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RESEARCH**

APPLICATION NUMBER:

021879Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Dextromethorphan(DM) + Quinidine(Q)
NDA:	21-879
PRODUCT (Brand Name):	Zenvia®
DOSAGE FORM:	Capsules
DOSAGE STRENGTHS:	DM 30mg/Q 10mg, DM 20mg/Q 10 mg
INDICATION:	Pseudobulbar affect (PBA)
NDA TYPE:	Complete Response (Priority)
SUBMISSION DATES:	4/23/2010, 5/5/2010, 6/28/2010, 7/16/2010, 7/19/2010, 7/20/2010, 8/5/2010, 8/23/2010, 9/1/2010
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1.0 EXECUTIVE SUMMARY

The sponsor is seeking for approval of Zenvia (Dextromethorphan (DM)/ Quinidine (Q), previously called AVP-923 or Neurodex) for the treatment of Pseudobulbar Affect (PBA). This submission (NDA 21879) is a complete response (CR) to the deficiencies listed in the Approvable Letter issued on 10/30/2006 for Zenvia. The original application for Zenvia (DM30mg/Q30mg) was submitted on 1/27/2006. Due to the safety concern of QT prolongation, the agency recommended the sponsor conducting a clinical efficacy and safety trial with lower doses of Q (15mg or 10mg). This CR was submitted on 4/23/2010 and was under the priority review classification. The (b)(4) product is a gelatin capsule, with (b)(4) strengths of DM 30 mg/ Q 10 mg (Zenvia 30/10) and DM 20 mg/ Q 10 mg (Zenvia 20/10). The (b)(4) dosing regimen is one capsule (at either dose) per day taken orally for the first 7 days. On the eighth day and thereafter, the daily dose should be increased by taking a second capsule approximately 12 hours after first dose.

Zenvia is a combination drug product containing two currently available drugs: DM and Q. It is known that DM is quickly eliminated due to extensive metabolism yielding low exposure even at high doses. As DM is metabolized primarily through CYP2D6 and Q is a potent inhibitor of CYP2D6, the sponsor utilized enzyme inhibitory property of Q to increase the exposure of DM without needing to apply high doses of both components. The exact mechanism of action of DM for PBA is unknown; however, the sponsor states it is postulated to act by controlling glutamate excitatory activity through the modulation of sigma-1 and *N*-methyl-D-aspartate (NMDA)-receptor activities.

In this submission, the sponsor submitted one new efficacy pivotal clinical study report, three clinical pharmacology/biopharmaceutic study reports, one population pharmacokinetic analysis, one thorough QT report and four in vitro inhibition/induction study reports to support the appropriate dosing, safety and the proposed claim for Zenvia.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed this submission and found it is acceptable from a Clinical Pharmacology point of view provided the sponsor agrees with the Agency's labeling recommendations.

Labeling recommendations outlined in the Detailed Labeling Recommendations section of the review should be conveyed to the sponsor.

1.2 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

In the present submission, the following clinical pharmacology related studies had been submitted and reviewed:

- 06-AVR-121 A DDI study with paroxetine
- 06-AVR-122 A DDI study with memantine

- 07-AVR-123 An efficacy pivotal study for lower doses (including PK)
- 07-AVR-125 A PK study with different dose formulation and regimen
- 08-AVR-126 A thorough QT study
- 09-AVR-127 A population PK study
- DMQ-142 An in vitro inhibition study for DM
- DMQ-143 An in vitro inhibition study for Q
- DMQ-144 An in vitro induction study for DM
- DMQ-145 An in vitro induction study for Q

The overall summary of the clinical pharmacology and biopharmaceutics findings are as follows:

Intrinsic Factors:

Population Pharmacokinetics:

The sponsor conducted the population PK analysis demonstrating that none of the following covariates, height, weight, BMI, age, race and gender, were considered significantly correlated with any of the PK parameters of DM, DX, and Q. *The sponsor's conclusion is consistent with that shown in the original submission and the sponsor's population PK model is acceptable.*

Pharmacogenetics:

CYP2D6 poor metabolizers (PMs; 5-10% of the Caucasian population) potentially do not benefit from the CYP2D6 inhibitory properties of Q. PK, efficacy, and safety endpoints were evaluated according to CYP2D6 metabolic status in 89% of subjects in 07-AVR-123 (N=290). CYP2D6 PMs were excluded from or represented a small proportion of the population in clinical studies that were previously submitted. Considering the totality of data, DM exposures in PMs receiving DM monotherapy or DM/Q tend to be similar to or greater than DM exposures in extensive metabolizers (EMs) receiving DM/Q. Q does not further inhibit CYP2D6 metabolism in PMs. Genetic effects on efficacy or safety findings are inconclusive in 07-AVR-123 given the small sample size, but no consistent differences were apparent across the genotype groups. The Q component may expose PMs to an unnecessary risk since Q is not adding any benefit. Prescribers should consider the potential risk for Q-related AEs relative to the benefit of administering the DM/Q combination product (vs. DM alone) in known CYP2D6 PMs.

Extrinsic Factors:

Drug-drug Interactions:

- **Paroxetine:** When DM 30 mg/Q 30 mg was added to steady state of paroxetine, 1.7-fold increase of paroxetine exposure was observed, while there was no significant change for DM and Q. There was 2.3-, 1.5- and 1.4-fold increase of AUC_{0-τ} for paroxetine, DM and Q, respectively when paroxetine was added to

steady state of DM/Q. Consideration should be given to initiating treatment with a lower dose of paroxetine if given with Zenvia. The dose of paroxetine can then be adjusted based on clinical response, however dosage above 35mg/day is not recommended.

- **Memantine:** Coadministration of 10 mg BID memantine with DM 30 mg/Q 30 mg BID resulted in no significant changes in PK of memantine, DM, DX and Q. Although both DM and memantine are antagonists of the NMDA receptors, no significant PD changes were observed except that the incidence of dizziness was greater when DM/Q was added to memantine than when memantine was given alone, as measured by VAS Dizziness. No dose adjustment is needed when memantine is coadministered with Zenvia.

In vitro inhibition/induction potential:

Inhibition:

- DM showed no inhibition potential for CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 at clinically relevant concentrations.
- Q showed no inhibition potential for CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1 and 3A4 at clinically relevant concentrations except that it is a potent inhibitor for CYP2D6.

Induction:

- Both DM and Q showed no induction potential for CYP1A2, 2B6 and 3A4 at therapeutic concentrations.

Biopharmaceutics:

The (b) (4) Zenvia (DM 30 mg/Q 10 mg and DM 20 mg/Q 10 mg capsules) are identical to those used in the pivotal Phase 3 study (07-AVR-123), which established safety and efficacy at these doses.

These DM30/Q10 and DM20/Q10 are composition-proportional to the DM30/Q30, which was used in the clinical pharmacology studies in the original submission.

Thorough QT results:

The effect of therapeutic dose of Zenvia 30/10 on QTc prolongation was evaluated in a randomized, double-blind (except for moxifloxacin), placebo-, and positive-controlled (400-mg moxifloxacin) crossover thorough QTc study in 50 fasted normal healthy men and women with CYP2D6 extensive metabolizer (EM) genotype. The results showed that the maximum mean difference of QT interval between Zenvia 30/10 and placebo was 10.2 ms with 95% CI upper bound of 12.6ms.

Analytical Assays:

The assays used to measure DM, DX and Q are considered validated.

Findings from the original review which are still applied to the whole NDA:

- The selection of Q dose was based on the urinary DM/DX ratio in Phase 1 studies. The selected dose (30 mg Q) converted 8/8 extensive metabolizers of drugs metabolized by CYP2D6 (EMs) to the poor metabolizer (PM) phenotype. It should be noted that a 10 mg dose of Q converted 6/7 subjects to PMs. This resulted in a mean 20-fold increase in exposure compared to DM alone. However, a dose-response evaluation for efficacy has not been conducted, and the efficacy of the Q/DM combination that would result in lower exposures has not been thoroughly evaluated.
- Exposure to DM (C_{max} or AUC) or Q (C_{max}) was not increased in subjects with mild/moderate renal impairment after NEURODEX administration for 6 days, and an increase in DX exposure was within the range of concentrations observed when DM is given at an OTC dose in the absence of Q. Q AUC increased by approximately 3%. No dosage adjustment is needed for mild-moderate renal impairment. NEURODEX has not been evaluated in severe renal impairment.
- Exposure to Q was not increased in mild to moderate hepatic impairment. Exposure to DM was increased less than 20% in mild to moderate hepatic impairment. There was an increase in common adverse events in subjects with moderate impairment. No dosage adjustment is needed for mild-moderate hepatic impairment, but in moderate impairment patients should be closely evaluated for adverse events. NEURODEX has not been evaluated in severe hepatic impairment.
- Quinidine is a strong inhibitor of CYP2D6. An interaction study showed a 5-6 fold increase in exposure to the sensitive CYP2D6 substrate desipramine after coadministration with NEURODEX.
- Quinidine is a substrate of CYP3A4. The literature shows a 1.6-fold increase in Q C_{max} and a 2.4-fold increase in AUC in the presence of a strong CYP3A inhibitor, itraconazole, *in vivo*.
- BE was demonstrated for AUC and C_{max} for DM and for Q following administration of NEURODEX under fasting conditions or with a high fat meal. NEURODEX can be taken without regard to meals.

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2.0 QUESTION BASED REVIEW

Most clinical pharmacology/biopharmaceutics studies were reviewed in the original submission. This review will mainly focus on the newly submitted reports to avoid repetition. The QBR section of the clinical pharmacology review for the original submission is attached in the Appendix II.

2.1 GENERAL ATTRIBUTES

Zenvia is a combination of two commercially available drugs: dextromethorphan hydrobromide (DM) and quinidine sulfate (Q). Two different dosages, 30 mg or 20 mg of DM and 10 mg of Q (Zenvia 30/10 and Zenvia 20/10), are developed ^{(b) (4)}. DM is an OTC antitussive to be given 30 mg every 6 to 8 hours up to 120 mg per day. Q is indicated for reduction of frequency of atrial fibrillation/flutter beginning at doses of 200 mg every 6 hours, conversion of atrial fibrillation/flutter to sinus rhythm beginning at doses of 400 mg every 6 hours, and treatment of *P. falciparum* malaria.

2.1.1 *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?*

Dosage Form/Strengths: DM 30 mg/Q 10mg and DM 20 mg/Q 10mg capsules

Indication: Zenvia (30/10 and 20/10) is indicated for the treatment of pseudobulbar affect (PBA).

Pharmacologic Class: **DM:** antagonist of the *N*-methyl-D-aspartate (NMDA) receptor and modulator of sigma-1 receptor

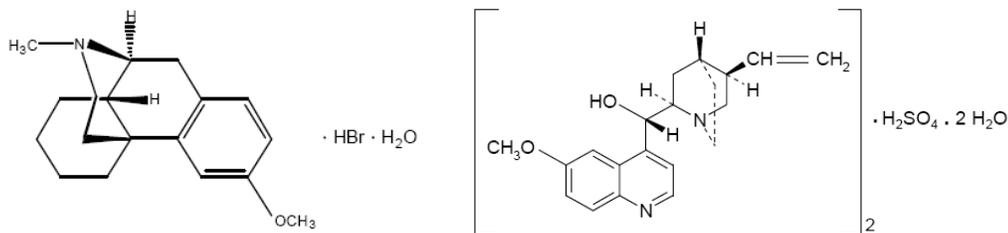
Chemical Name: **DM:** Morphinan, 3-methoxy-17-methyl-, (9 α , 13 α , 14 α)-, hydrobromide monohydrate.
Q: Cinchonan-9-ol, 6'-methoxy-, (9 S) sulfate (2:1), (salt), dehydrate.

Molecular formula: **DM:** C₁₈H₂₅NO.HBr.H₂O. Its molecular weight is 370.33.
Q: (C₂₀H₂₄N₂O₂)₂. H₂SO₄. 2H₂O. Its molecular weight is 782.96.

Chemical structure:

DM:

Q:



Formulation: An immediate release solid oral-dosage form (hard gelatin capsule) with two strengths (Zenvia 30/10 and Zenvia 20/10). The qualitative composition of both strengths is the same. The compositions (b) (4) are identical to those used in the Phase 3 study that established safety and efficacy at these doses. The composition of Zenvia capsules is shown in the Table below. Amounts of actives are presented in the anhydrous form.

Table 2.3.P.1-1 Components and Composition of Zenvia Capsules

Ingredient	Quality Standard	Function	Amount per Capsule (mg)			
			DM 20/Q 10	DM 30/Q 10		
Dextromethorphan Hydrobromide	USP, EP	Active	20.00*	30.00*		
Quinidine Sulfate	USP, EP	Active	10.00*	10.00*		
Croscarmellose Sodium	NF, EP, JP	Dispersant	(b) (4)			
Microcrystalline Cellulose (b) (4)	NF, EP, JP	Filler				
Lactose Monohydrate (b) (4)	NF, EP, JP	Filler				
Colloidal Silicon Dioxide	NF, EP, JP	Glidant				
Magnesium Stearate	NF, EP, JP	Lubricant				
					(b) (4)	
					(b) (4)	
Total			335	335		

EP = European Pharmacopeia; JP = Japanese Pharmacopeia; NF = National Formulary; USP = United States Pharmacopeia.

(b) (4)

2.1.2 What are the proposed dosages and route of administration?

The (b) (4) starting dose is one Zenvia 20/10 (b) (4) capsule per day for first 7 days; starting on the eighth day, the daily dose should be increased by taking a second capsule of ZENVIA 20/10 (b) (4) approximately 12 hours after taking the first dose. The proposed indication is the treatment of Pseudobulbar Affect (PBA).

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the clinical studies used to support dosing or claims and what are their design features?

This is a complete response for the deficiencies outlined in the Approvable Letter for Zenvia on 10/30/2006. The content of this submission includes one new pivotal efficacy study, three clinical pharmacology/biopharmaceutics studies, one population PK study, one thorough QT study and four in vitro inhibition/induction studies.

The pivotal study (07-AVR-123) was designed to evaluate the efficacy of lower doses of Q (DM 30 mg/Q 10 mg and DM 20 mg/Q 10 mg) per the Agency's recommendations in the Approvable Letter to reduce the potential risk of the exposure related QT prolongation by Q. The clinical pharmacology program included two in vivo drug-drug interaction studies. One DDI study was with paroxetine (06-AVR-121), a CYP2D6 substrate and a potent CYP2D6 inhibitor. The other was DDI study with memantine (06-AVR-122) due to the potential PD interaction as both DM and mamantine are antagonists of the *N*-methyl-D-aspartate (NMDA) receptors. One formulation/combination evaluation PK study (07-AVR-125) supported the selected doses (Zenvia 30/10 and Zenvia 20/10) to be given BID as maintaining doses. The detailed design features are provided in section 2.4.3.

2.2.2 What are the clinical endpoints and how are they measured in clinical pharmacology and clinical studies?

For the pivotal clinical study (07-AVR-123), the following variables were used in the evaluation of effectiveness.

The 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 key secondary efficacy endpoints were:

- mean change in CNS-LS score for the assessment of PBA status: CNS-LS score is a 7-item self-report questionnaire that measures the frequency and severity of PBA episodes
- mean change in Neuropsychiatric Inventory (NPI) score: NPI is a retrospective (to 1 month) caregiver-informant interview assessing frequency and severity of 12 neuropsychiatric symptom domains. The NPI score is based on the sum of the

- severity ratings (0 = absent, 1 = mild to 3 = severe). The 12 neuropsychiatric symptom 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.
- mean change in SF-36 Health Survey Medical Outcomes (SF-36) score: 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.
 - mean change in BDI-II score: BDI-II is a 21-item self-report instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV).
 - mean change in the PRS score in MS subjects: 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.
 - Caregiver Strain Index (CSI): 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.

For the DDI study with memantine (06-AVR-122), the following variables were used in the evaluation of pharmacodynamics.

- Choice Reaction Time (CRT): test of psychomotor function. The subject was presented with an onscreen equivalent of the numeric keypad. The subject was instructed to press the button on the keypad that corresponded with the key illuminated on the screen.
- Divided Attention (DA): simultaneous manual tracking and visual target detection tasks. Participants were instructed to use a joystick to maintain the image of an airplane over an image of a randomly curving road, while at the same time responding as quickly as possible to a visual target presented at random delays and display locations on the screen. Participants were to use the trigger button on the joystick to enter the response to the visual target. There were 16 targets presented during each trial. Each test consisted of three 1-minute trials over different road courses.
- Postural Stability: assessment of stability. The test was conducted using the commercially available AMTI AccuSway PLUS® force platform and the associated Balance Clinic software. Subjects were instructed to stand on the platform for over 1 minute, first with their eyes open and then with their eyes closed.
- Visual Analog Scale (VAS) for Nausea and Dizziness: assessment of nausea and dizziness. Participants were instructed to click and drag the computer mouse to the appropriate position according to how they felt at that moment (with respect to

the statement presented above the line). Each scale was scored as an integer from 0 to 100

- Beck Depression Inventory–II (BDI-II): assessment of depression. The BDI-II consisted of a 21-item test that measured presence and degree of depression in subjects. Each item in the inventory consisted of a list of four statements arranged in increasing severity about a particular symptom of depression. The items were consistent with descriptions of the depression contained in the psychiatric literature.
- Beck Anxiety Inventory (BAI): assessment of multiple symptoms of anxiety. The scale consisted of 21 items, each describing a common symptom of anxiety. The subject was asked to rate on a 4-point scale (ranging from 0 to 3) how much he or she has been bothered by each symptom over the past week. The items were summed to obtain a total score (ranging from 0 to 63).
- Leads Sleep Evaluation Questionnaire (LSEQ): Assessment of sleep quality. The LSEQ was comprised of ten self-rating 100-mm-line analog questions concerned with aspects of sleep and early morning behaviour. The questionnaire was used to monitor subjectively perceived changes in sleep during the psychopharmacological investigations.

2.2.3 What are the characteristics of exposure/effectiveness relationships?

In clinical study 07-AVR-123 comparing Zenvia 30/10 and Zenvia 20/10 to placebo, both doses of Zenvia were effective in reducing crying episodes when analyzed separately or together. Decreases from baseline to Day 84 in laughing and crying episodes were statistically significant between the DM 30 mg/Q 10 mg group and placebo group ($p = 0.0099$) and between the DM 20 mg/Q 10 mg group and placebo group ($p = 0.0048$).

Table 11-1. Primary Endpoint: Mean Change from Baseline to Day 84 in Laughing and Crying Episode Rates (ITT Population)

Visit	AVP-923-30 (n = 110)	AVP-923-20 (n = 107)	Placebo (n = 109)
Laughing and crying			
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	

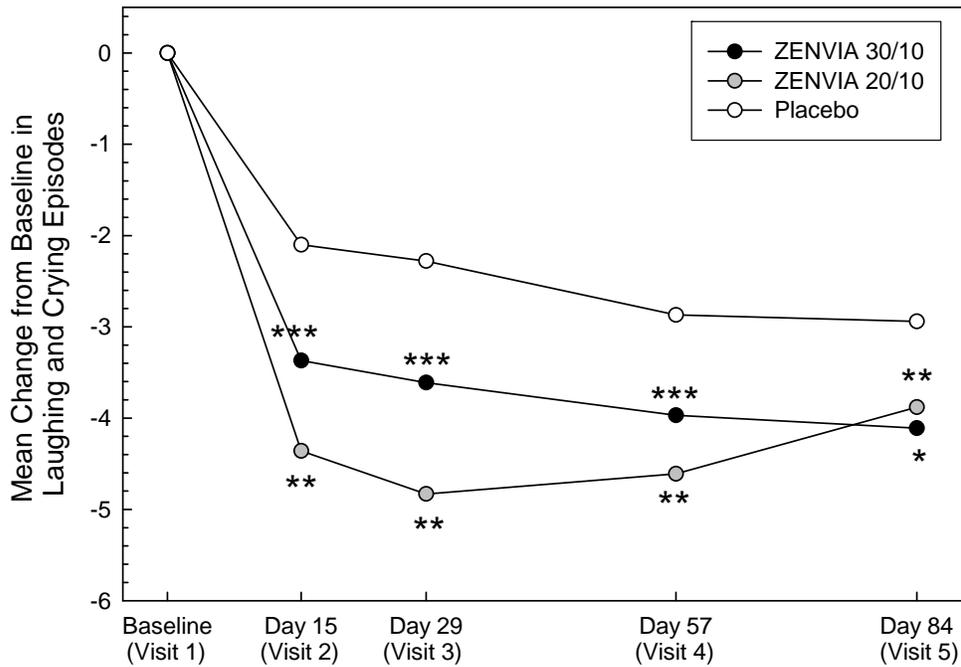
Source: DB phase, Section 14.1, Table 11.1.

ITT = intent to treat; SD = standard deviation.

^aBaseline episode rate was determined from the subject pretreatment diary entries.

^bP-value for Wilcoxon rank-sum test comparing active treatment to placebo.

In addition, when evaluated over time at day 15, day 29, day 57 and day 84, the laughing and crying episode changes from baseline for Zenvia 30/10 did not show greater improvement than Zenvia 20/10 (see figure below).



* $p < 0.05$ vs placebo

** $p < 0.01$ versus placebo

*** $p < 0.001$ versus placebo

Note: Figure is based on an analysis of daily episode rates using a Wilcoxon rank-sum test comparing active treatment to placebo.

While exposure of DM increased as the dose increased from 20 mg to 30 mg (table below), no improvement was observed regarding the primary endpoint. . Based on these findings, there is no dose/exposure-response relationship observed for the effectiveness.

Table 11-4. Summary of Plasma Levels of Dextromethorphan, Dextrorphan, and Quinidine, by Visit, Double-Blind Phase (ITT Population)

Visit/Analyte	Plasma Levels (ng/mL)	
	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: [Appendix 16.1.13](#); [Section 14.1](#), [Table 23.2](#).

ITT = intent to treat; SD = standard deviation.

2.2.4 What are the characteristics of exposure-safety relationships in clinical pharmacology studies?

DM can cause dizziness and gastrointestinal disturbances such as nausea. The most frequent adverse reactions for Q are gastrointestinal disturbances, including diarrhea, nausea, vomiting, and heartburn or esophagitis. Evaluation of common treatment-emergent adverse events (TEAEs) in the pivotal phase 3 Study 07-AVR-123 suggests that treatment of PBA patients with DM 20 mg/Q 10 mg or DM 30 mg/Q 10 mg is associated with DM-dose-dependent increases in the frequency of dizziness and dry mouth, and a smaller, non-dosedependent increase in the incidence of diarrhea. Incidences of other common TEAEs were similar for placebo and DM/Q treatment groups. There is no exposure-safety analysis conducted in this submission.

