Std Dev)	7.1 (69.25)	7.1 (87.70)	-12.9 (77.17)	0.3 (78.53)
95% C.I.	(-7.39, 21.62)	(-11.74, 25.86)	(-28.98, 3.16)	(-9.19, 9.73)
Min, Max	-143.0, 300.0	-233.0, 440.0	-283.0, 282.0	-283.0, 440.0
Median	0.5	2.9	-1.0	0.0
Creatinine (umol/L)				

Change from Baseline to Day 84				
N	96	90	96	282
Mean (Std Dev)	0.1 (9.30)	-0.3 (10.57)	-0.4 (10.49)	-0.2 (10.09)
95% C.I.	(-1.75, 2.02)	(-2.47, 1.96)	(-2.56, 1.69)	(-1.37, 1.00)
Min, Max	-26.0, 26.0	-27.0, 27.0	-44.0, 35.0	-44.0, 35.0
Median	0.0	0.0	0.0	0.0
Urea Nitrogen (mmol/L)				
Change from Baseline to Day 29				
N	105	94	101	300
Mean (Std Dev)	0.1 (1.36)	0.0 (1.57)	-0.1 (1.30)	-0.0 (1.41)
95% C.I.	(-0.21, 0.32)	(-0.30, 0.34)	(-0.35, 0.16)	(-0.17, 0.16)
Min, Max	-4.3, 5.0	-6.8, 4.6	-3.9, 2.9	-6.8, 5.0
Median	0.0	0.0	0.0	0.0
Change from Baseline to Day 84				
N	96	90	96	282
Mean (Std Dev)	0.3 (1.36)	0.0 (1.33)	0.0 (1.34)	0.1 (1.34)
95% C.I.	(0.06, 0.61)	(-0.25, 0.31)	(-0.23, 0.31)	(-0.02, 0.30)
Min, Max	-2.9, 4.7	-6.1, 2.8	-3.2, 4.3	-6.1, 4.7
Median	0.3	0.1	0.0	0.0
Serum Potassium (mmol/L)				
Change from Baseline to Day 84				
N	96	89	95	280
Mean (Std Dev)	0.1 (0.42)	0.1 (0.38)	0.0 (0.37)	0.0 (0.39)
95% C.I.	(-0.03, 0.13)	(-0.01, 0.15)	(-0.05, 0.10)	(0.00, 0.09)
Min, Max	-1.5, 0.9	-1.2, 1.1	-0.9, 0.9	-1.5, 1.1
Median	0.1	0.1	0.0	0.1
Serum Uric Acid (umol/L)				
Change from Baseline to Day 84				
N	96	90	96	282
Mean (Std Dev)	4.0 (42.91)	-5.2 (43.72)	3.0 (42.09)	0.7 (42.94)
95% C.I.	(-4.65, 12.74)	(-14.33, 3.98)	(-5.55, 11.51)	(-4.30, 5.77)
Min, Max	-108.0, 89.0	-113.0, 113.0	-179.0, 137.0	-179.0, 137.0
Median	6.0	-6.0	0.0	0.0

Range of median values at baseline: ALT 21-25; AST 22-26; Alk phosphate 66-74; GGT 22-29; Total bilirubin 7.00-10.26; Bicarbonate 21-28; CK 80.0-164; Potassium 4.10-4.30.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Study Report; Table 31.1-31.3

Shifts in laboratory parameters from baseline

I reviewed the shift tables for laboratory parameters from baseline in the pooled controlled studies (Pool 3) and in Study 123. Shift table for between treatment comparisons of selected (reviewer selected) clinical laboratory parameters in the double-blind phase of Study 123 is summarized in the following table. With the exception of a few laboratory parameters (highlighted) discussed in the following paragraphs, there were no apparent differences between the treatment groups for shifts for other laboratory parameters in the pooled controlled studies or in Study 123.

Table 70: Shift table for between treatment comparisons of selected clinical laboratory values in the double-blind phase of Study 123.

Lab Test Baseline value	End of Study Increased	 Decreased	 No Change	P-value [1]
ALT (SGPT) (U/L)				
AVP-923-30	7 (6.4%)	12 (10.9%)	74 (67.3%)	0.0395
AVP-923-20	5 (4.7%)	5 (4.7%)	82 (76.6%)	0.7057
Placebo	3 (2.8%)	4 (3.7%)	86 (78.9%)	
AST (SGOT) (U/L)				
AVP-923-30	5 (4.5%)	6 (5.5%)	80 (72.7%)	0.6236
AVP-923-20	2 (1.9%)	1 (0.9%)	87 (81.3%)	0.3530
Placebo	3 (2.8%)	4 (3.7%)	83 (76.1%)	

Alkaline Phosphatase (U/L)				
AVP-923-30	2 (1.8%)	1 (0.9%)	96 (87.3%)	0.5953
AVP-923-20	2 (1.9%)	3 (2.8%)	90 (84.1%)	0.9987
Placebo	2 (1.8%)	3 (2.8%)	93 (85.3%)	
GGT (U/L)				
AVP-923-30	5 (4.5%)	8 (7.3%)	86 (78.2%)	0.0215
AVP-923-20	5 (4.7%)	3 (2.8%)	87 (81.3%)	0.0714
Placebo	0 (0.0%)	3 (2.8%)	95 (87.2%)	
Total Bilirubin (umol/L)				
AVP-923-30	0 (0.0%)	2 (1.8%)	91 (82.7%)	0.6098
AVP-923-20	4 (3.7%)	4 (3.7%)	84 (78.5%)	0.2578
Placebo	1 (0.9%)	2 (1.8%)	91 (83.5%)	
Creatinine (umol/L)				
AVP-923-30	1 (0.9%)	4 (3.6%)	94 (85.5%)	0.4052
AVP-923-20	0 (0.0%)	1 (0.9%)	94 (87.9%)	0.6158
Placebo	1 (0.9%)	1 (0.9%)	96 (88.1%)	
Urea Nitrogen (mmol/L)				
AVP-923-30	3 (2.7%)	0 (0.0%)	96 (87.3%)	0.0937
AVP-923-20	0 (0.0%)	5 (4.7%)	90 (84.1%)	0.0803
Placebo	5 (4.6%)	4 (3.7%)	89 (81.7%)	
Cholesterol (High Performance)				
AVP-923-30	9 (8.2%)	14 (12.7%)	76 (69.1%)	0.7405
AVP-923-20	5 (4.7%)	8 (7.5%)	82 (76.6%)	0.1336
Placebo	12 (11.0%)	12 (11.0%)	74 (67.9%)	
Triglycerides (GPO) (mmol/L)				
AVP-923-30	8 (7.3%)	6 (5.5%)	85 (77.3%)	0.3131
AVP-923-20	3 (2.8%)	7 (6.5%)	85 (79.4%)	0.7304
Placebo	4 (3.7%)	10 (9.2%)	84 (77.1%)	

End of Study is Visit 5 (Day 84) or Early Termination.
[1] P-value is based on chi-square test for row mean scores differ comparison between active treatment and placebo.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Study Report; Table 33.1 - 33.3

Outliers and Clinically Important Laboratory parameter Values

Across the controlled trials, there were very few subjects (1 - 3 per treatment arm) who met the criteria for clinically significant abnormality (CSA). The incidence of potentially clinically important laboratory results by treatment for reviewer-selected laboratory parameters is reproduced in the table below. The incidences of subjects with a clinically important value in ALT, AST, alkaline phosphatase and total bilirubin were numerically greater in the DM/Q dose groups compared to placebo group. For the remaining laboratory parameters, the between treatment group differences were fairly similar.

Table 71: Incidence of potentially clinically important laboratory results by treatment in the controlled trials of PBA (Pool 3)

Parameter and Assessment	AVP-923 20 mg DM/ 10 mg Q (N=107)	AVP-923 30 mg DM/ 10 mg Q (N=110)	AVP-923 All doses with 10 mg Q (N=217)	AVP-923 All doses with 30 mg Q (N=146)	AVP-923 All AVP-923 (N=363)	Placebo (N=183)	DM 30 mg (N=33)	Q 30 mg (N=37)
ALT >=3X ULN								
Day 29	1/77 (1.3%)	2/92 (2.2%)	3/169 (1.8%)	1/108 (0.9%)	4/277 (1.4%)	0/146 (0.0%)	0/28 (0.0%)	0/34 (0.0%)
Day 84/85	0/80 (0.0%)	0/91 (0.0%)	0/171 (0.0%)	0/54 (0.0%)	0/225 (0.0%)	0/139 (0.0%)	0/0	0/0
ET Visit	0/11 (0.0%)	0/7 (0.0%)	0/18 (0.0%)	0/31 (0.0%)	0/49 (0.0%)	0/28 (0.0%)	0/1 (0.0%)	0/2 (0.0%)
Final Visit	0/86 (0.0%)	0/99 (0.0%)	0/185 (0.0%)	0/106 (0.0%)	0/291 (0.0%)	0/144 (0.0%)	0/29 (0.0%)	0/34 (0.0%)
End of Study	0/97 (0.0%)	0/106 (0.0%)	0/203 (0.0%)	0/137 (0.0%)	0/340 (0.0%)	0/174 (0.0%)	0/30 (0.0%)	0/36 (0.0%)
Any Visit	1/97 (1.0%)	2/106 (1.9%)	3/203 (1.5%)	1/137 (0.7%)	4/340 (1.2%)	0/174 (0.0%)	0/30 (0.0%)	0/36 (0.0%)
ALT >=5X ULN								
Day 29	1/77 (1.3%)	2/92 (2.2%)	3/169 (1.8%)	0/108 (0.0%)	3/277 (1.1%)	0/146 (0.0%)	0/28 (0.0%)	0/34 (0.0%)
Day 84/85	0/80 (0.0%)	0/91 (0.0%)	0/171 (0.0%)	0/54 (0.0%)	0/225 (0.0%)	0/139 (0.0%)	0/0	0/0
ET Visit	0/11 (0.0%)	0/7 (0.0%)	0/18 (0.0%)	0/31 (0.0%)	0/49 (0.0%)	0/28 (0.0%)	0/1 (0.0%)	0/2 (0.0%)
Final Visit	0/86 (0.0%)	0/99 (0.0%)	0/185 (0.0%)	0/106 (0.0%)	0/291 (0.0%)	0/144 (0.0%)	0/29 (0.0%)	0/34 (0.0%)
End of Study	0/97 (0.0%)	0/106 (0.0%)	0/203 (0.0%)	0/137 (0.0%)	0/340 (0.0%)	0/174 (0.0%)	0/30 (0.0%)	0/36 (0.0%)
Any Visit	1/97 (1.0%)	2/106 (1.9%)	3/203 (1.5%)	0/137 (0.0%)	3/340 (0.9%)	0/174 (0.0%)	0/30 (0.0%)	0/36 (0.0%)
ALT >=10X ULN								
Day 29	0/77 (0.0%)	1/92 (1.1%)	1/169 (0.6%)	0/108 (0.0%)	1/277 (0.4%)	0/146 (0.0%)	0/28 (0.0%)	0/34 (0.0%)
Day 84/85	0/80 (0.0%)	0/91 (0.0%)	0/171 (0.0%)	0/54 (0.0%)	0/225 (0.0%)	0/139 (0.0%)	0/0	0/0
ET Visit	0/11 (0.0%)	0/7 (0.0%)	0/18 (0.0%)	0/31 (0.0%)	0/49 (0.0%)	0/28 (0.0%)	0/1 (0.0%)	0/2 (0.0%)
Final Visit	0/86 (0.0%)	0/99 (0.0%)	0/185 (0.0%)	0/106 (0.0%)	0/291 (0.0%)	0/144 (0.0%)	0/29 (0.0%)	0/34 (0.0%)
End of Study	0/97 (0.0%)	0/106 (0.0%)	0/203 (0.0%)	0/137 (0.0%)	0/340 (0.0%)	0/174 (0.0%)	0/30 (0.0%)	0/36 (0.0%)
Any Visit	0/97 (0.0%)	1/106 (0.9%)	1/203 (0.5%)	0/137 (0.0%)	1/340 (0.3%)	0/174 (0.0%)	0/30 (0.0%)	0/36 (0.0%)
AST >=3X ULN								
Day 29	1/76 (1.3%)	2/91 (2.2%)	3/167 (1.8%)	0/108 (0.0%)	3/275 (1.1%)	0/145 (0.0%)	0/28 (0.0%)	0/34 (0.0%)
Day 84/85	0/78 (0.0%)	0/89 (0.0%)	0/167 (0.0%)	0/54 (0.0%)	0/221 (0.0%)	0/138 (0.0%)	0/0	0/0
ET Visit	0/11 (0.0%)	0/7 (0.0%)	0/18 (0.0%)	0/31 (0.0%)	0/49 (0.0%)	0/28 (0.0%)	0/1 (0.0%)	0/2 (0.0%)
Final Visit	0/86 (0.0%)	0/99 (0.0%)	0/185 (0.0%)	0/106 (0.0%)	0/291 (0.0%)	0/144 (0.0%)	0/29 (0.0%)	0/34 (0.0%)
End of Study	0/97 (0.0%)	0/106 (0.0%)	0/203 (0.0%)	0/137 (0.0%)	0/340 (0.0%)	0/174 (0.0%)	0/30 (0.0%)	0/36 (0.0%)
Any Visit	1/97 (1.0%)	2/106 (1.9%)	3/203 (1.5%)	0/137 (0.0%)	3/340 (0.9%)	0/174 (0.0%)	0/30 (0.0%)	0/36 (0.0%)
AST >=5X ULN								
Day 29	0/76 (0.0%)	1/91 (1.1%)	1/167 (0.6%)	0/108 (0.0%)	1/275 (0.4%)	0/145 (0.0%)	0/28 (0.0%)	0/34 (0.0%)
Day 84/85	0/78 (0.0%)	0/89 (0.0%)	0/167 (0.0%)	0/54 (0.0%)	0/221 (0.0%)	0/138 (0.0%)	0/0	0/0
ET Visit	0/11 (0.0%)	0/7 (0.0%)	0/18 (0.0%)	0/31 (0.0%)	0/49 (0.0%)	0/28 (0.0%)	0/1 (0.0%)	0/2 (0.0%)
Final Visit	0/86 (0.0%)	0/99 (0.0%)	0/185 (0.0%)	0/106 (0.0%)	0/291 (0.0%)	0/144 (0.0%)	0/29 (0.0%)	0/34 (0.0%)
End of Study	0/97 (0.0%)	0/106 (0.0%)	0/203 (0.0%)	0/137 (0.0%)	0/340 (0.0%)	0/174 (0.0%)	0/30 (0.0%)	0/36 (0.0%)
Any Visit	0/97 (0.0%)	1/106 (0.9%)	1/203 (0.5%)	0/137 (0.0%)	1/340 (0.3%)	0/174 (0.0%)	0/30 (0.0%)	0/36 (0.0%)
Alkaline Phosphatase >=2X ULN								
Day 29	1/80 (1.3%)	0/97 (0.0%)	1/177 (0.6%)	0/108 (0.0%)	1/285 (0.4%)	0/149 (0.0%)	0/28 (0.0%)	0/34 (0.0%)
Day 84/85	0/82 (0.0%)	0/96 (0.0%)	0/178 (0.0%)	0/54 (0.0%)	0/232 (0.0%)	0/143 (0.0%)	0/0	0/0
ET Visit	0/11 (0.0%)	0/7 (0.0%)	0/18 (0.0%)	0/31 (0.0%)	0/49 (0.0%)	0/28 (0.0%)	0/1 (0.0%)	0/2 (0.0%)
Final Visit	0/87 (0.0%)	0/101 (0.0%)	0/188 (0.0%)	0/106 (0.0%)	0/294 (0.0%)	0/146 (0.0%)	0/29 (0.0%)	0/34 (0.0%)
End of Study	0/98 (0.0%)	0/108 (0.0%)	0/206 (0.0%)	0/137 (0.0%)	0/343 (0.0%)	0/176 (0.0%)	0/30 (0.0%)	0/36 (0.0%)
Any Visit	1/98 (1.0%)	0/108 (0.0%)	1/206 (0.5%)	0/137 (0.0%)	1/343 (0.3%)	0/176 (0.0%)	0/30 (0.0%)	0/36 (0.0%)
GGT >=3X ULN								
Day 29	1/80 (1.3%)	0/97 (0.0%)	1/177 (0.6%)	1/108 (0.9%)	2/285 (0.7%)	2/149 (1.3%)	0/28 (0.0%)	0/34 (0.0%)
Day 84/85	0/82 (0.0%)	0/96 (0.0%)	0/178 (0.0%)	0/54 (0.0%)	0/232 (0.0%)	1/142 (0.7%)	0/0	0/0
ET Visit	0/11 (0.0%)	1/7 (14.3%)	1/18 (5.6%)	1/31 (3.2%)	2/49 (4.1%)	0/28 (0.0%)	0/1 (0.0%)	0/2 (0.0%)
Final Visit	0/87 (0.0%)	0/101 (0.0%)	0/188 (0.0%)	0/106 (0.0%)	0/294 (0.0%)	1/146 (0.7%)	0/29 (0.0%)	0/34 (0.0%)
End of Study	0/98 (0.0%)	1/108 (0.9%)	1/206 (0.5%)	1/137 (0.7%)	2/343 (0.6%)	1/176 (0.6%)	0/30 (0.0%)	0/36 (0.0%)
Any Visit	2/98 (2.0%)	1/108 (0.9%)	3/206 (1.5%)	3/137 (2.2%)	6/343 (1.7%)	2/176 (1.1%)	0/30 (0.0%)	0/36 (0.0%)
Total Bilirubin >1.5X ULN								
Day 29	1/78 (1.3%)	0/93 (0.0%)	1/171 (0.6%)	2/108 (1.9%)	3/279 (1.1%)	0/146 (0.0%)	1/28 (3.6%)	0/34 (0.0%)
Day 84/85	1/80 (1.3%)	0/91 (0.0%)	1/171 (0.6%)	0/54 (0.0%)	1/225 (0.4%)	0/139 (0.0%)	0/0	0/0
ET Visit	0/11 (0.0%)	0/7 (0.0%)	0/18 (0.0%)	0/30 (0.0%)	0/48 (0.0%)	0/28 (0.0%)	0/1 (0.0%)	0/2 (0.0%)
Final Visit	1/86 (1.2%)	0/99 (0.0%)	1/185 (0.5%)	2/106 (1.9%)	3/291 (1.0%)	0/144 (0.0%)	1/29 (3.4%)	0/34 (0.0%)
End of Study	1/97 (1.0%)	0/106 (0.0%)	1/203 (0.5%)	2/136 (1.5%)	3/339 (0.9%)	0/174 (0.0%)	1/30 (3.3%)	0/36 (0.0%)
Any Visit	2/97 (2.1%)	0/106 (0.0%)	2/203 (1.0%)	2/136 (1.5%)	4/339 (1.2%)	0/174 (0.0%)	1/30 (3.3%)	0/36 (0.0%)
Total Bilirubin >=2.0X ULN								
Day 29	1/78 (1.3%)	0/93 (0.0%)	1/171 (0.6%)	0/108 (0.0%)	1/279 (0.4%)	0/146 (0.0%)	1/28 (3.6%)	0/34 (0.0%)
Day 84/85	0/80 (0.0%)	0/91 (0.0%)	0/171 (0.0%)	0/54 (0.0%)	0/225 (0.0%)	0/139 (0.0%)	0/0	0/0
ET Visit	0/11 (0.0%)	0/7 (0.0%)	0/18 (0.0%)	0/30 (0.0%)	0/48 (0.0%)	0/28 (0.0%)	0/1 (0.0%)	0/2 (0.0%)
Final Visit	0/86 (0.0%)	0/99 (0.0%)	0/185 (0.0%)	0/106 (0.0%)	0/291 (0.0%)	0/144 (0.0%)	1/29 (3.4%)	0/34 (0.0%)
End of Study	0/97 (0.0%)	0/106 (0.0%)	0/203 (0.0%)	0/136 (0.0%)	0/339 (0.0%)	0/174 (0.0%)	1/30 (3.3%)	0/36 (0.0%)
Any Visit	1/97 (1.0%)	0/106 (0.0%)	1/203 (0.5%)	0/136 (0.0%)	1/339 (0.3%)	0/174 (0.0%)	1/30 (3.3%)	0/36 (0.0%)
Triglycerides >300 mg/dL (3.39 mmol/L)								
Day 29	7/81 (8.6%)	8/97 (8.2%)	15/178 (8.4%)	6/108 (5.6%)	21/286 (7.3%)	9/149 (6.0%)	3/28 (10.7%)	3/34 (8.8%)
Day 84/85	4/82 (4.9%)	7/96 (7.3%)	11/178 (6.2%)	4/54 (7.4%)	15/232 (6.5%)	11/143 (7.7%)	0/0	0/0
ET Visit	0/11 (0.0%)	1/7 (14.3%)	1/18 (5.6%)	4/30 (13.3%)	5/48 (10.4%)	2/28 (7.1%)	0/1 (0.0%)	0/2 (0.0%)
Final Visit	4/87 (4.6%)	8/101 (7.9%)	12/188 (6.4%)	8/106 (7.5%)	20/294 (6.8%)	10/146 (6.8%)	3/29 (10.3%)	4/34 (11.8%)
End of Study	4/98 (4.1%)	9/108 (8.3%)	13/206 (6.3%)	12/136 (8.8%)	25/342 (7.3%)	12/176 (6.8%)	3/30 (10.0%)	4/36 (11.1%)
Any Visit	10/98 (10.2%)	13/108 (12.0%)	23/206 (11.2%)	14/136 (10.3%)	37/342 (10.8%)	19/176 (10.8%)	3/30 (10.0%)	4/36 (11.1%)

Note: Treatment categories are not mutually exclusive. Thus, patients may contribute to more than one treatment category.

Note: Percentage = 100* (the number of patients who met the criterion for markedly abnormal at the visit/ the number of patients who had data at the indicated visit for the parameter).
Note: The early termination (ET) visit includes measurements collected on the last on-treatment date where labs were collected for non-completers.
Note: The final visit includes the last on-treatment measurements for completers.
Note: The end of study visit includes the last on-treatment measurements for all completers and non-completers.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS; Table 42.3.3

In the Approvable Letter, and during the Type C meeting (minutes dated 3/26/07), the Agency expressed concern that although there do not seem to be important systematic laboratory changes induced by treatment with DM/Q, there was the occurrence of significant hepatic injury in subject # 136-9004 (narrative provided below) who became jaundiced after 2 ½ months of treatment with study drug. In the paragraphs below, I discuss the liver function tests in detail, the Applicant's Response and my conclusions. I also discuss other laboratory tests of interest.

Liver function tests: The median changes from baseline in the liver function tests were fairly similar between treatment groups in the pooled controlled studies and the double-blind phase of Study 123, as discussed above. The pooled controlled studies did not show any differences between treatment groups for abnormal shifts in liver function tests. However, in Study 123 (Table 70), subjects in DM 30 mg/Q 10 mg group who had shifts in ALT and AST from normal at baseline to abnormally high at End of Study (Day 84) were numerically higher than either the DM 20 mg/Q 10 mg dose group or the placebo group. There were more subjects in the DM 20 mg/Q 10 mg group compared to placebo group who had shifts in total bilirubin from normal at baseline to abnormally high at End of Study.

I discuss below the narratives for subjects experiencing liver-related adverse events and subjects with outlier liver functions tests.

> Subject # 136-9004 (USUBJID: 109-136-004) was a 58-year old black male enrolled in Study 109 (a 13-week, double-blind, placebo-controlled study in subjects with diabetic peripheral neuropathy pain) experienced hepatitis. His medical history was significant for diabetes mellitus, neuropathy, dyslipemia, hypertension, and two cerebrovascular accidents. Concomitant medications at the time of the event included metformin 1000 BID, Actos 45 mg daily, Pravachol 40 mg daily, warfarin 2 to 5 mg daily, Humalog 75/25 varied dose SC daily, and Lantus 44 units SC daily. He began taking DM 45/Q 30 mg on 12/1/05, and his last dose was on 2/15/06 (77 days). On (b) (6)) he presented to the Emergency Room with complaints of dark urine, diarrhea, abdominal distension with pain, and was hospitalized for further evaluation. Abnormal laboratory findings included total bilirubin 5.6 mg/L (Screening 3.0 mg/L; reference range: 1 – 10 mg/L) with direct bilirubin 3.6 mg/L, ALT 673 IU/L (Screening 20 IU/L), AST 720 IU/L (Screening 18 IU/L), alkaline phosphatase 206 IU/L and serum albumin 2.7 mg/dL. He was treated for coagulopathy secondary to Coumadin with four units of fresh frozen plasma and Vitamin K. His liver enzymes peaked by 2/18/06 to ALT of 953 IU/L and AST of 1270 IU/L, and thereafter, decreased throughout his hospital stay to values of ALT of 110 IU/L, AST of 63 IU/L, and alkaline phosphatase of 146 IU/L and an INR of 2.5 on 2/27/06. A hepatitis viral panel was negative. An abdominal ultrasound revealed no stone in the common duct. A CT scan of the abdomen revealed multiple small stones in the gall bladder. During the course of his hospital stay, his distended abdomen and jaundice showed improvement, and remained afebrile. He was discharged on (b) (6). He was not rechallenged with DM/Q, and he withdrew consent. The subject did well after his hospitalization according to the primary care physician with no recurrence of liver problems. The investigator, after considering the input from a gastroenterology specialist, felt that, retrospectively, based on the clinical presentation and outcome, the subject did not have an episode of hepatotoxicity or liver failure, and that he had a gall bladder stone that spontaneously passed.

Across the integrated controlled trials (Pool 1), there was one subject (#123-106-724) with ALT elevated ≥ 3 times the upper limit of normal and bilirubin elevated ≥ 2 times the upper limit of normal in the context of infectious mononucleosis (narrative below).

Subject #123-106-724, is a 54 year old female with MS, who was enrolled in the double-blind phase of Study 123. She was randomized to DM 20 mg/Q 10 mg and experienced abnormally elevated liver function parameter values on Day 29. These parameters are summarized in the following table. Both ALT and AST were elevated ≥ 5-fold the upper limit of normal, with a concomitant ≥ 2-fold the upper limit of normal elevation for total bilirubin. An AE of infectious mononucleosis was reported on Day 24, and an AE of arthralgia was reported on Day 31. Concomitant medications included interferon beta (Avonex), modafinil, tizanidine, lotrel, gabapentin, celecoxib, azithromycin and bactrim. The only medication prescribed around the time of the AEs (Day 34) was celecoxib which she continued to take at least until Day 61. By Day 49, the liver functions tests became normal. She continued taking DM 20 mg/Q 10 mg, and went on to complete the 12-week open-label phase of Study 123 (DM 30 mg/Q 10 mg). Narrative was not provided and was requested. In response, the Applicant states that the elevated liver enzymes were attributed to infectious mononucleosis as the Epstein Barr virus test was positive.

Liver function test	**Ref range**	**Laboratory day**							
		-16	**29**	**49**	**56**	**84**	**99**	**127**	**169**
Alkaline Phosphatase	35-123 U/L	70	415	118	101	84	77	72	68
ALT	6-34 U/L	32	294	28	20	17	17	25	45
AST	9-34 U/L	28	140	26	17	15	23	25	62
Total Bilirubin	3-21 UMOL/L	3	46	7	5	5	5	7	7

Source: LB1 dataset.Eval Y.Subset by STUDYID 123OLE.Subset USUBJID 106-724; Tabulate (LBTEST to rows, LBDY2 as Grouping columns, AVAL as Analysis columns, OUNIT, LBSTNRLO and LBSTNRHI as Grouping columns. Similar analysis for LB2 dataset, join tables.

Reviewer's comments: Elevated liver function tests and infectious mononucleosis were reported as AEs; no other liver-related AEs including hepatitis were reported. A negative rechallenge with DM/Q argues against a relationship with DM/Q, and in favor of infectious mononucleosis as the underlying etiology.

Other than the two subjects noted above, there were no other subjects who died due to, or experienced a non-fatal hepatic-related SAE or abnormal liver function values as an SAE in the integrated clinical studies (Pool 1). In Pool 1, discontinuations due to hepatic AEs (abnormally elevated liver function tests reported as AEs) occurred in 8 subjects: 3 subjects in open-label Study 107 (DM 30 mg/Q 30 mg), 4 subjects in Study 109 (3 on DM 45 mg/Q 30 mg and 1 on DM 30 mg/Q 30 mg), and 1 subject in the open-label phase of Study 123. Two of these 8 subjects had ALS, 2 MS, and 4 had diabetic peripheral neuropathy pain. In 5 of the subjects, hepatic AEs leading to discontinuation were recorded as 'liver function test abnormal' or 'hepatic enzyme increased'. Two subjects had elevated levels of alkaline phosphatase, GGT, ALT and AST, and one patient had elevated levels of GGT only. These subjects are briefly summarized below.

Subject 107-007-004 in Study 107 (DM 30 mg/Q 30 mg) was a 52 year old female with MS who was discontinued from the study on Day 29 for hepatic enzyme increased. Concomitant medications included interferon beta, oxybutynin, loratidine and glucosamine. The maximum value for these liver function tests which occurred on Day 29 for ALT and AST, on Day 40 for alkaline phosphatase, and Day 71 for total bilirubin were: ALT = 108 U/L (Baseline = 17 U/L; Reference range: 8-43 U/L); AST = 74 U/L (Baseline = 20 U/L); alkaline phosphatase = 178 U/L (Baseline = 87 U/L); total bilirubin = 5.4 µMol/L (Baseline = 7.18 µMol/L; Reference range 3.8 – 21.9 µMol/L). This AE was not serious, and the investigator considered probably related to study drug. The subject recovered.

Subject 107-016-008 in Study 107 (DM 30 mg/Q 30 mg) was 55 year old female with MS who discontinued from the study on Day 33 for liver function test abnormal. Concomitant medications include clonazepam, fluoxetine, copaxone, loraditine and rizatriptan. The maximum value for these liver function tests which occurred on Day 33 were: ALT = 142 U/L (Baseline = 22 U/L; Reference range: 8-43 U/L); AST = 96 U/L (Baseline = 44 U/L); alkaline phosphatase = 216 U/L (Baseline = 73 U/L); total bilirubin = 6.6 µMol/L (Baseline = 5.9 µMol/L; Reference range 3.8 – 21.9 µMol/L). This AE was not serious, and the investigator considered this AE to be probably related to study drug. The subject recovered.

Subject 107-021-007 in Study 107 (DM 30 mg/Q 30 mg) was 53 year old female with primary lateral sclerosis who discontinued from the study on Day 124 for liver function test abnormal. Concomitant medications include riluzole. The maximum value for these liver function tests were ALT = 209 U/L (Baseline = 15 U/L; Reference range: 8-43 U/L); AST = 85 U/L (Baseline = 17 U/L); alkaline phosphatase = 303 U/L (Baseline = 61 U/L); total bilirubin = 32.2 µMol/L (Baseline = 8.2 µMol/L; Reference range 3.8 – 21.9 µMol/L). Cholestatic jaundice was reported as an AE. This AE was not serious, and the investigator considered this AE to be probably related to study drug. The subject recovered by Day 211. Reviewer's comments: bilirubin was elevated but not > 2 times the upper limit of normal. "Cholestatic jaundice" was reported as an AE suggesting an obstructive pathology rather than hepatocellular. No further details are provided in the narrative.

Subject 109-141-003 (old ID 141-9003) in Study 109 (DM 45 mg/Q 30 mg) was a 59-year old male with diabetic peripheral neuropathy, coronary artery disease and hypertension. Concomitant medications were insulin, glucophage and lipitor. He discontinued from the study on Day 49 due to ALT, AST, GGT, and blood alkaline phosphatase increased. The maximum value for these liver function tests which occurred on Day 48 were: ALT = 289 U/L (Baseline = 21 U/L; Reference range: 8-20 U/L); AST = 106 U/L (Baseline = 21 U/L); alkaline phosphatase = 556 U/L (Baseline = 101 U/L); total bilirubin = 17 µMol/L (Baseline = 10 µMol/L; Reference range 2 – 17 µMol/L). These AEs were mild in intensity, not serious, and the investigator considered them definitely related to study drug. The subject recovered.

Subject 109-141-010 in Study 109 (DM 30 mg/Q 30 mg) was a 65-year old male diabetic peripheral neuropathy who discontinued from the study on Day 29 for ALT, AST, GGT, and blood alkaline phosphatase increased. The maximum value for these liver function tests which occurred on Day 29 were: ALT = 194 U/L (Baseline = 35 U/L; Reference range: 8-20 U/L); AST = 79 U/L (Baseline = 27 U/L); alkaline phosphatase = 170 U/L (Baseline = 83 U/L); total bilirubin = 19 µMol/L (Baseline = 12 µMol/L; Reference range 2 – 17 µMol/L). These AEs were all mild in intensity, not serious, and the investigator considered them definitely related to study drug. The subject recovered.

Subject 109-145-001 in Study 109 (DM 45 mg/Q 30 mg) was 62-year old male with diabetic peripheral neuropathy who discontinued from the study on Day 50 for GGT increased. The maximum value for GGT and other liver function tests which occurred on Day 50 for GGT, Day 29 (total bilirubin) and on Days 50-55 for ALT, AST and alkaline phosphatase were: GGT = 272 U/L (Baseline = 20 U/L; Reference range: 2 – 65 U/L); ALT = 42 U/L (Baseline = 19 U/L; Reference range: 8-20 U/L); AST = 28 U/L (Baseline = 15 U/L); alkaline phosphatase = 139 U/L (Baseline = 65 U/L); total bilirubin = 9 µMol/L (Baseline = 7 µMol/L; Reference range 2 – 17 µMol/L). This AE was moderate in intensity, not serious, and the investigator considered probably related to study drug. The subject recovered.

Subject 109-156-007 in Study 109 (DM 45 mg/Q 30 mg) was a 77-year old male diabetic peripheral neuropathy who discontinued from the study on Day 28 for liver function test abnormal. The maximum value for these liver function tests which occurred on Day 28 were: ALT = 243 U/L (Baseline = 50 U/L; Reference range: 8-20 U/L); AST = 106 U/L (Baseline = 49 U/L); alkaline phosphatase = 227 U/L (Baseline = 81 U/L); total bilirubin = 7 µMol/L (Baseline = 5 µMol/L; Reference range 2 – 17 µMol/L). This AE was severe in intensity, not serious, and the investigator considered probably related to study drug. The subject recovered.

Subject 123-135-503 in the open-label phase of Study 123 (DM 30 mg/Q 10 mg) was a 35-year old male with ALS who was discontinued on Day 46 of the open-label phase (or Day 127 from randomization to the

double-blind phase) due to abnormal liver function tests. The subject was on placebo during the double-blind phase. Relevant concomitant medications included Prilosec (omeprazole) 40mg QD), guaifenesin, Zyrtec (cetirizine hydrochloride) PRN, propranolol 160mg QD, calcium, vitamin D, Maxalt (rizatriptan) PRN, and Super B complex. On Day 127, ALT was 243 U/L (Baseline for the double-blind phase = 43 U/L); AST = 174 U/L (Baseline = 36 U/L); total bilirubin = 7 µMol/L. DM 30 mg/Q 10 mg was discontinued on Day 134. Approximately, one month later (Day 166), the liver function parameters were almost normal. At no point, did the total bilirubin was abnormally elevated. These AEs were moderate and the investigator considered possibly related to drug.

Liver function tests	Ref range	Study day				
		96	127	131	148	166
Alkaline Phosphatase	31-129 U/L	79	92	89	83	76
ALT	6-43 U/L	50	243	181	64	74
AST	11-36 U/L	37	174	76	43	53
Total Bilirubin	3-21 UMOL/L	15	7	7	9	12

LB2.Eval Y.Subset by STUDYID 123OLE.Subset USUBJID 135-503

In the pooled controlled trials of PBA (Pool 3), the incidences of hepatobiliary AEs (including elevated liver enzymes) were 6 (2.8%) in subjects exposed to DM any dose/Q 10 mg, 4 (2.7%) in subjects exposed to DM any dose/Q 30 mg, and 4 (2.2%) in the placebo group; no meaningful between-treatment group differences were seen in ALS or MS subjects. In the double-blind phase of Study 123, the number of subjects with hepatobiliary AEs was: 0 subjects in DM 30 mg/Q 10 mg, 1 in DM 20 mg/Q 10 mg, and 2 in placebo group. Since riluzole and interferon may cause elevations in liver enzymes, the Applicant conducted sub-analyses in Pool 3 of concomitant use of riluzole in subjects with ALS as the primary disease, and of medications commonly used to treat MS (i.e., glatiramer acetate, beta interferons) in the subjects with MS as the primary disease. No increases in hepatobiliary disorders or elevated liver enzymes were seen in patients receiving DM/Q with these concomitant medications. In the double-blind phase of Study 123, there were three subjects, all with MS on either Avonex or Copaxone, with multiple abnormal liver function values which were reported as AEs in Study 123.

Subject 123-202-703 (DM 30 mg/Q 10 mg) had MS and was on Copaxone. On study Day 29, increased ALT, AST, and GGT were reported as AEs in. These AEs were mild in intensity, not serious, and resolved.

Subject 123-106-724 (DM 20 mg/Q 10 mg) had MS and was on Avonex. On Day 29, increased alkaline phosphatase, ALT, AST, GGT, and lactate dehydrogenase (LDH) were reported as AEs. These AEs were moderate in intensity, not serious, and resolved.

Subject 123-111-708 (DM 20 mg/Q 10 mg) had MS and was on Avonex. On Day 32, increased ALT, AST, and GGT were reported as AEs in. These AEs were mild in intensity, not serious, and did not resolve by the end of the study. No further abnormalities in clinical laboratory parameters were reported for this subject.

In Pool 1, there were two subjects with ALT or AST values ≥ 10 times the upper limit of normal but without a concomitant ≥ 2-fold the upper limit of normal increase in total bilirubin. One subject had bilirubin values > 2 times the upper limit of normal but without accompanying ≥ 3 fold elevation of ALT or AST values. These subjects are briefly discussed.

Subject 107-003-007 (DM 30 mg/Q 30 mg) enrolled in Study 107, a 25-year old female with MS, had ALT or AST values ≥ 10 times the upper limit of normal but without a concomitant ≥ 2-fold the upper limit of normal increase in total bilirubin. By Day 1373, ALT was 737 U/L (Baseline = 23 U/L; Reference range: 8

– 43 U/L), AST was 539 U/L, and total bilirubin was only 6.6 µMol/L (Baseline = 5.8 µMol/L; Reference range 3.8 – 21.9 µMol/L). By Day 1437 (unscheduled visit), the ALT values had decreased to 364 U/L and AST values to 369 U/L. The maximum total bilirubin value was 12.9 µMol/L on Day 705.

Subject 123-306-702 (DM 30 mg/Q 10 mg) enrolled in Study 123, a 29-year old female with MS, had ALT or AST values ≥ 10 times the upper limit of normal. ALT was 327 U/L on Day 14 (Baseline = 57 U/L; Reference range: 6 – 34 U/L), 425 U/L on Day 32, and had normalized at 23 U/L on Day 84. AST was 144 U/L on Day 14 (Baseline = 36), 200 U/L on Day 32 and normal (24 U/L) on Day 84. At no time point was total bilirubin abnormal; the highest value was 12 µMol/L on Days 32 and 84.

Subject 107-017-004 (DM 30 mg/Q 30 mg) enrolled in Study 107, was a 46-year old male with ALS who had total bilirubin values ≥ 2 times the upper limit of normal. The total bilirubin values were 50.9 µMol/L at open-label Baseline (Reference range: 3.8 – 21.9 µMol/L), and remained elevated at 62.2 µMol/L at the end of the study (Day 1384) with a maximum value of 72 µMol/L occurring at Day 372. The maximum ALT value was 44 on Day 1384 and the maximum AST value was 39 on Day 372.

Applicant's response: Both DM and Q, the component drugs for the combination product under review, are metabolized primarily by liver enzymes. In the over 50 years that DM has been marketed as an over-the-counter product at the recommended adult dose of 60-120 mg per day, there is no evidence that DM usage, even at high doses, is associated with liver toxicity. At the recommended maintenance dose of Q for cardiac arrhythmias of 200 mg to 400 mg 3 to 4 times daily (maximum dose not exceed 3-4 grams per day), a few cases of hepatotoxicity, including granulomatous hepatitis, have been reported (Quinidine Prescribing Information). All of these have appeared during the first few weeks of therapy, and most (not all) have remitted once Q was withdrawn. The daily dose of Q (20 mg) in DM/Q is 1-3% of a recommended antiarrhythmic dose of Q. In the development program, a review of all the clinical data revealed no evidence of hepatotoxicity with DM/Q 10 mg use.

Since riluzole, glatiramer, and interferon beta may elevate hepatic enzymes, sub-analyses were performed to assess the effects of riluzole use in subjects with ALS as the primary disease, and the effects of medications commonly used to treat MS (glatiramer acetate, beta interferons) in subjects with MS as the primary disease in Pool 3. Incidences of any AEs were similar between the DM any dose/Q 10 mg and placebo groups, or were lower in the DM/Q dose group.

Data obtained from Study 123 revealed no evidence of hepatotoxicity with DM/Q 10 mg use. The incidence of hepatobiliary AEs (including elevated liver enzymes) was low and most of the events were mild or moderate in intensity. Many subjects who showed elevated liver enzymes were taking concomitant medication known to increase liver function parameters (Rilutek, Avonex or Copaxone) as a part of the treatment of their underlying condition (ALS or MS). Mean laboratory parameters of ALT, AST, alkaline phosphatase, and GGT were comparable at baseline and showed no treatment-related differences at Day 84. The laboratory shift data from the controlled and uncontrolled PBA studies showed no remarkable trends in subjects exposed to the DM/Q combination. Thus, the evidence from the clinical program suggests that DM/Q does not cause drug related liver injury.

Reviewer's comments: Across the clinical studies, there was one case of hepatitis (#109-136-004) occurring after 77 days of exposure to DM 45 mg/Q 30 mg. Although gall bladder stone is a

potential explanation for this event, a relationship between DM/Q and hepatitis can not be entirely excluded. This subject was not rechallenged; however, recovered and did well thereafter with no recurrence of liver problems. Even assuming the worst case scenario that there was indeed a causal relationship between hepatitis and DM/Q, it appears that this adverse event is not only monitorable but, importantly, reversible. There was one subject (#123-106-724) with ALT elevated ≥ 3 times the upper limit of normal and bilirubin elevated ≥ 2 times the upper limit of normal in the context of infectious mononucleosis. Liver enzymes returned to normal after about 2-3 weeks. A negative rechallenge with DM/Q (subject went on to complete the study) argues against a relationship with DM/Q, and in favor of infectious mononucleosis as the underlying etiology.

Other than the two subjects noted above, there were no other subjects who died due to, or experienced a non-fatal hepatic-related SAE or abnormal liver function values as an SAE in the integrated clinical studies (Pool 1). In Pool 1, discontinuations due to hepatic AEs (abnormal liver function tests reported as AEs) occurred in 8 subjects. Most of these abnormal elevations of liver function tests occurred early during exposure between Study Day 28 – 50, and importantly, all subjects recovered. Controlled trials showed no excess of hepatic or abnormally elevated liver function tests in the DM/Q groups as compared to the placebo group.

In the integrated clinical studies, there were a two subjects who had ALT or AST values ≥ 10 times the upper limit of normal but without a concomitant ≥ 2-fold the upper limit of normal increase in total bilirubin (see section 7.4.2 of this review). One subject had bilirubin values > 2 times the upper limit of normal but without accompanying elevation of ALT or AST values.

Data in the pooled controlled studies did not show any differences between treatment groups for median change from baseline in liver function parameters. However, in Study 123, subjects in DM /Q 10 mg group who had shifts in ALT, AST and total bilirubin from normal at baseline to abnormally high at End of Study (Day 84) were numerically higher than in the placebo group.

Overall, based on the available data contained in safety database, the potential for DM/Q to cause severe drug induced liver injury is low.

Renal function: In his review of the original NDA submission, Dr. Farkas, discussed the increase of creatinine in the DM/Q arm versus placebo arm in Study 106 (MS subjects), and increase of urea in the DM/Q arms of both Study 102 and Study 106. Dr. Farkas concluded that overall, he found little evidence for overt renal toxicity from DM/Q but can not discount some effect of DM/Q on renal function. I reviewed all the laboratory data from Study 123 – unique to the Complete Response, and find that the median changes from baseline in the laboratory parameters including creatine and urea over time were fairly similar between treatment groups. There were also no apparent differences between the treatment groups for shifts from normal at baseline to abnormal in creatine or urea values in the pooled controlled studies or in Study 123. Across the integrated clinical trials (Pool 1), there were two subjects with acute renal failure.

> Subject #107-048-021 (Old ID: 48-4821) enrolled in Study 107 was an 18-year old male with MS, who discontinued due to an SAE of acute renal failure after (b) (6) days of exposure to DM 30 mg/Q 30 mg. Viral

encephalitis was suspected and he was given IV acyclovir for three days, at the end of which he developed acute renal failure which resolved after (b) days. Reviewer's comments: acute renal failure is most likely due to IV acyclovir.

Subject #109-133-009 was on placebo.

7.4.3 Vital Signs, O_2 saturation assessment and Physical examinations

Vital signs assessments were performed in clinical studies at all protocol-defined visits within each trial. In all three controlled trials and the two open-label trials of PBA, vital signs assessment included systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, respiration, temperature and weight. Orthostatic blood pressure measurements were not performed. Height was measured at the Screening Visit only in all the three controlled trials of PBA subjects. Vital Capacity was measured at the Screening Visit, Day 15 and Day 29 in Study 102 but not in other studies of PBA subjects. Complete physical examinations were conducted on the Screening Visit and Final Visit in Study 102, Study 106 and Study 123-DB. All vital sign assessments were considered for analyses, regardless of whether the assessment was scheduled or unscheduled.

Resting diurnal O_2 saturation was performed at Screening Visit, Days 15 and 84 during the double-blind phase, and on Day 1 and 84 of the OLE phase. Nocturnal O_2 saturation was performed at Screening Visit and Day 15 in the DB phase only. For the nocturnal O_2 saturation recordings these assessments were continuous. The subject (and/or caregiver) was instructed on how to operate the pulse oximeter while at home and how to record the O_2 saturation during sleep. No minimum and/or maximum recording time was required (the usual patient's sleep pattern was used). Once the device was received at the clinic, the reading was downloaded to a PC. The mean O2 saturation value was recorded in the CRF. Deviations from baseline were assessed by the investigators and reported as adverse events if appropriate as for any adverse event.

Physical examinations of subjects continuing on to the open-label Study 107 were performed annually and at the Termination Visit. Physical examination data were not specifically analyzed in the pooled safety data sets. However, abnormal findings from physical examinations reported as AEs are included in the AE sections.

The measures of central tendency for the change from baseline at the Final Visit for vital signs are summarized in the table below for all controlled studies of PBA. With the exception of pulse rate (discussed below), mean and median of change from baseline in vital sign parameters were fairly similar between treatment groups.

Table 72: Mean and median changes in vital sign parameters by treatment in PBA subjects (Pool 3)

	AVP-923							
Parameter and Assessment	20 mg DM/ 10 mg Q (N=107)	30 mg DM/ 10 mg Q (N=110)	All doses with 10 mg Q (N=217)	All doses with 30 mg Q (N=146)	All AVP-923 (N=363)	Placebo (N=183)	DM 30 mg (N=33)	Q 30 mg (N=37)

Systolic Blood Pressure

Final Visit Change from Baseline								
N	88	101	189	107	296	147	30	34
Mean	0.8	-0.5	0.1	0.6	0.3	-0.7	3.8	2.5
SD	11.71	12.31	12.02	12.84	12.30	11.59	15.60	12.45
Median	0.0	0.0	0.0	2.0	0.0	0.0	5.5	2.0
Minimum, Maximum	-25, 35	-53, 40	-53, 40	-34, 30	-53, 40	-30, 46	-36, 30	-18, 40

Diastolic Blood Pressure

Final Visit Change from Baseline								
N	88	101	189	107	296	147	30	34
Mean	0.0	0.6	0.3	-0.1	0.2	-1.4	2.6	-1.2
SD	8.06	10.20	9.25	8.69	9.03	9.24	8.10	7.13
Median	0.0	0.0	0.0	0.0	0.0	0.0	2.0	0.0
Minimum, Maximum	-20, 27	-32, 23	-32, 27	-18, 26	-32, 27	-26, 20	-20, 20	-18, 12

Pulse Rate

Final Visit Change from Baseline								
N	88	101	189	107	296	147	30	34
Mean	-3.8	-1.5	-2.6	0.2	-1.6	-0.8	3.6	-1.0
SD	10.16	10.31	10.28	11.49	10.80	9.00	12.15	10.36
Median	-4.0	-2.0	-3.0	0.0	-2.0	-1.0	2.0	0.0
Minimum, Maximum	-28, 24	-29, 30	-29, 30	-32, 48	-32, 48	-25, 24	-23, 32	-29, 28

Respiration

Final Visit Change from Baseline								
N	88	101	189	107	296	147	30	33
Mean	0.0	0.3	0.2	-0.2	0.0	0.1	1.1	0.0
SD	2.39	2.32	2.35	3.52	2.83	2.69	3.38	3.28
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Minimum, Maximum	-6, 7	-6, 8	-6, 8	-16, 12	-16, 12	-8, 8	-4, 9	-12, 8

Temperature

Final Visit Change from Baseline								
N	88	101	189	107	296	147	29	33
Mean	0.03	-0.05	-0.01	-0.01	-0.01	-0.01	0.00	-0.03
SD	0.450	0.409	0.429	0.496	0.454	0.466	0.608	0.560
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-0.10
Minimum, Maximum	-1.3, 1.2	-1.0, 1.2	-1.3, 1.2	-1.3, 1.4	-1.3, 1.4	-1.7, 1.2	-1.1, 1.4	-0.9, 1.3

Weight

Final Visit Change from Baseline								
N	88	100	188	103	291	144	29	34
Mean	-0.55	-0.63	-0.59	-0.36	-0.51	-0.53	-0.59	-1.84
SD	2.903	2.434	2.657	2.144	2.486	2.485	2.379	7.168
Median	0.00	0.00	0.00	-0.40	-0.20	-0.30	0.00	-0.50
Minimum, Maximum	-7.4, 11.5	-8.0, 6.0	-8.0, 11.5	-7.5, 8.0	-8.0, 11.5	-9.0, 10.0	-9.9, 2.2	-41.4, 3.1

Note: Treatment categories are not mutually exclusive. Thus, patients may contribute to more than one treatment category.
Note: DM = Dextromethorphan Hydrobromide USP; Q = Quinidine Sulfate USP. NOS = not otherwise specified. NA = Not Available.
Note: The early termination (ET) visit includes measurements collected on the last on-treatment date where vitals were collected for non-completers.
Note: The final visit includes the last on-treatment measurements for completers.
Note: The end of study visit includes the last on-treatment measurements for all completers and non-completers.
Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS; Table 43.1.3

Vital sign data from the original NDA submission (Study 102 and Study 106) was reviewed by Dr. Farkas. He noted an increase in median systolic blood pressure change from baseline across the three arms in Study 102 ALS trial (DM 30 mg/Q 30 mg, 4.0 mm; DM 30 mg, 6.0 mm; and Q 30 mg, 2.0 mm) but not in the MS study. Dr. Farkas concluded that the lack of concurrent placebo arm in this study hinders interpretation of this apparent blood pressure change. In the double-blind phase of Study 123, the mean and median change from baseline systolic BP for the ALS subjects in Study 123 is summarized in the following table. There are no consistent differences between treatment arms.

Table 73: Summary of change from baseline for systolic BP for the ALS population in double-blind phase of Study 123

VISIT		DM 20/Q 10	DM 30/Q 10	Placebo
DAY 15	Median (mmHg)	0	0	0
	Mean (mmHg)	-1.8	0.4	1.2

DAY 29	Median (mmHg)	4	2	0
	Mean (mmHg)	2.3	2.4	0.9
DAY 57	Median (mmHg)	0	2	0
	Mean (mmHg)	0.3	1.9	-0.7
DAY 84/85	Median (mmHg)	0	0	-1
	Mean (mmHg)	3.4	-0.1	-0.7

Source: NDA Complete Response 4/30/10; module 5.3.5.3; ISS; reviewer's analysis of VS dataset (subset Pool 3 Y and STUDYID 123); summary USUBJID, PDCAT, EXDOSTXT, AVISIT2, VSTESTCD, AVAL, MAVAL2 and ACHG; Tabulate VSTESTCD, PDCAT, AVISIT2 to rows and EXDOSTXT to columns; add ACHG to rows as analysis column: mean and median.

During the double-blind phase of Study 123, there was a small but consistent decrease in the median heart rate at every visit for both DM/Q dose groups compared to placebo subjects (see table below). However, with the exception of DM 20 mg/Q 10 mg and placebo at Day 84/84, the 95% confidence intervals between the DM/Q groups and placebo overlap. This decrease in pulse rate does not appear to be dose-related. The median decline was similar in magnitude for both the ALS and MS subsets (data not included in review).

Table 74: Summary of change from baseline for pulse rate in Study 123

Measure Visit	AVP-923-30 (N = 110)	AVP-923-20 (N = 107)	Placebo (N = 109)
Visit 2 (Day 15)			
Change from Baseline			
N	101	87	97
Mean (Std Dev)	-2.6 (10.90)	-1.9 (12.54)	0.3 (9.09)
95% C.I.	(-4.76, -0.45)	(-4.57, 0.78)	(-1.52, 2.14)
Min, Max	-25.0, 25.0	-28.0, 37.0	-21.0, 24.0
Median	-2.0	-3.0	1.0
Visit 3 (Day 29)			
Change from Baseline			
N	98	86	91
Mean (Std Dev)	-1.7 (10.48)	-3.0 (9.83)	0.7 (8.63)
95% C.I.	(-3.80, 0.41)	(-5.07, -0.86)	(-1.07, 2.52)
Min, Max	-28.0, 28.0	-21.0, 26.0	-17.0, 27.0
Median	-1.5	-4.0	1.0
Visit 4 (Day 57)			
Change from Baseline			
N	95	83	90
Mean (Std Dev)	-2.5 (11.76)	-2.9 (10.70)	0.7 (9.65)
95% C.I.	(-4.85, -0.06)	(-5.22, -0.54)	(-1.37, 2.68)
Min, Max	-34.0, 24.0	-26.0, 22.0	-19.0, 32.0
Median	-4.0	-3.0	1.0
Visit 5 (Day 84)			
Change from Baseline			
N	92	83	81
Mean (Std Dev)	-1.7 (10.79)	-4.1 (10.42)	0.1 (8.54)
95% C.I.	(-3.91, 0.56)	(-6.35, -1.80)	(-1.80, 1.97)
Min, Max	-29.0, 30.0	-28.0, 24.0	-20.0, 24.0
Median	-3.0	-4.0	-2.0

Source: NDA Complete Response 4/30/10; module 5.3.5.3; Study 123 Study Report, Table 34

Shifts in vital signs from baseline

In controlled studies in PBA subjects (Pool 3), there were more number of shifts for systolic blood pressure, which increased from <140 mmHg at baseline to >140 mmHg during treatment,

in both the DM/Q 10 mg (22.5%) and DM/Q 30 mg (16.4%) dose groups as compared to pooled placebo arm (9.4%), and did not appear to be related to the Q dose in the DM/Q combination. There were no apparent differences between the treatment groups for shifts in pulse rate.

Outliers and Clinically Important Vital Sign Values

Across the controlled trials, there were very few subjects (1 or 2 per treatment arm) with clinically important vital sign values, limiting any meaningful conclusions about differences between treatment arms. Based on the measures of central tendencies, shifts and clinically important values, decreases in heart rate, decreases and increases in systolic and diastolic blood pressure deserve further discussion.

Decreases in heart rate / bradycardia: Bradycardia is a known association with the use of Q. The Applicant defined clinically important heart rate decrease as a heart rate under 50 bpm and decreased by at least 15 bpm compared with baseline. Across all controlled trials of PBA (Pool 3), subjects who met this criterion were as follows: placebo (1/180 = 0.6%), and no subject met the criteria in any of the DM/Q, DM or Q treatment groups.

Since the Applicant-defined criteria for clinically important heart rate decrease (heart rate under 50 bpm ***and*** decreased by at least 15 bpm compared with baseline) appears restrictive, I used a criteria for a change from baseline of ≤ -20 to identify outliers. The following table summarizes these subjects in the pooled controlled trials (Pool 3) and double-blind phase of Study 123. In Pool 3, the incidences of subjects with a change from baseline in pulse rate of ≤ -20 in either DM/Q 10 mg groups were numerically higher than the DM/Q 30 mg group and the placebo group. In the double-blind phase of Study 123, however, the incidence of subjects with a change from baseline in pulse rate of ≤ -20 in either of the DM/Q 10 mg groups was over five-fold that in the placebo group.

Table 75: Incidence of subjects with a change from baseline in pulse rate of ≤ -20 in the controlled trials of PBA (Pool 3) and double-blind phase of Study 123

DM 20/Q 10 N=107 n (%)	DM 30/Q 10 N=110 n (%)	DM 30/Q 30 N=146 n (%)	Placebo N=183 n (%)	DM 30 N=33 n (%)	Q 30 N=37 n (%)
Pool 3					
14 (13.1)	11 (10)	11 (7.5)	12 (6.6)	1 (3)	5 (13 5)
Study 123 double-blind phase					
14 (13.1)	11 (10)	NA	2/109 (1.8)	NA	NA

Source: NDA Complete Response 4/30/10; Reviewer's analysis of VS dataset (subset Placebo 3 Y, select row state for ACHG2 ≤ -20)' Tabulate

Across all the integrated clinical trials (Pool 1), there were 15 subjects who experienced 'bradycardia' as an AE and one additional subject who experienced 'heart rate reduced'. None of the bradycardia events were classified as a SAE. In Pool 1, there were four subjects who discontinued due to bradycardia or sinus bradycardia. These subjects are discussed under Bradycardia in section 7.3.5 of this review. In the pooled controlled trials of PBA (Pool 3), the incidence of subjects experiencing bradycardia, sinus bradycardia or heart rate decreased were, 1 (1/107 = 0.9%) subject in the DM 20 mg/Q 10 mg group, 2 (2/146 = 1.4%) subjects in the DM 30 mg/Q 30 mg group and 2 (2/183 = 1.1%) in the placebo group. In the double-blind phase of Study 123, there was one subject each in the DM 20 mg/Q 10 mg and placebo groups.

Decreases in systolic and or diastolic blood pressure / hypotension: Hypotension is a known association with the use of Q. The Applicant defined clinically important decreases in systolic and diastolic blood pressure as systolic blood pressure under 90 mm Hg and decreased by at least 20 mm Hg compared with baseline, or a diastolic blood pressure under 50 mm Hg and decreased by at least 15 mm Hg compared with baseline. In Pool 3, subjects who met the criteria for decreases in systolic blood pressure were as follows: any dose of DM/Q 10 mg (1/209 = 0.5%), any dose of DM/Q 30 mg (1/140 = 0.7%), placebo (0/180), and Q 30 alone (1/37 = 2.7%). For reductions in diastolic blood pressure, subjects who met the criteria were: any dose of DM/Q 10 mg (1/209 = 0.5%), any dose of DM/Q 30 mg (0/140 = 0.7%), placebo (1/180 = 0.6%), and none in the remaining treatment groups.

Since the Applicant's criteria appeared restrictive, I used the criteria of a change from baseline of ≤ -20 to identify outliers for systolic hypotension and ≤ -15 for diastolic hypotension. The following table summarizes these subjects in the pooled controlled trials (Pool 3) and double-blind phase of Study 123. The incidence of subjects with a change from baseline in systolic BP ≤ -20 in any DM/Q dose groups were numerically higher than in the placebo group in Pool 3 and in the double-blind phase of Study 123. In contrast, the incidence of subjects with a change from baseline in diastolic BP ≤-15 was higher in the placebo group than in any DM/Q dose group in Pool 3 and in Study 123.

Table 76: Incidence of subjects with a change from baseline in systolic BP and diastolic BP in the controlled trials of PBA (Pool 3) and double-blind phase of Study 123

	DM 20/Q 10 N=107 n (%)	DM 30/Q 10 N=110 n (%)	DM 30/Q 30 N=146 n (%)	Placebo N=183 n (%)	DM 30 N=33 n (%)	Q 30 N=37 n (%)
Pool 3						
Systolic BP ≤ -20	19 (17.8)	17 (15.5)	21 (14.4)	21 (11.5)	4 (12.1)	4 (10.8)
Diastolic BP ≤ -15	17 (15.9)	14 (12.7)	13 (8.9)	34 (18.6)	1 (3)	3 (8.1)
Study 123 double-blind phase						
Systolic BP ≤ -20	19 (17.8)	17 (15.5)	0	14/109 (12.8)	NA	NA
Diastolic BP ≤ -15	17 (15.9)	14 (12.7)	0	21/109 (19.3)	NA	NA

Source: NDA Complete Response 4/30/10; Reviewer's analysis of VS dataset (subset Placebo 3 Y, select row state for ACHG ≤ -20 for systolic BP and ≤ -15 for diastolic BP); Tabulate

Across the integrated clinical trials (Pool 1), there were no subjects who experienced hypotension or blood pressure reduced as SAEs. There was one subject who discontinued due to hypotension (narrative provided below). In the pooled controlled trials (Pool 3), the incidence of subjects with a TEAE of hypotension, blood pressure systolic decreased or blood pressure diastolic decreased was 1 subject (1/110 = 0.9%) in DM 30 mg/Q 10 mg group, 4 (4/183 = 2.2%) in placebo group and none in other DM/Q groups. There were no subjects who experienced SAEs or discontinued due to decreases in systolic or diastolic blood pressure or hypotension in Study 123.

> Subject #109-147-006: 68-year old male with painful diabetic neuropathy enrolled in Study 109 discontinued on Day 8 of DM 90 mg/Q 60 mg due to ***hypotension*** and tachycardia. A more detailed narrative provided in section 7.3.5 of this review. Symptoms resolved upon discontinuation. Reviewer's comments: A temporal relationship between these events and ***high dose*** of DM/Q (DM 90 mg/Q 60 mg) is likely present.

Increases in systolic or diastolic blood pressure / hypertension: Although there were no significant between-treatment group differences in the measures of central tendencies for increase from baseline in systolic blood pressure, there were more number of shifts for systolic blood pressure, which increased from <140 mmHg at baseline to >140 mmHg during treatment, in both the DM/Q 10 mg (22.5%) and DM/Q 30 mg (16.4%) dose groups as compared to pooled placebo arm (9.4%). In Pool 3, the incidence of potentially clinically important increases from baseline in *systolic* blood pressure was comparable between the DM/Q 10 mg (5/209 = 2.4%) and placebo group (4/180 = 2.2%); and for *diastolic* blood pressure, the numbers of subjects were low in treatment groups (DM/Q 10 mg group, 3/209 = 1.4%; DM/Q 30 mg, 2/140 = 1.4%; and placebo group, 0/180).

Across the integrated clinical trials (Pool 1), there were four subjects who experienced hypertension, hypertensive crisis or blood pressure increased as SAEs. Five other subjects on DM/Q discontinued due to blood pressure increased, or hypertension. The narratives for these subjects are provided below. In the controlled trials (Pool 3), the incidence of subjects experiencing a TEAE of blood pressure increased, blood pressure systolic increased or hypertension was, 1 (1/107 = 0.9%) subject in the DM 20 mg/Q 10 mg group, 2 (2/110 = 1.8%) in the DM 30 mg/Q 10 mg group, 3 (3/146 = 2.1%) in the DM/Q 30 mg group, and 2 (2/183 = 1.1%) in the placebo group. There were no subjects who experienced SAEs or discontinuations due to increases in systolic or diastolic blood pressure or hypertension in Study 123.

> Subject #109-133-001 (old ID: 133-9001): 78-year old Caucasian female with painful diabetic peripheral neuropathy was enrolled in Study 109. Medical history included diabetes, myocardial infarction, angioplasty, cardiac murmur, hypertension, GERD and hyperlipidaemia. Concomitant medications at the time of the event included premarin cream topical, aspirin 325 mg, valsartan, Toprol XL 100 mg daily, Prevacid, multivitamin, L-thyroxine, Amaryl 8 mg daily, metformin 1000 mg BID, Lipitor, hydrochlorothiazide 25 mg daily, and amlodipine 10 mg daily. Dosing with DM 45 mg/Q 30 mg began on 9/30/05. On Day 29, the investigator noted that the subject's blood pressure had increased from a baseline pressure of 120/80 mmHg to 158/95 mmHg. The subject reported self-measured blood pressure readings in the high 180s systolic, and high 80s to 100s diastolic, accompanied by headaches. Study drug was discontinued on Day 32, and the subject's blood pressure improved. On Day (b) (6), a myocardial perfusion scan revealed abnormal perfusion with a small mild fixed septal defect. On Day (b) (6), she was hospitalized for management of ***hypertensive crisis*** and chest discomfort. Urine for amphetamine and for pheochromacytoma was unremarkable. She was discharged two days later, and the hypertensive crisis resolved. The Investigator considered the hypertensive crisis to have a possible relationship to study drug, respectively. Reviewer's comments: Although increase in blood pressure following start of study drug suggests a temporal relationship with DM/Q, pre-existing hypertension makes it difficult to ascertain causality.
>
> Subject #107-016-028 (Old ID: 16-1628): 65-year old Caucasian female with ALS was enrolled in Study 107. Other medical history included hypertension for at least 20 years prior to randomization. During hospitalization for PEG placement due to dysphagia, she developed chest pain and hypertension (on Day (b) (6) of DM 30 mg/Q 30 mg). Cardiac evaluation was negative. ***Hypertension*** was successfully treated with the addition of nifedepine to concomitant metoprolol, and was discharged. She continued in the study for a total of 556 days. The investigator determined that hypertension was not related to the study drug.
>
> Subject #107-028-013 (Old ID: 28-2813): 53-year old Caucasian female with ALS was enrolled in Study 107. Other medical history included hypertension, diabetes, GERD, anxiety disorder and gastroparesis. Concomitant medications included Cozaar, glucophage, Zoloft, Norvasc and Nexium. On Day (b) (6) of DM

30 mg/Q 30 mg, she was hospitalized for chest pain and severe headache. Cardiac evaluation was negative, and GERD was considered the likely cause of her symptoms. She was discharged (b) (6) days later. She was terminated early due to non-compliance. The narrative does not mention blood pressure abnormality. However, the CRF indicates "***elevated blood pressure***" that was not thought to be serious (may have been wrongly coded in the AE dataset as serious). Vital sign dataset reading of BP is 163/83.

Subject #106-017-006 (Old ID: 17-1709): 50-year old Caucasian female with MS was enrolled in Study 106. Other medical history included mitral valve prolapse, palpitations, panic anxiety and hypothyroid disorder. During a visit (Day (b) (6) of DM 30 mg/Q 30 mg treatment), she complained of "pain in chest as if someone is sitting on my chest". The subject's ***blood pressure*** was 146/92 which was ***elevated*** compared to her usual of 110/60. She was evaluated in the hospital; cardiac work up was negative. She was discharged on nitroglycerin. She continued in the study. The investigator thought relationship between DM/Q and this event was unlikely.

Subject #109-147-004 (old ID: 147-9004) is a 47 year-old female subject with painful diabetic neuropathy who was enrolled in Study 109. On Day 2 of DM 90 mg/Q 60 mg she discontinued due to diarrhea, ***hypertension*** exacerbation, nausea, and tachycardia. The study drug was discontinued and the events resolved. A more detailed narrative is provided in section 7.3.5 of this review. Reviewer's comments: A temporal relationship between hypertension and ***high dose*** of DM/Q (90 mg/60 mg) is likely present.

