

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross Discipline Team Leader Review

Date	September 20, 2010
From	Ronald Farkas, MD, PhD
Subject	Clinical Team Leader Review Memo
NDA#	21879
Applicant	Avanir
Date of Submission	4/30/2010
PDUFA Goal Date	10/30/2010
Proprietary Name / Established (USAN) names	Nuedexta Dextromethorphan 20 mg/Quinidine 10 mg (b) (4)
Dosage forms / Strength	Dextromethorphan 20 mg/Quinidine 10 mg (b) (4)
Proposed Indication(s)	Pseudobulbar Affect
Recommended:	Approval

1. Introduction

Pseudobulbar affect (PBA) is characterized by episodes of involuntary laughing or crying that do not reflect the true emotional state of the patient. The condition occurs in patients with a variety of underlying neurological disorders or injury, including amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Alzheimer disease (AD), and traumatic brain injury (TBI), but the underlying pathology is poorly understood. There is no currently approved therapy for PBA.

Nuedexta is a combination drug containing dextromethorphan (DM) and quinidine (Q). DM is considered to be the component that is responsible for efficacy, while Q is included in the combination to inhibit CYP2D6, which results in higher exposure to DM, which would otherwise ordinarily be metabolized rapidly to dextrophan. In the original NDA submission, the drug was formulated as DM 30 mg/Q 30 mg. Due to safety concerns about both the cardiac effects of 30 mg Q, and concern about adverse effects of 30 mg DM, the sponsor has investigated two lower dose formulations of Nuedexta, DM 30 mg/Q 10 mg, and DM 20 mg/Q 20 mg, and submits the report of this study in the current Complete Response, along with arguments addressing the other issues raised in an Approvable Letter issued by the Division in 2006 (see *Background* below). Neither Nuedexta nor similar drug combinations are approved in any country.

Other names used by the sponsor to refer to the DM/Q combination include AVP-923, Neurodex, and Zenvia.

2. Background

Development of Nuedexta was conducted under IND 56,954. The original NDA submitted 1/30/06 received an Approvable Letter communicated on 10/30/06. Between the issuance of

the Approvable letter and the sponsor's current Complete Response submission of 4/30/10, there were several regulatory interactions and agreements between the sponsor and the Division that are discussed below and in the body of this review where relevant.

February 26, 2007 Type C Meeting, (filed 3/26/2007)

Major agreements:

- The Division agreed that the DM 30/Q 30 formulation had been shown to be more effective than either component
- The efficacy data submitted to date for the 30 mg quinidine formulation of Zenvia, in combination with a single adequate positive study of lower dose-combinations, would support the efficacy of the new formulation.
- If the adverse effects of DM/Q, such as falls and vomiting, could be adequately minimized through a reformulation, the Division would consider such a decrease as evidence against an unacceptable rate of death from the combination.
- The Division agreed that CYP2D6 inhibition was, of itself, not an unacceptable safety risk for many patient populations. However, the Division stated that the sponsor must still demonstrate safety in the target population for Nuedexta, which is composed of patients taking multiple medications including CYP3A4 inhibitors and drugs such as oxycodone that might reach unacceptable exposures particularly in the presence of both CYP2D6 and CYP3A4 inhibitors.
- The Division noted that clinical experience with DM/Q in stroke, AD, and ALS was very limited, but stated that if a short-term controlled trial in patients from these groups was conducted, long-term safety studies might not be necessary to complete before approval.

November 18, 2009 Type C Meeting

(Note: The sponsor had no questions after receiving the preliminary minutes for this meeting, accepted the minutes as final, and the face-to-face meeting was not held.)

Major Agreements:

- The Division agreed that positive findings on review of study 07-AVR-123, as designed, combined with previously submitted data, would be adequate to support the efficacy of the new formulation of Zenvia with 10 mg quinidine. [note: the protocol had also undergone SPA review.]
- The Division stated that the number of human subjects exposed and the duration of exposure [from study 07-AVR-123 combined with the previous studies] was potentially adequate to support approval, but the division reiterated that the simple absence of an adverse event in the exposed population was not necessarily adequate to address the adverse events of special interest identified in previous communications.

- The Division agreed that no additional clinical pharmacology studies would be required before approval.
- The Division agreed that if additional non-clinical studies were required, they could be submitted post-approval

3. CMC

Dr. Thomas Wong conducted the primary CMC review, and Dr. Ramesh Sood conducted the secondary review. At the time of filing of the CMC review Dr. Wong stated there were deficiencies in the DMF which had not been resolved, and that the Office of Compliance had not issued a final overall recommendation regarding the cGMP inspections. However, Dr. Wong confirmed that both these issues were later resolved.

CMC had no recommendations for phase 4 commitments.

CDTL conclusion: No CMC issues preclude approval.

4. Nonclinical Pharmacology/Toxicology

Dr. D. Charles Thompson conducted the primary nonclinical review, and Dr. Lois Freed conducted the secondary review.

The following non-clinical issues, as summarized by Dr. Thompson in his current review, were raised in the 2006 Approvable Letter:

1. The potential for Zenvia [note: previous trade name of Nuedexta] to induce apoptotic neurodegeneration during development (corresponding to the human period of vulnerability of the last trimester through postnatal ages 2- 3) needs to be assessed via a juvenile neurotoxicology study in an appropriate animal species. This study may be conducted post-approval.
2. Dose range-finding studies in rat and rabbit should be repeated in order to select adequate doses for the potential necessity of repeating definitive reproductive toxicology studies in rat (fertility and early embryonic development, embryofetal development, and pre- and post-natal development) and rabbit (embryofetal development).
3. The final study report for the 2-year carcinogenicity study in rat should be submitted as soon as possible.
4. Zenvia needs to be evaluated in a chronic study in non-rodent, either in dog or in some other appropriate non-rodent animal model.

Dr. Thompson notes that the sponsor adequately addressed the first issue by committing to conduct a juvenile neurotoxicology study in rats, and to submit a protocol for this study by 3 months post approval.

For the second issue, the sponsor submitted in July 2008 results of dose-ranging studies for developmental/reproductive toxicology studies in rats and rabbits. Review at that time concluded that the pre- and post-natal development study in rats and also the embryo-fetal development study in rabbits needed to be repeated using a high dose of 50 mg/kg/day dextromethorphan in combination with 100 mg/kg/day quinidine. The Division also stated that these studies could be conducted post-approval. The sponsor has adequately addressed this issue by committing to conduct the studies on the timeline specified by the Division. Relevant findings from developmental/reproductive toxicology studies conducted by the sponsor to date will be included in labeling.

The sponsor adequately addressed the third issue by submitting an adequate 2-year carcinogenicity study in rat. The FDA conclusion was that there were no biologically significant neoplastic findings for dextromethorphan and quinidine, alone or in combination, under the conditions tested.

The sponsor adequately addressed the fourth issue with a 39-week study in dogs, along with 1- and 5-week dose-finding studies. Dr. Thompson concludes that toxicity was largely CNS-related, with additional cardiovascular (ECG) findings. There was focal squamous metaplasia in the trachea/larynx of an incidence and severity only slightly increased over background. The relationship, if any, to drug might have been related to the known epithelial irritancy of quinidine.

The nonclinical team concluded that the data submitted support approval of Nuedexta, with approval contingent on formal agreement to post marketing requirements for submission of protocols and conduct of the following phase 4 studies:

- juvenile neurotoxicology study in rats
- repeat pre- and post-natal development study in rats
- embryo-fetal development study in rabbits

CDTL conclusion: No nonclinical issues preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Ju-Ping Lai conducted the primary Clinical Pharmacology review, and Dr. Angela Men conducted the secondary review. Drs. Joo-Yeon Lee and Yaning Wang conducted the pharmacometrics review, and Drs. Li Zhang and Michael Pacanowski conducted the genomics review. Dr. Lai concludes that the sponsor's Complete Response is acceptable to Clinical Pharmacology provided that the sponsor agrees with FDA labeling recommendations.

In the 2006 Approvable Letter, the Division communicated the following Clinical Pharmacology requirement to the sponsor:

1. The following *in vitro* studies should be conducted preferably prior to approval to be included in labeling.

- Evaluate quinidine as an inhibitor and as an inducer of P450s
- Evaluate dextromethorphan (DM) as an inhibitor and as an inducer of P450s

Dr. Lai notes that the sponsor conducted four *in-vitro* inhibition/induction studies that showed no new induction or inhibition potential beyond the known inhibition of CYP2D6. These studies adequately address the issue raised by the Division in the 2006 Approvable Letter.

Due to safety concerns about both the cardiac effects of 30 mg Q, and concern about adverse effects of 30 mg DM, the sponsor investigated two lower dose formulations of Nuedexta, DM 30 mg/Q 10 mg, and DM 20 mg/Q 10 mg, and submits the report of this study (study 07-AVR-123) in the current Complete Response. In addition the sponsor submitted 3 new clinical pharmacology/biopharmaceutic study reports, one population PK analysis, and one thorough QT study report (**CDTL note: the thorough QT study is discussed in Section 8, Safety**).