Table 2.7.4-8. Incidence of Common Treatment-Emergent Adverse Events by Body System and Treatment in Double-Blind Phase of Study 07-AVR-123 (≥ 5% of Patients 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)
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			
Fatigue	11 (10.3)	9 (8.2)	10 (9.2)

Source: 5.3.5.3 Table 6.1.6

DM = dextromethorphan hydrobromide USP; Q = quinidine sulfate USP.

In clinical DDI study 06-AVR-121 with paroxetine, 83% of adverse events was observed when paroxetine was added to the steady state of DM 30 mg/Q 30 mg, which is higher than that of DM 30 mg/ Q 30 mg alone (30%). Adding DM 30 mg/Q 30 mg to paroxetine didn't show increase of incidence of adverse events (64%) when compared to paroxetine alone (78%). This finding suggests that adding paroxetine to DM/Q treatment may give rise to an increased incidence of AEs.

Table 12.2.2-1. Incidence of Treatment-Emergent Adverse Events by System Organ Class and Treatment for Group 1

	Treatment at Onset of Adverse Event	
	Paroxetine 20 mg qd (N=14)	Paroxetine 20 mg qd + AVP-923 30 mg bid (N=14)
Any System Organ Class		
Any Event	11 (78.6%)	9 (64.3%)

Table 12.2.2-2. Incidence of Treatment-Emergent Adverse Events by System Organ Class and Treatment for Group 2

	Treatment at Onset of Adverse Event	
	AVP-923 30 mg bid (N=13)	AVP-923 30 mg bid+ Paroxetine 20 mg qd (N=12)
Any System Organ Class		
Any Event	4 (30.8%)	10 (83.3%)

The exposure of paroxetine, DM and Q increased 2.3-, 1.5, and 1.4-fold when paroxetine was coadministered with DM 30mg/Q 30 mg, the increased incidence of AEs may be due to the increased exposure.

Exposure by fold change when paroxetine was added to DM 30mg/Q 30mg (AVP)

	Paroxetine	Dextromethorphan	Dextorphan	Quinidine
	AVP+P/P alone	AVP+P/AVP alone	AVP+P/AVP alone	AVP+P/AVP alone
AUC0-24	2.26	1.50	0.86	1.39
Css,max	2.07	1.44	0.82	1.32
Css,min	2.50	1.66	0.88	1.66

Exposure by fold change when DM 30mg/Q 30mg (AVP) was added to paroxetine

	Paroxetine	Dextromethorphan	Dextorphan	Quinidine
	P+AVP/P alone	P+AVP/AVP alone	P+AVP/AVP alone	P+AVP/AVP alone
AUC0-24	1.70	1.11	0.66	1.01
Css,max	1.48	1.08	0.67	0.91
Css,min	1.66	1.24	0.65	1.34

2.2.5 How the exposure levels of the new formulation (DM 30/Q 10 and DM 20/Q 10) compare to previously studies dose (DM 30/Q 30)?

Exposure of Q following administration of DM 30mg/Q 10mg and DM 20mg/Q 10mg appeared to be approximately one third of DM 30mg/Q 30mg dose indicating dose proportionality of Q. Following the administration of DM 30mg/Q 10mg and DM 30mg/Q 30mg, there is no significant change of the DM exposure.

Study		123		121	122
Doses	(DM/Q)	20/10	30/10	30/30	
Mean C _{max,ss} (ng/ml)	DM	53	85	88	96
	DX	74	129	84	70
	Q	54	62	159	152

Study		123		121	122
Doses	(DM/Q)	20/10	30/10	30/30	
Mean AUC _{ss} (ng.h/ml)	DM	525	883	852	943
	DX	772	1392	857	725
	Q	401	471	1065	968

2.2.6 Does this drug prolong QT or QTc interval?

The effect of therapeutic dose of Zenvia 30/10 on QTc prolongation was evaluated in a randomized, double-blind (except for moxifloxacin), placebo-, and positive-controlled (400-mg moxifloxacin) crossover thorough QTc study in 50 fasted normal healthy men and women with CYP2D6 extensive metabolizer (EM) genotype. The results showed that the maximum mean difference of QT interval between Zenvia 30/10 and placebo was 10.2 ms with 95% CI upper bound of 12.6ms. Below is the summary from IRT-QT review.

Dextromethorphan / quinidine significantly prolongs QTc interval, as evident by the results from two thorough QT studies. Study 05-AVR-119, which was reviewed by QT-IRT on 15 September 2006, was a thorough QT study using two supratherapeutic doses of dextromethorphan / quinidine (i.e., 30 mg / 30 mg and 60 mg / 60 mg). Study 08-AVR-126, which is currently submitted, used the therapeutic dose of dextromethorphan / quinidine (i.e., 30 mg / 10 mg). The results were summarized as the follows:

- For Study 05-AVR-119, the largest upper bounds of the 2-sided 90% confidence interval (CI) for the mean baseline-corrected QTcF between the difference of dextromethorphan / quinidine (30 mg / 30 mg and 60 mg / 60 mg) and placebo ($\Delta\Delta\text{QTcF}$) were 14.6 and 22.7 ms, respectively.
- For Study 08-AVR-126, the largest upper bounds of the 2-sided 90% CI for the mean $\Delta\Delta\text{QTcF}$ between dextromethorphan / quinidine (30 mg / 10 mg) and placebo was 12.6 ms at 3 hours after dose. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established.

Study 08-AVR-126 is a randomized, double-blind (except for moxifloxacin), placebo-controlled, positive-controlled, multiple-dose, 3-treatment crossover study of the ECG effects of dextromethorphan / quinidine (30 mg / 10 mg) administered in fasted normal healthy men and women with CYP2D6 extensive metabolizer (EM) genotype. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for AVP-923 (30 mg DM/10 mg Q) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hrs)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Dextromethorphan / Quinidine (30 mg / 10 mg)	3	10.2	(7.8, 12.6)
Moxifloxacin 400 mg*	4	12.3	(9.9, 14.7)

*: Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 3 timepoints is 9.1 ms.

The exposure tested in Study 08-AVR-126 represented the steady state concentrations following the therapeutic dose of dextromethorphan / quinidine (i.e., 30 mg / 10 mg) in subjects with CYP2D6 EM genotype. In the general population, approximately 7-10% of Caucasians and 3-8% of African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PMs), whereas the rest are intermediate, extensive metabolizer. Supratherapeutic doses were evaluated in Study 05-AVR-119. Maximum concentrations (C_{max}) of dextromethorphan and quinidine for the dextromethorphan / quinidine (30 mg / 30 mg) BID arm following the last dose were 89 and 177 ng/mL, respectively. Likewise, C_{max} of dextromethorphan and quinidine for the dextromethorphan and quinidine (60 mg / 60 mg) BID arm following the last dose were 211 and 355 ng/mL, respectively. C_{max} for dextromethorphan / quinidine (60 mg / 60 mg) BID arm were 3.5-fold and 6.0-fold higher than steady-state C_{max} for dextromethorphan and quinidine, respectively, for the dose in this study (dextromethorphan / quinidine 30 mg/10 mg BID). This fold increase in C_{max} and AUC for dextromethorphan / quinidine (60 mg / 60 mg) BID exceeds expected increases in quinidine or dextromethorphan due to drug interactions, hepatic impairment, or renal impairment.

2.2.7 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes. The assay validations for the measurement of DM, DX and Q concentrations in human plasma and urine were reviewed at original submission and were considered acceptable. One newly submitted validation report for Q with lower detection limits is also reviewed and acceptable.

A summary of all analytical methods is given in the analytical section 2.6 of this review.

2.2.8 What are the general ADME characteristics of Zenvia?

The key ADME characteristics of Zenvia had been summarized in the original clinical pharmacology review. There is no additional new ADME information provided in this submission.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Based on what is known about exposure response relationships and their variability, is dosage adjustment needed for any of the subgroups?

Population PK

The sponsor conducted a population PK analysis to determine the population PK parameters of Q, DM and its metabolite DX in plasma after single and multiple doses of AVP-923. This analysis also identified covariates on the population PK parameter estimates. The data from studies 07-AVR-123, 07-AVR-125, 08-AVR-126 were included in the analysis and five other studies (99-AVR-100, 99-AVR-101, 04-AVR-111, 04-AVR-115 and 04-AVR-116) were used for an external validation of the model. The key question to be addressed is shown below.

Is there any significant covariate which influences AVP-923 PK?

Once a structural model was selected, covariate analysis was performed to evaluate if some of them could improve the pharmacokinetic model. The covariates investigated for inclusion in the model were either continuous data (age, body mass index (BMI), weight and height) or categorical data (gender and race). The impact of covariates was initially assessed graphically by performing a linear regression on the parameter values vs. covariates (for continuous covariates) or by making box plots for categorical covariates. None of the available covariates of height, weight, BMI, age, race and gender were considered significantly correlated with any of the PK parameters.

Pharmacometrics Reviewer's comment:

- *The sponsor's conclusion is consistent with that shown in the original submission.*
- *The sponsor's population PK model is acceptable.*

CYP2D6 Pharmacogenetic Interactions

Approximately 5% to 10% of the Caucasian population has genetically reduced CYP2D6 activity. CYP2D6 poor metabolizers (PMs) potentially do not benefit from the CYP2D6

inhibitory properties of Q. Based on data available from 07-AVR-123 and clinical pharmacology studies included in the previous submission, the sponsor has proposed descriptive language related to the influence of CYP2D6 poor metabolism on DM/Q exposure and safety in the *Adverse Reactions* and *Clinical Pharmacology*, suggesting that AE rates do not differ according to CYP2D6 genotype and that dose adjustments are not required.

Studies submitted in the previous NDA submission demonstrated that plasma concentrations of DM when DM is administered alone are generally highest in PMs and are similar to concentrations observed in EMs when DM is administered with Q (99-AVR-102). Urinary DM:DX metabolic ratios do not change substantially between single and multiple dosing of DM/Q in PMs whereas they increase in EMs, suggesting that Q is not adding to the level of CYP2D6 inhibition in PMs (99-AVR-101). Post-dose plasma concentrations (ng/ml) of DM and DX by CYP2D6 metabolic status following DM 30 mg/Q 10 mg treatment in trial 07-AVR-123 are shown in the table below. Consistent with the findings of other studies, on Day 29, PMs tended to have the highest DM concentrations at the DM 30 mg/ Q 10 mg dose, whereas UMs had the lowest. The findings at Day 57, as presented in the sponsor’s proposed labeling, were generally consistent.

DM and DX plasma concentrations on Day 29 of DM/Q in 07-AVR-123

		UM	EM	IM	PM
DM 30 mg/ Q 10 mg		n=1	n=83	n=9	n=4
	DM				
	Mean (SD)	35 (9.4)	79 (41)	117 (26)	123 (41)
	Median (range)	36 (24, 45)	70 (8.6, 280)	117 (52, 156)	132 (66, 163)
	DX				
	Mean (SD)	126 (14)	145 (48)	83 (25)	45.3 (27)
Median (range)	132 (109, 145)	147 (26, 322)	83 (50, 137)	48 (10, 75)	
DM 20 mg/ Q 10 mg		n=1	n=79	n=9	n=3
	DM				
	Mean (SD)	19	50 (27)	62 (55)	79 (27)
	Median (range)	19	46 (6.6, 140)	68 (2.0, 127)	79 (59, 98)
	DX				
	Mean (SD)	109	76 (28)	55 (34)	28 (14)
Median (range)	109	72 (30, 177)	66 (7.3, 98)	28 (18, 39)	

Source: 07-AVR-123 study report

CYP2D6 genotype relationships with efficacy- or safety-related endpoints are inconclusive given the small number of PMs enrolled in trial 07-AVR-123. However, SAEs, drug-related AEs, and AEs leading to discontinuation do not appear to differ substantially according to CYP2D6 metabolic status in 07-AVR-123 (shown below) or the pooled PBA safety population.

DM/Q (combined dose groups) AEs in 07-AVR-123 by CYP2D6 metabolic status

	DM/Q				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	1	66	5	3	2	19	3	2

treatment	(50%)	(50.3%)	(31.3%)	(60%)	(33.3%)	(31.6%)	(42.9%)	(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)

Source: Reviewer analysis of 07-AVR-123 safety population

Genomics reviewer comments:

- Adding Q to DM appears to be of limited utility in PMs from a pharmacokinetic standpoint.
- Treatment effects (efficacy or safety) for DM/Q do not appear to differ in a consistent manner across CYP2D6 metabolic groups, but the findings are inconclusive because of the small database for PMs. AE rates appeared similar across CYP2D6 metabolic groups receiving DM/Q. Use of DM/Q may expose PMs to an unnecessary risk for QT-prolongation since Q is not adding any benefit.
- Prescribers should consider the potential risk for Q-related AEs relative to the benefit of administering the DM/Q combination product (vs. DM alone) in known CYP2D6 PMs.

2.4 EXTRINSIC FACTORS

2.4.1 Are dextromethorphan and quinidine a substrate, inhibitor or inducer of CYP enzymes?

Regarding whether DM and Q are substrate of the CYP enzymes, information was provided in the original review.

Regarding whether DM and Q are inhibitors or inducers of CYP enzymes, the Agency requested additional studies in the Approvable Letter and four in vitro studies were conducted to evaluate the potential of DM and Q to be an inhibitor or an inducer of CYP450s iso-enzymes as this information was lacking in the original submission.

Inhibitor:

The inhibitory potential of DM and Q towards the metabolism of CYP-specific substrates was determined in human liver microsomes pooled from adult males and females. DM up to 5 µM showed neither direct nor time-dependent inhibition potential for CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. Similarly, Q up to 5 µM showed neither direct nor time-dependent inhibition potential for CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1 and 3A4. It is well known that Q is a potent inhibitor of CYP2D6.

Inducer:

Cultured human hepatocytes from 3 donors were utilized for this study. The potential for DM and Q to induce human hepatocytes at 0.048 µM, 0.48 µM, and 4.8 µM DM and Q had no effect on CYP1A2, 2B6 and 3A4 activities.

2.4.2 What extrinsic factors (such as herbal products, diet, smoking and alcohol) influence exposure and or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of extrinsic factors like herbal products and smoking have not been conducted.

2.4.3 Are there any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered? If yes, is there a need for dosage adjustment?

Two in vivo drug-drug interaction studies were newly submitted to determine the potential drug-drug interactions of PK and/or PD effects on Zenvia or the concomitant drugs.

Paroxetine

Selective serotonin reuptake inhibitors (SSRIs) such as paroxetine may be prescribed to patients with neurologic disorders for the treatment of depression. Paroxetine is a CYP2D6 substrate as well as a potent CYP2D6 inhibitor. This drug interaction study was conducted to study the potential for DM/Q to affect the metabolism of non-target CYP2D6 substrates, and the potential for another CYP2D6 inhibitor to affect the PK of DM/Q. The study was conducted with DM 30 mg/Q 30 mg BID rather than (b) (4) (DM 30 mg/Q 10 mg BID, and DM 20 mg/Q 10 mg BID). 27 healthy subjects (19-55 years old) were randomized into two treatment groups:

- Group 1: Paroxetine 20 mg once daily for 12 days, followed by the addition of DM 30 mg/Q 30 mg BID for 8 days (N=14)
- Group 2: DM 30 mg/Q 30 mg BID for 8 days, followed by the addition of paroxetine 20 mg once daily for 12 days (N=13).

Steady state PK of paroxetine, DM, DX and Q were evaluated when taken DM/Q and paroxetine concomitantly versus taken DM/Q or paroxetine alone. PK parameters for paroxetine, DM, DX and Q are summarized in the tables below. The data are shown in two separated analyses. The *Evaluable Population* included all subjects who completed the study without major protocol violations. An additional *Sub-Group Analysis* was performed to exclude outliers, including unexpectedly low concentrations and poor CYP2D6 metabolizer. *Sub-Group* population was used by the reviewer for PK analysis.

Table 2.7.2-22. Summary of Steady-State PK Parameters for Paroxetine, in the Evaluable and Sub-group Populations. Boxed sections are within group comparisons (Study 06-AVR-121)

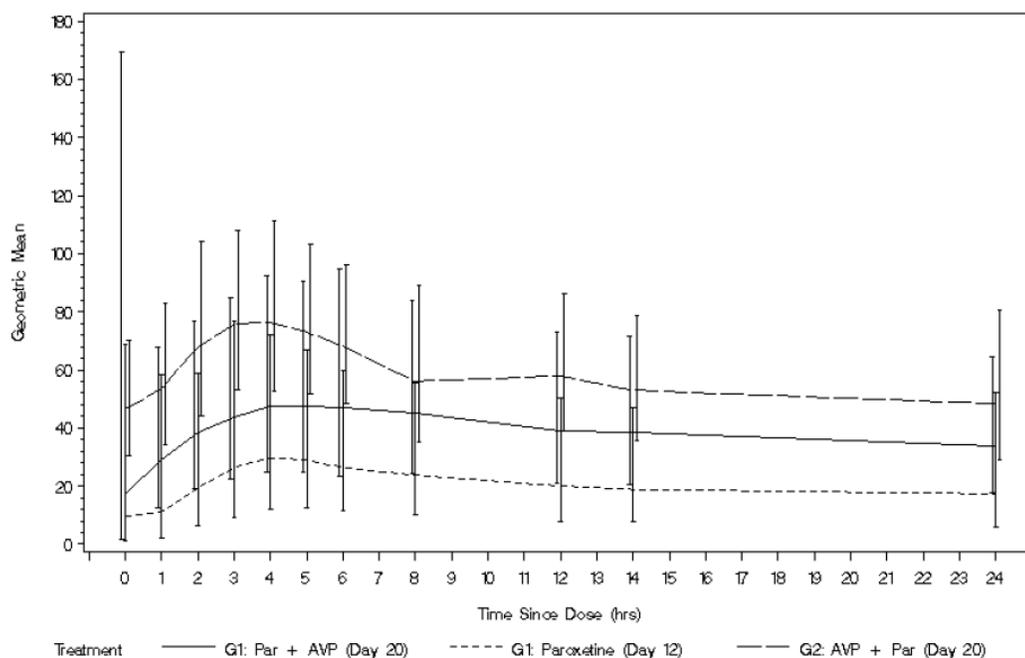
Parameters		Evaluable Population			Sub-Group* Analysis		
		Group 1 Day 12 (Par)	Group 1 Day 20 (Par + DM/Q)	Group 2 Day 20 (DM/Q + Par)	Group 1 Day 12 (Par)	Group 1 Day 20 (Par + DM/Q)	Group 2 Day 20 (DM/Q + Par)
N		12	12	10	9	9	9
AUC _{0-24h} (ng·h/mL)	Arithmetic	651.25	869.91	1408.43	648.08	1099.92	1463.68
	Mean (SD)	(411.98)	(626.53)	(457.24)	(452.03)	(535.89)	(448.18)
C _{SSmax} (ng/mL)	Arithmetic	41.39	46.99	80.77	40.08	59.37	83.04
	Mean (SD)	(24.35)	(33.97)	(23.20)	(25.97)	(29.33)	(23.40)
C _{SSmin} (ng/mL)	Arithmetic	22.09	28.99	52.39	21.90	36.35	54.79
	Mean (SD)	(16.76)	(21.52)	(18.39)	(18.36)	(19.24)	(17.76)
t _{max} (h)	Median	4.0	4.0	4.0	4.0	5.0	4.0
	(Range)	(2.0-6.0)	(1.0-6.1)	(3.0-5.0)	(3.0-6.0)	(4.0-6.1)	(3.0-5.0)
t _{1/2} (h)	Arithmetic	40.28	56.73	44.81	41.63	68.63	47.54
	Mean (SD)	(35.76)	(57.03)	(27.64)	(39.01)	(61.85)	(27.85)

Source: 5.3.3.4 06-AVR-121 Table 11.4.2-1.

AUC₀₋₂₄ = area under the plasma concentration versus time curve from 0 to 24 h; C_{SSmax} = steady-state maximum concentration; C_{SSmin} = steady-state minimum concentration; DM/Q = dextromethorphan hydrobromide/quinidine sulfate; Par = paroxetine; t_{max} = time of maximum measured plasma concentration; t_{1/2} = terminal elimination half-life; SD = standard deviation.

*Sub-group Population is defined in 5.3.3.4 06-AVR-121 Section 9.8.

Figure 11.4.2-2. Geometric Mean (SD) plasma concentration curves for paroxetine (ng/mL) for the *Sub-group Population



Source: Figure 14.2.1

* Sub-group Population is defined in Section 9.8.