Subject #109-118-031 (old ID: 118-9031) is a 52 year-old female subject with painful diabetic neuropathy who was enrolled in Study 109. Medical history included iron deficiency anemia, diabetes and hypertension. Concomitant medications at the time of the events included Glucophage, Avandia 8 mg daily, glimepiride 4 mg daily, Lotrel 10/20 one tablet daily, and ferrous sulfate. On Day 5 of DM 30 mg/Q 30 mg, she experienced dyspnea and dizziness; study drug was discontinued. The next day (1 day after discontinuation), she experienced ***hypertension***. All adverse events resolved over the next 1-2 days. The investigator considered the hypertension to have a possible relationship to study drug.

Subject #107-034-026 (old ID: 3426) is a 61 year-old female subject with history of small fiber neuropathy and PBA, hypertension, hypercholesterolemia and diabetes who was enrolled in Study 107. She developed mild dizziness on Day 1 of DM 30 mg/Q 30 mg, diarrhoea on Day 2, mild memory impairment on Day 11, headache on Day 18, mild disorientation on Day 23, and moderate ***blood pressure increased*** on Day 31. She discontinued study medication because of these AEs. Her blood pressure was 158/86 mmHg at screening, 158/82 mmHg on Day 1, and 210/98 on Day 31. Her enalapril was increased from 10 mg QD to 10 mg BID on Day 31. The investigator indicated that the event of 'blood pressure increased' was not related to study medication.

Subject #107-030-011 (old ID: 3011) is a 77 year-old male subject with stroke and PBA, high cholesterol and hypertension who was enrolled in Study 107. Concomitant medications included lisinopril, dyazide, Aggrenox and paroxetine. He developed mild hypertension on Day 8 of DM 30 mg/Q 30 mg. He discontinued study medication because of this AE and recovered on Day 19. His systolic/diastolic blood pressure was 140/90 mm Hg at screening, 158/88 mm Hg on Day 1, and 134/82 mm Hg at his termination visit on Day 27 (BP reading on Day 8 is not provided in the narrative or the dataset). The investigator indicated that this subject's hypertension had an unlikely relationship to study medication.

Subject #107-017-017 (old ID: 1717) is a 58 year-old female subject with stroke and PBA, epilepsy and fatigue who was enrolled in Study 107. Concomitant medications included phenytoin and ibuprofen. She developed abdominal distension, abdominal pain upper, mild dry mouth and throat, and mild dizziness on Day 2 of DM 30 mg/Q 30 mg. She developed moderate weakness and mild dyspnoea on Day 7, and mild blood pressure increased on Day 10. She discontinued because of these events. She had not recovered from these AEs as of her final contact on Day 12. Her blood pressure was 125/83 mmHg at screening, 132/87 mmHg on Day 1, and 132/92 mmHg on Day 11. The investigator indicated that event of 'blood pressure increased', had a possible relationship to study medication.

Applicant's conclusions: The number of patients with bradycardia was low in all treatment groups. The incidences of subjects with negative shifts in systolic blood pressure or diastolic blood pressure were low, and showed no differences between treatment groups. There was a slight trend for the number of subjects with increases in systolic and/or diastolic blood pressure to be higher in PBA patients exposed to DM/Q than for placebo.

Reviewer's comments: In both Pool 3 and double-blind phase of Study 123, there was a small but consistent decrease in the median heart rate at every visit for the DM/Q dose groups compared to placebo subjects. This decrease in pulse rate does not appear to be dose-related. With the exception of DM 20 mg/Q 10 mg and placebo at Day 84 in the double-blind phase of Study 123, the differences in the change from baseline in heart rate decrease between treatment groups appear to be a chance finding. The incidence of outliers for heart rate reduction using a less restrictive criterion (change from baseline of ≤ -20 beats per min) in the DM/Q 10 mg groups in the double-blind phase of Study 123 was more than five-fold that in the placebo group. This excess of outliers for heart rate reduction in the DM/Q groups compared to placebo group was also present in Pool 3 but was less striking. Across all the integrated clinical trials (Pool 1), no subject experienced bradycardia as an SAE, and four subjects discontinued due to bradycardia or sinus bradycardia. With the exception of one subject in Study 123 who discontinued DM 20 mg/Q 10 mg treatment due to sinus bradycardia and first degree AV block in the context of history of left anterior hemiblock, the remaining three subjects were taking the higher Q dose (DM 30 mg/Q 30 mg). There were no between treatment group differences in the incidences of subjects experiencing related AEs in the pooled controlled trials or the double-blind phase of Study 123. Overall, there were no clinically significant reductions in heart rate or bradycardia with the DM/Q 10 mg doses.

There were no significant between-treatment group differences in the measures of central tendencies for decrease from baseline in systolic or diastolic blood pressure, or shifts from normal at baseline to abnormally low values post treatment. While the number of subjects experiencing reduction from baseline in *diastolic* blood pressure was comparable between-treatment groups, the incidence of subjects with a decrease from baseline in *systolic* blood pressure in the DM/Q groups were numerically higher than in the placebo group. Across all the integrated clinical trials (Pool 1), no subject experienced blood pressure decreases or hypotension as SAE, and the one subject who discontinued due to hypotension was on a high dose of study drug (DM 90 mg/Q 60 mg). There were no between-treatment group differences in the incidences of subjects experiencing hypotension/decreased blood pressure-related AEs in the pooled controlled trials. Thus, the potential for DM/Q 10 mg doses to cause clinically significant reductions in blood pressure or hypotension is very low.

Although there were no significant between-treatment groups differences in the measures of central tendencies for increase from baseline in systolic blood pressure, there were more numbers of shifts from normal at baseline to abnormally high post-treatment for systolic blood pressure in the DM/Q groups compared to the pooled placebo group. The incidence of potentially clinically important increases from baseline in *systolic* blood pressure was comparable between treatment groups, however, for diastolic blood pressure, the incidences in DM/Q groups were low and numerically higher than in placebo group. Across the integrated clinical trials (Pool 1), there

were four subjects who experienced hypertension, hypertensive crisis or blood pressure increased as SAEs and five subjects who discontinued. Causality in the SAEs were confounded by the intercurrent illnesses and concomitant medications; two of these subjects continued on in the study uneventfully. In several of these discontinuations, a possible temporal relationship is suggested by the occurrence of the AEs of interest relatively soon after the start of the study drug; one of these subjects was given on a high dose of DM/Q (DM 90 mg/Q 60 mg). Overall, the potential for DM/Q 10 mg doses to cause clinically significant elevations in blood pressure or hypertension remains uncertain.

O_2 saturation assessments: O_2 saturation assessments were performed in Study 123. During the double-blind phase, resting diurnal O_2 saturation was performed at Screening Visit, Days 15 and 84, and nocturnal O_2 saturation was performed at Screening Visit and Day 15. The results of these assessments are summarized in the following tables. With the exception of the DM 30 mg/Q 10 mg dose group in nocturnal saturation, the O_2 saturation was trending to lower values across time in all treatment groups. Compared to placebo group, the change from baseline in nocturnal O_2 saturation in the DM 20 mg/Q 10 mg dose group was statistically significant ($p = 0.019$); however, in the higher dose group, DM 30 mg/Q 10 mg, the trend at later time point was the opposite with a small mean increase. The clinical significance of this discrepancy or the small changes from baseline is not apparent. The mean changes from baseline in diurnal O_2 saturation were numerically comparable between the treatment groups.

Table 77: Diurnal O_2 saturation among ALS subjects during the double-blind phase of Study 123

Variable	Zenvia 30/10 (n=65)	Zenvia 20/10 (n=68)	Placebo (n=64)
Percent Oxygen Saturation, mean ± standard deviation (minimum, maximum)			
Baseline	96.3 ± 1.5 (90.0, 100.0)	96.6 ± 1.3 (94.0, 100.0)	96.5 ± 1.2 (93.0, 99.0)
Day 15	95.5 ± 1.5 (92.0, 99.0)	96.0 ± 1.7 (90.0, 98.0)	96.0 ± 1.8 (90.0, 99.0)
Day 84	95.4 ± 1.8 (92.0, 99.0)	95.5 ± 2.6 (83.0, 98.0)	96.0 ± 1.6 (92.0, 99.0)
Change from baseline (95% confidence interval)			
Baseline to Day 15	-0.8 (-1.2, -0.4)[a]	-0.6[e] (-1.0, -0.1)[c]	-0.5[f] (-0.9, -0.1)
Baseline to Day 84	-0.9 (-1.3, -0.5)[b]	-1.1 (-1.8, -0.4)[d]	-0.5 (-1.0, -0.1)

[a]:P=0.319; [b]: P=0.198; [c]: P=0.868; [d]: P=0.197 (versus placebo)
[e]: erroneous value of -0.06 in the original table
[f]: erroneous value of -0.05 in the original table
Source: NDA Complete Response 4/30/10; module 5.3.5.3.ISS; Respiratory Report, modified from Table 13, page 38

Table 78: Nocturnal O_2 saturation among ALS subjects during the double-blind phase of Study 123

Variable	Zenvia 30/10 (n=65)	Zenvia 20/10 (n=68)	Placebo (n=64)
Percent Oxygen Saturation, mean ± standard deviation (minimum, maximum)			
Baseline	93.4 ± 6.7 (43.0, 98.0)	94.5 ± 2.1 (88.0, 99.0)	93.9 ± 2.0 (86.0, 98.0)
Day 15	93.8 ± 2.1 (88.0, 98.0)	93.6 ± 2.6 (85.0, 97.0)	93.8 ± 1.8 (89.0, 97.0)

Change from baseline (95% confidence interval)			
Baseline to Day 15	0.4[i] (-0.99, 0.17)[g]	-0.9 (-1.4, -0.3)[h]	-0.1 (-0 5, 0.4)

[g]: P=0.329; [h]: P = 0.019 (versus placebo)
[i]: erroneous value of -0.4 in the original table; therefore, the p-value (g) is erroneous
Source: NDA Complete Response 4/30/10; module 5.3.5.3.ISS; Respiratory Report, modified from Table 14, page 38

Reviewer's comments: The changes from baseline in O_2 saturation are small and numerically comparable between treatment groups. A consult with Division of Pulmonary, Allergy and Rheumatology Products to assess deaths in ALS (which are largely respiratory-related) and O_2 saturation assessments has not been finalized.

7.4.4 Electrocardiograms (ECGs)

ECGs (12-lead) were performed at the Screening Visit and the Final Visit (Day 29) in Study 102; and at the Screening Visit, Day 29 and Final Visit in Study 106. However, in Study 123, ECGs (12-lead with 2-minute rhythm strip) were performed more frequently: at Screening Visit, Days 1, 15, 29, 57 and 84 of the double-blind phase, and on Days 1, 15, 42, and 84 of the open-label phase. Additional ECGs were obtained at the discretion of the investigator. ECGs in the controlled studies of PBA were performed during scheduled clinic visits without regard to the timing of the dose.

ECG parameters included in the integrated safety data sets were heart rate, PR interval, QRS complex, QT interval, QTc interval, QTcB (Bazett's correction) and QTcF (Fridericia's correction). For clinically important values and changes for analysis, the most abnormal value recorded on any particular day was used in each analysis.

Thorough QT studies in healthy volunteers:
The Applicant conducted two thorough QT studies in healthy volunteers to evaluate the potential of DM/Q to cause cardiac repolarization abnormalities. Study 119 was the subject of review during the original NDA submission. Two DM/Q doses were evaluated in Study 119: DM 30 mg/Q 30 mg and DM 60 mg/Q 60 mg, both administered twice daily. Following the Agency's recommendation to reduce the dose of Q in the formulation, Study 126 was conducted to evaluate the potential for the new formulation, DM 30 mg/Q 10 mg, to cause cardiac repolarization abnormalities.

Study 119: A total of 36 healthy volunteers (27 male and 9 female), aged 19-55 years, received study drugs during 3 double-blind treatment periods (DM 30 mg/Q 30 mg, or DM 60 mg/Q 60 mg, or placebo, twice daily for 7 consecutive doses) in a randomized 3-way crossover sequence. In the fourth treatment period, all subjects received an open-label, single dose of 400 mg moxifloxacin as a positive control. The treatment periods were separated by 3 days. Holter and bedside ECGs were recorded during each treatment period; all ECG readers were blinded to all treatments in the study (including the positive control). A total of 33 subjects completed the study; reasons for non-completion (n = 3) were unrelated to study drug.

A single dose of oral moxifloxacin 400 mg confirmed assay sensitivity for the study. At the daily dose of DM 30 mg/Q 30 mg, the drug was associated with a maximum mean paired placebo and baseline subtracted QTcF of about 10 msec (3 hours post-dose), with a 95% upper bound one-sided confidence interval of about 15 msec. This QT prolongation persisted throughout the dosing interval. Over 4% of the ECGs in patients who received this recommended dose had QTc intervals that were increased between 30-60 msec above baseline, compared to 0.9% of those ECGs in the placebo arm. For the "supratherapeutic" daily dose of DM 60 mg/Q 60 mg, the maximum mean paired placebo and baseline subtracted QTcF was about 19 msec (6 hours post-dose), with a 95% upper bound one-sided confidence interval of about 25 msec. At the supratherapeutic dose of the combination, 7.2% of the ECGs were associated with an increase in QTc of 30-60 msec.

Study 126: Randomized, double-blind (except for open-label moxifloxacin), placebo-controlled, positive controlled, multiple dose, 3-treatment, crossover study. A total of 50 healthy volunteers (34 male and 16 female), aged 19 - 45 years, received 3 treatments in a randomized 3-way crossover sequence. The 3 treatments were DM 30 mg/Q 10 mg BID for 7 doses, placebo capsules BID for 7 doses, and placebo capsules BID for 3 days followed by a single 400-mg tablet of moxifloxacin on the fourth day. The treatments were double-blind except for moxifloxacin. The treatment periods were separated by 4 days. ECGs were recorded during each treatment period. The primary ECG endpoint was the individually corrected QT (QTcI), with QTcB and QTcF as secondary endpoints. A total of 47 subjects completed the study; 3 subjects withdrew consent and discontinued from the study.

A single dose of oral moxifloxacin 400 mg confirmed assay sensitivity for the study. The maximal mean placebo-corrected change from baseline for the various corrected QT intervals is summarized in the following table. The maximum mean placebo-corrected change from baseline QTcF for *DM 30 mg/Q 10 mg* in Study 126 (10.4 msec; upper bound 95% CI 14.4) is about the same as that seen for *DM 30 mg/Q 30 mg* in Study 119 (10.1 msec; upper bound 95% CI 15.1), but clearly less than for *DM 60 mg/Q 60 mg* in Study 119 (18.8 msec; upper bound 95% CI 24.5).

Table 79: Maximal mean placebo-corrected change from baseline QT interval in Study 126

	Hour	Estimate[a] (msec)	N	Upper (lower) bound of one-sided 95% CI (msec)
dQTcI				
DM 30 mg/Q 10 mg BID	3	10.3	50	14.3
Moxifloxacin (positive control)	1.5	12.2	49	(8.3)
dQTcF				
DM 30 mg/Q 10 mg BID	3	10.4	50	14.4
Moxifloxacin (positive control)	1.5	12.6	49	(8.6)
dQTcB				
DM 30 mg/Q 10 mg BID	3	8.9	50	13.7
Moxifloxacin (positive control)	1	14.8	49	(10.1)

CI = confidence interval; dQTcI = maximal mean placebo-subtracted rate-corrected QT interval using individual correction factors; dQTcB = maximal mean placebo-subtracted rate-corrected QT interval using Bazett's formula; dQTcF = maximal mean placebo-subtracted rate-corrected QT interval using Fridericia's formula; QTc = corrected QT interval

[a] Mixed Effects General Linear Model is fit for placebo-adjusted baseline-corrected and includes terms for: treatment, time, sex, a time be treatment and a sex by treatment interactions and baseline value.

Source: NDA Complete Response 4/30/10; module 5.3.5.3.ISS, Table 50, page 198

There was no significant effect of 30 mg/10 mg BID on heart rate, AV conduction or cardiac depolarization as measured by the PR interval and QRS complex durations. Incidences of subjects with clinically important changes in the QT interval are summarized in the table below. No subject in any group had QTcI, QTcB or QTcF absolute values that exceeded 480 msec, or change from baseline in these parameters that exceeded 60 msec. However, there was more than a 2-fold excess of ECGs with QTc intervals that were increased between 30-60 msec above baseline in subjects who received DM 30 mg/Q 10 mg compared those ECGs in the placebo arm.

Table 80: QTc Data from the clinical thorough QT Study 126

	DM/Q (30 mg/10 mg) (N =50)	Moxifloxacin (400 mg) (N = 49)	Placebo (N = 49)
Quinidine C_{max} (ng/mL)	59	-	-
dQTcI (msec)	7.2	8.3	-1.7
QTcI >480 msec: n (%)	0	0	0
dQTcI >60 msec: n (%)	0	0	0
dQTcI >30 msec: n (%)	3 (6.0)	8 (16.3)	0
dQTcB (msec)	5.2	11.5	0.1
QTcB >480 msec: n (%)	0	0	0
dQTcB >60 msec: n (%)	0	0	0
dQTcB >30 msec: n (%)	4 (8.0)	15 (30.6)	2 (4.1)
dQTcF (msec)	6.8	9.1	-1.3
QTcF >480 msec: n (%)	0	0	0
dQTcF >60 msec: n (%)	0	0	0
dQTcF >30 msec: n (%)	3 (6.0)	6 (12.2)	1 (2.0)
Abnormal U waves: n (%)	0	0	0
ST segment depression: n (%)	0	0	0
T wave inversion: n (%)	0	1 (2.0)	3 (6.1)

dQTcI = change in QTcI from baseline; dQTcB = change in QTcB from baseline; dQTcF = change in QTcF from baseline

Source: NDA Complete Response 4/30/10; module 5.3.5.3.ISS, Table 49, page 198

Population PK/PD analysis of clinical QT study data: The mean PK parameters for Q in Studies 119 and 126 are summarized in the following table. The C_{max} and AUC values of Q administered in combination with DM were dose proportional, and smaller standard deviations were observed with lower doses of Q. Therefore, the Applicant argues that these data indicate that the plasma exposure for Q in the DM/Q combinations is linear and predictable.

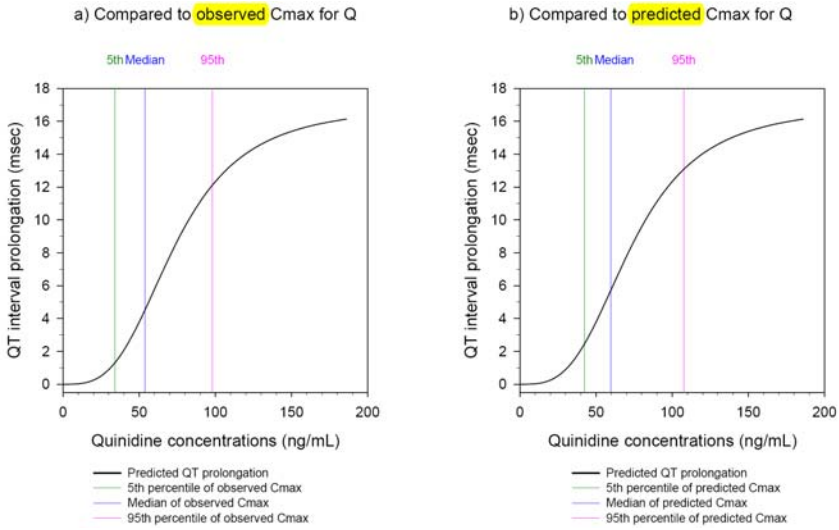
Table 81: Mean (SD) parameters for Q in thorough QT Studies 126 and 119

Parameter	Units	Study 126	Study 119	
		10 mg	30 mg	60 mg
Cmax	(ng/mL)	59.4 (27.6)	177 (50.3)	355 (102)
Tmax[a]	(hr)	1.50	2.33	2.33
AUC0-12[b]	(ng*hr/mL)	393 (138)	1,320 (416)	2,530 (778)

[a]Median (min, max) shown for Tmax.
[b]AUC_{0-12} equivalent to AUC_{tau}
Source: NDA Complete Response 4/30/10; module 5.3.5.3; Cardiac safety report: modified from Tables 3-4, page 21-23.

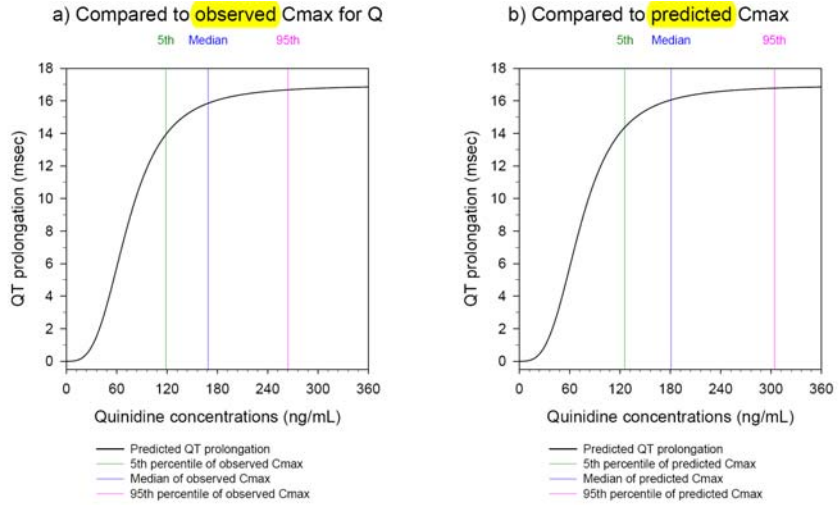
The Applicant used the data from the 2 clinical thorough QT studies to create a population PK/PD model using a non-linear mixed effect modeling. The predicted QT interval change from baseline as a function of Q concentrations (both observed and predicted) derived from the population PD model for DM 30 mg/Q 10 mg (Figure 9) and for DM 30 mg/Q 30 mg (Figure 10) are presented graphically below.

Figure 9: Predicted QT interval changes over the observed Q concentrations from clinical thorough QT studies with ***DM 30 mg/Q 10 mg*** (Studies 119 and 126)



Source: NDA Complete Response 4/30/10; module 5.3.5.3; Cardiac safety report: Figure 1, page 25.

Figure 10: Predicted QT interval changes over the observed Q concentrations from clinical thorough QT studies with ***DM 30 mg/Q 30 mg*** (Studies 119 and 126)



Source: NDA Complete Response 4/30/10; module 5.3.5.3; Cardiac safety report: Figure 2, page 26.

Based on the results of the population PK/PD analysis, the population mean maximal QT prolongation induced by Q is 17.0 msec and the Q plasma concentration required to reach half this maximum value is 73.6 ng/mL. For Q 10 mg at steady-state, the mean observed Cmax was 59.4 ng/mL corresponding to a predicted QT prolongation of 5.67 msec, and the 95th percentile of the observed Cmax was 98.1 ng/mL corresponding to a predicted QT prolongation of 12.1 msec. The Applicant states that this model supports the conclusion that changes in QT interval with low doses of Q are concentration-related and predictable, because plasma Q levels are at the low end of the concentration-response curve.

In the thorough QT studies (119 and 126), while there were no cases where the change from baseline in QTc interval was >60 msec or the absolute QTc interval was >480 msec, there was a QT dose-dependent increase in the incidence of subjects with QTcF of > 30-60 msec (see table below).

Table 82: Outlier analyses for thorough QT Studies 119 and 126

Study Dose DM/Q (mg)	Percent of Subjects with QTcF >450 msec	Percent of Subjects with dQTcF >60 msec	Percent of Subjects with dQTcF >30 msec	Percent of ECGs with dQTcF >30 msec
08-AVR-126 DM 30 mg/Q 10 mg	2	0	6	0.5
05-AVR-119 DM 30 mg/Q 30 mg	0	0	22	4.2
05-AVR-119 DM 60 mg/Q 60 mg	5.9	0	38	7.2

Source: NDA Complete Response 4/30/10; module 5.3.5.3; Cardiac safety report: Table 7, page 30.

Based on the results of the clinical thorough QT studies, the Applicant concludes that Q in DM/Q has the potential to prolong the QTc interval, and that compared to DM/Q at higher dose formulations (30 to 60 mg Q), DM 30 mg/Q 10 mg offers an improved safety margin.

Electrocardiogram assessments in clinical trials:
I reviewed the measures of central tendency for change from baseline for ECG parameters over time in the pooled controlled trials of PBA (Pool 3). The following table summarizes the central tendencies for the change from baseline for the ECG parameters. There was a small reduction in the heart rate in the DM/Q 10 mg and the pooled DM/Q 30 mg dose groups compared to pooled placebo subjects. This small reduction was consistent across time (reviewed but not included in the table), and did not appear dose-related. PR interval and QRS complex showed no consistent time-dependent or dose-dependent changes. Median increases in QTcF were present in an apparent dose-dependent manner in the DM/Q groups compared to the pooled placebo group at the *Final Visit*. There were similar median increases in QTcF in the DM/Q dose groups compared to the pooled placebo group at several but not all *earlier* time points, and without a consistent relationship to DM/Q dose. In the double-blind phase of Study 123, the mean QTcF interval change from baseline to Day 84 was greater in the DM 30 mg/Q 10 mg group (4.8 msec) than in either the DM 20 mg/Q 10 mg (1.0 msec) or the placebo group (1.0 msec).

Table 83: Mean changes in ECG parameters by treatment in controlled trials of PBA (Pool 3)

	AVP-923							
Parameter and Assessment	20 mg DM/ 10 mg Q (N=107)	30 mg DM/ 10 mg Q (N=110)	All doses with 10 mg Q (N=217)	All doses with 30 mg Q (N=146)	All AVP-923 (N=363)	Placebo (N=183)	DM 30 mg (N=33)	Q 30 mg (N=37)
Heart Rate								
Final Visit Change from Baseline								
N	84	100	184	105	289	147	30	33
Mean	-3.6	-1.9	-2.7	-1.8	-2.3	-0.3	-1.9	3.0
SD	10.09	9.94	10.02	10.39	10.15	9.24	14.51	10.59
Median	-2.0	-1.0	-2.0	-1.0	-1.0	0.0	-2.0	2.0
Minimum, Maximum	-32, 21	-41, 22	-41, 22	-35, 26	-41, 26	-38, 28	-35, 36	-16, 28
PR Interval								
Final Visit Change from Baseline								
N	84	100	184	105	289	147	30	33
Mean	-1.9	-1.9	-1.9	-0.1	-1.2	-1.5	0.4	-3.1
SD	14.13	12.00	12.98	13.26	13.09	11.07	12.18	11.66
Median	-1.0	0.0	-0.5	0.0	0.0	-2.0	0.0	-3.0
Minimum, Maximum	-38, 44	-33, 29	-38, 44	-40, 44	-40, 44	-41, 30	-44, 24	-26, 15
QRS Complex								
Final Visit Change from Baseline								
N	84	100	184	105	289	147	30	33
Mean	1.0	0.4	0.7	0.2	0.5	1.6	1.4	0.3
SD	11.32	9.48	10.34	7.34	9.35	10.00	11.20	10.08
Median	2.0	0.0	1.0	0.0	0.0	1.0	1.0	0.0
Minimum, Maximum	-50, 29	-47, 20	-50, 29	-26, 16	-50, 29	-28, 50	-18, 26	-19, 21
QTcF Interval								
Final Visit Change from Baseline								
N	84	100	184	105	289	147	30	33
Mean	1.8	4.9	3.5	5.0	4.1	1.1	-2.9	-1.0
SD	16.46	18.22	17.46	14.93	16.58	15.35	14.62	14.88
Median	2.5	3.0	3.0	6.0	4.0	0.0	-2.9	0.8
Minimum, Maximum	-48, 51	-41, 57	-48, 57	-38, 37	-48, 57	-39, 54	-26, 27	-38, 35

Note: Treatment categories are not mutually exclusive. Thus, patients may contribute to more than one treatment category.
Note: The final visit includes the last on-treatment measurements for completers.
Source: NDA Complete Response 4/30/10; module 5.3.5.3, ISS, modified from Table 44.1.1

Shifts in ECGs from baseline

The following table summarizes the shifts in QTcF from baseline to most abnormal post-baseline result by treatment for controlled trials of PBA (Pool 3). The proportions of subjects who showed a shift from <450 msec in QTcF at baseline to ≥450 msec during treatment for the DM/Q 10 mg dose groups were comparable to or marginally greater than the placebo group. No such shifts were seen in the pooled DM/Q 30 mg dose group.

Table 84: Shifts in QTcF values from baseline to most abnormal post-baseline result in controlled trials of PBA (Pool 3)

Parameter and Shift Criterion	Baseline Value	Most Abnormal On-Treatment Value	DM 20 mg/Q 10 mg (N=107) [1]	DM 30 mg/Q 10 mg (N=110) [1]	All doses with 10 mg Q (N=217) [1]	All dose with 30 mg Q (N=146) [1]	Placebo (N=183) [1]
QTCF>=450 ms		N [2]	97	107	204	139	178
	< 450 ms	>=450 ms	4 (4.1%)	6 (5.6%)	10 (4.9%)	0	7 (3.9%)
	>=450 ms	>=450 ms	0	1 (0.9%)	1 (0.5%)	0	2 (1.1%)
	<450 ms	<450 ms	91 (93.8%)	100 (93.5%)	191 (93.6%)	139 (100%)	169 (94.9%)

	>=450 ms	<450 ms	2 (2.1%)	0	2 (1.0%)	0	0
QTCF>=480 ms		N [2]	97	107	204	139	178
	< 480 ms	>=480 ms	0	0	0	0	1 (0.6%)
	>=480 ms	>=480 ms	0	0	0	0	0
	<480 ms	<480 ms	97 (100%)	107 (100%)	204 (100%)	139 (100%)	177 (99.4%)
	>=480 ms	<480 ms	0	0	0	0	0
QTCF>=500 ms		N [2]	97	107	204	139	178
	< 500 ms	>=500 ms	0	0	0	0	0
	>=500 ms	>=500 ms	0	0	0	0	0
	<500 ms	<500 ms	97 (100%)	107 (100%)	204 (100%)	139 (100%)	178 (100%)
	>=500 ms	<500 ms	0	0	0	0	0

Note: Treatment categories are not mutually exclusive. Thus, patients may contribute to more than one treatment category.
Note: Percentages are 100*(the number who experienced the indicated shift)/(the number of patients who had at least one on-treatment value).
Note: Patients who are missing a baseline value are included and are assumed to be not clinically significant at baseline.
[1] Number of patients in the population.
[2] Number of patients who had at least one on-treatment value for the parameter (included in analysis).
Source: NDA Complete Response 4/30/10; module 5.3.5.3, ISS, modified from Table 44.2.2

Clinically significant ECG changes

The incidence of clinically significant ECG parameters across the controlled trials of PBA (Pool 3) is summarized in the following table. The proportions of subjects with an increase in heart rate > 100 beats per min (bpm) and change from baseline ≥ 15 bpm were low and numerically higher in the DM/Q 30 mg dose group at most time points than in the DM/Q 10 mg dose group or the placebo group. No subjects in any DM/Q (10 or 30 mg) groups had a decrease in heart rate < 50 bpm and change from baseline ≤ 15 bpm (reviewed but not included in the table below). There were more subjects in the DM/Q 10 mg group with an increase in either the PR interval value ≥ 210 msec and change from baseline > 0 msec, or QRS interval value ≥ 120 msec and change from baseline > 0 msec at most time points than in either the DM/Q 30 mg or the placebo group.

Clinically significant prolongation of QTcF was defined as ≥470 msec in women, ≥450 msec in men, or increased by ≥30 msec in either sex. The proportions of subjects with a change from baseline in QTcF of ≥ 30 and < 60 msec were numerically higher in the DM/Q 10 mg dose group at several time points than in the DM/Q 30 mg dose group or the placebo group. Subjects experiencing an absolute value of ≥ 450 msec in QTcF in the DM/Q 10 mg group were comparable to those in the placebo group; none in the DM/Q 30 group had absolute value of ≥ 450 msec. There were no subjects in any of the DM/Q (10 or 30 mg) groups that had a change from baseline of ≥ 60 msec or absolute value of ≥ 480 msec in QTcF at any time point (reviewed but not included in the table below).

Table 85: Incidence of clinically significant ECG parameters by treatment in controlled trials of PBA (Pool 3)

	AVP-923							
Variable(unit) and Criterion	20 mg DM/ 10 mg Q (N=107)	30 mg DM/ 10 mg Q (N=110)	All doses with 10 mg Q (N=217)	All doses with 30 mg Q (N=146)	All AVP-923 (N=363)	Placebo (N=183)	DM 30 mg (N=33)	Q 30 mg (N=37)
Heart Rate								

Increased: Value >100 and Change from BL >=15								
Day 15	0/87 (0.0%)	1/105 (1.0%)	1/192 (0.5%)	0/0	1/192 (0.5%)	0/100 (0.0%)	0/0	0/0
Day 29	0/84 (0.0%)	0/103 (0.0%)	0/187 (0.0%)	0/108 (0.0%)	0/295 (0.0%)	3/150 (2.0%)	0/29 (0.0%)	2/33 (6.1%)
Day 57	0/80 (0.0%)	0/92 (0.0%)	0/172 (0.0%)	0/0	0/172 (0.0%)	0/91 (0.0%)	0/0	0/0
Day 84/85	0/78 (0.0%)	0/96 (0.0%)	0/174 (0.0%)	1/54 (1.9%)	1/228 (0.4%)	0/139 (0.0%)	0/0	0/0
ET Visit	0/13 (0.0%)	0/7 (0.0%)	0/20 (0.0%)	1/33 (3.0%)	1/53 (1.9%)	0/31 (0.0%)	0/1 (0.0%)	1/2 (50.0%)
Final Visit	0/84 (0.0%)	0/100 (0.0%)	0/184 (0.0%)	2/106 (1.9%)	2/290 (0.7%)	0/147 (0.0%)	0/30 (0.0%)	2/33 (6.1%)
End of Study	0/97 (0.0%)	0/107 (0.0%)	0/204 (0.0%)	3/139 (2.2%)	3/343 (0.9%)	0/178 (0.0%)	0/31 (0.0%)	3/35 (8.6%)
Any Visit	0/97 (0.0%)	1/107 (0.9%)	1/204 (0.5%)	4/139 (2.9%)	5/343 (1.5%)	3/178 (1.7%)	0/31 (0.0%)	3/35 (8.6%)
PR INTERVAL								
Increased: Value >=210 and Change from BL >0								
Day 15	2/87 (2.3%)	0/105 (0.0%)	2/192 (1.0%)	0/0	2/192 (1.0%)	0/100 (0.0%)	0/0	0/0
Day 29	2/84 (2.4%)	0/103 (0.0%)	2/187 (1.1%)	0/108 (0.0%)	2/295 (0.7%)	0/150 (0.0%)	0/29 (0.0%)	0/33 (0.0%)
Day 57	1/79 (1.3%)	1/92 (1.1%)	2/171 (1.2%)	0/0	2/171 (1.2%)	2/91 (2.2%)	0/0	0/0
Day 84/85	2/78 (2.6%)	1/96 (1.0%)	3/174 (1.7%)	1/54 (1.9%)	4/228 (1.8%)	1/139 (0.7%)	0/0	0/0
ET Visit	1/13 (7.7%)	0/7 (0.0%)	1/20 (5.0%)	0/33 (0.0%)	1/53 (1.9%)	0/31 (0.0%)	0/1 (0.0%)	0/2 (0.0%)
Final Visit	2/84 (2.4%)	1/100 (1.0%)	3/184 (1.6%)	1/106 (0.9%)	4/290 (1.4%)	1/147 (0.7%)	0/30 (0.0%)	0/33 (0.0%)
End of Study	3/97 (3.1%)	1/107 (0.9%)	4/204 (2.0%)	1/139 (0.7%)	5/343 (1.5%)	1/178 (0.6%)	0/31 (0.0%)	0/35 (0.0%)
Any Visit	6/97 (6.2%)	2/107 (1.9%)	8/204 (3.9%)	1/139 (0.7%)	9/343 (2.6%)	2/178 (1.1%)	0/31 (0.0%)	0/35 (0.0%)
QRS INTERVAL								
Increased: Value >=120 and Change from BL >0								
Day 15	2/87 (2.3%)	2/105 (1.9%)	4/192 (2.1%)	0/0	4/192 (2.1%)	1/100 (1.0%)	0/0	0/0
Day 29	2/84 (2.4%)	4/103 (3.9%)	6/187 (3.2%)	2/108 (1.9%)	8/295 (2.7%)	1/150 (0.7%)	0/29 (0.0%)	0/33 (0.0%)
Day 57	1/80 (1.3%)	4/92 (4.3%)	5/172 (2.9%)	0/0	5/172 (2.9%)	1/91 (1.1%)	0/0	0/0
Day 84/85	2/78 (2.6%)	3/96 (3.1%)	5/174 (2.9%)	0/54 (0.0%)	5/228 (2.2%)	2/139 (1.4%)	0/0	0/0
ET Visit	0/13 (0.0%)	0/7 (0.0%)	0/20 (0.0%)	1/33 (3.0%)	1/53 (1.9%)	0/31 (0.0%)	0/1 (0.0%)	0/2 (0.0%)
Final Visit	2/84 (2.4%)	3/100 (3.0%)	5/184 (2.7%)	1/106 (0.9%)	6/290 (2.1%)	2/147 (1.4%)	0/30 (0.0%)	0/33 (0.0%)
End of Study	2/97 (2.1%)	3/107 (2.8%)	5/204 (2.5%)	2/139 (1.4%)	7/343 (2.0%)	2/178 (1.1%)	0/31 (0.0%)	0/35 (0.0%)
Any Visit	3/97 (3.1%)	6/107 (5.6%)	9/204 (4.4%)	3/139 (2.2%)	12/343 (3.5%)	2/178 (1.1%)	0/31 (0.0%)	0/35 (0.0%)
QTCF								
>=450 ms								
Day 15	3/87 (3.4%)	3/105 (2.9%)	6/192 (3.1%)	0/0	6/192 (3.1%)	1/100 (1.0%)	0/0	0/0
Day 29	0/84 (0.0%)	2/103 (1.9%)	2/187 (1.1%)	0/107 (0.0%)	2/294 (0.7%)	2/150 (1.3%)	0/29 (0.0%)	0/33 (0.0%)
Day 57	1/80 (1.3%)	1/92 (1.1%)	2/172 (1.2%)	0/0	2/172 (1.2%)	1/91 (1.1%)	0/0	0/0
Day 84/85	1/78 (1.3%)	2/96 (2.1%)	3/174 (1.7%)	0/54 (0.0%)	3/228 (1.3%)	4/138 (2.9%)	0/0	0/0
ET Visit	0/13 (0.0%)	0/7 (0.0%)	0/20 (0.0%)	0/33 (0.0%)	0/53 (0.0%)	1/31 (3.2%)	0/1 (0.0%)	0/2 (0.0%)
Final Visit	1/84 (1.2%)	2/100 (2.0%)	3/184 (1.6%)	0/106 (0.0%)	3/290 (1.0%)	4/147 (2.7%)	0/30 (0.0%)	0/33 (0.0%)
End of Study	1/97 (1.0%)	2/107 (1.9%)	3/204 (1.5%)	0/139 (0.0%)	3/343 (0.9%)	5/178 (2.8%)	0/31 (0.0%)	0/35 (0.0%)
Any Visit	4/97 (4.1%)	6/107 (5.6%)	10/204 (4.9%)	0/139 (0.0%)	10/343 (2.9%)	7/178 (3.9%)	0/31 (0.0%)	0/35 (0.0%)
Change >=30 ms and <60ms								
Day 15	2/87 (2.3%)	8/105 (7.6%)	10/192 (5.2%)	0/0	10/192 (5.2%)	2/100 (2.0%)	0/0	0/0
Day 29	3/84 (3.6%)	6/103 (5.8%)	9/187 (4.8%)	5/107 (4.7%)	14/294 (4.8%)	8/150 (5.3%)	0/29 (0.0%)	1/33 (3.0%)
Day 57	5/80 (6.3%)	6/92 (6.5%)	11/172 (6.4%)	0/0	11/172 (6.4%)	3/91 (3.3%)	0/0	0/0
Day 84/85	2/78 (2.6%)	11/96 (11.5%)	13/174 (7.5%)	3/54 (5.6%)	16/228 (7.0%)	8/138 (5.8%)	0/0	0/0
ET Visit	0/13 (0.0%)	0/7 (0.0%)	0/20 (0.0%)	2/33 (6.1%)	2/53 (3.8%)	0/31 (0.0%)	0/1 (0.0%)	0/2 (0.0%)
Final Visit	3/84 (3.6%)	11/100 (11.0%)	14/184 (7.6%)	5/106 (4.7%)	19/290 (6.6%)	7/147 (4.8%)	0/30 (0.0%)	1/33 (3.0%)
End of Study	3/97 (3.1%)	11/107 (10.3%)	14/204 (6.9%)	7/139 (5.0%)	21/343 (6.1%)	7/178 (3.9%)	0/31 (0.0%)	1/35 (2.9%)
Any Visit	9/97 (9.3%)	17/107 (15.9%)	26/204 (12.7%)	11/139 (7.9%)	37/343 (10.8%)	12/178 (6.7%)	0/31 (0.0%)	1/35 (2.9%)

Note: Treatment categories are not mutually exclusive. Thus, patients may contribute to more than one treatment category.
Note: Percentage = 100*(the number of patients who met the criterion for markedly abnormal at the visit/ the number of patients who had at least one on-treatment value).
Note: The early termination (ET) visit includes measurements collected on the last on-treatment date where ECGs were collected for non-completers.
Note: The final visit includes the last on-treatment measurements for completers.
Note: The end of study visit includes the last on-treatment measurements for all completers and non-completers.
Source: NDA Complete Response 4/30/10; module 5.3.5.3, ISS, modified from Table 44.3.2

In the double-blind phase of Study 123, more subjects had increases from baseline to Day 84 in QTcF of 30–60 msec in the DM 30 mg/Q 10 mg group (11/110; 10%) compared with the DM 20 mg/Q 10 mg (2/107; 1.9%) and placebo groups (4/109; 3.7%). There were no subjects exposed to any DM/Q 10 mg group in Study 123 with changes ≥60 msec. At Day 84, more subjects in the placebo group (5/109; 4.6%) had QTcF intervals >450 msec compared to the DM 30 mg/Q 10 mg (3/110; 2.7%) and DM 20 mg/Q 10 mg (1/107; 0.9%) groups; and no subjects had QT, QTcB, or QTcF intervals >500 msec.

Across the integrated clinical studies (Pool 1), the incidences of clinically significant prolongation of QTcB and QTcF in subjects exposed to any dose of the DM/Q combination [70 subjects (5.6%), and 25 subjects (2.0%), respectively] were similar to those in the placebo group [16 subjects (5.5%), and 6 subjects (2.0%), respectively].

In Pool 1, 5 (0.4%) of 1251 subjects showed a shift from <500 msec at baseline to ≥500 msec during treatment. These subjects are briefly summarized below:

- Subject #103-001-039 in Study 103 (DM 45 mg/Q 60 mg), a healthy male subject, had a shift from a baseline QTcF of 367 to 534 msec at Day 8. No concomitant medications were recorded at the time of the QTc shift. However, when these ECGs were reread by a central laboratory, QTcF was 364 msec.

- Subject #107-003-008 in Study 107 (DM 30 mg/Q 30 mg), a female with MS, had a shift from a baseline QTcF of 455 to 505 msec at the end of study visit. Approximately one year before the time of the QTcF shift, before study entry, the subject had a history of prolonged QT, recorded as ongoing. No concomitant medications were recorded at the time of the QTcF shift.

- Subject #107-003-017 in Study 107 (DM 30 mg/Q 30 mg), a male with MS, had a shift from a baseline QTcB of 422 to 506 msec at Week 156. Approximately 5 months later, the subject had a shift from a baseline QTcB of 422 msec to 526 msec and a shift from a baseline QTcF of 413 to 506 msec. The subject did not have a known cardiac history; however, elevated cholesterol and smoking 1 to 1.5 packs of cigarettes/per day were recorded in the history. No concomitant medications were recorded at the time of these shifts. This subject completed the study and enrolled in the extension phase until the Applicant terminated the study.

- Subject #109-150-002 in Study 109 (DM 30 mg/Q 30 mg), a male patient with diabetic peripheral neuropathy pain, had a shift from a baseline QTcB of 428 to 502 msec at Day 29. During screening, QTcB ranged from 464 to 479 msec. The QTcB at Day 92 and end of study was 466 msec. In addition to diabetes, this subject had a history of hyperlipidemia and hypertension. No concomitant medications known to prolong the QT interval were recorded at the time of the QTcB shift.

- Subject #123-208-502 in Study 123 (*placebo*) had a shift from a baseline QTcB of 492 to 501 msec at Day 15. The subject did not have a history of any diagnoses that would predispose to QT interval prolongation and was not receiving any concomitant medications known to prolong the QT interval at the time of the QTcB shift.

Deaths potentially due to cardiovascular AEs and arrhythmias are discussed in section 7.3.5. Across the integrated clinical trials (Pool 1), there were no SAEs due to abnormal ECG parameters. In Pool 1, there were 4 subjects who discontinued due to abnormalities in an ECG parameter:

- Two subjects with 'ECG QT prolonged':
  - #107-003-004 with MS in Study 107 discontinued after being on DM 30 mg/Q 30 mg for (b) (6) days due to QT interval prolongation of 530 msec and QTcF of 493 msec. The baseline value for QTcF at randomization was 455 msec and at baseline prior to enrollment in the open-label Study 107 was 460 msec.
  - # 109-108-013 with diabetic painful neuropathy in Study 109 was on *placebo*
- One subject with 'ECG PR prolongation': #109-102-009 in Study 109 with diabetic painful neuropathy discontinued due to PR interval of 280 msec (baseline value was 267 msec) on Day (b) of DM 30 mg/Q 30 mg;
- One subject with 'ECG T wave inversion': #123-135-510 with ALS in the open-label phase of Study 123 was discontinued on Day (b) (6) (DM 30 mg/Q 10) due to 'Negative T wave inversion possible ischemia'. There was no evidence for delayed ventricular repolarization (i.e., no QTc interval prolongation). This T-

wave change did not resolve upon discontinuation of DM/Q, and the investigator considered a relationship to medication unlikely.

Applicant's conclusions: In the thorough QT clinical trials, Q (10 - 60 mg) in combination with DM did not increase QTc intervals greater than 60 msec, and the incidence of QTc intervals greater than 450 msec was not different from placebo. The evaluation of the frequencies of clinically significant QTc prolongation in subjects exposed to any dose of DM/Q showed no increases compared with placebo. In addition, analysis of QTc intervals showed no evidence for clinically significant changes in QTc interval duration in PBA subjects treated with DM 20 mg/Q 10 mg and DM 30 mg/Q 10 mg in Study 123. These data are consistent with a low level of I_{kr} inhibition and a small degree of QTc prolongation during treatment with DM/Q. These assessments suggest that DM/Q predictably prolongs the QTc interval, but the risk of arrhythmia is low.

Reviewer's comments: DM 30 mg/Q 10 mg clearly prolongs QT interval. There is some merit to the Applicant's argument that the degree of QT prolongation is finite and predictable. In the double-blind phase of Study 123, the mean QTcF interval change from baseline to Day 84 was greater in the DM 30 mg/Q 10 mg group (4.8 msec) than in either the DM 20 mg/Q 10 mg (1.0 msec) or the placebo group (1.0 msec), and more subjects had increases from baseline to Day 84 in QTcF of 30–60 msec in the DM 30 mg/Q 10 mg group (11/110; 10%) compared with the DM 20 mg/Q 10 mg (2/107; 1.9%) and placebo groups (4/109; 3.7%). There were no subjects with a change from baseline of ≥ 60 msec. There were no significant effects on the PR and QRS intervals suggesting that the pro-arrhythmic potential on sinus, AV and ventricular conduction is low. Arrhythmia is discussed in section 7.3.5 of this review.

7.4.5 Special Safety Studies/Clinical Trials

Two thorough QT studies were conducted. These studies were discussed in section 7.4.4 of this review.

7.4.6 Immunogenicity

Q labels contain warnings about Q-mediated immunogenic thrombocytopenia. As discussed in section 2.4 of this review, Quinine sulfate – a related compound mostly used off label for the treatment of leg cramps in the US, recently received a black box warning about the occurrence of serious and life-threatening hematological reactions including thrombocytopenia and hemolytic uremic syndrome/thrombocytopenic purpura, in the context of the absence of evidence of its effectiveness in treatment of leg cramps. Even though there were no cases of Q-mediated thrombocytopenia in the DM/Q development program, Zenvia label will need reflect what is generally known about Q-mediated immunogenic thrombocytopenia in the Warnings section.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Overall, the incidences of subject discontinuations and those experiencing common TEAEs were higher in the DM 30 mg/Q 30 mg dose groups compared to DM/Q 10 mg dose groups.

Within the DM/Q 10 mg dose groups, the incidence of subjects with any TEAE in the DM 30 mg/Q 10 mg group (82.7%) was numerically higher than in the DM 20 mg/Q 10 mg group (78.5%). In ALS subjects, the incidence of subjects with any TEAE in the DM 30 mg/Q 10 mg group (90.8%) compared to DM 20 mg/Q 10 mg group (82.4%); between dose group differences were similar in the MS subjects (Table 63and Table 64). Importantly, dizziness was clearly dose-related, particularly in the MS subjects (Table 52 and Figure 8). In the double-blind phase of Study 123, the incidence of ALS subjects with falls in the DM 30 mg/Q 10 mg group (27.7%) was higher than in the DM 20 mg/Q 10 mg group (14.7%). In the double-blind phase of Study 123, compared to placebo group (1/109 = 0.9%), subjects who experienced syncope/presyncope were numerically higher in the DM 30 mg/Q 10 mg (4/110 =3.6%) and comparable in the DM 20 mg/Q 10 mg group (1/107 = 0.9%).

In the double-blind phase of Study 123, the mean QTcF interval change from baseline to Day 84 was greater in the DM 30 mg/Q 10 mg group (4.8 msec) than in either the DM 20 mg/Q 10 mg (1.0 msec) or the placebo group (1.0 msec), and more subjects had increases from baseline to Day 84 in QTcF of 30–60 msec in the DM 30 mg/Q 10 mg group (11/110; 10%) compared with the DM 20 mg/Q 10 mg (2/107; 1.9%) and placebo groups (4/109; 3.7%).

Among subjects receiving concomitant medications of special interest, the incidence in the DM 30 mg/Q 30 mg or DM 30 mg/Q 10 mg groups appeared to be higher than in the DM 20 mg/Q 10 mg group (Table 86).

However, other data suggest a better safety profile for the DM 30 mg/Q 10 mg dose than in DM 20 mg/Q 10 mg dose. The overall incidence of subjects with any SAE in the double-blind phase of Study 123 was numerically higher, particularly in the ALS subjects, in the DM 20 mg/Q 10 mg group (9/68 = 13.2%) than in the DM 30 mg/Q 10 mg group (7/65 = 10.8%). Similarly, the incidence of subjects who discontinued was higher in the DM 20 mg/Q 10 mg group (9/107 = 8.4%) than in the DM 30 mg/Q 10 mg group (5/110 = 4.5%).

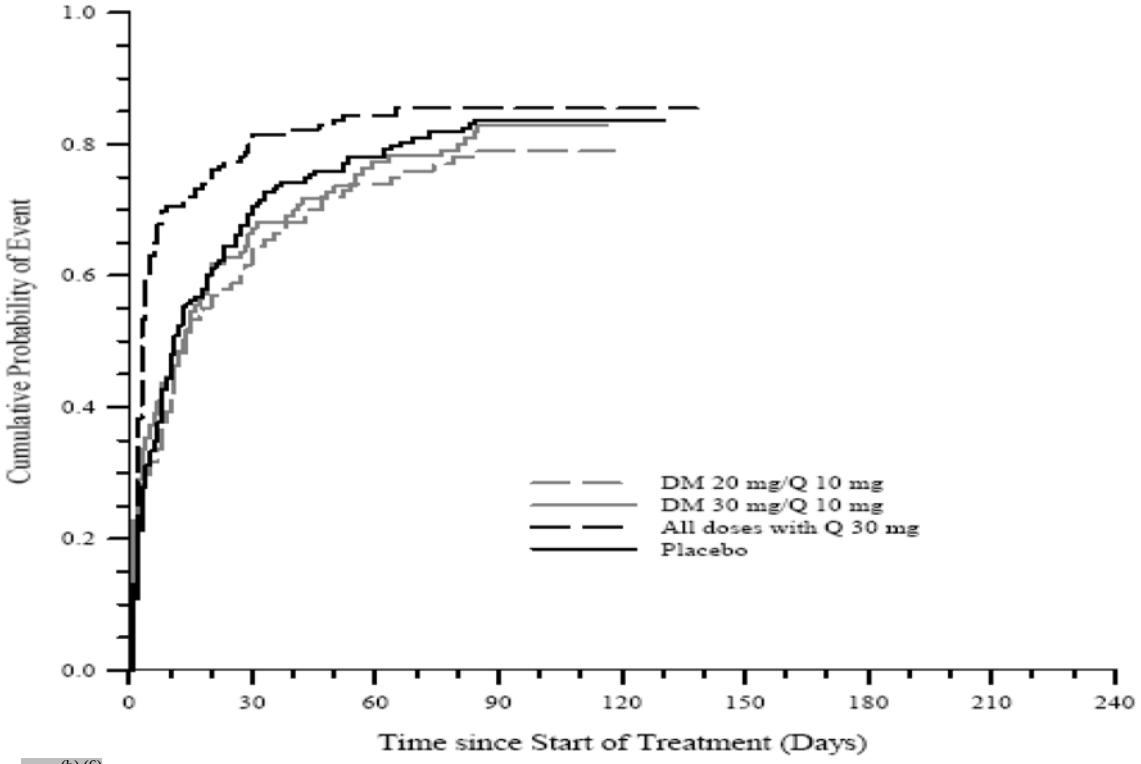
Reviewer's Conclusion: Although the differences between DM 20 mg/Q 10 mg and DM 30 mg/Q 10 mg doses in safety were not consistent, the preponderance of evidence in the overall safety data suggest that DM 20 mg/Q 10 mg has a better safety profile than DM 30 mg/Q 10 mg.

7.5.2 Time Dependency for Adverse Events

The cumulative incidence of AEs in controlled studies of PBA (Pool 3) is shown in the following figure. The cumulative incidence of AEs was highest for the group taking any dose of DM/Q 30

mg. The cumulative incidences for placebo, DM 30 mg/Q 10 mg and DM 20 mg/Q 10 mg groups appear similar, although the lowest cumulative incidence appears to be in DM 20 mg/Q 10 mg group.

Figure 11: Kaplan-Meier plot of cumulative incidence of any AE by treatment and time to first occurrence in Pool 3.



Source: (b) (6) Plot was used to create the figure from the integrated database.
The plots show cumulative incidence of any AE during treatment and up to 30 days after the last dose.
Source: NDA Complete Response 4/30/10; module 5.3.5.3.ISS, Figure 4, page 159

Among the most common TEAEs, nausea and dizziness have a higher incidence of occurrence in the first 1 and 2 weeks, respectively, before leveling off for the remainder of the duration. This is further discussed in section 7.3.5 of this review.

7.5.3 Drug-Demographic Interactions

Age, sex and race: There do not appear to be any significant differences in safety profile of DM/Q between PBA subjects <65 years of age and those ≥65 years of age, or between Caucasian and non-Caucasian PBA subjects, or between gender with respect to the incidences of SAEs, discontinuations due to AEs, or TEAEs.

PK and safety of 10 mg Q in subjects who are genetically poor metabolizers of CYP2D6: In the general population, approximately 7-10% of Caucasians and 3-8% of Black/African Americans lack the capacity to effectively metabolize CYP2D6 substrates and are classified as poor

metabolizers. The distribution of CYP2D6 phenotypes in the clinical studies was: 88% (373/425) of subjects genotyped in clinical studies of DM/Q were extensive metabolizers and 5% (19/425) were slow metabolizers. In the poor metabolizers, the combination of DM and Q does not raise levels of DM significantly above those seen when DM is administered alone. In the double-blind phase of Study 123, the plasma level of DM in poor metabolizer given DM 30 mg/Q 10 mg was higher (131 ng/mL; n=4) than the plasma level of DM in extensive metabolizers (78 ng/mL; n=83).

The incidence of SAEs, AEs leading to discontinuation and TEAEs in the poor metabolizers and normal metabolizers were fairly similar. Because there is no difference in the safety profile of Zenvia by CYP2D6 metabolizer status, and the genetic tests are relatively expensive, the Applicant believes that genetic prescreening is not necessary. Even if a subject is confirmed to be a poor metabolizer, the safety and efficacy of the use of DM alone for the treatment of PBA in this setting is unknown. However, since there is a potential risk of adverse events associated with Q, the Applicant proposes statements in the product labeling indicating that laboratory tests are available to identify CYP2D6 poor metabolizers.

7.5.4 Drug-Disease Interactions

The Applicant conducted two studies in special populations – one study each in subjects with hepatic impairment and in subjects with renal impairment.

Hepatic impairment Study 115: An open-label, multiple dose, parallel group study to evaluate the PK and safety of DM 30 mg/Q 30 mg in subjects with mild or moderate hepatic impairment and healthy volunteers. Each subject received 13 doses of DM 30 mg/Q 30 mg (BID for 6 consecutive days and once in the morning on Day 7). A total of 21 subjects were enrolled: 6 with mild hepatic impairment, 6 with moderate hepatic impairment, and 9 healthy subjects (matched for age, sex and weight). All subjects completed the study.

No deaths or SAEs were reported in this study. No subject was discontinued from the study due to an AE. Ten subjects reported at least one AE: 1 subject (11%) with normal hepatic function, 3 subjects (50%) with mild hepatic impairment, and 6 subjects (100%) with moderate impairment. All AEs were mild in severity with the exception of one AE (headache – moderately severe). The most common AEs were somnolence, headache, nausea and diarrhea. No subjects showed clinically significant changes in serum chemistry or hematology, or urinalysis values. No clinically significant ECG changes were observed. Mild or moderate hepatic impairment did not seem to have a significant clinical effect on the pharmacokinetic and elimination profiles of dextromethorphan, its metabolite dextrorphan, or quinidine.

Based on these study results, the Applicant concludes that Zenvia appears to be safe in patients with mild to moderate hepatic impairment, and no dosing adjustments of Zenvia necessary in patients with moderate or lesser hepatic impairment. No subjects with severe hepatic impairment have been studied. The Applicant recommends that Zenvia should be used with caution in patients with severe hepatic impairment.

Renal impairment Study 116: An open-label, multiple dose, parallel group study to evaluate PK and safety of DM 30 mg/Q 30 mg in subjects with various states of renal insufficiency and healthy adult volunteers. Each subject received 13 doses of DM 30 mg/Q 30 mg (BID for 6 consecutive days and once in the morning on Day 7). A total of 21 subjects were enrolled: 6 with mild renal impairment, 6 with moderate renal impairment, and 9 healthy subjects (matched for age, sex and weight). All subjects completed the study.

No deaths or SAEs were reported in this study. No subjects discontinued from the study. A total of six (6, 28.6%) subjects reported at least one adverse event: 4 (44.4%) in normal group and 2 (33.3%) mild impairment group. No subject in the moderate renal category reported any AE. Somnolence was reported in two subjects, both of whom had normal renal function. No subjects showed clinically significant changes in serum chemistry, hematology, or urinalysis values. No clinically significant ECG changes were observed. Patients with moderate renal impairment showed a statistically significant 2-fold increase in steady-state AUC (p-value = 0.0153) and C_{max} (p-value = 0.0267) values for total dextrorphan as compared to subjects with normal renal function. This was accompanied by a greater than 2-fold decrease in renal clearance. However, these changes were not associated with any adverse events.

Based on these study results, the Applicant concludes that the administration of Zenvia appears to be safe in patients with mild to moderate renal impairment, and no dosing adjustments of Zenvia are considered necessary in patients with moderate or lesser renal impairment. The Applicant proposes in the label that Zenvia should be used with caution in patients with severe renal impairment. Reviewer's comments: Given the statistically significant increase of exposure in subjects with moderate renal impairment, there likely will be greater increases in exposure in subjects with severe renal impairment. This will need to be appropriately reflected in the label.

7.5.5 Drug-Drug Interactions

In the Approvable Letter, the Agency expressed concern regarding potential drug interactions between DM/Q and other drugs that are metabolized by CYP2D6 and or CYP3A4.

In response to the recommendation of the Agency, the Applicant reformulated the DM/Q formulation with a lower Q (10 mg) dose. Three drug-drug interaction studies were conducted using the tricyclic antidepressant desipramine (a CYP2D6 substrate), the selective serotonin reuptake inhibitor paroxetine (a CYP2D6 substrate and inhibitor) and memantine (an NMDA receptor antagonist). The Applicant conducted an analysis on the clinical database to identify the most common concomitant medications in PBA patients and evaluate the potential safety issues related to drug interactions with those medications. The Applicant also reviewed the literature to evaluate the potential for DM and Q to interact with CYP3A4 inhibitors and substrates, and the potential for DM and Q to inhibit or induce cytochrome P450 isozymes in vitro.

Study 112 (desipramine): Since antidepressants are frequently administered to patients with neurological disorders to treat concomitant depressive symptomatology, and since desipramine

(CYP2D6 substrate) has narrow therapeutic index (other tricyclic antidepressants are metabolized to a greater extent by other CYP450 enzymes), the Applicant chose desipramine to study drug-drug interactions with DM/Q. Fourteen subjects (9 males and 5 females) were given 25 mg dose of desipramine once a day for 16 days (usual dose for depression is 150 – 300 mg/day). Starting from Day 8, DM 30 mg/Q 30 mg was administered q12h for 9 days (from Days 8 to 16).

At steady-state, C_{max} and AUC values were 17.6 ng/mL, and 257 ng*h/mL, respectively. Co-administration of DM 30 mg/Q 30 mg resulted in an increase of desipramine mean C_{max} to 117 ng/mL (7-fold) and AUC to 2093 (8-fold).

There were no deaths or serious adverse events. The investigator withdrew two subjects due to adverse events: one subject due to high bacteria count and pus in urine, and the other subject (#4) who experienced arrhythmia (ECG showed ventricular bigeminy) that commenced about 12 hours on Day 12. Subject #4 was subsequently placed on telemetry which showed periods of bigeminal PVCs (subject was asymptomatic). About 5 weeks later, a 24-hour Holter monitor was obtained. The Cardiologist reading the Holter which showed frequent PVCs recommended further evaluation to assess if these events were benign or due to an underlying structural or ischemic cardiac disease. However, it is unknown if this subject underwent such an evaluation. In the overall safety population, the frequency of AEs such as headache, dizziness, somnolence, nausea, and fatigue increased with the addition of DM 30 mg/Q 30 mg to desipramine.

Median QRS showed increases from Day 7 (88.5 msec) to Day 16 (91.5 msec). Median QTc interval showed increases from Day 7 (420 msec) to Day 16 (423.5 msec). One female subject (#7) experienced palpitations/tachycardia, commencing approximately 3.4 hours after dosing on Day 10, and 54 minutes after dosing on Day 11, lasting from 3 - 7.5 hours. No therapy was required to treat these events. Two male subjects (#8 and #12) experienced tachycardia each between 6.2 hours and 1.3 days after dosing between Days 10 and 18, lasting between 5 minutes and 6.9 days. No therapy was required to treat tachycardia.

The Applicant states that Study 112 was conducted with a higher dose of Q (DM 30 mg/Q 30 mg) than contained in Zenvia (Q 10 mg), so the observed changes may have been greater than would be observed with Zenvia. Increased desipramine exposure may result in changes in cardiac and vital sign parameters, which, if occurring in a more severe form than in Study 112, have the potential to be serious. The Applicant concludes that depending on the expected change in exposure and therapeutic index, CYP2D6 substrates should be used with caution in patients receiving Zenvia, and a dose adjustment may be advisable.

Study 121 (paroxetine): Paroxetine, a SSRI used as an antidepressant, is a substrate of CYP2D6 and weak inhibitor of CYP3A4; therefore the Applicant chose it for a drug interaction study with DM/Q. A total of 27 healthy male and female volunteers (all but were extensive CYP2D6 metabolizers) were divided into 2 groups. Group 1 (14 subjects) received 20 mg paroxetine once daily for 12 days; starting on Day 13, the subjects additionally received DM 30 mg/Q 30 mg BID for a further 8 days. Group 2 (13 subjects, including one poor metabolizer) received DM 30

mg/Q 30 mg BID for 8 days; starting on Day 9, the subjects additionally received 20 mg paroxetine QD for a further 12 days.

In Group 1, when DM 30 mg/Q 30 mg was added to paroxetine at steady state, paroxetine mean C_{max} increased from 41 ng/mL to 47 ng/mL (15%) and mean AUC_{0-24} increased from 651 ng*h/mL to 870 ng*h/mL (34%). In Group 2, when paroxetine was added to DM 30 mg/Q 30 mg at steady state, DM mean C_{max} increased from 94 ng/mL to 132 ng/mL (41%) and mean AUC_{0-12} increased from 915 ng*h/mL to 1336 ng*h/mL (46%); Q mean C_{max} increased from 160 ng/mL to 210 ng/mL (31%) and mean AUC_{0-12} increased from 1070 ng*h/mL to 1490 ng*h/mL (39%).

No deaths or SAEs were reported. Three subjects (narratives provided below) were withdrawn from the study due to an AE: one subject in Group 1 and 2 subjects in Group 2. In the overall safety population, the overall incidence 5/14 (35.7%) of subjects with any AE when DM 30 mg/Q 30 mg was added to paroxetine (Group 1) of was comparable to the incidence 4/12 (33.5%) when paroxetine was added to DM 30 mg/Q 30 mg (Group 2). The addition of DM 30 mg/Q 30 mg to steady-state paroxetine (Group 1) resulted in one severe event of non-cardiac chest pain (#9010), and the addition of paroxetine to steady-state levels of DM 30 mg/Q 30 mg resulted in two severe events of mood swing and bizarre behavior leading to withdrawals (see narratives).

> Subject #9010 was a 55-year old female in Group 1 who experienced chest pains about 5 days after DM 30 mg/Q 30 mg was added to paroxetine. The chest pains were diagnosed to be due to acid-related disorders, and resolved with Maalox and Nexium.
>
> Subjects #9039 was a 24-year old female in Group 2 who experienced erratic mood swings approximately 10 days after the addition of paroxetine to DM 30 mg/Q 30 mg and lasted about 6 hours. She was withdrawn from the study due to this AE, which resolved without drug therapy.
>
> Subject #9055 was a 25-year old male in Group 2 who experienced bizarre behavior in the form of hyperactivity approximately 8 days following the addition of paroxetine to DM 30 mg/Q 30 mg lasting nearly 6 hours, and was deemed to be probably related to the study drugs. He was withdrawn due to this AE, which resolved without drug therapy.