Dr. Lai had the following major findings regarding the new lower dose formulations and the new drug-interaction studies:

- None of the covariates of height, weight, BMI, age, race and gender were considered significantly correlated with any of the PK parameters of DM, DX, and Q
- Q exposure was dose-proportional between the 10 mg and 30 mg dose, and DM was close to, but slightly lower than dose proportional with the 30 mg DM /10 mg Q versus 30 mg DM /30 mg Q. This suggests that the 10 mg Q dose inhibits CYP2D6 nearly as well as the 30 mg dose.
- Drug-drug interaction studies showed the following:
 - No clinically meaningful PK interaction between Nuedexta and memantine, but possible worsening of dizziness
 - Increased exposure of paroxetine, DM, and Q when paroxetine is co-administered with Nuedexta
- In study 123, DM and DX concentrations were similar across CYP2D6 genotypes, although precision of findings was greatly limited by data from only 3 poor metabolizers (PMs) and 1 ultra-rapid metabolizer.
- Adverse events in study 123 were examined by CYP2D6 genotype, as shown in the table below (**CDTL: the small number of PM's [5 in DM/Q] limits ability to make meaningful safety conclusions related to CYP2D6 status**)

	DM/Q (combined dose groups)				Placebo			
	UM (n=2)	EM (n=131)	IM (n=16)	PM (n=5)	UM (n=6)	EM (n=60)	IM (n=7)	PM (n=7)
SAE	0 (0)	11 (8.4%)	2 (12.5%)	2 (40%)	1 (16.7%)	6 (10%)	2 (28.6%)	0 (0)
AE attributed to treatment	1 (50%)	66 (50.3%)	5 (31.3%)	3 (60%)	2 (33.3%)	19 (31.6%)	3 (42.9%)	2 (28.6%)

Discontinuation due to AE	0 (0)	10 (7.6%)	1 (6.3%)	2 (40%)	0 (0)	0 (0)	1 (14.3%)	0 (0)
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Pharmacogenomics: Dr. Zhang noted the following for pharmacogenomics:

- Q in Nuedexta adds potential risk without adding benefit in CYP2D6 PMs, and this should be communicated in Nuedexta labeling.
- Genetic effects on safety and efficacy are inconclusive in study 123 because of the small sample size.

CDTL: I agree that there are no unresolved Clinical Pharmacology/Biopharmaceutics issues precluding approval of Nuedexta.

As discussed in greater detail in *Section 8, Safety*, in the 2006 Approvable Letter, the Division expressed concern about the potential for increased adverse drug interactions due to CYP2D6 inhibition by Nuedexta. However, at the February 26, 2007 Type C Meeting with the sponsor, the Division agreed that CYP2D6 inhibition was not itself an unacceptable safety risk, but that the sponsor would still need to demonstrate that an unacceptable incidence of drug-drug interactions did not occur in studies of Nuedexta.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Tristan Massie was the primary statistical reviewer, and Dr. Kun Jin the secondary statistical reviewer. The primary clinical reviewer for efficacy was Dr. Jillapalli. Both Dr. Massie and Dr. Jillapalli conclude that study 07-AVR-123 demonstrates statistically significant benefit for both the 20/10 and 30/10 dose arms versus placebo. Similarly, both conclude that no difference in efficacy between the two drug doses can be ascertained from the study data.

Issues regarding efficacy in the current submission include a) efficacy concerns expressed by the Division in the Approvable Letter that had not been adequately addressed in communications with the Division prior to submission of the sponsor's Complete Response [*See Section 2, Background, for major agreements*], and b) efficacy analysis of the new clinical study (07-AVR-123) of two lower dose DM/Q combinations, 30 mg DM/10 mg Q, and 20 mg DM/ 10 mg Q.

a) The efficacy issues in the Approvable Letter are as follows:

- *Combination Drug Rule:* The Division expressed concern in the Approvable Letter that there was not enough evidence to conclude that the 'combination drug rule' had

been satisfied. However, prior to the current submission, the Division concluded at the 2/26/2007 post-action meeting that the combination rule had been adequately satisfied.

- *Primary Outcome Measure:* The Division noted in the 2006 Approvable letter that it preferred use of laughing and crying episode counts as a primary endpoint, and not the CNS-LS as the sponsor had used in the MS and ALS studies submitted in the first NDA cycle. This issue was adequately addressed before the current Complete Response submission, as the sponsor agreed to use laughing and crying counts as the primary outcome in study 07-AVR-123, and the Division had agreed to the design of that study at the 11/18/2009 Type C meeting.

CDTL: I conclude that approval of Nuedexta depends on efficacy analysis of study 07-AVR-123, and that the other efficacy concerns expressed by the Division in the 2006 Approvable Letter have been resolved previously. Importantly, the Division also previously agreed that the design of study 07-AVR-123 was adequate, from an efficacy standpoint, for approval if positive.

b) Efficacy analysis of study 07-AVR-123

- 326 subjects were randomized: 110 to DM 30/Q 10, 107 to DM 20/Q 10, and 109 to placebo.
- About 60% of subjects in each arm had ALS, and 40% had MS
- 283 subjects (86.8%) completed the study.
- Of the 43 subjects who withdrew, 19 were on DM 20/Q 10, 15 on placebo, and 9 on DM 30/Q 10.

Study quality and integrity

Dr. Jillapalli, through his own audits of the data and consideration of findings of DSI, found no issues with study quality and integrity that would meaningfully diminish confidence in efficacy findings.

Baseline Imbalance

Time from diagnosis of ALS at randomization was markedly different among the 3 treatment groups: 22 months for AVP-923-30, 16 months for AVP-923-20, and 13 months for placebo. Other demographic factors, including percent with bulbar onset, were similar across groups.

Given the above baseline imbalances, Dr. Jillapalli asked Dr. Massie to analyze if subjects with longer disease duration had more events, and if there was a greater treatment effect in those with more baseline events. Dr. Massie's did not find evidence to support either of these possibilities.

Primary Efficacy Analysis

Dr. Massie's overall conclusion is that efficacy data from study 07-AVR-123 suggest that both the DM 30/Q 10 and DM 20/Q 10 doses were superior to placebo for the primary endpoint, 'laughing plus crying episodes,' in the mixed ALS and MS populations enrolled. Dr. Massie observes that the statistical model used for the primary analysis in the study, a longitudinal analysis of daily episode counts, may have led to underestimation of p-values, but

that this underestimation is not so great as to alter the statistical significance of the comparison of both dose arms to placebo. Dr. Massie presents the sponsor's analysis that subjects in the DM 30/Q 10 arm experienced about half as many episodes, 53%, as subjects receiving placebo ($p < 0.0001$), and similarly that subjects in the DM 20/ Q 10 arm experienced about half as many episodes, 51%, as subjects receiving placebo ($p < 0.0001$). Dr. Massie conducted a number of his own sensitivity analyses that showed, in general, that findings of efficacy were robust for both dose arms. The efficacy conclusions were robust to analysis by site, and were not sensitive to the exclusion of data from any one site. Similarly, findings were robust to sensitivity analysis for missing data. However, sensitivity analysis imputing a high episode count for patients that died showed a non-significant p-value for DM 20/ Q 10 of 0.21, while the DM 30/ Q 10 arm remained significant, at $p = 0.017$.

Analysis by Underlying Disease

Dr. Massie found that the statistical model used for the primary analysis (longitudinal negative binomial model) seemed to suggest that for MS patients placebo was superior to the DM 20/ Q 10 dose (but not the DM 30/ Q 10 dose). However, other statistical models indicated that, at least numerically, the DM 20/ Q 10 dose was, in fact, superior to placebo. Furthermore, Dr. Massie was concerned that the model used for the primary analysis did not fit well the MS data due to a large number of zero episode counts, further decreasing concern about nominally negative finding for the DM 20/ Q 10 dose in MS.

Analysis of Laughing Alone

Dr. Massie states that there is some evidence that Nuedexta may be less effective for treatment of laughing episodes than for treatment of crying episodes. However, he stresses that the study was only powered for the analysis of combined events. Based on sensitivity analysis of laughing episodes only in study 123, neither dose was superior to placebo. Similarly, analysis of the 'laughing items' from the CNS-LS did not show efficacy for either dose group. In contrast, nominal statistical significance was reached for both crying episodes alone and 'crying items' from the CNS-LS, for both doses. Dr. Massie also notes that in the previous ALS study (102) of the higher dose formulation (DM 30/ Q 30) a similar pattern occurred.

Secondary Endpoint

The key secondary endpoint was score on the Center for Neurologic Study-Lability Scale (CNS-LS). Both doses were significant compared to placebo.

CDTL Discussion and Conclusions, Efficacy:

As noted in Section 2, Background, the Division previously agreed that positive findings for study 07-AVR-123 would be adequate to support the efficacy of the new, lower dose formulation if the study was otherwise positive. Both Dr. Massie and Dr. Jillapalli conclude that this study was positive, and that efficacy of the 20/10 dose was similar to efficacy of the 30/10 dose. As discussed in more detail below, I agree with their findings, and conclude that study 07-AVR-123, combined with previous studies 102 and 106, adequately support the efficacy of Nuedexta.

Baseline imbalance

A potential concern with efficacy findings is the baseline imbalance in time from diagnosis of ALS patients, who made up 60% of enrollment. Depending on the natural history of PBA, the baseline imbalance in time from diagnosis could have biased efficacy conclusions in favor of the drug arms, as a type of ‘lead time bias.’ For example, if the natural history of PBA is worsening for about a year after diagnosis, followed by improvement, the treatment arms in study 123 might have been improving spontaneously, while the placebo arm had not yet reached the time in the course of the disease when such improvement would begin. I find, however, that this type of bias was unlikely to have affected efficacy findings.