Table 2.7.2-23. Summary of Steady-State PK Parameters for DM, in the Evaluable and Sub-group Populations. Boxed sections are within group comparisons. (Study 06-AVR-121)

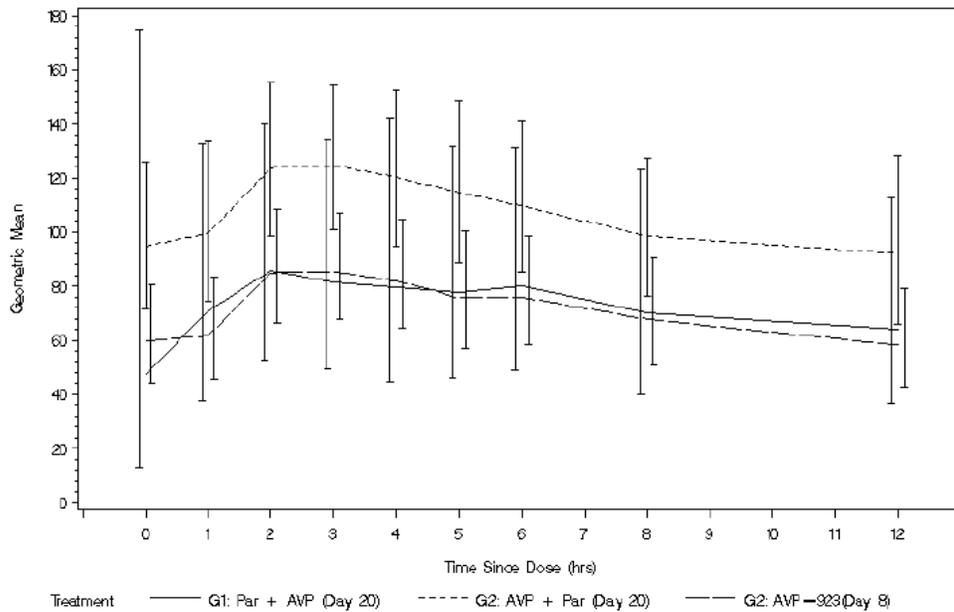
Parameters		Evaluable Population			Sub-Group* Analysis		
		Group 2 Day 8 (DM/Q)	Group 2 Day 20 (DM/Q + Par)	Group 1 Day 20 (Par + DM/Q)	Group 2 Day 8 (DM/Q)	Group 2 Day 20 (DM/Q + Par)	Group 1 Day 20 (Par + DM/Q)
N		10	10	12	9	9	9
AUC ₀₋₁₂ (ng·h/mL)	Arithmetic Mean (SD)	914.59 (225.08)	1335.93 (287.734)	813.27 (429.02)	876.20 (201.03)	1310.31 (292.84)	976.01 (351.87)
C _{SSmax} (ng/mL)	Arithmetic Mean (SD)	93.39 (21.40)	132.11 (23.83)	82.60 (40.26)	89.88 (19.40)	129.68 (23.92)	97.28 (34.65)
C _{SSmin} (ng/mL)	Arithmetic Mean (SD)	59.80 (16.47)	96.36 (24.95)	58.75 (31.00)	56.89 (14.49)	94.40 (25.63)	70.29 (25.73)
t _{max} (h)	Median (Range)	2.5 (2.0-4.0)	2.5 (2.0-3.0)	2.0 (0.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-3.0)	2.0 (1.0-4.0)
t _{1/2} (h)	Arithmetic Mean (SD)	17.30 (5.60)	26.08 (17.21)	20.45 (7.93)	16.90 (5.78)	25.54 (18.17)	21.25 (7.80)

Source: 5.3.3.4 06-AVR-121 Table 11.4.2-2.

AUC₀₋₂₄ = area under the plasma concentration versus time curve from 0 to 12 h; C_{SSmax} = steady-state maximum concentration; C_{SSmin} = steady-state minimum concentration; DM/Q = dextromethorphan hydrobromide/quinidine sulfate; Par = paroxetine; t_{max} = time of maximum measured plasma concentration; t_{1/2} = terminal elimination half-life; SD = standard deviation.

*Sub-group Population is defined in 5.3.3.4 06-AVR-121 Section 9.8.

Figure 11.4.2-4. Geometric Mean (SD) plasma concentration curves for dextromethorphan (ng/mL) for the *Sub-group Population



Source: Figure 14.2.2

* Sub-group Population is defined in Section 9.8.

Table 2.7.2-24. Summary of Steady-State Pharmacokinetic Parameters for Dextrophan, in the Evaluable Population (Study 06-AVR-121)

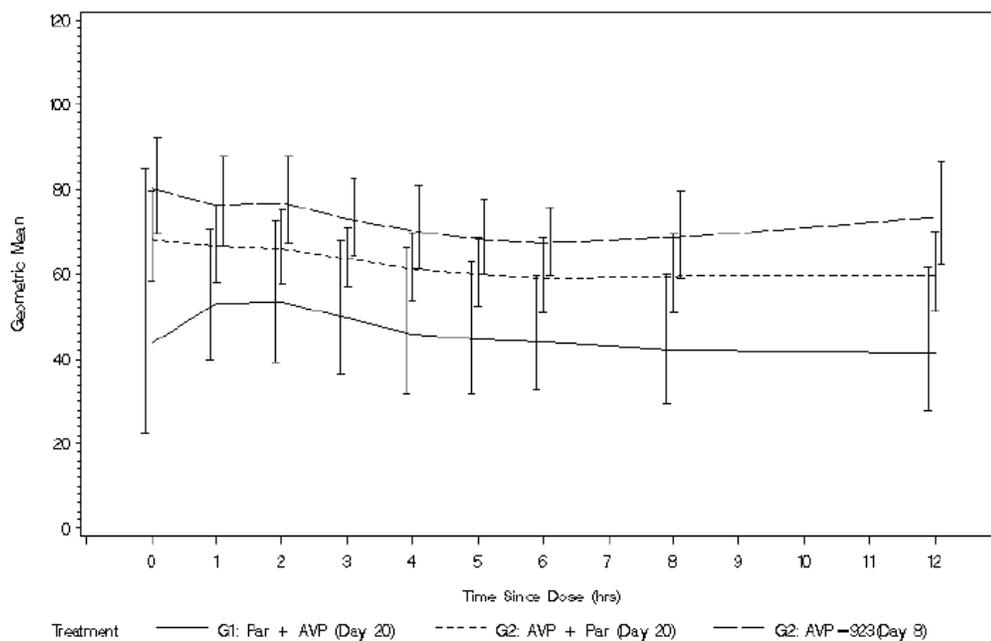
		Group 2		Group 1
		Day 8 (DM/Q)	Day 20 (DM/Q + Par)	Day 20 (Par + DM/Q)
N		10*	10*	12*
AUC₀₋₁₂ (ng·h/mL)	Arithmetic Mean (SD)	818.21 (174.31)	717.82 (127.93)	586.85 (171.35)
C_{SSmax} (ng/mL)	Arithmetic Mean (SD)	80.39 (15.17)	67.06 (12.04)	63.95 (24.00)
C_{SSmin} (ng/mL)	Arithmetic Mean (SD)	61.65 (13.51)	55.56 (10.14)	43.55 (13.43)
t_{max} (h)	Median (Range)	0.48 (0.0-12.0)	0.0 (0.0-5.0)	1.0 (0.0-2.0)
t_{1/2} (h)	Arithmetic Mean (SD)	43.55 (19.74) (N=3)	57.78 (25.57) (N=8)	36.73 (36.20) (N=10)

Source: 5.3.3.4 06-AVR-121 Table 11.4.2-3.

AUC₀₋₁₂ = area under the plasma concentration versus time curve from 0 to 12 h; C_{SSmax} = steady-state maximum concentration; C_{SSmin} = steady-state minimum concentration; DM/Q = dextromethorphan hydrobromide/quinidine sulfate; DX = dextrophan; Par = paroxetine; t_{max} = time of maximum measured plasma concentration; t_{1/2} = terminal elimination half-life; SD = standard deviation.

* Except for t_{1/2} values

Figure 11.4.2-6. Geometric Mean (SD) plasma concentration curves for dextrophan (ng/mL) for the *Sub-group Population.



Source: Figure 14.2.3

*Sub-group Population is defined in Section 9.8.

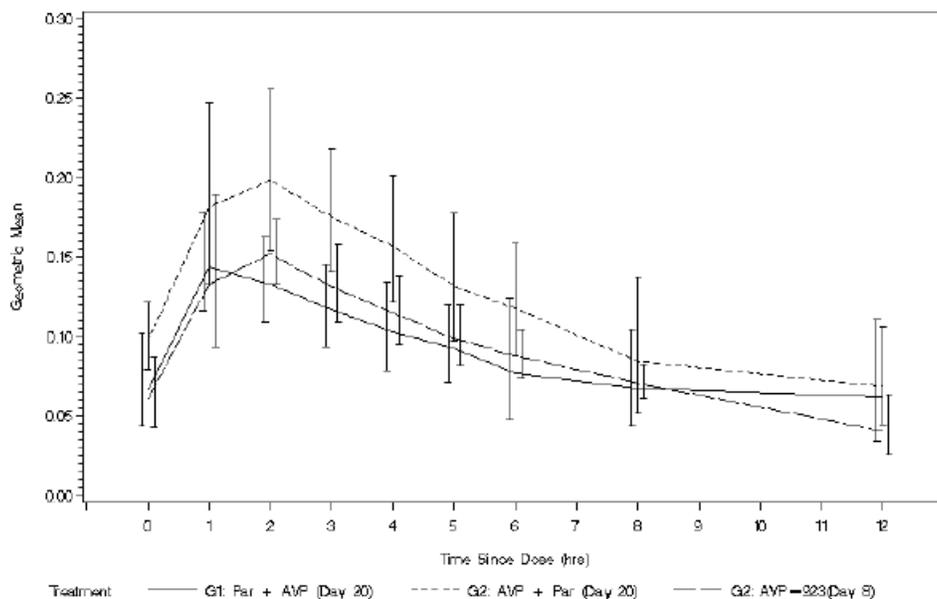
Table 2.7.2-25. Summary of Steady-State Pharmacokinetic Parameters for Q, in the Evaluable Population (Study 06-AVR-121)

		Group 2		Group 1
		Day 8 (DM/Q)	Day 20 (DM/Q + Par)	Day 20 (Par + DM/Q)
AUC_{0-12} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	Arithmetic Mean (SD) (N)	1.075 (0.178) (10)	1.488 (0.380) (10)	0.919 (0.434) (12)
C_{SSmax} ($\mu\text{g}/\text{mL}$)	Arithmetic Mean (SD) (N)	0.161 (0.023) (10)	0.209 (0.047) (10)	0.136 (0.038) (11)
C_{SSmin} ($\mu\text{g}/\text{mL}$)	Arithmetic Mean (SD) (N)	0.042 (0.019) (10)	0.073 (0.022) (10)	0.050 (0.026) (12)
t_{max} (h)	Median (Range) (N)	1.98 (1.0-2.0) (10)	1.98 (1.0-2.0) (10)	1.0 (0.0-2.0) (11)
$t_{1/2}$ (h)	Arithmetic Mean (SD) (N)	7.16 (2.62) (10)	6.84 (1.65) (10)	9.40 (3.57) (9)

Source: 5.3.3.4 06-AVR-121 Table 11.4.2-4.

AUC_{0-12} = area under the plasma concentration versus time curve from 0 to 12 h; C_{SSmax} = steady-state maximum concentration; C_{SSmin} = steady-state minimum concentration; DM/Q = dextromethorphan hydrobromide/quinidine sulfate; Par = paroxetine; t_{max} = time of maximum measured plasma concentration; $t_{1/2}$ = terminal elimination half-life; SD = standard deviation.

Figure 11.4.2-8. Geometric Mean (SD) plasma concentration curves for quinidine ($\mu\text{g}/\text{mL}$) for the *Sub-group Population.



Source: Figure 14.2.4

*Sub-group Population is defined in Section 9.8.

The addition of DM 30 mg/Q 30 mg to steady-state of paroxetine resulted in an increased steady-state levels of paroxetine (1.7 fold in AUC and 1.5 fold in C_{max}). Steady-state levels of DX were decreased by approximately 30 %. There is no significant change of the exposure of DM and Q.

Adding paroxetine to steady-state levels of DM 30 mg/Q 30 mg resulted in an increased AUC_{0-τ} of paroxetine (2.3 fold), DM (1.5-fold) and Q (1.4-fold). Furthermore, steady-state levels of DX were decreased by approximately 15 % following co-administration of paroxetine.

Safety Assessments

The addition of DM/Q to paroxetine gave rise to less pronounced AE effects than did the addition of paroxetine to DM/Q, in terms of the overall incidence, the incidence of maximum severity, and maximum relationship to study drugs.

The addition of paroxetine to DM/Q was associated with an incidence of 16.7% (2/12) severe AEs (classified by maximum intensity), compared to an incidence of none when DM/Q was given alone. The severe AEs included psychomotor hyperactivity (in the Nervous System Disorders SOC) and mood swings (in the Psychiatric Disorders SOC).

Consideration should be given to initiating treatment with a lower dose of paroxetine if given with Zenvia. The dose of paroxetine can then be adjusted based on clinical response, however dosage above 35mg/day is not recommended.

Memantine

DM and memantine are both antagonists of the NMDA receptors. Therefore, coadministration could result in an additive effect at NMDA receptors and potentially an increased incidence of side effects. A drug-drug interaction study between DM 30 mg/Q 30 mg and memantine was conducted to explore the potential for PK and PD interactions. 52 healthy subjects (19-55 years old) were randomized into two treatment groups (34 completed the study):

- Group 1 (memantine + DM/Q): Memantine was titrated to a dose of 10 mg/twice daily (20 mg/day). The starting dose was 5 mg, with weekly incremental increases of 5 mg. The subjects then continued administrations of memantine for 11 days to allow steady-state levels to be reached before starting treatment with DM 30 mg/Q 30 mg BID for 8 days.
- Group 2 (DM/Q + memantine): DM 30 mg/Q 30 mg was administered BID for 8 days, which allowed steady state levels to be reached. Subsequently, while continuing to administer DM/Q, memantine was titrated up to 20 mg/day, as indicated for Group 1. Once the target dose of memantine was reached, subjects took memantine and DM/Q for an additional 11 days.

Steady state PK of memantine, DM, DX and Q were evaluated when administering DM/Q and memantine concomitantly versus giving DM/Q or memantine alone. PK results showed that the addition of DM/Q to memantine did not alter the steady-state PK of memantine in healthy volunteers. Similarly, the addition of memantine to DM/Q did not alter the steady-state PK of DM and DX in healthy volunteers. Plasma concentrations of Q were slightly higher (20-30%) when memantine was added to AVP-923 than when AVP-923 was given alone. The 90% confidence interval ratios of geometric means for all

pharmacokinetic parameters (AUC_{0-12} , C_{SSmax} , and C_{SSmin}) of memantine, DM, DX and Q are listed below.

In-Text Table 1. Comparison of Steady State Pharmacokinetic Analysis for Memantine

	Estimate of Ratio of Geometric Means	90% Confidence Interval for Ratio
Group 1: Memantine (Day 40 - Day 32)		
AUC_{0-12h}	0.938	(0.850 - 1.036)
C_{SSmax}	0.936	(0.849 - 1.033)
C_{SSmin}	0.935	(0.826 - 1.059)

In-Text Table 2. Comparison of Steady State Pharmacokinetic Analysis for Dextromethorphan

	Estimate of Ratio of Geometric Means	90% Confidence Interval for Ratio
Group 2: Dextromethorphan (Day 40 - Day 8)		
AUC_{0-12h}	1.0991	(1.0413 - 1.1601)
C_{SSmax}	1.1077	(1.0579 - 1.1600)
C_{SSmin}	1.1698	(1.0758 - 1.2720)

Data extracted from [Table 14.2.2.3](#)

In-Text Table 3. Comparison of Steady State Pharmacokinetic Analysis for Dextrorphan

	Estimate of Ratio of Geometric Means	90% Confidence Interval for Ratio
Group 2: Dextrorphan (Day 40 - Day 8)		
AUC_{0-12h}	1.091	(1.020 - 1.167)
C_{SSmax}	1.115	(1.026 - 1.211)
C_{SSmin}	1.073	(0.993 - 1.160)

Data extracted from [Table 14.2.2.3](#)

In-Text Table 4. Comparison of Steady State Pharmacokinetic Analysis for Quinidine

	Estimate of Ratio of Geometric Means	90% Confidence Interval for Ratio
Group 2: Quinidine (Day 40 - Day 8)		
AUC_{0-12h}	1.24735	(1.15321 - 1.34918)
C_{SSmax}	1.19738	(1.13028 - 1.26847)
C_{SSmin}	1.31638	(1.14508 - 1.51330)

Data extracted from [Table 14.2.2.3](#)

PD measures, which included choice reaction time, divided attention test, postural stability, visual analog scale (VAS) for nausea, VAS for dizziness, Beck Depression Inventory-II, Beck Anxiety Inventory, and Leeds Sleep Evaluation Questionnaire, were evaluated. No clinically significant PD changes were observed except that the incidence of dizziness was greater when DM/Q was added to memantine compared with memantine alone, when measured at 2 and 4 hours post-dose.

Safety Assessments

There was no indication of AE differences in incidence, severity, or maximum relationship to study drugs when DM/Q was co-administered with memantine.

No dose adjustment is required for patients taking concomitant administration of memantine.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 What is the relative bioavailability of the [REDACTED] (b) (4) [REDACTED] formulation to the pivotal clinical trial?

The [REDACTED] (b) (4) products of Zenvia (DM 30 mg/Q 10 mg and DM 20 mg/Q 10 mg capsules) are identical to those used in the pivotal Phase 3 study (07-AVR-123).

Two clinical pharmacology studies (06-AVR-121, 06-AVR-122) used higher strengths (30/30), a previous formulation. The dissolution testing was utilized during development to evaluate the effect of material attributes, processing conditions (including scale of manufacture) and product storage on drug dissolution rates. Both drugs dissolved rapidly and completely from the capsules and proposed controls for routine monitoring of commercial product are identical to the specifications and methods used for testing of clinical batches. The compositions of all formulations used in the clinical studies are listed in the Table below.

Table 2.3.P.2-2 Compositions of Dosage Forms Used in Clinical and Other Development Programs Compared to (b) (4) Product (Formula 6)

Ingredient	Formula 1	Formula 2	Formula 3	Formula 4	Formula 5	Formula 6	
	mg						
Dextromethorphan HBr*	30	30	30	30	30	30	20
Quinidine Sulfate*	2.5 – 75	30	30	30	30	10	
Crosscarmellose Sodium	(b) (4)						
Microcrystalline Cellulose (b) (4)							
Lactose (b) (4)							
Colloidal Silicon Dioxide							
Magnesium Stearate (b) (4)							

2.6 ANALYTICAL

2.6.1 What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

The assay validations for the measurements of DM, DX and Q concentrations in human plasma and urine (Reports: 12730, 12730-2.01, 12730-3.01, 27267 and 22004-1) were reviewed at original submission and were considered acceptable. One newly submitted validation report (AA42125-01) for measurement of Q concentrations in plasma with lower detection limits is also reviewed and considered acceptable. Analytical validation methods are summarized in the table below.

Table: Summary of all analytical validation methods

Report number	Biological fluid	Analyte	Method	LLOQ	Calibration range
12732-2.01	Plasma	DM/DX	HPLC	DM: 0.2 (ng/mL) DX: 25 (ng/mL)	DM: 0.2 – 20 (ng/mL) DX: 25 - 1000 (ng/mL)
12730-3.01	Plasma	DM/DX	HPLC	DM: 0.2 (ng/mL) DX: 2.5 (ng/mL)	DM: 0.2 - 20 (ng/mL) DX: 2.5 - 500 (ng/mL)
27267-1	Plasma	DM/DX	LC/MS/MS	DM: 0.2 (ng/mL) DX: 2.5 (ng/mL)	DM: 0.2 - 200 (ng/mL) DX: 2.5 - 2500 (ng/mL)
22004-1	Plasma	Q	HPLC	0.05 (µg/mL)	0.05 – 10.0 (µg/mL)
12730	Urine	DM	Chromato-graphic	DM: 0.05 (µg/mL) DX: 0.05 (µg/mL)	DM: 0.05 – 15 (µg/mL) DX: 0.05 – 15 (µg/mL)
AA42125-01	Plasma	Q	HPLC	2.0 (ng/mL)	2.0 - 250 (ng/mL)

Study AA42125-01 is a validation report of a HPLC method with mass spectrometric detection for the determination of Q in human plasma (heparin).

Assessment of selectivity, sensitivity, accuracy, precision, matrix effect, stability (long-term, short-term, freeze and thaw, stock, and post-preparative), and response function and supporting assessments including the evaluation of recovery, dilution integrity, and processed sample integrity were conducted with respect to quinidine and internal standard, quinine, for the plasma quinidine assay. The results of the above assessments are considered acceptable per the FDA “Bioanalytical Method Validation” guidance.

3.0 DETAILED LABELING RECOMMENDATION

The reviewer's labeling recommendations are shown by track changes to the sponsor proposed label. These labeling changes should be incorporated in the revised label:

30 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.0 APPENDIX

4.1 APPENDIX I

INDIVIDUAL STUDY REVIEW

4.1-1. BIOPHARMACEUTICS STUDIES 4.1-1.1 Comparative BA/BE

Study 07-AVR-125: Randomized, Double-blind, Placebo-Controlled Pharmacokinetic Evaluation of Various Combinations and Regimens of Dextromethorphan and Quinidine Given for Eight Consecutive Days to Healthy Volunteers.

The sponsor evaluated PK of various combinations and regimens intended to justify which dose combinations would be recommended for further clinical development. Based on previous experiences, the sponsor used DM 45 mg/Q 30 mg BID as a reference when making the comparisons.

A brief overview of some essential components of the study design is given below:

Study Design	Double-blind, placebo-controlled, randomized, parallel-group study								
Study Population	79 subjects were randomized, 71 completed the study. Non-extensive metabolizers of CYP2D6 were not enrolled in the study.								
		Treatment Group							
	Trait		A	B	C	D	E	Placebo	Overall
	Gender	Female	5	5	2	3	5	4	24
		Male	9	9	12	11	8	6	55
	Race	Black					2		2
		Caucasian	3	2	2	4	1	1	13
		Hispanic	11	12	12	10	10	9	64
	Age (yrs)	N	14	14	14	14	13	10	79
		Mean	34.57	35.50	34.14	34.50	36.62	36.30	35.2
		SD	12.966	15.124	11.245	10.818	12.440	9.405	11.9
		Median	31.00	30.50	33.50	33.50	33.00	36.00	33.0
		Minimum	21.0	20.0	21.0	20.0	20.0	23.0	20.0
		Maximum	61.0	60.0	56.0	53.0	60.0	48.0	61.0
	Weight (kg)	N	14	14	14	14	13	10	79
		Mean	68.63	69.67	68.42	70.04	72.26	68.39	69.6
		SD	7.384	8.323	6.946	7.529	7.453	6.963	7.4
		Median	68.00	70.65	65.40	69.15	73.60	67.20	69.2
		Minimum	59.2	57.0	60.1	56.2	62.5	60.7	56.2
		Maximum	81.1	86.6	80.2	84.0	82.7	78.2	86.6
Height (cm)	N	14	14	14	14	13	10	79	
	Mean	167.07	165.43	167.00	167.36	168.85	164.60	166.8	
	SD	9.523	6.284	8.152	10.203	7.105	8.113	8.2	
	Median	166.50	164.50	167.00	170.00	167.00	167.00	167.0	
	Minimum	147.0	154.0	151.0	145.0	159.0	151.0	145.0	
	Maximum	182.0	178.0	181.0	182.0	185.0	176.0	185.0	
Dosage and Administration	79 subjects were randomized into 1 of 5 Treatment Groups as shown below. 2 subjects received placebo at each group.								
	Treatment Group	Dose Levels DM/Q	Dosing Regimen	Duration	Number of Subjects				
	A	45 mg/30 mg	b.i.d.	Days 1-8*	16				
	B	30 mg/10 mg	b.i.d.	Days 1-8*	16				
	C	30 mg/10 mg	t.i.d.	Days 1-8*	16				
	D	60 mg/15 mg	b.i.d.	Days 1-8*	16				
	E	60 mg/15 mg	q.d.	Days 1-8*	15				
	*The subjects received only the first dose on Day 8								
	Subjects were required to fast for at least 2 hours before and 1 hour after each dosing. 240 mL water was taken during each study drug administration.								