The Applicant concludes that the addition of DM 30 mg/Q 30 mg to steady-state levels of paroxetine resulted in increased steady-state levels of paroxetine, and the addition of paroxetine to steady-state levels of DM 30 mg/Q 30 mg resulted in increased steady-state levels of DM. Paroxetine is a CYP2D6 substrate, and the increase in paroxetine exposure during co-administration of DM 30 mg/Q 30 mg is consistent with inhibition of CYP2D6 by Q. The increase in DM exposure during co-administration of paroxetine and DM 30 mg/Q 30 mg suggests that CYP2D6-mediated metabolism of DM is not completely inhibited by Q 30 mg BID, and that the altered PK profile of DM is due to more complete inhibition of CYP2D6-mediated metabolism in the presence of paroxetine. The reason for the increased Q exposure may be related to the weak CYP3A4 inhibition caused by paroxetine; however, such potential interactions of paroxetine with CYP3A4 substrates are not considered clinically significant at recommended clinical doses. Analysis of AEs indicates that co-administration of paroxetine and DM/Q may have an impact on AE emergence and severity. It is therefore considered advisable to use Zenvia with caution in patients receiving paroxetine. Reviewer's comments: There do not

appear to be significant differences between the AE emergence following co-administration in Group 1 or Group 2.

Study 122 (memantine): The drug interaction study between DM 30 mg/Q 30 mg and memantine was conducted primarily to explore the potential for pharmacodynamic interactions since both are antagonists of the NMDA receptor. A total of 52 healthy volunteers (all extensive CYP2D6 metabolizers) were divided into 2 groups. Group 1 (23 subjects) began a 21-day titration period with 5 mg QD in Week 1, 5 mg BID in Week 2, 5 mg AM and 10 mg PM in Week 3, and then 0 mg BID for 11 days; starting on Day 33, the subjects in Group 1 additionally received DM 30 mg/Q 30 mg BID for 8 days. Group 2 (29 subjects) received DM 30 mg/Q 30 mg BID for 8 days; starting on Day 9, they began a 21-day dose titration period of memantine as above, and thereafter received 10 mg memantine BID for 11 days.

The addition of DM 30 mg/Q 30 mg to memantine did not alter the steady-state PKs of memantine, and the addition of memantine to DM/Q did not alter the steady-state PK of DM or Q.

There were no deaths or SAEs were reported. There was one subject in Group 1 and three subjects in Group 2 who withdrew due to AEs (see narratives below). There were no differences in AE incidence, severity, or maximum relationship between when co-administration or when drugs were given alone.

> Subject #9105 was a 54-year old female who withdrew on Day 10 of memantine (DM 30 mg/Q 30 mg was not yet co-administered) due to several AEs: lightheadedness "spaced out", constipation, insomnia, dizziness, abdominal pain, emotionally labile, nausea, and loose stools. All were mild and reported as resolved, with the exception of loose stools, because the subject was lost to follow-up.
>
> Subject #9125 was a 38-year old male who experienced 5 AEs (nausea, abdominal discomfort, headache, low energy and severe vomiting) which began 2 days after dosing with DM 30 mg/Q 30 mg (memantine was not yet co-administered) and withdrew. All AEs were reported as resolved.
>
> Subject #9130 was a 30-year old male who experienced several AEs (general weakness, vertigo, nausea, headache, somnolence, muscle tightness and diarrhea), 3 – 5 days after dosing with DM 30 mg/Q 30 mg (memantine was not yet co-administered) and withdrew. All AEs were reported as resolved.
>
> Subject 9204 was a 28-year old female who experienced continuous nausea which occurred 1 day after beginning DM 30 mg/Q 30 mg alone, lasted 2 days, and resolved without any treatment, and withdrew. AE resolved without other therapy.

The Applicant concludes that no precautions are advised for patients taking concomitant Zenvia and memantine.

Drug-drug interactions with CYP3A4: The Applicant draws conclusions regarding potential drug-drug interactions with Q and other CYP3A4 inhibitors from the Q label and published PK studies. The Q label states that concomitant administration of Q with drugs that inhibit CYP3A4

has the potential to increase Q concentrations by 40%. Citing a publication (*Kaukonen K, 1997*), the Applicant states that in healthy volunteers receiving a single dose of Q 100 mg, itraconazole (CYP3A4 inhibitor) 200 mg/day increased plasma C_{max} of Q by 60%, and the plasma AUC value by 2.4-fold. Another study (*Damker P, 1999*) showed that itraconazole and grapefruit juice decreased Q clearance but did not increase C_{max}, while erythromycin raised Q C_{max} by only 39%. The Applicant therefore expects that, depending on the specific CYP3A4 inhibitor, Q C_{max} may be elevated 40% to 60%.

The mean C_{max} for DM/Q 10 mg doses is 59 ng/mL (mean AUC_{0-12} = 393 ng*h/mL). A conservative assumption that the maximum effect of a CYP3A4 inhibitor will be a 2.4-fold increase in Q exposure, yields a mean C_{max} of 142 ng/mL (59*2.4), which is below that obtained during BID dosing with DM 30 mg/Q 30 mg (Cmax = 177 ng/mL). The Applicant states that in this situation, the QTc effect would be similar to that seen with the DM 30 mg/Q 30 mg dose when dosing with DM/Q 10 mg in the presence of a strong CYP3A4 inhibitor.

The Applicant concludes that CYP3A4 inhibition is unlikely to raise Q concentrations into the antiarrhythmic therapeutic range given the small dose of Q in Zenvia. However, that this potential interaction should still be taken into consideration when prescribing Zenvia, and therefore, proposes to include a Warning to exercise caution when concomitantly administering Zenvia with a strong CYP3A4 inhibitor.

Oxycodone as a concomitant medication of special interest: The Applicant considered oxycodone to be a concomitant medication of special interest. Oxycodone is metabolized in the liver, with the production of two metabolites: oxymorphone (via O-demethylation by CYP2D6) – a potent analgesic, and noroxycodone (via N-demethylation by 3A) – a mild analgesic. Across the integrated clinical studies, there were two deaths in subjects in whom oxycodone was a concomitant medication (narratives provided below). Of the 7 subjects in Study 123 who received oxycodone and DM/Q 10 mg, 4 subjects experienced AEs (nausea, vomiting, and constipation) that might be associated with oxycodone; none of these events were serious. There were several other concomitant medications in these subjects that are also potentially associated with these AEs, so it is difficult to ascribe causality. In addition, the Applicant also considered two published studies, and states that Q, despite being an inhibitor of CYP2D6, would not significantly affect the PK of oxycodone.

> Subject #106-003-002 was a 43-year old female MS patient who was enrolled in Study 107. In addition to MS, other medical history included an ongoing depressive disorder. On Day (b) (6) of DM 30 mg/Q 30 mg, she was found dead in her home. Autopsy results found oxycodone blood level 0.69 mg/L (690 µg/mL). The prescribed dose of oxycodone was 5 mg TID for headaches; at steady-state levels of this dose, the mean peak Cmax is expected to be15.5 ng/mL (mean trough 7.4 ng/mL). The levels found at autopsy were 50–100 times greater than the expected level. In addition to oxycodone, the toxicology results found other drugs in the blood: methorphan (50 ng/mL), fluoxetine (360 ng/mL), and caffeine (detected) but quinidine was not detected in the blood (50 ng/mL was the lower limit of quantitation). Several drugs were present in the urine: nicotine, caffeine, fluoxetine, diphenhydramine, methorphan, nortriptyline, oxycodone, and quinidine. The coroner suspected that this subject died of an ***intentional overdose of oxycodone***, consistent with the plasma levels of oxycodone found at autopsy. Reviewer's comments: The Q levels in the blood were undetectable. The death appears to be as a result of oxycodone overdose.

Subject #107-028-011 was a 64-year-old Caucasian male with ALS who was enrolled in Study 107. Other medical history included hypertension. Concomitant medications included lorazepam, atenolol, celecoxib, quinine sulfate, riluzole, minocycline, lioresal, sertaline and tamusoline. On Day (b) (6), he was taken to the ER because of respiratory distress. He was intubated and was placed on a ventilator. After his wife confirmed a "do not resuscitate" status, the ventilator was discontinued and he died a short time later. He had taken a single dose of oxycodone on Day 111 and had finished a 10-day course of erythromycin on Day 31. The longest QTc interval for this subject was 430 msec on Day 29. The Applicant concludes that the time sequence of events does not support concomitant drug use as a predisposing event to the respiratory failure. Reviewer's comments: I agree with the Applicant's conclusion.

Analysis of concomitant medications and potential drug interactions in integrated studies of subject with PBA:

The most common concomitant medications in Pool 3 in ≥ 10% of PBA subjects in the ALS subjects were: riluzole, ascorbic acid, tocopherol, baclofen, creatine, ubidecareonone, acetylsalicylic acid and ibuprofen. In MS subjects, the most common concomitant medications were: glatiramer acetate, interferon beta (all types), baclofen, paracetamol, ibuprofen, gabapentin, clonazepam, Vigran and calcium. Only two these medications (acetylsalicylic acid and clonazepam) are CYP3A4 substrates. None of these medications are metabolized by, and do not inhibit CYP2D6 or CYP3A4 pathways.

In the integrated studies, the Applicant identified any concomitant medication (regardless of its frequency of use) that is an inducer, substrate, or inhibitor of CYP2D6 or CYP3A4 enzymes. Analyses were then conducted to identify if there was an excess of SAEs, AEs leading to discontinuation or common TEAEs in the DM/Q groups compared to the placebo group among subjects who were on these concomitant medications in the pooled controlled studies (Pool 3). These analyses also included other drugs affecting ECG, opiates/opioids and SSRIs. The incidences of *SAEs and AEs leading to discontinuations* in subjects with PBA in controlled studies receiving these concomitant medications were similar between subjects receiving any dose of DM/Q and placebo (tables not included in the review).

The following table summarizes the incidences of *TEAEs* by treatment and concomitant use in Pool 3. Compared to the placebo group, the incidence of subjects experiencing any TEAE with the concomitant use of ***CYP2D6 inhibitors*** in the DM 20 mg/Q 10 mg is similar, and numerically higher in the DM 30 mg/Q 10 mg and DM 30 mg/Q 30 mg dose groups. Within each Body System Organ Class, most of these subjects experienced Gastrointestinal disorders-related adverse events, followed by Nervous System disorders, General Disorders and Administration site conditions, Injury, poisoning and Procedural Complications, and Investigations; the incidences for most Body System classes in the DM 20 mg/Q 10 mg dose group appears numerically less than the DM 30 mg/Q 10 mg or DM 30 mg/Q 30 mg groups, and comparable to the placebo group. In the Cardiac disorders, the absolute numbers of subjects in any dose group was ≤ 1. In the Respiratory, Thoracic and Mediastinal disorders, the incidences of subjects were 4 (21%) in the DM 20 mg/Q 10 mg group, 6 (37.5%) in the DM 30 mg/Q 10 mg group, 4 (19%) in the DM 30 mg/Q 30 mg group, and 8 (23.5%) in the placebo group. Similar incidences were seen in the ALS and MS subsets in Pool 3.

Among subjects using concomitant ***CYP2D6 substrates*** in Pool 3, compared to the placebo group, the overall incidence of subjects with any TEAE was numerically lower in the DM 20 mg/Q 10 mg group, and higher than or comparable to in the DM 30 mg/Q 10 mg or DM 30 mg/Q 30 mg groups. In the Cardiac disorders, the absolute numbers of subjects were small: 2 (8%) in the DM 20 mg/Q 10 mg group, 1 (2.9%) in the DM 30 mg/Q 10 mg group, 1 (3.1%) in the DM 30 mg/Q 30 mg group, and 2 (4.5%) in the placebo group. In the ALS subjects, the proportions of subjects with any Respiratory-related TEAE were higher in the DM/Q groups [8 (44.4%) in the DM 20 mg/Q 10 mg group; 8 (38.1%) in the DM 30 mg/Q 10 mg group; 4 (40%) in the DM 30 mg/Q 30 mg group] compared to 3 (18.8%) in the placebo group. The most common CYP2D6 substrates used concomitantly in ALS subjects were: amitryptyline, ondansetron, paroxetine and metoclopramide.

The absolute numbers of subjects using concomitant ***CYP3A4 inhibitors*** in Pool 3 were small, without any clear between-treatment group differences. The most common medications in this category were ciprofloxacin, donepezil, and fluconazole.

There were no differences in the incidences between treatment groups among subjects in Pool 3 with the concomitant use of medications known to prolong QT interval (most common were: tizanidine/tizanidine, diphenhydramine, levofloxacin, ciprofloxacin, and azithromycin), opiate, SSRI, riluzole or MS medications.

Table 86: Incidence of TEAEs by treatment and concomitant medication use in the controlled trials of PBA (Pool 3)

	AVP-923							
System Organ Class/ Preferred Term	20 mg DM/ 10 mg Q (N=19)	30 mg DM/ 10 mg Q (N=16)	All doses with 10 mg Q (N=35)	All doses with 30 mg Q (N=21)	All AVP-923 (N=56)	Placebo (N=34)	DM 30 mg (N=5)	Q 30 mg (N=6)
Primary Disease = All Diagnoses : CYP2D6 Inhibitors = YES								
Any Adverse Event	18 (94.7%)	16 (100.0%)	34 (97.1%)	21 (100.0%)	55 (98.2%)	33 (97.1%)	2 (40.0%)	5 (83.3%)
Primary Disease = All Diagnoses : CYP2D6 Substrates = YES								
Any Adverse Event	21 (84.0%)	31 (91.2%)	52 (88.1%)	31 (96.9%)	83 (91.2%)	40 (90.9%)	2 (40.0%)	3 (75.0%)
Primary Disease = All Diagnoses : CYP3A4 Inhibitors = YES								
Any Adverse Event	5 (100.0%)	6 (100.0%)	11 (100.0%)	5 (100.0%)	16 (100.0%)	8 (100.0%)	1 (100.0%)	0
Primary Disease = All Diagnoses : Medications Known To Prolong QT Interval = YES								
Any Adverse Event	33 (94.3%)	36 (94.7%)	69 (94.5%)	28 (90.3%)	97 (93.3%)	60 (89.6%)	4 (80.0%)	2 (66.7%)
CARDIAC DISORDERS	1 (2.9%)	2 (5.3%)	3 (4.1%)	1 (3.2%)	4 (3.8%)	2 (3.0%)	0	0
Primary Disease = All Diagnoses : Opiates/Opioidss = YES								
Any Adverse Event	13 (81.3%)	19 (95.0%)	32 (88.9%)	22 (100.0%)	54 (93.1%)	29 (96.7%)	1 (100.0%)	4 (100.0%)
CARDIAC DISORDERS	1 (6.3%)	1 (5.0%)	2 (5.6%)	2 (9.1%)	4 (6.9%)	1 (3.3%)	0	0
Primary Disease = Amyotrophic Lateral Sclerosis (ALS) : Opiates/Opioidss = YES								
Any Adverse Event	10 (83.3%)	13 (100.0%)	23 (92.0%)	6 (100.0%)	29 (93.5%)	11 (100.0%)	1 (100.0%)	4 (100.0%)
CARDIAC DISORDERS	1 (8.3%)	1 (7.7%)	2 (8.0%)	0	2 (6.5%)	0	0	0
Primary Disease = All Diagnoses : SSRIs = YES								

Any Adverse Event	8 (100.0%)	9 (100.0%)	17 (100.0%)	2 (100.0%)	19 (100.0%)	13 (100.0%)	0	1 (100.0%)
ALS Subjects Only Riluzole Use								
Any Adverse Event	36 (78.3%)	43 (89.6%)	79 (84.0%)	40 (87.0%)	119 (85.0%)	33 (86.8%)	14 (70.0%)	14 (66.7%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	13 (28.3%)	11 (22.9%)	24 (25.5%)	8 (17.4%)	32 (22.9%)	7 (18.4%)	3 (15.0%)	4 (19.0%)
MS Subjects Only MS Medication Use								
Any Adverse Event	10 (66.7%)	17 (77.3%)	27 (73.0%)	17 (94.4%)	44 (80.0%)	28 (80.0%)	0	0

Source: NDA Complete Response 4/30/10; module 5.3.5.3.ISS, section 3.5.15 modified from Tables 30.1.21 – 40.3.4

Applicant's conclusions: Q is a substrate for CYP3A4, and plasma concentrations may be increased if administered with other drugs that are CYP3A4 inhibitors such as ketoconazole. However, Q is given in very low doses with Zenvia administration (10 mg/dose), and effective plasma concentrations (0.05-0.06 µg/mL) are well below the antiarrhythmic therapeutic range of 2 to 5 µg/mL. Although CYP3A4 inhibition is unlikely to raise Q concentrations into the antiarrhythmic therapeutic range, or even, 3-fold to the concentrations utilized with the previous formulations, the potential interaction should still be taken into consideration when prescribing Zenvia. Caution should be exercised when prescribing strong CYP3A4 inhibitors and we have proposed labeling language to address this concern

Reviewer's comments: In clinical studies, the incidences of AEs in subjects receiving DM/Q with inhibitors or substrates of CYP2D6 or CYP3A4, or opiates/opioids, or drugs known to affect QT interval, were similar between DM/Q dose groups and placebo group, or were numerically too small for meaningful between treatment-group comparisons. I agree that the potential for altered drug effects resulting from co-administration of ZENVIA with drugs that undergo extensive CYP2D6 metabolism (based on the results of the interaction study with desipramine), and the potential interaction between Zenvia and strong CYP3A4 inhibitors need to be communicated in the label.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Across the integrated clinical studies (Pool 1), there were 3 cases of breast cancer, 1 case of skin cancer, 1 case of thyroid neoplasm, 1 case of acute monocytic leukemia (in an MS subject who was being treated with Novantrone) and several benign neoplasms.

7.6.2 Human Reproduction and Pregnancy Data

The effects of DM/Q on pregnancy, labor, and delivery are not known. No pregnancies were reported during any clinical study with DM/Q. Both DM and Q are individually classified as

Pregnancy Category C because animal developmental and reproductive toxicology studies had not been conducted.

The Applicant conducted developmental and reproductive toxicology studies with DM and Q in combination. See pharmtoxicology review for appropriate description of these studies in the label.

7.6.3 Pediatrics and Assessment of Effects on Growth

Assessment of growth in pediatric subjects is not applicable in this NDA.

Deferral of pediatric studies: The Applicant submitted a request for deferral of pediatric studies. During the meeting between the Agency and the Applicant on 9/14/02 the Agency stated that they were uncertain about the prevalence of PBA in children and indicated that a deferral of pediatric studies would be considered until after NDA approval. The Applicant states that the incidence of PBA is unknown in the pediatric population. Reviewer's comments: It appears that involuntary laughter or crying occurs in children with autism as young as 2.5 years old (*http://www.autism-pdd.net/testdump/test22874.htm*).

The Applicant states that the request for deferral of pediatric studies is made because the Applicant has not yet determined whether there is an unmet medical need in pediatric patients and must first consult with pediatric neurology and psychiatry experts post-approval of the adult indication to better understand the incidence, prevalence, etiology, and nature of an affective disinhibition syndrome in children. The Applicant anticipates that there will be sufficient information to support a Written Request by two years post-approval.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Across the clinical trials, there were no cases of intentional overdose of DM/Q combination product.

The Applicant states that although a few cases of toxicity following overdose have been reported, no fatalities have occurred with over-the-counter DM, even with doses exceeding 100 times the normal adult dose; however, 5 deaths in teenagers were reported with powdered DM abuse. Central nervous system-related AEs are most prevalent with DM overdose and include hyperexcitability, euphoria, excitation, severe irritability, confusion, toxic psychosis, auditory and visual hallucinations, stupor, coma, ataxia, dystonia, nystagmus, blurred vision, and changes in muscle reflexes. Respiratory depression, tachycardia, seizures, and severe nausea and vomiting can also occur at very high doses. The Applicant states that treatment for DM overdose includes symptomatic and supportive measures, and parenteral administration of naloxone hydrochloride.

The Applicant reports one death with a 5-gram dose of Q in a child, and an overdose of 8 grams of Q in an adolescent who reportedly survived after repeated gastric lavage. The Applicant states

that the most clinically significant AEs associated with acute Q overdoses are ventricular arrhythmias and hypotension. Symptoms of a Q overdose include coma, confusion, delirium, irritability, vomiting, seizures, difficulty breathing, fainting, diplopia, tiredness, syncope, ataxia, hypotension, and tachyarrhythmias. Q has a narrower therapeutic index than DM, and an overdose of Q is a medical emergency that can be fatal. In the event of overdose, the Applicant recommends employing the usual supportive measures (e.g., clinical monitoring and supportive therapy) as dictated by the patient's clinical status.

See CSS review for abuse potential and withdrawal.

7.7 Additional Submissions

All clinical trials included in the Complete Response were completed. Consequentially, there was no 120-day safety update. There were several requests from this reviewer regarding clarifications and requests for additional information. The submissions detailing the Applicant's responses to these requests were reviewed.

8 Postmarket Experience

DM/Q has not been approved for marketing.

9 Appendices

9.1 Literature Review/References

References and literature review are cited and discussed, respectively, within the relevant sections of this review.

- Wortzel HS, et al. Pathological laughing and crying. Epidemiology, pathophysiology and treatment. CNS Drugs 2008:22(7);531-545
- Miller RG, et al. Practice parameter update: The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review). Neurology. 2009;73:1227-1233
- Bradley WG, et al. (editors). Neurology in Clinical Practice. Philadelphia: Butterworth-Heinemann, 2008; pages 1165, 1589.
- Murray B and Mitsumoto H. Amyotrophic lateral sclerosis. In Katirji B et al. (editors). Neuromuscular Disorders in Clinical Practice. Boston: Butterworth-Heinemann, 2002; 418.

- Ropper AH, et al. (editors). Adams and Victor's Principles of Neurology (9th Ed). New York: McGraw Hill, 2009; chapters 35, 36 and 39.

- Kaukonen K, et al. Itraconazole increases plasma concentrations of quinidine. Clin Pharmacol Ther 1997;62:510-7.

- Damker P, et al. Effect of diclofenac, disulfiram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinidine. Br J Clinical Pharmacol 1999;48:829-838.

9.2 Labeling Recommendations

(b) (4)

9.3 Advisory Committee Meeting

A pre-approval Advisory Committee Meeting was not held.

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/s/

DEVANAND JILLAPALLI
10/06/2010

RONALD H FARKAS
10/09/2010

Review and Evaluation of Clinical Data

NDA (Serial Number)	**N21-879**
Sponsor:	**Avanir**
Drug:	**Zenvia (formerly Neurodex)**
Proposed Indication:	**Pseudobulbar affect**
Material Submitted:	**Meeting Package, Response to Action Letter**
Meeting Date:	**February 26, 2007**
Reviewer:	**Ronald Farkas Medical Reviewer, DNP, ODE I**

1. Introduction

An Approvable Action was taken on NDA 21-879 for Zenvia (formerly Neurodex) on October 30, 2006. This meeting addresses the initial response of the sponsor to issues raised in the Approvable Letter about the safety and efficacy of Zenvia.

Portions of the Approvable Letter are presented below in italics before corresponding sponsor comments, numbered to correspond with the sponsor's presentation in this meeting package. The sponsor's supporting arguments are briefly reviewed following each question. Draft answers to the sponsor's questions appear in Section 3, "Response to Clinical Questions."

2. Meeting Questions

Sponsor Questions:

(1). Study 102, in patients with Amyotrophic Lateral Sclerosis (ALS), was designed to establish the contribution of each component. We also acknowledge that the contrasts between the combination and the individual components reached statistical significance on the protocol specified primary outcome measure, the CNS-LS. However, as you also know, we had repeatedly expressed to you a preference for the designation of laughing and crying episodes as the primary outcome variable.

1. Sponsor Question: The CNS-LS is an acceptable primary outcome measure for Studies 99-AVR-102 and 02-AVR-106. Does FDA agree?

The sponsor presents the following supporting arguments:

- The sponsor notes that the Division agreed at the end-of-phase 2 meeting that the CNS-LS score was acceptable for the proposed MS trial.
- The sponsor notes previous arguments they have made in favor of using the CNS-LS score as the primary outcome, including clinical relevance,

correlation with episode counts, reproducibility, and normal distribution of scores.

(2)We note that your protocol specified that you would analyze these episodes using Poisson regression.

However, as you acknowledge, the distribution of the episode data did not support the use of the Poisson regression model. Although your protocol did not specify an alternative analysis in this case, you have chosen to analyze the episode data using the NB1 negative binomial model (variance proportional to the mean).

Given the lack of a prespecified alternative to the Poisson model and the fact that there is no single well-established parametric alternative, we performed a Cochran-Mantel-Haenszel (CMH) test with modified ridit scores on the combination-DM comparison; regardless of whether the data for the one outlier patient 08-016 (see below) are included (p=0.13) or excluded (p=0.19), the results do not achieve significance.

2. Sponsor Question: While there are limitations associated with relying on episode counts as a primary outcome measure in clinical studies, Avanir recognizes the importance of understanding episode count effects for clinical relevance. The NB1 model analysis of episode counts, prespecified for study 02-AVR-106 and accepted by FDA, achieved statistical significance for the comparison of DM/Q to DM when applied to Study 99-AVR-102. This finding supports the clinically [sic] effectiveness of DM/Q compared to DM in the prespecified secondary endpoint of episode counts. Does the FDA agree.

Comments: see statistical review

(3) We also investigated the NB2 negative binomial model (variance depends on the square of the mean). We believe that the NB2 negative binomial model also provides a reasonable alternative to the Poisson model. This model is less sensitive than the NB1 model in terms of measures of overall model fit to the inclusion of the one outlier in the Dextromethorphan (DM) group (patient 08-016, who had a total of 3010 laughing episodes during the study). In addition, with the NB1 model, the difference between the combination and the DM group increases when this patient's data are excluded, which is counterintuitive. In contrast, with the NB2 model, the difference between these groups decreases when this patient's data are excluded, as is expected. Therefore, we have analyzed the episode data using this latter model.

3. Sponsor Question: In summary, the NB1 model is valid and provides an acceptable fit for the data and valid basis for statistical inference. The other methods do not represent the data, and thus do not enable valid statistical inference. Therefore, the statistical methods used by the Sponsor are appropriate for analyzing the impact of Zenvia on the reduction of laughing and/or crying episode counts. Using these

methods, Zenvia produced positive results for the secondary outcome measure of episode count reduction in studies 99-AVR-102 and 02-AVR-106. Does FDA agree?

Comments: see statistical review

(4) We acknowledge that you have submitted the results of two randomized controlled trials that purport to establish substantial evidence of effectiveness of Zenvia in patients with Pseudobulbar Affect (PBA). We agree that Study 106, in patients with Multiple Sclerosis (MS), clearly can be considered one "positive" study contributing to such a finding. However, as you know, this study was not capable by design of establishing the contribution of the individual components of the product, as required by 21CFR300.50 (Fixed-combination prescription drugs for humans).

4. Sponsor Question: The effectiveness of Zenvia in the treatment of IEED has been demonstrated in two adequate and well-controlled clinical trials, Studies 99-AVR-102 and 02-AVR-106. The clinical assessment of IEED using the CNS-LS and the results of the statistical analyses of laughing and crying events are acceptable to support the effectiveness of Zenvia in patients with IEED. Furthermore, based on Study 99-AVR-102, it has been conclusively established that Zenvia is more effective than either component. Does FDA agree?

The sponsor argues that at the pre-NDA meeting the Division agreed that the efficacy data from studies 102 and 106 would be sufficient to support the indication of IEED.

(5) Numerous findings in the safety database raise serious concerns about the safety in use of this product.

First, we note that quinidine is well known to be associated with serious ventricular arrhythmias, including torsades de pointes. These arrhythmias can occur at low quinidine doses in susceptible patients (e.g., those with congenital prolonged QT syndrome), but higher quinidine doses can also be associated with serious cardiac events, presumably in a dose related fashion.

In this regard, we note the results of Study 119, your thorough QT study. This study demonstrated that at the daily dose of the combination that you propose, the drug is associated with a maximum mean paired placebo and baseline subtracted QTcF of about 10 msec, with a 95% upper bound one-sided confidence interval of about 15 msec (we presume this increase is directly a result of the quinidine component), and that the prolongation persists throughout the dosing interval. You suggest that this is of little consequence because Agency guidance states that this degree of increase is "inconclusive" regarding its clinical significance. However, we disagree with your conclusion. In our view, quinidine poses a known proarrhythmic risk, and as such this degree of QT interval increase raises serious concerns. In this regard, we also note that, in this study, over 4% of the EKGs in patients who received the recommended dose had QTc intervals that were increased between 30-60 msec above baseline, compared to 0.9% of those EKGs in the placebo arm.

5. Sponsor Question: A reformulation of Zenvia containing a reduced amount of quinidine (10 mg) would be expected to reduce the proarrhythmic risk of quinidine. PK/PD modeling alone is valid for predicting changes in QTc interval. Does FDA agree?

The sponsor has data from study 99-AVR-100 on the pharmacokinetics of Q at 10 mg, showing about 4-fold reduced Cmax and 6-fold reduced AUC. The sponsor cites a publication that the QT-prolongation induced by Q is dose-dependent.

(6) In this case, the combination-DM comparison is nominally significant (p=0.017) when this patient's data are included, but not if these data are excluded (p=0.34), or if the next worst episode count in the database (398) is imputed (p=0.13). We recognize that this outcome measure is a secondary measure, but, again, we remind you that, on numerous occasions, we strongly suggested that it be deemed the primary outcome. The results we have obtained suggest that the combination may not provide an additional benefit beyond that provided by the DM component itself. You will need to adequately address this concern before we can conclude that the combination policy has been met. It is also worth noting that this finding raises the possibility that a much lower exposure to DM than is achieved with this product might be effective in controlling laughing or crying episodes in these patients (see below).

6. Sponsor Question: A reformulation of Zenvia containing a reduced amount of quinidine (10 mg) would be expected to produce DM levels that are substantially higher than DM alone. PK/PD modeling alone may be used to predict clinical efficacy. Does FDA agree?

The sponsor has data from study 99-AVR-100 on the PK of DM with 10 mg Q. The sponsor combines efficacy (PD) data from study 102 and 106 with DM blood levels for modeling efficacy at lower DM doses.

[Reviewer comment: The sponsor does not present PK/PD modeling from study 102 alone, and the dose/response effect in study 102 appears weaker than for study 106. In addition, the sponsor focuses on the dose/response curve between 0 and 100 ng/ml DM, which is somewhat arbitrary. For example, in the 102 data (not including study 106 data), the dose-response curve appears to be an 'inverted U' shape between 0 and 100 ng/ml DM. Considerable uncertainty is likely to exist about efficacy derived from any modeling given the lack of any pre-specified analysis, and what appears to differences in 'efficacy' depending on relatively small differences in the way the modeling is carried out.]

(7) Further, and equally, if not more, disturbing, the maximum mean paired placebo and baseline subtracted QTcF was about 18 msec (upper bound of the 95% CI was 25 msec) at the supratherapeutic dose of the combination, which was only twice that of the

recommended dose (at this dose, 7.2% of the EKGs were associated with an increase in QTc of 30-60 msecs). Given that quinidine is metabolized by CYP3A4, and given the availability and use of numerous 3A4 inhibitors, we expect that, in practice, many patients may be exposed to levels of quinidine that were achieved with the supratherapeutic dose used in this study (or higher), and that these levels will be associated with serious cardiovascular consequences. In addition, we have performed PK/PD modeling of quinidine's effect on the QT interval; we have determined that 5% of the population who receives the recommended dose of Zenvia would be expected to experience a prolongation of the QTc interval of about 19 msec.

7. Sponsor Question: A reduction in the dose of Q from 30 mg to 10 mg in the combination product would result in reduced plasma concentrations of Q, consequently resulting in lower Cmax even in the presence of a CYP3A4 inhibitor. Does FDA agree?

Comment: Refer to clinical pharmacology review.

(8) In addition, quinidine's potent inhibition of CYP2D6 poses additional risks, especially in this vulnerable population. For example, we are aware of a death in the database that appeared likely related to elevated plasma levels of oxycodone, a substrate for both 3A4 and 2D6. The patient was also receiving, in addition to Zenvia, a potent 3A4 inhibitor (clarithromycin). The combination of 3A4 and 2D6 inhibition was likely responsible for the dangerously elevated oxycodone levels in this patient. We also note that at least one other patient in the data base was receiving oxycodone, Zenvia and another potent 3A4 inhibitor (erythromycin). These cases highlight the dangers that are potentially associated with the use of Zenvia, especially when it is used in association with other metabolic inhibitors and CYP2D6 substrates, as would be expected in the relatively sick populations in whom PBA may occur. We are very concerned that labeling statements warning against such use would not be entirely successful in preventing such concomitant drug use.

8. Sponsor Question: Although close evaluation of these cases indicates lack of a relationship of concomitant drug administration to the serious adverse event in question, reducing the dose of Q to 10 mg in Zenvia would further reduce the risk of adverse consequences in this vulnerable population. Does FDA agree?

The sponsor addresses two subjects with adverse events. The sponsor does not discuss CYP 2D6 inhibition from 10 mg vs. 30 mg of quinidine.

[Reviewer comment: A reasonable interpretation of the data is that the oxycodone level in subject 107-03-002 reached a fatal level through the contribution of a drug interaction with Zenvia. In subject 107-28-011 the time sequence of events does not support concomitant drug use as a predisposing event to the patient's death. However, this second case does confirm that the patient population that would be exposed to Zenvia is at potential risk for concomitant use of Zenvia, oxycodone, and CYP 3A4 inhibitors.]

[Reducing the Q dose to 10 mg would not greatly decrease the risk of drug interaction in this vulnerable population. Most patients would be fully CYP 2D6-inhibited with the 10 mg Q dose.]

(9) Finally, quinidine is known to be particularly dangerous in patients who are moving in and out of atrial flutter/fibrillation, due to the risk both of torsades de pointes, and of supraventricular tachychardia from quinidine effects on atrio-ventricular conduction. In this regard, we note at least one case in the database of a patient who entered the trial with a history of atrial flutter who became symptomatic (i.e., experienced palpitations) on treatment. The population in whom PBA is common may include many such patients, and we are concerned that these patients will be particularly vulnerable to serious ventricular arrythmias if treated with Zenvia.

9. Sponsor Question: Although close monitoring of susceptible patients with cardiac history may be required, reducing the dose of Q to 10 mg in Zenvia would further reduce the risk of cardiac arrhythmias in susceptible patients. Does FDA agree?

The sponsor appears to suggest that cardiac risk from a reformulation of Zenvia would be adequately addressed through physician inquiry about family and personal history, and 'close monitoring' of susceptible patients.

The sponsor also points out that quinidine is used to treat atrial fibrillation/flutter

[Reviewer comment: The sponsor does not present any evidence beyond simple assertion that the cardiac risk of Zenvia would be adequately addressed by physician and patient behavior.]

(10) We note the occurrence of 48 deaths in the open-label experience, many in ALS patients, presumably due to respiratory failure. However, you have not provided evidence that this number of deaths, from this cause, would be expected in this time period in this population.

10. Sponsor Question: The death rate for ALS patients in the open label experience study of Zenvia is comparable to the published and expected death rate for patients with ALS; therefore, the deaths reported do not constitute a safety signal with respect to the use of this product. Does FDA agree?

The sponsor notes that about 50% of ALS patients die within 2 years of diagnosis. The sponsor argues that the death rate in the Zenvia long-term trial was similar to this expected death rate. The sponsor compares the Zenvia death rate to that for Riluteck, and argues that the rates are the same (71% at 12 months). Several other studies are cited with survival at 12 months ranging from 66% to 80%.

[Reviewer comment: Review of the Zenvia safety data identified specific adverse effects of Zenvia (e.g. cardiac effects) that plausibly contributed to patient deaths. The fact that disease progression is undeniably a major factor in the deaths of a high overall percentage of patients with ALS does not meaningfully argue for the safety of Zenvia; instead, the

large number of expected deaths only increases the difficulty of identifying possibly drug-related deaths. The controlled ALS trial, while too short and too small to provide much data on mortality, in fact showed one death in the Zenvia arm, and no deaths in the Q only and DM only arms.]

(11) We are concerned that the very high levels of DM produced by Zenvia in this vulnerable population may have contributed to respiratory depression in these patients. We also note the occurrence of a relatively large number of respiratory depression and failure events, categorized as serious adverse events. You will need to address our concern that this product may be associated with respiratory depression and failure in this vulnerable population (we include in this vulnerable population other populations in whom PBA may occur, including patients with stroke and Alzheimer's Disease, groups in whom you have obtained very little clinical experience).

11. Sponsor Question: Although close evaluation of these cases indicates a lack of relationship of respiratory failure to Zenvia, reducing the dose of Q to 10 mg in Zenvia would reduce both Q and DM exposure and provide an even higher margin of safety in this vulnerable population. Does FDA agree?

The sponsor argues that the Zenvia studies revealed no adverse respiratory effects. The sponsor states that in controlled trials, Zenvia (or DM) had about half the rate of respiratory AEs as placebo or Q alone [data referred to not presented by sponsor]. The sponsor states that there was no evidence of decreased respiratory rate, no evidence of increased respiratory SAEs, no evidence of increased discontinuation due to respiratory AEs, and no evidence of increased death rate for ALS patients in Zenvia trials compared to that reported in the Rilutek label.

[Reviewer comment: In study 102, three SAEs occurred in the Zenvia arm (dysphagia, aspiration, respiratory failure [fatal]), none in the DM arm, and 1 in the Q arm (pneumonia). This meeting submission does not contain detailed explanation of how controlled trial data supports the lack of respiratory depression from Zenvia. The respiratory rate data appears to have been collected with bias towards specific respiratory rates (16 and 20 respirations/minute), and therefore may not be adequately reliable to address this question. The single death in the ALS controlled trial (in any arm) was due to respiratory depression, which clearly is not reassuring of the lack of relationship of Zenvia with respiratory failure. It is difficult to see how inadequate safety data on respiration from the current formulation of Zenvia could, without additional data, support the safety of a new formulation of Zenvia with 10 mg Q in terms of respiratory effects.

(12) We also note a 6% incidence of vomiting in the patients treated with Zenvia in Study 102 compared to no vomiting in the other treatment groups. We further note a 33% incidence of nausea in the Zenvia treated patients in this study, compared to 6-8% in the other treatment groups. These findings are particularly worrisome in vulnerable populations because of the risk of aspiration, especially in those patients with difficulty swallowing, in whom the risk of aspiration is even greater. Further, we believe the risk for aspiration may be especially great in these patients, given the 13% incidence of

somnolence in the Zenvia treated patients compared to 3% in the DM patients and 0 in the quinidine treated patients in Study 102 (we also note a 5% incidence of somnolence compared to 1% in the placebo group in Study 106).

12. Sponsor Question: We acknowledge that the incidence rates for nausea, vomiting, and somnolence are higher in Zenvia than with the individual components or placebo. We have investigated the incidence of episodes of aspiration and find them to be an infrequent occurrence that may be related to the patient's underlying neurological condition. Nevertheless, reducing the dose of Q to 10 mg in Zenvia should provide an improved safety profile. Does FDA agree?

The sponsor notes that aspiration is a common cause of death in late-stage ALS and MS, but that in Zenvia trials only 0.64% of patients (N=626) were reported to have 'aspiration' or 'aspiration pneumonia.' The sponsor notes that 3 of 4 patients with aspiration or aspiration pneumonia did not report nausea, and that none reported vomiting.

The sponsor notes that nausea, vomiting, and somnolence were less common as causes of discontinuation than as overall reported adverse events.

[Reviewer comment: The evidence the sponsor cites does not appear capable of establishing the safety of Zenvia in light of the common adverse events of vomiting, nausea, and somnolence. This is particularly so given that aspiration was an SAE reported in the Zenvia arm of trial 102, but not in the other arms. This case represents the only case of aspiration reported in study 102, but this largely only illustrates the overall lack of sufficient controlled trial safety experience in ALS patients.]

(13) We are also greatly concerned about the risk of falls in these patients. We have re-calculated the incidence of falls in both controlled trials, including those patients whose adverse event was categorized as an injury, but who clearly sustained their injuries as a result of falls. In Study 102, the incidence of falls was 13% in the Zenvia group, 12% in the DM group, and 0 in the quinidine group. A similar re-calculation of the incidence of falls in Study 106 yielded a 5% incidence of falls in the Zenvia group compared to a 3% incidence in the placebo group. The number of falls in Study 106 was too small to serve as a reliable indicator of risk in the MS population; however, Study 102 suggests that Zenvia increases the risk of fall in the ALS population.

Further, we calculated the incidence of an increased risk of falls in both studies, by adding the incidences of events that could reasonably be considered to predispose to falls. In this analysis, we combined various event terms, including disoriented, dizzy, lightheaded, shaky, unstable, etc. (we acknowledge that these calculations presuppose that each event reported occurred in separate individuals; this, of course, may not be true). When these events were combined, the incidence of events in Study 102 that could be considered to predispose to falls was 43% in the Zenvia group, 27% in the DM group, and 5% in the quinidine group. In Study 106, the incidence of these predisposing events

was 41% in the Zenvia group, and 23% in the placebo group. Although the specific terms to include in these calculations could be a matter for discussion, we believe grouping appropriate terms is clinically meaningful (an examination of dizziness alone shows a 20% incidence in the Zenvia group, a 15% incidence in the DM group, and a 3% incidence in the quinidine group in Study 102 and a 26% incidence in the Zenvia group and a 9% incidence in the placebo group in Study 106). These numbers are disturbing, given the potential serious consequences of falls in these populations. Please address these concerns.

13. Sponsor Question: A thorough evaluation of these cases indicates a lack of relationship of falls to Q administration. However, reducing the dose of Q to 10 mg in Zenvia should result in reduced DM levels as well as Q levels. The lower levels of DM would likely result in decreased CNS AEs, and thus, reduce the risk of adverse consequences such as falls in this vulnerable population. Does FDA agree?

The sponsor seems to acknowledge that in Zenvia studies there appears to be an association of falls with Zenvia common AEs. The sponsor attributes much of the risk of fall to underlying disease. The sponsor concludes that labeling statements that inform prescribing physicians and patients of the risk of falls associated with these AEs are warranted. The sponsor does not, however, find that labeling should distinguish between fall associated with Zenvia and fall associated more generally with underlying disease.

[Reviewer comment: Insufficient data has been presented for us to conclude that a reformulation of Zenvia with 10 mg Q would be associated with fewer CNS adverse events or falls. Importantly, 10 mg Q would still convert most subjects to poor metabolizer status, so that even though the average DM concentration in a population would likely decrease, for the majority of patients the DM concentration might not be decreased as compared to the 30 mg Q formulation. Thus, the overall risk to the population attributable to DM level might be reduced only by a relatively small fraction.]

(14) Although we acknowledge that there do not seem to be important systematic laboratory changes induced by treatment with Zenvia, we are particularly concerned about the occurrence of significant hepatic injury in patient 136-9004 who became jaundiced after 2 ½ months of treatment with study drug. This patient had significant elevations in AST, ALT, and bilirubin, with a mild increase in alkaline phosphatase. No viral or chemical cause for these changes was found, and, although this patient was receiving treatment with numerous concomitant medications, none would have been expected to have caused this injury. The pattern of injury seen in this patient is very similar to that seen with other drugs known to result in hepatic failure. For these other drugs, the incidence of hepatic failure in general use is about 10% of the incidence of the finding of hepatic injury in clinical trials (e.g., in this case, the incidence of the finding of hepatic injury is about 1/1000 patients; the incidence of hepatic failure in general use, if this case is drug related, would be expected to be about 1/10,000). We recognize that, typically, such cases of drug-induced serious liver injury occur in the setting of a general, systematic increase in liver function tests, which did not occur here. Nonetheless, this

case is troubling, and raises the concern that Zenvia is hepatotoxic. Please address this concern. We note that, if this patient was receiving active drug, it will be critical to closely follow him, to determine if an alternative underlying explanation for these findings emerges (e.g., episodes of alcohol abuse, underlying malignancy, etc.).

14. Sponsor Question: The investigator, in review of all the documents along with input from a gastroenterologist, felt that retrospectively, based on the clinical presentation and outcome, patient 136-9004 had a gall bladder stone that spontaneously passed. Detailed review of this case indicates that study drug was not involved, and the underlying explanation of passage of a gall bladder stone is logical and sound. Does FDA agree?

The sponsor has provided additional listings of laboratory studies for this subject, and the patient's Case Report Form is included in the meeting submission. The narrative for the SAE is also included. The sponsor's argument that the hepatitis was related to gallstones seems mainly to be based on CT scan showing multiple small stones remaining in the gall bladder. The sponsor acknowledges that abdominal ultrasound performed during the hospitalization showed no stone in the common duct, but suggests that this exam was inconclusive for etiology because it was conducted five days after admission, and at that time liver enzymes were decreasing.

[Reviewer comment: Evidence for a gall stone etiology is not adequately compelling to dismiss drug-induced liver injury. For example, in addition to studies negative for evidence of a common duct stone, the large elevation in AST and ALT in conjunction with modest increases in alkaline phosphatase is more typical of non-cholestatic hepatocellular injury. The presence of gall bladder stones on CT is not compelling evidence of cholestatic disease as the etiology of liver injury.]

(15) These concerns, taken together, raise serious questions about the safety of Zenvia in the vulnerable populations for whom it is intended, and, as described above, these concerns will need to be addressed before the drug can be approved. Further, we note, again, that numerous vulnerable populations (e.g., patients with Alzheimer's Disease) have not been adequately studied, and we believe that they will need to be before the drug can be approved.

15. Sponsor Question: We agree that additional safety and efficacy studies in other populations will provide critical information regarding the use of Zenvia. These studies would be appropriate to continue post approval (e.g., in stroke or Alzheimer's disease). Does FDA agree?

The sponsor lists 39 patients with stroke and 11 with Alzheimer's disease currently enrolled in the long-term Zenvia study. The sponsor states agreement that additional safety and efficacy data in other populations will provide critical information regarding the use of Zenvia, but wishes to conduct such studies post-approval

[Reviewer comment: Given the adverse effects associated with Zenvia, particularly in ALS subjects, evidence of safety in other diseases including stroke and Alzheimer's should be obtained before approval.]

(unnumbered) We also again note that lower doses of both the quinidine and DM components of the combination may result in a product that is equally effective, and potentially much safer, than the current proposed product (we remind you that the results of the analyses of the laughing/crying episodes at least suggest that [substantially] lower exposures of DM may control these events). We recognize that you have chosen your dose of quinidine based on a finding that this dose converted 8/8 extensive metabolizers of 2D6 (EMs) into poor metabolizers (PMs), as assessed by urinary metabolic ratio. We remind you, however, that a 10 mg dose of quinidine converted 6/7 EMs to PMs. It is clear that the lowest dose of quinidine that will give the desired effect is much to be preferred; this is similarly true for the dose of DM, and further dose finding to identify the lowest effective doses of each component should be undertaken.

Unnumbered Sponsor Comment:

The sponsor refers to the section of this meeting submission containing PK/PD modeling of the efficacy of 30 mg DM/10 mg Q.

3. Response to Clinical Questions (Draft)

The text below addresses the clinical issues raised in your meeting questions (questions 1-15), in a format designed to best communicate both the unresolved issues in the Zenvia NDA, along with possible remedies for these issues. Numbers of your specific meetings questions are referred to above areas of corresponding text.

In the Approvable Letter for Zenvia, we raised issues of concern regarding both the safety and the efficacy of Zenvia. In your current submission, you propose to address several of the key safety issues through a reformulation of Zenvia containing 10 mg quinidine instead of 30 mg quinidine. We agree that a different formulation of Zenvia might have fewer safety risks while being efficacious. You have not outlined in this meeting package arguments or proposals for collecting additional data that we are likely to lead to a finding of safety for the 30 mg Q formulation of Zenvia. Given data in the NDA that we find raises serious questions about the safety of the current formulation, we believe that establishing safety of the current formulation may be impossible. We believe, therefore, that the current discussion for this meeting should focus mainly on the additional data that would be necessary for you to demonstrate the safety and efficacy of a new formulation of Zenvia.

Efficacy
[questions 1, 2, 3, 4]

We will accept that Zenvia (30 mg Q formulation) has been shown to be more effective than either component. We include below detailed statistical comments intended only to clarify our interpretation, not to qualify our acceptance.

[question 2]
While the NB1 model does lend some support there is no general consensus that the NB1 model is the backup model of choice for overdispersed Poisson episode count data. Some other possible backup models for the 102 episode count data lead to different conclusions. This is problematic since the NB1 model was not pre-specified as the backup.

[question 3]
The prespecified model for the count data in study 102 was inadequate as it greatly underestimated the variability in the data which makes tests based on it anti-conservative. There was no back-up model pre-specified to handle this possibility and there is no general consensus on what the most appropriate backup model should be. The NB1 negative binomial model favored by the sponsor was post-hoc for study 102 and it is not clear that it is the only reasonable choice for the appropriate back-up model. The NB2 model is also reasonable. It has a higher log likelihood than the NB1 model and the deviance residuals from the NB2 model fit are approximately normally distributed which suggests that tests based on it are also valid. Unlike the NB1 model, results based on the NB2 model suggest that Zenvia was not superior to both components of the combination in terms of the episode counts. A nonparametric test, the Cochran Mantel Haenszel test,which may be reasonable given the uncertainty surrounding the true distribution of the count data, also found that the AVR vs. DM comparison was not statistically significant (p=0.145). It is true, as the sponsor argues, that episode rates estimated on the basis of a shorter period may have different variability than those based on a longer period which might make this latter test sub-optimal. However, only 15% of patients had less than 21 of the 29 planned days of observation and the assumptions of any test are usually only approximately true. Furthermore, this simple nonparametric approach is sometimes used by sponsors in the analysis of seizure rates which has the same problem of patients having different lengths of periods of observation due to dropping out.

SafetyThe major safety issues raised in the Approvable letter are as follows: (a) cardiac effects of quinidine, (b) drug interactions involving CYP 2D6 and CYP 3A4, (c) possible respiratory depression from Zenvia as a contributing factor in the deaths of ALS patients, (d) nausea and vomiting in populations at risk for aspiration, and increased falls in populations already at risk from falls (e) lack of adequate clinical experience in stroke, Alzheimer's disease, and other diseases in which Zenvia is intended for use, and (f) possible case of severe drug-induced liver injury.

(a) *cardiac effects of quinidine*
[questions 5, 7, 9]

We agree that for a reformulation of Zenvia containing 10 mg quinidine, modeling alone can be used to predict changes in QTc interval. However, 10 mg quinidine may have cardiac adverse effects not adequately described by QTc interval alone. For example, we are still concerned about potential adverse effects of 10 mg quinidine in patients with atrial fibrillation/flutter. You must still present evidence that 10 mg quinidine is acceptably safe in the intended patient population. You should incorporate in your response effects on quinidine levels of concomitant CYP 3A4 inhibitors. You should also specifically present a risk/benefit assessment of 10 mg quinidine in patients that are genetic CYP 2D6 poor metabolizers, in whom quinidine would have no benefit, but would presumably retain those risks not directly related to CYP inhibition. Given the availability of tests to determine CYP 2D6 metabolizer status, you should either incorporate such testing in labeling, or present a compelling argument why this apparent risk-reduction method should not be used.

Following are detailed comments regarding PK/PD modeling of QTc interval change [question 10]:

1. We agree that PK/PD modeling can be used for predicting changes in QTc interval. However, we still recommend periodic monitoring of ECGs and electrolytes in your clinical trials.
2. A PKPD model for quinidine using the data from your TQT study was developed by the agency. Our assumption was QT prolongation observed for Zenvia is due to only to quinidine and its metabolites. Both direct- and delayed-effect linear models were used to describe the relationship between quinidine concentrations and the change in the QTcI interval.
3. A model-based predicted mean and 90% confidence interval for various quinidine doses is summarized in the following table. The mean and 90% confidence interval for the prediction was computed by multiplying the mean Cmax by the mean and 90% confidence interval of the slope.

Quinidine Dose (Mean Cmax)	Mean (90% Confidence Interval)		
	FDA's Direct Effect Model1	FDA's Delayed Effect Model2	E14 Metric
30 mg (179 ng/ml)	8 (5, 10)	10 (7, 13)	10 (5, 15)3
60 mg (356 ng/ml)	15 (10, 20)	20 (14, 26)	18 (13, 25)4
10 mg (60 ng/ml)5	3 (2, 3)	3 (2, 3)	Not applicable

1. Slope (90% CI): 42.8 (29.1, 56.4) ms per 1000 ng/l
2. Slope (90% CI): 55.6 (38.8, 72.4) ms per 1000 ng/l
3. Max mean change occurred at 6 h post dose
4. Max mean change occurred at 5 h post dose
5. Predicted Cmax value assuming linear pharmacokinetics

(b) *drug interactions involving CYP 2D6 and CYP 3A4*
[questions 7, 8]
Your pharmacokinetic studies examining quinidine inhibition of CYP 2D6 suggest that most patients taking 10 mg quinidine would be converted to phenotypic poor metabolizers. Therefore, the risk of adverse drug interactions involving CYP 2D6 metabolized drugs may be little changed for most patients by a reformulation of Zenvia containing 10 mg quinidine
Following are detailed comments regarding Q and CYP 3A4 inhibitors:

> We believe that the pharmacokinetics of quinidine are linear, and the mean Cmax for a 10 mg dose is expected to be approximately 60 ng/ml. We note that the mean Cmax of 40 ng/ml reported in Table 2 (page 24) of your briefing document may not be accurate as this concentration is below the limit of quantitation for the analytical assay (LLQ = 50 ng/ml). With a potent inhibitor such as ketoconazole, a 40% increase in Q is seen (according to the labeling of Q).

[question 11]
Concomitant use of Zenvia with oxycodone and CYP 3A4 inhibitors occurred relatively frequently in your NDA studies (for example, subject 107-03-002, who died of oxycodone overdose). Higher than intended levels of oxycodone from drug interactions might also occur with a reformulation of Zenvia since most patients are converted to CYP 2D6 poor metabolizers from 10 mg quinidine. While CYP 2D6 inhibition is not, of itself, an unacceptable safety risk for many patient populations, you must address how this risk can be acceptably mitigated in the target population of Zenvia, neurologically compromised patients taking multiple medications including oxycodone and CYP 3A4 inhibitors.

(c) *possible respiratory depression from Zenvia as a contributing factor in the deaths of ALS patients*
[question 10]
We remain concerned that Zenvia might cause respiratory depression, even a modest degree of which might be a meaningful risk in a population such as ALS with compromised respiratory function. Additionally, adverse drug interactions between Zenvia and other medications used by this population (such as oxycodone), might further increase the risk of respiratory depression.

Part of your argument that Zenvia (with 30 mg quinidine) does not cause respiratory depression is based on respiratory rate measurements submitted in your NDA. However, these respiratory rate measurements appear to be distributed in a biologically implausible pattern, with a large percentage recorded as 16- or 20 breaths/minute. The value of this data in assessing respiratory effects of Zenvia is therefore doubtful. Collecting more objective respiratory data with the reformulated Zenvia would help to clarify this issue.

The expected rate of death from respiratory failure in ALS is very high, such that to confidently exclude even a clearly meaningful increase in death rate (from any cause) would require a large, long term placebo-controlled study. Because of the high 'background' rate of death, comparison of death rates across different open-label ALS studies appears to us incapable of persuasively excluding even a clinically meaningful affect on death rate. Specific deaths in Zenvia development appear plausibly related to adverse effects of Zenvia. If the adverse effects of Zenvia (such as falls and vomiting) can be adequately minimized through a reformulation, we would consider such a decrease as evidence against an unacceptable rate of death from Zenvia.

(d) *nausea and vomiting in populations at risk for aspiration, and increased falls in populations already at risk from falls*
[questions 2,3,4,6,12,15]
The proposed reformulation of Zenvia with 10 mg quinidine might be associated with less nausea, vomiting, and fall than the current formulation, but this can only be adequately determined through a controlled clinical trial. If the incidence of these adverse events were not meaningfully decreased in a new formulation of Zenvia, safety risks might still outweigh benefits, despite the decreased exposure to Q.

We strongly encourage you to explore several exposure levels for dextromethorphan, including lower exposures (lower beyond the decrease expected from 10 mg instead of 30 mg quinidine).
PK/PD modeling of effectiveness and safety (dose-limiting toxicities) may be useful for selecting doses for the next clinical trial. You have performed exposure-effectiveness modeling which suggests a rather flat relationship, implying lower exposure/doses might also provide effectiveness. However, we reiterate that modeling efficacy of a reformulated Zenvia from current data is not of itself adequate evidence of efficacy

The efficacy data submitted to date for the 30 mg quinidine formulation of Zenvia, in combination with a single adequate positive study, would support the efficacy of the new formulation. As is our general policy, controlled trials for a chronic indication for Zenvia should be at least 3 months duration.

The bioavailability of the new dose/formulation will need to be established. This can be done by obtaining full PK profiles in a subset of the subjects (e.g. n=24) in the phase 3 clinical trial. We also recommend that sparse PK samples are collected in all subjects to allow for establishing an exposure response relationship, both for safety and efficacy. The PK should evaluate DM, dextrorphan, and quinidine, and will require a more sensitive quinidine assay than was used for the original studies. Please submit your proposal for evaluation.

(e) *lack of adequate clinical experience in stroke, Alzheimer's disease, and other diseases in which Zenvia is intended for use*
[questions 1,15]
The clinical experience with Zenvia in stroke, Alzheimer's Disease, and other populations in which it would be used is currently very limited. Although a matter of

discussion, if you conduct a short-term controlled trial of a new formulation of Zenvia with enough patients from several patient groups including stroke, Alzheimer's Disease, and ALS, additional long-term experience with the new formulation might not have to be complete before approval.

For any additional Zenvia efficacy studies, we prefer counts of laughing and crying episodes as the primary outcome variable. We are willing to accept CNS-LS as the primary outcome variable, but will consider episode counts as a key secondary outcome. Episode count data is particularly valuable for describing efficacy of Zenvia given the lack of clarity in definition (and naming) of pseudobulbar affect/IEED. We suggest that any new study be designed to measure baseline episode rates.

(f) *possible case of severe drug-induced liver injury*
[question 14]
The case of possible drug-induced liver injury in the Zenvia NDA (patient 136-9004) remains of concern. Evidence for a gall stone etiology is not adequately compelling to discount drug-induced liver injury. Imaging studies were largely negative for a common duct stone, and the large elevation in AST and ALT in conjunction with modest increase in alkaline phosphatase appears typical of non-cholestatic hepatocellular injury.

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/s/

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CLINICAL REVIEW

Application Type: NDA
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Reviewer Name: Ronald Farkas, M.D., Ph.D.
Review Completion Date:

Established Name:
(Proposed) Trade Name: Neurodex
Therapeutic Class:
Applicant: Avanir

Priority Designation: P

Formulation: AVP-923
Dosing Regimen: 1 tablet twice daily
Indication: Pseudobulbar Affect
Intended Population: Adults

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Neither the efficacy nor the safety of AVP-923 has been adequately demonstrated for the proposed indication and patient population. Therefore AVP-923 should not be approved.

1.2 Recommendation on Postmarketing Actions

None

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

Pseudobulbar affect (PBA) affects children secondary to various neurological conditions, at a prevalence that has not been well established. The Agency requested a pediatric program be included in a generalized claim for PBA. Given the difficulty of conducting studies in pediatric patients with PBA, these studies could be deferred until after NDA approval.

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Avanir developed AVP-923/Neurodex for the generalized claim of PBA.[1] PBA is a secondary manifestation of a variety of neurologic conditions including amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Alzheimer Disease (AD), stroke, traumatic brain injury (TBI), and others. PBA is estimated to occur in up to 50% of patients with ALS, 10% of patients with MS, 40% of patients with AD, and 15% of patients with stroke. Although variation exists in definitions of PBA, the syndrome's key manifestation is pathologic and inappropriate crying and/or laughing. The cause of PBA is unknown. Unapproved treatments for PBA include levodopa, antidepressants, amantadine, methylphenidate and thyrotropin releasing hormone. PBA has no FDA approved treatment.

AVP-923 is a combination drug containing dextromethorphan hydrobromide (DM), 30 mg, combined with quinidine sulfate (Q), 30 mg, for twice daily oral dosing.

Dextromethorphan is an antagonist of N-methyl-D-aspartate (NMDA) receptors. Dextromethorphan is structurally related to morphine, but has no classical analgesic properties. Dextromethorphan is metabolized primarily by CYP 2D6.

Quinidine is a class Ia antiarrhythmic. Quinidine inhibits CYP 2D6, and is used in AVP-923 to increase blood levels of dextromethorphan through CYP 2D6 inhibition.

Two pivotal trials were conducted with AVP-923, one in patients with ALS (study 99-AVR-102, $N = 70$ in AVP-923 arm) and one in patients with MS (study 02-AVR-106, $N = 76$ in AVP-923 arm). The ALS study was not *placebo* controlled, but instead compared AVP-923 to dextromethorphan alone and to quinidine alone. The MS study compared AVP-923 to a placebo arm, but not to the individual drug components. A long-term, single-arm, open label safety study (02-AVR-107) examined AVP-923 mainly in ALS (≈36%) and MS (≈46%) patients, but also included stroke (≈5%), traumatic brain injury (≈3%), and a smaller number of patients with other neurological diseases that manifest PBA. The overall safety database for AVP-923 also contained small studies in painful diabetic neuropathy (01-AVR-105, $N = 36$, uncontrolled open label), and PBA (CNS-93, $N = 12$, placebo controlled).

1.3.2 Efficacy

The sponsor did not adequately demonstrate efficacy of AVP-923 for the generalized claim

[1] Avanir, in the NDA application, is seeking to change the name of the indication to "Involuntary Emotional Expression Disorder," a novel term that is intended to replace PBA for this disease (see *Labeling* section of this review for further discussion). The generally accepted term 'PBA' will be used in this review.

of PBA. In addition, efficacy was not adequately demonstrated for a more limited claim in ALS and/or MS.

PBA is a secondary manifestation of multiple disparate neurological conditions, from traumatic brain injury to AD. Given the many differences among these underlying conditions, little to no evidence supports the assumption that the efficacy of AVP-923 is substantially the same regardless of the underlying cause of PBA. While efficacy trials in *every* PBA population would not be practical or expected for approval, at least some evidence of efficacy of AVP-923 should be shown in other PBA populations.

To show efficacy of AVP-923 in PBA, the sponsor submitted one study in ALS patients, and one study in MS patients. The sponsor concluded that AVP-923 was efficacious in both studies. However, I find that the study in ALS patients did not adequately demonstrate efficacy. As discussed in Section 6, the study in ALS patients was deficient in several key aspects, including inadequate length of the study, lack of placebo arm (study arms were AVP-923, quinidine, DM), and excessive patient dropout rate. The trial in MS patients provided statistically significant evidence of efficacy of AVP-923. However, a variety of deficiencies weakened the overall findings in this MS study:

- The rate at which patients stopped taking medication was very high for a study in the MS population. During 12 weeks, ≈34% of patients in both arms stopped medication. Deviations from random are impossible to exclude, and could have had a large impact on study findings due to this high percentage of patients stopping medication.
- The Agency considered the 'patient-reported outcome (PRO)' instrument used as primary outcome measure inferior to direct count of pathological laughing/crying episodes. The Agency considered the PRO susceptible to confounding effects from mild depression, and to contain some elements with questionable applicability to PBA. The 'episode count' endpoint was used as a secondary outcome, but was collected without baseline data, weakening statistical interpretation, particularly in light of the high dropout rate.
- The secondary outcome measures, 'quality of life' and 'quality of relationships,' provide little additional support for efficacy due to deficiencies in the PRO instruments used and possible lack of independence from the primary outcome measure.
- The trial compared AVP-923 to placebo, and thus did not establish superiority of AVP-923 to its individual components, as required by the combination drug rule.

1.3.3 Safety

The safety of AVP-923 has not been demonstrated in 5 major areas:

1. Cardiac/arrhythmia
2. Aspiration
3. Fall

4. Adverse drug interaction
5. Undefined safety in major PBA populations

Cardiac/arrhythmia risk

As a Class Ia antiarrhythmic quinidine induces multiple clinically important and potentially deleterious cardiac effects. The sponsor argues that the dose of quinidine in AVP-923 is sufficiently low compared to the usual 'cardiac' dose that clinically meaningful adverse cardiac effects do not occur. However, I find that the cardiac safety of AVP-923 has not been adequately demonstrated, and in fact, that evidence suggests that AVP-923 may pose a clinically important cardiac risk in PBA patients.

Known quinidine risks

- Quinidine increases the risk of life-threatening arrhythmia, including torsade de pointe (TdP). Multiple genetic and environmental factors contribute to the risk of TdP, such that even 'low' blood levels of quinidine can induce TdP in certain patients and settings (Thompson et al., Clin Pharmacol Ther 1988;43:636-42; Mathis and Gandhi, Annals of Phamacotherapy, 2002;36:1156-1161; Roden et al., Am Heart J. 1986;111:1088-93). Key risk factors for quinidine-induced TdP, such as hypokalemia, can occur in almost any patient, increasing the difficulty of limiting exposure of 'at risk' patients.
    - The average serum quinidine level in one series of cardiac patients with TdP was ≈1.6 ± 1 μg/mL (N = 19, Thompson et al., Clin Pharmacol Ther 1988;43:636-42). AVP-923, *on average*, produces quinidine levels that are ≈1/10th this level, but importantly, quinidine levels up to ≈2 μg/mL occurred as high outliers in the relatively small number of patients treated with AVP-923
    - While hypokalemia was not documented in AVP-923 development, concern remains that hypokalemia might occur in patients on AVP-923. For example, vomiting is a common adverse effect of AVP-923 that can induce hypokalemia. Detecting hypokalemia related to vomiting during a trial might be difficult because serum potassium was not generally measured proximate to vomiting.
- Quinidine affects atrio-ventricular (A-V) conduction, and when given alone (without other cardioactive drugs) to patients with atrial fibrillation or flutter can result in a hemodynamically unsustainable rapid ventricular response. Atrial arrhythmia occurs commonly, spontaneously, and largely unpredictably in the middle-aged and elderly population affected by PBA. The effect of quinidine levels induced by AVP-923 on atrio-ventricular conduction is unknown.
- The risk of TdP after quinidine-induced conversion of atrial arrhythmia to sinus rhythm is high, likely 10% or more (Hohnloser et al., J. Am. Coll. Cardiol. 1995;26:852-8). In addition to the above effects on A-V conduction, AVP-923 might increase the risk of TdP in spontaneously occurring conversion from atrial arrhythmia to sinus rhythm.
- Quinidine also causes a high incidence of other severe and potentially life-threatening adverse effects, including autoimmune thrombocytopenia (1 per 1,000 patient years) and hypersensitivity reactions involving the liver (2%). These

adverse effects are thought to correlate poorly with dose.

AVP-923 clinical study findings suggestive of cardiac/arrhythmia risk

- The incidence of arrhythmia/possible arrhythmia was higher for AVP-923 than for control arms (6 vs. 2 events).
- Cardiovascular-related dropouts were higher for AVP-923 than for control arms (2 vs. 0 events).
- Several adverse events in AVP-923 treated patients were associated with arrhythmia/possible arrhythmia, including sudden death in one patient, and syncope in another patient with QTc increase >60 ms.
- QTc outliers occurred in the AVP-923 database, with cases of both >60 ms QTc increase, and >500 ms absolute QTc increase.
- AVP-923 was found in a 'thorough QT' study to prolong QTc by an average of ≈10 ms, with a 95% confidence interval up to ≈15 ms. While QTc prolongation is an imperfect predictor of arrhythmic risk, the fact that quinidine is already known to be pro-arrhythmic increases the likelihood that this degree of QT prolongation from 'low dose' quinidine represents a clinically meaningful increase in risk.

Aspiration Risk

Much of the PBA patient population may be at high risk of aspiration due to underlying neurological disease. In ALS patients, AVP-923 induced high rates of nausea (33%) and vomiting (6%). Vomiting from high dose DM alone (without quinidine) can be intractable (Hollander et al., Ann Neurol 1994;36:920-4). In a phase 1 study of AVP-923, a normal subject died after suffering intractable vomiting thought by the investigator to be drug-related (although the proximate cause of death, small bowel obstruction, may not have been drug-related). Even though the AVP-923 exposure in ALS was very small, with only 4 total serious adverse events in all three arms combined, one serious adverse event in the AVP-923 arm was aspiration, with no similar event in the other two study arms.