- **The imbalance in time from diagnosis was large (about 6 months) between the two DM/Q arms, yet both were still superior to placebo, which increases the constraints that any model of spontaneous improvement would have to meet to have biased results, thus decreasing plausibility.**
- **The imbalance between the placebo and 20/10 arm was only 3 months, while the baseline episode rate was *worse* for the 20/10 arm versus placebo, again further constraining the exact timing and rate of improvement that would be necessary for lead-time bias to have been a factor, and decreasing plausibility.**
- **Critically, most of the improvement in episodes occurred by the first post-treatment visit, which is inconsistent with a model in which differential improvement due to time-from-diagnosis occurred over the 3-month double-blind period.**

Dose Selection

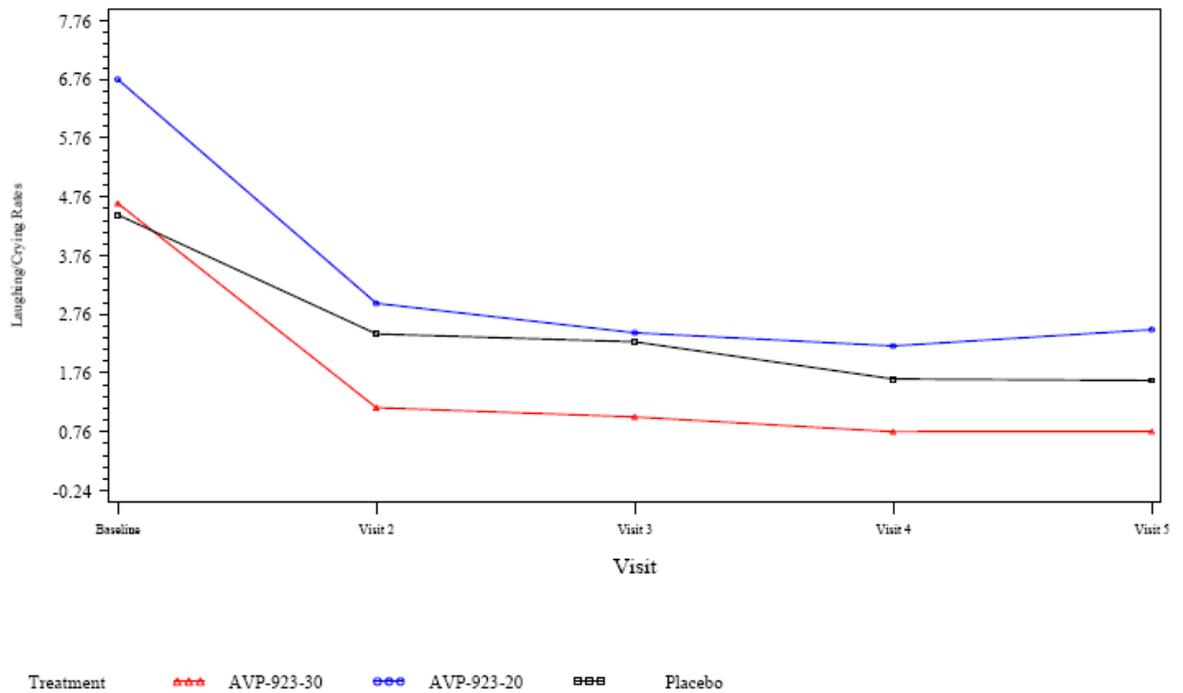
The Division expressed concerns not only about the safety of the Q component of Nuedexta, but also about the safety of the DM dose. The sponsor therefore included in study 123 both the previously studied 30 mg Q dose, and a lower DM 20 mg formulation of Nuedexta. While study 123 was not powered to differentiate between the efficacy of the two doses tested, similar findings for the two doses would suggest that safety findings would then be the major determinant of dose selection. I agree with Dr. Massie and Jillapalli that the overall data suggest that efficacy was similar for both doses. Most importantly, the DM 30/Q 10 and DM 20/ Q 10 doses showed very similar reduction of episodes on the pre-specified primary analysis (about 50% for each). Some sensitivity analyses suggested that results for the 30/10 dose were more robust than for the 20/10 dose, but others suggested the opposite.

The descriptive analysis in the figures below also provides support for the similarity of efficacy in the two arms. There were some differences between arms, particularly in baseline values, but overall efficacy in both dose arms appears similar:

- **Laughing/crying rates over time show a baseline difference, with more events/day in the 20/10 arm (Figure 1). The CNS-LS score also showed a similar baseline imbalance (Figure 5). Such baseline differences confound assessment of relative efficacy of the two drug arms.**

Figure 1

Figure 1
Laughing/Crying Rates Over Time by Treatment Group
(ITT Population)



- **Absolute change in episode rates was greater in the 20/10 than 30/10 arm for the first 4 visits, but showed little difference by the last study visit. (Figure 2, from study 123 report, below). However, while the absolute change in the 20/10 arm was large than in the 30/10 arm over most time points, the percent change was strikingly similar at all visits (Figure 3 from study 123 report)**

Figure 2, from study 123 report

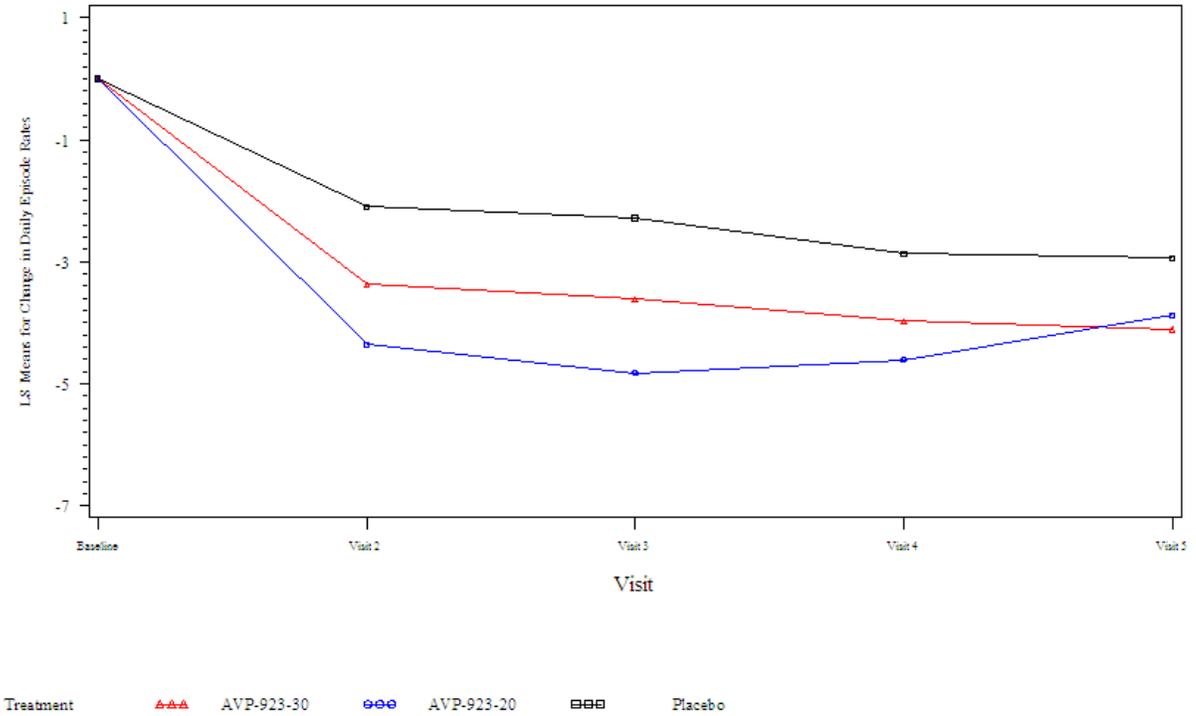
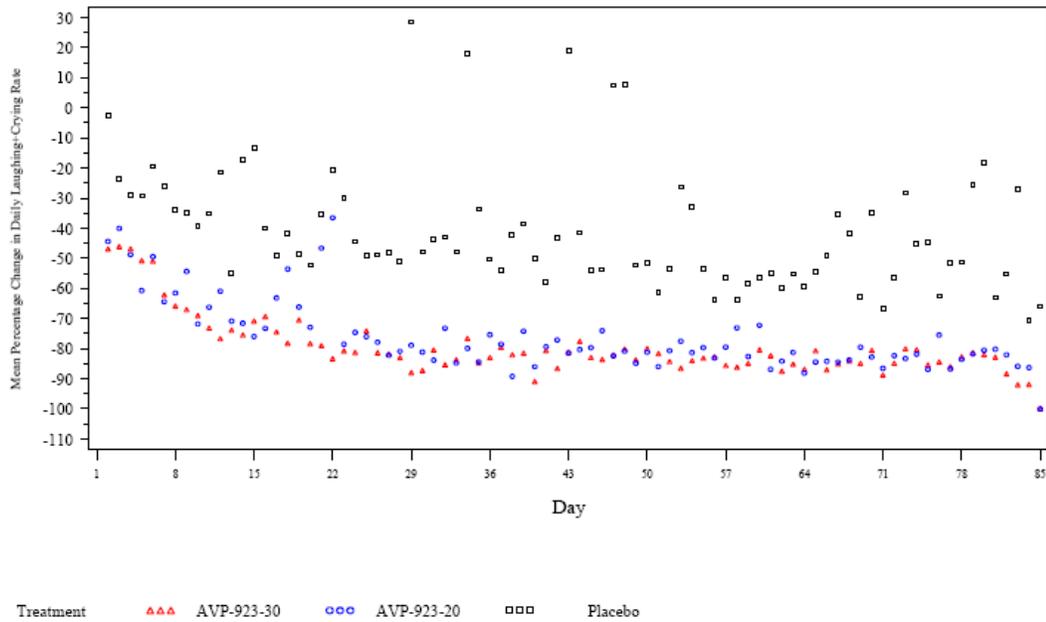


Figure 3 from study 123 report

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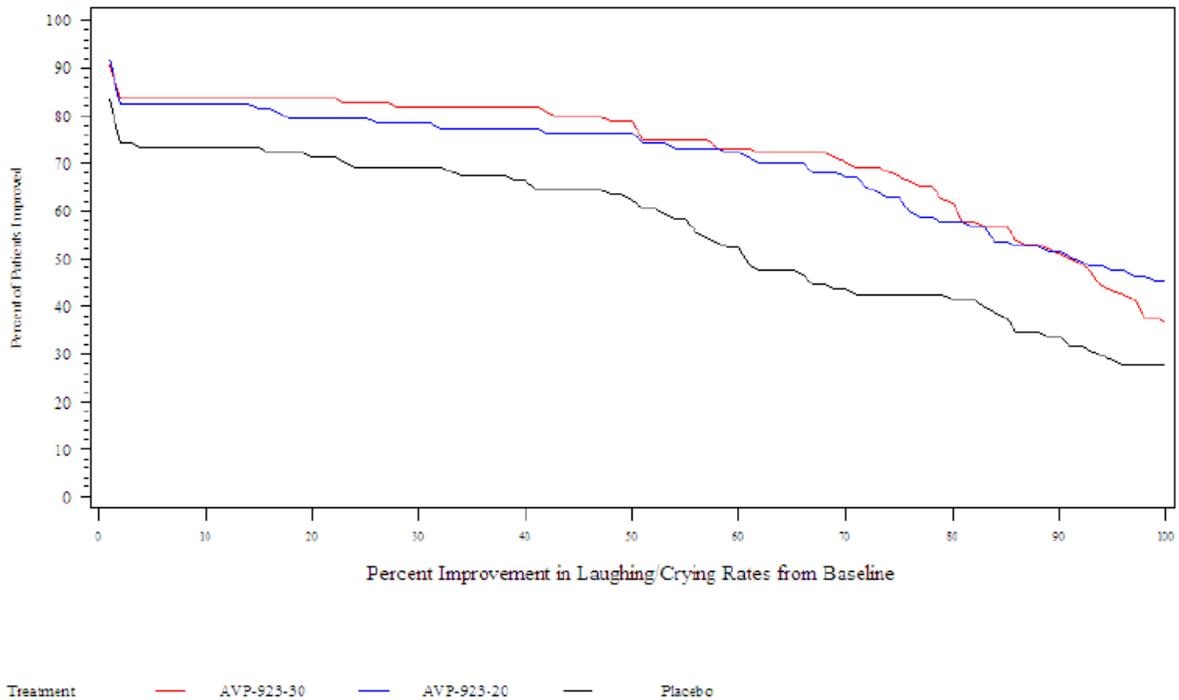
Figure 3.4
 Daily Laughing/Crying Rate Percentage Change from Baseline Over Time by Treatment Group
 (ITT Population)



- Responder analysis of the primary endpoint showed little difference between dose arms (Figure 4 Responder analysis in combined ALS and MS patients).