Zenvia (Dextromethorphan/Quinidine) capsules
N21-879

	<p>Test Products: AVP-923 (Dextromethorphan HBr/Quinidine Sulfate) 45/30 mg capsules Manufactured by (b) (4) Lot No.: PD109A-001 Manufacture date: May 2005</p> <p>AVP-923 (Dextromethorphan HBr/Quinidine Sulfate) 30/10 mg capsules Manufactured by (b) (4) Lot No.: PD261-003 Manufacture date: March 2007</p> <p>AVP-923 (Dextromethorphan HBr/Quinidine Sulfate) 60/15 mg capsules Manufactured by (b) (4) Lot No.: C7K01601 Manufacture date: November 2007</p> <p>AVP-923 (Dextromethorphan HBr/Quinidine Sulfate) Placebo Manufactured by (b) (4) Lot No.: PD110A-001 Manufacture date: May 2005</p> <p><u>Diet:</u> Water was not permitted from 2 hours before until 1 hour after dosing, but was allowed at all other times.</p> <p>Subjects was prohibited from the following foods and/or beverages:</p> <ul style="list-style-type: none"> • Xanthines: 24 hours before dosing and throughout the period of sample collection; • Alcohol: 48 hours before dosing and throughout the period of sample collection; • Grapefruit: 10 days before dosing and throughout the study; • Vitamins: throughout the confinement period. • High-fiber products (may affect absorption) <p>No medication or herbal were permitted during blood sample collection.</p>								
<p>Sampling: Plasma</p>	<p>For dextromethorphan, dextrorphan, and quinidine (Plasma): Day 1: predose (0 hour), and 1, 2, 3, 4, 6, 8 and 12 hours post-dose. Day 6 and 7: Prior to the morning dose Day 8: predose (0 hour), and 1, 2, 3, 4, 6, 8, 12, 24 and 36 hours post-dose</p>								
<p>Analysis (Plasma)</p>	<p><u>Method</u> LC-MS/MS</p> <p><u>Lower Limits of Quantitation</u></p> <table data-bbox="418 1192 966 1325"> <thead> <tr> <th></th> <th><u>Plasma</u></th> </tr> </thead> <tbody> <tr> <td>Dextromethorphan</td> <td>0.200 ng/mL</td> </tr> <tr> <td>Dextrorphan</td> <td>2.50 ng/mL</td> </tr> <tr> <td>Quinidine</td> <td>2.00 ng/mL</td> </tr> </tbody> </table> <p><u>Dextromethorphan:</u> Linear range : 0.200-200 ng/mL in plasma (heparin) Inter-day Precision (%CV for Quality Controls) : < 6.0% Inter-day accuracy: 2.7% Short term Stability: 27 hours in propylene tubes at ambient temperature under white light</p> <p><u>Dextrorphan:</u> Linear range : 2.50-2500 ng/mL in plasma (heparin) Inter-day Precision (%CV for Quality Controls) : < 5.8% Inter-day accuracy: 0.7-2.7% Short term Stability: 27 hours in propylene tubes at ambient temperature under white light</p> <p><u>Quinidine:</u></p>		<u>Plasma</u>	Dextromethorphan	0.200 ng/mL	Dextrorphan	2.50 ng/mL	Quinidine	2.00 ng/mL
	<u>Plasma</u>								
Dextromethorphan	0.200 ng/mL								
Dextrorphan	2.50 ng/mL								
Quinidine	2.00 ng/mL								

	Linear range : 2-250 ng/mL in plasma (heparin) Inter-day Precision (%CV for Quality Controls) : < 5.2% Inter-day accuracy: -1.6 % to 1.2% Short term Stability: 28 hours at ambient temperature under white light
PK Assessment	Day 1: AUC _{0-t} , AUC _{inf} , AUC/AUC _{inf} , C _{max} , T _{max} , kel, and t _{1/2} . Day 8: AUC _{0-t} , AUC ₀₋₂₄ , AUC ₀₋₁₂ , C _{max} , C _{min} , T _{max} , C _{ssav} and Flux.
Safety Assessment	Assessment of adverse events, clinical laboratory results, physical examinations, vital signs and electrocardiograms

Results:

Pharmacokinetics

Pharmacokinetics of Dextromethorphan:

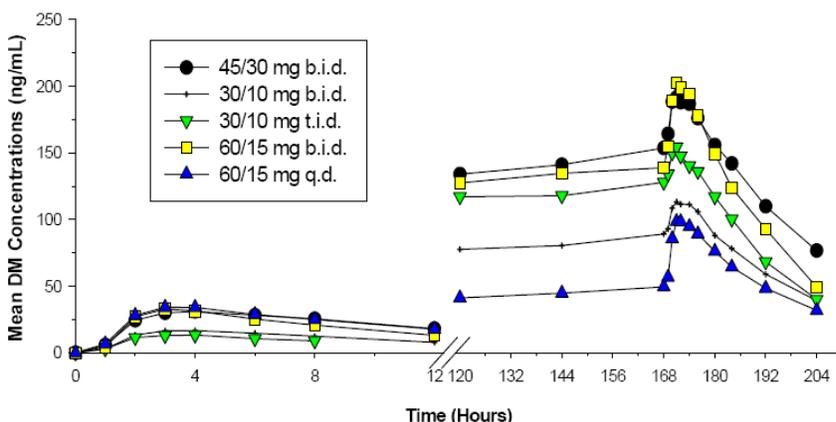
The pharmacokinetic parameters of dextromethorphan are summarized in the following table:

Table 11.4.3.1.1:3 Comparison of Dextromethorphan PK Parameters between Day 1 and Day 8

Day	PK Parameters	DM/Q 45/30 mg b.i.d.	DM/Q 30/10 mg b.i.d.	DM/Q 30/10 mg t.i.d.	DM/Q 60/15 mg b.i.d.	DM/Q 60/15 mg q.d.
1	AUC _{0-t} (ng-h/mL)	258.9 (34.1)	128.8 (40.0)	71.7 (36.7)	240.7 (27.2)	251.5 (61.7)
	C _{max} (ng/mL)	30.74 (35.5)	17.28 (37.5)	13.16 (39.5)	32.92 (25.3)	33.13 (52.0)
8	AUC _{0-t} (ng-h/mL)	2075.1 (20.1)	1183.9 (34.6)	1074.8 (35.8)	2062.8 (29.9)	1520.8 (57.2)
	C _{max} (ng/mL)	192.37 (22.1)	113.04 (32.7)	147.27 (35.5)	200.8 (27.5)	93.37 (41.4)

The concentration-time profiles of dextromethorphan are shown in the following figure:

Figure 11.4.3.1.1:1 Mean Plasma Dextromethorphan



- The PK profile obtained at the 60/15 mg b.i.d. of DM/Q combination appeared to be similar to that of the reference treatment (45/30 mg b.i.d.) on Day 8.

- Compared to the reference values, mean AUC₀₋₂₄ values were approximately 43%, 22% and 63% lower than those of DM/Q combinations of 30/10 mg b.i.d., 30/10 mg t.i.d and 60/15 mg q.d, respectively.
- Median T_{max} values ranged from 3.00 to 4.00 hours over the DM/Q combinations studied.
- Mean half-life values were 23.2 and 15.0 hours at 45/30 mg b.i.d. and 60/15 mg b.i.d., respectively.
- Approximately 6.0 to 14.8-fold and 2.8 to 11.2-fold increases were observed in AUC and C_{max} values, respectively, on Day 8 compared to Day 1.

Pharmacokinetics of Dextrophan:

The pharmacokinetic parameters of dextrophan are summarized in the following table:

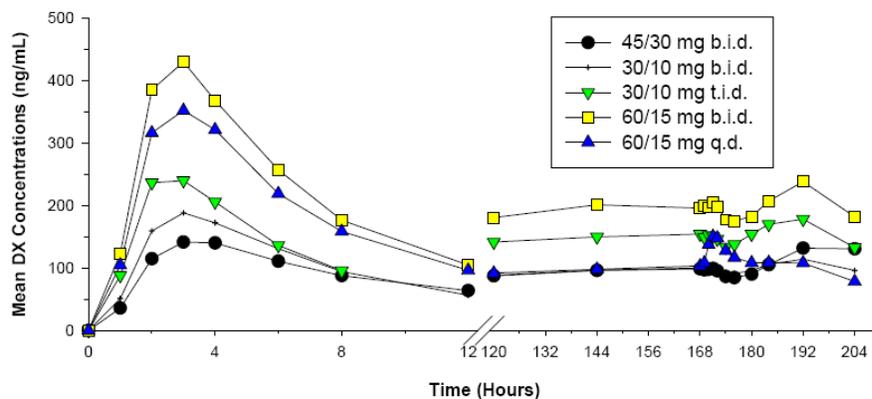
Table 11.4.3.1.2:3 Comparison of Dextrophan PK Parameters between Day 1 and Day 8

Day	PK Parameters	DM/Q 45/30 mg b.i.d.	DM/Q 30/10 mg b.i.d.	DM/Q 30/10 mg t.i.d.	DM/Q 60/15 mg b.i.d.	DM/Q 60/15 mg q.d.
1	AUC _{0-t} (ng·h/mL)	1029.0 (44.8)	1232.4 (40.0)	1205.0 (22.5)	2650.7 (26.4)	1808.9 (136.0)
	AUC _{inf} (ng·h/mL)	NC	1819.7 (13.2)	1834.7 (12.3)	3473.9 (23.0)	3738.6 (24.3)
	C _{max} (ng/mL)	132.8 (52.0)	179.3 (48.7)	244.3 (27.4)	413.7 (32.3)	261.9 (149.9)
8	AUC _{tau} (ng·h/mL)	1065.1 (24.1)	1124.0 (30.7)	1132.0 (19.2)	2201.0 (20.9)	2527.1 (58.9)
	C _{max} (ng/mL)	98.1 (24.8)	103.4 (31.5)	153.6 (21.0)	206.7 (24.4)	138.3 (61.6)

NC: Not calculated

The mean concentration-time profiles of dextrophan are shown in the following figure:

Figure 11.4.3.1.2:1 Mean Plasma Dextrophan



- The PK profile obtained at the 30/10 mg b.i.d. of DM/Q combination appeared to be similar to that of the reference treatment (45/30 mg b.i.d.).

- Mean AUC₀₋₂₄ values were approximately 59%, 107% and 19% greater than those of DM/Q combinations of 30/10 mg t.i.d., 60/15 mg b.i.d. and 60/15 mg q.d., respectively, compared to the reference treatment value.
- Median T_{max} values ranged from 0.50 to 3.00 hours over the DM/Q combinations studied.
- Mean half-life values ranged from 23.4 to 31.1 hours over the DM/Q combinations of 30/10 and 60/15 mg studied.
- C_{max} values generally decreased by approximately 26% to 50% between Days 1 and 8 over the dose range studied of DM/Q combinations.
- AUC values (AUC_{inf} vs. AUC_{tau}) generally decreased by approximately 33% to 39% over the dose ranges of 30/10 to 60/15 mg of DM/Q combinations.

Pharmacokinetics of Quinidine:

The pharmacokinetic parameters of quinidine are summarized in the following table:

Table 11.4.3.1.3:3 Comparison of Quinidine PK Parameters between Day 1 and Day 8

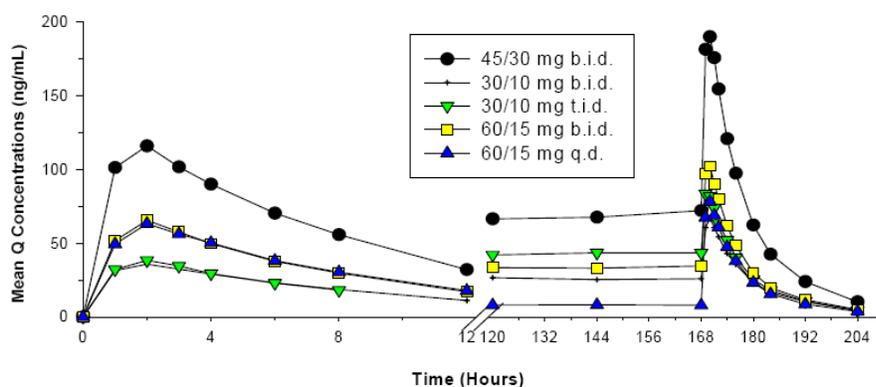
Day	PK Parameters	DM/Q 45/30 mg b.i.d.	DM/Q 30/10 mg b.i.d.	DM/Q 30/10 mg t.i.d.	DM/Q 60/15 mg b.i.d.	DM/Q 60/15 mg q.d.
1	AUC _{0-t} ** (ng·h/mL)	795.5 (25.8)	255.2 (27.9)	206.3 (21.7)	436.9 (20.1)	426.6 (31.5)
	AUC _{inf} ** (ng·h/mL)	1003.2 (17.7)	287.4 (21.3)	327.4* (21.3)	530.9 (22.0)	541.3 (42.4)
	C _{max} ** (ng/mL)	113.6 (34.1)	36.6 (30.3)	37.8 (24.6)	64.9 (15.3)	62.6 (33.0)
8	AUC _{tau} ** (ng·h/mL)	1390.3 (36.7)	488.0 (38.8)	473.8 (34.3)	740.2 (21.8)	703.5 (34.7)
	C _{max} ** (ng/mL)	188.5 (33.9)	66.3 (32.8)	81.0 (34.5)	103.4 (18.4)	76.8 (38.4)

*n = 1 (value not used for comparison between dose levels)

**Geometric mean

The mean concentration-time profiles of quinidine are shown in the following figure:

Figure 11.4.3.1.3:1 Mean Plasma Quinidine



- Mean AUC₀₋₂₄ values were approximately 65%, 49%, 47% and 75% lower than those of DM/Q combinations of 30/10 mg b.i.d., 30/10 mg t.i.d., 60/15 mg b.i.d. and 60/15 mg q.d., respectively.
- Median T_{max} values ranged from 1.0 to 2.00 hours over the DM/Q combinations studied.

- Mean half-life values remained constant over the DM/Q combinations studied (values ranged from 9.27 to 9.62 hours).
- Systemic exposure of Q increased by approximately 39% for the DM/Q combinations of 45/30 mg b.i.d. and 60/15 mg b.i.d.. It also increased approximately 70% and 30% for DM/Q 30/10 mg b.i.d. and 60/15 mg q.d., respectively.
- Cmax values increased by approximately 66%, 81, 114, 59 and 23% at the DM/Q combinations of 45/30 mg b.i.d., 30/10 mg b.i.d., 30/10 mg t.i.d., 60/15 mg b.i.d. and 60/15 mg q.d., respectively.

Statistical Results for AUC0-24 on Day 8

ANOVA Results for AUC₀₋₂₄

Summary of ANOVA Results for AUC₀₋₂₄ on Day 8

	Ratios of LSM%		
	Dextromethorphan	Dextrorphan	Quinidine
B/A% (30/10 mg b.i.d.) / (45/30 mg b.i.d.)%	57.1%	105.5%	35.1%
C/A% (30/10 mg t.i.d.) / (45/30 mg b.i.d.)%	77.7%	159.4%	51.1%
D/A% (60/15 mg b.i.d.) / (45/30 mg b.i.d.)%	99.4%	206.6%	53.2%
E/A% (60/15 mg q.d.) / (45/30 mg b.i.d.)%	36.6%	118.6%	25.3%
Intrasubject CV%	37.9%	34.2%	34.9%

- The comparison of different DM/Q combinations to the reference treatment (B vs. A, C vs. A, D vs. A, and E vs. A) showed that the AUC0-24 ratios of dextromethorphan (60/15 mg b.i.d.) / (45/30 mg b.i.d.), dextrorphan ((30/10 mg b.i.d.) / (45/30 mg b.i.d.)), and dextrorphan (60/15 mg q.d.) / (45/30 mg b.i.d.) were within 80.0-125.0%.
- These results suggest that the AUC0-24 of dextromethorphan at the 60/15 mg b.i.d. and that of dextrorphan at 30/10 mg b.i.d. and 60/15 mg q.d. were not different to those of the reference treatment (45/30mg b.i.d.).

Adverse Events

Incidence of adverse events in each group is summarized below.

Table 12.2.3:1 Subjects (%) Reporting Adverse Events at Each Dose Level

Treatment	Dose Levels*	Number of subjects (%) with AEs
A	45 mg DM / 30 mg Q b.i.d. for 7 days (n=14)	12 (86%)
B	30 mg DM / 10 mg Q b.i.d. for 7 days (n=14)	9 (64%)
C	30 mg DM / 10 mg Q t.i.d. for 7 days (n=14)	12 (86%)
D	60 mg DM / 15 mg Q b.i.d. for 7 days (n=14)	13 (93%)
E	60 mg DM / 15 mg Q q.d. for 7 days (n=13)	11 (85%)
Placebo	Matching placebo (n=10)	5 (50%)

Source data: [Table 14.3.1.1](#)

*Subjects received only the first dose on Day 8

Withdrawal

Five subjects were withdrawn from the study by the PI. Subject No. 12 (treatment A) was withdrawn by the Investigator due to AEs (Chills approximately 1.8 hours post dose, on Day 1, followed by diarrhea 44 minutes later. On Day 3, the subject experienced mydriasis, dizziness, dry mouth, palpitations, skin warm, hyperhidrosis and tachycardia approximately 4 hours after the last dose on Day 2. Approximately 6.8 hours later the subject reported nausea, followed by a headache approximately 1.5 hours later. All AEs were mild in severity and resolved without treatment.). Subject No. 49 (treatment D) was withdrawn by the sponsor due to pre-existing junctional rhythm, and Subject No. 75 (treatment D) was withdrawn due to ectopic atrial rhythm, and Subject Nos. 64 and 73 (treatment D) were withdrawn by the PI due to AEs. Subject Nos. 57, 61 and 78 withdrew for personal reasons. All subjects underwent their appropriate post-study procedures.

- Group D (DM 60mg/Q15mg) BID appeared to have highest incidences of AEs (93%).
- Group B (DM 30mg/Q 10mg) BID have lower AEs (64%) and closest to the incidences of AEs in placebo (50%).
- Four out of five withdrawals come from group D.

Conclusions:

- Although the 60/15 mg b.i.d. dose group provides the closest PK match for DM levels, DX levels are elevated more than two-fold compared to that of the reference treatment and its use was associated with a higher incidence of AEs and discontinuations.
- The next closest match to the PK properties of DM was provided with 30/10 mg t.i.d. treatment. The AUC₀₋₂₄ for DM on Day 8 was only 22% less than that for the reference treatment, and the AUC₀₋₂₄ for DX was only about 59% higher. With the 30/10 mg t.i.d. treatment, the AUC₀₋₂₄ for Q is 49% lower than with the 45/30 mg b.i.d. treatment. It is therefore predicted that, with 30/10 mg t.i.d. DM/Q treatment, the efficacy observed with 45/30 treatment should be maintained while potential risk associated with Q will be decreased.
- Exposure levels of DM following 30/10 b.i.d. treatment are 43% lower than those with the 45/30 mg b.i.d. treatment. DX levels are equivalent to the 45/30 mg b.i.d. treatment and the Q exposures are 65% reduced. Because it was better tolerated than the 45/30 mg b.i.d. reference and the other test formulations, the 30/10 b.i.d. treatment regimen also merits further study.

Reviewer's note:

As the doses and dosing regimens have been chosen for the clinical trials, this study did not serve for the decision making purpose. However, instead, it provides supportive evidence for the selection of the dose used in the pivotal clinical trial.

4.1-2. IN VITRO STUDIES

4.1-2.1 In vitro metabolism

Study DMQ 142:

GLP *In Vitro* Assessment of Human Liver Cytochrome P450 Inhibition Potential of Dextromethorphan Hydrobromide

Objective

To assess the potential of dextromethorphan hydrobromide (DM) to inhibit the catalytic activity associated with the formation of metabolites produced by CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4.

Test System

Human liver microsomes pooled from 15 individuals (male and females)

Methods

Cytochrome P450-specific probe substrates were incubated with pooled human liver microsomes in the presence and absence of standard inhibitors or DM (0, 0.05, 0.1, 0.5, 1 and 5 μM). DM was pre-incubated for 30 minutes with pooled human liver microsomes before the addition of the CYP450-specific probe substrate to assess potential time-dependent inhibition. The effects of standard inhibitors and of DM on the rate of production of the relevant probe substrate metabolites were evaluated. When inhibition reached significant levels, IC_{50} values for both direct and time-dependent inhibition were determined.

The maker substrates, metabolites, internal standards, positive control inhibitors and vendors for the chemicals utilized in each CYP450 assay are summarized in the table below.

Table 3: List of Substrate Probes, Inhibitors and Incubation Conditions to Assess Human Microsomal CYP450 Activity

Isoform Monitored	Marker Substrate	Substrate Conc. (µM)	Incubation Time (min)	Protein Conc. (mg/mL)	Metabolite	Positive Control Inhibitor (Direct)	Direct Inhibitor Conc. (µM)	Mechanism-Based Inactivation (MBI) Positive Control Inhibitor	MBI Inhibitor Conc. (µM)
CYP1A2	Phenacetin	50	30	0.1	Acetaminophen	Furafylline	50	Furafylline	50
CYP2A6	Coumarin	1	5	0.025	7-Hydroxycoumarin	Tranylcypromine	10	NA*	NA*
CYP2B6	Bupropion	125	20	0.25	Hydroxybupropion	Thio-TEPA	75	NA*	NA*
CYP2C8	Paclitaxel	5	10	0.075	6 α -Hydroxypaclitaxel	Quercetin	10	Phenelzine	100
CYP2C9	Diclofenac	5	4	0.05	4'-Hydroxydiclofenac	Sulfaphenazole	20	Tienilic Acid	10
CYP2C19	(S)-Mephenytoin	50	30	0.1	4'-Hydroxymephenytoin	Ticlopidine	1	Ticlopidine	1
CYP2D6	Dextromethorphan	5	15	0.2	Dextrophan	Quinidine	10	3,4-Methylenedioxy-methamphetamine (MDMA)	250
CYP2E1	Chlorzoxazone	50	20	0.1	6-Hydroxychlorzoxazone	Clomethiazole	100	NA*	NA*
CYP3A4 [†]	Midazolam	5	4	0.025	1'-Hydroxymidazolam	Ketoconazole	1	Mifepristone	10
CYP3A4 [†]	Testosterone	50	7	0.05	6 β -Hydroxytestosterone	Ketoconazole	1	Mifepristone	10

(b) (4) recommends that at least two assays be used to assess CYP3A4 interactions. This is due to reports describing a steroid binding site and a benzodiazepine binding site on the enzyme (8, 9).