Fall Risk

Much of the PBA population may be at high risk of fall due to underlying neurological disease. The fall rate in ALS patients was 18% for AVP-923, 14% for dextromethorphan, and 0% for quinidine. Absence of a control arm hampers unequivocal interpretation of this data, but a reasonable interpretation is that AVP-923 and dextromethorphan substantially increase fall risk compared to quinidine. The only death in the ALS trial was associated with broken ribs in a patient taking AVP-923 who experienced dizziness and fell (this also represents a possible signal for 'excess death' in general in the AVP-923 arm).

In the controlled trial in MS patients 'fall' occurred in 4/76 (5%) of AVP-923 patients and 2/74 (3%) placebo patients. While the total number of events was small, this suggests an increased risk of fall also may exist for MS patients. 'Dizziness' affected 26% of MS patients on AVP-923, and only 9% on placebo.

Evidence that dizziness from AVP-923 shows adaptation in either the ALS or MS population is not persuasive (Section 7.1.5.6)

Adverse drug interactions
The quinidine in AVP-923 is designed to fully inhibit CYP 2D6, which metabolizes approximately 25% of all commonly used medications, including many cardiovascular drugs, antidepressants, antipsychotics, and analgesics used by PBA patients. Lack of CYP 2D6 activity can cause serious adverse drug reactions. The role of CYP 2D6 in the metabolism of many drugs is incompletely understood, particularly with regard to the role of active drug metabolites.

A drug interaction study (04-AVR-112) of AVP-923 and the tricyclic antidepressant desipramine found, not unexpectedly, a 7- to 8-fold increase in desipramine levels. These levels were associated with increased QT and QRS intervals, palpitations, tachycardia, and cardiac arrhythmia. In the AVP-923 safety study (02-AVR-107) a patient died from overdose of oxycodone while taking AVP-923 with another CYP inhibitor that together block both major pathways of oxycodone metabolism (CYP 2D6 and 3A4).

Many common drugs increase quinidine levels, including erythromycin, which was associated with a sudden death in AVP-923 studies. The thorough QT study of AVP-923 found that QTc prolongation was strongly dose related for AVP-923 (twice the dose associated with near doubling of QTc). Even small increases in quinidine levels from AVP-923 might therefore substantially increase the risk of TdP and other adverse cardiac actions.

In addition to absolute quinidine level, the pro-arryhthmic risk of quinidine is likely to be increased by concomitant use of other drugs that prolong QTc or that are otherwise pro-arrhythmic. As noted above, erythromycin is of particular concern because it both increases quinidine levels and is itself a QT-prolonging drug (labeled under erythromycin ADVERSE REACTIONS: Erythromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes).

Quinidine also inhibits the drug efflux pump p-glycoprotein, an effect not addressed in the NDA submission. The clinically important interaction between quinidine and digoxin is thought to occur through this mechanism.

Undefined safety risk in PBA populations
PBA occurs in many different disease populations in addition to ALS and MS, including stroke, traumatic brain injury, Alzheimer Disease and others. The risk/benefit profile for AVP-923 might differ among these PBA populations. In fact, the current AVP-923 database suggests that AVP-923 might be more poorly tolerated in ALS than MS patients. Similarly, the death (as mentioned above) of an otherwise healthy elderly volunteer in phase I testing suggests that an elderly population might be at increased risk from AVP-923. Few patients over the age of 75 were included in AVP-923 studies, particularly in controlled studies.

Specific disease populations commonly take disease-specific drugs, such as memantine for AD. Adverse interaction between AVP-923 and memantine is of particular concern because both drugs are NMDA antagonists, and have overlapping adverse event profiles

including dizziness, fatigue, nausea, and vomiting.

The U.S. prevalence of Alzheimer Disease, Stroke, and traumatic brain injury are each about 100-fold greater (3-4 million) than the prevalence of ALS (30,000), and 10-fold greater than the prevalence of MS (300,000). The total number of patients with PBA in the U.S. likely approaches 1 million, with only about 5% of this total representing the ALS and MS patients included in AVP-923 controlled trails (and composing ≈80% of the safety trial). Thus, the current safety database is only informative about a small minority of patients who would be treated with AVP-923.

Additional important safety issues:

1. *Lack of benefit but maintained risk of quinidine in CYP 2D6 poor metabolizers*: Seven to ten percent of Caucasians completely lack CYP 2D6 activity ("poor metabolizers) and gain no benefit from the quinidine in AVP-923, while remaining at risk for many of quinidine's adverse effects. No testing is proposed by the sponsor to detect such patients or prevent their use of AVP-923. Such patients can be identified by genetic testing, and should be excluded from AVP-923 use (section 7.5.1).
2. *Respiratory depression*
   Dextromethorphan is a respiratory depressant at high doses (USP Drug Information). Adequate data was not presented that AVP-923 is safe in populations with compromised respiratory function, such as in ALS.
3. *Cough suppression*
   Patients with PBA often have reduced ability to clear respiratory secretions. Dextromethorphan inhibits cough, and could lead to increased risk of respiratory infections and respiratory failure. Inadequate data is presented to evaluate this possibility.
4. *Hepatotoxicity*
   Subsequent to submission of the NDA and safety update, a single patient in ongoing IND studies of AVP-923 developed acute hepatotoxicity of unknown etiology, in a pattern consistent with 'Hy's law.' Possible relationship to AVP-923 can not be excluded. Additional clinical information should be provided by the sponsor (see section 7.1.7.5).
5. *Abuse potential of AVP-923*
   The abuse potential of AVP-923 has not been adequately defined (See section 7.1.13, *Withdrawal Phenomena and/or Abuse Potential*).

1.3.4 Dosing Regimen and Administration

Each AVP-923 tablet contains dextromethorphan 30 mg and quinidine 30 mg, for twice daily dosing.

1.3.5 Drug-Drug Interactions

Drug interactions are a major safety risk of AVP-923, as summarized in section 1.3.3.

1.3.6 Special Populations

As discussed in the *Executive Summary*, a large number of neurological diseases secondarily manifest PBA, including ALS, MS, PD, stroke, Huntington disease (HD), mental retardation, traumatic brain injury, dementia, schizophrenia, and a number of less common neurodegenerative disorders. Tremendous heterogeneity exists among these patient populations. Inadequate evidence supports the safety and efficacy of AVP-923 in most populations for which it is intended.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

AVP-923 is a combination drug containing dextromethorphan hydrobromide USP, 30 mg, and quinidine sulfate USP, 30 mg quinidine on an anhydrous basis. It is intended for twice daily oral dosing.

AVP-923 is intended for treatment of PBA in adults.

Dextromethorphan is an antagonist of N-methyl-D-aspartate (NMDA) receptors. While dextromethorphan is structurally related to morphine, it has no classical analgesic properties.

Quinidine is a class Ia antiarrhythmic. Quinidine inhibits CYP 2D6, and is used in AVP-923 to increase blood levels of dextromethorphan through this inhibition.

2.2 Currently Available Treatment for Indications

PBA is marked by loss of normal emotional control, manifested as crying and/or laughing that is not congruent with internal emotional state. PBA can significantly impair social and occupational function, and can be distressing and disabling. Although estimates of incidence vary widely, PBA may occur in up to 50% of patients with ALS, 10% of patients

with MS, 40% of patients with AD, and 15% of patients with stroke. In the U.S., the incidence of new cases might be >1 million/year (Arciniegas et al., *CNS Spectr*. 2005;10:1-14) The cause of PBA is unknown.

No treatment is FDA approved for PBA. Unapproved treatments include levodopa, antidepressants, amantadine, methylphenidate and thyrotropin releasing hormone. No large, well-controlled trials have been conducted in PBA other than in AVP-923 development.

2.3 Availability of Proposed Active Ingredient in the United States

The two active components of AVP-923, quinidine and dextromethorphan, are both marketed in the United States.

Dextromethorphan
Dextromethorphan is a centrally acting cough suppressant, and is an ingredient in many over-the-counter cough and cold remedies. It was approved by FDA in 1958, and is the subject of an FDA monograph (41 Fed. Reg. 38312, Sept. 9, 1976). Labeling requirements regarding the antitussive efficacy of dextromethorphan are contained in 21 C.F.R. 341.14(1)(3), 341.74(d)(1)iii). Dextromethorphan has been investigated in multiple neurological disorders including PD, stroke, acute brain injury, ALS (no benefit found in disease progression), neuropathic pain, and others.

FDA has expressed concern about the abuse potential of dextromethorphan (FDA Talk Paper, May 20, 2005). The Controlled Substances Act specifically excluded dextromethorphan from any of the Schedules in 1970 because of a lack of significant opiate-like abuse potential [21 USC 811(g)(2), "Dextromethorphan shall not be deemed to be included in any schedule by reason of enactment of this subchapter unless controlled after October 27, 1970 pursuant to the foregoing provisions of this section."].

Quinidine
Quinidine was introduced in 1918 as a stereoisomer of quinine, and has been widely used as a cardiac drug since the mid 19th century. Quinidine is a class Ia antiarrhythmic, currently used mainly to treat life-threatening arrhythmias. It is FDA approved for conversion of atrial fibrillation/flutter to sinus rhythm, reduction of frequency of relapse into atrial fibrillation/flutter, and suppression of ventricular arrhythmia. Quinidine inhibits CYP 2D6, the major route of dextromethorphan metabolism, and is used in AVP-923 for this effect [Note: the experimental design of pivotal trials of AVP-923 prevents concluding that quinidine has no effect separate from increasing dextromethorphan levels].

Quinidine is pro-arrhythmic secondary to direct myocardial depression and conduction delay affecting myocardial repolarization. When used for maintenance of sinus rhythm after cardioversion, quinidine is estimated to triple death rate (Coplen et al., Circulation 1990, 82:2248-50), although this estimate was based on small absolute numbers. Quinidine

increases QT interval in a dose-dependent fashion, but the risk of arrhythmia from quinidine is present at low drug levels, ≤ 2 μg/mL (Mathis & Gandhi, Annals of Pharmacotherapy, 2002;36:1156-1161). Quinidine increases QT dispersion (QTd), an experimental measure of pro-arryhthmic potential. Quinidine induces a greater increase in QTd at low levels, < 1.5 μg/ml than at high levels (quinidine levels up to 2 μg/mL were produced by AVP-923).

2.4 Important Issues With Pharmacologically Related Products

None.

2.5 Presubmission Regulatory Activity

AVP-923 was developed for the indication of PBA under IND 56,954. Studies of AVP-923 for the indication of neuropathic pain are being conducted under IND (b) (4) in the Division of Anesthesia, Analgesia, and Rheumatology Products.

Major Amendment/Goal Date Extension
On June 29, 2006, FDA received Avanir's June 26, 2006 submission of the final study report for a thorough QT study in healthy volunteers, which was considered a major amendment to this application. The receipt date was within 3 months of the user fee goal date. The goal date was extended by three months to provide time for a full review of the submission. The extended user fee goal date was October 30, 2006.

Filing Issues
The NDA application was submitted under a rolling review procedure. The Division initially 'Refused to File' (Aug 25, 2005) the completed application, but this decision was later rescinded by the Division (Sept 13, 2005). Upon further review, the Division determined that the NDA submission of August 9, 2005 did not contain a comprehensive Integrated Summary of Safety (ISS) and could not be considered the final submission to this application (Oct 19, 2005 letter). A revised ISS was submitted and the NDA was filed with a 6-month review schedule, ending July 30th 2006.

General Indication of PBA
During development, the Agency indicated that studying PBA in two different diseases would be adequate for filing a marketing application for the general indication of PBA.

Primary endpoint
The Division strongly encouraged the sponsor to use counts of episodes of pathological laughing and crying as the primary endpoint. The sponsor selected a patient-reported outcome instrument, the Center for Neurologic Study-Lability Scale (CNS-LS). The Division agreed at the End of Phase 2 (EOP-2) meeting to consider studies using CNS-LS

as the primary endpoint.

Controlled trial length
In the EOP-2 meeting, the Division indicated that controlled trials of 3 months duration were generally required for chronic therapies such as for PBA, instead of the 28 day duration of study 99-AVR-102.

Placebo control
In the EOP-2 meeting the Division indicated that the lack of a placebo in study 99-AVR-102 hindered study interpretation.

Statistical Issues
The Division noted that the sponsor's plan to record CNS-LS score beginning on Day 15 was problematic (submission 027 and 028, see review of Dr. Kevin Prohaska, 03-Apr-2002). Patients withdrawing before day 15 would not provide information to the ITT data set. The agency suggested more data be collected before Day 15. The sponsor did not follow this suggestion, and a high number of dropouts occurred in both pivotal studies, undermining study findings.

Dose/response
The Division communicated to the sponsor that the dose/response of dextromethorphan/quinidine for the treatment of PBA should be explored (submission 028). However, dose/response studies were not carried out.

Abuse potential of AVP-923
In the pre-NDA meeting, the Division indicated that no additional studies would be required before regulatory filing to assess the abuse liability of AVP-923.

Trade Name
DMETS recommended against the use of the proprietary name, Neurodex, due to the availability of Neurodex in other countries (Mexico, Antirheumatic Corticosteroid Combination; Singapore and Indonesia, vitamin B combination) containing different active ingredients (and one additional name, 'Neurobex,' with the potential for look-alike confusion with Neurodex). The DMETS consult to DNP noted that recent post-marketing experience demonstrates FDA should not allow the use of the same name for different products containing different active ingredients. DNP recommended that the Sponsor submit an alternate proprietary name. The sponsor appealed in a letter dated June 23, 2006.

2.6 Other Relevant Background Information

None

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

For additional assessment of the CMC data, see Dr. Gurpreet Gill-Sangha's CMC review of this application.

3.2 Animal Pharmacology/Toxicology

Nonclinical studies suggest CNS, kidney, and liver as target organs of toxicity for AVP-923. The major CNS toxicity in nonclinical studies was generalized CNS depression. The sponsor also noted minor, reversible changes in lung and thyroid. An acute exposure study was reported as negative for Olney lesions. Kidney toxicity was evident as increased urinary volume and kidney weights in rats. Kidney histopathology showed transient tubular dilation. Liver toxicity was evident as increased liver weight and minimal centrilobular hepatocellular hypertrophy that was plausibly a physiological response to the physiological demand of metabolizing the administered drugs.

For additional assessment of the nonclinical data, see Dr. Kathleen Young's Pharmacology/Toxicology review of this application.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Clinical data supporting AVP-923 safety and efficacy was mainly from trials conducted by the applicant (Table 1). A full study report was also submitted for the investigator-sponsored study CNS-93, a small randomized controlled trial in a total of 12 PBA patients. Literature-derived studies, also listed in Table 1, contributed to the review of safety but were not used by the sponsor to support efficacy.

Table 1: Clinical Studies Providing Exposure to Combination dextromethorphan and

quinidine
(from Table 2-1, NEW ISS AVP-923.pdf)

Study No./ Reference	Study Type	Subject Population	Number of Study Participants Exposed to Combination of DM and Q			Study Report Location
			AVP-923*	DM Daily Dose	Q Daily Dose	
Avanir-Sponsored						
04-AVR-111	Biopharmaceutic, PK, food effect	Healthy volunteers	18	NA	NA	5.3.1.1 (CTD)
99-AVR-100	Clinical pharmacology PK, dose-ranging	Healthy volunteers	NA	39		5.3.3.1 (CTD)
				30, 60 mg	5-150 mg	
99-AVR-101	Clinical pharmacology PK	Healthy volunteers	10	NA	NA	5.3.3.1 (CTD)
00-AVR-103	Clinical pharmacology PK, dose-ranging	Healthy volunteers	NA	48		5.3.3.1 (CTD)
				90, 120 mg	60, 90, 120 mg	
04-AVR-115	Hepatic impairment PK and safety	Healthy volunteers and patients with mild and moderate hepatic impairment	21	NA	NA	5.3.3.3 (CTD)
04-AVR-116	Renal impairment PK and safety	Healthy volunteers and patients with mild and moderate renal impairment	21	NA	NA	5.3.3.3 (CTD)
04-AVR-112	Drug interaction PK and safety	Healthy volunteers	15	NA	NA	5.3.3.4 (CTD)
99-AVR-102	Controlled efficacy and safety	ALS patients with PBA	70	NA	NA	5.3.5.1 (CTD)
02-AVR-106	Controlled efficacy and safety	MS patients with PBA	76	NA	NA	5.3.5.1 (CTD)
02-AVR-107	Open-label safety	Patients with PBA	463†	NA	NA	5.3.5.2
01-AVR-105	Open-label safety	Patients with PDN	NA	36		5.3.5.2 (CTD)
				30, 45, 60, 90, 120 mg	30, 60, 90, 120 mg	
Investigator-Sponsored						
CNS-93	Controlled efficacy	Patients with PBA‡	NA	12		5.3.5.1 (CTD)
				60 mg	150 mg	
Studies Published in the Literature§						
Schadel et al. (1995)[24]	Clinical pharmacology PK	Healthy volunteers	NA	5		NA
				30 mg	100 mg	
Capon et al. (1996)[25]	Clinical pharmacology PK	Healthy volunteers	NA	6		NA
				30 mg	50 mg	
Abdul-Manap et al. (1999) [26]	Clinical pharmacology PK	Healthy volunteers	NA	22		NA
				30 mg	50 mg	
Desmeules et al. (1999)[27]	Clinical pharmacology PK	Healthy volunteers	NA	7		NA
				50 mg	50 mg	
Zhang et al. (1992)[28]	Clinical pharmacology PK	ALS patients	NA	8		NA
				15-120 mg	150, 300 mg	
Metman et al. (1998b)[29]	Efficacy (for treatment of PD)	Patients with PD	NA	6		NA
				30-180 mg	200 mg	
Metman et al. (1998a)[30]	Efficacy (for treatment of PD)	Patients with PD	NA	18		NA
				30-180 mg	200 mg	

Source: Table 5.1, Section 5.2 (CTD).

Note: Study participants in Study 99-AVR-101 also participated in Study 99-AVR-100, and approximately 20% of patients in Study 02-AVR-107 will also have participated in Study 99-AVR-102 or Study 02-AVR-106.
ALS = amyotrophic lateral sclerosis; CTD = Common Technical Document; DM = Dextromethorphan Hydrobromide USP; MS = multiple sclerosis; NA = not applicable; PBA = pseudobulbar affect; PD = Parkinson's disease; PDN = painful diabetic neuropathy; PK = pharmacokinetic(s); Q = Quinidine Sulfate USP. * The daily dose of AVP-923 (30 mg DM and 30 mg Q, twice daily) was 60 mg DM and 60 mg Q for all studies except Study 04-AVR-111; study participants received only one capsule of AVP-923.
† As of interim cutoff date, 31 October 2005.
‡ CNS-93 enrolled 8 patients with ALS and 4 patients with other neurological diseases.
§ Literature was searched by using the following search terms: pseudobulbar affect, pseudobulbar palsy, pathological laughing and crying, emotional lability, dextromethorphan, and quinidine.

4.2 Tables of Clinical Studies

See section 4.1

4.3 Review Strategy

All trials conducted by the sponsor were analyzed for efficacy and safety in this review. Literature sources were used to evaluate safety of both the individual components and their use in combination.

Both safety and efficacy portions of the review were performed by a single primary reviewer.

4.4 Data Quality and Integrity

For both the ALS (99-AVR-102) and MS (02-AVR-107) studies, I analyzed the consistency of the primary outcome results (change in CNS-LS score) across study sites. I also examined the dropout rate by site. In the following analysis, I imputed change in CNS-LS score differently than the sponsor: all patients that did not continue medication for at least 90% of the study length were assigned a change in CNS-LS score of zero (discussed in detail in section 6, Integrated Review of Efficacy). While wide differences in efficacy and non-completer rate were present among sites, I found no evidence to suggest that this was due to factors other than chance.

Study 99-AVR-102
In study 99-AVR-102, center #8, the second largest site with 17 total patients, was the most important favoring AVP-923 (Table 2, only largest sites shown). Center #8 had few dropouts compared to other centers.

Table 2: Study 99-AVR-102, Outcome (CNS-LS) by Site

		AVP-923		DM		Q		Median difference CNS-LS score#	
site	Total	enrolled	Stopped drug*	enrolled	Stop drug	enrolled	Stop drug	AVP-DM	AVP-Q
03	8	4	1/4	2	0/2	2	1/2	-1	2
13	8	4	2/4	2	0/2	2	0/2	-.25	2
14	8	4	0/4	2	0/2	2	0/2	1.25	5.25
06	9	5	3/5	2	0/2	2	0/2	-8.75	-2
01	15	7	1/7	4	1/4	4	2/4	7.25	6.25
07	15	8	2/8	3	0/3	4	1/4	.05	5.5
08	17	9	0/9	4	0/4	4	0/4	9.5	8.5
11	21	10	4/10	6	0/6	5	1/5	-6.25	-.75

* completed less than 11 weeks treatment
# CNS-LS score calculated using 'no change' for patients completing less than 11 weeks treatment
Shaded rows indicate sites with major effect on efficacy outcome.

Site #08 was selected for DSI inspection based on this analysis
Benjamin Brooks, MD
ALS Clinical Research Center
University of Wisconsin
H6/563 Clinical Science Center
600 Highland Avenue
Madison, WI 53782

DSI inspection revealed that the investigator did not adhere to the investigational plan in that subject 0817 was randomized to the study despite taking quinine sulfate, a prohibited medication. The data from the site otherwise appeared acceptable in support of the respective indication.

Study 02-AVR-106
In study 02-AVR-106, center #34, the largest site, contributed the most to evidence of AVP-923 efficacy, in terms of both size and degree of superiority of AVP-923 versus placebo (Table 3, only largest sites shown).

Table 3: Study 02-AVR-106, Outcome (CNS-LS) by Site

Site #	AVP-923		Placebo		Total enrolled	Median difference CNS-LS score# (AVP - placebo)
	enrolled	Stopped drug*	enrolled	Stopped drug		
2	4	1/4	5	1/5	8	1.1
3	4	0/4	5	0/5	9	5.25
8	6	4/6	5	4/5	11	-2.6
15	4	1/4	4	2/4	8	1.5
17	9	3/9	10	3/10	19	-4.6
18	6	3/6	5	2/5	11	1.1
21	5	3/5	6	1/6	11	-4.1
34	12	2/12	10	1/10	22	6.1

* defined as completing less than 11 weeks treatment
# CNS-LS score calculated using 'no change' for patients completing less than 11 weeks treatment
Shaded rows indicate sites with major effect on efficacy outcome.

Site #34 was selected for DSI inspection based on this analysis.
PI: Gary Pattee, MD
Neurological Associates, P.C.
2631 South 70th St.
Lincoln, NE 68506
402-483-6498

DSI inspection found that the data appeared acceptable in support of the relevant indication.

Protocol Amendments
Study 99-AVR-102
The protocol for study 99-AVR-102 was amended twice, including the following substantive changes:

- Poor metabolizers were removed from the efficacy analysis. This was done because poor metabolizers in the DM arm of the study would have had similar DM levels as subjects in the AVP-923 arm.

  [Comment: Administering quinidine to CYP 2D6 null patients imparts no efficacy benefit, but remains a safety risk for these patients. The CYP 2D6 genotype should be determined for all patients to exclude homozygote null patients *before* instituting AVP-923 therapy.]

- The washout period for fluoxetine, a disallowed medication, was changed from 4 weeks to 2 weeks.

The second amendment occurred on June 5, 2001 and affected the following areas of the protocol:

- The inclusion/exclusion criterion that permitted subjects 18 to 75 years of age to

enroll in the study was changed to permit subjects 18 to 80 years of age.
- Vital capacity requirements were changed from ≥ 60 % to ≥ 50 %.
- The prolongation of the QT_c interval was changed from ≥ 430 msec to ≥ 450 msec and the requirement for a QRS ≥ 110 msec was deleted.
- The requirement that the Day-15 visit be held in the clinic was waived.
- Quinine, St. John's Wort, anticoagulants, and antiarrhythmic medications were added to the list of disallowed medications.
- The washout period for all disallowed medications was reduced to 1 week.

These changes appear acceptable.

4.5 Compliance with Good Clinical Practices

The sponsor states that standards for good clinical practice (GCP), as outlined by regional regulations, were adhered to for all procedures in the studies.

4.6 Financial Disclosures

The HHS form, *Certification: Financial Interests and Arrangements of Clinical Investigators* was submitted, and indicated that, per checkbox #1, no study investigators had significant financial interest in AVP-923.

5. CLINICAL PHARMACOLOGY

Key Conclusions
A therapeutic 'cardiovascular' blood level of quinidine is generally considered to be as low as 1,000 ng/ml. Plasma levels of quinidine in AVP-923 studies were as high or higher than 300 ng/ml, *not* timed for Cmax, in about 5% of patients (N = 70 for ALS study, N = 76 in MS study). Quinidine level in one patient was over 2,000 ng/ml (Table 4, Table 5). This patient had a 32 ms QTcF increase, and was taking hydrochlorothiazide, which reduces renal elimination of quinidine and can thus increase serum levels. TdP from quinidine can occur at levels below 2,000 ng/ml.

Table 4: Quinidine, Random Levels, ALS study 99-AVR-102

Patient Number	Study Arm	Quindine (μg/ml)
1408	AVP-923	2.21
0810	DM	0.606*
0101	AVP-923	0.373
1403	AVP-923	0.327
1501	AVP-923	0.322
0609	AVP-923	0.262
0107	AVP-923	0.255
1505	AVP-923	0.239

* The DM/DX ratio is what would be expected from a patient only on DM, and is not expected from a patient also on quinidine. No other sample on a different date was taken to serve as a comparison. There's no indication that the patient was taking another source of quinidine or was a protocol violation.

Table 5: Quinidine, Random Levels, MS study 02-AVR-106

Patient Number	Study Arm	Quinidine (μg/ml)
3202	AVP-923	0.4770
1807	AVP-923	0.4669
1802	AVP-923	0.3953
2100	AVP-923	0.3741
0806	*	0.3490

*not specified in sponsor's data table

For additional information, see the Clinical Pharmacology review by Dr. Sally Yasuda for this application.

5.1 Pharmacokinetics

Dextromethorphan
Dextromethorphan is used widely as an antitussive. The usual adult dose is 30 mg every 6 to 8 hours. Dextromethorphan is extensively metabolized by the P450 2D6 enzyme to dextrorphan (DX), which has CNS effects, and several other metabolites that have been less intensively studied. In extensive metabolizers (93% of Caucasian population) greater than 90% of dextromethorphan is metabolized via the P450 2D6. Approximately 7% of the US population has no activity of P450 CYP2D6, and are termed 'poor metabolizers.' Quinidine does not further decrease metabolism of dextromethorphan in poor metabolizers.

Quinidine
Quinidine is a Class Ia cardiac antiarrhythmic drug most often used to maintain sinus rhythm after cardioversion of atrial fibrillation, or for the suppression of supraventricular and ventricular arrhythmias. Oral quinidine is rapidly absorbed, with a T_{max} of about 1.5 hours. Quinidine is metabolized by P450 CYP3A4, and inhibits CYP2D6. The plasma half-

life is about 6 to 8 hours. The usual adult dose of quinidine is 200 to 400 mg three or four times daily based on clinical response.

Considerable intersubject and intrasubject variability in the pharmacokinetics of quinidine has previously been documented. For example, the half-life can range from about 1 to 16 hours. Urinary excretion of quinidine is dependent on urinary pH, such that increased quinidine levels can occur from drugs that increase urinary pH, such as sodium bicarbonate, some antacids, and carbonic anhydrase inhibitors.

Effect of CYP 2D6 inhibition on other drugs
A drug interaction study (04-AVR-112) found that CYP 2D6 inhibition by AVP-923 greatly increased adverse effects of desipramine, a tricyclic antidepressant (see Section 8.2, *Drug-Drug Interactions*).

5.2 Pharmacodynamics

Aside from studies examining the dose of quinidine required to inhibit CYP 2D6, pharmacodynamic studies of quinidine and DM were not conducted in support of the AVP-923 NDA application. While the mechanism of action of dextromethorphan in PBA is hypothesized to relate to NMDA receptor effects, this mechanism remains largely theoretical.

5.3 Exposure-Response Relationships

Only one dose combination was examined in pivotal studies.

6. INTEGRATED REVIEW OF EFFICACY

6.1 Indication

6.1.1 Methods

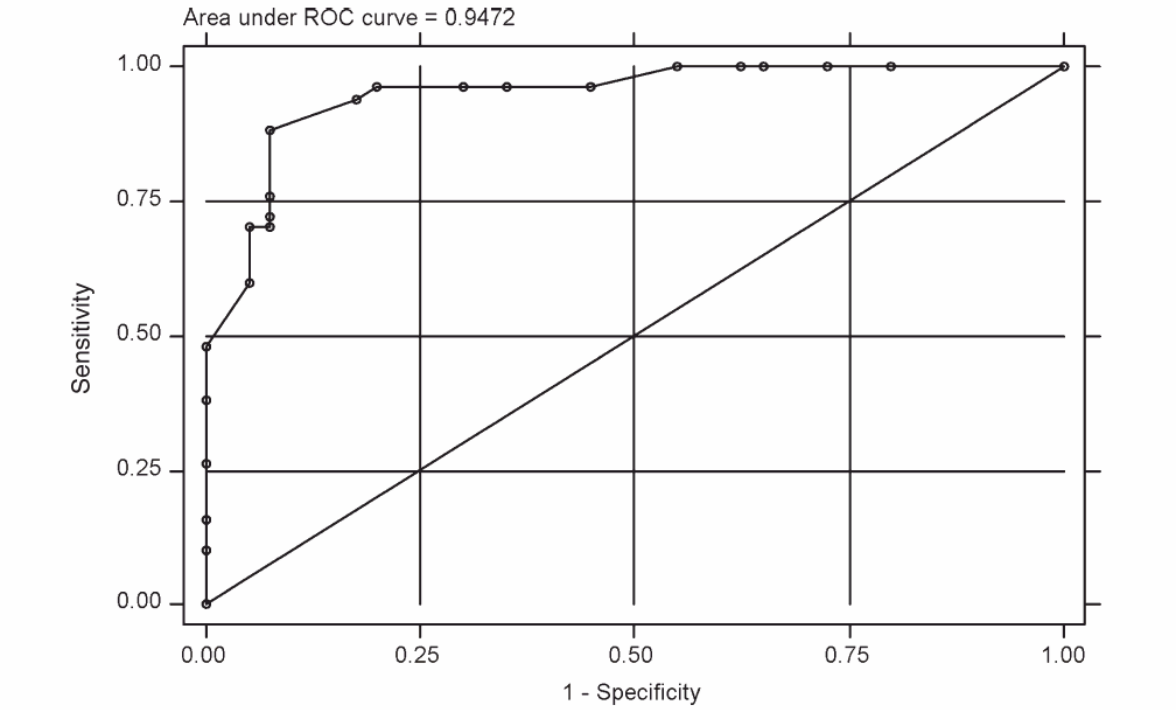
Two placebo controlled pivotal studies were submitted as support of the efficacy of AVP-923: 99-AVR-102 and 02-AVR-106.

6.1.2 General Discussion of Endpoints

Primary endpoint: CNS-LS
The primary efficacy endpoint in studies 99-AVR-102 and 02-AVR-106 was 'change from baseline in Center for Neurologic Study-Lability Scale (CNS-LS) score.' The CNS-LS is an abbreviated modification of the investigator-administered Pathologic Laughter and Crying Scale (PLACS), an 18-item measure that has been used to evaluate pseudobulbar affect after stroke.

The CNS-LS is a 7-item self-report measure that provides a score for total PBA severity (Figure 2). The range of possible scores is 7 (least severe) to 35 (most severe). The sponsor enrolled only patients with a score of ≥13, which, for ALS patients, accurately predicts a neurologists' diagnoses for 82% of participants with a sensitivity of 0.84 and a specificity of 0.81 (Moore et al., J. Neurosurg. Psychiatry, 1997;63:89-93). In contrast, for MS, a higher CNS-LS score, ≥17 performed best at predicting the diagnosis of PBA (Smith et al., Mult. Scler. 2004;10:679-85), with a sensitivity of 0.94 and a specificity of 0.83. Despite this, the sponsor used the same minimum CNS-LS score for inclusion in the MS study as used in the ALS study. A score of 13 in MS patients corresponds to a sensitivity of about 96%, but a specificity of only about 55% (interpolated from Figure 1). In both study arms, more than 1/5 of patients had CNS-LS baseline scores less than 17.

Figure 1:CNS-LS in MS, ROC curve
(From Smith et al., 2004)



Smith et al. 2004 identify key points in the ROC curve as follows: "The upper-leftmost points in Figure 1 correspond to CNS-LS scores of 16, 17, and 18. Using each of these in turn as a cut-off produces sensitivities of 96%, 94%, and 88% and specificities of 80%, 83%, and 93%, respectively. In this sample, the positive predictive values were 86%, 87%, and 94%, while the negative predictive values were 94%, 92%, and 86%." Since the lowest score for the CNS-LS is 7, I interpret the right-most point as 7, with the point 7th from the right corresponding to a score of 13.

Figure 2: CNS-LS Patient Form

CNS-LS (Patient Completes)

(b) (4)

During AVP-923 development, the Agency recommended using counts of pathological laughing/crying episodes as the primary outcome variable. Dr Paul Andreason from the Division of Psychiatry Products noted in a consult (April 26, 1999) that investigators have used episode counts previously without problems. Dr. Mani, the primary reviewer from Neurology Products also recommended episode counts as the primary endpoint instead of CNS-LS: (1) He did not agree with the sponsor that patients could not adequately quantify their attacks. (2) He thought that a CNS-LS form completed episodically during follow up visits would be less reliable than a daily diary completed during the treatment period. (3)

He felt that although the scale appears to be valid in diagnosing PBA when compared to an examination by a neurologist, he did not believe it was the best instrument to determine the frequency of episodes. (4) He felt that despite the sponsor's plan to exclude patients with severe depression it seemed likely that milder forms of depression might confound the study results (also a concern of Dr. Andreason). (5) He felt question number 5 appeared to be assessing the tendency to have "happy or funny thoughts" as opposed to externally visible laughter and crying, the later of which are fundamental to what is conventionally considered to be pathological. (6) Finally, he did not agree with the sponsor that the scale has the ability to assess the severity of individual episodes of pathological laughter and crying.

I agree with the concerns of Drs. Mani and Andreason. I have the related concern that the correlation between pathological episodes and CNS-LS score appears to be weak. For example, fully 1/3 (11 of 33) subjects in the dextromethorphan arm (a 'control' arm) of study 99-AVR-102 had 4 or fewer pathological episodes over the entire 4 week study period, with 4 of these eleven having no pathological episodes at all, despite all patients having met the enrollment criterion for CNS-LS score of 13 or more. PBA is largely defined by the episodes of pathological laughing and crying themselves, such that I am concerned that the CNS-LS is not, in fact, measuring PBA severity very well.

Secondary endpoints
Secondary endpoints for 99-AVR-102 were:

- Pathological laughing/crying episode counts
- Quality of life (QOL) [this is the sponsor's nomenclature – I do not consider this instrument to measure QOL (see below)(Figure 3)]
- Quality of relationships (QOR) [this is the sponsor's nomenclature – I do not consider this instrument to measure QOR (see below)(Figure 4)]

An additional endpoint for study 02-AVR-106 was assessment of MS-associated pain, by the *Pain Intensity Rating Scale* (PIRS).

Episode Counts
As noted in the discussion of CNS-LS above, the Agency favored episode counts as the primary outcome variable. Importantly, the sponsor did not collect actual baseline episode counts, but only historical data. The lack of reliable baseline data impedes interpretation of the episode count data:

- For sensitivity analysis, dropouts might be assigned episode rates equal to baseline if this information was reliable.
- Without baseline data, determining if differential dropouts occurred associated with baseline episode count is not possible.
- The statistical analysis of episode counts was pre-specified in the SAP as based on a Poisson regression model. The data collected showed strong evidence of more variability than the Poisson model would predict (overdispersion), and consequent lack of fit. The sponsor's statistician states: "This particular departure from the Poisson model understates standard errors, so p-values for treatment effects are too small (over-significant). A valid but conservative approach (which

may sacrifice considerable power) in this case is to fit the Poisson model, but to rescale the standard errors using the deviance or Pearson chi-squared statistic. When this is done in the AVP-923 data, the treatment effects are no longer statistically significant" for study 99-AVR-102 (From NDA section 7.5.1, Notes on Episode-Count Models, study-99-avr-102.pdf).

Quality of Life

Figure 3 shows the form presented to patients to measure what the sponsor denotes as "Overall Quality of Life," a secondary outcome measure. This instrument, however, does not measure 'overall quality of life,' but instead addresses only the much narrower concept of how much overall quality of life is affected by uncontrollable laughter, tearfulness, or anger. I find three major weaknesses of this outcome variable that preclude use:

1. The measure focuses narrowly only on how uncontrollable laughter, tearfulness, or anger affect overall quality of life. The measure is therefore almost certainly highly correlated with the 'CNS-LS' and 'episode count' outcome variables, thus providing little additional evidence of efficacy. The measure would have been far more informative if it did, in fact, measure 'overall quality of life.'
2. The measure includes *anger*, which is not a generally accepted key component of PBA.
3. Although the measure, strictly interpreted, focuses only on the effect of uncontrollable laughter etc. on quality of life, the presentation to the patient is potentially misleading due to the title, "*overall quality of life.*"

Figure 3: 'Overall Quality of Life' Patient Form

OVERALL QUALITY OF LIFE

Quality of Relationships

Figure 4 shows the form presented to patients to measure what the sponsor denotes as "Quality of Relationships," a secondary outcome measure. I find similar serious

weaknesses in this measure:

1. The measure is narrowly focused on uncontrollable emotions, and is therefore correlated with the other primary and secondary outcome variables.
2. *Anger* is inappropriately included as a key measure of PBA.
3. The measure could easily be misinterpreted by patients based on the 'title' being a more general concept than the actual question.

Figure 4: 'Quality of Relationships' Patient Form

QUALITY OF RELATIONSHIPS

(b) (4)

Pain Intensity
MS patients in study 02-AVR-106 were assessed for "Pain Intensity." The sponsor does not adequately address the relationship between 'pain' and PBA, such that the endpoint adds little to the overall interpretation of the study.

6.1.3 Study Design

Study 99-AVR-102
A Double-Blind Controlled, Multicenter Phase 2/3 Study to Assess the Safety and Efficacy of AVP-923 (Dextromethorphan/Quinidine) in the Treatment of Pseudobulbar Affect in Patients with Amyotrophic Lateral Sclerosis.

- 17 study centers
- Double blind, controlled [Note: the study had no *placebo* arm]
- Arms:
  - 30 mg dextromethorphan hydrobromide combined with 30 mg quinidine sulfate (AVP-923) orally twice daily
  - 30 mg dextromethorphan orally twice daily

  - 30 mg quinidine orally twice daily

- Key Inclusion Criteria
  - 18 to 80 years of age, inclusive.
  - Confirmed diagnosis of ALS or probable ALS according to the World Federation of Neurology (WFN) criteria.
  - Clinical history of pseudobulbar affect.
  - CNS-LS score on Day 1 was ≥ 13.
  - HRSD score was ≤ 16 on the 21-item scale (allowing inclusion of patients with possible moderate depression).
  - Vital capacity of ≥ 50%.
  - ECG (obtained and read within 4 weeks before entry in the study) with no evidence of: a) heart block, including prolongation of P-R interval (> 210 msec), right or left bundle branch block or any intraventricular conduction delay with QRS duration of 120 msec; second degree heart block; or complete heart block; b) prolongation of Q-Tc interval (≥ 450 msec); c) sinus bradycardia (< 50 bpm) or history of sick sinus syndrome; or d) ventricular tachycardia or ventricular ectopic beats (> 5 per minute).

- Efficacy
  - All efficacy variables involving a change were determined by the baseline score being subtracted from the mean of the scores on Days 15 and 29.

- Statistical Analysis
  - Both paired comparisons of AVP-923 (AVP-923 vs DM; AVP-923 vs Q) had to show statistically significant differences in favor of AVP-923 for it to be judged superior to DM or Q.

Safety
(see also Schedule of Assessments,

Table 6)

- adverse events
- physical examinations
- vital signs
- clinical laboratory values
- resting electrocardiography.

Table 6: Schedule of Assessments, 99-AVR-102
(From table 1, 99-AVR-102, final study report)

Event	Screen	Day 1	Days 2-14	Day 15[a]	Days 16-28	Day 29[b]/ET[c]
Medical history and physical assessment	X					X
Record vital signs	X	X		X		X
Review of inclusion and exclusion criteria	X	X				
Resting ECG	X					X
Dispense medication		X				
Chemistry, hematology, and urinalysis	X					X
Urinary hCG	X	X				X
Blood sample for genotyping	X					
Distribute diary card		X		X		
Review previous and concomitant medication	X	X		X		X
Complete CNS-LS	X	X		X		X
Quality of Life (VAS)		X		X		X
Quality of Relationships (VAS)		X		X		X
Clinical psychologist administer HRSD	X					X
Subject takes A.M. medication			X	X	X	X
Subject takes P.M. medication		X	X	X	X	
Review AEs				X		X
Review diary card		X		X		X
Collect diary card				X		X
Blood sample for DM, D, and Q quantitation						X
Return study medication						X

[a] Day 15 refers to the on treatment visit that occurred any time between Day 13 A.M. and Day 17 A.M.
[b] Day 29 refers to the final visit that occurred at any time between Day 26 A.M. and Day 32 A.M.
[c] ET = early termination.

Study 02-AVR-106
A Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of AVP-923 (Dextromethorphan/Quinidine) in the Treatment of Pseudobulbar Affect in Patients with Multiple Sclerosis.

- Double blind, placebo controlled
- 22 study centers (18 in the U.S., 4 in Israel)
- Key Inclusion Criteria
  - 18 to 68 years of age, inclusive.
  - Confirmed diagnosis of MS or probable MS (McDonald criteria).
  - Clinical history of pseudobulbar affect.
  - CNS-LS score at baseline ≥ 13 [see discussion of this cutoff in section 6.1.2,

General Discussion of Endpoints].

- Efficacy
  - All efficacy variables involving a change were determined by the baseline score being subtracted from the mean of the scores on Days 15, 29, 57, and 85.

- Statistical Analysis
  - AVP-923 outcome variables were compared to those of the placebo control.

- Safety (see also Schedule of Assessments, Table 7)
  - AEs.
  - Clinical laboratory values.
  - Vital signs.
  - Physical examinations.
  - ECGs.

Table 7: Schedule of Assessments, 02-AVR-106

Event	Screen	Day 1	Day 15	Day 29	Day 57	Day 85a
Physical assessment	X					X
Record vital signs	X	X	X	X	X	X
Review of inclusion and exclusion criteria	X	X				
Resting ECG	X			X		X
Chemistry, hematology, and urinalysis	X			X		X
Urinary pregnancy test (human chorionic gonadotropin, hCG)		X		X	X	X
Blood sample for genotyping		X				
Review previous and concomitant medication	X	X	X	X	X	X
Distribute medication		X		X	X	
Distribute diary card		X	X	X	X	
Complete CNS-LS	X	X	X	X	X	X
Complete Visual Analog Scale: Overall Quality of Life		X	X	X	X	X
Complete Visual Analog Scale: Quality of Relationships		X	X	X	X	X

Complete Pain Intensity Rating Scale		X	X	X	X	X
Review adverse events (AEs)			X	X	X	X
Review/collect diary card			X	X	X	X
Blood sample for quantitation of DM, DX, and Qb				X		X
Review compliance and collect drug card as appropriate			X	X	X	X

[a] Or at early termination.
[b] DM = dextromethorphan, DX = dextrorphan, Q = quinidine.

6.1.4 Efficacy Findings

Baseline Characteristics of Study Populations

ALS study 99-AVR-102

Table 8 shows the baseline characteristics for subjects in study 99-AVR-102. The arms of the study are *not well balanced* (**Table 8**). These imbalances are large enough to affect study outcome:

- The quinidine arm had a much higher percentage of bulbar onset patients, a possibly meaningfully distinct ALS patient category.
- The dextromethorphan arm had higher episode count of pathological laughing and crying, and lower HRSD score (less depression)
- The AVP-923 arm had less severe PBA (by CNS-LS, VAS-QOL, and VAS-QOR score)

Table 8: Baseline Characteristics, 99-AVR-102

	AVP-923 **N=65**	**DM** **N=30**	**Q** **N=34**	**p-value** **AVP-923 vs. DM**	**p-value** **AVP-923 vs. Q**
Bulbar onset	44.6%	46.7%	61.8%	0.8341	0.0793
Limb onset	55.4%	53.3%	38.2%		
Episode Count [#]	22.18	38.93	19.35	0.0897	0.7043
HRSD	5.37	4.27	5.70	0.1404	0.7066
CNS-LS	20.06	21.40	22.46	0.3202	0.0705
VAS-QOL	35.05	47.57	46.56	0.0209	0.0261
VAS-QOR	31.77	41.07	42.18	0.1435	0.0646

#baseline episode counts collected retrospectively
Major imbalances between groups are shaded

MS study 02-AVR-106

Table 9 and Table 10 show baseline characteristics for subjects in study 02-AVR-106. PBA was less severe in the AVP-923 arm versus the control arm to a degree that might have influenced study outcome. For example, baseline episode counts of pathological laughing/crying collected as historical estimates were 23% higher in the control group.

Table 9: Baseline Characteristics, 02-AVR-106 (Scaled instruments)
(From 02-AVR-106 study report)

Table 21. Baseline Characteristics — ITT Population

Scale	Statistic	AVP-923 (N=76)	Placebo (N=74)	P-value[b]
Screening CNS-LS[a]	n	71	71	0.3581
	Mean	21.1	22.0	
	SD[c]	5.90	5.18	
	Median	20.0	21.0	
	Min/Max	13/35	13/35	
Day 1 CNS-LS	n	76	74	0.1683
	Mean	20.3	21.4	
	SD	5.02	5.09	
	Median	20.0	22.0	
	Min/Max	13/35	13/35	
Day 1 VAS,[d] Overall Quality of Life	n	76	74	0.4206
	Mean	50.4	54.1	
	SD	28.40	27.49	
	Median	50.0	57.0	
	Min/Max	0/100	2/98	
Day 1 VAS, Quality of Relationships	n	76	74	0.4233
	Mean	45.6	49.2	
	SD	28.76	27.49	
	Median	46.5	48.5	
	Min/Max	2/98	0/100	
Day 1 Pain Intensity Rating Scale	n	76	74	0.8206
	Mean	1.4	1.4	
	SD	1.02	0.99	
	Median	1.0	2.0	
	Min/Max	0/3	0/4	

[a] CNS-LS = Center for Neurologic Study - Lability Scale
[b] P-values to compare means were computed by using t-tests.
[c] SD = Standard deviation.
[d] VAS = Visual analog scale.

Table 10: Baseline characteristics, study 02-AVR-106, (Episode counts)
(From 02-AVR-106 study report)

Table 9. Multiple Sclerosis and Pseudobulbar Affect History — ITT Population

Characteristic	Statistic	AVP-923 (N=76)	Placebo (N=74)	P-value[a]
Years with Multiple Sclerosis	n	76	74	0.5751
	Mean	10.3	9.6	
	SD[b]	8.59	7.36	
	Median	7.5	8.0	
	Min/Max	1/40	1/31	
Weekly Episodes of Pathological Laughing and/or Crying	n	75	74	0.4048
	Mean	14.1	17.3	
	SD	20.36	25.24	
	Median	7.0	9.5	
	Min/Max	1/140	1/140	

[a] P-values to compare means for continuous variables were computed by using t-tests. P-values for categorical variables were computed by using chi-square tests.

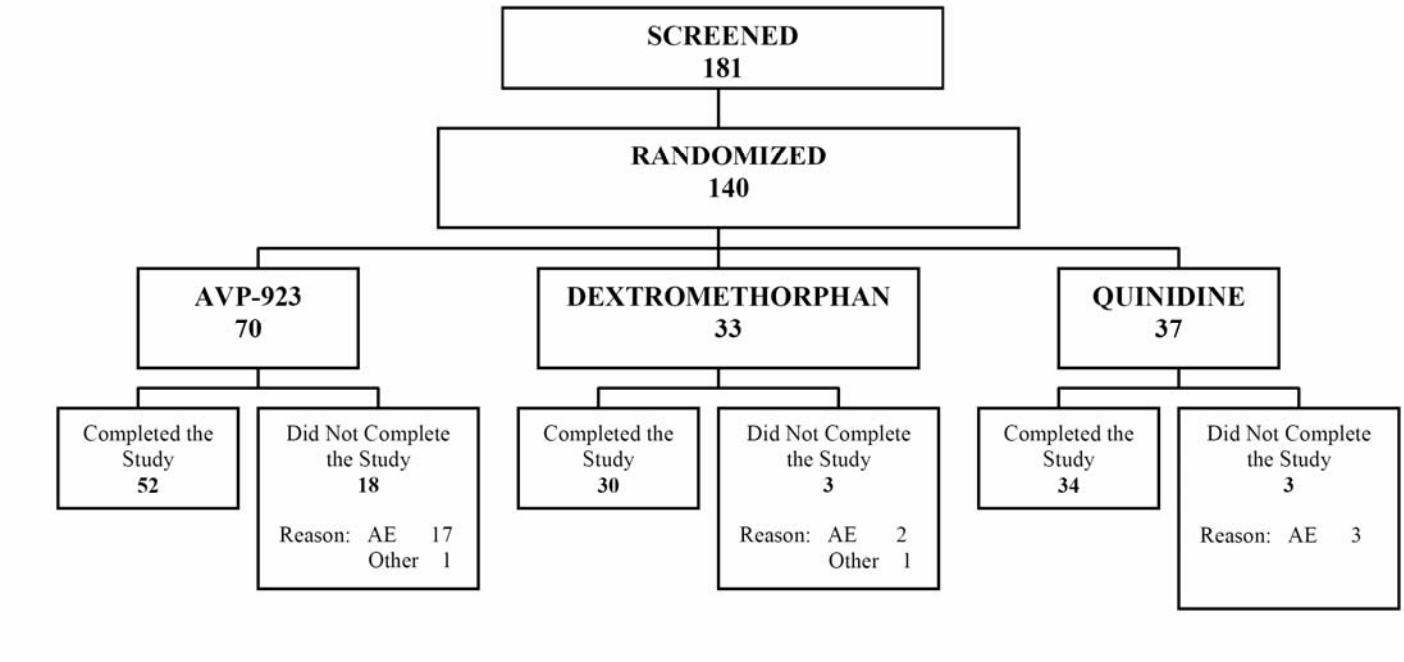
[b] SD = Standard deviation.

Dropouts/Patient Disposition

ALS study 99-AVR-102

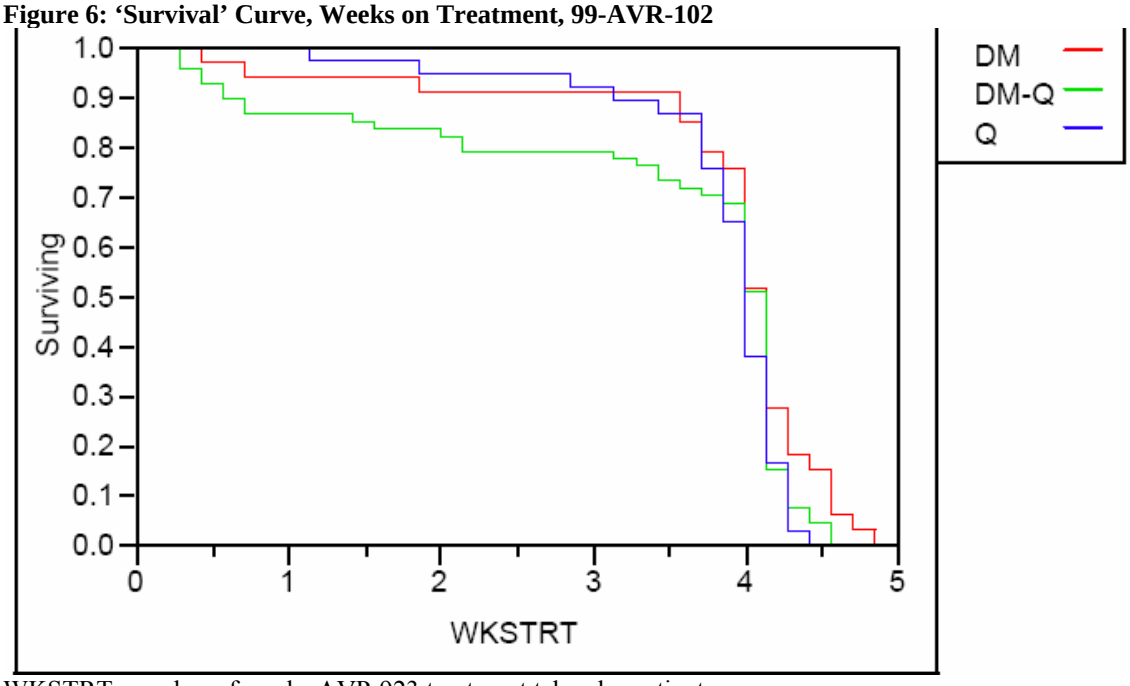
Figure 5 shows the disposition of subjects in study 99-AVR-102. The sponsor indicates that 18 of 70, or 26% of patients in the AVP-923 arm did not complete the study, while the two other study arms had much lower non-completer rates, 3 of 33 (9%) for dextromethorphan alone, and 3 of 37 (8%) for quinidine alone. The high and unequal dropout rate weakens efficacy findings because assumptions have to be made about missing data that may or may not be true.

Figure 5: Disposition of Subjects, 99-AVR-102
(from NDA application, study 99-AVR-102, Figure 1)



In **Figure 6**, I plot as a survival curve from the sponsor's data table [EFF102] the number of weeks of treatment received by subjects in study 99-AVR-102. Dropouts are more numerous for the DM-Q arm (AVP-923) throughout the study.

Figure 6: 'Survival' Curve, Weeks on Treatment, 99-AVR-102



WKSTRT: number of weeks AVP-923 treatment taken by patient

MS study 02-AVR-106

Figure 7 shows the subject disposition for study 02-AVR-106. The sponsor indicates that 21/76 patients (28%) for AVP-923, and 21/ 74 patients (28%) for placebo arms discontinued.

Figure 7: Subject Disposition, Study 02-AVR-106
(from study 02-AVR-106 final report)

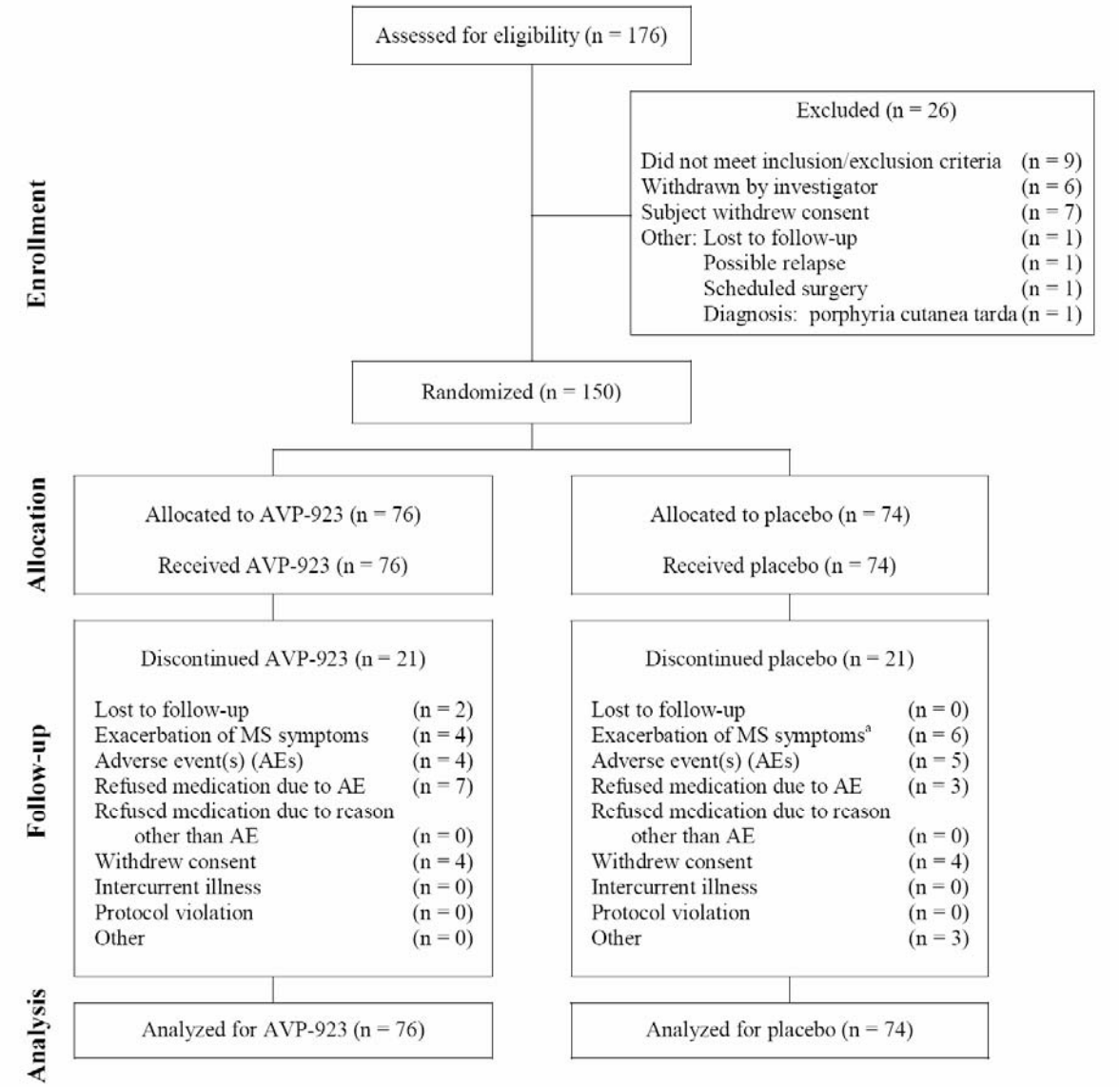
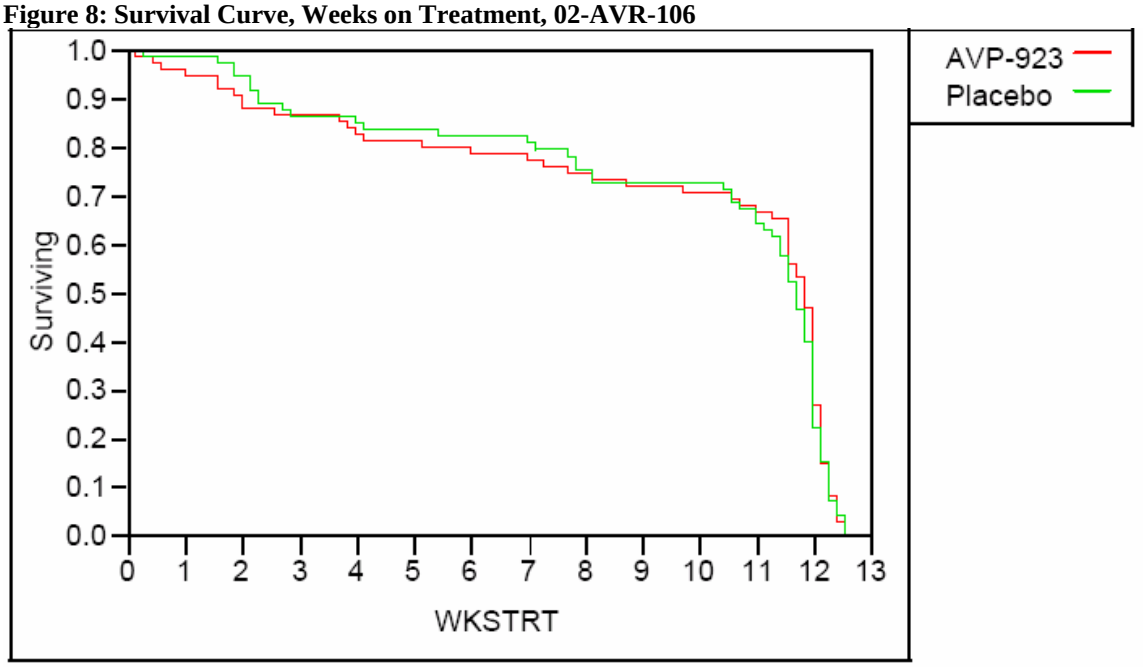


Figure 1. Disposition of Subjects

[a] One additional subject (1901) was treated for an MS exacerbation during the study but completed study treatment (Section 3.1.1).

In **Figure 8**, I plot a survival curve from the sponsor's data table [EFF106] the number of weeks of treatment received by patients in study 02-AVR-106. Early dropouts (weeks 0-2) appear to be more numerous in the AVP-923 arm, but not strikingly so.

Figure 8: Survival Curve, Weeks on Treatment, 02-AVR-106



WKSTRT: number of weeks AVP-923 treatment taken by patient

Efficacy Results

Study 99-AVR-102

The sponsor states AVP-923 was statistically better than either compound alone for the following outcomes:

- CNS-LS
- Pathological laughing/crying episode counts
- Quality of life
- Quality of relationships

Table 11 shows the sponsor's efficacy calculations for primary and secondary outcome variables in study 99-AVR-102. The sponsor claims statistical superiority of AVP-923 versus DM and Q on the primary outcome of change in CNS-LS score, and the three secondary outcome variables - change in episode counts, QOL, and QOR measures. As discussed below, I disagree with the sponsor's statistical analysis, and find study endpoints to not show statistically significant superiority of AVP-923 over its components.

Table 11: Sponsor-Calculated Efficacy Endpoints, 99-AVR-102

Summary of Efficacy Parameters in Study 99-AVR-102

	AVP-923 (N=65)	DM (N=30)	AVP-923 vs. DM p-value	Q (N=34)	AVP-923 vs. Q p-value
CNS-LS (Change in Score)					
Mean (SE)*	7.4 (0.6)	4.1 (0.9)	0.001	3.7 (0.8)	<0.001
Episodes Laughing and Crying (Number/Week)					
Mean	6.7	39.6	0.004	12.5	<0.001
QOL (Change in Score)					
Mean (SE)*	24.1 (2.5)	11.2 (3.6)	0.002	12.2 (3.3)	0.001
QOR (Change in Score)					
Mean (SE)*	22.6 (2.4)	6.6 (3.4)	<0.001	8.6 (3.2)	<0.001

Source(s): Table 12, Final Study Report 99-AVR-102; Brooks et al., 2004
CNS-LS = Center for Neurologic Study-Lability Scale; DM = Dextromethorphan Hydrobromide USP; Q = Quinidine Sulfate USP; QOL = quality of life; QOR = quality of relationships; SE = standard error.
* Values listed are least-squares means, adjusting for baseline levels and center effects, except for episode counts.

Study 99-AVR-102, *Re-Analysis of Efficacy Results*

The sponsor used a method similar to 'last observation carried forward' (LOCF), with day 15 measurement alone used if the day 28 measure was missing. This method makes assumptions about similarity between test and control arms that may or may not be true.

Dr. Tristan Massie, the statistician analyzing this submission, performed sensitivity analyses for the primary outcome variable of study 99-AVR-102. In some sensitivity analyses, AVP-923 did not show statistical superiority. Two different imputation methods were used to analyze the primary outcome variable in the ITT population, change in CNS-LS scale:

- 'No change' in CNS-LS score was imputed for dropouts. Dropouts were defined as 'last assessment of CNS-LS score before study day 25.' This imputation yielded a P-value of 0.08 for AVP-923 versus dextromethorphan, and 0.01 for AVP-923 versus quinidine.
- 'Negative efficacy of 4 points on the CNS-LS' was imputed for dropouts as above. This represents the worst observed outcome for completing patients. This imputation yielded a P-value of 0.25 versus dextromethorphan, and 0.03 versus quinidine.

As discussed in Section 6.12, *General Discussion of Endpoints*, the secondary outcome based on pathological laughing/crying episode counts appears not to yield a valid result due to more variability than predicted by the pre-specified Poisson model. The *sponsor's* statistician reanalyzed the endpoint using a more appropriate method, and found a statistically non-significant effect.

I find the additional secondary outcomes 'Quality of Life' and 'Quality of Relationships' do not support AVP-923 efficacy because of unclear meaning, as discussed in Section 6.12,

Study 02-AVR-106, Efficacy Results,

The sponsor states AVP-923 was statistically better than placebo for all outcome variables:

- Change in CNS-LS (primary outcome)
- Pathological laughing/crying episode counts
- Quality of life
- Quality of relationships
- Pain intensity rating scale

Efficacy results for study 99-AVR-102 are shown in Table 12, calculated by the sponsor using an LOCF analysis for non-completers. While I find that interpretation of efficacy is problematic because of the high dropout rate, dropouts occurred about equally between study arms, and the imputation method for missing data does not make a large difference in statistical interpretation, per the analysis of Dr. Massie.

Table 12: Efficacy Results, Sponsor's Analysis, 02-AVR-106
(from summary-clin-efficacy-pseudobulbar-affect.pdf, Table 2.7.3-6.)

Parameters	AVP-923 (N=76)	Placebo (N=74)	p-value*
Primary Efficacy Variable			
CNS-LS†	n=73	n=74	
Mean	7.9	4.3	
SD	5.32	5.26	
Adjusted mean‡	7.7	3.3	<0.0001
SE	0.57	0.58	
Secondary Efficacy Variables			
QOL†	n=73	n=74	
Mean	32.5	17.5	
SD	26.64	28.15	
Adjusted mean‡	32.1	14.9	<0.0001
SE	2.71	2.72	
QOR†	n=73	n=74	
Mean	27.9	15.5	
SD	29.87	29.13	
Adjusted mean‡	31.0	16.1	0.0001
SE	2.87	2.84	
PIRS†	n=73	n=74	
Mean	0.5	0.2	
SD	0.79	0.82	
Adjusted mean‡	0.4	0.2	0.0271
SE	0.09	0.09	
Episode rates§			
Crying and Laughing, Combined	n=75	n=73	
Mean	4.7	11.5	0.0002
SD	10.93	19.43	
Crying	n=75	n=73	
Mean	2.2	6.7	<0.0001
SD	4.94	10.81	
Laughing	n=75	n=73	
Mean	2.5	4.8	0.0077
SD	8.36	13.39	

Source(s): Table 22, Table 23, Table 24, Table 25, and Table 26 in Final Study Report 02-AVR-106.
CNS-LS = Center for Neurologic Study-Lability Scale; DM = Dextromethorphan Hydrobromide USP; ITT = intent-to-treat; PIRS = pain intensity rating scale; Q = Quinidine Sulfate USP; QOL = quality of life; QOR = quality of relationships; VAS = visual analog scale.

* For QOL, QOR, and PIRS, p-values were computed by using linear regression according to Frison and Pocock analysis of covariance method and adjusting for baseline VAS and center. For episode rates, p-values were computed by using negative binomial regression.

† Change in CNS-LS, QOL, QOR, or PIRS was defined as baseline value minus the mean of the scores on Day 15, 29, 57, and 85.

‡ Values listed are least-squares means, adjusting for baseline levels and center effects. For each patient, the change in score was evaluated as the baseline score subtracted from the mean of the scores for Days 15, 29, 57, and 85.