Figure 4 Responder analysis in combined ALS and MS patients

Figure 11-3. Laughing/Crying Rates - Responder Analysis by Treatment Group (ITT Population)

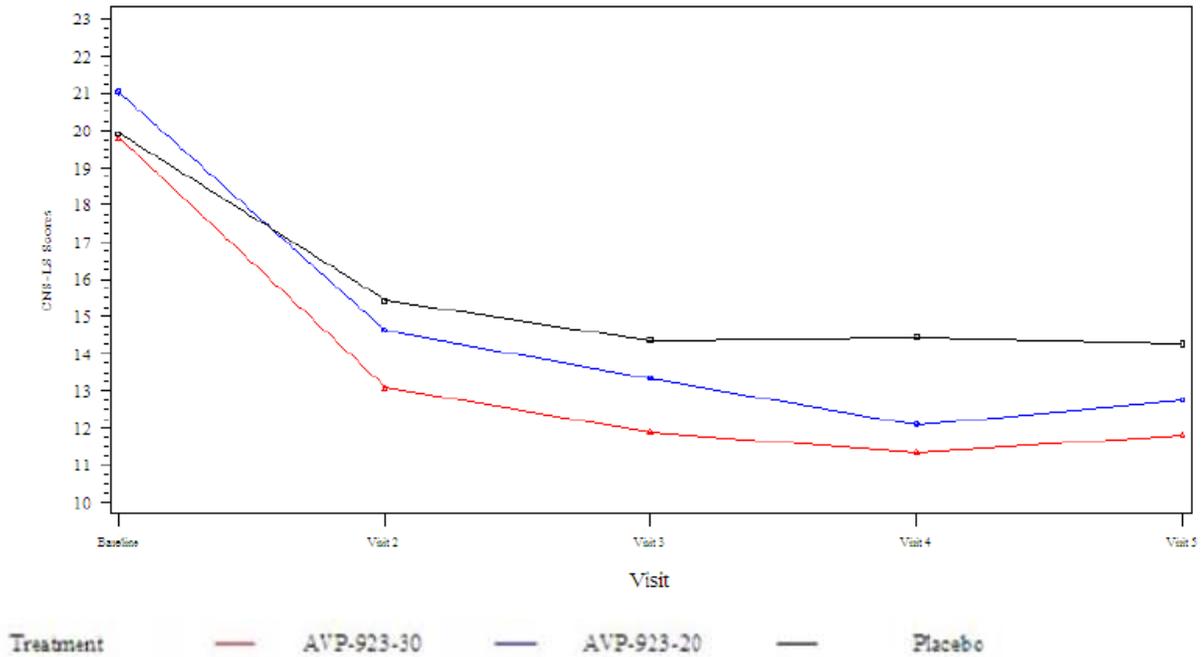


Source: DB phase, Section 14.1, Figure 4.1. ITT = intent to treat.

For the key secondary endpoint, CNS-LS score, the decrease over time might be interpreted as being similar for both dose arms, but with the baseline imbalance (20 mg arm with higher score at baseline) explaining the lower absolute score for the 30 mg DM arm (Figure 5). Alternatively, the lower absolute score achieved in the 30 mg DM arm might be taken as supportive of superiority of that arm. However, given the baseline imbalance in CNS-LS score between dose arms, with the 20 mg DM arm worse at baseline, such evidence is extremely weak.

Figure 5

Figure 11-4. CNS-LS Scores over Time in the DB Phase by Treatment Group (ITT Population)

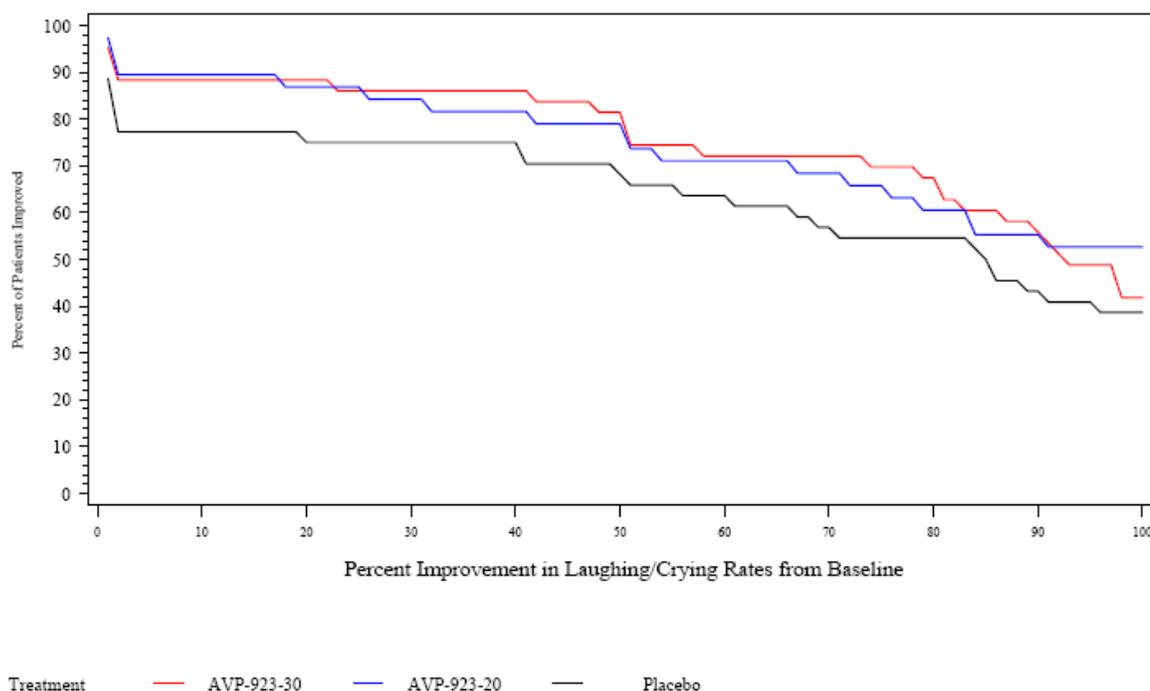


Analysis by underlying disease

While Dr. Massie rightly points out that study 123 was not powered to detect efficacy separately for ALS and MS, it is still a question of interest. Dr. Massie, after considering sensitivity analyses, ultimately concludes that both doses were at least numerically superior to placebo for MS. Descriptive statistics support this, as shown by the responder analysis in MS patients alone (Figure 6). Importantly, study 106, which examined the 30 mg DM/30 mg Q formulation in MS, was clearly positive. This provides evidence that the combination of DM/Q, if not necessarily the dose, is effective in PBA from underlying MS.

Figure 6

Figure 4.3
Laughing/Crying Rates - Responder Analysis by Treatment Group
(ITT Population - MS Patients)



Analysis by Laughing and Crying episodes Separately

Dr. Massie finds little evidence that Nuedexta is effective for treatment of laughing episodes, with efficacy evidence largely based on effect on crying episodes. However, he notes that it is important to consider that neither the current nor previous studies were powered to detect an effect on laughing separately. Given the overall benefit shown in PBA in ALS and MS, and the very weak nature of the evidence that Nuedexta may not be effective for laughing episodes, I do not think this analysis affects the current approvability of Nuedexta. I find it reassuring that ‘number of episode free days’ was statistically significantly in favor of Nuedexta (as discussed in section 6.1.6 of Dr. Jillapalli’s review), and ‘no episodes’ also, by necessity, means no laughing episodes.

However, as discussed directly below, I do think that potential doubts about efficacy for laughing episodes could increase concern about using the current data to generalize efficacy to PBA from other underlying neurological conditions.

Overall generalizability of findings to PBA

While I conclude that efficacy in ALS and MS has been adequately demonstrated by the combination of current and previous studies, evidence that Nuedexta is effective in all conditions in which PBA occurs is quite weak. The underlying pathophysiology of PBA is poorly understood even in ALS and MS, and is even less studied in other neurological conditions. Given the clearly large differences in mechanisms and manifestations of the underlying neurological diseases, the possibility of important differences in PBA

pathophysiology, or modifiers of its expression, seems difficult to dismiss. For example, Dr. Massie's analysis indicates that there is little evidence of efficacy for Nuedexta for laughing episodes, and I am not aware of evidence that the relative frequency of laughing versus crying episodes is constant for PBA across different underlying conditions. This would seem an important issue to address before considering a generalized claim in PBA.

Importantly, while many factors (like similarity of pathophysiology) affect the evidence needed for a generalized claim, from a statistical viewpoint two positive findings does not provide much reassurance that efficacy would hold in all cases. Since evidence of generalizability greatly increases with each additional confirmatory finding, requiring efficacy evidence from at least 3 different underlying diseases appears to provide an appropriate compromise between level of evidence and practicability.

8. Safety

Dr. Jillapalli conducted the primary safety review. His recommended regulatory action is approval.