*NA – Not applicable; No MBI Positive control utilized.

Results

Following table indicates shows the estimated IC₅₀ values for DM CYP450 isoform-specific inhibition.

Summary of the Estimated IC₅₀ Values for Inhibition of CYP450 by Dextromethorphan Hydrobromide

P450 Isoform	Substrate	Estimated IC ₅₀ (µM)	
		Direct Inhibition	Time-dependent (MBI) Inhibition
CYP1A2	Phenacetin	>5	>5
CYP2A6	Coumarin	>5	>5
CYP2B6	Bupropion	>5	>5
CYP2C8	Paclitaxel	>5	>5
CYP2C9	Diclofenac	>5	>5
CYP2C19	(S)-Mephenytoin	>5	>5
CYP2D6	Dextromethorphan	>5	>5
CYP2E1	Chlorzoxazone	>5	>5
CYP3A4	Midazolam	>5	>5
CYP3A4	Testosterone	>5	>5

- No inhibition was observed for DM at concentrations up to 5 μ M for CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 (midazolam) and 3A4 (testosterone).
- Following a 30 minute pre-incubation with NADPH, DM at concentrations up to 5 μ M showed no significant changes in IC50 values for CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 (midazolam) and 3A4 (testosterone), indicating DM is not likely a time-dependent inhibitor of these isoforms.

Conclusions:

- DM at concentrations up to 5 μ M is unlikely to play a role in clinical drug-drug interactions related to inhibition of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4 metabolism.

Study DMQ 143:

***GLP In Vitro Assessment of Human Liver Cytochrome P450 Inhibition
Potential of Quinidine Sulfate***

Objective

To assess the potential of quinidine sulfate (Q) to inhibit the catalytic activity associated with the formation of metabolites produced by CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4.

Test System

Human liver microsomes pooled from 15 individuals (male and females)

Methods

Cytochrome P450-specific probe substrates were incubated with pooled human liver microsomes in the presence and absence of standard inhibitors or Q (0, 0.05, 0.1, 0.5, 1 and 5 μM). Q was pre-incubated for 30 minutes with pooled human liver microsomes before the addition of the CYP450-specific probe substrate to assess potential time-dependent inhibition. The effects of standard inhibitors and of Q on the rate of production of the relevant probe substrate metabolites were evaluated. When inhibition reached significant levels, IC₅₀ values for both direct and time-dependent inhibition were determined.

The maker substrates, metabolites, internal standards, positive control inhibitors and vendors for the chemicals utilized in each CYP450 assay are summarized in the table below. These are acceptable per the FDA guidance “Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro” and draft guidance “Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling”.

Table 3: List of Substrate Probes, Inhibitors and Incubation Conditions to Assess Human Microsomal CYP450 Activity

Isoform Monitored	Marker Substrate	Substrate Conc. (µM)	Incubation Time (min)	Protein Conc. (mg/mL)	Metabolite	Positive Control Inhibitor (Direct)	Direct Inhibitor Conc. (µM)	Mechanism-Based Inactivation (MBI) Positive Control Inhibitor	MBI Inhibitor Conc. (µM)
CYP1A2	Phenacetin	50	30	0.1	Acetaminophen	Furafylline	50	Furafylline	50
CYP2A6	Coumarin	1	5	0.025	7-Hydroxycoumarin	Tranylcypromine	10	NA*	NA*
CYP2B6	Bupropion	125	20	0.25	Hydroxybupropion	Thio-TEPA	75	NA*	NA*
CYP2C8	Paclitaxel	5	10	0.075	6α-Hydroxypaclitaxel	Quercetin	10	Phenelzine	100
CYP2C9	Diclofenac	5	4	0.05	4'-Hydroxydiclofenac	Sulfaphenazole	20	Tienilic Acid	10
CYP2C19	(S)-Mephenytoin	50	30	0.1	4'-Hydroxymephenytoin	Ticlopidine	1	Ticlopidine	1
CYP2D6	Dextromethorphan	5	15	0.2	Dextrophan	Quinidine	10	3,4-Methylenedioxy-methamphetamine (MDMA)	250
CYP2E1	Chlorzoxazone	50	20	0.1	6-Hydroxychlorzoxazone	Clomethiazole	100	NA*	NA*
CYP3A4 [†]	Midazolam	5	4	0.025	1'-Hydroxymidazolam	Ketoconazole	1	Mifepristone	10
CYP3A4 [†]	Testosterone	50	7	0.05	6β-Hydroxytestosterone	Ketoconazole	1	Mifepristone	10

^{(b) (4)} recommends that at least two assays be used to assess CYP3A4 interactions. This is due to reports describing a steroid binding site and a benzodiazepine binding site on the enzyme (8, 9).

*NA – Not applicable; No MBI Positive control utilized.

Results

Following table shows the estimated IC₅₀ values for Q CYP450 insoform-specific inhibition.

Summary of the Estimated IC₅₀ Values for Inhibition of CYP450 by Quinidine Sulfate

P450 Isoform	Substrate	Estimated IC ₅₀ (µM)	
		Direct Inhibition	Time-dependent (MBI) Inhibition
CYP1A2	Phenacetin	>5	>5
CYP2A6	Coumarin	>5	>5
CYP2B6	Bupropion	>5	>5
CYP2C8	Paclitaxel	>5	>5
CYP2C9	Diclofenac	>5	>5
CYP2C19	(S)-Mephenytoin	>5	>5
CYP2D6	Dextromethorphan	<0.05	<0.05
CYP2E1	Chlorzoxazone	>5	>5
CYP3A4	Midazolam	>5	>5
CYP3A4	Testosterone	>5	>5

- No inhibition was observed for Q at concentrations up to 5 µM for CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1, 3A4 (midazolam) or 3A4 (testosterone).

- Q inhibit CYP2D6 at all concentrations examined.
- Following a 30 minute pre-incubation with NADPH, Q at concentrations up to 5 μ M showed no significant changes in IC50 values for CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1, 3A4 (midazolam) or 3A4 (testosterone), indicating Q is not likely a time-dependent inhibitor of these isoforms.
- Q inhibits CYP2D6 by > 50% upon pre-incubation.

Conclusions:

- Q at concentrations up to 5 μ M is unlikely to play a role in clinical drug-drug interactions related to inhibition of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1 or 3A4 metabolism.
- Q plays a significant role in clinical drug-drug interactions related to the inhibition of CYP2D6.

Study DMQ 144:

GLP In Vitro Assessment of the Induction Potential of Dextromethorphan Hydrobromide in Primary Cultures of Human Hepatocytes

Objective

To utilize primary cultures of human hepatocytes to evaluate the potential of dextromethorphan hydrobromide to induce liver microsomal cytochrome P450 (CYP450) enzymes

Test System

Primary cultures of human hepatocytes were prepared from human liver tissue from three donors

Methods

Dextromethorphan hydrobromide (DM) and known CYP450 inducers, 3-methylcholanthrene (3-MC), phenobarbital (PB), and rifampicin (RIF), were incubated with cultures of human hepatocytes from three separate donors for three consecutive days. *In situ* samples were collected, and enzymatic activities for CYP1A2, CYP2B6, and CYP3A4 were determined using selective metabolite markers. Messenger RNA (mRNA) levels for CYP1A2, CYP2B6, and CYP3A4 were also analyzed using TaqMan®-based quantitative real time-polymerase chain reaction (qRT-PCR).

Concentrations for dosing solutions of DM (0.048, 0.48, and 4.8 μM) and positive controls, 3-MC (2 μM), PB (1000 μM), and RIF (10 μM) are summarized in the table below. At these concentrations, the positive controls induce maximal CYP450 activity without causing cytotoxicity. Negative control cultures were treated with vehicle (0.1% DMSO).

Table 2.4.1: Treatment Protocol to Assess Enzyme Induction by Dextromethorphan Hydrobromide in Primary Human Hepatocyte Cultures

Group #	Comprehensive Study	Concentration
1	Control	0.1% DMSO
2	3-Methylcholanthrene (3-MC)	2 μM
3	Phenobarbital (PB)	1000 μM
4	Rifampicin (RIF)	10 μM
5	Dextromethorphan hydrobromide	0.048 μM
6	Dextromethorphan hydrobromide	0.48 μM
7	Dextromethorphan hydrobromide	4.8 μM

Cell culture medium containing the appropriate CYP450 marker substrates for CYP1A2, CYP2B6, and CYP3A4 was added directly to the monolayers. ^{(b) (4)}

where they were processed for LC-MS/MS analysis. In each analytical run, at least six calibration standards and 12 quality control (QC) samples (at three

different concentrations) were used to evaluate the quality of the analytical runs. Substrate probes and assay conditions are described in the table below.

Table 2.6.1: Substrate Probes and Assay Conditions for Assessment of Human *In Situ* CYP450 Activity

Enzyme	Substrate	Concentration	Incubation Time	Marker Metabolite
CYP1A2	Phenacetin	100 µM	15 min	Acetaminophen
CYP2B6	Bupropion	500 µM	20 min	Hydroxybupropion
CYP3A4	Testosterone	200 µM	14 min	6β-Hydroxytestosterone

Results

The activity results from the three preparations of human hepatocytes are summarized as the % positive control activity and fold induction in the tables below.

Summary of Enzyme Activity (% Positive Control) after Treatment with Dextromethorphan Hydrobromide

Treatment	CYP1A2			CYP2B6			CYP3A4		
	Hu684	Hu689	Hu693	Hu684	Hu689	Hu693	Hu684	Hu689	Hu693
3-Methylcholanthrene (3-MC; 2 µM)	100	100	100	2.9	1.8	12.3	-2.1	-6.1	-2.7
Phenobarbital (PB; 1000 µM)	2.0	2.9	1.0	100	100	100	32.7	38.6	37.2
Rifampicin (RIF; 10 µM)	0.87	2.5	1.7	38.6	14.0	71.4	100	100	100
Dextromethorphan hydrobromide (0.048 µM)	0.27	0.14	1.2	1.4	0.20	4.6	2.2	0.34	4.5
Dextromethorphan hydrobromide (0.48 µM)	0.55	0.73	1.1	1.6	0.68	2.1	0.56	2.2	1.8
Dextromethorphan hydrobromide (4.8 µM)	0.28	0.60	0.73	3.9	1.9	0.14	1.9	1.6	0.73

Summary of Enzyme Activity (Fold Induction) after Treatment with Dextromethorphan Hydrobromide

Treatment	CYP1A2			CYP2B6			CYP3A4		
	Hu684	Hu689	Hu693	Hu684	Hu689	Hu693	Hu684	Hu689	Hu693
3-Methylcholanthrene (3-MC; 2 µM)	154.4	68.1	113.1	1.6	1.4	1.7	0.6	0.5	0.7
Phenobarbital (PB; 1000 µM)	4.1	2.9	2.2	19.9	25.7	6.9	7.2	4.1	4.7
Rifampicin (RIF; 10 µM)	2.3	2.7	3.0	8.3	4.5	5.2	20.0	8.9	11.0
Dextromethorphan hydrobromide (0.048 µM)	1.4	1.1	2.4	1.3	1.1	1.3	1.4	1.0	1.4
Dextromethorphan hydrobromide (0.48 µM)	1.9	1.5	2.2	1.3	1.2	1.1	1.1	1.2	1.2
Dextromethorphan hydrobromide (4.8 µM)	1.4	1.4	1.8	1.7	1.5	1.0	1.4	1.1	1.1

The results for mRNA are summarized as the % positive control activity and fold induction in the tables below.

Summary of mRNA Content (% Positive Control) after Treatment with Dextromethorphan Hydrobromide

Treatment	CYP1A2			CYP2B6			CYP3A4		
	Hu684	Hu689	Hu693	Hu684	Hu689	Hu693	Hu684	Hu689	Hu693
3-Methylcholanthrene (3-MC; 2 µM)	100	100	100	3.6	1.8	3.6	-1.1	-7.8	-7.3
Phenobarbital (PB; 1000 µM)	0.24	0.43	0.31	100	100	100	49.4	72.1	55.6
Rifampicin (RIF; 10 µM)	0.02	0.05	0.45	68.9	38.1	79.4	100	100	100
Dextromethorphan hydrobromide (0.048 µM)	0.49	0.62	0.54	1.4	2.5	-0.11	0.37	4.4	3.7
Dextromethorphan hydrobromide (0.48 µM)	0.72	0.52	0.27	1.1	0.42	-2.2	0.22	-1.5	-3.1
Dextromethorphan hydrobromide (4.8 µM)	0.57	0.32	-0.07	3.7	2.0	1.1	0.89	-5.9	0.83

Summary of mRNA Content (Fold Induction) after Treatment with Dextromethorphan Hydrobromide

Treatment	CYP1A2			CYP2B6			CYP3A4		
	Hu684	Hu689	Hu693	Hu684	Hu689	Hu693	Hu684	Hu689	Hu693
3-Methylcholanthrene (3-MC; 2 µM)	190	203	169	2.44	1.31	1.72	0.345	0.405	0.287
Phenobarbital (PB; 1000 µM)	1.38	1.73	1.53	42.0	22.8	20.2	25.5	5.41	5.69
Rifampicin (RIF; 10 µM)	0.964	0.968	1.76	29.2	9.24	16.2	50.8	7.16	9.51
Dextromethorphan hydrobromide (0.048 µM)	1.85	2.11	1.90	1.57	1.46	1.00	1.09	1.17	1.24
Dextromethorphan hydrobromide (0.48 µM)	2.29	1.91	1.46	1.45	1.01	0.604	1.01	0.800	0.652
Dextromethorphan hydrobromide (4.8 µM)	2.01	1.50	0.875	2.49	1.35	1.22	1.35	0.526	0.987

CYP1A2:

- A marked induction of CYP1A2-catalyzed APAP formation from phenacetin was observed with the positive control, 3-MC (2 µM), in all three human hepatocyte preparations (68.1- to 154.4-fold greater than vehicle control), demonstrating that the culture systems of hepatocytes were responding appropriately to a prototypical CYP1A-type inducer.
- No marked concentration-related increases and no significant induction responses ($\geq 40\%$ of adjusted positive control) of CYP1A2 enzyme activity were observed with any of the concentrations of DM examined in any of the human donor preparations (Hu684, Hu689, and Hu693). Percent increases in enzyme activity ranged between 0.14 and 1.2 percent of the adjusted positive control response across all hepatocyte cultures treated with DM.
- Analysis of CYP1A2 mRNA content also demonstrated that the positive control, 3-MC (2 µM), induced CYP1A2 expression as expected in all three hepatocyte preparations, and DM treatment resulted in no marked CYP1A2 mRNA induction. Overall, these data suggest that dextromethorphan hydrobromide has a very low potential to induce CYP1A2 enzyme activity at the concentrations examined.

CYP2B6:

- A marked induction of CYP2B6-catalyzed OHBP formation from bupropion was observed with the positive controls, PB (1000 µM) and RIF (10 µM), in all three human hepatocyte preparations (6.9- to 25.7-fold and 4.5- to 8.3-fold greater than vehicle control, respectively), demonstrating that the culture systems of hepatocytes were responding appropriately to prototypical CYP2B inducers.
- No marked concentration-related increases and no significant induction responses ($\geq 40\%$ of adjusted positive control) of CYP2B6 enzyme activity were observed with any of the concentrations of dextromethorphan hydrobromide examined in any of the human donor preparations (Hu684, Hu689, and Hu693). Percent increases in enzyme activity ranged between 0.14 and 4.6 percent of the adjusted positive control response across all hepatocyte cultures treated with dextromethorphan hydrobromide.
- Analysis of CYP2B6 mRNA content also demonstrated that the positive controls, PB (1000 µM) and RIF (10 µM), induced CYP2B6 expression as expected in all three hepatocyte preparations and dextromethorphan hydrobromide treatment resulted in no

marked CYP2B6 mRNA induction. Overall, these data suggest that dextromethorphan hydrobromide has a very low potential to induce CYP2B6 enzyme activity at the concentrations examined.

CYP3A4:

- A marked induction of CYP3A4-catalyzed 6 β T from testosterone was observed with the positive controls, RIF (10 μ M) and PB (1000 μ M), in all three human hepatocyte preparations (8.9- to 20.0-fold and 4.1- to 7.2-fold, respectively, greater than vehicle control), demonstrating that the culture systems of hepatocytes were responding appropriately to prototypical CYP3A inducers.
- No marked concentration-related increases and no significant induction responses (\geq 40% of adjusted positive control) of CYP3A4 enzyme activity were observed with any of the concentrations of dextromethorphan hydrobromide examined in any of the human donor preparations (Hu684, Hu689, and Hu693). Percent increases in enzyme activity ranged between 0.34 and 4.5 percent of the adjusted positive control response across all hepatocyte cultures treated with dextromethorphan hydrobromide.
- Analysis of CYP3A4 mRNA content also demonstrated that the positive controls, RIF (10 μ M) and PB (1000 μ M), induced CYP3A4 expression as expected in all three hepatocyte preparations and dextromethorphan hydrobromide treatment resulted in no marked CYP3A4 mRNA induction. Overall, these data suggest that dextromethorphan hydrobromide has a very low potential to induce CYP3A4 enzyme activity at the concentrations examined.

Conclusions:

- DM is unlikely to play a role in clinical drug-drug interactions related induction of CYP1A2, CYP2B6, and CYP3A4 at the concentrations examined (0.048, 0.48, and 4.8 μ M).

Study DMQ 145:

GLP In Vitro Assessment of the Induction Potential of Quinidine Sulfate in Primary Cultures of Human Hepatocytes

Objective

To utilize primary cultures of human hepatocytes to evaluate the potential of quinidine sulfate to induce liver cytochrome P450 (CYP450) enzymes

Test System

Primary cultures of human hepatocytes were prepared from human liver tissue from three donors

Methods

Quinidine sulfate (0.048, 0.48, and 4.8 μM) and known CYP450 inducers, 3-methylcholanthrene (3-MC), phenobarbital (PB), and rifampicin (RIF) were incubated with cultures of human hepatocytes from three separate donors for three consecutive days. *In situ* samples were collected, and enzymatic activities for CYP1A2, CYP2B6, and CYP3A4 were determined using selective metabolite markers. Messenger RNA (mRNA) levels for CYP1A2, CYP2B6, and CYP3A4 were also analyzed using TaqMan®-based quantitative real time-polymerase chain reaction (qRT-PCR).

Concentrations for dosing solutions of Q (0.048, 0.48, and 4.8 μM) and positive controls, 3-MC (2 μM), PB (1000 μM), and RIF (10 μM) are summarized in the table below. At these concentrations, the positive controls induce maximal CYP450 activity without causing cytotoxicity. Negative control cultures were treated with vehicle (0.1% DMSO).

Table 2.4.1: Treatment Protocol to Assess Enzyme Induction by Quinidine Sulfate in Primary Human Hepatocyte Cultures

Group #	Comprehensive Study	Concentration
1	Control	0.1% DMSO
2	3-Methylcholanthrene (3-MC)	2 μM
3	Phenobarbital (PB)	1000 μM
4	Rifampicin (RIF)	10 μM
5	Quinidine Sulfate	0.048 μM
6	Quinidine Sulfate	0.48 μM
7	Quinidine Sulfate	4.8 μM

Cell culture medium containing the appropriate CYP450 marker substrates for CYP1A2, CYP2B6, and CYP3A4 was added directly to the monolayers. ^{(b) (4)}

where they were processed for LC-MS/MS analysis. In each analytical run, at least six calibration standards and 12 quality control (QC) samples (at three

different concentrations) were used to evaluate the quality of the analytical runs. Substrate probes and assay conditions are described in the table below.

Table 2.6.1: Substrate Probes and Assay Conditions for Assessment of Human *In Situ* CYP450 Activity

Enzyme	Substrate	Concentration	Incubation Time	Marker Metabolite
CYP1A2	Phenacetin	100 µM	15 min	Acetaminophen
CYP2B6	Bupropion	500 µM	20 min	Hydroxybupropion
CYP3A4	Testosterone	200 µM	14 min	6β-Hydroxytestosterone

Results

The activity results from the three preparations of human hepatocytes are summarized as the % positive control activity and fold induction in the tables below.

Summary of Enzyme Activity (% Positive Control) after Treatment with Quinidine Sulfate

Treatment	CYP1A2			CYP2B6			CYP3A4		
	Hu684	Hu689	Hu693	Hu684	Hu689	Hu693	Hu684	Hu689	Hu693
3-Methylcholanthrene (3-MC; 2 µM)	100	100	100	2.9	1.8	12.3	-2.1	-6.1	-2.7
Phenobarbital (PB; 1000 µM)	2.0	2.9	1.0	100	100	100	32.7	38.6	37.2
Rifampicin (RIF; 10 µM)	0.87	2.5	1.7	38.6	14.0	71.4	100	100	100
Quinidine Sulfate (0.048 µM)	0.00	-0.01	0.29	0.80	0.49	1.7	1.0	0.85	-0.41
Quinidine Sulfate (0.48 µM)	0.69	0.78	0.95	2.4	1.1	-2.5	0.60	0.38	0.02
Quinidine Sulfate (4.8 µM)	0.51	-0.02	1.1	0.84	-1.1	-6.9	0.84	-3.7	-1.3

Summary of Enzyme Activity (Fold Induction) after Treatment with Quinidine Sulfate

Treatment	CYP1A2			CYP2B6			CYP3A4		
	Hu684	Hu689	Hu693	Hu684	Hu689	Hu693	Hu684	Hu689	Hu693
3-Methylcholanthrene (3-MC; 2 µM)	154.4	68.1	113.1	1.6	1.4	1.7	0.6	0.5	0.7
Phenobarbital (PB; 1000 µM)	4.1	2.9	2.2	19.9	25.7	6.9	7.2	4.1	4.7
Rifampicin (RIF; 10 µM)	2.3	2.7	3.0	8.3	4.5	5.2	20.0	8.9	11.0
Quinidine Sulfate (0.048 µM)	1.0	1.0	1.3	1.2	1.1	1.1	1.2	1.1	1.0
Quinidine Sulfate (0.48 µM)	2.1	1.5	2.1	1.4	1.3	0.9	1.1	1.0	1.0
Quinidine Sulfate (4.8 µM)	1.8	1.0	2.3	1.2	0.7	0.6	1.2	0.7	0.9

The results for mRNA are summarized as the % positive control activity and fold induction in the tables below.