§ Episode rates were reported as episodes per week, computed as the total number of episodes divided by the total number of weeks on treatment (weeks were computed to the nearest day).

According to the 'LOCF analysis' used by the Sponsor, AVP-923-treated patients had, versus placebo:

- More than two-fold greater decrease in CNS-LS score (7.7 points versus 3.3

points).
- Approximately half as many episodes of laughing, crying, and laughing and crying combined.
- 2.2-times higher improvement for QOL
- 1.9 times higher improvement for QOR

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

Efficacy of AVP-923 was not adequately demonstrated in the study in ALS patients, 99-AVR-102:

- The trial was only 28 days in length, too short a period to adequately establish the efficacy of chronic treatment of PBA by AVP-923.
- Baseline imbalances between study arms occurred, in such key patient characteristics as PBA severity.
- Patient dropouts were much higher in the AVP-923 arm than the other study arms, such that study interpretation depended largely on the imputation used for missing data.
- Sensitivity analysis indicated that the study did not adequately demonstrate superiority of AVP-923 to its components.
- A true placebo arm was lacking.

The study in MS patients, 02-AVR-106, suggested efficacy of AVP-923 for PBA in MS, but the study had important shortcomings:

- The patient dropout rate was high, possibly introducing bias through loss of randomization.
- The primary outcome measure was a patient-reported outcome instrument the Agency considered inferior to direct count of pathological laughing/crying episodes. The instrument might have been confounded by mild depression, and some questions have questionable applicability to PBA. The 'episode count' endpoint was used as a secondary outcome, but was collected without baseline data, weakening statistical interpretation, particularly in light of the high dropout rate.
- The secondary outcome measures, 'quality of life' and 'quality of relationships,' provide little additional support for efficacy due to several important deficiencies in the measurement instruments used.
- The study only examined AVP-923 versus placebo, and not versus the individual drug components.

7. INTEGRATED REVIEW OF SAFETY

Major safety conclusions are first summarized below, followed by additional safety information about quinidine and DM derived from current individual use. Detailed review of safety data submitted with the AVP-923 application is then presented.

Safety Conclusions [Note: the same discussion and conclusions were presented in Section 1.3.3, Safety]

The safety of AVP-923 has not been demonstrated in 5 major areas:

1. Cardiac/arrhythmia
2. Aspiration
3. Fall
4. Adverse drug interaction
5. Undefined safety in major PBA populations

Cardiac/arrhythmia risk
As a Class Ia antiarrhythmic quinidine induces multiple clinically important and potentially deleterious effects. The sponsor argues that the dose of quinidine in AVP-923 is sufficiently low compared to the usual 'cardiac' dose that clinically meaningful adverse cardiac effects do not occur. However, I find that the cardiac safety of AVP-923 has not been adequately demonstrated, and in fact, that substantial evidence suggests that AVP-923 poses a clinically important cardiac risk in PBA patients.

Known quinidine risks

- Quinidine increases the risk of life-threatening arrhythmia, including torsade de pointe (TdP). Multiple genetic and environmental factors contribute to risk of TdP, such that even 'low' blood levels of quinidine can induce TdP in certain patients and settings (Thompson et al., Clin Pharmacol Ther 1988;43:636-42; Mathis and Gandhi, Annals of Phamacotherapy, 2002;36:1156-1161; Roden et al., Am Heart J. 1986;111:1088-93). Key risk factors for quinidine-induced TdP, such as hypokalemia, can occur in almost any patient, increasing the difficulty of limiting exposure of 'at risk' patients.
    - The average serum quinidine level in one series of cardiac patients with TdP was ≈1.6 ± 1 μg/mL (N = 19, Thompson et al., Clin Pharmacol Ther 1988;43:636-42). AVP-923, *on average*, produces quinidine levels that are ≈1/10th this level, but importantly, quinidine levels associated historically with TdP occur in a substantial number of patients treated with AVP-923
    - The theoretical risk of hypokalemia in patients on AVP-923 may be high. Vomiting is a common adverse effect of AVP-923 that can induce hypokalemia, and many PBA patients use medications, such as diuretics,

that induce hypokalemia.

- Quinidine affects atrio-ventricular (A-V) conduction, and when given alone (without other cardioactive drugs) to patients with atrial fibrillation or flutter can result in a hemodynamically unsustainable rapid ventricular response. Atrial arrhythmia occurs commonly, spontaneously, and largely unpredictably in the middle-aged and elderly population affected by PBA. The effect of quinidine levels induced by AVP-923 on atrio-ventricular conduction is largely unknown.
    - The risk of TdP after quinidine-induced conversion of atrial arrhythmia to sinus rhythm is high, likely 10% or more (Hohnloser et al., J. Am. Coll. Cardiol. 1995;26:852-8). In addition to the above effects on A-V conduction, AVP-923 might increase the risk of TdP in spontaneously occuring conversion from atrial arrhythmia to sinus rhythm.
- Quinidine also causes a high incidence of other severe and potentially life-threatening adverse effects, including autoimmune thrombocytopenia (1 per 1,000 patient years) and hypersensitivity reactions involving the liver (2%). These adverse effects are thought to correlate poorly with dose.

AVP-923 clinical study findings suggestive of cardiac/arrhythmia risk

- The incidence of arrhythmia/possible arrhythmia was higher for AVP-923 than for control arms.
- Cardiovascular-related dropouts were higher for AVP-923 than for control arms.
- Several adverse events in AVP-923 treated patients, including sudden death and syncope (in a patient with QTc increase >60 ms) were associated with arrhythmia/possible arrhythmia.
- QTc outliers occurred in the AVP-923 database, with cases of both >60 ms QTc increase, and >500 ms absolute QTc increase.
- AVP-923 was found in a 'thorough QT' study to prolong QTc by an average of ≈10 ms, with a 95% confidence interval of up to 15 ms. While QTc prolongation is an imperfect predictor of arrhythmic risk, the fact that quinidine is already known to be pro-arrhythmic increases the likelihood that this degree of QT prolongation from 'low dose' quinidine represents a clinically meaningful increase in risk.

Aspiration Risk

Particularly in ALS patients, AVP-923 induced very high rates of nausea (33%) and vomiting (6%). Vomiting from high dose DM alone (without quinidine) can be intractable (Hollander et al., Ann Neurol 1994;36:920-4). In a phase 1 study of AVP-923, an elderly normal subject died after suffering intractable vomiting thought by the investigator to be drug-related (although the proximate cause of death, small bowel obstruction, may not have been drug-related). Much of the PBA patient population is at high risk of aspiration due to underlying neurological disease. A 6% rate of vomiting in an ALS population is, on face, an unacceptable safety risk. Even though the AVP-923 exposure in ALS was very small, one serious adverse event in the AVP-923 arm was aspiration, with no similar event in the other two study arms.

Fall Risk

Much of the PBA population is at high risk of fall due to underlying neurological disease.

The fall rate in ALS patients was 18% for AVP-923, 14% for dextromethorphan, and 0% for quinidine. Absence of a control arm hampers unequivocal interpretation of this data, but a reasonable interpretation is that AVP-923 and dextromethorphan substantially increase fall risk compared to quinidine. The only death in the ALS trial was associated with broken ribs in a patient taking AVP-923 who experienced dizziness and fell (this also represents a possible signal for 'excess death' in general in the AVP-923 arm).

In the controlled trial in MS patients, 'fall' occurred in 3/76 (4%) of AVP-923 patients and 2/74 (3%) placebo patients. The absolute number of events is small, but suggest a 50% increase in risk of fall.

Evidence that dizziness from AVP-923 shows adaptation in either the ALS or MS population is not persuasive (Section 7.1.5.6)

Adverse drug interactions

The quinidine in AVP-923 is designed to fully inhibit the drug metabolizing enzyme CYP 2D6. CYP 2D6 metabolizes approximately 25% of all commonly used medications, including many cardiovascular drugs, antidepressants, antipsychotics, and analgesics used by PBA patients. Lack of CYP 2D6 activity can cause serious adverse drug reactions by increasing exposure (e.g. tricyclic antidepressants), or decreasing exposure to active metabolites (e.g. codeine or tamoxifen [Goetz et al., J. Clin. Oncol. 2005;23:9312-8]).

A drug interaction study (04-AVR-112) of AVP-923 and the tricyclic antidepressant desipramine found, not unexpectedly, a 7- to 8-fold increase in desipramine levels. These levels were associated with increased QT and QRS intervals, palpitations, tachycardia, and cardiac arrhythmia. In the AVP-923 safety study (02-AVR-107) a patient died from overdose of oxycodone while taking AVP-923 with another CYP inhibitor that together block both pathways of oxycodone metabolism.

Many common drugs increase quinidine levels, including erythromycin, which was associated with a sudden death in AVP-923 studies. The thorough QT study of AVP-923 found that QTc prolongation was strongly dose related for AVP-923 (twice the dose associated with near doubling of QTc). Even small increases in quinidine levels from AVP-923 might therefore substantially increase the risk of TdP and other adverse cardiac actions.

In addition to absolute quinidine level, the pro-arryhthmic risk of quinidine is likely to be increased by concomitant use of other drugs that prolong QTc or that are otherwise pro-arrhythmic. As noted above, erythromycin is of particular concern because it both increases QTc and is itself pro-arrhythmic.

Quinidine also inhibits the drug efflux pump p-glycoprotein, an effect not addressed in the NDA submission. The clinically important interaction between quinidine and digoxin is thought to occur through this mechanism.

Undefined safety risk in PBA populations

PBA occurs in many different disease populations in addition to ALS and MS, including stroke, traumatic brain injury, Alzheimer Disease and others. The risk/benefit profile for AVP-923 might differ among these PBA populations. In fact, the current AVP-923 database suggests that AVP-923 might be more poorly tolerated in ALS than MS patients. Similarly, the death of an otherwise healthy elderly volunteer in phase I testing suggests that an elderly population might be at increased risk from AVP-923. Few patients over the age of 75 were included in AVP-923 studies, particularly in controlled studies.

Specific disease populations commonly take disease-specific drugs, such as memantine for AD. Adverse interaction between AVP-923 and memantine is of particular concern because both drugs are NMDA antagonists, and have overlapping adverse event profiles including dizziness, fatigue, nausea, and vomiting.

The U.S. prevalence of Alzheimer Disease, Stroke, and traumatic brain injury are each about 100-fold greater (3-4 million) than the prevalence of ALS (30,000), and 10-fold greater than the prevalence of MS (300,000). The total number of patients with PBA in the U.S. likely approaches 1 million, with only about 5% of this total representing the ALS and MS patients included in AVP-923 controlled trails. Thus, the current safety database is only informative about a small minority of patients who would be treated with AVP-923.

Additional important safety issues:

1. *Lack of benefit but maintained risk of quinidine in CYP 2D6 poor metabolizers*:
   Seven to ten percent of Caucasians completely lack CYP 2D6 activity ("poor metabolizers) and gain no benefit from the quinidine in AVP-923, while remaining at risk for many of quinidine's adverse effects. Such patients can be identified by genetic testing, and should be excluded from AVP-923 use (section 7.5.1).
2. *Respiratory depression*
   Dextromethorphan is a respiratory depressant at high doses (USP Drug Information). Respiratory rate data from AVP-923 studies did not show respiratory depression. However, the measurement method for respiratory rate appeared biased for 'round number' rates (e.g. 16 breaths/minute), and might not have been adequately sensitive to detect respiratory depression.
3. *Cough suppression*
   Patients with PBA often have reduced ability to clear respiratory secretions. Dextromethorphan inhibits cough, and could lead to increased risk of respiratory infections and respiratory failure.
4. *Abuse potential of AVP-923*
   The abuse potential of AVP-923 has not been adequately defined (See section 7.1.13, *Withdrawal Phenomena and/or Abuse Potential*).

Quinidine Common Adverse Effects

Common adverse effects of quinidine listed in current labeling are shown in Table 13. Gastrointestinal symptoms are often dose-limiting.

Table 13: Quinidine Common Adverse Effects

Adverse Experiences in a 245-Patient PVC Trial

	Incidence (%)
diarrhea	85 (35)
"upper gastrointestinal distress"	55 (22)
light-headedness	37 (15)
headache	18 (7)
fatigue	17 (7)
palpitations	16 (7)
angina-like pain	14 (6)
weakness	13 (5)
rash	11 (5)
visual problems	8 (3)
change in sleep habits	7 (3)
tremor	6 (2)
nervousness	5 (2)
discoordination	3 (1)

Dextromethorphan Adverse Effects
Serious adverse effects from DM are rare. Common adverse effects include drowsiness, dizziness, and GI disturbances such as nausea and vomiting.

High dose DM has been studied in several settings including neurosurgery and stroke as a possible neuroprotectant. Plasma levels of 400-600 ng/ml are associated with somnolence, agitation, and confusion. Higher levels of 1,000 ng/ml and higher are associated with hypotension, stupor, and hypoventilation (Albers et al., Stroke 1995; 26:254-8). Plasma DM levels from AVP-923 are generally about 100 ng/ml. Death or irreversible injury from DM overdose is rare in both adults and children, but can occur with DM abuse.

A potentially fatal serotonergic syndrome can result from combination of DM with monamine oxidase inhibitors, but this appears to be very rare.

7.1 Methods and Findings

7.1.1 Deaths

Adverse events from AVP-923 studies should be interpreted in the context of the very small safety database, particularly that portion derived from controlled trials. In controlled trials, only 146 patients were exposed to AVP-923, for either 4 weeks (ALS study) or 12 (MS study) weeks. About one-fourth to one-third of patients in the controlled studies were non-completers, so the exposure was even less than just stated.

One death occurred in the AVP-923 controlled trials, and one death occurred in phase 1 development. A possible safety signal for increased mortality from AVP-923 is therefore

present. Forty eight deaths occurred in the open-label safety study. Listed below are 4 deaths of particular interest that occurred in the course of AVP-923 development. The remaining deaths are discussed under '*Uncontrolled trial deaths, study 02-AVR-107*.'

Death #1

Study 99-AVR-100
Subject 23
Healthy volunteer

This death occurred in a PK study examining the dose/response effect of quinidine on dextromethorphan metabolism.

The subject was an otherwise healthy 86-year old woman. She received 4 doses of 30 mg dextromethorphan/75 mg quinidine over (b) (6) days. On the (b) (6) day, she experienced nausea and vomiting beginning ≈1.5 hours after the third dose. The investigator coded the adverse events of nausea and vomiting as "almost certainly" related to study drug. The next day 'dry heaves' continued, accompanied by abdominal pains. The patient was then withdrawn from the study.

Two days later the patient returned for an 'early termination exam.' She was noted to have dry mouth, reduced skin turgor, and episodic vomiting. At that time, 51.5 hours post-dose, blood dextromethorphan and dextrorphan concentrations were 16.66 and 57.10 ng/mL, respectively. Serum quinidine was less than the lower limit of detection (0.5 µg/mL)(earlier drug levels were not obtained). Dextromethorphan and dextrophan, still present in circulation, might have contributed to the ongoing adverse events.

The evening of the early termination visit, the subject presented to the hospital with dehydration and continued vomiting. She was treated with intravenous fluids and Compazine. Three days later, a firm, bloated abdomen was noted. Abdominal x-rays and CT of the abdomen showed a "high-grade small-bowel obstruction at the terminal ilium." Six days after last dose, the subject "vomited and aspirated stomach contents into her lungs. She then "coded, suffered myocardial infarction, and died as a result of the aspiration," per the sponsor.

Sponsor's interpretation of the death:

> "the AEs leading to discontinuation likely related to study drug due to the relationship to dosing [my underline]. The mechanical bowel obstruction, however, is difficult to attribute to study drug because the subject had discontinued the medication (b) (6) days prior to the hospitalization and 5 days prior to the bowel obstruction. The most common cause of mechanical small-bowel obstruction is adhesions. In this case, scar tissue from previous surgery is a possibility, because the subject has a history of surgery for colon cancer, appendectomy, and hysterectomy. Bowel inflammation and impacted feces remain in the differential, but are less likely because her examinations were relatively benign, and she was adequately rehydrated in the hospital 3 days prior to the event.

Nausea and vomiting are common adverse effects of both dextromethorphan and quinidine. The intractable nausea and vomiting leading to discontinuation might have been caused by study drug, as assessed by the sponsor. No known adverse effect of AVP-923 causes small bowel obstruction, or a similar clinical picture, but the possibility remains that this event represents a first occurrence of such a syndrome. Also, the possibility can not be excluded that AVP-923 adversely affected the clinical course of an otherwise unrelated small bowel obstruction.

This subject received 75 mg Q instead of the 30 mg Q used in the final formulation of AVP-923. PK studies by the sponsor show that quinidine doses higher than 30 mg do not lead to meaningfully higher DM levels. However, prominent side effects of quinidine are nausea and vomiting, such that the higher quinidine dose might have caused more nausea and vomiting than the dose ultimately used in AVP-923.

Death #2

Study 02-AVR-107
Subject 34-033
Primary lateral sclerosis

A 48-year-old woman with primary lateral sclerosis died suddenly on day (b)(6) of AVP-923 treatment:

> "Her husband assisted her to the couch and set up her breakfast tray and morning medications. After leaving her alone for a short while, he returned to find her lying supine on the couch with her head back. Her eyes and mouth were open, and she was not breathing."

Concurrent medication included erythromycin, a CYP 3A4 inhibitor that also prolongs QT, and venlafaxine, which is metabolized by CYP 2D6 and also has a weak effect on QT prolongation. Venlafaxine and quinidine levels would have been elevated from CYP 2D6 and CYP 3A4 inhibition, respectively. Additive QT prolongation from erythromycin, venlafaxine, and quinidine could therefore have occurred, leading to arrhythmia. Torsade de pointes has been documented to result from the combination of erythromycin and quinidine (Lin and Quasny, Pharmacotherapy 1997,17,3:626-30).

The sponsor attributes cause of death as follows:

> "Because the exact cause of death is unknown, it might have been caused by either a cardiac disorder or by her progressively reported dysphagia."

No autopsy was performed.

Death #3

Study 02-AVR-107

Subject 03-002
MS

A 43-year-old woman with MS in was found dead on the couch at home on day (b) (6) of AVP-923 treatment. The official cause of death was "Intentional Overdose" from oxycodone. The main evidence of intentional overdose was the blood level of oxycodone. The patient had a history of depression, but there was no evidence of suicidal intent (e.g. patient note, conversation with physician). The sponsor suggests that suicidal intention might be suggested because the death occurred on the patient's birthday. The blood level of oxycodone at autopsy was 0.69 mg/L, a level high enough to cause death. Oxycodone is metabolized by CYP 2D6 and CYP 3A4. For study 02-AVR-107, the patient was taking AVP-923, which blocks CYP 2D6. Beginning 5 days before the patient's death, she took clarithromycin for bronchitis. Clarithromycin is a potent inhibitor of CYP 3A4. The patient was also taking fluoxetine, a less potent, but possibly clinically significant CYP 3A4 inhibitor. Blocking CYP 2D6-mediated *O*-demethylation of oxycodone causes a compensatory increase in *N*-demethylation of oxycodone by CYP 3A4 (Heiskanen et al., Clin. Pharmacol. & therapeut., 1998, 64:6, 603- 611). This pathway would have been blocked, however, by clarithromycin (and fluoxetine). Given that both metabolic pathways of oxycodone were blocked, I conclude that the fatal blood level of oxycodone might have resulted in part from AVP-923.

Death #4

Study 99-AVR-102
Subject 19-001
ALS

A 53-year-old woman enrolled in the ALS controlled trial with a vital capacity of 51%. She experienced 'mild dizziness,' a common adverse effect of AVP-923. She fell on day (b) (6), sustaining rib fracture. The patient died of respiratory failure on Day (b) (6).

Uncontrolled trial deaths, study 02-AVR-107

Forty eight deaths occurred in the long-term AVP-923 safety study, 02-AVR-107. The sponsor considered all deaths unrelated to, or unlikely related to AVP-923. Thirty of the deaths were attributed to respiratory failure in ALS patients. I reviewed individually the clinical summaries of each death in the long-term study. I paid particular attention to deaths that occurred early after treatment initiation, and deaths of MS patients, since MS is not usually fatal in the time period of the studies. In the first 60 days, 8 patients died (5 ALS, 1 MS, 1 stroke, 1 primary lateral sclerosis)[an additional early death was reported in the 120-day safety update].

One ALS patient (subject 28-011) died on study day (b) (6) of respiratory failure. While this is not unexpected in ALS, the patient was taking oxycodone concomitantly with AVP-923, (a CYP 2D6 inhibitor), and erythromycin (a CYP 3A4 inhibitor). This combination of medications is almost the same as that taken by subject 03-002, described as Death #3 above, suggesting that this type of adverse interaction can occur in the ALS and MS patient

populations. Increased oxycodone blood levels could have contributed to respiratory depression and death in this patient.

An MS patient (subject ID 29-006) experienced a series of adverse events in the setting of multiple possible drug interactions with AVP-923: diltiazem inhibits 3A4, thiazide diuretic inhibits renal elimination of quinidine, metoprolol is associated with increased (5-fold) adverse events in 2D6 poor metabolizers, and furosemide leads to hypokalemia which increases arrhythmia risk with quinidine. The patient deteriorated rapidly on AVP-923, and died of apparent MI (b) (6) days after stopping AVP-923.

Table 14 lists early deaths (less than 60 days exposure) in AVP-923 studies.

Table 14: Deaths, less than 60 days exposure (from ISS table 8-1)

Subject ID	Primary Disease	Study Day of Onset (b) (6)	Event
Study 99-AVR-100			
01-023	Normal volunteer		Bowel obstruction, aspiration, myocardial infarction
Study 99-AVR-102			
19-001	ALS		Respiratory failure
Study 01-AVR-105			
04-006	PDN		Arrhythmia, myocardial infarction
Study 02-AVR-107			
19-003	ALS		Respiratory failure
25-002	ALS		Infection of unknown source
25-012	ALS		Respiratory arrest
25-025	ALS		Respiratory failure due to ALS
29-006	MS		Acute myocardial infarction
30-021	ALS		Respiratory failure secondary to ALS
34-033	Other (primary lateral sclerosis)		Death of unknown cause
34-039	Stroke		Possible stroke

ALS = amyotrophic lateral sclerosis; MS = multiple sclerosis; PDN = painful diabetic neuropathy.

7.1.2 Other Serious Adverse Events

Controlled Trials

ALS study 99-AVR-102
The ALS study was very short, 28 days, and as a result the overall number of SAEs was low for an ALS population. However, even though the SAE data is limited, I find evidence of increased risk of SAEs from AVP-923. Three of the four SAEs were in the AVP-923 arm, including one each of 'dysphagia,' 'aspiration,' and 'respiratory failure' (note: the

subject with respiratory failure died shortly after a fall involving broken ribs, as described under 'Deaths'). The remaining SAE, 'pneumonia' was in the quinidine arm.

MS Controlled Studies

The number of SAEs in the MS study was low. Two SAEs occurred in the AVP-923 arm (optic neuritis and vaginal hemorrhage) and four occurred in the control arm (cellulitis, pneumonia, leg fracture, and 'multiple sclerosis aggravated'). Optic neuritis is listed in quinidine labeling under 'other adverse reactions occasionally reported,' raising concern that AVP-923 could increase the risk of this common manifestation of MS. However, independent verification of this association is essentially absent from published literature.

Uncontrolled trials

In the safety trial, 02-AVR-107, 117 PBA patients developed SAEs. The most common SAEs are shown in Table 15. Most were either related to the major diseases affecting the patients (e.g. respiratory failure in ALS), or are common in the general population. I detected no drug-related SAEs. However, the power of this uncontrolled data to detect drug-related SAEs is weak given the high expected rate of SAEs in this type of patient population.

Table 15: Common SAEs, Long Term Safety Study 02-AVR-107Most common SAEs, 02-AVR-107, by high level term

Respiratory (mainly resp. failure)	29
Gastrointestinal (mainly dysphagia, G-tube)	16
Demyelinating diseases (MS aggravated)	10
Lung infections	7
Muscle tone (spasm/spasticity)	5
Coronary artery disease	7
Motor neuron disease (all forms)	4
Joint related	3
Lower limb fractures and dislocations	3
Device failure or malfunction	2
Infections	2
Nausea and vomiting	2
Non site specific injuries	2
Pancreatitis	2
Physical examination procedures	2
Seizures and seizure disorders	2
Suicidal or self-injurious behaviour	2

Ventricular arrhythmias and cardiac arrest	2
Peripheral embolism, thrombosis and stenosis	2

7.1.3 Dropouts and Other Significant Adverse Events

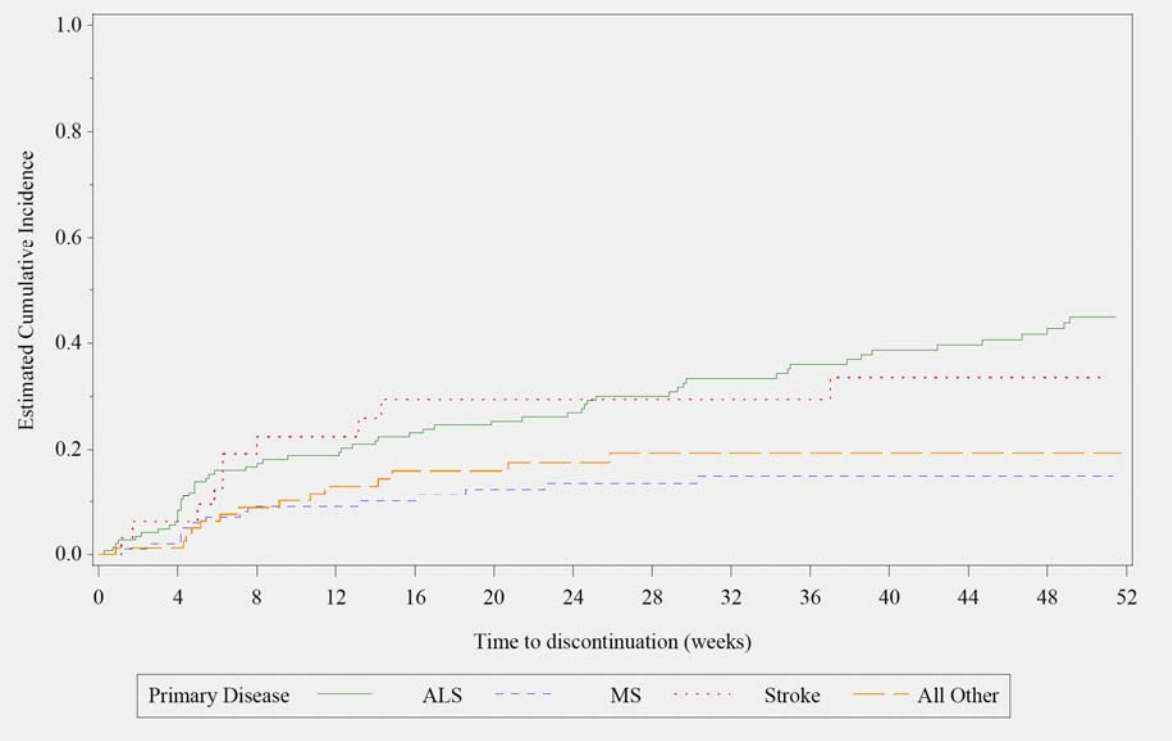
7.1.3.1 Overall profile of dropouts

In both the ALS and MS controlled trials, the dropout rate in the AVP-923 arms due to adverse events was higher than in the control arms. The excess dropout rate was particularly striking in the ALS study, in which at least 24% of subjects in the AVP-923 arm dropped out due to adverse events, while only 6% and 5%, of subjects in the dextromethorphan and quinidine arms, respectively, were dropouts,.

In the MS study, 14% of subjects in the AVP-923 arm dropped out due to adverse events, compared to 11% in the placebo arm. The overall high dropout rate in both arms acted to obscure differences between drug and control. In an attempt to 'filter out' dropouts more likely to be unrelated to drug, I excluded those categories reported by only a single patient. This revealed about a 4-fold excess of dropouts secondary to gastrointestinal disorders in the AVP-923 arm, 9-fold excess due to 'general disorders' consisting mainly of fatigue/weakness terms, and 7-fold excess due to nervous system disorders, preponderantly dizziness, somnolence, and related terms. The only such category with a greater representation in the placebo arm versus the AVP-923 arm was 'psychiatric disorders,' with a 4-fold excess in the placebo arm.

Safety Trial, 02-AVR-107
Figure 9 shows the cumulative incidence of discontinuations by underlying disease in the long-term safety trial. A large number of dropouts occurred in the first few weeks, mainly due to very similar types of adverse events as the 'common adverse events' caused by AVP-923, such as nausea, dizziness, etc. Later causes of dropout tended to be for reasons more directly related to underlying disease, such as respiratory failure in ALS.

Figure 9: Cumulative Dropouts, 02-AVR-107



7.1.3.2 Adverse events associated with dropouts

Controlled trials, 99-AVR-102 and 02-AVR-106

Cardiovascular-related Dropouts
Although small in absolute number, an excess of dropouts due to cardiovascular disorders occurred in the AVP-923 arms. One subject in the AVP-923 arm of the ALS study dropped out due to 'atrial flutter,' (Table 16) and one subject in the AVP-923 arm of the MS study dropped out due to 'bradycardia' (from Table 15-17, 'NEW ISS'), while no subjects in the placebo arm dropped out for cardiovascular disorders.

The patient with atrial flutter (05-001) was diagnosed *on enrollment* with 'atrial flutter with varying degree of AV conduction.' Therefore quinidine did not cause the patients baseline condition. However, quinidine might have caused or worsened symptoms from the pre-existing atrial flutter . Quinidine in atrial flutter reduces atrioventricular block and can result in rapid ventricular rate, syncope, and even death. Patients with atrial fibrillation/flutter placed on quinidine should be given concomitant medication for ventricular rate control, but this patient apparently received no concomitant medications.

The bradycardia event resulting in dropout was not well-documented. However, quinidine can cause or worsen bradycardia (or, paradoxically, cause rate *increase* due to

anticholinergic effects).

Gastrointenstinal-related Dropouts
Gastrointestinal adverse events are among of the most common adverse events in the AVP-923 controlled studies, and this is reflected in the dropout data. In the ALS study, 5 subjects in the AVP-923 arm dropped out due to such adverse events, compared to 1 in the DM arm and none in the Q arm. In the MS study, 3 subjects dropped in the AVP-923 arm, versus 1 in the placebo arm (Table 16).

Table 16: Adverse Events Resulting in Discontinuation, 02-AVR-106 and 99-AVR-102

Table 15-17. Incidence of Adverse Events Leading to Discontinuation in Avanir-Sponsored Controlled Studies in PBA Patients (Study 99-AVR-102 and Study 02-AVR-106)

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Incidence of Adverse Events Leading to Discontinuation
Controlled Phase 2/3 PBA Studies (99-AVR-102, 02-AVR-106)

		99-AVR-102 (ALS)						02-AVR-106 (MS)				Combined	
System Organ Class	Preferred Term	AVP-923 N=70		DM N=33		Q N=37		AVP-923 N=76		Placebo N=74		AVP-923 N=146	
N(%) OF SUBJECTS WITH AE		17	(24)	2	(6)	2	(5)	11	(14)	8	(11)	28	(19)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		0	(0)	0	(0)	0	(0)	1	(1)	1	(1)	1	(1)
	ANAEMIA NOS	0	(0)	0	(0)	0	(0)	1	(1)	1	(1)	1	(1)
CARDIAC DISORDERS		1	(1)	0	(0)	0	(0)	1	(1)	0	(0)	2	(1)
	ATRIAL FLUTTER	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
	BRADYCARDIA NOS	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	1	(1)
EAR AND LABYRINTH DISORDERS		1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
	TINNITUS	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
GASTROINTESTINAL DISORDERS		5	(7)	1	(3)	0	(0)	3	(4)	1	(1)	8	(5)
	ABDOMINAL PAIN LOWER	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)
	DIARRHOEA NOS	3	(4)	1	(3)	0	(0)	1	(1)	0	(0)	4	(3)
	DRY MOUTH	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	1	(1)
	DYSPEPSIA	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)
	NAUSEA	4	(6)	1	(3)	0	(0)	2	(3)	1	(1)	6	(4)
	TONGUE DISORDER NOS	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
	VOMITING NOS	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		4	(6)	1	(3)	0	(0)	7	(9)	1	(1)	11	(8)
	CHEST PAIN NEC	0	(0)	0	(0)	0	(0)	1	(1)	1	(1)	1	(1)
	FATIGUE	3	(4)	0	(0)	0	(0)	3	(4)	0	(0)	6	(4)
	FATIGUE AGGRAVATED	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	1	(1)
	FEELING HOT AND COLD	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	1	(1)
	PYREXIA	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	1	(1)
	SHIVERING	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
	WEAKNESS	1	(1)	1	(3)	0	(0)	2	(3)	0	(0)	3	(2)
INVESTIGATIONS		1	(1)	0	(0)	0	(0)	1	(1)	0	(0)	2	(1)
	HAEMATURIA PRESENT	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	1	(1)

INVESTIGATIONS	NEUTROPHIL COUNT INCREASED	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	1	(1)
	WEIGHT DECREASED	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
	WHITE BLOOD CELL INCREASED	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	1	(1)
METABOLISM AND NUTRITION DISORDERS		4	(6)	1	(3)	0	(0)	0	(0)	1	(1)	4	(3)
	ANOREXIA	3	(4)	1	(3)	0	(0)	0	(0)	0	(0)	3	(2)
	APPETITE DECREASED NOS	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
	HYPOKALAEMIA	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS		5	(7)	0	(0)	1	(3)	2	(3)	1	(1)	7	(5)
	JOINT STIFFNESS	3	(4)	0	(0)	0	(0)	0	(0)	0	(0)	3	(2)
	MUSCLE CRAMPS	1	(1)	0	(0)	1	(3)	1	(1)	0	(0)	2	(1)
	MUSCLE SPASMS	1	(1)	0	(0)	0	(0)	1	(1)	0	(0)	2	(1)
	MUSCLE STIFFNESS	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
	PAIN IN LIMB	1	(1)	0	(0)	0	(0)	0	(0)	1	(1)	1	(1)
NERVOUS SYSTEM DISORDERS		12	(17)	2	(6)	0	(0)	5	(7)	0	(0)	17	(12)
	BALANCE IMPAIRED NOS	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
	DISTURBANCE IN ATTENTION NEC	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	1	(1)
	DIZZINESS (EXC VERTIGO)	1	(1)	2	(6)	0	(0)	2	(3)	0	(0)	3	(2)
	DYSARTHRIA	2	(3)	0	(0)	0	(0)	0	(0)	0	(0)	2	(1)
	GAIT ABNORMAL NOS	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
	HEADACHE NOS	4	(6)	0	(0)	0	(0)	0	(0)	0	(0)	4	(3)
	HYPERTONIA	2	(3)	0	(0)	0	(0)	1	(1)	0	(0)	3	(2)
	INCREASED ACTIVITY	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	1	(1)
	INSOMNIA NEC	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
	NEURASTHAENIA	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
	SEDATION	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
	SOMNOLENCE	2	(3)	1	(3)	0	(0)	1	(1)	0	(0)	3	(2)
	TREMOR NEC	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
PSYCHIATRIC DISORDERS		1	(1)	0	(0)	0	(0)	1	(1)	3	(4)	2	(1)
PSYCHIATRIC DISORDERS	ABNORMAL DREAMS	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	1	(1)
	APATHY	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	1	(1)
	HALLUCINATION NOS	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)
	IRRITABILITY	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	1	(1)
	MOOD ALTERATION NOS	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)
	NERVOUSNESS	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
	PANIC ATTACK	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
	SUICIDAL IDEATION	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
	RESPIRATORY FAILURE (EXC NEONATAL)	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)
SKIN & SUBCUTANEOUS TISSUE DISORDERS		2	(3)	0	(0)	1	(3)	1	(1)	1	(1)	3	(2)
	DERMATITIS NOS	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)
	PRURITUS NOS	0	(0)	0	(0)	1	(3)	0	(0)	0	(0)	0	(0)
	SWEATING INCREASED	2	(3)	0	(0)	0	(0)	1	(1)	0	(0)	3	(2)
VASCULAR DISORDERS		0	(0)	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)
	HYPOTENSION NOS	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)

Safety Trial, 02-AVR-107

Cardiovascular-related Dropouts

Subject 02-007, a 47-year-old Caucasian female diagnosed with MS in 1999, had a history of clinically insignificant bradycardia of 54 bpm. Her rate on AVP-923 at day 29 was 43 bpm, causing her withdrawal. The investigator considered the bradycardia possibly AVP-923-related.

Subject 28-005, a 51-year-old Caucasian female with MS, experienced palpitations and other adverse events (dry heaves, dry mouth, metal taste in mouth) on day 1, resulting in withdrawal from the study. She was also taking erythromycin. Erythromycin increases quinidine levels by inhibiting CYP 3A4, and erythromycin itself prolongs QT. The combined cardiac effects of quinidine and erythromycin might have caused arrhythmia manifesting as 'palpitations.' Of concern, concomitant erythromycin and AVP-923 was

associated with a study death that might have been secondary to arrhythmia (Death #2 above). Torsade de pointes has been documented to result from the combination of erythromycin and quinidine (Lin and Quasny, Pharmacotherapy 1997,17,3:626-30).

7.1.3.3 Other significant adverse events

Arrhythmia
Table 17 is a tabulation of arrhythmia recorded as AEs. Importantly, many of the most important events possibly due to arrhythmia were not captured as such in AE reports (e.g. sudden death, palpitations, syncope), but the data still suggests excess arrhythmia associated with AVP-923. This excess is particularly apparent in the ALS study, with 3 events in the AVP-923 arm, and none in the dextromethorphan or quinidine arms. [note: this data suggests that AVP-923 may have a greater risk of arrhythmia than quinidine alone.]

Table 17: Arrhythmia, Controlled Trials

	Study 99-AVR-102 ALS			Study 02-AVR-106 MS	
Preferred Term	**AVP-923 N = 70**	**DM N = 33**	**Q N = 37**	**AVP-923 N = 76**	**Placebo N = 74**
Atrial flutter	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Bradycardia NOS	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)
Bundle branch block, left	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Sinus bradycardia	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Sinus tachycardia	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)
Supraventricular tachycardia	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)

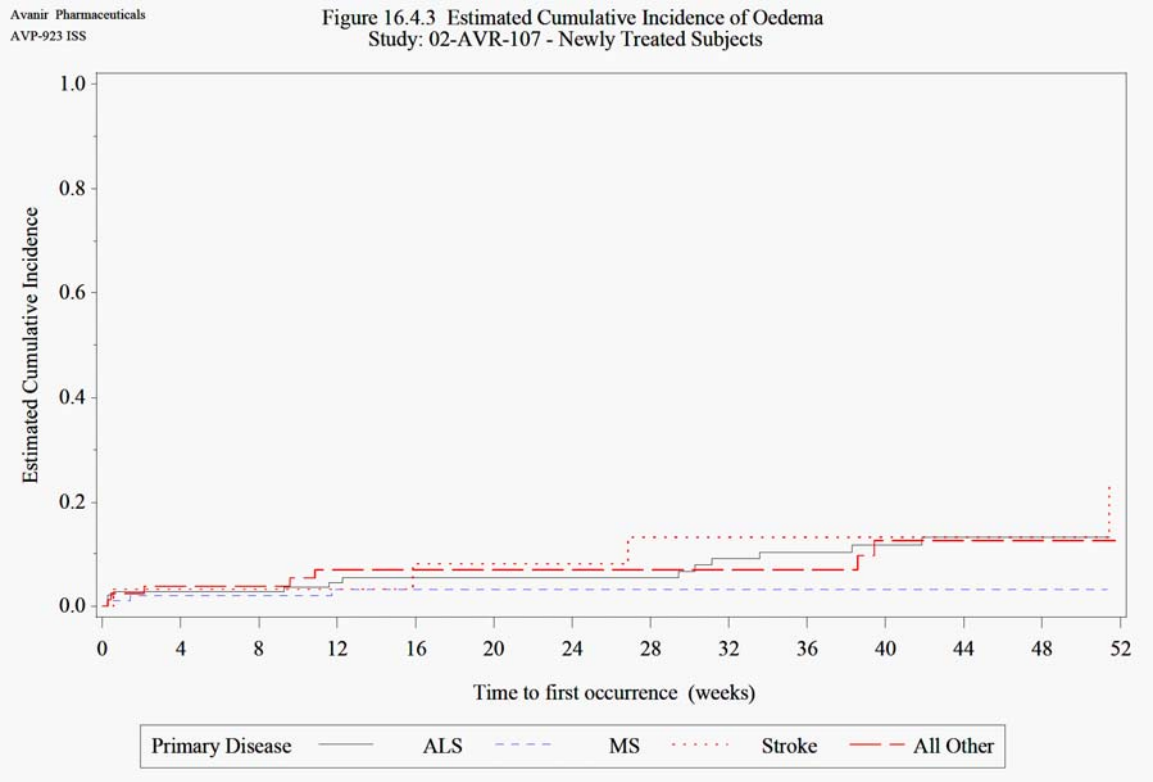
Syncope
Three subjects in uncontrolled studies reported the adverse event of syncope, one of which was associated with QTc increase of > 60 ms. Increased QTc from quinidine is associated with syncope (an effect commonly termed 'quinidine syncope'). This degree of QTc increase is large enough to suggest a possible cardiac origin of the syncopal event in that patient.

I did not find an increased incidence of syncope in AVP-923 controlled trials. No reports of syncope occurred in Study 99-AVR-102, while in Study 02-AVR-106 one case occurred in the AVP-923 arm and one in the control arm.

Peripheral Edema
Peripheral edema was a common adverse event in the long-term safety study, occurring in ≈6% of patients. Peripheral edema was not observed in excess in the controlled trials. In the long-term study, I individually reviewed the clinical summaries of each of these patients, and found that peripheral edema appeared to occur mainly in the course of ongoing debilitation, or with a previous history of peripheral edema, which are both expected settings arguing against a clear contributory effect of AVP-923. Figure 10 shows the cumulative incidence of peripheral edema in the long term study, with few early cases

and a steady accumulation over the 1 year period.

Figure 10: Peripheral Edema Incidence, 02-AVR-107



7.1.4 Other Search Strategies

Risk of Fall

99-AVR-102
I selected all patients that actually fell, per the verbatim term:

AVP	9 patients: 307, 701, 705, 707, 804, 1120, 1303, 1703, 1901
DM	4 patients: 202, 1112, 1305, 1407
Q	zero patients

My tabulation of patients that fell included 3 additional patients in the AVP arm (307, 701, 804), and 2 patients in the DM arm (202, 1112) that were not included in the sponsor's tabulation. The verbatim terms for these patients were:

AVP

307	'laceration head secondary to fall'
701	'(L) shoulder trauma secondary to fall'
804	'(R) hip pain after fall'

DM
202 'fell secondary to unsteady'
1112 '(fall) bruised back'

I calculate the risk of fall to be 9/70 (13%) for AVP, 4/33 (12%) for DM, and zero percent for Q. These percentages are based on all enrolled patients, but the study had a high percentage of dropouts, particularly from the AVP arm. I therefore normalized the above fall risk using 'number of doses taken' per patient for each study arm.

AVP:	43 doses/patient
DM:	52 doses/patient
Q:	52 doses/patient

Since study drug was taken twice daily in each arm, the risk of fall for each individual patient was:

AVP: 0.6% per day of treatment (13%/21.5 days)
18% per month-long study

DM: 0.46% per day of treatment (12%/26 days)
13.8% per month-long study

Q: 0% per day of treatment
0% per month-long study

My overall conclusion is that study 99-AVR-102 demonstrated that AVP-923 poses a safety risk from increased fall in ALS patients.

I then explored in more detail adverse events that possibly could increase the risk of fall. First, I selected all adverse event verbatim terms with even a broad possible relationship to fall or risk of fall. The most common terms for this analysis, out of a total of 50 selected terms, were: fatigue, dizziness, fall, tired, drowsiness, disoriented, shaky, lightheaded, and unstable. For this broad selection of AEs, the percentage of patients affected was 38/70 (54%) for AVP-923, 12/33 (36%) for DM, and 10/37 (27%) for Q.

From the above 50 AEs possibly related to fall, I next selected the following terms that might be more directly related to risk of fall: fall/fell etc, disoriented, dizzy/dizziness etc, drowsy/drowsiness etc, groggy etc, lightheaded etc, vertigo, neurasthenia, off-balance, faint, sedation, shaky, somnolence, sleepy etc, unstable, unsteady. For these terms, the percentage of patients affected by study arm was 30/70 (43%) for AVP-923, 9/33 for DM (27%), and 2/37 (5%) for Q.

MS study 02-AVR-106

I selected all patients that actually fell per the verbatim term or preferred term:
AVP: 303, 3417, 3420, 3411
Placebo: 902, 1507

Although the number of events is small, AVP-923 might increase the risk of fall in MS patients to a clinically important extent.

I then explored in more detail adverse events that possibly could be related to fall in MS subjects. Seventy four verbatim AE's were selected as 'broadly related to fall,' including the following most frequent terms: fatigue, lightheaded, dizziness, weakness, tired, fall, lethargy, sleepiness, difficulty thinking, and feeling intoxicated. I also included verbatim terms indicating accidental injury, although not enough information was submitted to determine that injury resulted from fall. The percentage of patients affected was 41/76 (54%) for AVP-923 and 29/74 (39%) for placebo. I next identified the following terms that may be more directly related to fall, identifying 51 total AE verbatim terms. These terms, in general order of prevalence, were: dizzy, lightheaded, fall, difficulty thinking/confusion/feeling intoxicated/drunk/disoriented etc., and various acute injuries (e.g. burn, laceration, fracture). The percentage of patients affected was 31/76 (41%) for AVP-923 and 17/74 (23%) for placebo.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Table 18 and Table 19 show the safety assessments conducted in the Avanir-sponsored controlled trials and safety trial.

Table 18: Safety Assessments, Controlled Trials
(From New ISS, Table 2-3)

Study ID Study Title Link to Schedule of Assessments	Safety Variables				
	Adverse Events	Clinical Laboratory Values	Vital Signs	Physical Examination	Electrocardiogram
99-AVR-102 A Double-Blind Controlled, Multicenter Phase 2/3 Study to Assess the Safety and Efficacy of AVP-923 (Dextromethorphan Hydrobromide 30 mg and Quinidine Sulfate 30 mg) in the Treatment of Pseudobulbar Affect in Patients with Amyotrophic Lateral Sclerosis Table 1: Schedule of Assessments; Clinical Study Report	Patients received a diary in which they recorded any AEs that had occurred since the last visit. On Day 15 and Day 29, patients were questioned regarding any AEs that might have occurred since their previous visit.	Blood and urine were collected at the screening visit and Day 29 for clinical chemistry, hematology, urinalysis, and pregnancy testing. The lists of assessments for clinical chemistry, hematology, and urinalysis are found in Section 2.11.2.2 of the Clinical Study Report.	The following values were obtained at the screening visit, Day 15, and Day 29 (or the final visit): • Systolic blood pressure (mm Hg) • Diastolic blood pressure (mm Hg) • Heart rate (bpm) • Respiration rate (breaths/minute) • Vital capacity • Body weight • Temperature • Height (screening only)	Complete physical examinations were conducted at the screening visit and on Day 29 (or the final visit).	Electrocardiography (12-lead) was performed at the screening visit and on Day 29 (or the final visit).
02-AVR-106 A Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of AVP-923 (Dextromethorphan/ Quinidine) in the Treatment of Pseudobulbar Affect in Patients with Multiple Sclerosis Table 1: Schedule of Assessments; Clinical Study Report	Patients were instructed to keep a diary of any AEs experienced. On Days 15, 29, 57, and 85, patients were questioned regarding any AEs that might have occurred since their previous visit.	Blood and urine were collected at screening, Day 29, and Day 85 (or the final visit) for clinical chemistry, hematology, and urinalysis. Urine was collected on Day 1, Day 29, Day 57, and Day 85 for pregnancy testing. The lists of assessments for clinical chemistry, hematology, and urinalysis are found in Section 2.8.1.2 of the Clinical Study Report.	The following values were obtained at the screening visit and at all study visits Day 15, Day 29, Day 57, and Day 85, (or the final visit): • Systolic blood pressure (mm Hg) • Diastolic blood pressure (mm Hg) • Heart rate (bpm) • Respiration rate (breaths/minute) • Temperature • Body weight • Height (screening visit only)	Complete physical examinations were conducted at screening and on Day 85 (or the final visit).	Electrocardiography (12-lead) was performed at screening, on Day 29, and on Day 85 (or the final visit). Additional ECGs were obtained at the discretion of the investigator or in accordance with requirements of local IRBs (identified in the data listings as "unscheduled").

Table 19: Safety Assesments, Open Label Safety Study (02-AVR-107)
(From NEW ISS Table 2-3)

Study ID Study Title Link to Schedule of Assessments	Safety Variables				
	Adverse Events	Clinical Laboratory Values	Vital Signs	Physical Examination	Electrocardiogram
02-AVR-107 An Open-Label Multicenter Study to Assess the Safety of AVP-923 (Dextromethorphan/Quinidine) in the Treatment of Patients with Pseudobulbar Affect Table 1: Schedule of Assessments; Clinical Study Report	Patients were given a diary to record any AEs experienced. At each clinic visit from Day 29 onward, patients were questioned regarding any AEs that had occurred since their previous visit. In months with no scheduled clinic visit, patients were contacted by telephone and questioned about AEs. Patients who entered the optional extension phase visited the clinic every 4 months and were contacted by telephone in every month without a clinic visit.	Blood and urine were collected for clinical chemistry, hematology, and urinalysis at screening, Day 29, and Week 52 (or the final visit). Urine was collected for pregnancy testing on Day 1, Day 29, Week 16, Week 34, and Week 52 or the final visit. Patients participating in the extension phase provided blood and urine samples at the extension termination visit. The lists of assessments for clinical chemistry, hematology, and urinalysis are found in Section 2.9.2 of the Clinical Study Report.	The following values were obtained at all study visits (Day 29, Week 16, Week 34, and Week 52 or the final visit). • Systolic blood pressure (mm Hg) • Diastolic blood pressure (mm Hg) • Heart rate (bpm) • Respiration rate (breaths/minute) • Temperature • Body weight	Complete physical examinations were conducted at screening and at Week 52 (or the final visit) of the treatment phase, and for patients who continued in the extension phase, at the extension termination visit.	Electrocardiography (12-lead) was performed at screening, Day 29, and Week 52 (or the final visit). For patients participating in the extension phase, ECGs were performed at the extension termination visit.

AE = adverse event; bpm = beats per minute; ECG = electrocardiogram; ID = identification.

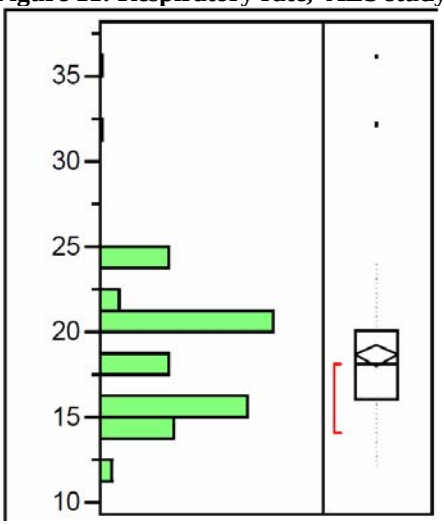
The sponsor states:

> "Study participants in the Avanir-sponsored studies recorded AEs daily in patient diaries and were assessed for AEs at every clinic visit or during regularly scheduled phone contacts."

No checklist or other structured method of eliciting AEs was used. This would act, in particular, to underestimate AEs that patients are hesitant to volunteer, such as sexual dysfunction, and would likely underestimate even common AEs. Standard questions were not used to elicit AEs, raising the concern of large variation between study sites.

Respiratory rate showed no change from AVP923, but the data appeared inadequate. The respiratory rate data clusters strongly around either 16 respirations/minute or 20 respirations/minute (with few or no patients at 'odd' rates), possibly due to subjective bias in collection (generated from m5\datasets\99-AVR-102\listings\vitals.xpt). Figure 11 is a representative example of respiratory rate for all patients in the ALS study.

Figure 11: Respiratory rate, ALS study, Day 1



Vital capacity data collected was of limited use due to a high number of patient dropouts (see Table 28).

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

I examined the 'verbatim' and corresponding 'preferred' terms for AEs in the controlled AVP-923 trials, and found inappropriate coding of events for 'fall.' Adverse events resulting from falls were in some cases coded only by the related injury, and not under "fall." I addressed this through my own analysis presented in Section 7.1.4, *Other Search Strategies*.

7.1.5.3 Incidence of common adverse events

Controlled Trials

ALS, study 99-AVR-102
Importantly, the ALS study did not have a placebo arm, but only 'dextromethorphan-only' and 'quinidine-only' arms. These other two study arms do not fill the important role of a 'no drug' placebo arm in adverse events analysis. That stated, AVP-923 was associated with a high percentage of excess common adverse events in ALS patients, above that observed in the DM and Q arms (Table 20).

Nausea occurred in 33% of the AVP-923 treated patients, and vomiting occurred in 6%. Vomiting may be a safety risk in a neurologically compromised population with high aspiration risk and low respiratory reserve, such as ALS patients and other populations with

PBA.

'Fall,' appeared increased by AVP-923 (discussed in detail in Section 7.1.4).

MS, study 02-AVR-106

AVP-923 was also associated with excess common adverse events in the MS population (Table 20).

'Fall,' appeared increased by AVP923, although the overall number of events was small (Section 7.1.4). Dizziness (excluding vertigo) was more clearly increased by AVP-923, affecting 26% of subjects on AVP-923, and only 9% on placebo.

Open-label Safety Study
The long-term safety trial was composed mainly of ALS (N=147) and MS (N=102) patients, with a much smaller number of stroke (N=32), traumatic brain injury (N=16), Alzheimers (N=8), and 'other diseases' (N=59) patients [≈40 additional patients reported in the 120-day safety update were distributed similarly among the underlying diseases]. As in the controlled trials, nausea was frequent in the safety trial, affecting about 20-30% of all patients (Table 21). 'Dizziness' affected about 15-25% of patients across disease groups, while 'fall' occurred in about 10-20%. Somnolence affected about 10-20% of patients, but less in MS, with 4% affected. Fatigue and weakness affected about 15-20% of all subjects. Lower limb edema was reported by about 5-10% of subjects, but as discussed elsewhere, patient debility was probably the major contributing factor, although a contributory effect of AVP-923 can not be excluded.

7.1.5.4 Common adverse event tables

Table 20: Common Adverse Events, Controlled Studies
(From Table 4-2, NEW ISS)

		99-AVR-102 (ALS)						02-AVR-106 (MS)			
System Organ Class	Preferred Term	AVP-923 N=70		DM N=33		Q N=37		AVP-923 N=76		Placebo N=74	
EYE DISORDERS	VISION BLURRED	1	(1)	0	(0)	0	(0)	3	(4)	0	(0)
GASTROINTESTINAL DISORDERS	ABDOMINAL PAIN NOS	1	(1)	0	(0)	0	(0)	5	(7)	3	(4)
	CONSTIPATION	5	(7)	2	(6)	0	(0)	3	(4)	4	(5)
	DIARRHOEA NOS	11	(16)	7	(21)	4	(11)	6	(8)	6	(8)
	DRY MOUTH	2	(3)	1	(3)	1	(3)	6	(8)	1	(1)
	NAUSEA	23	(33)	2	(6)	3	(8)	17	(22)	11	(15)
	VOMITING NOS	4	(6)	0	(0)	0	(0)	3	(4)	6	(8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	FALL	6	(9)	2	(6)	0	(0)	4	(5)	2	(3)
	FATIGUE	13	(19)	3	(9)	4	(11)	11	(14)	6	(8)
	FATIGUE AGGRAVATED	1	(1)	0	(0)	1	(3)	4	(5)	9	(12)
	WEAKNESS	4	(6)	1	(3)	4	(11)	8	(11)	4	(5)
INFECTIONS AND INFESTATIONS	UPPER RESPIRATORY TRACT INFECTION NOS	3	(4)	1	(3)	2	(5)	5	(7)	6	(8)
METABOLISM AND NUTRITION DISORDERS	ANOREXIA	4	(6)	1	(3)	0	(0)	0	(0)	1	(1)
	APPETITE DECREASED NOS	3	(4)	1	(3)	0	(0)	3	(4)	0	(0)
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS	JOINT STIFFNESS	7	(10)	0	(0)	1	(3)	1	(1)	2	(3)
	MUSCLE CRAMPS	5	(7)	2	(6)	1	(3)	4	(5)	3	(4)
	MUSCLE STIFFNESS	3	(4)	0	(0)	0	(0)	1	(1)	0	(0)
NERVOUS SYSTEM DISORDERS	BALANCE IMPAIRED NOS	2	(3)	1	(3)	0	(0)	3	(4)	3	(4)
	DIZZINESS (EXC VERTIGO)	14	(20)	5	(15)	1	(3)	20	(26)	7	(9)
	HEADACHE NOS	11	(16)	4	(12)	4	(11)	12	(16)	22	(30)
	HYPERTONIA	5	(7)	0	(0)	1	(3)	2	(3)	2	(3)
	PARAESTHESIA NEC	2	(3)	0	(0)	0	(0)	3	(4)	2	(3)
	SOMNOLENCE	9	(13)	1	(3)	0	(0)	4	(5)	1	(1)
PSYCHIATRIC DISORDERS	ANXIETY NEC	3	(4)	0	(0)	3	(8)	1	(1)	2	(3)
	DEPRESSION NEC	2	(3)	0	(0)	1	(3)	2	(3)	3	(4)
	NERVOUSNESS	2	(3)	1	(3)	1	(3)	2	(3)	0	(0)
SKIN & SUBCUTANEOUS TISSUE DISORDERS	DERMATITIS NOS	3	(4)	1	(3)	0	(0)	2	(3)	6	(8)
	SWEATING INCREASED	4	(6)	0	(0)	1	(3)	3	(4)	1	(1)

Program: aesum.sas Data Source: ae.sas7bdat 20OCT05

ALS = amyotrophic lateral sclerosis; DM = Dextromethorphan Hydrobromide USP; EXC = excluding; MS = multiple sclerosis; NEC = not elsewhere classified; NOS = not oth
PBA = pseudobulbar affect; Q = Quinidine Sulfate USP.

* Adverse events reported by more than 2% of patients in the combined AVP-923 group and that were more frequent, within either study, in AVP-923 group then in a control group.

Table 21: Common Adverse Events (>5%), Safety Study 02-AVR-107

		Primary Disease											
		ALS N=147		MS N=102		Stroke N=32		Traumatic Brain Injury N=16		Alzheimers N=8		Other N=59		All Patients N=364	
System Organ Class	Preferred Term														
CARDIAC DISORDERS	OEDEMA LOWER LIMB	11	(7)	5	(5)	3	(9)	0	(0)	0	(0)	6	(10)	25	(7)
GASTROINTESTINAL DISORDERS	CONSTIPATION	25	(17)	4	(4)	1	(3)	0	(0)	1	(13)	7	(12)	38	(10)
	DIARRHOEA NOS	25	(17)	15	(15)	4	(13)	2	(13)	2	(25)	8	(14)	56	(15)
	DRY MOUTH	10	(7)	8	(8)	2	(6)	0	(0)	0	(0)	7	(12)	27	(7)
	DYSPHAGIA	31	(21)	2	(2)	2	(6)	0	(0)	0	(0)	2	(3)	37	(10)
	NAUSEA	40	(27)	24	(24)	6	(19)	1	(6)	1	(13)	11	(19)	83	(23)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	FALL	30	(20)	11	(11)	3	(9)	3	(19)	1	(13)	5	(8)	53	(15)
	FATIGUE	19	(13)	17	(17)	2	(6)	5	(31)	1	(13)	9	(15)	53	(15)
	WEAKNESS	29	(20)	13	(13)	2	(6)	1	(6)	0	(0)	2	(3)	47	(13)
INFECTIONS AND INFESTATIONS	NASOPHARYNGITIS	12	(8)	13	(13)	3	(9)	2	(13)	0	(0)	4	(7)	34	(9)
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS	ARTHRALGIA	10	(7)	10	(10)	1	(3)	0	(0)	0	(0)	5	(8)	26	(7)
	BACK PAIN	15	(10)	11	(11)	2	(6)	0	(0)	1	(13)	4	(7)	33	(9)
	PAIN IN LIMB	12	(8)	10	(10)	2	(6)	0	(0)	0	(0)	5	(8)	29	(8)
NERVOUS SYSTEM DISORDERS	DIZZINESS (EXC VERTIGO)	23	(16)	23	(23)	7	(22)	2	(13)	1	(13)	8	(14)	64	(18)
	HEADACHE NOS	32	(22)	28	(27)	6	(19)	5	(31)	1	(13)	12	(20)	84	(23)
	INSOMNIA NEC	23	(16)	5	(5)	5	(16)	0	(0)	0	(0)	4	(7)	37	(10)
	SOMNOLENCE	16	(11)	4	(4)	6	(19)	2	(13)	0	(0)	13	(22)	41	(11)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	COUGH	22	(15)	5	(5)	1	(3)	2	(13)	0	(0)	3	(5)	33	(9)
	DYSPNOEA NOS	16	(11)	2	(2)	2	(6)	2	(13)	0	(0)	4	(7)	26	(7)
	NASAL CONGESTION	11	(7)	6	(6)	1	(3)	1	(6)	0	(0)	2	(3)	21	(6)
	RESPIRATORY FAILURE (EXC NEONATAL)	33	(22)	0	(0)	0	(0)	0	(0)	0	(0)	1	(2)	34	(9)
SKIN & SUBCUTANEOUS TISSUE DISORDERS	ECCHYMOSIS	18	(12)	8	(8)	1	(3)	1	(6)	0	(0)	7	(12)	35	(10)

Program: caesum.sas Data Source: ae.sas7bdat 21NOV05

ALS = amyotrophic lateral sclerosis; EXC = excluding; MS = multiple sclerosis; NEC = not elsewhere classified; NOS = not otherwise specified.
* Adverse events reported by more than 5% of patients in the all patients group.
† Patients not previously enrolled in Study 99-AVR-102 or Study 02-AVR-106.

7.1.5.5 Identifying common and drug-related adverse events

Discussed under other *Adverse Events* sections.

7.1.5.6 Additional analyses and explorations

Nausea, Exploration for Adaptation
Nausea is a common, strongly drug-related adverse effect of AVP-923. Figure 12 and Figure 13 show the cumulative incidence of nausea in the ALS (99-AVR-102) and MS (02-AVR-106) studies. Importantly, the figures used in this section represent only the exact AE term specified, and thus under-represent the total of related terms. For example, patient 04-002 had no nausea event, but had 2 episodes of vomiting, while patient 15-1501 complained of nausea and vomiting early in the study, then subsequently complained only

of vomiting on three different dates. While most patients reported nausea in the first 1-2 weeks of AVP-923 use, the incidence of nausea continued to increase relative to placebo/other study arms for the duration of the studies. Figure 14 and Figure 15 show the same data in the form of event graphs for each study patient. This representation of adverse events is possibly biased downward by the tendency of patients to decrease reporting of a continued adverse event over time. However, I think the figures show that nausea is not limited to the early phase of treatment.