Dr. Jillapalli assessed the risks and benefits of Nuedexta in the context of the deficiencies outline in the 2006 Approvable Letter, and in the context of the new data submitted in the sponsor's current Complete Response.

In the 2006 Approvable letter, the Division expressed concern with the following safety issues:

1. Potential for adverse effect on survival in ALS, particularly due to effects on respiration
2. Risk of aspiration secondary to drug-associated nausea, vomiting, and somnolence
3. Risk from falls
4. Potential for drug-induced hepatotoxicity
5. Adverse drug interactions resulting from CYP2D6 and CYP3A4 inhibition
6. Potential adverse cardiac affects of Q, including QTc prolongation and adverse effects on cardiac conduction
7. Generalizability of Safety Findings to Other Populations

The following is the sponsor's response to the above concerns, along with FDA analysis of the issues.

1. Deaths:

In the 2006 Approvable Letter, the Division expressed the following concern about deaths in studies of the DM 30/Q 30 formulation:

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).

In response to this concern, the sponsor compared the death rate in the overall development program to reported rates in the literature, and concluded that the rate was not higher than expected.

In the new study of the lower dose formulation, study 123, there were 10 deaths in the combined controlled and open label periods. Seven of these deaths occurred in the 12-week placebo-controlled period, with 3 deaths in each active drug arm, and 1 death in the placebo arm. The sponsor argues that the number of deaths in study 123 is expected given the underlying diagnosis of ALS, and that the cause of all deaths was respiratory failure. The sponsor suggests that the imbalance of deaths in treatment versus placebo arms may have been due in part to imbalances in the time from diagnosis to randomization in the treatment arms versus placebo arm, as duration of disease is an important predictor of death in ALS. The time from diagnosis to enrollment was 12 months in the DM 30 mg/Q 10 mg group; 9.5 months in DM 20 mg/Q 10 mg group; 6.5 months in placebo group.

Dr. Jillapalli generally agrees with the sponsor's conclusions that the deaths in study 123 appear to be related to respiratory failure according to expectations in an ALS population. He notes that with even if one more death had occurred in the placebo arm, there would be essentially no appearance of an imbalance. He does not, however, find comparisons of death rates to historical rates to be informative, and concludes that there is not enough data to validate the sponsor's argument that differential time from diagnosis to enrollment was responsible for the imbalance of deaths. He notes that the argument about differential time from diagnosis to enrollment would be supported if deaths in each arm all clustered around the same time from diagnosis, but with only 3 deaths in each drug arm and one death in placebo, there is not enough data to estimate average time between diagnosis and death.

While he expresses some concern about a potential adverse effect of DM/Q on the progression of the underlying ALS, Dr. Jillapalli concludes that such an adverse effect, if it occurred, should be detectable as an increase in non-fatal adverse events. Importantly, however, he finds that non-fatal respiratory-related adverse events were actually equal to or even lower in the DM/Q arms than in the placebo arm, suggesting that there is little to no evidence supporting an adverse effect of Nuedexta on ALS. The incidence of non-fatal respiratory-related adverse events experience by 2 or more subjects in the double-blind phase of study 123 was 4.4% for the 20/10 arm, 6.2% for the 30/10 arm, and 6.3% for the placebo arm.

Dr. Jillapalli's overall conclusion is that a) the deaths were due to respiratory failure, b) that respiratory failure in most cases occurred after the patient had stopped taking the drug, and c) that the imbalance could reasonably have occurred by chance.

CDTL Discussion

I agree with Dr. Jillapalli that the totality of data does not suggest that Nuedexta increases the risk of death in ALS patients.

Even before considering the details of the deaths in study 123, the size of the imbalance is small, and as Dr. Jillapalli points out in his review, if there was even one more death in the placebo arm, the imbalance would have appeared clearly due to chance. As Dr. Jillapalli notes, Dr. Massie performed a post-hoc statistical analysis (Fisher's exact test) of the imbalance in deaths observed between the two treatment arms and the placebo arm, finding that the probability of an imbalance in deaths of the observed size or larger is 0.28 based on the null hypothesis that there is no true difference in the risk of death in either drug or placebo arms, and based on a one-sided test. This calculation helps put into perspective just how weak the imbalance is as evidence that there is an adverse effect of Nuedexta on death rate. Moreover, the probability that the study would have shown the *reverse* imbalance, with more deaths in the placebo arm than the drug arms is also 0.28, so that the odds are greater than 50:50 that an imbalance of this size (but not necessarily in this direction) would have been encountered purely by chance in a study of this design.

Dr. Jillapalli also notes that 3 of the deaths (two in the 30/10 arm and one in the placebo arm) in study 123 occurred about a month after stopping DM/Q, and that the deaths are therefore less likely to be drug-related. I would also add that one death in the 20/10 arm occurred 19 days after stopping drug, and one death in the 30/10 arm occurred 12 days after stopping, similarly decreasing plausibility that the deaths were drug-related.

The sponsor suggests that the imbalance of deaths may have been due to imbalances in the time from diagnosis to randomization in the treatment arms versus placebo arm, as duration of disease is an important predictor of death in ALS. While Dr. Jillapalli correctly states that this hypothesis is not testable given the low number of deaths, I do find it to be plausible.

Perhaps most compellingly, Dr. Jillapalli notes that death in ALS is usually part of a continuum of the spectrum of respiratory dysfunction in ALS patients. Therefore, non-fatal respiratory adverse events and other measures of respiratory function should serve as a surrogate for risk of death. Importantly, at the February 2007 meeting with the sponsor, the Division stated that if adverse effects of DM/Q could be adequately minimized through a lower dose reformulation, the Division would consider such a decrease as evidence against an unacceptable rate of death from the combination. Dr. Jillapalli finds that the incidence of subjects experiencing any respiratory-related TEAEs in the placebo group was comparable to or even higher than in either DM/Q 10 mg dose group, decreasing concern that the imbalance in ALS deaths between treatment groups in Study 123 was more than a chance finding. In addition, as discussed in the next

section under *Pulmonary Consult*, Dr. Lydia Gilbert-McClain also concluded that the deaths in study 123 were consistent with progression of ALS. I believe that this mechanism-based assessment of risk for death also adequately addresses the concern expressed in the 2006 Approvable letter specifically about the deaths in the previous open-label experience reviewed at that time.

Pulmonary Consult

In the 2006 Approvable letter, DNP expressed concern that while deaths would be expected in clinical studies of ALS patients, the sponsor had not presented adequate evidence that DM/Q had not adversely affected the death rate. The Approvable letter specifically expressed concern about respiratory depression from DM/Q because in high doses, DM can depress respiration. To address the issue of respiratory depression, in study 07-AVR-123, the sponsor collected oxygen saturation data in ALS patients. DNP consulted the Pulmonary Division to assist in interpretation of this oxygen saturation data, particularly in the context of the patients that died during the study, and in interpreting the overall respiratory risk associated with Nuedexta.

Dr. Lydia Gilbert-McClain was the primary pulmonary consultant, with Dr. Badrul Chowdhury providing concurrence.

Diurnal oxygen saturation was measured at baseline, day 15 and day 84, and nocturnal oxygen saturations was measured at baseline and day 15. Dr. Gilbert-McClain notes, however, that measurements of oxygen saturation over short time periods are not very informative of the overall patient status in terms of adequate tissue oxygenation.

Dr. Gilbert-McClain finds that the values obtained for ALS patients were within the 90% range of normal limits, and that although there were shifts in both the diurnal and nocturnal oxygen saturation values, the values did not appear to have fallen to low enough levels to be of clinical concern. She concluded that findings for the DM 30/Q 10 and DM 20/ Q 10 doses were similar, and not meaningfully different from placebo values.

Dr. Gilbert-McClain concluded after review of the deaths in study 07-AVR-123 that they were consistent with progression of ALS, and did not suggest a treatment-related effect. She notes that only 2 of the patients that died were actually still on active treatment at the time of death, decreasing the plausibility of causal association. She also notes the absence of a dose-response effect between the two Nuedexta arms: there were 3 deaths in each.

CDTL: I agree with Dr. Gilbert-McClain's analysis and conclusions. While the sensitivity of oxygen saturation measurements to detect adverse effects of Nuedexta may have been low, the patient narratives provide no compelling evidence of an adverse effect of Nuedexta on respiration.

2. Aspiration, Nausea, Vomiting, Somnolence

In the 2006 Approvable Letter, the division expressed concern about a higher incidence of nausea, vomiting, and somnolence in patients treated with the DM 30/ Q 30 formulation of Nuedexta versus those treated with placebo, and that these adverse events might be associated

with the more serious adverse event of aspiration/aspiration pneumonia. The Approvable Letter stated the following:

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).

In response, the sponsor argues that the causal association between nausea/vomiting and aspiration is weak. The sponsor asserts that since there is no temporal association of aspiration/aspiration pneumonia with events of nausea, vomiting, or somnolence, these events are not causally related.

Dr. Jillapalli finds that in study 123, there were only 2 patients with aspiration/aspiration pneumonia, one in the placebo arm, and one in the 30/10 arm, and that this low number of events precluded any conclusions about drug-relatedness. He also found that for adverse events potentially increasing the risk of aspiration/aspiration pneumonia, there is little evidence of drug-relatedness. He notes that there was a higher incidence of nausea in the DM 30/ Q 10 (but not DM 20/ Q 10) MS arm versus placebo (6%, 0%, 3%, respectively), and a higher incidence of vomiting in the 20/10 group in ALS subjects versus 30/10 and placebo (5%, 1%, 1%, respectively). Somnolence was in the range of 4-to 6% in all arms, and only 1 patient across all arms had an adverse event of sedation.

CDTL: I agree with Dr. Jillapalli that there is little evidence of either adverse events that increase the risk of aspiration, or of aspiration pneumonia. The imbalances in nausea and vomiting in study 123 are small and follow a pattern that is not convincing of occurrence other than by chance; in each case one drug arm is either less than or equal to placebo (and for vomiting, it is the *higher* dose arm that is equal to placebo), arguing against a discernable relationship to drug. Somnolence was almost the same across study arms and disease sub-categories, and sedation was essentially absent.