Summary of mRNA Content (% Positive Control) after Treatment with Quinidine Sulfate

Treatment	CYP1A2			CYP2B6			CYP3A4		
	Hu684	Hu689	Hu693	Hu684	Hu689	Hu693	Hu684	Hu689	Hu693
3-Methylcholanthrene (3-MC; 2 µM)	100	100	100	3.6	1.8	3.6	-1.1	-7.8	-7.3
Phenobarbital (PB; 1000 µM)	0.24	0.43	0.31	100	100	100	49.4	72.1	55.6
Rifampicin (RIF; 10 µM)	0.02	0.05	0.45	68.9	38.1	79.4	100	100	100
Quinidine Sulfate (0.048 µM)	0.44	-0.01	-0.21	1.7	-0.09	-1.8	0.28	-4.9	-3.8
Quinidine Sulfate (0.48 µM)	0.88	0.79	0.57	3.3	2.5	-1.1	3.8	-1.9	-0.96
Quinidine Sulfate (4.8 µM)	2.1	1.6	-0.12	4.0	3.0	0.19	10.5	16.7	9.9

Summary of mRNA Content (Fold Induction) after Treatment with Quinidine Sulfate

Treatment	CYP1A2			CYP2B6			CYP3A4		
	Hu684	Hu689	Hu693	Hu684	Hu689	Hu693	Hu684	Hu689	Hu693
3-Methylcholanthrene (3-MC; 2 µM)	190	203	169	2.44	1.31	1.72	0.345	0.405	0.287
Phenobarbital (PB; 1000 µM)	1.38	1.73	1.53	42.0	22.8	20.2	25.5	5.41	5.69
Rifampicin (RIF; 10 µM)	0.964	0.968	1.76	29.2	9.24	16.2	50.8	7.16	9.51
Quinidine Sulfate (0.048 µM)	1.77	0.836	0.640	1.66	0.894	0.665	1.04	0.588	0.587
Quinidine Sulfate (0.48 µM)	2.60	2.46	1.96	2.34	1.47	0.815	2.78	0.774	0.834
Quinidine Sulfate (4.8 µM)	4.97	4.02	0.800	2.60	1.57	1.06	6.15	1.94	1.77

CYP1A2:

- A marked induction of CYP1A2-catalyzed APAP formation from phenacetin was observed with the positive control, 3-MC (2 µM), in all three human hepatocyte preparations (68.1- to 154.4-fold greater than vehicle control), demonstrating that the culture systems of hepatocytes were responding appropriately to a prototypical CYP1A-type inducer.
- No marked concentration-related increases and no significant induction responses ($\geq 40\%$ of adjusted positive control) of CYP1A2 enzyme activity were observed with any of the concentrations of Q examined in any of the human donor preparations (Hu684, Hu689, and Hu693). Percent increases in enzyme activity ranged between -0.02 and 1.1 percent of the adjusted positive control response across all hepatocyte cultures treated with Q.
- Analysis of CYP1A2 mRNA content also demonstrated that the positive control, 3-MC (2 µM), induced CYP1A2 expression as expected in all three hepatocyte preparations. Q treatment resulted in extremely small concentration-related increases in CYP1A2 mRNA content; however induction levels failed to reach significant levels ($\geq 40\%$ of adjusted positive control). Overall, these data suggest that Q has a very low potential to induce CYP1A2 enzyme activity at the concentrations examined.

CYP2B6:

- A marked induction of CYP2B6-catalyzed OHBP formation from bupropion was observed with the positive controls, PB (1000 µM) and RIF (10 µM), in all three human hepatocyte preparations (6.9- to 25.7-fold and 4.5- to 8.3-fold greater than vehicle control, respectively), demonstrating that the culture systems of hepatocytes were responding appropriately to prototypical CYP2B inducers.
- No marked concentration-related increases and no significant induction responses ($\geq 40\%$ of adjusted positive control) of CYP2B6 enzyme activity were observed with any of the concentrations of Q examined in any of the human donor preparations (Hu684, Hu689, and Hu693). Percent increases in enzyme activity ranged between -6.9 and 2.4 percent of the adjusted positive control response across all hepatocyte cultures treated with Q.

- Analysis of CYP2B6 mRNA content also demonstrated that the positive controls, PB (1000 μ M) and RIF (10 μ M), induced CYP2B6 expression as expected in all three hepatocyte preparations. Q treatment resulted in extremely small concentration-related increases in CYP2B6 mRNA content; however induction levels failed to reach significant levels ($\geq 40\%$ of adjusted positive control). Overall, these data suggest that Q has a very low potential to induce CYP2B6 enzyme activity at the concentrations examined.

CYP3A4:

- A marked induction of CYP3A4-catalyzed 6 β T formation from testosterone was observed with the positive controls, RIF (10 μ M) and PB (1000 μ M), in all three human hepatocyte preparations (8.9- to 20.0-fold and 4.1- to 7.2-fold, respectively, greater than vehicle control), demonstrating that the culture systems of hepatocytes were responding appropriately to prototypical CYP3A inducers.
- No marked concentration-related increases and no significant induction responses ($\geq 40\%$ of adjusted positive control) of CYP3A4 enzyme activity were observed with any of the concentrations of Q examined in any of the human donor preparations (Hu684, Hu689, and Hu693). Percent increases in enzyme activity ranged between -3.7 and 1.0 percent of the adjusted positive control response across all hepatocyte cultures treated with Q.
- Analysis of CYP3A4 mRNA content also demonstrated that the positive controls, RIF (10 μ M) and PB (1000 μ M), induced CYP3A4 expression as expected in all three hepatocyte preparations. Q treatment resulted in small concentration-related increases in CYP3A4 mRNA content; however induction levels failed to reach significant levels ($\geq 40\%$ of adjusted positive control). Overall, these data suggest that Q has a very low potential to induce CYP3A4 enzyme activity at the concentrations examined.

Conclusions:

- There is a very low potential for drug-drug interactions associated with quinidine sulfate due to enzyme induction of CYP1A2, CYP2B6, and CYP3A4 at the concentrations examined (0.048, 0.48, and 4.8 μ M).

4.1-3. HUMAN PK STUDIES

4.1-3.1 Patient PK

Study 07-AVR-123: A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy and to Determine the Pharmacokinetics of Two Doses of AVP-923 (Dextromethorphan/Quinidine) in the Treatment of Pseudobulbar Affect (PBA) in Patients with Amyotrophic Lateral Sclerosis and Multiple Sclerosis

This is the new pivotal clinical study supporting the efficacy of lower doses (Zenvia 30/10 and Zenvia 20/10) for the treatment of PBA. Since PK portion was also included, this review will focus on evaluating the PK results and briefly on safety from a clinical pharmacology perspective. The efficacy results and details on safety of this study will be carefully reviewed by relevant review teams.

A brief overview of some essential components of the study design is given below:

Study Design	Double-blind, randomized, placebo-controlled study		
Study Population	<p>For DB phase: 326 subjects randomized (197 with amyotrophic lateral sclerosis (ALS) and 129 with multiple sclerosis (MS)), 326 treated, and 283 completed.</p> <p>For OLE phase: 253 subjects (146 subjects with ALS and 107 subjects with MS); 235 completed.</p> <p>For PK portion: 72 patients were enrolled; however, only 41 patients consented (27 patients available, see below).</p>		
		Group 1 N=14	Group 2 N=13
	Age (years)		
	Mean (SD)	33.6 (9.22)	33.5 (9.65)
	Median	35.5	30.0
	Range	19 - 55	23 - 50
	Sex		
	Male	12 (85.7%)	9 (69.2%)
	Female	2 (14.3%)	4 (30.8%)
	Race		
	White	4 (28.6%)	6 (46.2%)
	American Indian or Alaskan Native	0 (0.0%)	0 (0.0%)
	Asian	1 (7.1%)	0 (0.0%)
	Black or of African Descent	9 (64.3%)	3 (23.1%)
	Hispanic or Latino	0 (0.0%)	4 (30.8%)
	Native Hawaiian or other Pacific Islander	0 (0.0%)	0 (0.0%)
	Other	0 (0.0%)	0 (0.0%)
	Weight		
	Mean (SD)	75.34 (11.684)	73.28 (10.415)
	Median	77.00	77.40
	Range	55.1 - 96.7	55.3 - 91.3
	Height		
	Mean (SD)	172.43 (7.498)	170.58 (8.369)
	Median	170.50	171.50
	Range	163.0 - 190.0	159.0 - 181.5
Dosage and	ALS or MS patients with PBA were randomized into 1 of 2 dose levels or		

Administration	<p>placebo for 84 days.</p> <p>Patients received a single oral dose of their assigned treatment in the morning during the first week, and then they were given twice daily (b.i.d.) oral doses, every 12 hours for the remaining 11 weeks.</p> <table border="1" data-bbox="472 365 1349 554"> <thead> <tr> <th>Duration (Weeks)</th> <th>Treatment A AVP-923-30 (DM 30 mg/Q 10 mg)</th> <th>Treatment B AVP-923-20 (DM 20 mg/Q 10 mg)</th> <th>Treatment C Placebo</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>AVP-923-30 q.d.</td> <td>AVP-923-20 q.d.</td> <td>Placebo q.d.</td> </tr> <tr> <td>11*</td> <td>AVP-923-30 b.i.d.</td> <td>AVP-923-20 b.i.d.</td> <td>Placebo b.i.d.</td> </tr> </tbody> </table> <p>*Weeks 2-12</p> <p><u>Study medication:</u></p> <table border="1" data-bbox="472 653 927 848"> <thead> <tr> <th>Phase/Treatment</th> <th>Lot Numbers</th> </tr> </thead> <tbody> <tr> <td colspan="2">Double-blind phase</td> </tr> <tr> <td>AVP-923-30</td> <td>PD261M-001</td> </tr> <tr> <td>AVP-923-20</td> <td>PD284M-001</td> </tr> <tr> <td>Placebo</td> <td>PD110A-001</td> </tr> <tr> <td colspan="2">Open-label extension phase</td> </tr> <tr> <td>AVP-923-30</td> <td>PD261-001</td> </tr> </tbody> </table> <p><u>Restrictions for diet or medications:</u> Any drugs or dietary supplement that may have increased or decreased Q levels and that may have increased plasma levels when coadministered with Q were not allowed. Exceptions were made for digoxin, warfarin, modafinil, oral steroids (at stable doses), amantadine, and haloperidol, although doses of these drugs may have been adjusted. Drugs that may have produced serotonin syndrome when coadministered with DM (e.g., monoamine oxidase inhibitors) were also disallowed.</p>	Duration (Weeks)	Treatment A AVP-923-30 (DM 30 mg/Q 10 mg)	Treatment B AVP-923-20 (DM 20 mg/Q 10 mg)	Treatment C Placebo	1	AVP-923-30 q.d.	AVP-923-20 q.d.	Placebo q.d.	11*	AVP-923-30 b.i.d.	AVP-923-20 b.i.d.	Placebo b.i.d.	Phase/Treatment	Lot Numbers	Double-blind phase		AVP-923-30	PD261M-001	AVP-923-20	PD284M-001	Placebo	PD110A-001	Open-label extension phase		AVP-923-30	PD261-001
Duration (Weeks)	Treatment A AVP-923-30 (DM 30 mg/Q 10 mg)	Treatment B AVP-923-20 (DM 20 mg/Q 10 mg)	Treatment C Placebo																								
1	AVP-923-30 q.d.	AVP-923-20 q.d.	Placebo q.d.																								
11*	AVP-923-30 b.i.d.	AVP-923-20 b.i.d.	Placebo b.i.d.																								
Phase/Treatment	Lot Numbers																										
Double-blind phase																											
AVP-923-30	PD261M-001																										
AVP-923-20	PD284M-001																										
Placebo	PD110A-001																										
Open-label extension phase																											
AVP-923-30	PD261-001																										
Sampling: Plasma	For dextromethorphan, dextrophan, and quinidine (Plasma): At predose (0 hour), and 1, 2, 3, 4, 6, 8 and 12 hours post-AM dose (at day 29 visit).																										
Analysis (Plasma)	<p><u>Method</u> LC-MS/MS</p> <p><u>Lower Limits of Quantitation</u></p> <table data-bbox="467 1339 1015 1476"> <thead> <tr> <th></th> <th>Plasma</th> </tr> </thead> <tbody> <tr> <td>Dextromethorphan</td> <td>0.200 ng/mL</td> </tr> <tr> <td>Dextrophan</td> <td>2.50 ng/mL</td> </tr> <tr> <td>Quinidine</td> <td>2.00 ng/mL</td> </tr> </tbody> </table> <p><u>Dextromethorphan:</u> Linear range : 0.200-200 ng/mL in plasma (heparin) Inter-day Precision (%CV for Quality Controls) : < 6.2% Inter-day accuracy: 2.7 % to 4.0%</p> <p><u>Dextrophan:</u> Linear range : 2.50-2500 ng/mL in plasma (heparin) Inter-day Precision (%CV for Quality Controls) : < 6.1% Inter-day accuracy: -0.1 % to 2.5%</p>		Plasma	Dextromethorphan	0.200 ng/mL	Dextrophan	2.50 ng/mL	Quinidine	2.00 ng/mL																		
	Plasma																										
Dextromethorphan	0.200 ng/mL																										
Dextrophan	2.50 ng/mL																										
Quinidine	2.00 ng/mL																										

	<p><u>Quinidine:</u> Linear range : 2.00-250 ng/mL in plasma (heparin) Inter-day Precision (%CV for Quality Controls) : < 5.2% Inter-day accuracy: -1.6 % to 1.2%</p>
PK Assessment	AUC0-12, Cmax and Tmax at steady state
Efficacy Assessment	<p>Primary: Change in number of laughing and/or crying episodes from baseline Secondary: Changes from baseline in the Center for Neurologic Studies-Lability Scale (CNS-LS) total score, change in NPI score, change in SF-36 score, change in BDI-II score, change in PRS score (in subjects with MS) and the CSI index</p>
Safety Assessment	Assessment of physical examinations, vital signs, 12-lead ECGs with a 2-minute rhythm strip, AEs, SaO2, and clinical laboratory tests

Results:

Pharmacokinetics:

The pharmacokinetic parameters of dextromethorphan, dextrorphan and quinidine are summarized in the following table:

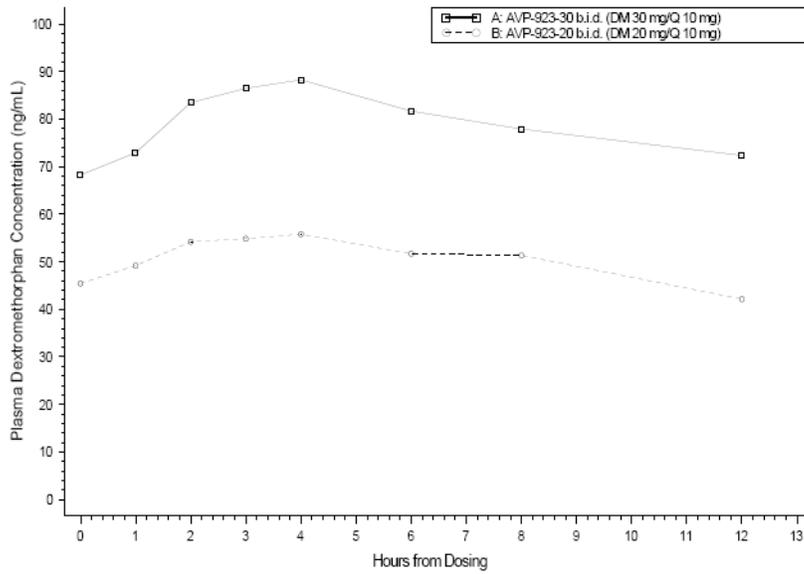
Table 11-4. Summary of Plasma Levels of Dextromethorphan, Dextrorphan, and Quinidine, by Visit, Double-Blind Phase (ITT Population)

Visit/Analyte	Plasma Levels (ng/mL)	
	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: [Appendix 16.1.13](#); [Section 14.1](#), [Table 23.2](#).
ITT = intent to treat; SD = standard deviation.

The concentration-time profiles of dextromethorphan are shown in the following figure:

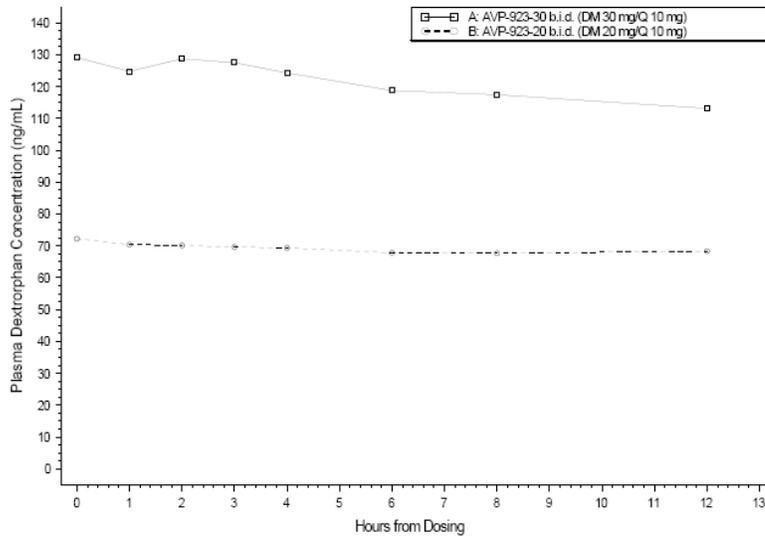
Figure 11-1 Mean Plasma Dextromethorphan Concentrations versus Time N=27



Source: Tables 14.2.1.1 and 14.2.1.2.

The concentration-time profiles of dextorphan are shown in the following figure:

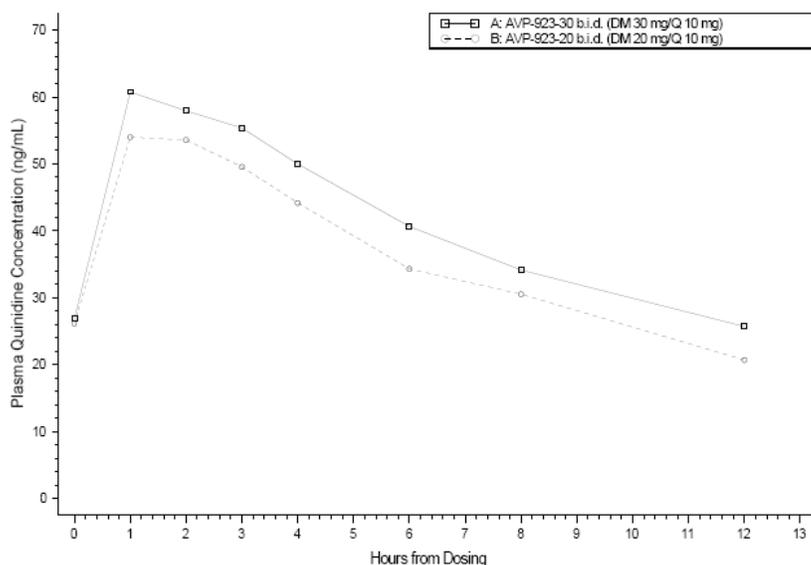
Figure 11-2 Mean Plasma Dextorphan Concentrations versus Time N=27



Source: Tables 14.2.2.1 and 14.2.2.2.

The concentration-time profiles of quinidine are shown in the following figure:

Figure 11-3 Mean Plasma Quinidine Concentrations versus Time N=24



Source: Tables 14.2.3.1 and 14.2.3.2.

- Exposure of quinidine for both dosages (30/10 and 20/10) are similar as the quinidine dose is the same in the two formulations.
- Exposure of DM and DX of 20/10 formulation are approximately two third of those for the formulation 30/10 indicating DM dose proportionality.

Summary of pharmacokinetic parameters of dextromethorphan by gender is provided below.

Table 11-5. Summary Geometric Mean and Median Plasma Dextromethorphan PK Parameters

DM Parameter		AVP-923-30	AVP-923-20
Geometric mean (CV%)			
AUC ₀₋₁₂ (ng·hr/mL)	Overall	882.9 (43.2)	524.9 (57.2)
	n	13	14
	Males	670.4 (36.5)	377.3 (41.6)
	n	6	7
	Females	1118 (32.0)	730.3 (46.9)
	n	7	7
C _{max} (ng/hr)	Overall	85.0 (40.0)	52.8 (48.3)
	n	13	14
	Males	65.7 (33.7)	40.2 (34.3)
	n	6	7
	Females	106 (29.6)	69.5 (42.9)
	n	7	7
Median (min, max)			
T _{max} (hr)	Overall	4.00 (0.00, 8.00)	2.98 (1.42, 4.00)
	n	13	14
	Males	3.58 (1.00, 6.22)	2.95 (1.42, 4.00)
	n	6	7
	Females	4.00 (0.00, 8.00)	3.00 (1.42, 4.00)
	n	7	7

Source: Appendix 16.1.13, Tables 14.2.1.4 through 14.2.1.5

- Comparing with females, males showed 38% and 40% lower C_{max} and AUC₀₋₁₂, respectively, in Zenvia 30/10 group and 42% and 48%, respectively, in Zenvia 20/10 group.

Summary of pharmacokinetic parameters of dextrorphan (DX) by gender is provided below.