Figure 12: Cumulative Incidence of Nausea, ALS Study 99-AVR-102
(From NEW ISS Figure 16.6.1)

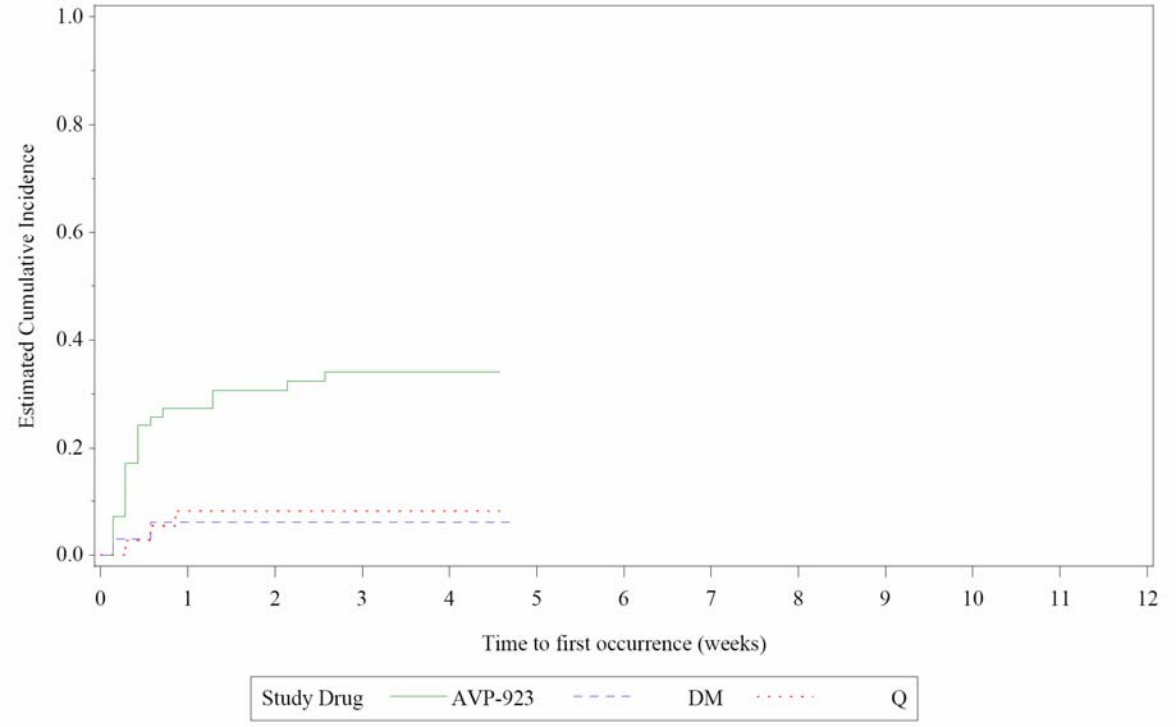


Figure 13: Cumulative Incidence of Nausea, MS Study 02-AVR-106
(From NEW ISS Figure 16.6.2)

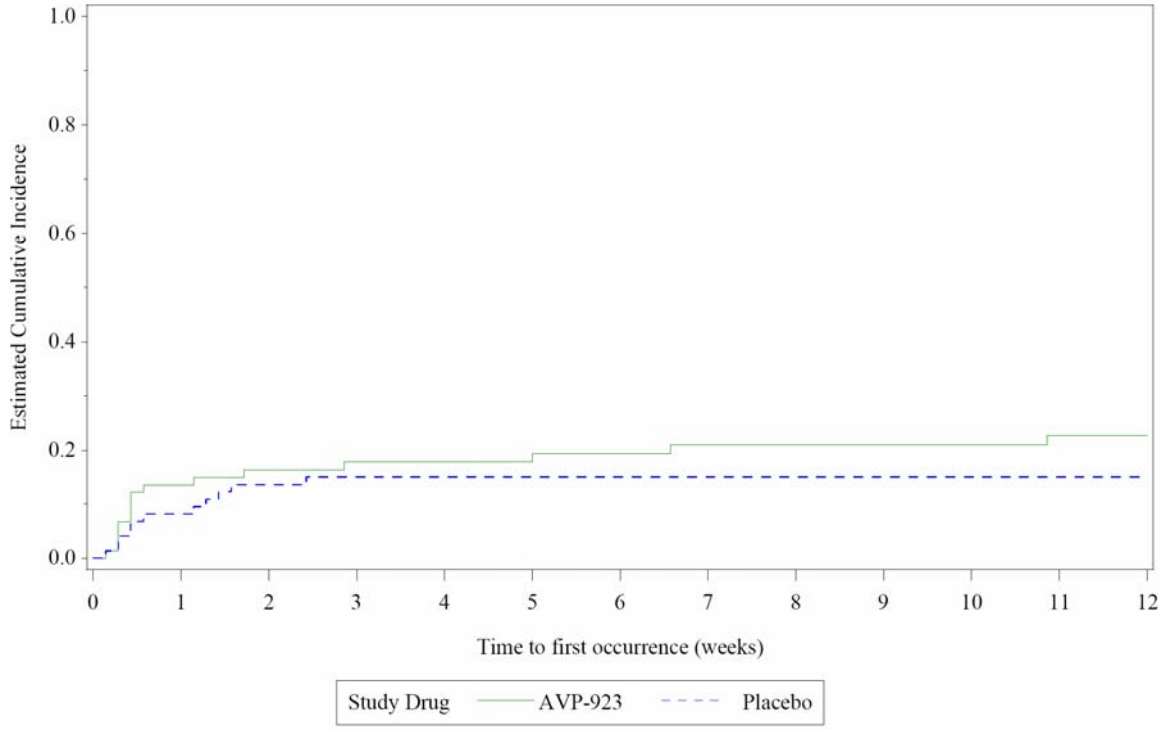
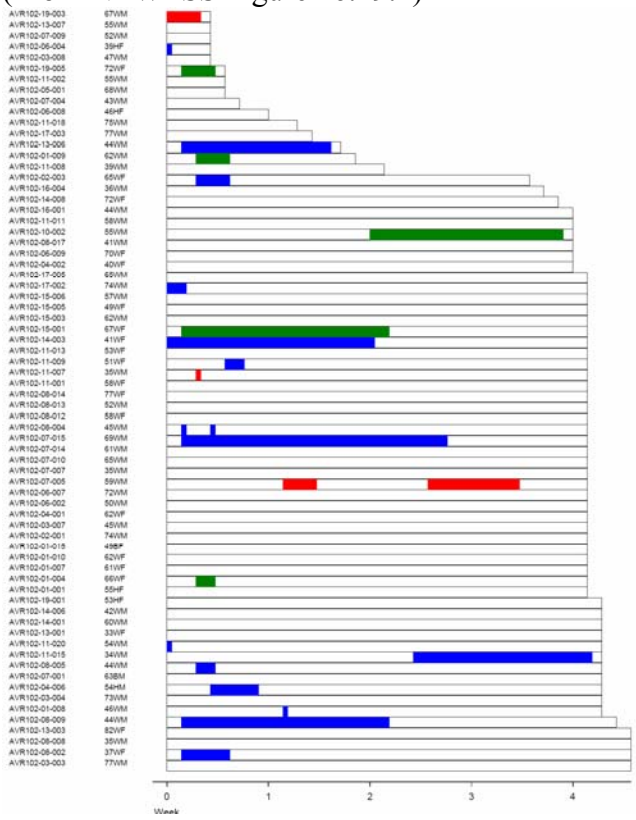
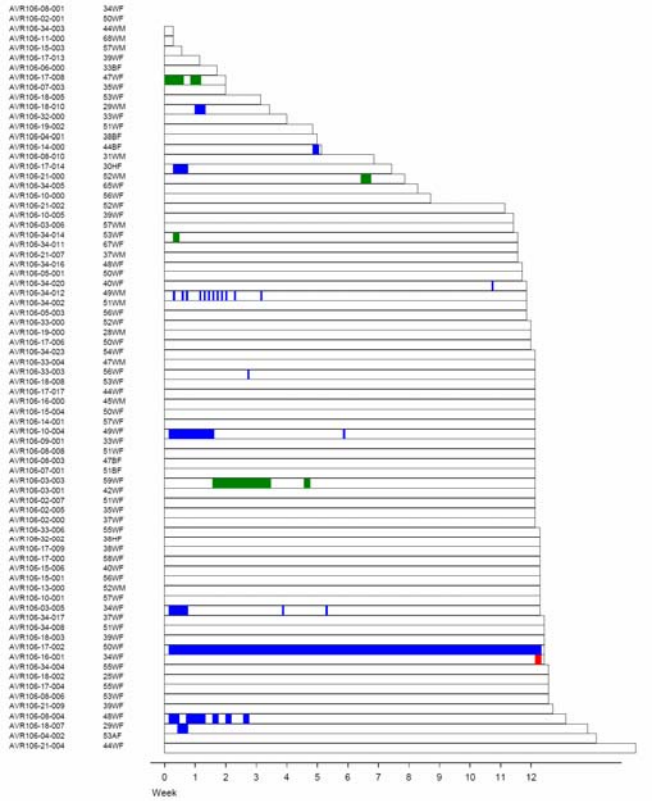


Figure 14: Nausea by Week, AVP Arm, ALS Study 99-AVR-102
(From NEW ISS Figure 16.19.1)



Blue - mild; Green – moderate; Red - Severe

Figure 15: Nausea by Week, AVP Arm, MS study 02-AVR-106



Blue - mild; Green – moderate; Red - Severe

Dizziness, Exploration for Adaptation

Dizziness and related AEs were common excess adverse events for the AVP-923 arms in both the ALS and MS studies. Figure 16 and Figure 17 show the cumulative incidence of dizziness in the ALS and MS studies, respectively. Figure 18 and Figure 19 show similar information, but graphically represent the AE as reported by each subject in the AVP-923 arm. The cumulative incidence shows a rapid early presentation of dizziness, but suggests that the incidence continues to rise even days to weeks after initiating drug, arguing against a strong effect of adaptation. The presence of dizziness over extended periods of time shown clearly in Figure 18 for ALS argues against adaptation to dizziness, while similarly Figure 19 for MS gives little evidence that dizziness is a transient adverse effect,even with the bias against continued AE reporting inherent in this 'spontaneous reporting only' AE monitoring method.

Figure 16: Cumulative Incidence of Dizziness, ALS study 99-AVR-102
(from NEW ISS Figure 16.7.1)

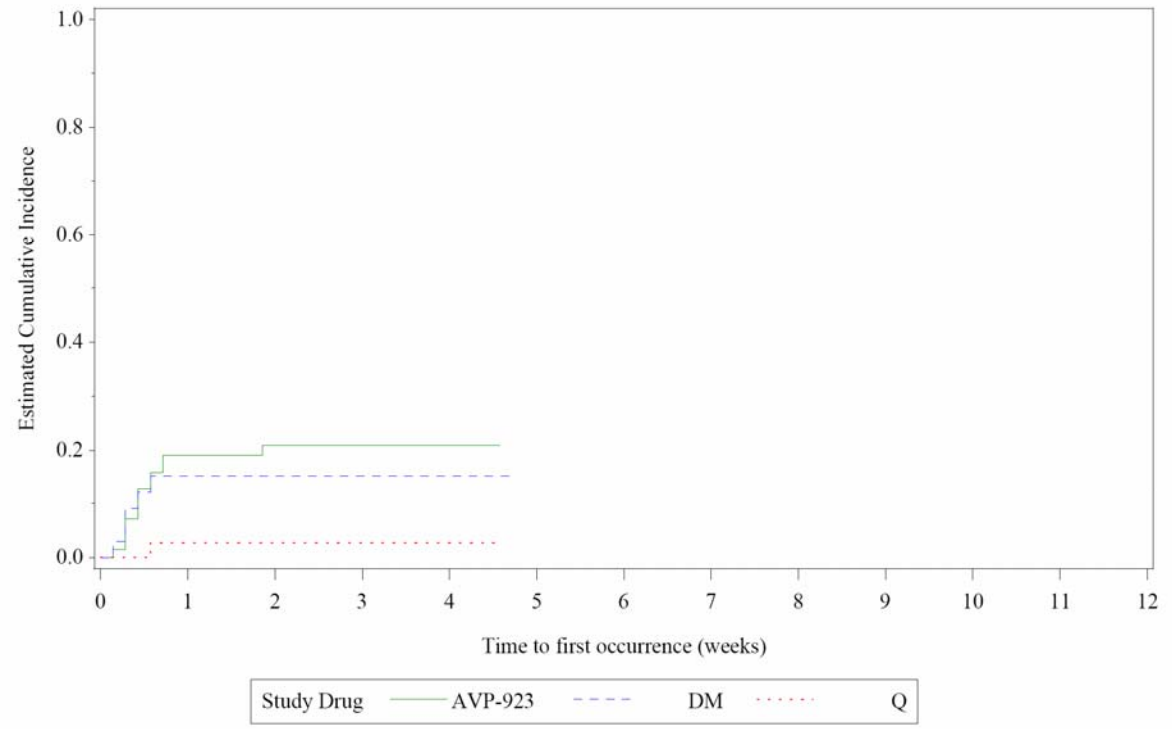


Figure 17: Cumulative Incidence of Dizzyness, MS Study 02-AVR-106
(From NEW ISS Figure 16.7.2)

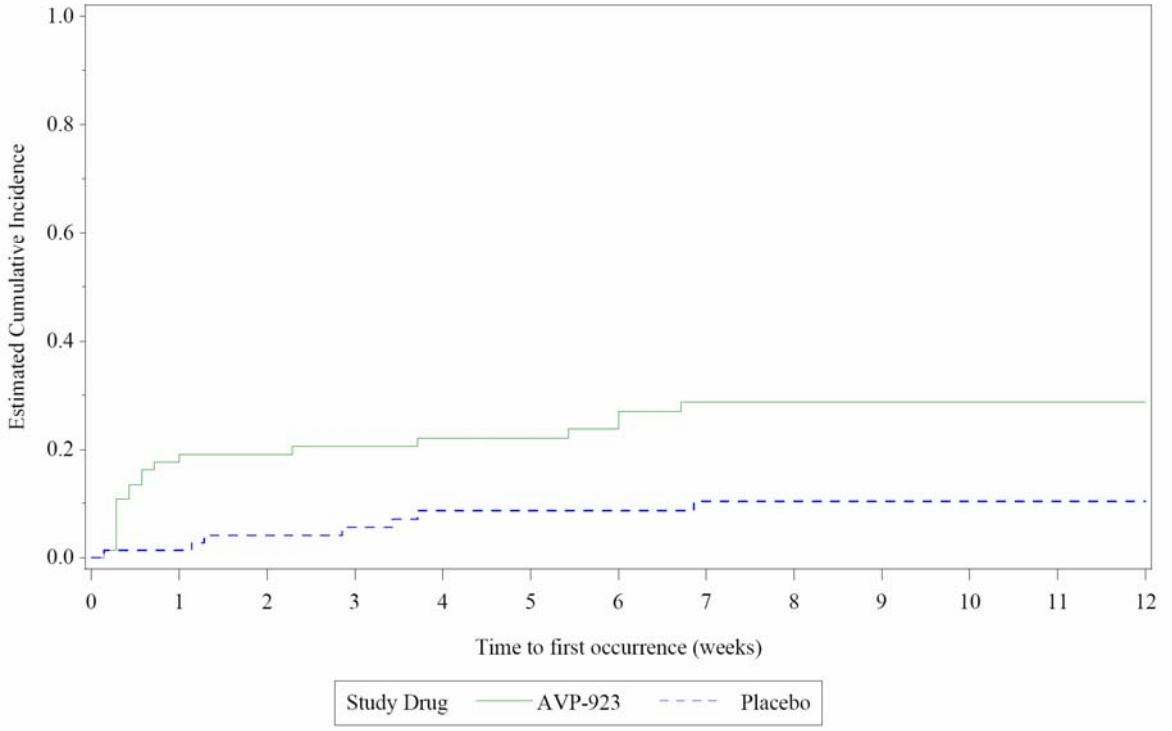
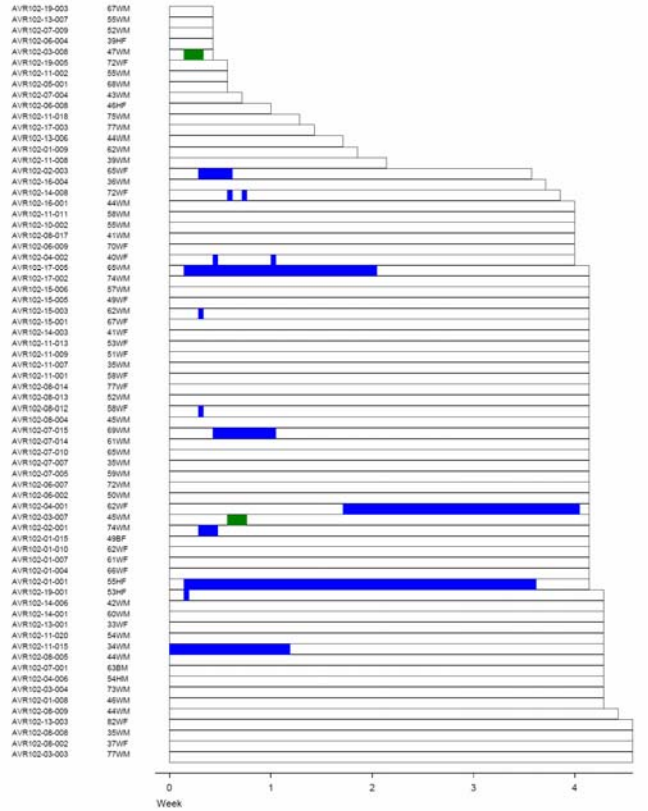
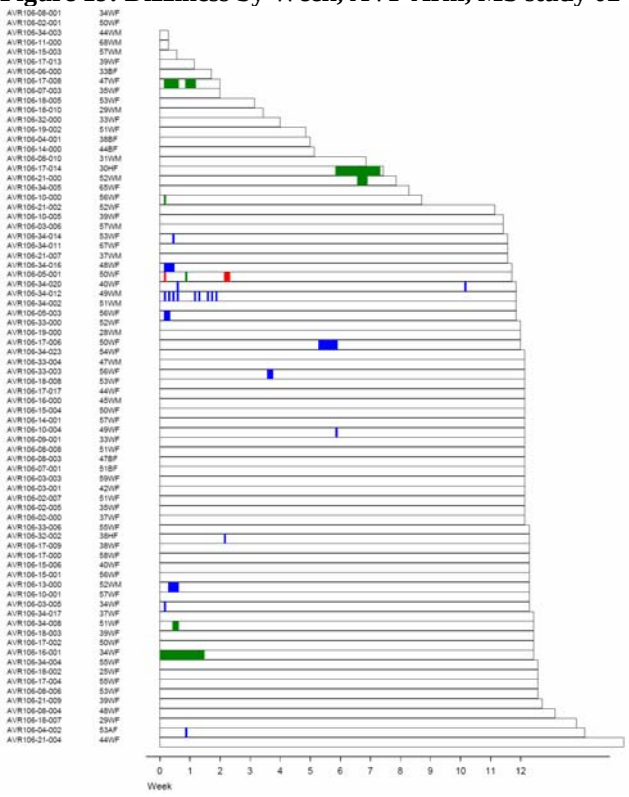


Figure 18: Dizziness by Week, AVP ARM, ALS study 99-AVR-102



Blue - mild; Green – moderate; Red - Severe

Figure 19: Dizziness by Week, AVP Arm, MS study 02-AVR-106



Blue - mild; Green – moderate; Red - Severe

7.1.6 Less Common Adverse Events

PBA patients experience a relatively large number of adverse events, decreasing the likelihood that any given uncommon adverse event will be identified as drug related. The AVP-923 safety trial (02-AVR-107) included patients with several very different underlying diseases, including ALS, MS, stroke, traumatic brain injury, etc., further complicating interpretation of AEs. A total of 140 SAEs were reported in the safety trial, most of which could be related to the underlying disease causing PBA (e.g. respiratory failure in ALS). I did not identify any SAEs classically associated with adverse drug effects (e.g. liver failure). Remaining SAEs included but were not limited to the following:

GI system:

Abdominal pain, gallstone pancreatitis (2), appendectomy, GI bleed, bowel impaction

Cardiovascular:

Coronary artery disease/myocardial infarction/angina (8), cardiac arrest (2), vein thrombosis (2), aneurysm, hypertension, hypotension, carotid stenosis, nose bleed

Pulmonary:

Bronchitis, asthma

Nervous system/psychiatric:

Suicide, migraine headache, recurrent adjustment reaction, seizure (2)
Endocrine:
Hypothyroidism, hyperglycemia, metabolic acidosis
Immune:
Cystitis (2), infection (3)

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory safety assessments conducted are listed in Table 18 and Table 19 above. Chemistry, hematology, and urinalysis were conducted in each of the Avanir-sponsored studies. The sponsor states that "results of the clinical laboratory assessments were evaluated with respect to whether they met predefined criteria of clinical concern" per FDA Guidance. All laboratory studies performed, and associated criteria of clinical concern, are included in Table 24.

Laboratory evaluation was conducted on 146 patients on AVP-923 in controlled trials. Overall, including the long-term safety study, laboratory evaluation was conducted on 557 patients taking AVP-923 [with an additional ≈40 patients reported in the 120-day safety update].

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

For this review, the controlled trials in ALS (99-AVR-102) and MS (02-AVR-106) were chosen for analysis of laboratory values, as well as the open-label safety study, (02-AVR-107). The controlled trials were short, particularly the ALS study which was only 4 weeks duration, greatly weakening the power of laboratory evaluations to detect adverse effects. Many PBA patients are severely affected by their underlying disease, increasing the difficulty of assigning causation to laboratory abnormalities in the long-term uncontrolled study. No long-term controlled studies on PBA patients have been conducted to use in comparison to the AVP-923 studies.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Chemistry

Table 22 shows the *median* changes in laboratory values for each treatment group in controlled trials, in terms of percent change, with shifts of possible concern in red.

Table 22: Chemistry, Median Percent Change From Baseline, Controlled Trials
(From Table 15-23, NEW ISS)

	99-AVR-102			02-AVR-106	
	AVP	DM	Q	AVP	Placebo
Albumin	-2.1	0.0	0.0	-1.4	-0.7
Alkaline Phos.	9.7	7.4	1.5	-3.9	-2.5
SGOT	0.0	4.1	-4.2	-2.2	-7.7
SGPT	0.0	7.2	-8.1	-4.3	0.0
Bicarbonate	0.0	1.9	0.0	1.2	-2.3
Calcium	-2.0	1.1	0.0	-2.0	0.0
CK	-7.4	-3.6	2.5	5.1	1.0
Cholesterol	-0.3	0.8	-3.4	1.5	-2.2
Chloride	0.0	0.0	0.5	0.0	0.0
Creatinine	0.0	0.0	0.0	6.5	0.0
GGT	0.0	0.0	-7.4	-8.1	0.0
Glucose	-1.0	0.6	0.0	-0.6	1.2
LDH	0.0	-1.8	-4.9	-2.9	-4.0
Potassium	0.0	0.0	0.0	0.0	0.0
Phosphorus	0.0	-1.2	2.6	0.0	-2.8
Sodium	-0.4	0.0	-0.7	-0.7	-0.7
Total bilirubin	0.0	-5.6	11.1	-10.4	-7.5
Total protein	0.0	-0.6	0.0	0.1	0.0
Triglycerides	-1.2	16.4	3.5	-6.8	-3.3
Uric acid	-1.1	-3.2	1.0	3.6	3.3
Urea	7.4	0.0	0.0	4.8	-1.4

Liver
Quinidine is known to be a cause of sporadic drug-induced hepatotoxicity, and was a target organ of toxicity in preclinical studies of AVP-923. However, the median laboratory values related to liver do not suggest a generalized toxic effect on the study population. Alkaline phosphatase was increased in the AVP arm in the ALS study, but not in the MS study. SGOT and SGPT were unchanged or slightly decreased in AVP arms of both studies, and total bilirubin was either unchanged (ALS study) or decreased (MS study).

Kidney
Creatinine was unchanged in the ALS study, but increased in the AVP arm of the MS

study. Urea was increased in the AVP arms of both studies. I examined the distribution of change of creatinine between screening and day 85, and found the AVP curve shifted to higher creatinine, but with no outliers. In the long-term safety trial, no patients had outlier values for creatinine. Overall, I find little evidence for overt renal toxicity from AVP-923, but can not discount some effect of AVP-923 on renal function.

Urinalysis

In the ALS study, no patients had hematuria, proteinuria, or white blood cells in urine. In the MS study, two AVP-923 patients had hematuria, and two had white blood cells in urine. One of these patients, subject 03-005, had a history of intermittent urinary tract infections. The other, subject 15-003, had concomitant elevated white blood cell count, but further information addressing possible urinary tract infection is not available. Overall, these findings may have arisen from underlying disease.

Hematology

Table 23 shows median change in hematology laboratory values for the controlled AVP-923 trials. The data does not reveal clinically meaningful changes in median values.

Table 23: Hematology Median Percent Change from Baseline, Controlled Trials
(From table 15-23, NEW ISS)

	AVP	DM	Q	AVP	Placebo
Platelets	-3.2	-0.5	-1.1	-2.7	-2.3
RBC	1.0	0.0	0.0	-0.3	0.7
WBC	0.0	-1.7	-4.0	-3.1	-5.8

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 24 shows outlier laboratory abnormalities for the controlled AVP-923 studies. In all categories (except triglycerides, which often shows high variability), at most a single study subject exhibited the outlier value. I examined the clinical narrative of each patient in the controlled studies with an outlier laboratory value, and found none to implicate clearly an effect of AVP-923. Patients with abnormal laboratory values of possible concern are listed below:

Patient 106-05-003

> "Elevation in ALT to 138 U/L at Day 29. Concomitantly obtained AST and GGT were also elevated (95 U/L and 108 U/L, respectively). All were reported as mild AEs from which the subject recovered 2 weeks later."

Patient 106-10-001

> GGT day 29, elevated to 182 U/L, but returned to normal on day 85.

Patient 106-34-023

"Elevation in GGT to 343 U/L that was noted during an unscheduled visit at approximately 2 months. At Day 85, it had decreased to 95 U/L. She subsequently rolled over into Study 02-AVR-107 as Subject 34-023 where additional follow-up labs showed an eventual decrease to normal. Concomitantly obtained AST and ALT were minimally elevated at this time (49 U/L and 69 U/L, respectively). Review of AEs and concomitant medications failed to identify a potential reason for this elevation."

Patient 106-33-000

"Severe decrease in sodium to 111 mmol/L at Day 29. She was asymptomatic. In follow-up 2 days later, her sodium had returned to normal (141 mmol/L)."

Patient 106-17-009

Low sodium (138 mmol/L), normal at end of study (140 mmol/L).

Patient 102-17-002

"hematocrit at screening of 38.0% was low for a male, but still outside the range of clinical concern. On Day 29, his hematocrit decreased to 36.6%. This barely just reached the level of clinical concern (<37% for a male). No additional hematocrit values are recorded for this subject."

Patient 106-34-008

"low WBC value of 1.7 × 103/μL on Day 29. This had normalized at Day 85. Review of AEs and concomitant medications failed to identify a potential cause for this decrease."

Patient 106-34-020

Single measurement of low WBC ($2.3X10^3$/mm) during safety extension after MS controlled study, normal on later measurements.

Table 24: Outlier Laboratory Abnormalities, Controlled Studies
(From Table 9-1, NEW ISS)

		99-AVR-102 (ALS)			02-AVR-106 (MS)		Combined
Parameter	Criteria	AVP-923 N=70	DM N=33	Q N=37	AVP-923 N=76	Placebo N=74	AVP-923 N=146
Albumin	Low <25 g/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Alkaline Phosphatase	High >400 U/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SGPT	High >3*ULN	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (1%)
SGOT	High >3*ULN	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Calcium	Low <1.75 mmol/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	High >3 mmol/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cholesterol	High >10.36 mmol/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CK	High >3*ULN	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Creatinine	High >176.8 umol/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
GGT	High >3*ULN	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Glucose	Low <2.775 mmol/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
	High >13.875 mmol/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Potassium	Low <3.0 mmol/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	High >5.5 mmol/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
LDH	High >3*ULN	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Sodium	Low <130 mmol/L	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (1%)
	High >150 mmol/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Triglyceride	High >3.39 mmol/L	2 (4%)	1 (5%)	0 (0%)	0 (0%)	2 (4%)	2 (2%)
Uric Acid	High M: >594.8 mmol/L F: >475.8 mmol/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Urea	High >10.71 mmol/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hematocrit	Low M: <37 % F: <32 %	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	1 (1%)
Hemoglobin	Low M: <115 g/L F: <95 g/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Platelets	Low <75 X10E9/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	High >700 X10E9/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
WBC	Low <2.8 X10E9/L	0 (0%)	0 (0%)	0 (0%)	1 (2%)	1 (2%)	1 (1%)
	High >16 X10E9/L	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Program: lababn.sas Data Source: lb.sas7bdat 02NOV05
Incidence of subjects who were normal at baseline and had any post-baseline value meeting criteria

ALS = amyotrophic lateral sclerosis; CK = creatine kinase; DM = Dextromethorphan Hydrobromide USP; F = female; GGT = gamma-glutamyltransferase; LDH = lactic dehydrogenase; M = male; MS = multiple sclerosis; PBA = pseudobulbar affect; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamate pyruvate transaminase; Q = Quinidine Sulfate USP; ULN = upper limits of normal; WBC = white blood cell.

Table 25 includes outlier laboratory abnormalities from both the controlled studies and the long-term safety trial. Overall, laboratory abnormalities were few. I reviewed the clinical narratives of all patients with outlier laboratory values (NEW ISS section 9.4, *Individual Subjects with Abnormal Laboratory Values*). Abnormal values, including liver indices, generally returned to normal while on drug. However, I note below cases suggesting that AVP-923 might cause elevations of liver enzymes that resolve upon drug discontinuation:

Subject 16-008

Increase in liver function tests (alkaline phosphatase, 216 U/L; AST 96 U/L; ALT, 142 U/L; GGT, 243 U/L) that returned to normal on drug

discontinuation. The increase was considered possibly related to study drug because of the timing of normalization.

Subject 29-004

"Abnormal laboratory values of clinical concern included elevations in SGOT, SGPT, and GGT, which began at approximately 10 weeks; 113 U/L, 275 U/L, and 308 U/L for SGOT, SGPT, and GGT, respectively. These elevations were documented as severe AEs and led to interruption of study drug dosing. At approximately 12 weeks, these values had decreased to 48 U/L, 127 U/L, and 217 U/L, respectively. At approximately 20 weeks all had normalized except for GGT, which remained mildly elevated at 85 U/L."

Subject 34-036

At Day 29 elevations in AST (147 U/L), ALT (169 U/L), and GGT (111 U/L) were noted. Following the initial elevation in liver enzymes on Day 29, study drug was interrupted and the abnormalities were reported as an AE. Additional follow-up on Day 54 showed persistent elevations for GGT at 149 U/L and triglycerides at 328 mg/dL. No subsequent laboratory values for these parameters were reported.

Table 25: Laboratory Abnormalities, All PBA Studies (99-AVR-102, 02-AVR-106 02-AVR-107)

Parameter	Criteria		AVP-923 N=557
Albumin	Low	<25 g/L	0 (0%)
Alkaline Phosphatase	High	>400 U/L	1 (0%)
SGPT	High	>3*ULN	8 (2%)
SGOT	High	>3*ULN	3 (1%)
Calcium	Low	<1.75 mmol/L	0 (0%)
	High	>3 mmol/L	0 (0%)
Cholesterol	High	>10.36 mmol/L	0 (0%)
CK	High	>3*ULN	1 (0%)
Creatinine	High	>176.8 umol/L	0 (0%)
GGT	High	>3*ULN	8 (2%)
Glucose	Low	<2.775 mmol/L	1 (0%)
	High	>13.875 mmol/L	0 (0%)
Potassium	Low	<3.0 mmol/L	0 (0%)
	High	>5.5 mmol/L	3 (1%)
LDH	High	>3*ULN	0 (0%)
Sodium	Low	<130 mmol/L	3 (1%)
	High	>150 mmol/L	3 (1%)
Triglycerides	High	>3.39 mmol/L	19 (5%)
Uric Acid	High	M: >594.8 mmol/L F: >475.8 mmol/L	1 (0%)
Urea	High	>10.71 mmol/L	0 (0%)
Hematocrit	Low	M: <37 % F: <32 %	4 (1%)
Hemoglobin	Low	M: <115 g/L F: <95 g/L	1 (0%)
Platelets	Low	<75 X10E9/L	0 (0%)
	High	>700 X10E9/L	0 (0%)
WBC	Low	<2.8 X10E9/L	3 (1%)
	High	>16 X10E9/L	0 (0%)

Program: lababn.sas Data Source: lb.sas7bdat 21NOV05
Incidence of subjects who were normal at baseline and had any post-baseline value meeting criteria

CK = creatine kinase; F = female; GGT = gamma-glutamyltransferase; LDH = lactic dehydrogenase; M = male; PBA = pseudobulbar affect; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamate pyruvate transaminase; ULN = upper limits of normal; WBC = white blood cell.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Discussed in Section 7.1.7.3.2, *Analyses focused on outliers or shifts from normal to abnormal*

7.1.7.4 Additional analyses and explorations

The limited controlled-trial data precluded meaningful additional analysis of laboratory values.

7.1.7.5 Special assessments

While several individual cases of elevated liver enzymes occurred in the NDA database, no cases of frank hepatotoxicity occurred. However, during review of this NDA, an adverse event from ongoing study 04-AVR-109 for painful diabetic neuropathy was reported to the IND. Subject 136-9004 experienced the SAE of 'hepatitis of unknown etiology,' associated with increased bilirubin (total bilirubin 5.6 g/l, direct bilirubin 3.6 g/l), AST (1270 U/L)and ALT (953 U/L) , and minimal elevation of alkaline phosphatase (202 IU/L). The patient was on concomitant pravastatin (for 3 years), piaglitozone (almost 1 year), metformin (2 years), and warfarin (2 years), all of which have rarely been associated with serious liver damage. Clear causation can not be assigned from the information in the adverse event report, but this case raises concern that AVP-923 might cause liver failure. Additional clinical data and analysis from the sponsor regarding possible relationship to AVP-923 is necessary.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Conclusions, Vital Signs
The controlled AVP-923 trials were small, and the ALS study did not include a control arm, weakening conclusions about vital signs. Very few vital signs outliers were recorded in controlled studies, with no meaningful excess in the AVP-923 arms. Average vital signs data was similar among study arms. In total, 5 patients developed bradycardia in uncontrolled trials (with an additional two in the open label 120-day safety update). These events were possibly related to AVP-923. Several of the patients experienced AEs possibly related to bradycardia, including 'lightheadedness.'

Vital signs assessments
Vital sign measurements assessed in Avanir-sponsored studies are listed in Table 18 (controlled trials) and Table 19 (open-label safety study).

Vital Signs of Specific Concern
The sponsor notes bradycardia as a possible adverse effect of Q, and thus of AVP-923.

Stating that:

> Bradycardia is a relative contraindication to treatment with Q and as an adverse effect of Q overdose. Symptomatic bradycardia is reason to discontinue Q. Q can cause severe bradycardia in patients with disease of the sinus node. Caution is advised regarding concomitant use of Q with other drugs that cause bradycardia or inhibit or compete for cytochrome P450 3A4.

The sponsor also notes that bradycardia has not been associated with DM, which has caused tachycardia in overdose.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

I analyzed the ALS (99-AVR-102) and MS (02-AVR-106) controlled studies for drug-control comparisons of vital signs, and also examined the open-label safety study and smaller open-label studies (e.g. study 01-AVR-105, painful diabetic neuropathy).

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Table 26 shows median blood pressure, and change in median blood pressure for controlled trials in ALS and MS. AVP-923 did not have a clinically meaningful affect on these parameters. An increase in median blood pressure occurred across all three arms in the ALS trial (AVP-923, 4.0 mm; DM, 6.0 mm; and Q, 2.0 mm), but not in the MS study. The lack of a true placebo arm in the ALS study hinders interpretation of this apparent blood pressure change.

Table 26: Mean Blood Pressure, Controlled Trials
From New ISS

Table 15-26. Mean Changes in Vital Sign Parameters at Time of Last Treatment in Avanir-Sponsored Controlled Studies (Study 99-AVR-102 and Study 02-AVR-106)

Avanir Pharmaceuticals

Mean Changes in Vital Signs at Time of Last Treatment
Controlled Phase 2/3 PBA Studies (99-AVR-102, 02-AVR-106)

			99-AVR-102 (ALS)			02-AVR-106 (MS)		Combined
Parameter			AVP-923 N=70	DM N=33	Q N=37	AVP-923 N=76	Placebo N=74	AVP-923 N=146
Systolic BP (mm Hg)	Value	n	54	31	36	68	71	122
		mean	130.6	129.9	126.4	123.3	117.7	126.6
		median	130.0	128.0	127.0	124.5	115.0	130.0
		SD	13.9	17.2	12.4	15.5	14.5	15.2
		min	105.0	100.0	102.0	96.0	95.0	96.0
		max	176.0	172.0	150.0	160.0	174.0	176.0
	Change from Baseline	n	54	31	36	66	71	120
		mean	2.1	3.7	1.8	-1.0	-0.1	0.4
		median	4.0	6.0	2.0	-2.0	0.0	2.0
		SD	14.5	16.0	12.2	12.8	11.2	13.6
		min	-40.0	-36.0	-18.0	-34.0	-30.0	-40.0
		max	30.0	30.0	40.0	39.0	32.0	39.0
Diastolic BP (mm Hg)	Value	n	54	31	36	68	71	122
		mean	79.3	81.4	77.8	77.2	75.6	78.1
		median	80.0	82.0	79.0	77.0	76.0	80.0
		SD	10.4	7.4	7.1	9.8	9.9	10.1
		min	58.0	70.0	56.0	60.0	60.0	58.0
		max	110.0	99.0	90.0	100.0	104.0	110.0
	Change from Baseline	n	54	31	36	66	71	120
		mean	0.4	1.8	-1.6	0.2	0.4	0.3
		median	0.0	2.0	0.0	0.0	2.0	0.0
		SD	8.3	8.4	7.2	9.3	10.0	8.8
		min	-16.0	-20.0	-18.0	-20.0	-26.0	-20.0
		max	20.0	20.0	12.0	26.0	18.0	26.0

Program: vitchg.sas Data Source: vitals.sas7bdat 21NOV05
Value selected is last on treatment value within 3 days after last dose

AVP-923 did not have a clinically meaningful effect on mean heart rate or respiratory rate (Table 27) [although the thorough QT study identified a decrease in heart rate of about 4-5 bpm]. Importantly, respiratory rate data appeared highly unreliable, with counts clustering around the two values of 16/minute and 20/minute (Figure 11) (these are typical values reported for patients in the general care setting that are nonetheless rarely accurate).

Table 27: Mean Heart Rate, Respiratory Rate, Controlled Trials
(From Table 15-26, NEW ISS)

			99-AVR-102 (ALS)			02-AVR-106 (MS)		Combined
Parameter			AVP-923 N=70	DM N=33	Q N=37	AVP-923 N=76	Placebo N=74	AVP-923 N=146
Heart Rate (beats/min)	Value	n	54	31	36	68	71	122
		mean	77.0	78.5	78.8	73.4	74.2	75.0
		median	80.0	80.0	79.0	72.0	73.0	75.0
		SD	12.0	10.2	9.5	10.8	11.4	11.5
		min	49.0	60.0	58.0	52.0	55.0	49.0
		max	103.0	100.0	100.0	120.0	118.0	120.0
	Change from Baseline	n	54	31	36	66	71	120
		mean	-0.1	2.5	-0.9	-0.3	-2.3	-0.2
		median	0.0	2.0	0.0	0.0	-2.0	0.0
		SD	12.4	11.2	10.1	10.6	10.7	11.4
		min	-29.0	-23.0	-29.0	-32.0	-25.0	-32.0
		max	48.0	32.0	28.0	24.0	27.0	48.0
Respiration Rate (resp/min)	Value	n	54	31	35	68	71	122
		mean	18.5	19.1	18.5	17.7	17.6	18.0
		median	18.0	18.0	20.0	18.0	17.0	18.0
		SD	3.3	3.5	4.0	2.2	2.6	2.8
		min	14.0	14.0	12.0	12.0	13.0	12.0
		max	28.0	28.0	32.0	24.0	24.0	28.0
	Change from Baseline	n	54	31	35	66	71	120
		mean	-0.2	0.9	-0.1	0.1	-0.0	-0.0
		median	0.0	0.0	0.0	0.0	0.0	0.0
		SD	3.7	3.0	3.3	2.5	2.9	3.1
		min	-16.0	-4.0	-12.0	-6.0	-8.0	-16.0
		max	12.0	6.0	8.0	6.0	8.0	12.0

Program: vitchg.sas Data Source: vitals.sas7bdat 21NOV05
Value selected is last on treatment value within 3 days after last dose

The effect of AVP-923 on vital capacity is shown in Table 28. A high percentage of missing data (25% for AVP-923 arm at day 29) hinders interpretation, as do baseline imbalances in vital capacity between study arms, and lack of a placebo arm. The data present show little change in vital capacity in the AVP-923 arm.

Table 28: Vital Capacity, 99-AVR-102
(from table 18.1, t vitlcap.pdf)

			AVP-923 (N=70)		DM (N=33)		Q (N=37)	
Parameter (unit)	Visit	Statistic	Actual Value	Percent Change	Actual Value	Percent Change	Actual Value	Percent Change
Vital Capacity (%)	Screening/Day 1	n	70		33		37	
		Mean	68.60		74.21		75.49	
		Std Dev	22.59		19.48		21.28	
		Median	69.50		74.00		74.00	
		Min/Max	18.0/121.0		32.0/107.0		40.0/157.0	
	Day 15	n	14	14	7	7	5	5
		Mean	61.50	9.91	60.57	5.90	79.80	-3.86
		Std Dev	21.65	43.88	8.02	28.21	18.02	7.26
		Median	61.50	2.07	63.00	-1.69	68.00	-4.41
		Min/Max	14.0/ 88.0	-28.9/150.0	50.0/ 72.0	-17.7/ 67.4	65.0/100.0	-10.7/ 6.3
	Day 29	n	53	53	28	28	29	29
		Mean	68.47	1.52	72.68	-3.09	67.00	-10.15
		Std Dev	22.22	23.60	20.59	12.98	26.84	20.94
		Median	70.00	-1.89	71.00	-3.81	66.00	-7.69
		Min/Max	25.0/122.0	-41.7/119.2	39.0/111.0	-29.3/ 30.4	23.0/158.0	-73.3/ 32.5

Note: Percent change was defined as the post-baseline value minus Day 1 (baseline) value divided by baseline times 100.
Cross-reference: Listing 20.
Data Extraction: 11JUN2002 Table Generation: 26JUN2006

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Blood Pressure and Heart Rate

Few outlier values for vital signs were associated with controlled AVP-923 studies, such that no effect of AVP-923 was discernable (**Table 26**). No cases of bradycardia were recorded in AVP-923 arms.

Table 29: Vital sign Outliers, Controlled Trials
(From table 10-1, NEW ISS)

		99-AVR-102 (ALS)			02-AVR-106 (MS)		Combined
		AVP-923 N=70	DM N=33	Q N=37	AVP-923 N=76	Placebo N=74	AVP-923 N=146
Systolic BP	>180 and increase>=20	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)
	<90 and decrease>=20	0 (0%)	0 (0%)	1 (3%)	1 (1%)	0 (0%)	1 (1%)
Diastolic BP	>105 and increase>=15	1 (1%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	2 (1%)
	<50 and decrease>=15	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Heart Rate	<50 and decrease>=15	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
	>120 and increase>=15	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)

Program: vital.sas Data Source: vs.sas7bdat 02NOV05

ALS = amyotrophic lateral sclerosis; BP = blood pressure; DM = Dextromethorphan Hydrobromide USP; MS = multiple sclerosis; PBA = pseudobulbar affect; Q = Quinidine Sulfate USP.

Three patients from the MS controlled study experienced bradycardia AEs separate from the vital signs data measured during clinic visits. Two of these events were in patients in the AVP arm, and the other was in the control arm. One of the two AVP patients with bradycardia (self-reported rate of 48 bpm) discontinued. This patient had taken AVP-923 for only 2 days, and reported the AE of 'lightheadedness' in addition to bradycardia.

Three additional AEs of bradycardia occurred in the long-term study, 02-AVR-107 (another was possibly a data recording error; Subject 18-014).

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

See section 7.1.8.3.2.

7.1.8.4 Additional analyses and explorations

The limited controlled trial data regarding vital signs precluded meaningful additional analysis.

7.1.9 Electrocardiograms (ECGs)

ECG studies, Conclusions
Based on findings in PK studies, I find that AVP-923 is likely to prolong QT interval to a clinically meaningful degree. This finding is in contrast to the sponsor's claim of no clinically meaningful effect.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

A 'thorough QT' study was submitted as an amendment to the submission, and is discussed in section 7.1.9.4, following discussion of studies included in the original submission.

ECG testing (other than thorough QT))
ECGs were examined near T_{max} in 3 phase 1 studies: 99-AVR-100, 99-AVR-101, and 00-AVR-103. In the ALS and MS controlled studies and in the long-term safety study, ECGs were examined during clinic visits independent of time after dose. For the open-label study in painful diabetic neuropathy, 01-AVR-105, the first ECG measurement was completed 1 hour after the first dose, with subsequent ECGs (Day 15 and Day 29) completed independent of time after dose.

ECG analysis was conducted as recommended by the Agency:

> "ECG data were collected according to the ICH E14 Guidance, Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs."
>
> "ECG analysis in Study 99-AVR-102, Study 01-AVR-105, Study 02-AVR-106, and Study 02-AVR-107 was performed by (b) (4) . All ECGs were machine-read and 'over-read' by a cardiologist blinded to the treatment arm."
>
> "For Studies 99-AVR-100, 99-AVR-101, 99-AVR-102, 00-AVR-103, 02 AVR-106, and 01-AVR-105, a second analysis was performed by the (b) (4) . ECG intervals were measured manually by a cardiologist, and all abnormal ECGs were read again by a second cardiologist. Both (b) (4) cardiologists were blinded to the study groups and the treatment arm, and the same physicians performed all ECG readings. The assessment was performed by on-screen analysis using digital calipers in accordance with the regulatory guidelines. The QTc interval was evaluated by both QTcB and QTcF corrections for all studies."

Study 99-AVR-100
This Phase 1 study in normal volunteers examined the lowest dose of quinidine which protects dextromethorphan from degradation by CYP 2D6 in extensive metabolizers.

Eight subjects per group were assigned the following treatments, starting with a P.M. dose on Day 1, at 12-hour intervals for the next 6 days, with a final A.M. dose on Day 8:

- 30 mg dextromethorphan (DM) + 0 mg quinidine (Q) (Treatment arm A)
- 30 mg DM + 2.5 mg Q (Treatment arm B)
- 30 mg DM + 10 mg Q (Treatment arm C)
- 30 mg DM + 25 mg Q (Treatment arm D)
- 30 mg DM + 50 mg Q (Treatment arm E)
- 30 mg DM + 75 mg Q (Treatment arm F)

A resting ECG was obtained on Day 1 prior to dosing and on Day 8, 1-4 hours after dosing. Subjects with any ECG abnormality were excluded from the study.

At the 75 mg Q dose (arm F), which is 2.5-fold higher than the dose of Q in AVP-923, QT was statistically significantly prolonged, by 46 ms (Table 30), as was QTcB, by 16 ms (Table 31), and QTcF, by 26 ms (Table 32). The Q dose in AVP-923 was not, in fact, used for one of the study arms, but would have fallen between the dose in arm 'D' and arm 'E'. As an approximation, the average change in QT value for arms 'D' and 'E' might therefore represent AVP-923, with QT increase of 14 ms, QTcB increase of 5 ms, and QTcF increase about 8 ms increase. These values are not 'statistically significant' largely due to the small study size, and I therefore find that QT interval is lengthened by Q doses similar to contained in AVP-923, by roughly 5-15 ms as indicated by the QT and QTc point estimates. Importantly, the plasma concentrations resulting from the 25 mg, 50 mg, and 75 mg Q doses show a large degree of overlap (Figure 20), such that many patients taking AVP-923 (30 mg Q) would experience Q levels that cause much more QT prolongation than the 'average' QT prolongation associated with that dose. In fact, the untimed Q levels from the controlled AVP-923 trials indicate that patients taking AVP-923 can achieve Q blood levels as high, or higher than the average level of the patients in the 75 mg arm of this study.

Figure 20: Quinidine levels after 25, 50, and 75 mg Quinidine (each with 30 mg DM)

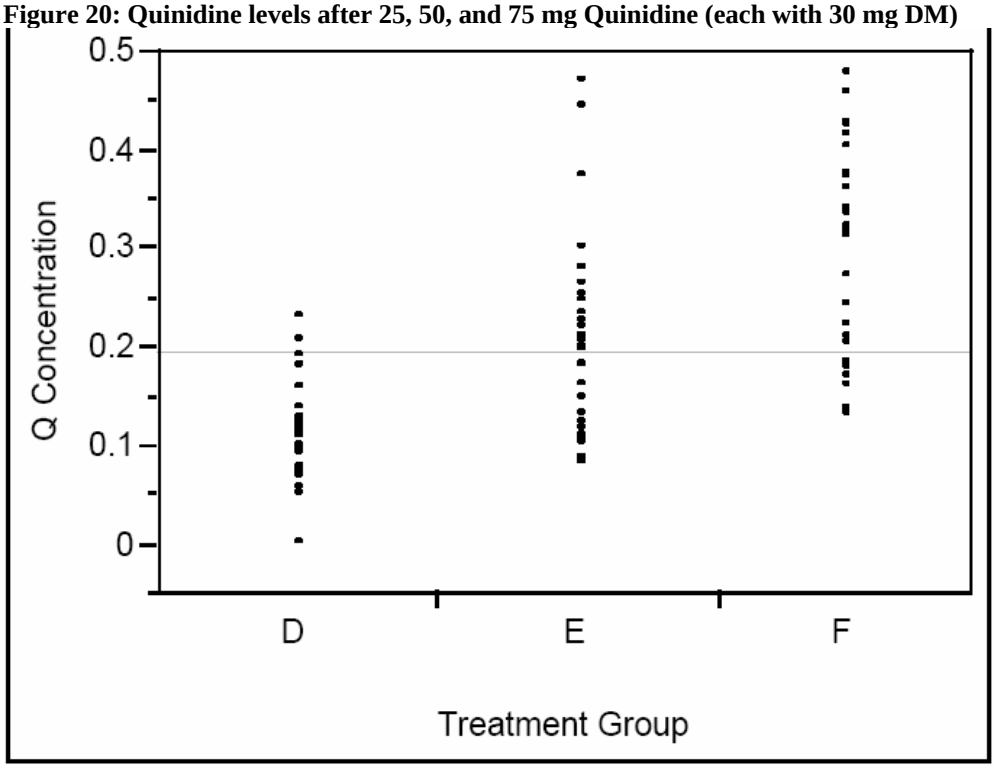


Table 30: QT Study ECG-AVR-100, Change from Baseline QT Interval
(From Table 9, study-ecg-avr-100.pdf)

Change from Baseline in QT Interval Measurements

Treatment	Timepoint	N	Mean	SD	Min	Median	Max	95% CI LCL	95% CI UCL	p-value
A	Part 2 D 8	5	-4	7	-11	-4	7	-12	5	.2883
B	Part 2 D 8	4	25	23	-5	27	49	-13	62	.1275
C	Part 2 D 8	5	10	27	-18	0	53	-23	43	.4424
D	Part 2 D 8	5	2	3	-3	2	5	-2	5	.2943
E	Part 2 D 8	5	26	27	-6	22	59	-7	60	.0967
F	Part 2 D 8	6	46	22	7	52	66	23	70	.0037

N: Number of observations
SD: Standard deviation
Min: Minimum value
Max: Maximum value
CI: Confidence interval
LCL: Lower confidence limit
UCL: Upper confidence limit
QT: Time from the onset of the QRS complex to the end of the T wave

Table 31:QT Study ECG-AVR-100, Change from Baseline QTc (Bazett) Interval
(From Table 10, study-ecg-avr-100.pdf)

Table 10

Change from Baseline in QTcB Measurements

Treatment	Timepoint	N	Mean	SD	Min	Median	Max	95% CI LCL	95% CI UCL	p-value
A	Part 2 D 8	5	-13	12	-28	-10	-1	-28	2	.0798
B	Part 2 D 8	4	-3	8	-10	-3	5	-15	10	.5339
C	Part 2 D 8	5	-8	18	-28	-7	20	-30	14	.3749
D	Part 2 D 8	5	-2	9	-9	-6	14	-14	10	.6557
E	Part 2 D 8	5	11	26	-23	13	43	-21	43	.3971
F	Part 2 D 8	6	16	6	6	16	24	9	22	.0016

N: Number of observations
SD: Standard deviation
Min: Minimum value
Max: Maximum value
CI: Confidence interval
LCL: Lower confidence limit
UCL: Upper confidence limit
QTcB: QT interval corrected for heart rate using Bazett's formula

Table 32: QT Study ECG-AVR-100, Change from Baseline QTc (Fridericia) Interval
(From table 11, study-ecg-avr-100.pdf)

Change from Baseline in QTcF Measurements

Treatment	Timepoint	N	Mean	SD	Min	Median	Max	95% CI LCL	95% CI UCL	p-value
A	Part 2 D 8	5	-10	9	-19	-11	1	-21	1	.0729
B	Part 2 D 8	4	6	4	0	7	10	-1	13	.0691
C	Part 2 D 8	5	-2	19	-18	-7	30	-25	21	.8052
D	Part 2 D 8	5	-1	6	-5	-4	9	-8	6	.7733
E	Part 2 D 8	5	16	24	-7	6	49	-14	46	.2078
F	Part 2 D 8	6	26	9	11	28	38	17	35	.0008

N: Number of observations
SD: Standard deviation
Min: Minimum value
Max: Maximum value
CI: Confidence interval
LCL: Lower confidence limit
UCL: Upper confidence limit
QTcF: QT interval corrected for heart rate using Fridericia's formula

Study 99-AVR-101
Eight extensive metabolizers (EMs) and two poor metabolizers (PMs) were dosed every 12 hours with AVP-923 for a week, with an additional dose on Day 8. The ECGs were taken on Day 1 (prior to dosing) and Day 8 (1-4 hrs. after the last dose).

Statistically significant changes were found in heart rate and QT. The mean QT change from Day 1 was 52 ± 29 ms with a mean HR change from Day 1 of -16 ± 12 bpm. The corrected QT intervals (QTcB and QTcF) did not show statistically significant changes, but the QTcF showed an increase of 17 ms (Table 33: ECG-AVR-101, QT Change).

One female subject had a QTcB value ≥ 450 ms and < 470 ms. One 1 male subject had a QTcB value ≥ 430 ms and < 450 ms, and one male subject had a QTcF value of 454 ms. No subjects had QT or QTc values ≥ 500 ms.

I conclude this small study supports that AVP-923 prolongs QT/QTc interval.

Table 33: ECG-AVR-101, QT Change
(From study-ecg-avr-101.pdf)

Table 7
QT/QTc change from Day 1

Treatment	Measure	Timepoint	N	Mean	SD	Min	Median	Max	95% CI LCL	95% CI UCL	p-value
AVP-923	QT	DAY 8	10	52	29	-4	54	99	31	72	.0023
	QTcB	DAY 8	10	-1	21	-29	0	35	-16	15	.8674
	QTcF	DAY 8	10	17	15	-3	12	37	6	27	.0848

N: Number of observations
SD: Standard deviation
Min: Minimum value
Max: Maximum value
CI: Confidence interval
LCL: Lower confidence limit
UCL: Upper confidence limit

Study ECG-AVR-103
This Phase 1 study determined the lowest dose of quinidine that protects dextromethorphan from metabolism by cytochrome P450 2D6, studied in two different doses of DM. Sixty five healthy male and female subjects were enrolled, all extensive metabolizers.

Subjects were randomly assigned to one of the following treatment arms:

- 60 mg DM + 0 mg Q (Treatment arm A)
- 60 mg DM + 30 mg Q (Treatment arm B)
- 60 mg DM + 45 mg Q (Treatment arm C)
- 60 mg DM + 60 mg Q (Treatment arm D)
- 45 mg DM + 0 mg Q (Treatment arm E)
- 45 mg DM + 30 mg Q (Treatment arm F)
- 45mg DM + 45 mg Q (Treatment arm G)
- 45 mg DM + 60 mg Q (Treatment arm H)

ECGs were recorded at screening, day 1, day 4, and day 8 (1-4 hours after last dose).

Table 34 shows change in QT/QTc between screening and day 8 for each treatment arm. The average increase in QT/QTc between 0 mg Q and 30 mg Q was about 11 ms.

Five subjects had an increase in QTc of 30 to 59 ms. One patient had an increase of 70 ms.

These findings for DM/Q combinations similar to that in AVP-923 suggest that AVP-923 is likely to increase QT interval on average, and result in clinically important QT outliers.

Table 34: QT/QTc Change, Day 8 vs. ScreeningQT/QTc interval change, screening versus day 8
(From study-ecg-avr-103.pdf, tables 9.7, 9.8, and 9.9)

ARM	Q dose (mg)	QT (ms)	QTcB (ms)	QTcF (ms)
A	0	24	-22	-6
B	30	27	-7	6
C	45	27	25	26
D	60	42	13	22
E	0	20	-13	-2
F	30	30	0	10
G	45	49	3	19
H	60	56	12	27

Study ECG-AVR-105
ECG-AVR-105 was a dose escalation study in 36 patients with painful diabetic neuropathy. An ECG was taken one hour after the first dose. Patients without ECG changes after the first dose were escalated to 4 capsules/day (120 mg Q) by day 29, if tolerated. On day 15 and 29, ECGs were not timed to time of drug dose. Thirteen patients did not tolerate the maximum dose of 120 mg Q, and received a range of doses, from 30 mg/day to 90 mg/day. These patients are not considered further here because few were in each dose level. Twenty-three patients reached the 120 mg/day dose. The maximum QT, QTcB, and QTcF changes were, respectively, 18 ms, 10 ms, and 11 ms. One subject had a QTcF prolongation of 31 ms. I find this data suggests these quinidine doses cause QT prolongation.

Five patients had treatment-emergent morphological abnormalities on ECG of uncertain significance (Table 35).

Table 35: 02-AVR-105, Treatment Emergent ECG Abnormalities
(from Table 8, report-ecg-02-avr-105.pdf)

ECG abnormality	DM		
	n	%	N
Borderline Left Atrial Enlargement	1 (60 mg)	20.00	5
Left Axis Deviation	1 (120 mg)	4.35	23
Non-specific T Wave Changes	1 (30 mg)	25.00	4
Ventricular Extra Systole (Unifocal)	2 (120 mg)	8.70	23

Studies with ECG not timed to Cmax: 99-AVR-102, 02-AVR-106, 02-AVR-107
Table 36 shows the change in QT interval for the 2 controlled studies and open-label safety study in PBA patients. ECGs were not timed to AVP-923 dose. The data shows high variability of QT measurements. In the ALS study, 99-AVR-102, AVP increased QT interval by about 8 or 9 ms, while the equivalent dose of Q *decreased* QT by up to about 6 ms. In contrast, in the MS study, 02-AVR-106, the two different ECG interpretations done by BMS and QECG showed poor agreement for AVP-923, with averages of 3.4 ms increase to 5.6 ms decrease, respectively, while both companies had a smaller range of change for placebo, of 3 or less ms centered around zero change.

In contrast to uncorrected QT, for QTcF and QTcB, the ALS study did not show increases, while the MS analysis showed an increase for AVP-923 of up to 6 or 7 ms.

Overall, I find the above data to be inconclusive, likely due to the manner of collection in an uncontrolled clinic setting. Studies in which ECG data was collected near Tmax should be relied upon for conclusions regarding QT prolongation.

Table 36: QT Change, Studies on PBA patients
(From NEW ISS, Table 12-1)

Table 12-1. ECG Readings from (b) (4) and (b) (4) Change from Screening for QT Intervals, QTcF Values, and QTcB Values in All Avanir-Sponsored Studies in PBA Patients (Studies 99-AVR-102, 02-AVR-106, and 02-AVR-107)

Variable (unit)	ECG Reading	Visit	Study 99-AVR-102						Study 02-AVR-106				Study 02-AVR-107*	
			AVP-923 (N = 67)		DM (N = 31)		Q (N = 33)		AVP-923 (N = 76)		Placebo (N = 74)		AVP-923 (N = 463)	
			Mean	Min/ Max	Mean	Min/ Max	Mean	Min/ Max	Mean	Min/ Max	Mean	Min/ Max	Mean	Min/Max
QT (ms)	(b) (4)	Day 29	7.5§	-47/81	0.7	-80/51	-5.9§	-61/42	0.1	-64/60	2.1	-50/66	2.6	-92/72
		Day 85	--	--	--	--	--	--	3.4	-70/66	0.0	-54/56	--	--
		Week 52	--	--	--	--	--	--	--	--	--	--	2.2	-82/84
		Extension	--	--	--	--	--	--	--	--	--	--	-0.8	-56/42
		Day 29	8.7	-39/109	3.0	-97/52	-1.3	-64/36	-5.6	-69/55	-1.0	-55/64	--	--
		Day 85	--	--	--	--	--	--	-0.6	-58/60	-3.0	-68/50	--	--
QTcF† (ms)		Day 29	--	--	--	--	--	--	4.8	-55/41	3.3	-35/36	3.1	-76/52
		Day 85	--	--	--	--	--	--	6.1‡*	-49/37	0.4‡*	-39/44	--	--
		Week 52	--	--	--	--	--	--	--	--	--	--	4.8	-48/66
		Extension	--	--	--	--	--	--	--	--	--	--	11.0	-12/46
		Day 29	2.0	-75/48	0.4	-47/54	3.7	-36/38	-0.1	-32/40	-0.8	-39/18	--	--
		Day 85	--	--	--	--	--	--	2.1	-30/33	-1.9	-41/30	--	--
QTcB (ms)		Day 29	-2.9	-46/34	-4.9	-57/27	2.5	-41/40	7.3	-53/50	4.1	-29/51	3.4	-65/69
		Day 85	--	--	--	--	--	--	7.5‡*	-37/38	0.5‡*	-46/55	--	--
		Week 52	--	--	--	--	--	--	--	--	--	--	6.4	-57/83
		Extension	--	--	--	--	--	--	--	--	--	--	14.1	-23/47
		Day 29	-1.6	-94/55	-1.0	-51/62	6.5	-47/41	2.8	-32/50	-0.4	-32/29	--	--
		Day 85	--	--	--	--	--	--	3.5	-30/38	-1.3	-38/29	--	--

Source: Study 02-AVR-106 Clinical Study Report, Table 18; Study 99-AVR-102 Clinical Study Report, Table 21; Study 99-AVR-102 Integrated (b) (4) Report, Table 49, Table 50, and Table 51; Study 02-AVR-107 Interim Study Report, Table 15.

(b) (4) = (b) (4) DM = Dextromethorphan Hydrobromide USP; PBA = pseudobulbar affect; Q = Quinidine Sulfate USP; QT = QT interval; QTcB = rate-corrected QT interval with Bazett's correction; QTcF = rate-corrected QT interval with Fridericia's correction.

* A second analysis by (b) (4) was not performed for Study 02-AVR-107.

† QTcF was not calculated in the (b) (4) analysis for Study 99-AVR-102.

‡ Significant p-value for difference between treatment groups ($p \leq 0.05$, *t* test).

§ Significant p-value for difference between AVP-923 and Q treatment groups ($p \leq 0.05$, ANOVA).

Table 37: QTc Abnormality, Outlier Analysis

Table 12-2. Incidence of QTc Abnormalities: Avanir-Sponsored Controlled Studies in PBA Patients (Studies 99-AVR-102 and 02-AVR-106)

		99-AVR-102 (ALS)			02-AVR-106 (MS)		Combined
		AVP-923 N=67	DM N=31	Q N=35	AVP-923 N=75	Placebo N=73	AVP-923 N=146
QTc Fredericia	> 450 ms	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)	0 (0%)
	> 480 ms	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
	> 500 ms	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Change >=30 ms	3 (4%)	0 (0%)	1 (3%)	8 (11%)	5 (7%)	11 (8%)
	Change >=60 ms	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
QTc Bazett	> 450 ms	1 (1%)	1 (3%)	1 (3%)	7 (9%)	7 (10%)	8 (6%)
	> 480 ms	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	> 500 ms	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Change >=30 ms	3 (4%)	0 (0%)	4 (11%)	15 (20%)	4 (5%)	18 (13%)
	Change >=60 ms	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Program: ecg.sas Data Source: eg.sas7bdat 05JAN06

ALS = amyotrophic lateral sclerosis; DM = Dextromethorphan Hydrobromide USP; MS = multiple sclerosis; Q = Quinidine Sulfate USP; QTc = rate-corrected QT.

QTc Values in Patients with Sudden Death or palpitations

QT prolongation can lead to sudden death through arrhythmia, and an attempt was therefore made to correlate the two. However, this analysis had little power to detect a correlation because insufficient QT data was available for patients that experienced sudden death (and the related adverse events discussed below). For example, subject 34-033 in study 02-AVR-107 died suddenly on day (b)(4) of AVP-923 treatment, possibly due to arrhythmia, but never had an ECG on treatment. Similarly, for all patients, ECGs were taken remotely in time from the occurrence of arrhythmias, without regard to peak quinidine levels, such that even if QT prolongation had been present during the event, the QT prolongation might not have been present during the ECG.

With such limitations in mind, the longest QTc value recorded in the pooled database for these 5 AVP-923-treated patients identified with sudden death was 430 ms QTcF (418 ms QTcB) recorded for Patient 107-28-011 at Day (b)(4), and the greatest increase in QTc was a QTcB of 18 ms (QTcF 16 ms) at Day (b)(4) in Patient 107-30-01 when the QTcB value was 420 ms (QTcF 418 ms).

QTc in patients with syncope
Ten AVP-923-treated patients were identified with syncope. I find one of these cases suggestive of a causal role of QT prolongation in the syncopal event. Patient 107-03-014 had a 61 ms increase in QTcB and 52 ms increase in QTcF at Day 29. The syncope event occurred on Day 5, but an ECG was not obtained on that date. The QTcB value at Day 29 was 410 ms (QTcF at Day 29 was 408 ms). The QTcB increase in this same patient at

Week 52 while still on AVP was 41 ms, with an increase of QTcF of 34 ms. The patient experienced multiple falls.

QTc in patients with palpitations
Palpitations were reported by 10 patients. The greatest increase in QTc among these 10 patients was a QTcF of 23 ms and QTcB of 15 ms in Patient 107-27-001 when the QTcF value was 419 ms and QTcB was 426 ms. One patient (28-005, study 02-AVR-107) developed palpitations on day 1 while taking both AVP-923 and erythromycin, a 3A4 inhibitor, and dropped out of the study with no on-drug ECG data available.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

7.1.9.3 Standard analyses and explorations of ECG data

See section 7.1.9.1.

7.1.9.3.1 Analyses focused on measures of central tendency

See section 7.1.9.1.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

See section 7.1.9.1.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

See section 7.1.9.1.

7.1.9.4 Additional analyses and explorations

Thorough QT study
The study was a randomized, double-blind, placebo controlled, crossover study in 36

healthy male and female volunteers to determine the electrocardiogram changes associated with 2 doses of AVP-923, with an open- label active control arm of oral moxifloxacin.

The primary endpoint was maximum mean change of the QT corrected for heart rate (HR) using the Fridericia formula (QTcF) from among the AVP-923 arm observation times during supratherapeutic (2 x standard dose [two capsules BID]) dose, subtracted by the mean change of QTcF at the matching placebo observation time. Secondary endpoints included analysis of the standard dose of AVP-923 [one capsule BID], and maximum mean change of QT intervals corrected for HR using Bazett's formula (QTcB). The relationship was also determined for the concentration of dextromethorphan (DM), dextrorphan (DX), and quinidine (Q) to the change of QTcF (dQTcF) for all observations during dosing.

Randomized treatments were administered on days 1, 8, and 15 and positive control on day 22. Baseline assessments were days 0, 7, 14 and pre-dose on day 22. Treatment assessments were made on days 4, 11, 18, and 22.

Moxifloxacin control values reached the criterion for valid assay sensitivity.

AVP-923 prolonged QTc (see Table 38):

> "The maximal mean placebo-subtracted QTcF change from baseline (dQTcF) for the supratherapeutic dose of AVP-923 was 18.81 msec, and the upper bound of the one-sided 95% CI was 24.50 msec. A standard dose of AVP-923, 30 mg dextromethorphan and 30 mg Q bid for 7 doses caused QTcF elevation, observable prior to the last dose and maximal at 3 hours postdose. The maximal mean placebo-subtracted QTcF change from baseline (dQTcF) for the standard dose of AVP-923 was 10.12 msec, and the upper bound of the one-sided 95% CI was 15.05 msec. A single dose of oral moxifloxacin 400 mg caused QTcF elevation, observable prior to the last dose and maximal at 1 hour postdose. The maximal mean placebo subtracted QTcF change from baseline (dQTcF) for the moxifloxacin was 14.35 msec, and the lower bound of the one-sided 95% CI was 9.73 msec." (from study-05-AVR-119-part-1.pdf).

Table 38: QTc Endpoints, Thorough QT Study

Maximum Mean, Paired, Placebo-subtracted dQTc Endpoints for Each Treatment						
dQTcF	Hour	Mean (msec)	SEM	N	p	Upper (lower) bound of 95% CI one-sided (msec)
Supratherapeutic	6	18.81	3.36348	34	<.0001	24.50
Standard	3	10.12	2.90739	31	0.0015	15.05
Pos. Contr.	1	14.35	2.72976	33	<.0001	9.73
dQTcB	Hour	Mean	SEM	N	p	Upper (lower) bound of 95% CI one-sided (msec)
Supratherapeutic	5	15.54	3.44091	34	<.0001	21.37
Standard	3	9.24	3.71446	31	0.0187	15.54
Pos. Contr.	3	17.22	3.46892	33	<.0001	11.35

Outliers

Table 39 shows QTc outliers for the thorough QT study. The maximal QTcF and maximal change in QTcF observed was 454 msec and 55 msec, respectively.