The data from study 123 for these adverse events are less concerning than the earlier findings with the DM 30/ Q 30 formulation, and reassuring of safety of the lower dose formulation of Nuedexta. Also, the concern expressed in the 2006 Approvable Letter was mainly that the events like nausea and vomiting might increase risk of aspiration. However, I agree with the sponsor and Dr. Jillapalli that such an association, while plausible, remains speculative and unsupported by the actual studies of Nuedexta. My overall conclusion is therefore that this concern has been adequately addressed.

3. Falls and Dizziness

In the 2006 Approvable Letter, the division expressed concern about an increased risk of fall in drug- versus placebo arms, and increased incidence of adverse events that might cause falls, such as dizziness. The Approvable Letter stated the following:

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.

The sponsor argues that data from study 123 indicate that falls are the result of the patient's underlying condition, and that while the incidence of dizziness is slightly higher in subjects treated with DM 30/ Q 10 or DM 20/ Q 10 combinations, any potential risk from this could be managed with appropriate labeling.

Dr. Jillapalli notes that in study 123 the incidence of falls was comparable between treatment groups, as follows:

ALS	DM 20/Q 10	15%
	DM 30 /Q 10	28%
	Placebo	28%
MS	DM 20 /Q 10	10%
	DM 30/Q 10	9%
	placebo	9%

Dr. Jillapalli does concludes that there is a clear dose-related effect of DM/Q on dizziness (Table 52 below), and considers this a factor that might influence falls, but he ultimately concludes that the data do not actually support such a conclusion. He notes, for example, that

across the integrated clinical trials (all DM/Q dose combinations), the odds of a fall in subjects who experienced any TEAE of dizziness is only 1.5 times that in subjects who did not experience any TEAE of dizziness, and that there was no discernable relationship between the temporal occurrence of dizziness and that of falls.

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%)

CDTL: I agree with Dr. Jillapapalli that study 123 does not provide evidence for an increase in falls associated with either DM/Q arm tested. While dizziness *does* appear to be a dose-related adverse effect of DM/Q, there is enough data from *actual falls* in the study to conclude that a large increase in actual falls did not occur due to Nuedexta. However, given that the study had limited power to detect an increased risk of fall related to Nuedexta, and the still plausible contribution of dizziness as a risk factor in fall, I recommend that the risk of dizziness and fall be described in labeling.

4. Hepatotoxicity

In the 2006 Approvable Letter, the Division acknowledged that that there did not seem to be systematic changes in laboratory values related to DM/Q, but expressed concern about a single patient who experienced increased AST, ALT, and bilirubin, with only mild increase in alkaline phosphatase, in a pattern similar to that expected from the type of drug-induced liver injury that is also associated with liver failure. The Approvable Letter stated the following:

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.).

The sponsor acknowledges that hepatotoxicity has been associated with Q. However, the sponsor notes the even lower doses of Q are in the current Nuedexta formulation in study 123, and states that neither average nor individual patient data from study 123 suggest liver injury from Nuedexta.

Dr. Jillapalli re-examined the case of hepatitis from the 30/30 study, and concludes that a relationship to DM/Q can not be excluded. However, he is reassured that the patient recovered, and believes that any potential liver injury from DM/Q is likely to be both detectable by monitoring, and reversible.

Dr. Jillapalli notes that there was one patient in study 123 (#123-106-724) with ALT elevated ≥ 3 times the upper limit of normal and bilirubin elevated ≥ 2 times the upper limit of normal. Liver enzymes returned to normal after about 2-3 weeks, and rechallenge with DM/Q did not produce abnormality, arguing against a causal relationship with DM/Q, and in favor of the sponsor's conclusion that infectious mononucleosis was the most likely underlying etiology.

CDTL: Hepatitis from Q, at doses used for cardiac indications, is well-documented. For example, Knobler et al (1986)¹ reviewed the charts of 1,500 patients receiving quinidine over a 10 year period, and found 33 with quinidine-associated hepatitis, or an incidence of about 2%. Histopathological findings generally consisted of a mixed picture of portal and parenchymal involvement, with both acute and chronic inflammation, and granuloma formation. Time to diagnosis was a mean of 14 days, and range of 3- to 44 days. The authors concluded that the hepatitis was easily recognized because in most cases fever preceded liver damage, and less commonly other signs of hypersensitivity reaction including gastrointestinal symptoms, rash, and thrombocytopenia. Symptoms were observed to resolve quickly and generally completely after discontinuation of Q, and to re-occur promptly in those patients that underwent re-challenge.

¹ Knobler, H, Levij, I, Gavish, D, Chajek-Shaul, T. *Quinidine-Induced Hepatitis: A Common and Reversible Hypersensitivity Reaction*. Arch Intern Med, 1986;146:526-528.

Dr. Jillapalli finds, and I agree, that it is not possible to exclude that the patient noted in the 2006 approvable letter had hepatitis related to quinidine. However, Dr. Jillapalli did not identify other suspect cases, or systematic changes in mean or outlier laboratory values, and concludes that, at least based on the Nuedexta clinical database, the risk of drug-induced hepatitis from Nuedexta is very low. Clearly, the incidence of hepatitis from Nuedexta is far lower than the 2% reported by Knobler et al., but I find there is insufficient exposure data for Nuedexta to conclude that the risk is absent. Given the minimal signal in the safety database for serious liver injury from Nuedexta, and the fact that liver toxicity from Q is thought to be reversible and readily diagnosed in the early stages, I conclude that this risk can be adequately addressed through labeling.

5. Adverse Drug Interactions based on CYP Inhibition

In the 2006 Approvable Letter, the Division expressed concern that inhibition of CYP2D6 by Nuedexta would increase adverse drug interactions, as follows. The Approvable Letter stated the following:

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.

The sponsor acknowledges that Nuedexta can alter the exposure to concomitant medications, but argues that this risk can be adequately addressed through labeling.

Dr. Jillapalli, while agreeing that Nuedexta, as a CYP2D6 inhibitor would increase the potential for adverse drug interactions, found little evidence in the safety database that patients that received concomitant CYP2D6 or CYP3A4 inhibitors, opiates, or drugs known to affect QT interval experienced an increased incidence of adverse events. He therefore concludes that the risk could be adequately addressed through labeling.

CDTL: I agree with Dr. Jillapalli that while Nuedexta, as a CYP2D6 inhibitor, can contribute to adverse drug interactions, this risk appears unexceptional in the context of overall risk of drug interaction in a population with high utilization of multiple types of medication; clearly such a population take many other drugs that inhibit CYP2D6. At the February 2007 Type C meeting with the sponsor, the Division previously agreed that CYP2D6 inhibition was, of itself, not an unacceptable safety risk, and would be acceptable if in this population safety could otherwise be demonstrated. Dr. Jillapalli's review of safety data did not find evidence that patients on Nuedexta experienced an

increase in adverse events from adverse drug interactions. I therefore find that the risk of CYP2D6 inhibition from Nuedexta can be adequately addressed through labeling.

6. *Cardiac Risk:*

In the 2006 Approvable Letter, the Division noted that QTc prolongation and risk of torsades de pointes (TdP) from Q was a safety concern that would need to be addressed before consideration of approval. The Division was also concerned about other potential adverse effects of Q, particularly on atrio-ventricular conduction, and in patients moving in and out of atrial fibrillation/flutter. The Approvable Letter stated the following:

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 msec). 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.

The sponsor argues in their Complete Response that the lower exposure to Q from the DM 30/ Q 10 and DM 20/ Q 10 formulations minimizes risk of adverse cardiac affects of Q. Furthermore, the sponsor states that while the new formulation has the potential to increase QTc, these changes are predictable. The sponsor concludes that labeling is adequate to address the QTc prolongation.

Dr. Jillapalli notes that the new formulations result in about one-third the exposure to Q as the previous formulation with 30 mg Q. He finds that while DM 30 mg/Q 10 mg clearly prolongs QT interval, that there is some merit to the applicant’s argument that the degree of QT prolongation is finite and predictable. He notes that in the double-blind phase of Study 123

there were no subjects with a change from baseline of ≥ 60 msec in QT interval. He notes the following pattern of QTcF 30–60 msec outliers: 10% in DM 30 mg/Q 10 mg, 2% in DM 20 mg/Q 10 mg, and 4% in placebo. **CDTL: The 30-60 msec outlier data was underpowered to show differences with much precision, but it is not unreasonable to consider that the average incidence of outliers in the DM/Q arms combined is almost the same as the incidence in placebo. While it is unlikely that the observed lower incidence of outliers in the 20/10 arm compared to placebo is due to anything other than random variation, that this was observed increases confidence in the safety of the 20/10 dose.**

Dr. Jillapalli also analyzed the incidence of syncope and palpitations in the clinical database as possible manifestations of cardiac arrhythmia. He notes that across all DM/Q combinations there were few subjects who experienced syncope/ presyncope or palpitations as an SAE or reason for discontinuation, and in those cases that occurred pre-existing risk factors confounded causality assessment. Dr. Jillapalli is reassured that 3 of 4 subjects who experienced SAEs related to syncope or palpitations continued on with DM/Q treatment without apparent recurrence of adverse effects. In the double-blind phase of Study 123, Dr. Jillapalli notes that 4% of subjects in the 30/10 arm experienced syncope/presyncope, versus only 1% in the 20/10 and placebo arms. **CDTL: While again this data was underpowered to show differences with much precision, the combined incidence in the DM/Q arms is not much higher than the placebo arm, and the 20/10 arm, considered alone, is the same as the placebo arm, which adds further reassurance of safety for the lower dose in particular.**

Dr. Jillapalli, considering also the conclusions of the Cardiology Division, finds that the cardiac risk of Nuedexta can be adequately addressed through labeling.

CDTL: I agree with Dr. Jillapalli that the cardiac risk of Nuedexta can be adequately addressed through labeling. This conclusion is addressed further below.

QT-IRT and Cardiology Consult

The primary review of the thorough QT study was conducted by Dr. Hao Zhu of the QT-IRT team. DNP additionally requested consultation from the Cardio-Renal Division on the cardiac safety of Nuedexta. The primary consultant was Dr. Suchitra Balakrishnan. Dr. Norman Stockbridge provided concurrence for both reviews.