Table 11-6. Summary Geometric Mean and Median Plasma Dextrorphan PK Parameters

Dextrorphan Parameter		AVP-923-30	AVP-923-20
Geometric mean (CV%)			
AUC ₀₋₁₂ (ng·hr/mL)	Overall	1392 (35.3)	771.5 (34.7)
	n	13	14
	Males	1295 (44.5)	764.2 (35.3)
	n	6	7
	Females	1481 (27.8)	778.8 (37.0)
	n	7	7
C _{max} (ng/hr)			
	Overall	129 (36.8)	73.5 (34.2)
	n	13	14
	Males	123 (47.3)	73.5 (33.8)
	n	6	7
	Females	134 (29.0)	73.5 (37.5)
	n	7	7
Median (min, max)			
T _{max} (hr)	Overall	1.17 (0.00, 6.00)	1.21 (0.00, 12.0)
	n	13	14
	Males	0.50 (0.00, 4.00)	2.00 (0.00, 4.00)
	n	6	7
	Females	2.00 (0.00, 6.00)	0.00 (0.00, 12.0)
	n	7	7

Source: [Appendix 16.1.13](#), [Tables 14.2.2.4](#) through [14.2.2.5](#)

- Male and female patients had comparable mean DX C_{max} and AUC₀₋₁₂ values following DM 20 mg/Q 10 mg and a comparable mean DX C_{max} following DM 30 mg/Q 10 mg. Following DM 30mg/Q10mg, males had 13% lower DX AUC₀₋₁₂ than females.

Summary of pharmacokinetic parameters of quinidine by gender is provided below.

Table 11-7. Summary Geometric Mean and Median Plasma Quinidine PK Parameters

Quinidine Parameter		AVP-923-30	AVP-923-20
Geometric mean (CV%)			
AUC ₀₋₁₂ (ng·hr/mL)	Overall	471.2 (37.1)	401.1 (44.3)
	n	11	13
	Males	375.6 (21.5)	344.6 (21.4)
	n	4	6
	Females	536.3 (38.5)	456.9 (56.7)
	n	7	7
C _{max} (ng/hr)			
	Overall	62.2 (34.0)	54.3 (43.8)
	n	11	13
	Males	50.3 (17.9)	47.6 (19.8)
	n	4	6
	Females	70.2 (35.7)	60.8 (57.7)
	n	7	7
Median (min, max)			
T _{max} (hr)	Overall	2.00 (1.00, 4.02)	1.42 (1.00, 4.00)
	n	11	13
	Males	2.08 (1.00, 4.02)	1.71 (1.00, 2.97)
	n	4	6
	Females	2.00 (1.00, 3.38)	1.42 (1.00, 4.00)
	n	7	7

Source: [Appendix 16.1.13](#), [Tables 14.2.3.4](#) through [14.2.3.5](#).

- Geometric mean values of Q Cmax and AUC0-12 obtained with both treatments appeared comparable, with less than 15% difference between treatments.
- Male patients had lower mean Q Cmax and AUC0-12 values than female patients by approximately 28% and 30%, respectively following DM 30 mg/Q 10 mg and by approximately 22% and 25%, respectively, following DM 20 mg/Q 10 mg.

Reviewer's note:

- *This finding might not be conclusive due to the small subject numbers. In addition, no gender effect was reported previously in either labels or the original submission of this NDA with larger population.*

Pharmacokinetics by genotyping groups:

Summary of pharmacokinetic parameters of DM by genotyping group is provided below.
Summary of the Plasma Dextromethorphan PK Parameters by Genotyping Group

DM/Q	DM Pharmacokinetic Parameters	Intermediate Metabolizers	Extensive Metabolizers	Ultra-Rapid Metabolizers
		Arithmetic Mean ± SD (N)	Arithmetic Mean ± SD (N)	Value* (N)
DM 30 mg/Q 10 mg	C _{max} (ng/mL)	138 ± 26.2 (2)	86.3 ± 28.7 (10)	45.1 (1)
	T _{max} (hr)	5.01 (4.02, 6.00) (2)	3.58 (0.00, 8.00) (10)	2.00 (1)
	AUC ₀₋₁₂ (ng*hr/mL)	1503 ± 298.9 (2)	897.5 ± 323.9 (10)	443.8 (1)
DM 20 mg/Q 10 mg	C _{max} (ng/mL)		58.4 ± 28.9 (14)	
	T _{max} (hr)		2.98 (1.42, 4.00) (14)	
	AUC ₀₋₁₂ (ng*hr/mL)		598.7 ± 334 (14)	

T_{max} is presented as median (minimum, maximum)
*Unique value
Source: Tables 14.2.1.6 through 14.2.1.9

- Zenvia 20/10 group consisted solely of extensive metabolizers (N = 14), whereas Zenvia 30/10 group included intermediate (N = 2), extensive (N = 10) and ultra-rapid (N = 1) metabolizers.
- When comparing the two groups for extensive metabolizers only, DM Cmax and AUC0-12 values generally increased as doses of DM increased from 20 to 30 mg.
- When comparing the DM PK parameters at the 30/10 mg DM/Q combination by genotyping group, the DM Tmax was earlier and the DM Cmax and AUC0-12 values were lower for the genotyping groups with more rapid metabolism.
- Although there was only 1 patient who was an ultra-rapid metabolizer, it can be noted that the PK parameter values for this patient appeared to be as expected, with an early Tmax of 2 hours and low Cmax and AUC0-12 values of 45.1 ng/mL and 443.8 ng*hr/mL, respectively.

Summary of pharmacokinetic parameters of DX by genotyping group is provided below.

Summary of the Plasma Dextrophan PK Parameters by Genotyping Group

DM/Q	DX Pharmacokinetic Parameters	Intermediate Metabolizers	Extensive Metabolizers	Ultra-Rapid Metabolizers
		Arithmetic Mean ± SD (N)	Arithmetic Mean ± SD (N)	Value* (N)
DM 30 mg/Q 10 mg	C _{max} (ng/mL)	77.4 ± 19.9 (2)	147 ± 39.6 (10)	145 (1)
	T _{max} (hr)	1.50 (1.00, 2.00) (2)	0.583 (0.00, 6.00) (10)	4.00 (1)
	AUC ₀₋₁₂ (ng*hr/mL)	860.8 ± 230.2 (2)	1573 ± 410.9 (10)	1571 (1)
DM 20 mg/Q 10 mg	C _{max} (ng/mL)		77.2 ± 24.6 (14)	
	T _{max} (hr)		1.21 (0.00, 12.0) (14)	
	AUC ₀₋₁₂ (ng*hr/mL)		812.7 ± 270.3 (14)	

T_{max} is presented as median (minimum, maximum)
*Unique value
Source: Tables 14.2.2.6 through 14.2.2.9

- When comparing the 2 treatments for extensive metabolizers, DX C_{max} and AUC₀₋₁₂ values generally increased as doses of DM increased from 20 to 30 mg in the DM/Q combinations.
- When comparing the DX PK parameters following the DM 30 mg/Q 10 mg combination by genotyping group, the DX C_{max} and AUC₀₋₁₂ values were higher for the genotyping groups with more rapid metabolism.
- For the one patient who was an ultra-rapid metabolizer, the individual C_{max} and AUC₀₋₁₂ values were similar to those of the extensive metabolizers.

Summary of pharmacokinetic parameters of Q by genotyping group is provided below.

Summary of the Plasma Quinidine PK Parameters by Genotyping Group

DM/Q	Q Pharmacokinetic Parameters	Intermediate Metabolizers	Extensive Metabolizers	Ultra-Rapid Metabolizers
		Value* (N)	Arithmetic Mean ± SD (N)	Value* (N)
DM 30 mg/Q 10 mg	C _{max} (ng/mL)	79.0 (1)	66.7 ± 24.6 (9)	42.2 (1)
	T _{max} (hr)	1.00 (1)	2.00 (1.00, 4.02) (9)	2.00 (1)
	AUC ₀₋₁₂ (ng*hr/mL)	547.2 (1)	514.1 ± 201.3 (9)	330.9 (1)
DM 20 mg/Q 10 mg	C _{max} (ng/mL)		58.8 ± 25.8 (13)	
	T _{max} (hr)		1.42 (1.00, 4.00) (13)	
	AUC ₀₋₁₂ (ng*hr/mL)		436.3 ± 198.5 (13)	

T_{max} is presented as median (minimum, maximum)
*Unique value
Source: Tables 14.2.3.6 through 14.2.3.9

- When comparing the two treatments for extensive metabolizers, Q C_{max} and AUC₀₋₁₂ values appeared to be comparable for DM 20 mg/Q 10 mg and DM 30 mg/Q 10 mg, with less than 15% difference in C_{max} and AUC₀₋₁₂.

- There is only one subject in the intermediate and ultra-rapid metabolizer groups. No robust comparison could be made for the Q PK parameters following the 30/10 mg DM/Q combination by genotyping group.

Adverse Events

Incidence of adverse events is summarized below.

Table 12-2. Summary of Adverse Events (Safety Population)

Category	DB Phase			Overall (N = 326)	OLE Phase ^a
	AVP-923-30 (n = 110)	AVP-923-20 (n = 107)	Placebo (n = 109)		AVP-923-30 (N = 253)
Number of AEs	337	292	312	941	1065
Number of subjects (%)					
With no AEs	19 (17.3)	22 (20.6)	19 (17.4)	60 (18.4)	67 (26.5)
With at least 1 AE	91 (82.7)	85 (79.4)	90 (82.6)	266 (81.6)	186 (73.5)
With serious AEs	8 (7.3)	9 (8.4)	10 (9.2)	27 (8.3)	14 (5.5)
With study drug-related AEs	43 (39.1)	37 (34.6)	29 (26.6)	109 (33.4)	71 (28.1)
With severe AEs	10 (9.1)	16 (15.0)	10 (9.2)	36 (11.0)	19 (7.5)
With AEs leading to dosing suspension or termination	7 (6.4)	16 (15.0)	8 (7.3)	31 (9.5)	11 (4.3)
Discontinuing due to AEs ^b	6 (5.5)	10 (9.3)	2 (1.8)	18 (5.5)	10 (4.0)
Who died	3 (2.7)	3 (2.8)	1 (0.9)	7 (2.1)	3 (1.2)

Source: DB phase, Section 14.1, Table 24; OLE phase, Section 14.2, Table 24.1.

DB = double blind; OLE = open-label extension; AE = adverse event.

^aIncludes only adverse events experienced since Visit 5 of the double-blind study or while on the OLE study.

^bAEs causing discontinuations included multiple sclerosis exacerbation, serious AE, AE causing noncompliance, or an intercurrent illness or AE.

- No dose-responses for AEs were observed.

Reviewer's note:

More deaths were found in both study drug treated groups when compared with placebo. The sponsor stated that all deaths were consistent with ALS disease progression. These safety data will be thoroughly reviewed by the safety reviewer to determine whether the death is not related to the study drugs..

Genotyping of CYP2D6 enzyme activity

Disposition of CYP2D6 activity of the subjects is displayed in the table below:

AVP-923-30 (N=110)			
Slow Metabolizers (N = 4)	Intermediate Metabolizers (N = 9)	Extensive Metabolizers (N = 83)	Ultra-Rapid Metabolizers (N = 1)

AVP-923-20 (N=107)			
Slow Metabolizers (N = 3)	Intermediate Metabolizers (N = 9)	Extensive Metabolizers (N = 79)	Ultra-Rapid Metabolizers (N = 1)

- For both dose groups of AVP-923, most subjects were extensive metabolizers (83 of 110 subjects in the AVP-923-30 group and 79 of 107 subjects in the AVP-923-20 group).

SAEs in poor metabolizers

- There were 4, 3, and 7 subjects were classified as poor metabolizers in the AVP-923-30, AVP-923-20, and placebo groups, respectively.
- No SAEs or discontinuations due to AEs occurred in the 7 subjects who were poor metabolizers receiving placebo.
- Of 7 subjects taking AVP-923 who were classified as poor metabolizers, 2 subjects experienced SAEs and 1 subject experienced AEs.

SAEs

- One subject, in the AVP-923-30 group (Subject 302-503) experienced syncope on Day 67 that was considered to be moderate in intensity and not related to study drug. At the time of the syncopal event, the subject had started taking a concomitant medication, tamsulosin, known to have the side effect of syncope. Tamsulosin was discontinued, and the subject recovered and completed the study.
- One subject in the AVP-923-20 group (Subject 133-501) experienced respiratory failure, a fatal event, on Day (b) (6). The SAE was considered not related to study drug.

AEs

- One subject (131-501) in the AVP-923-20 group was discontinued due to AEs of decreased appetite and insomnia of severe intensity and fatigue of moderate intensity on Day 1; all events were considered to be probably related to study drug. The subject recovered.

Reviewer's note:

No drug concentrations for these patients were available as they were not involved in the PK portion of the study. Evaluation of the correlations between AEs and drug plasma exposures is therefore impossible.

Conclusions:

- Mean C_{max} and AUC₀₋₁₂ values of DM and DX increased as doses of DM increased from 20 mg to 30 mg in the AVP-923-20 and AVP-923-30 groups. The mean C_{max} and AUC₀₋₁₂ values of Q appeared to be similar between treatments (with a less than 15% difference in C_{max} and AUC₀₋₁₂).
- The median T_{max} appeared to be similar between treatments for all analytes.

- Pharmacokinetic results showed lower mean C_{max} and AUC₀₋₁₂ values of plasma DM and Q for the male subjects. However, the inter-subject variability was high and the sample size was small. This finding should be interpreted with caution.
- No robust evaluation for the PK of DM, DX, and Q by genotyping groups was performed since the PK population consisted either solely (DM 20 mg/Q 10 mg) or mostly (DM 30 mg/Q 10 mg) extensive metabolizers.
- When comparing the 2 treatments for extensive metabolizers only, mean C_{max} and AUC₀₋₁₂ values of DM and DX increased as doses of DM increased from 20 to 30 mg in the DM/Q combinations, while mean C_{max} and AUC₀₋₁₂ values of Q after a 10 mg dose given with both treatments appeared comparable.
- Genotyping results obtained appeared to be as expected: the DM (parent drug) T_{max} was earlier and the DM C_{max} and AUC₀₋₁₂ values were lower for the genotyping groups with more rapid metabolism; consequently, the DX (metabolite) C_{max} and AUC₀₋₁₂ values were the lowest for the intermediate metabolizer group (group with the slowest metabolism in this study).
- Of subjects who were classified as poor metabolizers, no SAEs or discontinuations due to AEs occurred in the placebo group. Two subjects experienced SAEs (1 in the AVP-923-30 group and 1 in the AVP-923-20 group) and 1 subject (in the AVP-923-20 group) was discontinued due to AEs.

4.1-3. HUMAN PK STUDIES

4.1-3.2 Extrinsic factors

Study 06-AVR-121: A Multiple-Dose Pharmacokinetic Drug Interaction Study Between AVP-923 and Paroxetine in Healthy Adult Subjects

Since chronic pain is frequently accompanied by symptoms of depression, it is likely that patients treated for major depression may receive concurrent treatment for pain. AVP-923 is comprised of both dextromethorphan hydrobromide, which is metabolized by CYP2D6, and quinidine sulfate, a potent CYP2D6 inhibitor. AVP-923 may potentially interact with paroxetine, a marketed antidepressant drug (Paxil®), which itself is both a substrate and an inhibitor of the CYP2D6 enzyme. This study was conducted to determine both the effect of AVP-923 on the steady state pharmacokinetics of paroxetine and the effect of paroxetine on the steady state pharmacokinetics of AVP-923 in healthy adult volunteers.

A brief overview of some essential components of the study design is given below:

Study Design	open-label, randomized, parallel-group study		
Study Population	23 completed the study (Group 1 [n=13] and Group 2 [n=10]).		
		Group 1 N=14	Group 2 N=13
	Age (years)		
	Mean (SD)	33.6 (9.22)	33.5 (9.65)
	Median	35.5	30.0
	Range	19 - 55	23 - 50
	Sex		
	Male	12 (85.7%)	9 (69.2%)
	Female	2 (14.3%)	4 (30.8%)
	Race		
	White	4 (28.6%)	6 (46.2%)
	American Indian or Alaskan Native	0 (0.0%)	0 (0.0%)
	Asian	1 (7.1%)	0 (0.0%)
	Black or of African Descent	9 (64.3%)	3 (23.1%)
	Hispanic or Latino	0 (0.0%)	4 (30.8%)
	Native Hawaiian or other Pacific Islander	0 (0.0%)	0 (0.0%)
	Other	0 (0.0%)	0 (0.0%)
	Weight		
	Mean (SD)	75.34 (11.684)	73.28 (10.415)
	Median	77.00	77.40
	Range	55.1 - 96.7	55.3 - 91.3
	Height		
	Mean (SD)	172.43 (7.498)	170.58 (8.369)
	Median	170.50	171.50
	Range	163.0 - 190.0	159.0 - 181.5
Dosage and Administration	Twenty-seven subjects were randomized into 1 of 2 Treatment Groups Group 1 (N=14) and Group 2 (N=13).		

	<p style="text-align: center;">Paroxetine 20 mg, once daily (Days 1–20)</p> <p>Group 1 (N=14) AVP-923 30 mg, bid (Days 13–20)</p> <p>Group 2 (N=14) Paroxetine 20 mg, once daily (Days 9–20)</p> <p>AVP-923 30 mg, bid (Days 1–20)</p> <p>Subjects were required to fast (abstain from food) for approximately 8 hours prior to dosing (on days requiring post-dose PK sampling) or 2 hours prior to dosing (on all other study days) until approximately 1 hour post dosing (and post second dose administration, if applicable). 125 mL of non-carbonated water was taken during each study drug administration.</p> <p style="text-align: center;"><u>Lot No.</u></p> <p>AVP-923 capsules(30 mgDM+30mg Q): PD108A-001, expiration date 01-May-2008</p> <p>Paroxetine (Paxil®) tablets (20 mg): GSK, 5K001, expiration date 31-Sep-2008</p> <p><u>Diet:</u> Water was not permitted from 2 hours pre-dose (first dose administration) until 1 hour post-dose (post-second dose administration, if applicable).</p> <p>Subjects was prohibited from the following foods and/or beverages for at least 2 weeks prior to the first dose administration until final discharge: grapefruit juice/products, foods containing poppy seeds, Seville oranges and/or products (including supplements containing <i>Citrus aurantium</i> or “bitter orange”), apple or orange juice, vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), charbroiled meats, caffeine containing beverages and foods (e.g., coffee, Cola-products, chocolate), and/or drinks or foods containing quinine (e.g., tonic water).</p> <p>Alcohol was prohibited for 2 weeks prior to dosing until study completion.</p>										
<p>Sampling: Plasma</p>	<p>For paroxetine and AVP-923 (including dextromethorphan, dextrorphan, and quinidine (Plasma): At predose (0 hour), and 1, 2, 3, 4, 5, 6, 8, 12, 14, and 24 hours post-dose.</p>										
<p>Analysis (Plasma)</p>	<p><u>Method</u> LC-MS/MS</p> <p><u>Lower Limits of Quantitation</u></p> <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th></th> <th style="text-align: center;"><u>Plasma</u></th> </tr> </thead> <tbody> <tr> <td>Dextromethorphan</td> <td style="text-align: center;">0.200 ng/mL</td> </tr> <tr> <td>Dextrorphan</td> <td style="text-align: center;">2.50 ng/mL</td> </tr> <tr> <td>Quinidine</td> <td style="text-align: center;">0.05 µg/mL</td> </tr> <tr> <td>Paroxetine</td> <td style="text-align: center;">0.10 ng/mL</td> </tr> </tbody> </table> <p><u>Dextromethorphan:</u> Linear range : 0.200-200 ng/mL in plasma (heparin) Inter-day Precision</p>		<u>Plasma</u>	Dextromethorphan	0.200 ng/mL	Dextrorphan	2.50 ng/mL	Quinidine	0.05 µg/mL	Paroxetine	0.10 ng/mL
	<u>Plasma</u>										
Dextromethorphan	0.200 ng/mL										
Dextrorphan	2.50 ng/mL										
Quinidine	0.05 µg/mL										
Paroxetine	0.10 ng/mL										

	<p>(%CV for Quality Controls) : < 6.1% Inter-day accuracy: -4.5 % to 6.7% Short term Stability: 27 hours in propylene tubes at ambient temperature under white light</p> <p><u>Dextrophan:</u> Linear range : 2.50-2500 ng/mL in plasma (heparin) Inter-day Precision (%CV for Quality Controls) : < 6.3% Inter-day accuracy: -6.4 % to – 1.2% Short term Stability: 27 hours in propylene tubes at ambient temperature under white light</p> <p><u>Quinidine:</u> Linear range : 0.05-10 µg/mL in plasma (heparin) Inter-day Precision (%CV for Quality Controls) : < 3.4% Inter-day accuracy: -8.0 % to -1.3% Short term Stability: 24.5 hours at ambient temperature under white light</p> <p><u>Paroxetine:</u> Linear range : 0.10-50 ng/mL in plasma (EDTA) Inter-day Precision (%CV for Quality Controls) : < 5.1% Inter-day accuracy: 1.5 % to 3.0 % Short term Stability: 27 hours in propylene tubes at ambient temperature under white light</p>
PK Assessment (Primary endpoints)	<p>Paroxetine: AUC(0-24h) on Day 12 (paroxetine alone) and Day 20 (paroxetine with AVP-923) in Group 1 AVP-923(dextromethorphan, dextrophan, and quinidine): AUC(0-12h) on Day 8 (AVP-923 alone) and Day 20 (AVP-923 with paroxetine) in Group 2 Paroxetine and AVP-923: CSSmax, CSSmin, Tmax, and apparent t^{1/2}</p>
Safety Assessment (Secondary endpoints)	<p>Assessment of vital signs (sitting blood pressure, respiratory rate, pulse rate, oxygen saturation, and temperature), 12-lead electrocardiogram (ECG), adverse events and clinical laboratory tests (hematology, clinical chemistry, and urinalysis).</p>

Results:

The data are shown in two separated analyses. The *Evaluable Population* included all subjects who completed the study without major protocol violations. An additional *Sub-Group Analysis* was performed to exclude outliers, including unexpectedly low concentrations and poor CYP2D6 metabolizer. *Sub-Group* population was used for PK analysis.