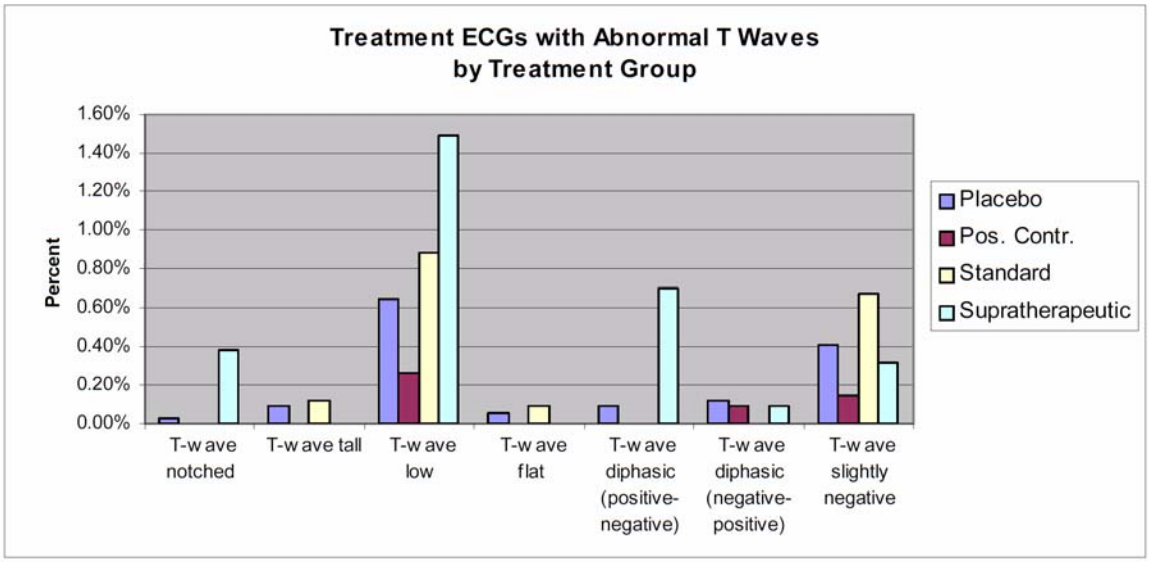
Table 39: QTc Outliers, Thorough QT Study

Value	Cat	Treatment	Count	Percent
dQTcB	30-60	Placebo	8	2.29%
dQTcB	30-60	Pos. Contr.	11	11.11%
dQTcB	30-60	Standard	13	3.90%
dQTcB	30-60	Supratherapeutic	27	7.74%
dQTcB	60-90	Pos. Contr.	1	0.29%

dQTcF	30-60	Placebo	3	0.86%
dQTcF	30-60	Pos. Contr.	3	3.03%
dQTcF	30-60	Standard	14	4.20%
dQTcF	30-60	Supratherapeutic	25	7.16%

The sponsor notes that there were few ECGs with abnormal ST segments and no trends for their appearance during therapy. T wave abnormalities likewise were very limited in frequency but there was a trend, especially for low T waves, favoring a greater number for the AVP-923 arms in a dose-related fashion (Figure 21). The study report notes that these T wave findings reinforce the interval results suggesting repolarization abnormalities.

Figure 21: Abnormal T Waves, Thorough QT Study (From CCSSREREPORTFINAL, Fig. 19)



Abnormal U waves were present in only 4 ECGs, all during baseline.

The AVP-923 treatments were also associated with an initial drop of HR of about 4 bpm at hour 2, with recovery by hour 3, and another drop of about 5 bpm at hour 14. At hour 22 HR values are at baseline levels.

No AEs beyond mild, non-serious occurred. Of note, 2 of 35 subjects reported 'euphoric mood' when receiving twice the recommended dose, with no similar reports from the other treatments, raising additional concern about potential liability for abuse of AVP-923.

[Day 18 results (below) showed differences in HR, QTcB and QTcF interval versus other treatment days, regardless of treatment or sequence. This might have arisen by chance, or from a systematic but undetected difference in the study volunteers on that day, possibly habituation or sensitization to the treatment environment.]

Treatment Day	dHR	dQTcB	dQTcF
4	1.41	2.85	1.41
11	-2.01	2.21	3.92
18	-1.10	5.77	6.94
Prob > F	<.0001	0.0057	<.0001

Dose/response effect of quinidine on QTc

Figure 22 and Figure 23 show that QTc prolongation increases as a function of quinidine concentration [of note, since quinidine and dextromethorphan were dosed only in fixed combination, and since a positive correlation existed between quinidine, dextromethorphan, and dextrophan levels, the dose/response of QTc for dextromethorphan and dextrorphan are similar to that for quinidine,].

Figure 22: Change in QTcB by Quinidine Concentration (Fig 22 and 23 from CCSSREPORTFINAL.doc, Figure 21)

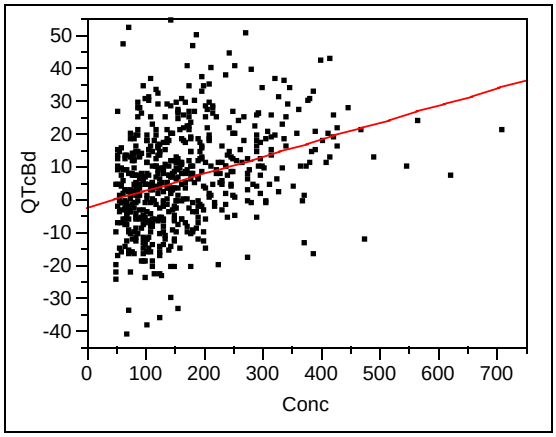
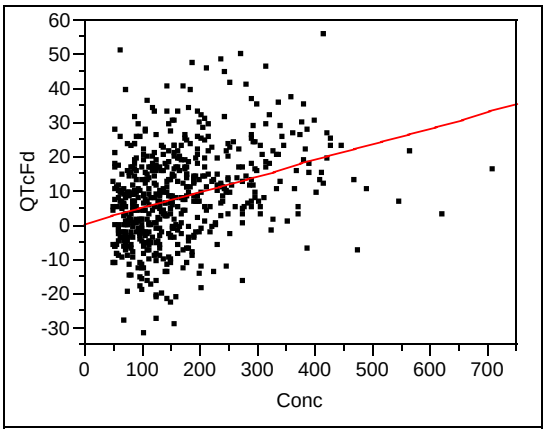


Figure 23: Change in QTcF by Quinidine Concentration



Conc, ng/ml; QT, ms

The sponsor concludes:

> The presence of quinidine in the formulation makes these findings predictable and expected. While the maximal mean placebo-subtracted dQTcF of 10.12 msec and the dQTcB value of 9.24 msec exceed the ICH guidance threshold for a positive thorough QT study, the magnitudes of these changes are well within the lower range, 10 to 20 msec, considered "inconclusive" in the ICH guidance. (from CCSSREPORTFINAL.DOC)

I disagree with the sponsor's minimization of the QTc findings as 'inconclusive,' as based on both incorrect interpretation of the ICH guidelines, and of the current results. The ICH guidelines are applicable for screening drugs without known proarrhythmic risk. QTc is an imperfect biomarker for proarrhythmic risk, such that not all drugs that increase QTc by 5- to 20-msec are proarrhythmic. Quinidine, in contrast, presents a known proarrhythmic risk. Therefore, a very different question is being addressed by this study: Given the known

proarrhythmic risk of quinidine at cardiac doses, is the lower dose in AVP-923 also proarrythmic. The data suggest that given the prior knowledge of quinidine's proarrhythmic risk at higher doses, the repolarization abnormality observed at the doses found in AVP-923 likely presents a clinically meaningful proarrhythmic risk. Given the strong dose-relationship of QTc prolongation, risk would be especially high for patients with levels of quinidine at the high end of the distribution (
Figure 22 and Figure 23).

7.1.10 Immunogenicity

Thrombocytopenia
Quinidine is associated with a high risk of autoimmune thrombocytopenia, at an incidence of about 1 per 1,000 patient years. The thrombocytopenia can be severe, requiring platelet transfusion or causing death. Thrombocytopenia did not occur in the AVP-923 safety database.

Lupus erythematosus-like syndrome
There are several well-documented reports of quinidine-induced lupus erythematosus-like syndrome. The syndrome involves polyarthritis with a positive antinuclear antibody test. Symptoms do not usually occur until several months after starting quinidine, and resolve slowly on withdrawing the drug. No cases of such a syndrome occurred in the AVP-923 safety database.

7.1.11 Human Carcinogenicity

An MS patient in the long-term AVP-923 study developed and died of acute monocytic leukemia. The patient was on concomitant Novantrone and interferon beta 1-a. A black box on Novantrone indicates that secondary AML has been reported in MS patients treated with Novantrone, at a rate of 0.25%.

7.1.12 Special Safety Studies

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The abuse of DM-containing OTC preparations is common. Adolescents are the primary population known to abuse DM. A mild stimulant effect of DM is reported at a dose of

between 100 and 200 mg (http://www.erowid.org). Dependence on DM is rarely described. An abstinence syndrome may be associated with cessation of DM abuse that is characterized by dysphoria and intense cravings.

Studies of the abuse potential of AVP-923 were not performed.

The sponsor asserts that the metabolic conversion of DM to dextrophan (DX) is required to achieve the intoxicating, 'positive' drug effects desired with drug abuse. The sponsor further argues that since Q inhibits this conversion, AVP-923 dose not have abuse potential:

> "In human abuse liability studies, drug liking was correlated with CYP2D6 activity in eight extensive metabolizers given DM, and some drug effects corresponded to plasma DX concentration (Zawertailo et al., J Clin Psychopharmacol, 1998;18(4):332-337). Extensive metabolizers who received DM reported an overall drug liking and positive subjective effects including euphoria, detachment, and spaciness. In contrast, poor metabolizers who received DM reported negative effects, such as sedation, dysphoria, and nausea, and drug toxicity primarily caused by DM, because no DX was detectable in the blood. In addition, extensive metabolizers coadministered Q and DM experienced decreased positive drug effects and increased negative drug effects, similar to poor metabolizers, compared with DM treatment alone (Zawertailo, L.A., Variations in CYP2D6 activity affect the pharmacokinetics and dynamics of dextromethorphan in humans, in Department of Pharmacology. 2002, University of Toronto. p. 292.). A recent report confirms that DX is the active metabolite that produces neurobehavioral effects, and DM does not produce the same effects. In that sense, DM is a prodrug, and the metabolic conversion of DM to DX is an important determinant of the abuse potential of DM in an individual (Boyer, E.W., Dextromethorphan abuse. Pediatr. Emerg. Care, 2004. 20:858-863)."

I find the sponsor's arguments insufficient to address the abuse potential of AVP-923. The Zawertailo study from 1998 cited above was *very* small (N = 4 EMs and 2 PMs), and while the results are suggestive, few broad conclusions can be drawn from only 2 patients. The study by the same author from 2002 is not provided or readily available. The sponsor does not give the citation for the assertion that DM dose did not produce neurobehavioral effects.

The sponsor notes that common AEs associated with drug abuse include euphoric mood, disorientation and confusion, all of which AVP-923 can produce. Euphoric mood was reported in 2 MS patients (3%) in Study 02-AVR-106, and in no placebo patients. In normal volunteers euphoric mood was reported once in the AVP-923 group (10%, 1/10), once in the DM group (4%, 1/26), and 5 times in the DM/Q combination (other than AVP-923) group (6%, 5/80). In the thorough QT study, 2 or 36 patients experienced euphoria when in the 'twice the recommended dose' arm of AVP-923, with non experiencing euphoria from the 'recommended dose,' placebo, or positive control.

While the sponsor argues that not enough DX is formed from AVP to produce positive drug effects, DX is still formed, at about 1/3 the blood level as occurs after DM alone.

7.1.14 Human Reproduction and Pregnancy Data

Quinidine is in pregnancy category C, and should be given in pregnant women only if clearly needed.

No adverse effects have been reported in infants from quinidine received through breast milk, and the American Academy of Pediatrics considers that quinidine is therefore usually compatible with breast feeding. A single report of administration of quinidine to a woman throughout pregnancy did not identify abnormalities in the infant.

Dextromethorphan is generally considered safe for use during pregnancy and breast feeding.

The effects of AVP-923 on pregnancy, labor, and delivery are not known.

7.1.15 Assessment of Effect on Growth

No data was presented on the effect of AVP-923 on growth.

7.1.16 Overdose Experience

No cases of AVP-923 overdose have occurred. The highest dose of quindine tested with dextromethorphan in AVP-923 development was 150 mg/day (2.5-fold the dose in AVP-923), and the highest dose of dextromethorphan tested with quinidine was 120 mg/day (2-fold the dose in AVP-923).

Quinidine
Quinidine has a narrow therapeutic index. A typical therapeutic concentration is up to 6 mg/L. The most clinically significant AEs associated with acute quinidine overdoses are ventricular arrhythmias and hypotension. Other signs/symptoms of acute overdose include vomiting, diarrhea, tinnitus, high-frequency hearing loss, vertigo, blurred vision, diplopia, photophobia, headache, confusion and delirium. Treatment of overdosage is symptomatic and supportive. Activated charcoal may be considered if the patient presents within 1 hour of ingestion. Serum quinidine levels can be monitored in overdose, but the electrocardiographic QTc interval is a better predictor of quinidine-induced ventricular arrhythmias

Cinchonism, characterized by headache, fever, visual disturbances, mydriasis, decreased hearing or tinnitus, nausea, vomiting, hot flushed skin, rash, and CNS impairment can occur from elevated plasma concentrations (5 mg/L or more) during chronic therapeutic use. Cinchonism can occur in the absence of cardiotoxicity, other than QT prolongation.

Death has been described after a 5-gram ingestion of quinidine by a toddler, while an adolescent survived after ingesting 8 grams of quinidine

Dextromethorphan
Dextromethorphan has a wide therapeutic index. No fatalities have been reported from OTC dextromethorphan, and death is unlikely even with doses exceeding 100 times the normal adult dose. Deaths have been reported from abuse of powdered dexromethorphan. Lethargy, ataxia, tachycardia, and nystagmus lasting 7 to 8 hours may occur with amounts of 10 mg/kg or more. CNS-related AEs are most prevalent with dexromethorphan overdose and include hyperexcitability, euphoria, excitation, severe irritability, confusion, toxic psychosis, auditory and visual hallucinations, stupor, coma, ataxia, dystonia, nystagmus, blurred vision, and changes in muscle reflexes Respiratory depression, tachycardia, seizures, and severe nausea and vomiting can also occur at very high doses.

Treatment for dexromethorphan overdose includes symptomatic and supportive measures. Anecdotal reports suggest parenteral naloxone may be helpful in reversing CNS and respiratory depressant effects.

Adverse effects of dexromethorphan overdoes might differ from the effects of dexromethorphan overdose in the presence of quinidine, due to relatively higher dexromethorphan versus DX blood levels.

7.1.17 Postmarketing Experience

AVP-923 or related DM/Q combinations are not marketed in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Section 7.2.1.1 lists the studies used for the safety evaluation, along with populations exposed and extent of exposure.

7.2.1.1 Study type and design/patient enumeration

The following tables list the clinical studies analyzed in this review:

Table 40: Food Effects on Pharmacokinetics, 04-AVR-111
(**Table 40-Table 52** are from NDA application table 5-1, 'Tabular Listing of all Clinical Studies')

Study ID Study Title No. Site(s) Country/IND Submission	Status Date Type of Study	Subject Population Total Number of Subjects Age: Range (y) Mean (y) Gender: M/F (%) Race: W/B/Other (%)	Design/Control* Objectives/Endpoint(s)	Test and Control Drugs Dose Regimen/ Route	Clinical Outcome Efficacy/Pharmacology Safety AEs SAEs
AVANIR-SPONSORED STUDIES					
Biopharmaceutic Study					
Study 04-AVR-111 A Randomized, Single-Dose, 2-Way Crossover Study to Determine the Effects of Food on the Pharmacokinetics of AVP-923 in Healthy Adult Volunteers 1 U.S./IND 56,954	Completed 01/31/04-05/04/04 Food Effects, PK and Safety	Population: Normal healthy volunteers Number of subjects: 18 subjects enrolled 18 subjects completed the study Age: Range: 19-53 Mean: 27 Gender: 11/7 (61%/39%) Race: 18/0/0 (100%/0%/0%)	Open-label, randomized, 2-way crossover, comparative bioavailability study under fed and fasting condition To determine the effect of food on the PK of DM, DX, and Q PK evaluation of AVP-923 under fed and fasting conditions	Regimen A: Single oral 30 mg DM and 30 mg Q dose, administered after fasting for at least 10 h Lot No. C0051B002 Regimen B: Single oral 30 mg DM and 30 mg Q dose, administered 30 minutes after administration of a standard high fat breakfast	PK: The $AUC_{0-\tau}$ values for DM, DX and Q were not significantly different for subjects administered AVP-923 under fed or fasting conditions. There was a slight delay in the (t_{max}) for DM and Q. Table 2.7.1-4 Table 2.7.1-5. AEs: Roughly equal numbers of subjects reported AEs under fasting (5 subjects) and fed conditions (4 subjects). All AEs were mild or moderate in severity and all AEs were unrelated to AVP-923. SAEs: None.

(Study 04-AVR-111 located in NDA application section 5.3.1.1.1)

Table 41: Drug interaction/Metabolism, 99-AVR-100

Study ID Study Title No. Site(s) Country/IND Submission	Status Date Type of Study	Subject Population Total Number of Subjects Age: Range (y) Mean (y) Gender: M/F (%) Race: W/B/Other (%)	Design/Control* Objectives/Endpoint(s)	Test and Control Drugs Dose Regimen/ Route	Clinical Outcome Efficacy/Pharmacology Safety AEs SAEs
AVANIR-SPONSORED STUDIES (continued)					
Clinical Pharmacology Studies					
99-AVR-100† Clinical Pharmacology Study to Determine the Lowest Dose of Quinidine which Protects Dextromethorphan from Degradation by Cytochrome P450 2D6 1 U.S./IND 56,954 SN 011	Completed 04/04/99-04/19/99 PK and Safety	Population: Healthy volunteers EMs included Number of subjects: Part 1: 58 subjects enrolled 50 subjects dosed All completed the study Part 2: 46 subjects enrolled 45 subjects completed the study Age: Part 1: Range: 20-86 Mean: 51 Part 2: Range: 20-86 Mean: 51 Gender: Part 1: 25/25 (50%/50%) Part 2: 22/24 (48%/52%) Race: Part 1: 39/3/8 (78%/6%/16%) Part 2: 37/2/7 (81%/4%/15%)	Two-part Phase 1 Study Part 1: open-label, single dose Part 2: open-label randomized, multiple dose Urine concentration of DM and DX Plasma concentration of DM, DX, and Q Evaluate safety during administration of DM and Q	Part 1: single oral dose of 30-mg DM capsule Lot No 981203-1 Part 2: 30 mg DM with 0, 2.5, 10, 25†, 50, or 75 mg of Q; given orally every 12 h for a total of 14 doses 30 mg DM: 0 mg Q Lot No. 981203-1; 25 mg† Q Lot No. 981215-1; 2.5 mg Q Lot No. 981210-2; 10 mg Q Lot No. 981214-1; 50 mg Q Lot No. 981216-1; 75 mg Q Lot No. 981217-1	PK: A 25-mg† dose of Q results in nearly maximal possible inhibition of CYP2D6 activity. Table 2.7.2-2. Modeling results confirm competitive inhibition of DM metabolism with 25 mg† Q (28.8 mg Quinidine Sulfate USP) as the optimal dose (addendum to Study 99-AVR-100 and Study 00-AVR-103 located in the final study report for Study 00-AVR-103). AEs: Part 1: One AE (headache, mild) was reported and resolved without intervention. Part 2: 150 AEs were experienced by 34 (74%) of 46 subjects. The most frequently reported AEs included headache, loose stool, lightheadedness, dizziness, and nausea. 120 of the 150 AEs were considered to be at least possibly drug related. There were no clinically significant trends regarding vital signs, physical examinations, or clinical laboratory tests. SAEs: One 87-year-old female discontinued from study because of protracted vomiting after four doses of 30 mg DM and 75 mg Q and was subsequently discontinued from the study. Two days later she was hospitalized for dehydration and vomiting. She received rehydration treatment and appeared to be progressing appropriately. On the third day of hospitalization, she was noted to have a firm, bloated abdomen. Ultrasound and computed tomography of the abdomen revealed a mechanical bowel obstruction at the terminal ileum. Before a nasogastric tube could be inserted, the subject vomited and aspirated stomach contents into the lungs. She then suffered myocardial infarction and ultimately died as a results of the aspiration. The death was not considered to be directly related to study drug.

(Study 99-AVR-100 located in NDA application section 5.3.3.1.1)

Table 42: Pharmacokinetics, 99-AVR-101

Study ID Study Title No. Site(s) Country/IND Submission	Status Date Type of Study	Subject Population Total Number of Subjects Age: Range (y) Mean (y) Gender: M/F (%) Race: W/B/Other (%)	Design/Control* Objectives/Endpoint(s)	Test and Control Drugs Dose Regimen/ Route	Clinical Outcome Efficacy/Pharmacology Safety AEs SAEs
AVANIR-SPONSORED STUDIES (continued)					
Clinical Pharmacology Studies (continued)					
99-AVR-101† A Single-Dose and Multiple-Dose Pharmacokinetic Study with a Product Containing Dextromethorphan and Quinidine (AVP-923) 1 U.S./IND 56,954 SN 011	Completed 05/09/99-05/24/99 PK and Safety	Population: Healthy volunteer EMs and PMs included Number of subjects: 10 subjects enrolled 9 subjects completed the study Age: Range: 36-74 Mean: 53 Gender: 5/5 (50%/50%) Race: 8/0/2 (80%/0%/20%)	Phase 1 Study An open-label, single and multiple dose PK and safety study To determine the PK parameters of DM upon administration of a single dose and multiple doses of AVP-923, the differences in these PK parameters between EMs and PMs, and to chronicle the occurrence of AEs during administration of AVP-923 Evaluate safety during administration of DM and Q Urine concentrations of DM and DX Plasma concentrations of DM, DX, and Q	30 mg DM and 25 mg† Q, given orally every 12 h for a total of 15 doses Lot No. 981215-1	PK: Low-dose Q inhibited the metabolism of DM resulting in increased systemic availability. Mean DM C_{max} and AUC_{0-12} values increased approximately sixfold and eightfold, respectively, between Days 1 and 8. In EMs, 30 mg DM and 25 mg† Q increases exposure to DM. Following administration of AVP-923, DM levels were higher in PMs than in EMs and DX levels were lower in PMs than in EMs. Table 2.7.2-3 The mean urinary DM/DX ratio increased at least 29-fold in EMs by Day 8 (compared to ratio after stopping dosing). Table 2.7.2-4 AEs: 16 treatment-emergent AEs were reported by 5 of the 10 (50%) subjects dosed. AEs considered drug related included asthenia, diarrhea, anorexia, nausea, vomiting, anxiety, depersonalization, insomnia, and somnolence. There were no clinically significant trends regarding vital signs, physical examinations, or clinical laboratory tests. SAEs: None.

(Study 99-AVR-101 located in NDA application Section 5.3.3.1.2)

Table 43: Drug interaction/metabolism, 00-AVR-103

Study ID Study Title No. Site(s) Country/IND Submission	Status Date Type of Study	Subject Population Total Number of Subjects Age: Range (y) Mean (y) Gender: M/F (%) Race: W/B/Other (%)	Design/Control* Objectives/Endpoint(s)	Test and Control Drugs Dose Regimen/ Route	Clinical Outcome Efficacy/Pharmacology Safety AEs SAEs
AVANIR-SPONSORED STUDIES (continued)					
Clinical Pharmacology Studies (continued)					
00-AVR-103 A Phase 1 Drug Interaction Study to Determine the Lowest Dose of Quinidine that Protects Dextromethorphan in Two Dose Levels from Metabolism by Cytochrome P450 2D6 1 U.S./IND 56,954 SN 025	Completed 02/23/01-03/24/01 PK and Safety	Population: Healthy volunteers (only) EMs included Number of subjects: 65 subjects enrolled 47 completed the study Age: 60-mg arm: Range: 19-47 Mean 26.3 45-mg arm: Range: 19-60 Mean: 29.5 Gender: 60-mg arm: 12/20 (38%/62%) 45-mg arm: 21/12 (64%/36%) Race: 60-mg arm: 32/0/0 (100%/0%/0%) 45-mg arm: 31/1/1 (94%/3%/3%)	Phase 1 Study: An open-label, parallel-group, multiple-dose, single-center, drug interaction study Determine the lowest dose of Q that effectively inhibits the conversion of 45 mg of DM to DX and the lowest dose of Q that effectively inhibits the conversion of 60 mg of DM to DX Evaluate safety during administration of DM and Q Urine concentration of DM, DX, and the DM/DX ratio Plasma concentration of DM, DX, and Q	60 mg DM with 0, 30, 45, or 60 mg of Q, given orally every 12 h for a total of 14 doses 60/0 Lot No. 1004F 60/30 Lot No. 2002F 60/45 Lot No. 2003F 60/60 Lot No. 2004F 45 mg DM with 0, 30, 45, or 60 mg of Q, given orally every 12 h for a total of 14 doses 45/0 Lot. No. 1003F 45/30 Lot. No. 1006F 45/45 Lot No. 1007F 45/60 Lot No. 1008F 30 mg DM capsule Lot No. M11007F (used for determining metabolizer type in urine)	PK: Q doses inhibited the metabolism of DM dosed at 45 and 60 mg, resulting in increased systemic availability of DM. The lowest effective dose of Q that inhibited the metabolism of 45 and 60 mg DM was 30 mg. At the 30-mg dose of Q as compared with 0 mg Q, the Day 8 plasma DM AUC was 46-fold higher and C_{max} was 33-fold higher after doses of 45 mg DM. A similar increase in DM AUC and C_{max} was seen with the 60-mg DM dose. At a given dose level of Q, DM exposure was slightly higher in the 60-mg DM group than in the 45-mg group. Table 2.7.2-5 through Table 2.7.2-10. Results from Study 00-AVR-103 were also combined with results from Study 99-AVR-100 and the proposed inhibition model for selecting the Q dose was confirmed to be valid (SN 025; Section 5.3.5.4.2.1). AEs: 279 treatment-emergent AEs were experienced by 48 of the 65 (74%) subjects dosed during the trial with more AEs experienced in those receiving 60 mg DM. AEs most commonly reported were dizziness, nausea, and headache. Seventeen subjects (12 receiving 60-mg DM treatments and 5 receiving 45-mg DM treatments) were discontinued from the trial because of the following drug-related AEs: dizziness, intoxication, feeling jittery, nausea, vomiting, tremor, loose stools, tinnitus, and paresthesia. SAEs: None.

(Study 00-AVR-103 located in NDA application Section 5.3.3.1.3)

Table 44: Hepatic Impairment Pharmacokinetics, 04-AVR-115

Study ID Study Title No. Site(s) Country/IND Submission	Status Date Type of Study	Subject Population Total Number of Subjects Age: Range (y) Mean (y) Gender: M/F (%) Race: W/B/Other (%)	Design/Control* Objectives/Endpoint(s)	Test and Control Drugs Dose Regimen/ Route	Clinical Outcome Efficacy/Pharmacology Safety AEs SAEs
AVANIR SPONSORED STUDIES (continued)					
Special Population Studies					
04-AVR-115 An Open-Label, Multiple-Dose, Multiple-Site, Parallel Group Study to Evaluate the Pharmacokinetics and Safety of AVP-923 (30 mg of Dextromethorphan Hydrobromide and 30 mg Quinidine Sulfate) in Patients with Hepatic Impairment and Healthy Adult Volunteers. 2 U.S./IND 56,954	Completed 04/06/04-05/28/04 Hepatic Impairment, PK and Safety	Population: Healthy (matched) volunteers (9) and patients with mild (6) and moderate (6) hepatic impairment Number of subjects: 21 subjects enrolled 21 subjects completed the study Age: Range: 44-62 Mean: 52.2 Gender: 11/10 (52%/48%) Race: 6/6/9 (28.5%/28.5/43%)	Phase 1 Study An open-label, multiple-dose, multiple-site, parallel group study Determine the steady-state PK and safety of AVP-923 in healthy (matched) subjects and subjects with mild and moderate hepatic impairment Primary endpoint: ratio of LSM of the PK parameters $AUC_{0-\tau}$ and C_{max} in patients with hepatic impairment (Group 2 and 3) compared with healthy (matched) subjects (Group 1) Secondary endpoints: other PK parameters and safety evaluation parameters	AVP-923 (30 mg DM and 30 mg Q) twice daily for 7 days Lot No. C0051B001	PK: Steady-state $AUC_{0-\tau}$ and C_{max} of DM in patients with mild and moderate hepatic impairment were comparable to those observed in subjects with normal hepatic function (LSM fell within 80%-125%), however, the ratios of the P parameters for unbound DM ($AUC_{0-\tau(u)}$ and $C_{max(u)}$) were not within 80%-125% for the mild or moderate impairment groups. Patients with moderate liver impairment displayed a 35% increase in $AUC_{0-\tau(u)}$ and a 34% increase in $C_{max\,(u)}$ for DM as compared to subjects with normal hepatic function. The lack of statistical significance ($p>0.05$) may result from the relatively small numbers of subjects per group. Changes in unbound $AUC_{0-\tau}$ and C_{max} of DM and Q did not significantly affect total DM exposure ($AUC_{0-\tau}$) in hepatically impaired subjects. Table 2.7.2-11. Table 2.7.2-12. For DX, no clinical significant differences in PK parameters were observed between subjects with normal hepatic function and those in patients with mild and moderate impairment. For Q, $AUC_{0-\tau}$, C_{max}, $AUC_{0-\tau(u)}$, $C_{max\,(u)}$ were all within 80%-125% for subjects with mild hepatic impairment, but the ration of LSM of Q C_{max} in the moderately hepatic impaired group was not within 80%-125%. A 30% decrease in C_{max} of Q was observed in the moderate hepatic group. A lack of statistical significance may be explained by the small number of subjects per group. Lower unbound oral clearance values for the hepatically impaired patients were consistent with the observation of slightly lower levels of plasma proteins in these patients. AEs: A total of 35 AEs occurred, of which 31 were considered drug related. Drug-related AEs occurred in 9 (42.9%) of 21 subjects: one (11.1%) subject in the normal group, two (33.3%) patients in the mild impairment group and 6 (100%) patients in the moderate impaired group. All drug-related AEs were considered mild or moderate in severity and not clinically significant. The most frequent AEs included: somnolence (5 subjects), headache (4 subjects) and nausea (5 subjects). SAEs: None.

(Study 04-AVR-115 from NDA application Section 5.3.3.3.1)

Table 45: Renal Insufficiency Pharmacokinetics, 04-AVR-116

Study ID Study Title No. Site(s) Country/IND Submission	Status Date Type of Study	Subject Population Total Number of Subjects Age: Range (y) Mean (y) Gender: M/F (%) Race: W/B/Other (%)	Design/Control* Objectives/Endpoint(s)	Test and Control Drugs Dose Regimen/ Route	Clinical Outcome Efficacy/Pharmacology Safety AEs SAEs
AVANIR SPONSORED STUDIES (continued)					
Special Population Studies					
04-AVR-116 An Open-Label, Multiple-Dose, Multiple-Site, Parallel Group Study to Evaluate the Pharmacokinetics and Safety Profile of AVP-923 (30 mg Dextromethorphan Hydrobromide and 30 mg Quinidine Sulfate) in Subjects with Various Stages of Renal Insufficiency and Healthy Volunteers. 2 U.S./IND 56,954	Completed 04/05/04-06/10/04 Renal Impairment, PK and Safety	Population: Healthy (matched) volunteers (9) and patients with mild (6) and moderate (6) renal impairment Number of subjects: 21 subjects enrolled 21 subjects completed the study Age: Range: 44-73 Mean: 60.6 Gender: 11/10 (52%/48%) Race: 11/4/6 (52.4%/19.0%/28.6%)	Phase 1 Study An open-label, multiple-dose, multiple-site, parallel group study Determine the steady-state PK and safety of AVP-923 in healthy subjects (matched) and patients with mild and moderate renal impairment Primary endpoint: ratio of LSM of the PK parameters $AUC_{0-\tau}$ and C_{max} of patients with renal impairment (Group 2 and 3) compared with healthy subjects (Group 1) Secondary endpoints: other PK parameters and safety	AVP-923 (30 mg DM and 30 mg Q) twice daily for 7 days Lot No. C0051B001	PK: Total and unbound PK parameters of DM, DX, and Q in subjects with normal renal function compared with patients with either mild or moderate renal impairment were approximately in the same range. Table 2.7.2-14 DX $AUC_{0-\tau}$ and C_{max} in patients with mild renal impairment increased by approximately 33% and 48%, respectively, and the corresponding ratios of the LSM and 90% CI were not within 80%-125%. Patients with moderate renal impairment, however, displayed a statistically significant twofold increase in steady-state $AUC_{0-\tau}$ ($p=0.0153$) and C_{max} ($p=0.0267$) of total DX as compared to subjects with normal renal function. Overall, the 90% CI ranges across PK parameters were large and may be explained by high intersubject variability and the relatively small number of study participants in each group. Table 2.7.2-15. Changes in PK parameters were not associated with any AEs. AEs: A total of 17 AEs occurred of which 12 were considered drug related. Ten of the 12 AEs occurred in subjects with normal renal function. Drug-related AEs occurred in 5 (23.8%) of 21 subjects: three (33.3%) subject in the normal group, two (33.3%) patients in the mild impairment group and 0 (0%) patients in the moderate impaired group. The most frequent drug-related AEs included the following: somnolence (2 subjects), nausea (1 subject), vomiting (1 subject), and diarrhea (2 subjects). Drug-related AEs were mild in severity. SAEs: None.

(Study 04-AVR-116 in NDA submission Section 5.3.3.3.2)

Table 46: Desipramine Interaction, 04-AVR-112

Study ID Study Title No. Site(s) Country/IND Submission	Status Date Type of Study	Subject Population Total Number of Subjects Age: Range (y) Mean (y) Gender: M/F (%) Race: W/B/Other (%)	Design/Control* Objectives/Endpoint(s)	Test and Control Drugs Dose Regimen/ Route	Clinical Outcome Efficacy/Pharmacology Safety AEs SAEs
AVANIR SPONSORED STUDIES (continued)					
Drug Interaction Study					
04-AVR-112 Drug Interaction Study between AVP-923 and Desipramine in Healthy Adult Subjects (CYP2D6 Extensive Metabolizers) 1 U.S./IND 56,954	Completed 02/28/04 - 03/17/04 Drug Interaction, PK and Safety	Population: Healthy volunteers Number of subjects: 16 subjects enrolled 14 subjects completed the study 13 included in PK analyses Age: Range: 19-42 Mean: 27 Gender: 9/5 (64%/36%) Race: 1/0/13 (7%/0%/93%)	A Phase 1 study A sequential-treatment, drug interaction study evaluating the effects of AVP-923 (30 mg of DM and 30 mg of Q) on steady-state plasma concentrations of desipramine Determine the impact of multiple administrations of AVP-923 on the steady-state PK of desipramine The endpoints ware 90% CI of the ratio of LSM of the PK parameters $AUC_{0-\tau}$ and C_{max} for desipramine on Day 16 to Day 7	An oral dose (25 mg, one tablet) of desipramine (Norpramin®) was administered every 24 h once daily for 16 days Lot No. 3025971 On Day 8, an oral dose of AVP-923 (30 mg DM and 30 mg Q) was administered every 12 h for 9 days (from Days 8 to 16) Lot No. C0051B001	PK: The steady-state concentration of desipramine was approximately eightfold higher and the C_{max} was approximately sevenfold higher, when AVP-923 was given concomitantly. Table 2.7.2-17 The ratios of LSM and the 90% CI derived from the analyses of the ln-transformed PK parameters $AUC_{0-\tau}$ and C_{max} were 815.0% (570.8 to 1163.9%) and 665.0% (493.8 to 895.6%), respectively. Table 2.7.2-18 AEs: A total of 109 AEs were recorded and all subjects reported at least one AE. All AEs, with one exception were judged at least remotely drug-related. Most AEs were judged mild in severity; one was judged moderate in severity. Seven (44%) subjects reported at least one AE after dosing with desipramine only, and 15 (100%) subjects reported at least one AE after dosing with desipramine and AVP-923. Twelve (11%) AEs occurred after dosing with desipramine, 97 (89%) AEs occurred after dosing with desipramine and AVP-923. The most frequent (>20%) AEs reported were the following: headache (11subjects, 69%); dizziness (10 subjects, 63%); somnolence (8 subjects, 50%); nausea (6 subjects, 38%); and fatigue (5, 31%). At 6 h post-dose, DBP was the only parameter with a significant statistical correlation with C_{max} ($p<0.05$) and a borderline statistically significant correlation with $AUC_{0-\tau}$. Globally, the absolute increase observed in the PK parameters appeared to have a positive correlation with absolute increase in DBP and QTc, and absolute change in QTc from baseline, at 6 h post-dose. SAEs: None.

(Study 04-AVR-112 in NDA submission Section 5.3.3.4.1)

Table 47: Patient Population Pharmacokinetics, 04-AVR-117

Study ID Study Title No. Site(s) Country/IND Submission	Status Date Type of Study	Subject Population Total Number of Subjects Age: Range (y) Mean (y) Gender: M/F (%) Race: W/B/Other (%)	Design/Control* Objectives/Endpoint(s)	Test and Control Drugs Dose Regimen/ Route	Clinical Outcome Efficacy/Pharmacology Safety AEs SAEs
AVANIR SPONSORED STUDIES (continued)					
Population Pharmacokinetic Analysis					
04-AVR-117 Population Pharmacokinetic Analysis of AVP-923 in Healthy Subjects and in Patient Populations (b) (4) Project No. AA19861 NA U.S./IND 56,954	Completed (04/21/05) Population PK Analysis	Subject Populations : Total, healthy and patient populations Studies: 99-AVR-100, 99-AVR-101, 00-AVR-103, 04-AVR-111, 04-AVR-115, 04-AVR-116, 99-AVR-102, 02-AVR-106, 02-AVR-107 Total population : 170 70 M; 100 F 3 PMs; 167 EMs 48.9 y mean age 51.0 y median age 19 to 82 y age range 76.4 kg mean body weight 168.2 cm mean height Healthy: 53 30 M; 23 F 2 PMs; 51 EMs 45.3 y mean age 52 y median age 19 to 69 y age range 75.9 kg mean body weight 170.1 cm mean height	Plasma concentrations of DM, DX and Q and urine concentrations of DM and DX from nine clinical studies were combined Objectives: To determine the population PK parameters of Q in plasma and DM and DX in plasma and urine after single and multiple doses of AVP-923; To identify the impact of demographic covariates on the population PK parameter estimates; To determine population PK parameters of DM, DX and Q in patient populations Compartmental analyses were performed using a general two-stage approach. Multiple compartmental models were constructed Covariates investigated in the model included: age, gender, body weight, ideal body weight, genotype, height, phenotype, and race	Only those subjects who received 30 mg DM and 30 mg Q were included in the population PK analysis	PK The PK of AVP-923 in healthy subjects was best described with a 1-compartment model for Q and a 2-compartment model for DM and DX. The model also included a CYP2D6 maximum inhibitory effect (as a function of Q concentration) preventing the biotransformation of DM to DX and also inhibiting the renal clearance of DX and DM (P-gp inhibition). Age and ideal body weight were significant covariates included in the final model, whereby PK parameters such as clearance and volume of distribution were adjusted for ideal body weight. The covariates of race and gender did not appear to affect the PK of DM and DX, although the effect of race was difficult to evaluate due to the small size of the non-Caucasian population. Age appeared to significantly affect the central volume of distribution of DX, resulting in a Vc/Fm of DX that increased with increasing age. The apparent increase in the Vc/Fm of DX associated with increasing age was likely a reflection of a decrease in the terminal elimination rate constant because total clearance was unaffected by age in this population of patients and healthy volunteers. Values for systemic clearance (CL/F) in healthy subjects and in patients were 1.04 L/h/kg and 0.699 L/h/kg, respectively. All other clearances values were comparable between the two groups, leading to a 30% difference in DM and DX CL_T between healthy subjects and patients. However, the ranges of CL_T values were similar.
04-AVR-117 (continued)		Patients: 117 40 M; 77F 1 PMs; 116 EMs 50.5 y mean age 51 y median age 25 to 82 y age range 60.6 kg mean body weight 167.2 cm mean height	Patients with sparse data were analyzed with MAP analysis. Population PK parameters of Q, DM, and DX as well as their respective variabilities obtained from the IT2S® and GTS analyses were used as "*a posteriori estimates*"		

(Study 04-AVR-117 in NDA application Section 5.3.3.5.1)

Table 48: ALS Pseudobulbar Affect, Efficacy, 99-AVR-102

Study ID Study Title No. Site(s) Country/IND Submission	Status Date Type of Study	Subject Population Total Number of Subjects Age: Range (y) Mean (y) Gender: M/F (%) Race: W/B/Other (%)	Design/Control* Objectives/Endpoint(s)	Test and Control Drugs Dose Regimen/ Route	Clinical Outcome Efficacy/Pharmacology Safety AEs SAEs
AVANIR SPONSORED STUDIES (continued)					
Controlled Efficacy Study in Pseudobulbar Affect					
99-AVR-102 A Double-Blind Controlled, Multicenter Phase 2/3 Study to Assess the Safety and Efficacy of AVP-923 (Dextromethorphan Hydrobromide 30 mg and Quinidine Sulfate 30 mg) in the Treatment of Pseudobulbar Affect in Patients with Amyotrophic Lateral Sclerosis 17 U.S./IND 56,954 SN 035	Completed (01/11/01-04/30/02) Safety and Efficacy	Population: Male and female ALS patients with clinically diagnosed PBA and a score ≥13 on the CNS-LS Number of patients: 140 patients enrolled 116 completed the study Population analyzed: ITT, N=129 Age: Range: 33-82 Mean: 54 Gender: 80/49 (62%/38%) Race: 114/2/13 (88%/2%/10%)	Phase 3 study A multicenter, randomized, double-blind, controlled, parallel-group study Control: 30 mg DM alone and 30 mg Q alone Compare and evaluate the efficacy, safety, and tolerance of AVP-923 relative to 30 mg DM and to 30 mg Q taken individually in a population of ALS patients with PBA Primary endpoint: change from baseline in CNS-LS score. Secondary endpoints: • Counts of laughing/crying episodes recorded in the patient diary • Change from baseline in QOL scores • Change from baseline in QOR scores. Primary and secondary endpoints were assessed at Day 1, Day 15, and Day 29.	AVP-923 (30 mg DM and 30 mg Q) or 30 mg DM or 30 mg Q Oral capsule self-administered every 12 hours for 28 days Number of patients by arm: AVP-923 (N=70) DM (N=33) Q (N=37) AVP-923 (DM/Q 30 mg/30 mg) Lot No. M11009F DM (30 mg) Lot No. M11007F Q (30 mg) Lot No. M11018F	Efficacy: AVP-923 was highly statistically significantly better than either DM (p=0.001) or Q (p<0.001) in improving PBA (as reflected in decreased scores in the CNS-LS, the primary endpoint). In terms of secondary endpoints, patients treated with AVP-923 compared with patients treated with DM or Q showed a reduction in the number of weekly episodes of laughing and crying (p<0.0001) recorded in the patient diary, as well as improvement in QOL (p=0.001) and QOR (p<0.001). **Table 1. Summary of Study 99-AVR-102 Efficacy Results – ITT Population** Adjusted Mean* (SE) / p-value AVP-923: 7.4 (0.6); DM: 4.1 (0.9); Q: 3.7 (0.8); AVP-923 vs. DM: 0.001; AVP-923 vs. Q: <0.001 **Secondary Efficacy Variables** QOL: 24.1 (2.5); 11.2 (3.6); 12.2 (3.3); 0.002; 0.001 QOR: 22.6 (2.4); 6.6 (3.4); 8.6 (3.2); <0.001; <0.001 Episode rates (no./week): DM vs. AVP-923 Ratio / 95%CI; Q vs. AVP-923 Ratio / 95%CI Combined Laughing and Crying: 1.89; 1.23-2.90; 2.13; 1.44-3.16; 0.004; <0.001 Crying: 1.98; 1.20-3.27; 3.32; 2.06-5.33; 0.007; <0.001 Laughing: 1.49; 0.87-2.54; 1.63; 1.00-2.67; 0.142; <0.050 Source(s): Brooks et al., 2004. See also Table 9, Table 12, Table 13, and Table 14 in Final Study Report 99-AVR-102. ITT = intent- to- treat; CI = confidence interval; CNS-LS = Center for Neurologic Studies-Lability Scale; DM = dextromethorphan; Q = quinidine; QOL = quality of life; QOR = quality of relationships. * Values listed are LSM, adjusting for baseline levels and center effects.
99-AVR-102 (continued)			Safety: AEs, physical exam, vital signs, ECG, and clinical laboratory assessments		For each patient, the change in score was evaluated as the baseline score subtracted from the mean of the scores for Day 15 and Day 29. For episode rates, the ratio between the DM rate or Q rate and the AVP-923 rate is listed. The ratios for combined crying and laughing episodes and laughing episodes omit one outlier in the DM group. PK: Significant increases in plasma DM concentrations and lower DX concentrations were linked to significant improvements in clinical signs of PBA in patients treated with AVP-923 (Table 2.7.3-3). AEs: AEs were within acceptable limits in this subject population, and there were no clinically relevant findings for any other safety variable. AEs for which there were statistically significant differences between groups included nausea, dizziness, somnolence, and loose stools. Loose stools occurred more frequently in the DM group. The other AEs occurred more frequently in the AVP-923-treated group. Seventeen patients in the AVP-923-treated group withdrew because of AEs. Only 2 of the 17 patients had severe AEs (headache, nausea, vomiting). ECG: There was no statistically significant difference between the treatment groups in QTc interval, pulse rate, or QRS duration. No patients had any QT and/or QTc value ≥ 500 msec. There was a statistically significant difference, at Day 29, in ventricular rate and QT interval between the AVP-923 and Q treatment groups (only); however, these changes were so small that they were not clinically relevant. SAEs: Three patients treated with AVP-923 experienced SAEs, one resulting in death, due to progression of ALS. All SAEs were considered not related to drug. One patient in the Q group experienced one SAE that was considered not related to drug.

(Study 99-AVR-102 in NDA application Section 5.3.5.1.1)

Table 49: MS, Pseudobulbar Affect, Efficacy, 02-AVR-106

Study ID Study Title No. Site(s) Country/IND Submission	Status Date Type of Study	Subject Population Total Number of Subjects Age: Range (y) Mean (y) Gender: M/F (%) Race: W/B/Other (%)	Design/Control* Objectives/Endpoint(s)	Test and Control Drugs Dose Regimen/ Route	Clinical Outcome Efficacy/Pharmacology Safety AEs SAEs
AVANIR SPONSORED STUDIES (continued)					
Controlled Efficacy Study in Pseudobulbar Affect (continued)					
02-AVR-106 A Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of AVP-923 (Dextromethorphan/ Quinidine) in the Treatment of Pseudobulbar Affect in Patients with Multiple Sclerosis 19 U.S. / 4 Israel; IND 56,954 SN 072 02-AVR-106 (continued)	Completed (12/10/02-03/30/04) Safety and Efficacy	Population: Male and female MS patients with clinically diagnosed PBA and CNS-LS ≥ 13 at baseline Number of patients: 150 patients randomized 150 treated 108 completed Population analyzed for safety and efficacy: ITT population (all randomized patients who received at least 1 dose of study medication); N=150 patients Age: Range: 21-71 Mean: 45 Gender: 26/124 (17%/83%) Race: 136/10/4 (90%/7%/3%)	Phase 3 study double-blind, placebo-controlled, multicenter study Evaluate and compare to placebo the safety, tolerability, and efficacy of AVP-923 Primary endpoint: change from baseline in CNS-LS Secondary endpoints: • Number of episodes as recorded in the patient diary • VAS response for QOL • VAS response for QOR • PIRS score Primary and secondary endpoints were assessed at Day 1 and Days 15, 29, 57, and 85 Safety: AEs, physical exam, vital signs, ECG, and clinical laboratory assessments	AVP-923 (30 mg DM and 30 mg Q) or placebo Study drug was administered orally two times a day every 12 hours for 12 weeks Number of patients by arm: AVP-923 (N=76) Placebo (N=74) Lot No. C0051001	Efficacy: Patients receiving AVP-923 had a statistically greater reduction in CNS-LS than those receiving placebo (p<0.0001). The secondary endpoints were also highly statistically significant in favor of AVP-923: the number of laughing, crying, or laughing and crying episodes (all p-values ≤ 0.0077); QOL (p<0.0001); QOR (p=0.0001), and PIRS (p=0.0271). **Table 2. Summary of Study 02-AVR-106 Efficacy Results – ITT Population** AVP-923 / Placebo **Primary Efficacy Variable** CNS-LS Mean (SE)* 7.7 (0.57) / 3.3 (0.58) / <0.0001 **Secondary Efficacy Variables** QOL Mean (SE)* 32.1 (2.71) / 14.9 (2.72) / <0.0001 QOR Mean (SE)* 31.0 (2.87) / 16.1 (2.84) / 0.0001 PIRS Mean (SE)* 0.4 (0.09) / 0.2 (0.09) / 0.0271 Episode rates (number/week) Combined Laughing and Crying Mean (SD) 4.7 (10.93) / 11.5 (19.43) / 0.0002 Crying Mean (SD) 2.2 (4.94) / 6.7 (10.81) / <0.0001 Laughing Mean (SD) 2.5 (8.36) / 4.8 (13.39) / 0.0077 Source(s): Table 22, 23, 24, 25, and Table 26 Final Study report 02-AVR-106. ITT = intent-to-treat; CNS-LS = Center for Neurologic Study-Lability Scale; DM = dextromethorphan; PIRS = pain intensity rating scale; Q = quinidine; QOL = quality of life; QOR = quality of relationships. * Values listed are LSM, adjusting for baseline levels and center effects. For each patient, the change in score was evaluated as the baseline score subtracted from the mean of the scores for Days 15, 29, 57, and 85. Nearly twice as many AVP-923-treated patients as compared with placebo-treated patients responded to treatment (84% versus 49%, respectively; p<0.001). Complete remission (no episodes) was observed in about 3 times as many AVP-923 patients as placebo patients from Day 7 until end of study (20.8% versus 6.9%, respectively; p=0.028); and complete remission (no episodes) was achieved in a significantly larger proportion of AVP-923 patients as early as Week 1 of treatment (21.9% versus 8.3%, p=0.036). PK: Significant increases in plasma DM concentrations were linked to significant improvements in clinical signs of PBA in patients treated with AVP-923 (Table 2.7.3-9). AEs: The nature, frequency, and intensity of AEs were within acceptable limits and, in general, were similar between treatment groups. Dizziness, nausea, and fatigue were reported by >5% of patients in both treatment groups. Eleven AVP-923 patients and 8 placebo patients experienced AEs resulting in discontinuation. Only 1 of the 19 patients who discontinued had a severe AE (somnolence). ECG: The ECG results suggested no clinically meaningful effect of AVP-923 on cardiac repolarization or on any ECG variable. No subject had a QTc value >500 msec during the study. The (b) analysis showed that the AVP-923 group had a statistically greater change than the placebo group in mean QTc (both Fridericia's and Bazett's) from screening to Day 85. In the (b) (4) analysis, there was no statistically significant difference between treatment groups in mean QTc (both Fridericia's and Bazett's). The mean changes in QTc, at Day 85, were very small for both the (b) (4) (<8 msec) and the Quintiles (<4 msec) Bazett's readings. The Fridericia's readings by (b) (4) (6.1 msec) and (b) (4) (2.1 msec) were even smaller. Only 1 subject, in the placebo group, had a QTc value >480 msec. Of the 2 subjects who were reported to have clinically significant QT prolongation during the study, 1 was receiving AVP-923, 1 was receiving placebo, and both of these subjects completed the study. SAEs: Two patients treated with AVP-923, and four placebo-treated patients experienced SAEs, but none were considered study drug related. No deaths were reported.

(Study 02-AVR-106 from NDA submission Section 5.3.5.1.2)

Table 50: Smith et al., Small Efficacy Trial, Emotional Lability, CNS-93

Study ID Study Title No. Site(s) Country/IND Submission	Status Date Type of Study	Subject Population Total Number of Subjects Age: Range (y) Mean (y) Gender: M/F (%) Race: W/B/Other (%)	Design/Control* Objectives/Endpoint(s)	Test and Control Drugs Dose Regimen/ Route	Clinical Outcome Efficacy/Pharmacology Safety AEs SAEs
INVESTIGATOR-SPONSORED STUDIES					
Controlled Efficacy in Pseudobulbar Affect (continued)					
CNS-93 The Treatment of Emotional Lability with Dextromethorphan (Smith et al., 1995) 1 U.S. Information amendment to IND 56,954 SN 039	Completed (03/10/93-12/13/93) Efficacy	Population: 8 ALS patients, 3 related neurological diseases (1 MND, 1 MSA, 1 PLS and 1 unclassified neurological disease) Number of patients: 19 screened 12 randomized and treated Population analyzed: ITT and safety population N=12 Age: Range: 33-72 Mean: 51 Gender: 8/4 (67%/33%) Race: No race information	Phase 2 study double-blind, crossover, placebo-controlled single-center study Control: placebo Objective: determine if a combination of DM and Q was effective in suppressing or eliminating PBA Endpoints: self-report measure of PBA (emotional lability score) Safety was assessed by recording all adverse reactions	Combination oral capsule 30 mg DM and 75 mg Q or placebo oral capsule All medications were self-administered orally once daily for 5 days followed by twice-daily dosing at 12-hour intervals throughout the remainder of the 4-week Treatment Period 9-week study: two 4-week double-blind Treatment Periods separated by a 1-week Washout Period Number of patients by arm: 6 in sequence one (DM/Q:Placebo) 6 in sequence two (Placebo:DM/Q)	Efficacy: The combination of DM and Q was highly statistically significantly more effective than placebo in treating PBA in patients with ALS. **Table 3. Summary of Study CNS-93 Efficacy Results – ITT Population** Mean (SD) of Total Emotional Lability Score Time Point: Placebo (N=12) / DM/Q (N=12) Baseline: 144.2 (42.34) / 142.1 (38.02) Post treatment: 154.1 (38.57) / 99.3 (27.85) Change: 9.8 (26.36) / -42.8 (31.25) Source: Table 11-4 in Final Study Report CNS-93. There was a statistically significant treatment effect (p=0.0001), a statistically significant sequence effect (p=0.0049), and no statistically significant period effect (p=0.5299). AEs/SAEs: No treatment-emergent AEs and no discontinuations were reported during the study. There were no deaths reported during the study.

Table 51: Open-Label Safety, 02-AVR-107

Study ID Study Title No. Site(s) Country/IND Submission	Status Date Type of Study	Subject Population Total Number of Subjects Age: Range (y) Mean (y) Gender: M/F (%) Race: W/B/Other (%)	Design/Control* Objectives/Endpoint(s)	Test and Control Drugs Dose Regimen/ Route	Clinical Outcome Efficacy/Pharmacology Safety AEs SAEs
AVANIR SPONSORED STUDIES (continued)					
Open-Label Safety Study in Pseudobulbar Affect					
02-AVR-107 An Open-Label Multicenter Study to Assess the Safety of AVP-923 (Dextromethorphan/ Quinidine) in the Treatment of Patients with Pseudobulbar Affect 31 U.S./IND 56,954 SN 038 (Protocol)	Ongoing since 03/03/03 Interim cut-off 02/28/05 Safety	At interim cutoff: Population: Male and female patients clinically diagnosed with PBA Number of patients: 294 in treatment phase 76 in extension phase Population analyzed: All patients analyzed for safety Age: Range: 18-86 Mean: 50.6 Gender: 118/176 (40.1%/59.9%) Race: 269/7/18 (92%/2%/6%)	Multicenter Open-Label Study Evaluate the safety and tolerability of AVP-923 following chronic administration Optional study extension: will allow subjects who feel as if they are benefiting from treatment to continue treatment past Week 52 Safety: AEs, physical examination, vital signs, clinical laboratory values, and resting ECG	AVP-923 (30 mg DM and 30 mg Q) one capsule two times a day (every 12 hours) for 12 months administered orally Lot No. GN01A	As of the interim cutoff, a total of 111 (37.8%) patients have completed one year of treatment with AVP-923 and 224 (76.2%) have completed 6 months of treatment with AVP-923‡ in this study. AEs/SAEs: Treatment phase: Of the 294 patients receiving AVP-923, 83.7% have experienced AEs, 24.5% have experienced SAEs, and 24.1% have experienced AEs resulting in discontinuation. Extension phase: Of the 76 patients receiving AVP-923, 51.3% have experienced AEs, 15.8% have experienced SAEs, and 6.6% have experienced AEs resulting in discontinuation The most common adverse events were nausea, headache, dizziness, diarrhea, fall, fatigue, weakness, and nasopharyngitis. The most common serious adverse events were respiratory failure, worsening of MS, progression of ALS, and dysphagia. The most common adverse events resulting in discontinuation were dizziness, somnolence, nausea, diarrhea, and respiratory failure. All subjects discontinuing due to respiratory failure died from this AE. A total of 28 deaths have occurred in both the treatment and extension phases. The most frequent cause of death was respiratory failure or a similar respiratory cause. ECG: No patients had a QTc interval >500 msec and 3 patients had changes from screening in QTc ≥ 60 msec. None of the 3 patients had an ECG abnormality rated clinically significant or reported as an AE. A total of 21 (7.1%) patients had ECG abnormalities judged by a reviewing cardiologist to be clinically significant; none of these ECG abnormalities were recorded as an AE, and no patients discontinued due to an ECG abnormality. Two patients had ECG readings recorded as AEs, even though they were identified as not clinically significant by a reviewing cardiologist. On average, corrected QT intervals increased slightly during study treatment (screening to Week 52), but these changes were small and of no clinical concern (Fridericia's [QTcF] 4.8 msec and Bazett's [QTcB] 7.1 msec.

(Study 02-AVR-107 in NDA application Section 5.3.5.2.1)

Table 52: Open Label Dose Escalation, Diabetic Painful Neuropathy, 01-AVR-105

Study ID Study Title No. Site(s) Country/IND Submission	Status Date Type of Study	Subject Population Total Number of Subjects Age: Range (y) Mean (y) Gender: M/F (%) Race: W/B/Other (%)	Design/Control* Objectives/Endpoint(s)	Test and Control Drugs Dose Regimen/ Route	Clinical Outcome Efficacy/Pharmacology Safety AEs SAEs
AVANIR SPONSORED STUDIES (continued)					
Open-Label Study in Painful Diabetic Neuropathy					
01-AVR-105 An Open-Label, Dose-Escalation Study of Dextromethorphan and Quinidine in Patients with Painful Diabetic Neuropathy 5 U.S./IND (b) (4) SN 017	Completed (09/06/02-03/28/03) Safety and Tolerability	Population: Male and female patients with painful diabetic neuropathy Number of patients: 36 patients enrolled 33 completed the study Age: Range: 22-78 Mean: 57.9 Gender: 19/17 (53%/47%) Race: 25/3/8 (70%/8%/22%)	Phase 2 study An open-label, dose escalation study Primary objective: evaluate the safety and tolerability of capsules containing DM and Q to the patient's MTD not to exceed 120 mg DM and 120 mg Q per day Secondary objective: to obtain a preliminary assessment of the efficacy of DM and Q in the treatment of pain associated with diabetic neuropathy Safety: AEs, laboratory values, vital signs, physical examinations, ECG, nerve conduction measurements Pain Intensity Rating Scale, Pain Relief Rating Scale, Peripheral Neuropathy Quality of Life (QOL) instrument, and rating scales for sleep, present pain intensity, activity, and average pain during the preceding 12 hours, completed daily in a diary	30 mg DM and 30 mg Q and/or 15 mg DM and 30 mg Q self-administered orally 30 mg DM and 30 mg Q, Lot No. 02-002 15 mg DM and 30 mg Q, Lot No. 02-003 Not to exceed 120 mg of each per day (30 mg DM and 30 mg Q for 29 days beginning with 1 capsule per day and escalating approximately weekly to a maximum dose of 4 capsules per day [120 mg/d]). Subjects who could not tolerate a dose level could return to the previous dose level; could substitute a capsule containing 15 mg DM and 30 mg Q; or, discontinue the study.	Safety: The safety results demonstrate that the combination of DM and Q, in the dose range from 30 mg DM and 30 mg Q to 120 mg DM and 120 mg Q, is safe and well tolerated in patients with pain associated with diabetic peripheral neuropathy. AEs: Sixty-four percent of the ITT population tolerated the highest permissible dose of DM (120 mg). The nature, frequency, and intensity of the AEs were consistent with this patient population, and there were no findings of clinical concern for any other safety variables. The most common AEs were nausea (28%), dizziness (25%), and headache (25%), which were classified as mild or moderate. Two patients withdrew from the study because of AEs. Both were SAEs (resection of pre-existing colonic polyp; and recurring, intermittent chest pain), and both were considered unrelated to study drug. ECG: The (b) (4) ECG analysis showed no statistically significant difference from baseline to Day 29 in PR, VR, or QRS in any MTD group. A statistically significant difference in the change from baseline to Day 29 in QT interval (11.6 msec; p=0.0131) and QTcB interval (11.3 msec; p=0.0102) was found in the 120-mg MTD group; a significant change in QTc was also found in all groups combined (8.2 msec, p=0.0213). A reviewing cardiologist concluded that there were no systematic changes in the ST segment and T-wave morphology and that the sporadic, minor changes observed would be considered clinically insignificant in the absence of symptoms. There were no ECGs in which an increase in QTc was associated with a morphological change in ST segment or T-wave. No systematic changes in QTc were noted. The (b) (4) analysis showed no statistically significant difference from baseline to Day 29 in PR, VR, QRS, or QTcB in any MTD group. A statistically significant difference in the change from baseline to Day 29 was found in QT interval in the 30-mg MTD group (−18 msec; p=0.0271) and QTcF interval in the 120-mg MTD group (6 msec; p=0.0177).
01-AVR-105 (continued)					SAEs: Three patients experienced five SAEs. Four of five SAEs were considered not related to drug. One SAE was considered possibly related to study drug (chest pain NEC, recovered). One patient died due to myocardial infarction and arrhythmia. This patient had a history of cigarette smoking (46 years); carotid artery occlusion (11 years); chronic, obstructive pulmonary disease (COPD; 10 years); and high cholesterol (8 years). He had an exacerbation of COPD at the time of his final visit on Day (b) (6) and was hospitalized that day. Four days after his final dose of study medication (Day 33) the subject suddenly died while still in the hospital.

(Study 01-AVR-105 in NDA application Section 5.5.5.2.2.1)

[Key below for **Table 40** through **Table 52**]

AE = adverse event; ALS = amyotrophic lateral sclerosis; AUC_{0-t} = area under the plasma concentration versus time curve from zero to the last measurable concentration; $AUC_{0-t(u)}$ = area under the unbound plasma concentration versus time curve from zero to the last measurable concentration; B = black; (b) (4); CI = confidence interval; CLf/F = systemic clearance of DM into DX; CL_T = total clearance; C_{max} = maximum measured plasma concentration $C_{max(u)}$ = maximum measured unbound plasma concentration; CNS-LS = Center for Neurologic Study-Lability Scale; CYP2D6 = cytochrome P450 isoenzyme 2D6; DBP = diastolic blood pressure; DM = dextromethorphan; DX = dextrorphan; ECG = electrocardiogram; EM = extensive metabolizer; F = female; GTS = general two-stage approach; ID = identification; IND = Investigational New Drug application; ITT = intent-to-treat; IT2S® = iterative two-stage methodology; LSM = least-squares means; M = male; MAP = *maximum a posteriori*; MND = motor neuron disease; MS = multiple sclerosis; MSA = multiple system atrophy; MTD = maximum tolerated dose; NA = not applicable; NEC = not elsewhere classified; PBA = pseudobulbar affect; PK = pharmacokinetic(s); PLS = primary lateral sclerosis; PM = poor metabolizer; PIRS = pain intensity rating scale; Q = Quinidine; (b) (4); QOL = quality of life; QOR = quality of relationships; QTc = corrected QT; SAE = serious adverse event; SN = serial number; U.S. = United States; VAS = visual analog scale; Vc/Fm = apparent central volume of the dissolution of DX; W = white. * All Avanir-sponsored studies were conducted under Good Clinical Practice. † In Studies 99-AVR-100 and 99-AVR-101, the Q content was protocol-specified to be 25 mg. However, it was learned that the actual amount was 28.8 mg per capsule (for the 25 mg Q dose group only in Study 99-AVR-100). ‡ The numbers for patient exposure from this study differ from the numbers in the integrated safety dataset, because the integrated safety dataset accounts for cumulative exposure during any Avanir-sponsored studies. In Study 02-AVR-107, patients were considered to have had 1 year of treatment if they either had a termination CRF page indicating that they had completed the study, or if they had an extension-phase drug-dispensing CRF page confirming that they had entered the extension phase. Patients were considered to have had 6 months of treatment if they either had 1 year of treatment according to the above rule, or had a telephone contact CRF at Week 22 or later. In the integrated safety dataset, subject exposure was calculated from the date of first dose to

the date of last dose; in the ongoing Study 02-AVR-107, the interim cutoff date of 28 February 2005 was considered date of last dose for study participants (PBA patients) still being treated with AVP-923; these study participants were segregated into groups receiving treatment for 180 days (6 months) or 360 days (12 months; including patients exposed for 6 months).

7.2.1.2 Demographics

Demographics for studies with PBA patients

Table 53 shows the demographics for all PBA patients in the combined Avanir-sponsored studies. Of note, few elderly (≥75 years) patients were included, a serious shortcoming of the data because elderly patients, particularly those with AD and stroke, would be treated in large numbers if AVP-923 is approved for the generalized indication of PBA.

Table 53: Demographics, All Avanir-Sponsored Studies in PBA Patients
(From NEW ISS, Table 3-2)

Table 3-2. Demographic Profile: All Avanir-Sponsored Studies in PBA Patients by Primary Disease (Studies 99-AVR-102, 02-AVR-106, and 02-AVR-107)

		Primary Disease						
		ALS N=222	MS N=220	Stroke N=32	Traumatic Brain Injury N=16	Alzheimers N=8	Other N=59	All Patients N=557
Age (yrs)	n	222	220	32	16	8	59	557
	mean	55.4	45.2	54.9	43.4	62.0	56.5	51.2
	median	56.0	47.0	56.0	40.5	67.5	59.0	51.0
	SD	11.9	10.3	10.2	14.4	14.1	12.6	12.5
	min	18.0	21.0	38.0	18.0	38.0	22.0	18.0
	max	82.0	71.0	77.0	72.0	79.0	86.0	86.0
Age Group (yrs)	<=54	101 (45%)	182 (83%)	15 (47%)	13 (81%)	2 (25%)	23 (39%)	336 (60%)
	55 - 64	66 (30%)	32 (15%)	10 (31%)	1 (6%)	1 (13%)	19 (32%)	129 (23%)
	65 - 74	46 (21%)	6 (3%)	6 (19%)	2 (13%)	4 (50%)	16 (27%)	80 (14%)
	>=75	9 (4%)	0 (0%)	1 (3%)	0 (0%)	1 (13%)	1 (2%)	12 (2%)
Sex	Not known	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
	Male	135 (61%)	51 (23%)	14 (44%)	8 (50%)	4 (50%)	28 (47%)	240 (43%)
	Female	87 (39%)	168 (76%)	18 (56%)	8 (50%)	4 (50%)	31 (53%)	316 (57%)
Race	Caucasian	198 (89%)	203 (92%)	27 (84%)	11 (69%)	8 (100%)	55 (93%)	502 (90%)
	Black	7 (3%)	8 (4%)	3 (9%)	1 (6%)	0 (0%)	1 (2%)	20 (4%)
	Asian	0 (0%)	1 (0%)	1 (3%)	0 (0%)	0 (0%)	1 (2%)	3 (1%)
	Hispanic	13 (6%)	7 (3%)	1 (3%)	3 (19%)	0 (0%)	2 (3%)	26 (5%)
	Other*	4 (2%)	1 (0%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)	6 (1%)

Program: demog2.sas Data Source: dm.sas7bdat 21NOV05

ALS = amyotrophic lateral sclerosis; MS = multiple sclerosis; PBA = pseudobulbar affect.
* Other primary neurological diseases are listed in Table 1-1.

ALS controlled trial, Study 99-AVR-102

Table 54shows demographics of subjects in 99-AVR-102. The study arms were not well-balanced for gender.