Background

In the 2006 Approvable Letter, the Division noted that QT prolongation and risk of TdP from Q in the combination was a safety concern that would need to be addressed before consideration of approval. The Division was also concerned about other potential adverse effects quinidine, particularly as it might effect atrio-ventricular conduction, and patients moving in and out of atrial fibrillation/flutter.

The Division noted that for the DM 30 mg/Q 30 mg combination, the thorough QT (TQT) study found a maximum mean QTcF increased of about 10 msec, with a 95% bound of about 15 msec. Additionally, over 4% of EKGs during DM/Q treatment showed QTc increased

between 30- to 60 msec, versus about 1% during placebo treatment. The Division acknowledged that the sponsor had argued that Agency guidance stated that this degree of QT prolongation is ‘inconclusive,’ but the Division, particularly noting that Q is known to cause TdP, concluded that these findings did, in fact, raise serious concern about risk of TdP from 30 mg Q. The Division expressed further concern that Q is a CYP3A4 substrate, and that the wide use of drugs that are CYP3A4 inhibitors would lead to even higher Q levels, and greater risk of TdP. At the 2-fold supratherapeutic dose containing 60 mg Q, QTc was increased by a mean of 18 msec, with a 95% bound of 25 msec.

Based in part on the sponsor’s observations that a 10 mg dose of Q converted 6/7 extensive metabolizers (EMs) to poor metabolizers (PMs), the Division concluded the Approvable Letter with the suggestion that a lower dose of Q (and DM) be explored to determine if a product that is equally effective but safer could be developed.

TQT Studies

The sponsor reformulated the DM/Q combination to contain 10 mg Q, and either 30 or 20 mg DM. In the sponsor’s Complete Response, data was submitted from a newly completed TQT study (08-AVR-126) of the DM 30 mg/Q10 mg formulation. Dr. Zhu notes that adequate QT data about supratherapeutic exposure is provided by the previous TQT study (05-AVR-119) which examined both DM 30/Q 30 and DM 60/Q 60 doses.

Dr. Zhu concludes that the DM 30/Q 10 formulation increases QTc by about 10 msec, with a 95% upper confidence bound of about 13 msec. The sponsor argues that the 10 mg Q dose is a pure IKr blocker, and that other known effects of Q on the heart, such as decrease in atrioventricular (AV) conduction and heart rate or ‘vagolytic’ effects are absent because the effects are mediated by sodium/calcium blockade, which only occurs at higher doses. To test this claim, mean changes and 25% outliers in PR and QRS intervals and in HR were examined by Dr. Zhu for the high-dose study (30/30 and 60/60 DM/Q). While there was a trend for decreased HR, Dr. Zhu’s analysis supported the sponsor’s contention that Q at 10 mg is unlikely to affect cardiac function other than through QTc prolongation.

Cardiology Review

The clinical assessment of the TQT studies, along with analysis of data including non-clinical and clinical studies of DM/Q, was addressed by Dr. Balakrishnan, who conducted the primary Cardiology review. Based on QTc, Dr. Balakrishnan concludes that ‘some slight risk for QT prolongation related AEs exists even at this dose,’ and that this risk would have to be considered in risk vs. efficacy considerations for this indication and population.

In addition to QTc, Dr. Balakrishnan considered in detail the other available non-clinical and clinical findings related to the overall cardiac safety of DM/Q, to determine if there was evidence of adverse events related to QTc prolongation or other cardiac effects of Q.

Dr. Balakrishnan found no clear evidence of cases of TdP or significant ventricular arrhythmias in the clinical studies, noting however, that the database was of modest size such that sensitivity for rare events was poor. She examined the 92 deaths that occurred in the overall development program (most patients on higher Q dose than 10 mg) for evidence of

cardiovascular causes, including particular focus on 7 patients whose deaths were considered sudden. All 7 of these patients were in open-label study 02-AVR-107, in which higher dose DM 30/Q30 was used. Dr. Balakrishnan concludes that while sudden cardiac death related to DM/Q can not be completely excluded, attribution to either underlying disease or other factors unrelated to DM/Q seemed reasonable.

Dr. Balakrishnan identified 4 subjects on DM/Q and 1 on placebo with QTc shift from <500 msec at baseline to ≥500 msec during treatment. Importantly, all 4 of the DM/Q subjects were treated with *higher Q* dose combinations than 10 mg. Dr. Balakrishnan notes, however, that infrequent ECG sampling and discrepancies between study site and central core lab ECG readings for one subject raise concerns that some outliers might not have been captured.

In study 07-AVR-123, which examined the 10 mg Q formulations, Dr. Balakrishnan notes that the number of cardiac adverse events were low, and that there were no adverse events related to QT prolongation. She notes that AEs related to cardiac disorder in the double-blind phase occurred in 3.6%, 2.8%, and 1.8%, respectively, in patients on DM 30/Q 10, DM 20/Q10, and placebo, as listed in the table below (from table 25, Cardiac Safety Report).

Adverse Events by System Organ Class and Preferred Term
 (Safety Population)

System Organ Class Preferred Term	AVP-923-30 (N=110) n (%)	AVP-923-20 (N=107) n (%)	Placebo (N=109) n (%)	Overall (N=326) n (%)
CARDIAC DISORDERS	4 (3.6%)	3 (2.8%)	2 (1.8%)	9 (2.8%)
SINUS BRADYCARDIA	1 (0.9%)	1 (0.9%)	0	2 (0.6%)
PALPITATIONS	0	1 (0.9%)	1 (0.9%)	2 (0.6%)
ATRIOVENTRICULAR BLOCK FIRST DEGREE	1 (0.9%)	1 (0.9%)	0	2 (0.6%)
VENTRICULAR EXTRASYSTOLES	0	0	1 (0.9%)	1 (0.3%)
TACHYCARDIA	1 (0.9%)	0	0	1 (0.3%)
SINUS TACHYCARDIA	1 (0.9%)	0	0	1 (0.3%)
MYOCARDIAL INFARCTION	0	0	1 (0.9%)	1 (0.3%)
ATRIAL FIBRILLATION	0	1 (0.9%)	0	1 (0.3%)

Note: A patient who reported 2 or more adverse events with the same preferred term was counted only once for that term.
 A patient who reported 2 or more adverse events with different preferred terms within the same system organ class was counted only once in the system organ class total.

Dr. Balakrishnan also notes that syncope and presyncope, which can have a cardiac origin, occurred at a similar rate across arms: 2 patients on DM 30/Q10, 3 patients on DM 20 / Q10, and 2 patients on placebo.

Dr. John Koerner reviewed non-clinical literature related to the *non*-QTc mediated cardiac effects of Q. He concludes that Q appears to be more potent on hERG and IKr than on sodium and calcium currents, which is consistent with QTc prolongation as the major concern, with lesser concern for other electrophysiological effects (e.g. atrioventricular block, decreased conduction velocity, decreased heart rate or blood pressure).

CDTL Discussion:

I agree with the interpretation and general recommendations for labeling of the Cardiology team. I interpret their overall conclusions as follows:

- **Even for high-dose formulations (Q 30 mg or higher), serious adverse events and deaths were not clearly associated with DM/Q.**
- **A slight risk of QTc-related AEs exists for the DM 20/Q 10 formulation.**
- **Other cardiac adverse effects of 10 mg Q are unlikely in patients without underlying cardiac disease, but patients with specific cardiac conditions are at risk and should not take the drug. Pro-arrhythmic risk from Nuedexta may be higher in some populations not studied.**
- **While cardiac risk from the low-dose formulation was not identified, power to detect AEs was low.**
- **Risk mitigation strategies are warranted for QTc prolongation.**

Specific suggestions for labeling were as follows:

- **Contraindications: long-QT syndrome, use with drugs that prolong the QT interval and that are metabolized by CYP2D6, and heart failure²**
- **ECG and clinical monitoring for patients taking QT-prolonging drugs, and correction of modifiable risk factors (e.g. hypokalemia) before initiating treatment**
- **Caution with strong CYP-3A4 and CYP-2D6 inhibitors.**

7. *Generalizability of Safety Findings to Other Populations*

In the 2006 Approvable Letter, the Division expressed the following concern about safety of Nuedexta across different patient populations:

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.

The sponsor seeks (b) (4) PBA, and notes the Division stated at a meeting on 7/16/07 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 sponsor notes that efficacy was demonstrate in both ALS and MS, and that in the overall database 85% of patients had either ALS or MS as the underlying condition, while 5% had stroke, 2% traumatic brain injury, and 2% dementia. The sponsor indicates their intention to educate prescribers. (b) (4) about the medical definition of PBA and those patients to which it applies. The sponsor considers that PBA occurs from ALS, MS, stroke, TBI, and “a number of other neurological conditions” that are not further specified.

Dr. Jillapalli notes that there is no controlled-trial experience with Nuedexta in diseases other than ALS and MS, and that the only exposure of patients with other underlying conditions was

² congestive heart failure reduces quinidine’s apparent volume of distribution and requires a reduction in dosage to prevent toxicity.

in open-label study 107, in which there was limited enrollment of patients who had diseases other than ALS or MS, as shown below:

ALS	MS	Other	AD	Stroke	TBI
176	223	73	14	45	21

Dr. Jillapalli expresses concern that subjects with several of these diseases are older and have additional intercurrent illnesses, particularly cardiac disease, and that without controlled-trial data it would be difficult to identify adverse drug effects from DM/Q.

Dr. Jillapalli cites a recent review (Wortzel HS et al, 2008) that estimates that the majority (and perhaps a large majority) of patients with PBA have Alzheimer disease as the underlying condition:

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	10%	9,000 - 24,000
	Southern US		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

Dr. Jillapalli therefore concludes that Nuedexta should be approved specifically for the treatment of PBA in ALS and MS subjects only.

CDTL: During development of Nuedexta, the sponsor and Division discussed what constitutes the symptoms and signs of the condition under study, what other patient groups beside ALS and MS the condition occurs in, and what is the most appropriate name to use in drug labeling for the condition. While a large number of underlying neurological diseases cause a disorder of affect, there remains considerable uncertainty about if these disorders are essentially the same, or instead differ in more fundamental ways. Similarly, there is considerable uncertainty about what patient populations are subsumed under a given disease name. The sponsor is making the argument that the name 'PBA' does *not* include, for example, patients with disordered affect resulting from AD. Thus, they defend the appropriateness of a 'global' claim in PBA by defining PBA narrowly, as occurring mainly in MS, ALS, stroke, and traumatic brain injury (TBI).

In the post-SPA Type A meeting of July 16, 2007, the Division stated that for the sponsor to use a seemingly broad term for PBA, like 'involuntary emotional expression disorder (IEED)' the sponsor would have to show at least that Nuedexta was safe and effective in the disordered affect that can occur in AD. The Division did express openness to considering a global claim for PBA based on the narrow definition of the condition as including MS, ALS, stroke and TBI patients:

“We have been considering your definition of PBA/IEED, and your argument that it occurs in a wide variety of neurological diseases, including Alzheimer Disease. The evidence you have presented to date may not be sufficient for us to determine the relationship between the ‘emotional lability’ that has been described in Alzheimer and some other types of cerebral disease, with what has been termed ‘pathological (pseudobulbar, forced, spasmodic) laughing and crying’ which appears to occur mainly in MS, ALS, bilateral stroke, and traumatic brain injury. We refer you, for example, to Adams and Victor’s Principles of Neurology Eight Edition (page 445), which states that “a patient whose cerebrum has been damaged – for example by a series of vascular lesions, may suffer...an emotional lability...[that] while excessive, does not reach the degree of forced emotionality of the special form of lability described as pseudobulbar.”

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.”

However, while the sponsor claims in their Complete Response that PBA is a condition limited to MS, ALS, stroke, TBI, and ‘a number of other neurological conditions’ ^{(b) (4)} the sponsor nearly simultaneously co-authored a paper reporting the results of study 123 (Pioro et al., Ann Neurol 2010) that contained an introduction that explicitly defines PBA as including AD, as follows:

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(from Pioro et al, 2010)

Also, as indicated by usage in other current scientific literature, PBA is generally accepted as a term that includes patients with underlying AD (e.g. Strowd et al, J. Neurol 2010). Additionally, PBA and IEED are consistently defined as interchangeable in current literature (e.g. Phuong et al., Parkinsonism and Related Disorders 2009).

I agree with Dr. Jillapalli that Nuedexta should be approved for use in PBA from underlying ALS and MS. In addition to unknown cardiac safety of Q from Nuedexta in elderly patients, the Division has also expressed concern about potential adverse effects of DM on memory in patients with AD. In addition, adverse drug interactions remain a

concern in AD; in study 122, a PK interaction study of DM 30 mg/ Q 30 mg and memantine, dizziness was significantly worsened by the combination (as measured by VAS, 90% CI). Therefore, before approval of Nuedexta under an indication that would include AD, it would be important to have safety data on concomitant use with drugs used to treat AD.

While the Division expressed willingness to consider approval for the generalized indication of PBA, this was contingent, at minimum, on the term reflecting the appropriate patient population. However, since the term PBA encompasses a broader patient population than safety and efficacy data supports, I find that it is not acceptable for labeling.

Note: the safety issues below do not represent issues from the 2006 Approvable Letter, but rather new analysis of data from study 123.

Thrombocytopenia and Other Hypersensitivity Reactions

Thrombocytopenia is a labeled adverse effect of Q, and was considered an adverse event of special interest in Dr. Jillapalli's review. However, Dr. Jillapalli did not identify any cases of Q-associated thrombocytopenia in the overall safety database, including study 123. He notes that one subject's platelet count dropped from 150,000 to 101,000 during hospitalization, but this appeared due to heparin-associated antibodies (subject #107-034-052).

CDTL: Thrombocytopenia from quinidine and (related drugs like quinine) is well-documented, but there was essentially no evidence of its occurrence in the Nuedexta database. While the possibility of thrombocytopenia as a rare adverse effect of Nuedexta can not be excluded, I find that the risk can be adequately addressed through labeling. In particular, while thrombocytopenia from Q can be serious and even fatal if not recognized, it generally resolves quickly once Q is withdrawn.

Serious Adverse Events:

Dr. Jillapalli notes that no non-fatal SAE in the placebo-controlled portion of study 123 was experienced by more than a single patient (table below from his review):

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

	D20/Q10		D30/Q10		Any DM/Q		Placebo	
	N = 68		N = 65		N = 133		N = 64	
ALS subjects with PBA	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
Dextromethorphan/Quinidine (Zenvia)								
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).

While relationship to drug can not be excluded, Dr. Jillapalli found the data unremarkable.

CDTL: I agree.

Withdrawals due to Adverse Events:

In study 123, 8% of patients in the 20/10 arm discontinued due to adverse events, compared to 5% in the 30/10 arm, and 5% in the placebo arm. While relationship to drug can not be excluded, Dr. Jillapalli found the data unremarkable.

CDTL: I agree.

Common Adverse Events:

Common adverse events from study 123 are shown in the table below. Dr. Jillapalli concluded that dizziness, dry mouth, and urinary tract infection were potentially dose-related adverse effects of Nuedexta.

Body System	DM 20 mg/ Q 10 mg (N=107) n (%)	DM 30 mg/ Q 10 mg (N=110) n (%)	Placbo (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			
Cough	5 (4.7)	4 (3.6)	2 (1.8)

CDTL: I agree, and concluded that the common adverse effects can be adequately addressed through labeling. (See also discussion of dizziness under issue #3 above).

Laboratory tests:

CDTL: Dr. Jillapalli's findings were generally unremarkable. (See additional discussion of hepatotoxicity under issue #4 above).

9. Advisory Committee Meeting

No advisory committee meeting was held.

10. Pediatrics

The Nuedexta pediatric plan was discussed at the Pediatric Review Committee Meeting on October 13, 2010. A waiver for pediatric patients age 2 and under was deemed acceptable, with deferral of studies for older children.

11. Other Relevant Regulatory Issues

Division of Scientific Inspections (DSI)

Dr. Antoine El-Hage conducted the DSI review. He notes that in the complete response the sponsor submitted results from one pivotal study, 07-AVR-123. Two investigator sites were inspected, each with 22 subjects listed. Dr. El-Hage lists in his review specific violations and discrepancies discovered, and concludes that they were isolated in nature and unlikely to significantly impact data integrity.

CDTL: I and Dr. Jillapalli reviewed the regulatory violations and agree that they are unlikely to significantly impact the safety and efficacy conclusions.

Executive CAC Committee

The committee concluded that the rat carcinogenicity study was adequate and that there were no biologically significant neoplastic findings for DM and Q, alone or in combination, under the conditions tested.

Controlled Substance Staff (CSS)

The CSS review was conducted by James Hunter, with secondary review by Dr. Lori Love.

In the 2006 Approvable Letter, the Division communicated the following Abuse Liability comments to the sponsor:

In addition to the proposed educational plan under your proposed Risk Minimization Plan (RiskMAP), 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; provide information on the frequency of reporting to the FDA on the outcomes of the proposed RiskMAP; and propose interventions if abuse or misuse of the product is determined.

The CSS review found that the abuse potential of Nuedexta could not be determined because the sponsor did not submit adequate animal or human data for this assessment. However, because the product will be available by prescription only, and for a narrow indication, CSS concluded that the abuse potential of Nuedexta will be less than currently marketed, widely available, over-the-counter products containing DM. CSS further concluded that there was insufficient data to support a claim of lower abuse potential of Nuedexta compared to DM alone.

12. Labeling

Division of Medication Error Prevention and Analysis (DMEPA)

Loretta Holmes conducted the primary review of the proprietary name. DMEPA found the name Nuedexta acceptable for this product.

CDTL: The proprietary name is acceptable to DNP.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

There are no unresolved issues from the 2006 Approval Letter, and no new safety or efficacy concerns raised by the new efficacy study, 07-AVR-123. I therefore recommend approval of Nuedexta.

I do not find any interpretable evidence of a difference in efficacy between the 30 mg DM and 20 mg DM formulations. Dizziness is likely more common with the 30 mg formulation, and while not clearly associated with an increased risk of fall in the available safety database, remains of particular concern in this population. I therefore recommend approval of the 20 mg DM dose only.

- Risk Benefit Assessment

Nuedexta both decreased average laughing and crying episodes, and increased number of days that treated patients were symptom-free. I therefore conclude that Nuedexta provides clinically meaningful benefit in PBA.

Even though Q has been reduced to 10 mg in the new formulation, Nuedexta is still associated with prolongation of QTc, and likely with a very small risk of torsade de pointes, particularly in patients with other risk factors, such as concomitant use of other QTc-prolonging drugs. However, I find that this risk is acceptable in the context of the drug's benefits, and that the risk can be adequately addressed through labeling.

In study 07-AVR-123, there were 3 deaths of ALS patients in each DM/Q arm, and only 1 death in the placebo arm. However, detailed evaluation of the circumstances of each death revealed essentially no evidence of causal association with Nuedexta. Similarly, while Nuedexta is clearly associated with some adverse effects (like dizziness and QTc prolongation), there was essentially no evidence that these adverse effects led to the imbalance in deaths observed. Importantly, an imbalance in deaths of the size observed (favoring either drug or placebo) is *more likely than not* to occur in a study of this design, even if there is no actual difference among treatment arms. I therefore conclude that for FDA approval, the risks of Nuedexta are acceptable in the context of its benefits.

- Recommendation for Postmarketing Risk Management Activities

I find that standard pharmacovigilance methods (e.g. reporting and analysis of spontaneous adverse event reports) are adequate for postmarketing risk management.

- Recommendation for Postmarketing Requirements

Nonclinical

The nonclinical team concluded that approval be contingent on formal agreement to submission of protocols and conduct of the following phase 4 studies:

- juvenile neurotoxicology study in rats
- repeat pre- and post-natal development study in rats
- embryo-fetal development study in rabbits

Pediatric

Pediatric studies under PREA will be waived for children ≤ 2 years, and deferred for children (b) (4)

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/s/

RONALD H FARKAS
10/28/2010