Table 54: Demographics, 99-AVR-102

(Table 6, final study report)

Category	AVP-923 (N=65)	DM (N=30)	Q (N=34)	P-values[a] AVP-923 vs DM	P-values[a] AVP-923 vs Q
Age (years)					
n	65	30	34		
Mean	54.82	53.77	55.32	0.7788	0.9976
Std Dev	12.79	11.25	9.47		
Median	55	54	58		
Min/Max	38/82	33/75	35/72		
Gender, n (%)					
Female	23 (35.4)	14 (46.7)	12 (35.3)	0.1549	0.8105
Male	42 (64.6)	16 (53.3)	22 (64.7)		
Race, n (%)					
Asian	0 (0)	1 (3.3)	0 (0)	0.2100	0.5522
Black	2 (3.1)	0 (0)	0 (0)		
Caucasian	58 (89.2)	25 (83.3)	31 (91.2)		
Hispanic	5 (7.7)	3 (10.0)	3 (8.8)		
Other	0 (0.00)	1 (3.3)	0 (0.00)		

[a] P-values to compare means for continuous variables are computed by using ANOVA with an adjustment for treatment and center to obtain overall F-tests. P-values for categorical values were computed by using Cochran-Mantel-Haenszel chi-square with an adjustment for center.

MS controlled trial, Study 02-AVR-106

Table 55shows the demographics of the MS controlled study, 02-AVR-106. Both arms were more than 80% female, as expected in MS.

Table 55: Demographics, MS Controlled Study 02-AVR-106

Table 8. Demographics — ITT Population

Characteristic (unit)	Category or Statistic	AVP-923 (N=76)	Placebo (N=74)	P-value[a]
Age (years)	n	76	74	0.1033
	Mean	46.3	43.7	
	SD[b]	9.78	9.95	
	Median	49.0	45.0	
	Min/Max	25/68	21/71	
Gender, n (%)	Male	14 (18.4)	12 (16.2)	0.7214
	Female	62 (81.6)	62 (83.8)	
Race, n (%)	Caucasian	68 (89.5)	68 (91.9)	0.7275
	Black	5 (6.6)	5 (6.8)	
	Asian	1 (1.3)	0 (0.0)	
	Hispanic	2 (2.6)	1 (1.4)	
	Other	0 (0.0)	0 (0.0)	

[a] P-values to compare means for continuous variables were computed by using t-tests. P-values for categorical variables were computed by using chi-square tests.

[b] SD = Standard deviation.

7.2.1.3 Extent of exposure (dose/duration)

Table 57 shows the exposure to AVP-923 in the controlled studies. Length of exposure was short for both studies, with a high percentage of patients not achieving the full planned exposure.

Table 57: Exposure, Controlled Studies (99-AVR-102, 02-AVR-106)
(From Table 2-4, NEW ISS)

	99-AVR-102 (ALS)			02-AVR-106 (MS)		Combined
Duration of Dosing	AVP-923 N=70	DM N=33	Q N=37	AVP-923 N=76	Placebo N=74	AVP-923 N=146
1-7 days	10 (14%)	1 (3%)	1 (3%)	3 (4%)	1 (1%)	13 (9%)
8-14 days	4 (6%)	2 (6%)	0 (0%)	4 (5%)	4 (5%)	8 (5%)
15-29 days	39 (56%)	20 (61%)	26 (70%)	2 (3%)	6 (8%)	41 (28%)
30-59 days	15 (21%)	10 (30%)	10 (27%)	7 (9%)	6 (8%)	22 (15%)
60-89 days	0 (0%)	0 (0%)	0 (0%)	53 (70%)	53 (72%)	53 (36%)
90-179 days	0 (0%)	0 (0%)	0 (0%)	2 (3%)	3 (4%)	2 (1%)
180-269 days	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
270-359 days	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
>=360 days	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown	2 (3%)	0 (0%)	0 (0%)	5 (7%)	1 (1%)	7 (5%)
Total	70 (100%)	33 (100%)	37 (100%)	76 (100%)	74 (100%)	146 (100%)

Program: expose.sas Data Source: ex.sas7bdat 20OCT05

ALS = amyotrophic lateral sclerosis; DM = Dextromethorphan Hydrobromide USP; MS = multiple sclerosis; PBA = pseudobulbar affect; Q = Quinidine Sulfate USP.

Exposure, Open Label Safety Trial

Table 58 shows the number of doses taken in the treatment phase (first 52 weeks) and extension phase of the open label safety trial. 'Days of exposure' for the safety trial is incorporated in

Table 56 shows AVP-923 exposure in all clinical Table 56, in the '90-days and above' exposures.

Table 58: Total Exposure, All Studies
(Table 2.5-3, NDA application, clinical overview)

Table 2-6. Study Drug Exposure: Integrated Avanir-Sponsored Studies (Studies 99-AVR-100, 99-AVR-101, 99-AVR-102, 00-AVR-103, 01-AVR-105, 02-AVR-106, and 02-AVR-107)

Duration of Dosing	AVP-923 N=603	DM N=57	DM/Q N=88	Q N=36	Placebo N=32
1-7 days	38 (6%)	6 (11%)	7 (8%)	1 (3%)	1 (3%)
8-14 days	34 (6%)	25 (44%)	81 (92%)	0 (0%)	3 (9%)
15-29 days	84 (14%)	16 (28%)	0 (0%)	25 (69%)	5 (16%)
30-59 days	53 (9%)	10 (18%)	0 (0%)	10 (28%)	4 (13%)
60-89 days	27 (4%)	0 (0%)	0 (0%)	0 (0%)	16 (50%)
90-179 days	55 (9%)	0 (0%)	0 (0%)	0 (0%)	2 (6%)
180-269 days	48 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
270-359 days	62 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
>=360 days	196 (33%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown	6 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Total	603 (100%)	57 (100%)	88 (100%)	36 (100%)	32 (100%)
>=180 days	306 (51%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
>=360 days	196 (33%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
>=540 days	100 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
>=720 days	60 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Program: expose.sas Data Source: ex.sas7bdat 21DEC05

Note: Some patients with painful diabetic neuropathy who are included in the AVP-923 group received multiple doses of AVP-923 up to 120 mg DM and 120 mg Q daily (Study 01-AVR-105, CTD Section 5.3.5.2.2.1).
DM = Dextromethorphan Hydrobromide USP; Q = Quinidine Sulfate USP.

Integrating data from the 120-day safety update, 326 PBA patients (54%) have been exposed to AVP-923 for more than 180 days. Patient exposed to AVP-923 for more than 180 days includes: 100 ALS patients, 154 MS patients, 21 stroke patients, 7 traumatic brain injury patients, 3 Alzheimer's disease patients, and 41 patients with other neurological conditions. Two-hundred thirty three PBA patients (39%) have been exposed to AVP-923 for more than 360 days. Patients exposed to AVP-923 for more than 360 days include: 62 ALS patients, 119 MS patients, 16 stroke patients, 6 traumatic brain injury patients, 1 Alzheimer's disease patient, and 29 patients with other neurological conditions. One-hundred twenty six PBA patients have been treated with AVP-923 for 540 days or more, and 77 PBA patients have been treated with AVP-923 for 720 days or more.
(from 120-day safety update).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

AVP-923 is a combination of two drugs with a long history of use. Secondary data sources, including drug labels and literature reports were used for the safety review of AVP-923. Secondary data sources were not used extensively for the review of AVP-923 efficacy.

7.2.2.2 Postmarketing experience

No postmarketing data is available for AVP-923 or related combinations of DM and Q.

7.2.2.3 Literature

The sponsor's review of the literature focused on studies of DM/Q combinations, and high dose DM/DM abuse, but did not adequately address the literature on quinidine adverse effects. Literature review indicates that serum quindine levels overlapping those caused by AVP-923 can induce fatal arrhythmia, including torsade de pointes (discussed in Section 1.1).

7.2.3 Adequacy of Overall Clinical Experience

Patient exposure and safety assessments for AVP-923 were not adequate:

- *Overall numbers of patients exposed*
  The controlled trials of AVP-923 were small and of short duration. The trial in ALS, in particular, was conducted for only 4 weeks, with only 52 subjects in the AVP arm completing the study. In the MS trial, only 55 patients in the AVP arm completed all 3 months of treatment. Serious adverse events, including death, occurred in the studies, but rates of these events could not be estimated adequately due to the short duration and small size of studies. The high dropout rate in both studies also weakens efficacy conclusions.

- *Patient subsets and demographics*
  The AVP-923 controlled studies examined only ALS and MS patients, and the long-term extension study examined mainly ALS and MS patients, with only a few individuals from other primary disease groups that manifest PBA. Additional

studies should be conducted to characterize the safety and efficacy of AVP-923 in primary diseases such as AD and stroke in which it will be commonly used if approved.

- *Study Design*
  The ALS trial was not placebo-controlled, greatly weakening both safety and efficacy assessments.

- *Dose*
  Only a single dose combination of DM and Q was examined in phase 3 trials. The dose selected was poorly tolerated and presents what I consider a serious safety risk. Lower doses or a different dose combination might have a better safety/efficacy profile.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Both dextromethorphan and quinidine have been used extensively in clinical settings over many years. CNS lesions (Olney lesions) were of particular concern given the NMDA-receptor binding of DM. Nonclinical studies of AVP-923, however, did not find neurodegenerative changes in the brain. Clinical findings or characteristics of the drugs in AVP-923 did not suggest the need for additional nonclinical testing.

7.2.5 Adequacy of Routine Clinical Testing

See section 7.1.7

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Drug interactions are a major inadequately addressed safety concern for AVP-923 (see Executive Summary)

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

See Executive Summary.

7.2.8 Assessment of Quality and Completeness of Data

7.2.9 Additional Submissions, Including Safety Update

Safety Update
New clinical data in the safety update is from the ongoing safety study (02-AVR-107) and a summary only of results from a thorough QT study (05-AR-119). The data cut-off data for the safety update was February 28, 2006. Forty-three new patients had been enrolled since the previous cutoff of October 31, 2005, and so have at most 4 months of exposure. Additional safety data was also collected from 259 ongoing subjects. The sponsor indicates no change to their previous safety conclusions from the updated data.

Population Studied
The newly enrolled patients mainly had as an underlying neurological diagnosis primary lateral sclerosis (15 patients), Parkinson's Disease (10 patients), or Cerebellar Ataxia (3 patients).

Arrhythmia
Three additional arrhythmias occurred: one right bundle branch block, two sinus bradycardia. Bradycardia is a potential adverse effect of quinidine. The two additional cases in the safety update do not alter my finding that bradycardia is a potential risk of AVP-923.

Syncope

QT outliers
One patient was identified in the safety update with QTc prolongation >500 ms. The patient (107-03-008) had a baseline QTcF of 455 ms, and a maximum of 505 ms, a 50 ms increase. The patient also had bradycardia, with rate changing from 70 at baseline to 55 on AVP-923. The patient discontinued the study due to ECG adverse events.

Thorough QT study, 05-AVR-119
In the 120-day safety update, a *summary only* of a 'thorough QT study' of AVP-923 was included, thus precluding appropriately detailed regulatory review.

The study was entitled:

> *"A Randomized, Double-Blind, Placebo Controlled Crossover Study in Healthy Volunteers to Determine the Electrocardiogram Changes Associated with 2 Doses of AVP-923 (AVP-923), with an Open-Label Active Control Arm of Oral Moxifloxacin."*

The study was a three-arm, randomized, placebo-controlled, double-blind crossover design examining either a single or two doses of AVP-923 and placebo. An additional open-label arm used moxifloxacin (400 mg) as positive control. ECG readers were blinded to all treatments. The study was intended to be in compliance with the current guidance described in "The Clinical Evaluation of QT/QTC Interval Prolongation and Proarrhythmic Potential For Non-Antiarrhythmic Drugs" (International Conference on Harmonization ("ICH") 2005).

AVP-923 increased QTc by about 10 ms, with an upper confidence interval of about 15 ms. Two doses of AVP-923 (supratherapeutic) increased QTc by more, by up to ≈19 ms, with an upper confidence interval of up to ≈25 ms (Table 59).

Table 59: Thorough QTc Study Endpoints
(From Table 12-17, 120-day-safety-update-report.pdf)

dQTcF	Hour	Mean (ms)	SEM	N	p	Upper (lower) bound of 95% CI one-sided (ms)
Supratherapeutic	6	18.81	3.36348	34	<.0001	24.50
Standard	3	10.12	2.90739	31	0.0015	15.05
Pos. Contr.	1	14.35	2.72976	33	<.0001	9.73
dQTcB	**Hour**	**Mean**	**SEM**	**N**	**p**	**Upper (lower) bound of 95% CI one-sided**
Supratherapeutic	5	15.54	3.44091	34	<.0001	21.37
Standard	3	9.24	3.71446	31	0.0187	15.54
Pos. Contr.	3	17.22	3.46892	33	<.0001	11.35

The sponsor concludes:

> "The presence of quinidine in the formulation makes these findings predictable and expected. While the maximal mean placebo-subtracted dQTcF of 10.12 ms and the dQTcB value of 9.24 ms exceed the ICH guidance threshold for a positive thorough QT study, the magnitudes of these changes are at the lower limit of the range of increase, (10 to 20 ms), which is considered "inconclusive" in the ICH guidance."

I conclude that this positive QT study suggests that a clinically meaningful pro-arrhythmic risk might remain from the 'low' quinidine dose in AVP-923. This study, combined with adverse events suggestive of arrhythmia in the current AVP-923 database, argues strongly that the cardiovascular safety of AVP-923 has not been established.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

- Arrhythmia

Serious cardiac adverse events from quinidine, including torsade de pointe, are thought to occur at levels caused by AVP-923. The thorough QT study of AVP-923 (submitted as a summary only) indicates that AVP-923 prolongs QT. Several adverse events in AVP-923 development might have been due to arrhythmia. Together, these factors indicate that cardiovascular safety of AVP-923 has not been satisfactorily established, and in fact present a possible positive signal of clinically meaningful cardiac risk.

- Adverse Drug Interaction

AVP-923 presents a definite risk of adverse drug interaction. Dangerous interactions could result from drugs that:

  - Are metabolized by CYP 2D6
  - Inhibit CYP 3A4
  - Prolong QT
  - Decrease renal elimination of quinidine
  - Decrease serum potassium and magnesium
  - Affect serotonin
    (Dextromethorphan enhances central serotonergic tone by blocking its reuptake and increasing its release. Cases of serotonin syndrome resulting from combining dextromethorphan with paroxetine and monoamine oxidase inhibitor medications have been reported).
  - Are eliminated by p-glycoprotein
    Quinidine inhibits p-glycoprotein, an interaction responsible for the well-known increase of digoxin observed with quinidine coadministration. This inhibition is particularly important at the blood-brain barrier. For example, quinidine dose of 600 mg increases CNS exposure to the anti-diarrheal loperamide through p-glycoprotein inhibition, resulting in respiratory depression. The risk from lower levels of quinidine has not been established, but merits investigation.

PBA patient populations commonly use specific medications to treat the underlying neurological disease that might interact adversely with AVP-923. Of particular concern, many AD patients take memantine, an NMDA antagonist similar to DM that induces common adverse events overlapping those of AVP-923.

- Fall risk

Most of the PBA population is at high risk of fall, such that the increased rate of both falls and common adverse effects such as dizziness that can cause falls would be an unacceptable safety risk. An increased risk of fall was observed in both the ALS and MS controlled studies. Quantifying the degree of increased risk in the ALS study is made difficult by the lack of a placebo arm, and the large difference in falls between the DM arm (14%) and Q arm (zero falls), compared to the higher risk in the AVP-923 arm (18%). A reasonable interpretation of this data is that both AVP-923 and DM cause a large increase in fall risk in ALS patients.

- Aspiration/Nausea/Vomiting

The ALS population appears particularly susceptible to AVP-923-induced nausea/vomiting/aspiration in comparison to the MS population. However, I find that the death associated with intractable vomiting in a normal volunteer in phase 1 testing of AVP923 suggests that not only ALS patients are at risk.

- Additional safety signals of possible concern
    - Renal: Creatinine appeared to be increased in the AVP-923 arm in the MS study. Increase of creatinine was not observed in the ALS study, but the short time period of the ALS study might have precluded detection of change. Urea was increased in the AVP-923 arms of both studies, which raises the level of concern for renal effects. Two diabetic patients developed renal failure in uncontrolled studies, but drug effect can not be separated from underlying disease status. Non-clinical testing identified kidney as experiencing toxicity.
    - Hepatic: Alkaline phosphatase was increased in the AVP arm in the ALS study, but not in the MS study. Quinidine is known to be a cause of sporadic drug-induced hepatotoxicity, and was a target organ of toxicity in preclinical studies of AVP-923.
    - Visual System: Blurry vision was reported by 5 patients treated with AVP-923 in controlled studies, and no patients in other arms. DM has been reported to cause blurry vision, and quinidine is labeled as associated with optic neuritis. If AVP-923 development continues, ophthalmic monitoring should be increased.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The clinical database for AVP-923 was small, and both MS and ALS were examined in controlled studies. The need for, and validity of pooling data across studies was therefore limited.

7.4.1.1 Pooled data vs. individual study data

The ALS and MS populations differ in many respects, limiting the meaningfulness of combined data.

7.4.1.2 Combining data

See section 7.4.1.1.

7.4.2 Explorations for Predictive Factors

Lack of data supporting safety in different patient groups is a major safety deficiency of this application (see section 1.3.3).

7.4.2.1 Explorations for dose dependency for adverse findings

Only one dose of AVP-923 was studied in controlled trials or the safety study, such that little data can address dose dependency for adverse findings.

7.4.2.2 Explorations for time dependency for adverse findings

Significant adaptation was not observed for major adverse effects (see section 7.1.5.6).

7.4.2.3 Explorations for drug-demographic interactions

Age
Only 40 of 290 patients enrolled in controlled studies were 65 years and older, with only 5 patients total in the MS study ≥ 65. In the ALS study, age ≥ 65 was associated with increased adverse events. Given the high risk of falls from AVP-923, it is particularly notable that the adverse event cluster 'Ataxia-Gait Disturbance-Loss of Balance' occurred in 15% of subjects ≥ 65, and in no younger subjects. The number of patients in the study was too small in general to comment meaningfully about age effect on other specific adverse events.

In all controlled and uncontrolled AVP-923 studies, there were about 500 PBA patients under 65 years of age and about 100 PBA patients 65 years and older. The incidence of AEs was greater in ALS and MS patients 65 years and older.

Gender
In the ALS study, the total incidence of AEs by gender was similar in both the AVP-923 and quinidine groups, and was slightly higher in females compared with males in the DM group. The total incidence of AEs in MS patients by gender was slightly higher in females in the AVP-923 group and slightly higher in males in the placebo group.

In all controlled and uncontrolled AVP-923 studies, there were about 260 male patients and about 340 female patients treated with AVP-923. A similar percentage of male and female PBA patients experienced AEs.

Race
Only 29 of 290 patients in controlled studies were non-Caucasian. Rates of AEs appeared similar by race.

In all controlled and uncontrolled AVP-923 studies, there were about 550 Caucasian PBA patients and 60 non-Caucasian PBA patients treated with AVP-923. There was little difference in the incidence of AEs in all PBA patients in the Caucasian subgroup (88%) and the non-Caucasian subgroup (91%).

7.4.2.4 Explorations for drug-disease interactions

Cardiac disease
Quinidine likely causes excess adverse events, including arrhythmia, in the setting of cardiac disease, as described in section 1.3.3, *Safety*.

7.4.2.5 Explorations for drug-drug interactions

Adverse drug interactions are a major safety risk of AVP-923, as discussed in detail (see section 1.3.3, *Safety*).

7.4.3 Causality Determination

Causality determination is addressed in the review in the context of each specific adverse event or effect.

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Aside from PK studies of CYP 2D6 inhibition by quinidine, dose-toxicity and dose-response data was not systematically studied in AVP-923 development.

8.2 Drug-Drug Interactions

Drug-drug interactions are a major safety concern of AVP-923, as summarized in section 1.3.3, *Safety.*

Below is first discussed a drug interaction study undertaken in AVP-923 development, followed by a discussion of drugs of particular interest for interaction with AVP-923.

A drug interaction study of AVP-923 and desipramine was undertaken in healthy volunteers, entitled:

> *Drug Interaction Study between AVP-923 (30 mg of Dextromethorphan Hydrobromide and 30 mg of Quinidine Sulfate) and Desipramine (25 mg Norpramin®) in Healthy Adult Subjects (CYP2D6 Extensive Metabolizers)*

Sixteen healthy adult 2D6 extensive metabolizers were studied. Desipramine was administered for 16 days. AVP-923 was administered from Days 8 to 16. With co-administration of AVP-923 and desipramine, $AUC_{0-\tau}$ and C_{max} for desipramine were greatly increased, 815.0% and 665.0% respectively.

Subjects receiving the combination of desipramine and AVP-923 reported about 10-times the number of adverse events (**Table 60**). One subject (subject 4) was withdrawn due to arrhythmia on day 12.

Table 60: Adverse Events From Concomitant Desipramine, 04-AVR-112 (Study 04-AVR-112, modified from Table 12.2.3.1)

Adverse Event Preferred Term	Treatment	
	Desipramine N (%)	Desipramine and AVP-923 N (%)
Headache	1 (6%)	10 (67%)
Dizziness	1 (6%)	10 (67%)
Somnolence	2 (13%)	6 (40%)
Nausea	0 (0%)	6 (40%)
Fatigue	2 (13%)	4 (27%)
Vision blurred	0 (0%)	4 (27%)
Tachycardia	0 (0%)	3 (20%)
Dry mouth	0 (0%)	3 (20%)
Asthenia	0 (0%)	3 (20%)
Decreased appetite	0 (0%)	3 (20%)
Pharyngolaryngeal pain	1 (6%)	1 (7%)
Dysgeusia	0 (0%)	2 (13%)
Insomnia	0 (0%)	2 (13%)
Dysuria	0 (0%)	2 (13%)

Desipramine 1 x 25mg
Desipramine 1 x 25mg + AVP-923 1 x 30/30 mg

Four subjects (25%) experienced cardiac-related adverse events (tachycardia, 3 subjects; palpitations and arrhythmia, 1 subject).

The primary investigator concluded that "the results from this study indicate potential cardiac safety concerns when desipramine is administered with AVP-923." I agree.

Other drug interactions of particular concern in PBA
Quinine
Forty-five subjects in the ALS and safety study took concomitant quinine for prophylaxis of muscle cramps. Quinidine is a stereoisomer of quinine, and the two drugs can have additive toxicities.

MAO inhibitors and serotonin re-uptake inhibitors
Drug interactions between DM and MAO inhibitors or serotonin re-uptake inhibitors may result in a serotonergic syndrome.

8.3 Special Populations

Renal Insufficiency
Accumulation of quinidine metabolites may occur in patients with renal dysfunction. Study 04-AVR-116 examined the PK and safety profile of AVP-923 in 6 subjects with mild renal impairment (creatinine clearance 50-80 mL/min) and 6 with moderate impairment (creatinine clearance 30-49 mL/min).

> "The study was open label, multiple-dose, parallel group. Subjects were given a single oral dose of AVP-923, twice a day from Days 1 to 6 and once in the morning on Day 7. PK blood samples were drawn on Days 1, 6 and 7 and PK urine samples on Days 1 and 7. Additional blood samples were taken for protein binding assessments. Laboratory assessments (hematology, serum chemistry and urinalysis) were performed at Screening, on Day -1 and at the end of the study. ECG readings were performed at Screening, as well as on Days 1 and 7. Adverse events and use of concomitant medications were monitored throughout the study." (from study synopsis)

No SAEs or severe AEs occurred during the study. The majority of adverse events (14 of 17) were reported by subjects in the normal renal function group. No adverse events were reported by patients in the moderate renal impairment group (Table 61).

Table 61: Renal Impairment, Adverse Events

		Renal Function							
		Normal Function (N=9)		Mild Impairment (N=6)		Moderate Impairment (N=6)		Overall (N=21)	
Body System	Adverse Event	N	%	N	%	N	%	N	%
Gastrointestinal disorders	Diarrhoea NOS	1	11.1	1	16.7	0	0.0	2	9.5
	Dyspepsia	0	0.0	1	16.7	0	0.0	1	4.8
	Nausea	1	11.1	0	0.0	0	0.0	1	4.8
	Toothache	0	0.0	1	16.7	0	0.0	1	4.8
	Vomiting NOS	1	11.1	0	0.0	0	0.0	1	4.8
Nervous system disorders	Dizziness	1	11.1	0	0.0	0	0.0	1	4.8
	Headache	1	11.1	0	0.0	0	0.0	1	4.8
	Somnolence	2	22.2	0	0.0	0	0.0	2	9.5
	Syncope	1	11.1	0	0.0	0	0.0	1	4.8
Skin and subcutaneous tissue disorders	Rash pruritic	1	11.1	0	0.0	0	0.0	1	4.8
Vascular disorders	Hypertension NOS	1	11.1	0	0.0	0	0.0	1	4.8

Clear trends were not observed for quinidine levels in renal impairment, possibly due to the small size of the study. The $AUC_{0-\tau}$ and C_{max} of quinidine in plasma in patients with mild renal impairment decreased by about 25%, while that $AUC_{0-\tau}$ in patients with moderate renal impairment increased by 5.7%, with Cmax decreasing by 13.4% when compared to subjects with normal renal function.

Patients with moderate renal impairment had a statistically significant 2-fold increase in $AUC_{0-\tau}$ and Cmax for total dextrorphan as compared to subjects with normal renal function.

The study results do not indicate that dose-adjustment is required for patients with mild or moderate renal impairment, but conclusions are limited by the small size of the study.

Hepatic Insufficiency
Hepatic impairment may affect protein binding and prolong quinidine's half-life. Markedly prolonged half-life resulting in quinidine toxicity has been reported in hepatic failure (Stanek et al., Pharmacotherapy 17:622-5).

Study 04-AVR-115 examined the PK and safety of AVP-923 in 6 patients with mild hepatic impairment (Child-Pugh class A) and 6 with moderate impairment (Child-Pugh class B). The study was an open-label, multiple-dose, parallel group study.

> "Subjects were given a single oral dose of AVP-923, twice a day from Days 1 to 6, and once in the morning on Day 7. PK blood samples were drawn on Days 1, 6 and 7 and PK urine samples on Days 1 and 7. Additional blood samples were taken for protein binding assessments. Laboratory assessments (hematology, serum chemistry and urinalysis) were performed at Screening on Day -1 and at the end of the study. ECG readings were performed at Screening, as well as on Days 1 and 7."(from study synopsis)

There were no serious or severe AEs. A greater number of AEs occurred in the moderate hepatic impairment arm than in the other two arms (Table 62).

Table 62: Hepatic Impairment, Adverse Events

		Hepatic Function							
		Normal (N=9)		Mild Impairment (N=6)		Moderate Impairment (N=6)		Overall (N=21)	
Body System	Adverse Event	N	%	N	%	N	%	N	%
Cardiac disorders	Sinus tachycardia	0	0.0	1	16.7	0	0.0	1	4.8
Gastrointestinal disorders	Diarrhoea NOS	0	0.0	1	16.7	2	33.3	3	14.3
	Dry mouth	0	0.0	1	16.7	0	0.0	1	4.8
	Nausea	0	0.0	2	33.3	3	50.0	5	23.8
	Vomiting NOS	0	0.0	1	16.7	1	16.7	2	9.5
Metabolism and nutrition disorders	Hyperglycaemia NOS	0	0.0	0	0.0	1	16.7	1	4.8
Nervous system disorders	Dizziness	1	11.1	1	16.7	1	16.7	3	14.3
	Headache	0	0.0	1	16.7	3	50.0	4	19.0
	Somnolence	0	0.0	1	16.7	4	66.7	5	23.8
	Tremor	0	0.0	0	0.0	1	16.7	1	4.8
Psychiatric disorders	Agitation	1	11.1	0	0.0	0	0.0	1	4.8

For DM, patients with moderate liver impairment displayed a 35% increase in AUC and a 34% increase in Cmax as compared to subjects with normal hepatic function.

For Q, a 30% decrease in Cmax was observed in the moderate hepatic group.

The sponsor concludes that these changes were the result of decreased protein binding of DM and Q, and that AVP-923 is safe in mild to moderate hepatic impairment. Given the increase in adverse events in hepatic impairment, particularly somnolence, nausea, and vomiting, I find that AVP-923 has not been demonstrated to be safe in either mild or moderate hepatic impairment.

8.4 Pediatrics

No studies were conducted with AVP-923 in the pediatric age group.

8.5 Advisory Committee Meeting

This application was not presented to an Advisory Committee.

8.6 Literature Review

Cardiac Risks of Quinidine

The risk of TdP from quinidine is often cited to be between 1% and 8% (Roden, 1994, Risks and Benefits of Antiarrhythmic Therapy, NEJM, 331:785-91; Roden, 2006, Long QT Syndrome: Reduced Repolarization Reserve and the Genetic Link, J. Intern. Med.; 259: 59-69). An important paper from which this rate estimate was derived was by Drs. Dan Roden and Raymond Woosley, recognized experts on the pro-arrhythmic risk of quinidine. They state:

> "We have had the opportunity to review our experience with a large series of patients (24 patients) with this entity [TdP] at our institution [Roden, Woosley, Primm, Am. Heart J., 1986]. On the basis of non-referral patients only, we estimated that 2 to 3% of patients starting quinidine therapy will develop this potentially lethal ventricular tachyarrhythmia. Approximately one-half of the quinidine concentrations were below 2 ug/ml, the lower limit of the usual therapeutic range, and most serum potassium concentrations in our series were below 4 mEq/liter, usually in association with diuretic therapy" (J. Am. Coll. Cardiol., 1986).

Possibly the most important risk determinant for many of these patients was recent conversion from atrial fibrillation to sinus rhythm. Of eight patients receiving quinidine for atrial fibrillation, the paper notes that fully six developed TdP after conversion to sinus

rhythm.

Concomitant digoxin is not mentioned in this paper in the list of 'other cardioactive medications,' apparently because it was used in all patients (digoxin levels within 24 hours of TdP are presented for 15/24 patients). The combination of quinidine and digoxin is thought to increase risk of TdP.

Other papers often cited to support the 1% to 8% incidence of TdP from quinidine similarly are 'confounded' for interpretation in the PBA population by a high percentage of cases of TdP immediately following cardioversion from atrial fibrillation (Ejvinsson and Orinius, 1980, Acta Med. Scand. 208:445-50; Radford and Evans, 1968, Br. Heart J. 30:91-6), and concomitant use of digoxin.

A late pro-arrhythmic effect of antiarrhythmics including quinidine in atrial fibrillation was identified in a re-analysis of data from the Stroke Prevention in Atrial Fibrillation Study (Flaker et al., 1992, JACC;20:527-32). Antiarrhythmic therapy was initiated for most patients before the study. Antiarrhythmic drug therapy was *not* randomly assigned (effects of warfarin and aspirin on stroke were the main purpose of the). Cardiac mortality and arrhythmic death were both increased about 2.5-fold by antiarrhythmic therapy, but, importantly, the risk was almost entirely limited to patients with a history of congestive heart failure, in whom the increased risk was about 4- to 5-fold.

In ventricular arrhythmia, quinidine also appears to be proarrhythmic. Morganroth and Goin (1991, Circulation;84:1977-1983) performed a meta-analysis of four trials of quinidine use in ventricular arrhythmia, with a total of 1,009 patients on quinidine compared to flecainide (n = 141), mexiltine (n = 246), tocainide (n = 67), and propafenone (n = 53). Quinidine increased the relative risk of dying by about 3-fold, with death specifically due to proarrhythmia roughly doubled. Interactions between quinidine and digoxin likely contributed to these findings, however.

8.7 Postmarketing Risk Management Plan

None.

8.8 Other Relevant Materials

None

9. OVERALL ASSESSMENT

9.1 Conclusions

The safety and efficacy of AVP-923 have not been adequately demonstrated.

9.2 Recommendation on Regulatory Action

Not approvable.

9.3 Recommendation on Postmarketing Actions

Not applicable.

9.3.1 Risk Management Activity

Not applicable.

9.3.2 Required Phase 4 Commitments

Not applicable.

9.3.3 Other Phase 4 Requests

Not applicable.

9.4 Labeling Review

General Comments
Neither the safety nor the efficacy of AVP-923 has been adequately established. The currently proposed labeling must therefore be considered preliminary.

In general, however, I find that the current proposed labeling unacceptably understates both the known and potential risks of AVP-923. For example, given the established risk of vomiting from AVP-923, labeling should warn against use of AVP-923 in patients at risk of aspiration. Similarly, the labeling states that 'dizziness' and 'falls' are common excess adverse events from AVP-923, but does not include specific warning about use in patients already at risk of fall from underlying neurological disease. While labeling is expected to change based on additional data that would need to be collected before approval, I recommend that the sponsor make all possible effort to define a more narrow patient population in whom the risks of AVP-923 might be acceptable.

PBA nomenclature for labeling
The sponsor proposes replacing the disease name 'pseudobulbar affect' with a novel name, "Involuntary Emotional Expression Disorder (IEED)." A variety of terms have been used in the literature for PBA, often with slightly varying definitions. However, PBA is a widely accepted and generally understood term. Other terms that are commonly understood to represent the same disease are: pathological laughing and crying, emotional lability, emotional incontinence, emotionalism, and involuntary crying. The sponsor does not provide adequate evidence that the novel name is currently known or accepted in the medical community, and that the diagnostic criteria are generally accepted.

The sponsor notes a recent journal article (Cummings et al., Defining and Diagnosing Involuntary Emotional Expression Disorder, CNS Spectrums 2006; 11:1-7) that argues for using the novel name 'Involuntary Emotional Expression Disorder' to replace previous nomenclature for PBA. The article was supported by a grant from the sponsor.

9.5 Comments to Applicant

Pending

10. APPENDICES

10.1 Review of Individual Study Reports

10.2 Line-by-Line Labeling Review

See section 9.4

REFERENCES

(within text)

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/s/

Ronald Farkas
10/30/2006 05:24:28 PM
MEDICAL OFFICER

Wilson Bryan
12/28/2006 03:58:32 PM
MEDICAL OFFICER

MEMORANDUM

DATE: October 30, 2006

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-879

SUBJECT: Action Memo for NDA 21-879, for the use of Zenvia (Dextromethorphan and Quinidine) in patients with Pseudobulbar Affect (PBA)

NDA 21-879, for the use of Zenvia (Dextromethorphan and Quinidine) in patients with Pseudobulbar Affect (PBA), was submitted on 1/30/06 by Avanir. The application contains reports of two randomized controlled trials, Studies 102 and 106, as well as safety data, and other requisite information (CMC, clinical pharmacology, non-clinical studies).

PBA is a clinical syndrome characterized by sudden outbursts of laughing or crying that appears in many settings of diffuse degenerative brain disease or injury. There are no approved treatments for PBA. Zenvia is a fixed combination product containing dextromethorphan 30 mg and quinidine 30 mg, given twice a day. The sponsor's belief is that the dextromethorphan (DX) is responsible for the control of the PBA symptoms; the quinidine (Q) is present in the product to maximally inhibit CYP2D6, the enzyme responsible for the metabolism of dextromethorphan. In this way, sufficient levels of dextromethorphan can reach the brain and produce the desired effect (sufficient dextromethorphan to produce the effect presumably cannot be given orally in the face of fully functioning CYP2D6).

This application has been reviewed by Dr. Ron Farkas, medical officer, Dr. Tristan Massie, statistician, Dr. Shari Targum, consultant cardiologist, Drs. Silvia Calderon and Geoffrey Zeldes, Controlled Substance Staff (CSS), Dr. Sally Yasuda, Office of Clinical Pharmacology, Dr. Mohammad Atiar Rahman, carcinogenicity statistical reviewer, Dr. Kathy Young, pharmacologist, Dr. Gurpreet Gill-Sangha, chemist, and Dr. Wilson Bryan, neurology team leader. In this memo, I will briefly review the effectiveness and safety data, and offer the rationale for the division's action.

EFFECTIVENESS

As noted above, the sponsor has submitted the results of two controlled trials, Studies 102 and 106. I will describe each briefly.

Study 102

This was a multi-center, double blind, parallel group trial in which patients with ALS and PBA were randomized to receive either Zenvia, dextromethorphan 30 mg, or quinidine 30 mg twice a day for 28 days. The primary outcome measure was the between-treatment difference of the change from baseline in the Center for Neurologic Study-Lability Scale (CNS-LC), a 7 item measure designed to assess labile laughter and tearfulness. Scores range from 7 (best) to 35 (worst). Patients were to have a score of at least 13 at baseline, and assessments were to be made on Days 15 and 28. The primary analysis was to be an ANCOVA on the average of the Day 15 and 28 scores. In order for the study to be considered "positive", each comparison of the combination to the individual components was to reach significance at the 0.05 level. The primary analysis was to be performed on the intent-to-treat population, excluding patients who were genetically deficient in CYP2D6 (poor metabolizers); these patients, about 7% of the US population, were not expected to be able to respond to the treatment.

Secondary measures included number of episodes of laughing or crying, a Visual Analogue Scale for Overall Quality of Life, and a Visual Analogue Scale of Quality of Relationships.

Results

A total of 140 patients were randomized in the following groups: Zenvia, 70; DX, 33; Q, 37. A total of 18 (26%) of Z patients did not complete the study (17 due to ADRs), compared to 3 (9%) of the DX and 3 (8%) of the Q groups.

There were numerous baseline differences among the groups.

The Q patients had about a 20% greater incidence of bulbar ALS compared to the other groups (62% vs 43% and 42%, Z and DX, respectively; p=0.06 compared to Zenvia). Also, the two VAS scores were worse in the DX and Q arms compared to those in the Z group (see Dr. Massie's review, page 16 for specific quantitation), and the Q group was almost significantly worse on the CNS-LC score compared to the Z group (22.3 vs 20.3, p=0.065).

The following table presents the sponsor's results of the primary analysis:

Treatment	Change from Baseline	Z vs DX	Z vs Q
Zenvia (N=65)	-7.4	-3.3	-3.7
DX (N=30)	-5.1		
Q (N=34)	-4.9		
P-value		0.001	0.0002

This analysis excluded the patients who were PMs (Z,5; DX,3; Q,3). Analyses including only the last value (as opposed to the mean of the Days 15 and 29 values) gave similar results.

Because of the large number of dropouts (especially in the Z group; 26%), Dr. Massie performed an analysis of completers (defined as anyone whose last assessment was after Day 22). The results of the two primary comparisons are robust to this analysis (see his Table 5, page 21).

As Dr. Massie notes, there were 4 patients in the Z group who had no post-baseline scores on the CNS-LC, compared to 0 such patients in either of the other treatment groups. In order to assess the effects of these patients on the overall outcome of the study, Dr. Massie performed several sensitivity analyses. He notes that the worst change from baseline score in any group during the study was +4 points (the worst change in the Z group was +1). Assigning a score of +5 to each of the Z patients who had no post-baseline data yielded a p-value for the Z vs DX comparison of 0.056 (the Z vs Q comparison is still very significant). Other sensitivity analyses of this kind yielded significant results for both comparisons.

If, however, the baseline score is carried forward for those patients with no post-baseline data, as well as for those patients whose last visit was before Day 23, the p-value for the Z vs DX comparison becomes 0.083, but if the baseline score is carried forward only for the 4 patients with no post-baseline scores, the Z vs DX contrast yields a p-value of 0.022, according to an analysis performed by Dr. Massie that is not described in his review.

A mixed-model repeated measures analysis also yielded strongly significant results (p=0.0002 and 0.006 for the DX and Q comparisons to Z, respectively).

Dr. Massie also analyzed the effects of Z on the individual components of the CNS-LC; that is the laughing and crying items separately. Four of the items relate to laughing, 3 to crying.

The following data are abstracted from his Table 7, page 25:

LAUGHING ITEMS CNS-LC

Tx	Change from Baseline	Z vs DX	Z vs Q
Zenvia	-3.5	-1.1	-0.4
DX	-2.4		
Q	-3.1		
P-value		0.096	0.53

The above analyses evaluate only the last observation carried forward; analyses of the mean of the two on-study evaluations yields nominal significance for the Z vs DX contrast (p=0.02) and not for the Z vs Q comparison (p=0.1).

Similar analyses for the Crying items all reach statistical significance (see Dr. Massie's Table 7, page 25).

Secondary Outcomes

Episode Counts

As both Drs. Farkas and Massie note, in discussions with the sponsor, the division repeatedly expressed a desire for the sponsor to make a comparison of the counts of PBA episodes the primary outcome. Ultimately, the sponsor decided not to do this, and the division agreed to accept an application in which the CNS-LC was designated as the primary outcome. However, Dr. Massie has analyzed these episodes.

In these studies, the pre-study episode count was reconstructed from historical data; that is, patients were asked to estimate how many episodes they experienced in the week prior to their enrollment in the study.

Dr. Massie notes that 13%, 12%, and 3% of the Z, DX, and Q groups, respectively, had no episodes during the treatment period, but that several of these patients had relatively minimal number of days of exposure to treatment. He calculates that, on average, patients on the individual treatments had about 3 days longer on treatment than those on Z (27 for DX, Q; 24 for Z).

The following table, taken from Dr. Massie's Table 9, page 26, displays the on-treatment episode data:

	Baseline		On-Treatment	
Tx	Mean	Median	Mean	Median
Z	23	13	9.4	2.5
DX	36	11	34.4	4.8
DX*	36	11	13	4.7
Q	21	14	13	6.3

*-excluding one outlier, with 3010 (laughing) episodes during the study, more than 9 times the number of such episodes in the next highest count.

As Dr. Massie notes, the protocol called for analyzing these data with a Poisson regression, but by the sponsor's own admission (with which Dr. Massie agrees), the data are not distributed appropriately for using the Poisson model).

In this case, then, Dr. Massie investigated the use of two different negative binomial models, which are apparently the most commonly used parametric models for count data (in the protocol, the sponsor did not identify any models to be used to analyze these data other than the Poisson). Although the sponsor suggests that one of these models, designated NB1, Dr. Massie does not agree that this model is most appropriate, and instead believes the alternative model, designated NB2, is more appropriate, in part because it is less sensitive to the inclusion/exclusion of the data from the outlier (see his detailed discussion of these matters on pages 26-31).

Using the latter (NB2) model, Dr. Massie calculates the following p-values for the various comparisons:

Comparison	P-value
Including DX outlier	
Z vs DX	0.02
Z vs Q	0.11
Excluding DX outlier	
Z vs DX	0.34
Z vs Q	0.09
Z vs DX*	0.13

*-imputing count of 398 for the outlier, the next highest count in the database.

Analyses of the Z vs DX comparison reach nominal significance using the NB1 model, regardless if the outlier is included or excluded (p=0.05 and 0.013, respectively).

As Dr. Massie notes, it is useful to examine non-parametric analyses of these data using rank sum data, which are relatively insensitive to such an extreme outlier. In this regard, he has performed Cochran-Mantel-Haenszel (CMH) tests on these count data. A CMH with modified ridit scores yields non-significant findings for the Z vs DX contrasts (with or without the outlier data). Analyses of the Z vs Q contrast reached significance (see his review, page 29).

As with the analyses of the individual episode types (laughing or crying) for the CNS-LC, no analyses of counts of laughing episodes reached significance, while the various analyses of the crying episodes did reach significance (see Dr. Massie's Table 12 and 13, pages 32-33).

Analyses of the two VAS scores (QoL, QoR) reached significance. As noted earlier, there were between-treatment baseline differences in these measures, although the protocol specified analysis, an ANCOVA, did adjust for these differences (see Dr. Massie's Table 14, page 34).

Study 106

This was a multi-center, double blind, parallel group study in which patients with MS and PBA were randomized to receive either Zenvia or placebo twice a day. The study duration was three months. The primary and secondary outcome measures were the same as in Study 102; in addition, a Pain Intensity Rating Scale, a 5 point Likert scale, was administered. Specifically, the primary analysis was to compare drug to placebo on the average of the CNS-LC for Days 15, 29, 57, and 85.

Results

A total of 150 patients were randomized; 76 to Z, 74 to placebo. In each group, 21 patients discontinued. In the Z group, 11 were related to ADRs, compared to 8 in the placebo group. The following chart displays the results of the primary analysis:

Drug	Baseline CNS-LC	Change in CNS-LC	P-value
Z	20.3	7.9	
Pla	21.4	4.3	<0.0001

Analyses of the number of episodes of laughing, crying, or total all yielded highly significant results (p=0.008, <0.0001, and 0.0002 for the NB1 model, respectively; see Dr. Massie's Table 19, page 41). Results of the NB2 model, as well as a CMH non-parametric model, yielded similar results. Additional analyses performed by Dr. Massie (last observation carried forward, MMRM, both yielded highly significant results; see his page 42). Various analyses designed to look at the effect of dropouts were performed, including a completers' analysis; all yielded highly significant results (see Dr. Massie's review, page 44).

Results of the VAS QoL and QoR scores also yielded significant results (see Dr. Massie's Table 23, page 46).

SAFETY

A total of 677 people have received at least one dose of Zenvia. Of these, 326 patients have received treatment for at least 6 months, and 233 patients have been exposed for at least one year. Of the patients exposed for at least 6 months, the following diagnoses were included: ALS-100; MS-154; Stroke-21; Other neurologic illnesses (excluding Alzheimer's Disease)-41. Of the patients exposed for at least 1 year, 181 had either ALS or MS. A total of 146 patients were treated with Zenvia in the two PBA controlled trials.

Deaths

A total of 50 subjects/patients died while receiving either the to be marketed combination or other version. One death occurred in a Phase 1 study, one occurred in the ALS controlled trial, and 48 deaths occurred in open-label safety studies.

Phase 1 death

This was an 86 year old woman who received 4 doses of a combination of DX 30 mg and quinidine 75 mg. On the (b) (6) of dosing, about 1 ½ hours after the first dose of that day, she developed nausea and vomiting. "Dry heaves" continued into the next day, and the drug was stopped. Two days later she was noted to be dehydrated with continued vomiting. At that time, her dextromethorphan and dextrorphan levels were about 17 and 57 ng/mL, respectively, and her quinidine levels were undetectable. She was treated with compazine and fluids, and several days later x-rays and abdominal CT showed intestinal obstruction at the terminal ileum. Several days later, she vomited and aspirated, and died.

ALS death

This occurred in a 53 year old woman after 2 days of treatment who experienced mild dizziness, fell, sustained a rib fracture, and died on day 30 of respiratory failure.

Other deaths

As noted by Dr. Farkas, several other deaths were of interest, including:

1) a 48 year old woman with primary lateral sclerosis who died suddenly on Day (b) (6) of treatment. This woman was also receiving erythromycin, a potent CYP3A4 inhibitor (quinidine is metabolized via 3A4).
2) A 43 year old woman with MS who died after (b) (6) days on drug, who was found to have a very elevated oxycodone level. This level was the basis for the official cause of death being listed as an intentional overdose (she

had a history of depression, but no other evidence that this was a suicide attempt). As Dr. Farkas notes, oxycodone is metabolized by 2D6 and 3A4, and, in addition to receiving Zenvia, this patient also started clarithromycin, a potent inhibitor of 3A4, 5 days before her death.

3) An ALS patient who died on day (b) (6) of treatment, whose death was attributed to respiratory failure, but who also was receiving oxycodone and erythromycin.
4) An MS patient who died of a myocardial infarction (b) (6) days after starting drug (and (b) (6) days after her last dose). This patient had been receiving diltiazem (a 3A4 inhibitor), a thiazide diuretic, which decreases the renal elimination of quinidine, metoprolol, which is known to result in increased adverse events in poor 2D6 metabolizers, and furosemide, which can result in hypokalemia (not documented here), which can increase the arrhythmia risk of quinidine.

Of the 48 deaths that occurred in the open-label experience, 30 were attributed to respiratory failure in patients with ALS. Of these, 4 (or perhaps 5) occurred in the first 60 days of treatment.

Serious Adverse Events

There were few serious adverse events noted in the controlled trials. As Dr. Farkas notes, 3 of the 4 SAEs in the ALS study occurred in the Zenvia group; one case each of dysphagia, aspiration, and respiratory failure (with one case of pneumonia in the quinidine arm). There were no obvious SAEs in the MS study that could reasonably be related to treatment with Zenvia.

In uncontrolled studies, there were numerous SAEs reported, including 29 cases of respiratory failure, 16 cases of GI events (mainly dysphagia), 7 cases of lung infections, and 3 cases of lower limb fractures and dislocations.

Discontinuations

In the ALS controlled trial, 24% of the Zenvia patients discontinued due to adverse events, compared to 5-6% in the other treatment arms. The following table displays the incidences of the most frequent ADRs responsible for discontinuation:

Event	Zenvia (N=70)	DX (N=33)	Q (N=37)
Nausea	6%	3%	0
Headache	6%	0	0
Diarrhea	4%	3%	0
Fatigue	4%	0	0

Anorexia	4%	3%	0
Joint Stiffness	4%	0	0
Dysarthria	3%	0	0
Somnolence	3%	3%	0

In the MS controlled trial, the most frequent reasons for discontinuation of treatment with Zenvia were as follows:

Event	Zenvia (N=76)	Placebo (N=74)
Nausea	3%	1%
Dizziness	3%	0
Fatigue	4%	0

In the open-label experience, Dr. Farkas describes a number of patients who discontinued treatment relatively soon after initiation of treatment, largely due to similar reasons as in the controlled trials (e.g., nausea, dizziness, etc.)

Other Adverse Events of Interest

Dr. Farkas describes a number of patients who discontinued treatment for specific reasons of potential concern, despite the fact that these were few in number.

Specifically, he describes a patient with atrial flutter prior to enrollment into study, but who developed palpitations (i.e., this patient became symptomatic) on treatment. As he notes, quinidine in the setting of atrial flutter/fibrillation can cause serious ventricular arrhythmias.

Another patient, a 51 year old woman with MS, experienced palpitations, dry mouth, and dry heaves on Day 1 and discontinued treatment. She was also receiving erythromycin, a potent CYP3A4 inhibitor.

In the ALS controlled trial, there were 3 reports of arrhythmia (one each of atrial flutter, sinus tachycardia, and supraventricular tachycardia) and none in the other treatment groups. In the MS trial, there were 3 arrhythmias in the Zenvia group (one each of bradycardia NOS, left bundle branch block, and bradycardia), and 2 in the placebo group (bradycardia NOS and sinus tachycardia). It is difficult to attribute any of these events to treatment with Zenvia.

Three (3) patients experienced syncope in the open-label experience, one apparently in the setting of an increase in the QTc interval of greater than 60 msec. There was no increase in the incidence of syncope in the Zenvia-treated patients in controlled trials.

Common Adverse Events

The following incidences of adverse events were seen in the two controlled trials.

ALS-Study 102

Event	Zenvia (N=70)	DX (N=33)	Q (N=37)
Nausea	33%	6%	8%
Dizziness	20%	15%	3%
Fatigue	19%	9%	11%
Diarrhea	16%	21%	11%
Headache	16%	12%	11%
Somnolence	13%	3%	0
Joint Stiffness	10%	0	3%
Fall	9%	6%	0
Constipation	7%	6%	0
Muscle Cramps	7%	6%	3%
Hypertonia	7%	0	3%
Vomiting	6%	0	0
Anorexia	6%	3%	0
Sweating Increased	6%	0	3%
Muscle Stiffness	4%	0	0
Appetite Decreased	4%	3%	0

MS-Study 106

Event	Zenvia (N=76)	Placebo (N=74)
Dizziness	26%	9%
Nausea	22%	15%
Fatigue	14%	8%
Weakness	11%	5%
Dry Mouth	8%	1%
Somnolence	5%	1%
Fall	5%	3%

Many of these events were seen commonly in the open-label study (e.g., of the 364 patients in the open-label study 107, 23% reported nausea, 18% reported dizziness and 15% reported falls and fatigue each). However, it is difficult to assess causality in this setting.

Falls

As noted above, falls were seen commonly in the open-label experience, as well as in Study 102 in patients with ALS. Dr. Farkas has looked more closely at this issue.

In particular, he has attempted to group adverse event terms that he believes could reasonably be considered to constitute a group of events that could increase patients' risk for fall. Included in this list of terms he considers disoriented, dizziness, groggy, lightheaded, faint, shaky, unstable, unsteady, etc. He calculates the incidence of these terms/events for the treatment groups, and obtains 43% for Zenvia, 27% for DX, and 5% for Q. He also recalculated the incidence of frank falls, including several patients that the sponsor did not include (in the Zenvia group, he added 3 patients who clearly fell, but whose primary event was mis-classified as an injury). His recalculation results in the following incidences for fall: Zenvia, 13%; DX, 12%, Q, 0. Finally, he calculated the risk of these events by patient month, given that there were many more early discontinuations in the Zenvia group compared to the number in the other treatment groups. This calculation resulted in an incidence of falls in the Zenvia group of 18% per month, in the DX group of 14% per month, and 0 in the Q group.

A similar calculation of "risk" for fall yielded an incidence of 41% in the Zenvia group in Study 106 compared to 23% in the placebo group. An analogous recalculation of the actual incidence of falls resulted in an incidence of fall of 12% in the Zenvia group and 8% in the placebo group.

Laboratory Changes

There did not appear to be any significant average changes in routine laboratory tests in patients being treated with Zenvia. However, several patients appeared to have experienced an elevation of liver function tests (LFTs) on treatment that resolved upon treatment withdrawal.

Specifically, Dr. Farkas describes three patients with elevated AST/ALT and GGT who recovered upon drug discontinuation (the greatest elevation of LFTs was about 300, and the greatest elevation of GGT was about 300). In two of these cases, the event began from 1-3 months of treatment initiation.

Of greater interest, however, was a patient with diabetic neuropathy who experienced severe elevations of LFTs and bilirubin whose treatment assignment is still blinded.

This was a 59 year old African American man being treated with study drug for 2 ½ months who presented with dark urine, abdominal distention and pain, and jaundice. He developed an ALT of 953, and AST of 1270, and alk phos of 206, a total bilirubin of 5.6 (direct 3.6) and an INR of 10.3. Abdominal ultrasound was reported to have shown fatty infiltration but no biliary obstruction. An evaluation for causes of the hepatitis, including viral screens, ANA, and ASMA, was negative. Lab tests were markedly improved by 2 weeks after presentation and drug discontinuation. The patient was receiving concomitant insulin, metformin, Actos, pravachol (for 3 years), and warfarin.

Vital Signs

There were no important apparent drug-related changes in vital signs.

EKG

Although the sponsor monitored EKG in the controlled trials, they performed a thorough QT study according to Agency guidelines. This study was a cross-over study in 36 healthy subjects and evaluated the recommended dose of Zenvia given BID for 7 doses, twice the recommended dose given BID for 7 doses, placebo given BID for 7 doses, and a single dose of 400 mg moxifloxacin as a positive control.

The maximum mean, paired, placebo and baseline subtracted QTcF was 19 msec for the supratherapeutic dose (upper bound of 95% CI of 25; seen at 6 hours after dosing); 10 msec for the recommended dose (upper bound of 95% CI of 15; seen at 3 hours after dosing); and 14 msec for moxifloxacin (seen at 1 hour after dosing). The mean QTcF remained elevated for up to 10 hours after dosing with the recommended dose. The following table presents the proportion of EKGs in each treatment group in which the QTcF reached outlier criteria (defined as an increase of QTcF of between 30-60 msec) by treatment:

Treatment	Number	Percent
Placebo	3	0.86%
Moxifloxacin	3	0.86%
Recommended	14	4.2%
Supratherapeutic	25	7.2%

Only 2 patients (both in the supratherapeutic group) achieved a QTcF of between 450-480 msec, and no patient experienced an increase in QTcF of >60 msec.

COMMENTS

The sponsor has submitted two randomized trials which they believe establish substantial evidence of effectiveness for Zenvia as a treatment for PBA. In addition, they believe that the safety data establish that Zenvia is safe in use at the recommended daily dose. I have the following comments.

Effectiveness

I agree that Study 106, in patients with Multiple Sclerosis (MS), clearly can be considered one "positive" study contributing to a finding of substantial evidence of effectiveness. However, this study was not capable by design of establishing the contribution of the individual components of the product, as required by 21CFR300.50 (Fixed-combination prescription drugs for humans).

Study 102, in patients with Amyotrophic Lateral Sclerosis (ALS), was designed to establish the contribution of each component. The contrasts between the combination and the individual components reached statistical significance on the protocol specified primary outcome measure, the CNS-LC. However, we had repeatedly expressed to the sponsor our preference for the designation of laughing and crying episodes as the primary outcome variable. The protocol specified that the sponsor would analyze these episodes using Poisson regression.

However, as the sponsor acknowledges, the distribution of the episode data did not support the use of the Poisson regression model. Although the protocol did not specify an alternative analysis in this case, the sponsor has chosen to analyze the episode data using the NB1 negative binomial model.

Dr. Massie believes that the NB2 negative binomial model is preferable to the NB1 model, because it is less sensitive to the inclusion of the one outlier in the Dextromethorphan (DM) group (patient 08-016, who had a total of 3010 laughing episodes during the study). In addition, with the NB1 model, the difference between the combination and the DX group increases when this patient's data are excluded, which is counterintuitive. In contrast, with the NB2 model, the difference between these groups decreases when this patient's data are excluded, as is expected. Therefore, he has analyzed the episode data using this latter model.

In this case, the combination-DX comparison is nominally significant (p=0.017) when this patient's data are included, but not if these data are excluded (p=0.34), or if the next worst episode count in the database (398) is imputed (p=0.13). He has also performed a Cochran-Mantel-Haenszel (CMH) test with modified ridit scores on this comparison; regardless of whether this patient's data are included (p=0.13) or excluded (p=0.19), the results do not achieve significance. Although

this outcome measure is a secondary measure, we had informed the sponsor on numerous occasions that we strongly suggested that it be deemed the primary outcome. The results of our re-analyses of the episode count data suggest that the combination does not provide an additional benefit beyond that provided by the DM component itself. This finding raises the possibility that a much lower exposure to DM (which could be achieved with a much lower dose of quinidine) than is achieved with this product might be effective in controlling laughing or crying episodes in these patients (see below).

I would make several other comments.

Dr. Farkas expresses concern that the large number of discontinuations from the Zenvia group, especially in Study 102, cast serious doubts on the analyses of the data. Although I acknowledge these concerns, I believe that the sensitivity analyses performed by Dr. Massie adequately establish that the dropouts did not materially affect the conclusions.

I also believe that, all other things being equal (which, given my comments above, they are not), these two studies could theoretically provide substantial evidence of effectiveness of Zenvia. That is, I believe that, if the contribution of the components could be shown in Study 102, such a demonstration would not need to be replicated. Further, although I agree that the pathophysiology of the laughing and crying episodes is not well understood, I believe that a robust finding of effectiveness in the two models studied here can reasonably be considered to support a claim for PBA, regardless of the clinical setting in which it occurs. I also believe that the disparate findings on the laughing or crying episodes seen in Study 102 should not be a bar to granting a claim to Zenvia for an effect on both types of episodes, given the robust findings in Study 106. Finally, I believe the relatively short duration of Study 102 also should not pose a bar to concluding that the drug is effective in chronic use; the very robust finding over the 3 months of Study 106 is adequate in this regard, in my view.

SAFETY

Numerous findings in the safety database raise serious concerns about the safety in use of this product.

First, quinidine is well known to be associated with serious ventricular arrhythmias, including torsades de pointes. These arrhythmias can occur at low quinidine doses in susceptible patients (e.g., those with congenital prolonged QT syndrome), but higher quinidine doses can also be associated with serious cardiac events, presumably in a dose related fashion.

In this regard, Study 119, the thorough QT study, demonstrated that at the daily dose of the combination that is proposed, the drug is associated with a maximum

mean paired placebo and baseline subtracted QTcF of about 10 msec, with a 95% upper bound one-sided confidence interval of about 15 msec (I presume this increase is directly a result of the quinidine component), and the prolongation persists throughout the dosing interval. Although the sponsor suggests that this is of little consequence because Agency guidance states that this degree of increase is "inconclusive" regarding its clinical significance, I agree with Dr. Farkas's view that, because quinidine poses a known proarrhythmic risk, it is reasonable to expect this degree of QT interval prolongation could result in significant cardiac adverse events. In this regard, I note that, in this study, over 4% of the EKGs in patients who received the recommended dose had QTc intervals that were increased between 30-60 msec above baseline, compared to 0.9% of those EKGs in the placebo and moxifloxacin arms.

Further, and equally, if not more, disturbing, the maximum mean paired placebo and baseline subtracted QTcF was about 18 msec (upper bound of the 95% CI was 25 msec) at the supratherapeutic dose of the combination, which was only twice that of the recommended dose (at this dose, 7.2% of the EKGs were associated with an increase in QTc of 30-60 msecs). Given that quinidine is metabolized by CYP3A4, and given the availability and use of numerous 3A4 inhibitors, we expect that, in practice, many patients may be exposed to levels of quinidine that were achieved with the supratherapeutic dose used in this study (or higher), and that these levels will be associated with serious cardiovascular consequences. In addition, the OCP reviewers have performed PK/PD modeling of quinidine's effect on the QT interval, and have determined that 5% of the population who receives the recommended dose of Zenvia would be expected to experience a prolongation of the QTc interval of about 19 msec.

In addition, quinidine's potent inhibition of CYP2D6 poses additional risks, especially in this vulnerable population. For example, we are aware of at least two deaths in the database that could reasonably be considered to be related to elevated plasma levels of oxycodone, a substrate for both 3A4 and 2D6. Both patients were also receiving, in addition to Zenvia, potent 3A4 inhibitors (erythromycin in one case, clarithromycin in the other). The combination of 3A4 and 2D6 inhibition was likely responsible for the dangerously elevated oxycodone levels in these patients. These cases highlight the dangers that are potentially associated with the use of Zenvia, especially when it is used in association with other metabolic inhibitors and 2D6 substrates, as would be expected in the relatively sick populations in whom PBA may occur. The review team and I are very concerned that labeling statements warning against such use would not be entirely successful in preventing such concomitant drug use.

Finally, quinidine is known to be particularly dangerous in patients who are moving in and out of atrial flutter/fibrillation. In this regard, we note at least one case in the database of a patient who entered the trial with a history of atrial flutter who became symptomatic (i.e., experienced palpitations) on treatment. The population in whom PBA is common may include many such patients, and,

again, the review team and I are concerned that these patients will be particularly vulnerable to serious ventricular arrhythmias if treated with Zenvia.

I note the occurrence of 48 deaths in the open-label experience, many in ALS patients, presumably due to respiratory failure. However, the sponsor has not provided evidence that this number of deaths, from this cause, would be expected in this time period in this population. I am concerned that the very high levels of DM produced by Zenvia in this vulnerable population may have contributed to respiratory depression in these patients. Dr. Farkas also notes the occurrence of a relatively large number of respiratory depression and failure events, categorized as serious adverse events. The sponsor will need to address our concern that this product may be associated with respiratory depression and failure in this vulnerable population (I include in this vulnerable population other populations in whom PBA may occur, including patients with stroke and Alzheimer's Disease, groups in whom the sponsor has obtained very little clinical experience).

As Dr. Farkas has pointed out, there is a 6% incidence of vomiting in the patients treated with Zenvia in Study 102, compared to no vomiting in the other treatment groups. He further notes a 33% incidence of nausea in the Zenvia treated patients in this study, compared to 6-8% in the other treatment groups. These findings are particularly worrisome in vulnerable populations because of the risk of aspiration, especially in those patients with difficulty swallowing, in whom the risk of aspiration is even greater. Critically, it is possible that the risk for aspiration is especially great in these patients, given the 13% incidence of somnolence in the Zenvia treated patients compared to 3% in the DM patients and 0 in the quinidine-treated patients in Study 102 (we note a 5% incidence of somnolence compared to 1% in the placebo group in Study 106).

I also agree with Dr. Farkas that there seems to be a relatively high risk of falls in these patients. He has re-calculated the incidence of falls in both controlled trials, including those patients whose adverse event was categorized as an injury, but who clearly sustained their injuries as a result of falls. In Study 102, the incidence of falls in the Zenvia group was 13%, in the DM group, 12%, and 0 in the quinidine group. A similar re-calculation of the incidence of falls in Study 106 yielded a 12% incidence of falls in the Zenvia group compared to an 8% incidence in the placebo group.

Further, he has calculated the incidence of an increased risk of falls in both studies, by adding the incidences of events that could reasonably be considered to predispose to falls. In this analysis, he combined various event terms, including disoriented, dizzy, lightheaded, shaky, unstable, etc. When these events were combined, the incidence of events in Study 102 that could be considered to predispose to falls was 43% in the Zenvia group, 27% in the DM group, and 5% in the quinidine group. In Study 106, the incidence of these predisposing events was 41% in the Zenvia group, and 23% in the placebo

group. Of course, the terms Dr. Farkas included in his re-analyses are subject to discussion, and his calculations presuppose that these events occurred in unique patients (that is, that no single patient experienced more than one of these events); of course, this could be wrong. Nonetheless, these numbers are disturbing, given the potential serious consequences of falls in these populations. The sponsor will need to address this concern.

Although there do not seem to be important systematic laboratory changes induced by treatment with Zenvia, I am particularly concerned about the occurrence of significant hepatic injury in patient 136-9004 who became jaundiced after 2 ½ months of treatment with study drug. This patient had significant elevations in AST, ALT, and bilirubin, with a mild increase in alkaline phosphatase. No viral or chemical cause for these changes were found, and, although this patient was receiving treatment with numerous concomitant medications, none would have been expected to have caused this injury. The pattern of injury seen in this patient is very similar to that seen with drugs known to result in hepatic failure with an incidence of hepatic failure about 10% of that of the incidence of the finding (in this case, the incidence of such a finding is about 1/700 patients; the incidence of hepatic failure, if this case is drug related, would be expected to be about 1/7000). I recognize that, typically, such cases of serious liver injury occur in the setting of a general increase in liver function tests, which did not occur here. Nonetheless, this case is troubling, and raises the concern that Zenvia is hepatotoxic. The sponsor will need to allay our concerns about the hepatotoxic potential of Zenvia (assuming this patient was treated with active drug). I note that, if this patient was receiving active drug, it will be critical to closely follow him, to determine if an alternative underlying explanation for these findings emerges (e.g., episodes of alcohol abuse, underlying malignancy, etc.).

These concerns, taken together, raise serious questions about the safety of Zenvia in the vulnerable populations for whom it is intended, and, as described above, in my view, these concerns will need to be addressed before the drug can be approved. Further, numerous vulnerable populations (e.g., patients with Alzheimer's Disease) have not been adequately studied, and, as pointed out by Dr. Farkas, I agree that these populations will need to be studied before the drug can be approved.

As I noted earlier, lower doses of both the quinidine and DM components of the combination may result in a product that is equally effective, and potentially much safer than the current proposed product (again, the results of the analyses of the laughing/crying episodes at least suggest that [substantially] lower exposures of DM may control these events). In this regard, I note the incidences of some significant ADRs (e.g., falls, dizziness), are much higher in the DX group than in the Q group in Study 102; this also suggests that exposures associated with a 30 mg dose of DX, *uninhibited*, may also be unsafe in this population, an issue the sponsor will need to address.

I recognize, as described by Dr. Yasuda, that the sponsor chose the dose of quinidine based on a finding that this dose converted 8/8 extensive metabolizers of 2D6 (EMs) into poor metabolizers (PMs). However, as Dr. Yasuda notes, a 10 mg dose of quinidine converted 6/7 EMs to PMs. It is clear that the lowest dose of quinidine that will give the desired effect is much to be preferred; this is similarly true for the dose of DM, and further dose finding to identify the lowest doses of each component should be undertaken.

Conclusions

Because of these fundamental questions about the safety and effectiveness of Zenvia, the application cannot be approved at this time. Although I will issue the attached Approvable letter, because of the fundamental concerns raised above, I do not believe we can draft product labeling at this time. Therefore, we have not included draft labeling with this letter.

Russell Katz, M.D.

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

/s/

Russell Katz
11/3/2006 09:39:51 AM
MEDICAL OFFICER