Pharmacokinetics of Paroxetine:

The pharmacokinetic parameters of paroxetine are summarized in the following table:

Table 11.4.2-1. Summary of steady state pharmacokinetic parameters for paroxetine, in the Evaluable and Sub-group Population. Boxed sections are within group comparisons

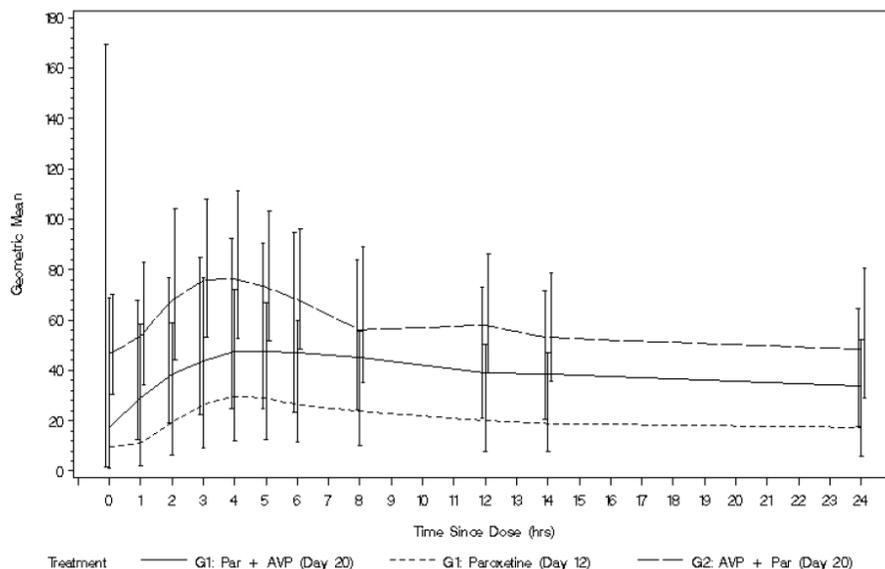
Parameters		Evaluable Population			Sub-Group* Analysis		
		Group 1 Day 12 (Par)	Group 1 Day 20 (Par + AVP-923)	Group 2 Day 20 (AVP-923 + Par)	Group 1 Day 12 (Par)	Group 1 Day 20 (Par + AVP-923)	Group 2 Day 20 (AVP-923 + Par)
N		12	12	10	9	9	9
AUC_(0-24h) (ng·h/mL)	Arithmetic Mean (SD)	651.25 (411.98)	869.91 (626.53)	1408.43 (457.24)	648.08 (452.03)	1099.92 (535.89)	1463.68 (448.18)
	Geometric Mean (CV)	503.74 (104.1%)	519.85 (235.3%)	1320.93 (43.0%)	478.09 (120.8%)	943.66 (72.5%)	1376.58 (43.2%)
C_{ssmax} (ng/mL)	Arithmetic Mean (SD)	41.39 (24.35)	46.99 (33.97)	80.77 (23.20)	40.08 (25.97)	59.37 (29.33)	83.04 (23.40)
	Geometric Mean (CV)	33.14 (92.0%)	29.28 (199.2%)	77.08 (35.6%)	31.01 (103.2%)	50.72 (73.6%)	79.21 (36.6%)
C_{ssmin} (ng/mL)	Arithmetic Mean (SD)	22.09 (16.76)	28.99 (21.52)	52.39 (18.39)	21.90 (18.36)	36.35 (19.24)	54.79 (17.76)
	Geometric Mean (CV)	12.70 (278.9%)	16.48 (256.6%)	48.65 (46.4%)	11.14 (381.0%)	28.88 (103.5%)	51.19 (45.7%)
T_{max} (h)	Median (range)	4.00 (2.0-6.0)	4.03 (1.0-6.1)	3.99 (3.0-5.0)	4.00 (3.0-6.0)	5.0 (4.0-6.1)	4.00 (3.0-5.0)
t_{1/2} (h)	Arithmetic Mean (SD)	40.28 (35.76)	56.73 (57.03)	44.81 (27.64)	41.63 (39.01)	68.63 (61.85)	47.54 (27.85)
	Geometric Mean (CV)	30.48 (85.5%)	41.32 (87.7%)	38.18 (64.2%)	30.97 (90.5%)	52.18 (82.9%)	40.97 (62.8%)

Source: Tables 14.2.2.1 and 14.2.4.1

*Sub-group Population is defined in Section 9.8.

The concentration-time profiles of paroxetine are shown in the following figure:

Figure 11.4.2-2. Geometric Mean (SD) plasma concentration curves for paroxetine (ng/mL) for the *Sub-group Population



Source: [Figure 14.2.1](#)

* Sub-group Population is defined in [Section 9.8](#).

A summary of pharmacokinetic analysis shown as Estimate of Ratio of Geometric Means are provided in the table below.

Paroxetine-Summary of pharmacokinetic analysis (Estimate of Ratio of Geometric Means)

	P+AVP/P alone G1-Day20/G1-Day12	AVP+P/P+AVP G2-Day20/G1-Day20	AVP+P/P alone G2-Day20/G1-Day12
AUC0-24	1.70		2.26
C _{ss,max}	1.48		2.07
C _{ss,min}	1.66	2.70	2.50

- Coadministration of paroxetine with AVP-923 exhibited higher exposure of paroxetine, shown as AUC(0-24h), CSS_{max}, and CSS_{min}, when compared with paroxetine alone at steady state.
- The 90% confidence intervals for AUC(0-24h) [1.53–2.55], CSS_{max} [1.35–1.98], and CSS_{min} [1.46–4.59] in Group 1 on Day 20 were all >1.25.
- When paroxetine was added to AVP-923 (G2), compared to when AVP-923 was added to paroxetine (G1), the exposure of paroxetine are even higher as shown by CSS_{min}. The reason for this is unclear.

Reviewer's note:

The variation seems to be very wide in most of the PK parameters.

Pharmacokinetics of Dextromethorphan:

The pharmacokinetic parameters of dextromethorphan are summarized in the following table:

Table 11.4.2-2. Summary of steady state pharmacokinetic parameters for dextromethorphan, in the Evaluable and Sub-group Population. Boxed sections are within group comparisons.

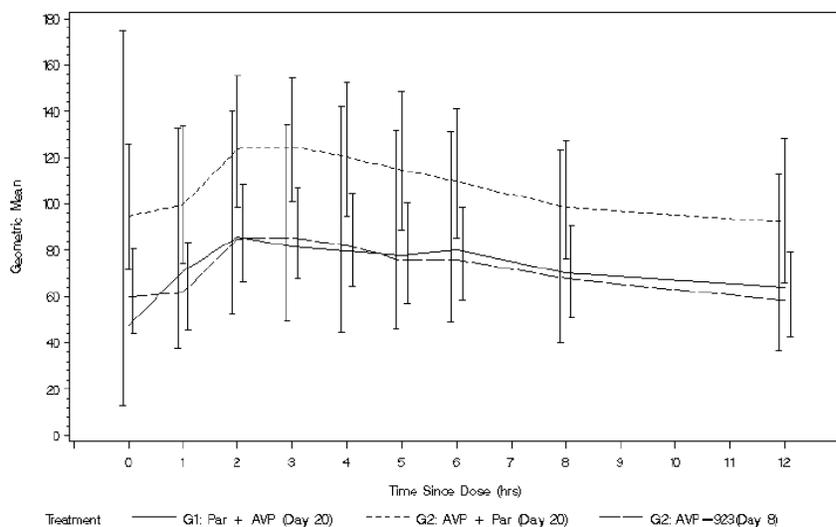
Parameters		Evaluable Population			Sub-Group* Analysis		
		Group 2 Day 8 (AVP-923)	Group 2 Day 20 (AVP-923 + Par)	Group 1 Day 20 (Par + AVP-923)	Group 2 Day 12 (Par)	Group 2 Day 20 (AVP-923 + Par)	Group 1 Day 20 (Par + AVP-923)
N		10	10	12	9	9	9
AUC_(0-12h) (ng-h/mL)	Arithmetic Mean (SD)	914.59 (225.08)	1335.93 (287.734)	813.27 (429.02)	876.20 (201.03)	1310.31 (292.84)	976.01 (351.87)
	Geometric Mean (CV)	885.97 (28.3%)	1302.17 (25.6%)	663.60 (87.9%)	851.96 (26.8%)	1275.70 (26.2%)	883.57 (59.3%)
C_{SSmax} (ng/mL)	Arithmetic Mean (SD)	93.39 (21.40)	132.11 (23.83)	82.60 (40.26)	89.88 (19.40)	129.68 (23.92)	97.28 (34.65)
	Geometric Mean (CV)	90.93 (25.6%)	129.83 (20.8%)	71.15 (68.8%)	87.77 (24.4%)	127.39 (21.1%)	89.11 (53.6%)
C_{SSmin} (ng/mL)	Arithmetic Mean (SD)	59.80 (16.47)	96.36 (24.95)	58.75 (31.00)	56.89 (14.49)	94.40 (25.63)	70.29 (25.73)
	Geometric Mean (CV)	57.57 (30.7%)	92.70 (32.1%)	47.20 (96.4%)	55.06 (28.7%)	90.59 (33.2%)	63.42 (60.7%)
T_{max} (h)	Median (range)	2.50 (2.0-4.0)	2.49 (2.0-3.0)	2.00 (0.0-4.0)	2.97 (2.0-4.0)	2.97 (2.0-3.0)	2.00 (1.0-4.0)
t_{1/2} (h)	Arithmetic Mean (SD)	17.30 (5.60)	26.08 (17.21)	20.45 (7.93)	16.90 (5.78)	25.54 (18.17)	21.25 (7.80)
	Geometric Mean (CV)	16.49 (33.7%)	22.77 (54.7%)	19.22 (37.9%)	16.06 (34.7%)	22.00 (57.0%)	20.32 (30.1%)

Source: Tables 14.2.2.2.1 and 14.2.4.2.1

* Sub-group Population is defined in Section 9.8.

The mean concentration-time profiles of dextromethorphan are shown in the following figure:

Figure 11.4.2-4. Geometric Mean (SD) plasma concentration curves for dextromethorphan (ng/mL) for the *Sub-group Population



Source: Figure 14.2.2

* Sub-group Population is defined in Section 9.8.

A summary of pharmacokinetic analysis shown as Estimate of Ratio of Geometric Means are provided in the table below.

Dextromethorphan-Summary of pharmacokinetic analysis (Estimate of Ratio of Geometric Means)

	AVP+P/AVP alone G2-Day20/G2-Day8	AVP+P/P+AVP G2-Day20/G1-Day20	P+AVP/AVP alone G1-Day20/G2-Day8
AUC0-12	1.50		1.11
Css,max	1.44		1.08
Css,min	1.65	2.00	1.24

- In group 2, adding paroxetine to AVP-923 exhibited higher exposure of dextromethorphan, shown as AUC(0-12h), CSSmax, and CSSmin, when compared with AVP-923 alone at steady state.
- The 90% confidence interval for geometric mean ratio in the Evaluable Population for AUC(0-12h) [1.37–1.57], CSSmax [1.34–1.52], and CSSmin [1.45–1.78], were > 1.25. The same result was observed for the Sub-group Population.
- When paroxetine was added to AVP-923 (G2), compared to when AVP-923 was added to paroxetine (G1), the exposure of dextromethorphan are higher by a factor of 2 folds as shown by CSSmin. The reason for this finding is unclear.
- The exposure of dextromethorphan did not show significantly increase when adding AVP-923 to paroxetine compared with AVP-923 alone.

Pharmacokinetics of Dextrophan:

The pharmacokinetic parameters of dextrophan are summarized in the following table:

Table 14.2.4.2.2
Summary of Steady State Pharmacokinetic Parameters : Dextrophan (ng/mL) - Subgroup Analysis*
Evaluable Population

	Group 2, Day 8 AVP-923 30mg bd N=9	Group 2, Day 20 AVP-923 30mg bd + Paroxetine 20mg od N=9	Group 1, Day 20 Paroxetine 20mg od+ AVP-923 30mg bd N=9
AUC (0-12h)			
N	9	9	9
Arithmetic Mean(SD)	862.95 (108.028)	744.72 (101.333)	573.28 (186.433)
Geometric Mean(CV)	856.80 (12.8%)	738.69 (13.6%)	545.43 (35.2%)
Median	891.18	718.76	591.32
Range	(729.6 - 995.5)	(619.8 - 885.6)	(299.3 - 905.5)
Cssmax			
N	9	9	9
Arithmetic Mean(SD)	84.64 (7.443)	69.61 (9.480)	57.08 (17.067)
Geometric Mean(CV)	84.36 (8.7%)	69.04 (13.7%)	54.95 (29.6%)
Median	84.20	66.30	55.50
Range	(75.1 - 96.9)	(55.5 - 82.7)	(37.1 - 90.7)
Cssmin			
N	9	9	9
Arithmetic Mean(SD)	65.16 (8.185)	57.64 (8.175)	42.62 (15.292)
Geometric Mean(CV)	64.70 (12.6%)	57.13 (14.4%)	40.02 (40.4%)
Median	64.40	55.30	44.40
Range	(55.6 - 75.4)	(45.9 - 67.7)	(19.0 - 70.1)
Tmax			
N	9	9	9
Median	0.00	0.00	1.00
Range	(0.0 - 12.0)	(0.0 - 5.0)	(0.0 - 2.0)
IQ Range	(0.00 - 1.00)	(0.00 - 0.00)	(1.00 - 1.02)
T1/2			
N	2	7	7
Arithmetic Mean(SD)	54.18 (10.062)	58.57 (27.513)	28.07 (9.316)
Geometric Mean(CV)	53.71 (18.8%)	52.28 (59.0%)	26.39 (42.6%)
Median	54.18	54.51	32.74
Range	(47.1 - 61.3)	(19.8 - 93.8)	(11.9 - 37.2)

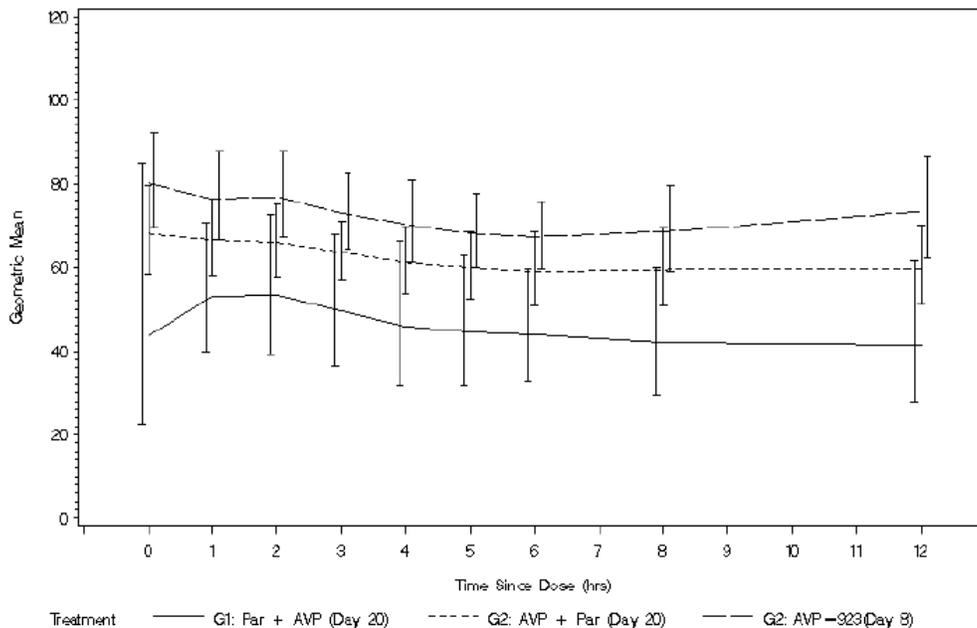
Note:

* Excluding Subjects 9009, 9019 and 9034 from Group 1 whose data showed unexpectedly low concentrations of the study drug

* Excluding Subject 9005 from Group 2 who was a poor metabolizer

The mean concentration-time profiles of dextrophan are shown in the following figure:

Figure 11.4.2-6. Geometric Mean (SD) plasma concentration curves for dextroprphan (ng/mL) for the *Sub-group Population.



Source: [Figure 14.2.3](#)

*Sub-group Population is defined in [Section 9.8](#).

A summary of pharmacokinetic analysis shown as Estimate of Ratio of Geometric Means are provided in the table below.

Dextroprphan-Summary of pharmacokinetic analysis (Estimate of Ratio of Geometric Means)

	AVP+P/AVP alone G2-Day20/G2-Day8	AVP+P/P+AVP G2-Day20/G1-Day20	P+AVP/AVP alone G1-Day20/G2-Day8
AUC0-12	0.86		0.66
Css,max	0.82		0.67
Css,min	0.88	1.56	0.65

- In group 2, adding paroxetine to AVP-923 exhibited lower exposure of dextroprphan, shown as AUC(0-12h), CSSmax, and CSSmin, when compared with AVP-923 alone at steady state.
- The lower limit of the 90% confidence interval for the ratio of geometric means for all parameters fell slightly below the [0.8, 1.25] interval.
- When paroxetine was added to AVP-923 (G2), compared to when AVP-923 was added to paroxetine (G1), the exposure of dextroprphan are higher by 56% as shown by CSSmin.

Pharmacokinetics of Quinidine:

The pharmacokinetic parameters of quinidine are summarized in the following table:

Table 14.2.4.2.3
Summary of Steady State Pharmacokinetic Parameters : Quinidine (µg/mL) - Subgroup Analysis*
Evaluable Population

	Group 2, Day 8 AVP-923 30mg bd N=9	Group 2, Day 20 AVP-923 30mg bd + Paroxetine 20mg od N=9	Group 1, Day 20 Paroxetine 20mg od+ AVP-923 30mg bd N=9
AUC (0-12h)			
N	9	9	9
Arithmetic Mean(SD)	1.08223 (0.186214)	1.50212 (0.400493)	1.09419 (0.339293)
Geometric Mean(CV)	1.06497 (20.2%)	1.43573 (36.2%)	1.02897 (43.1%)
Median	1.13578	1.56679	1.05894
Range	(0.6583 - 1.3160)	(0.6067 - 1.9854)	(0.3777 - 1.5648)
Cssmax			
N	9	9	9
Arithmetic Mean(SD)	0.16122 (0.024555)	0.21233 (0.048218)	0.14720 (0.030608)
Geometric Mean(CV)	0.15943 (16.3%)	0.20643 (27.1%)	0.14432 (21.5%)
Median	0.16500	0.23000	0.14900
Range	(0.1140 - 0.1970)	(0.1130 - 0.2760)	(0.0988 - 0.1980)
Cssmin			
N	9	9	9
Arithmetic Mean(SD)	0.04397 (0.018604)	0.07347 (0.023371)	0.05891 (0.024761)
Geometric Mean(CV)	0.04023 (48.3%)	0.06873 (45.1%)	0.05368 (51.2%)
Median	0.05210	0.08230	0.05600
Range	(0.0250 - 0.0698)	(0.0250 - 0.0950)	(0.0250 - 0.1030)
Tmax			
N	9	9	9
Median	1.98	1.98	1.00
Range	(1.0 - 2.0)	(1.0 - 2.0)	(1.0 - 2.0)
IQ Range	(1.00 - 1.98)	(1.97 - 1.98)	(1.00 - 1.00)
T1/2			
N	9	9	7
Arithmetic Mean(SD)	7.41 (2.640)	6.70 (1.689)	9.51 (3.840)
Geometric Mean(CV)	6.99 (37.9%)	6.45 (31.7%)	8.75 (48.8%)
Median	8.10	7.11	9.32
Range	(3.8 - 12.4)	(3.1 - 8.8)	(4.5 - 14.2)

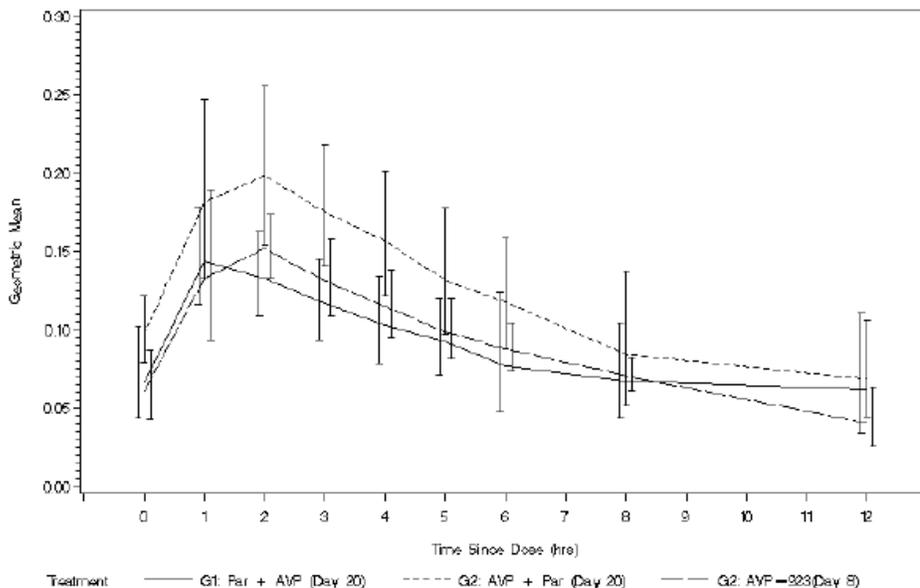
Note:

* Excluding Subjects 9009, 9019 and 9034 from Group 1 whose data showed unexpectedly low concentrations of the study drug

* Excluding Subject 9005 from Group 2 who was a poor metabolizer

The mean concentration-time profiles of quinidine are shown in the following figure:

Figure 11.4.2-8. Geometric Mean (SD) plasma concentration curves for quinidine ($\mu\text{g/mL}$) for the *Sub-group Population.



Source: [Figure 14.2.4](#)

*Sub-group Population is defined in [Section 9.8](#).

A summary of pharmacokinetic analysis shown as Estimate of Ratio of Geometric Means are provided in the table below.

Quinidine-Summary of pharmacokinetic analysis (Estimate of Ratio of Geometric Means)

	AVP+P/AVP alone G2-Day20/G2-Day8	AVP+P/P+AVP G2-Day20/G1-Day20	P+AVP/AVP alone G1-Day20/G2-Day8
AUC ₀₋₁₂	1.39		1.01
C _{ss,max}	1.32		0.91
C _{ss,min}	1.66	1.47	1.34

- In group 2, adding paroxetine to AVP-923 exhibited higher exposure of quinidine, shown as AUC(0-12h), CSS_{max}, and CSS_{min}, when compared with AVP-923 alone at steady state.
- The 90% confidence interval for geometric mean ratio reached above the [0.8, 1.25] interval for all parameters in the Sub-group Populations.
- When paroxetine was added to AVP-923 (G2), compared to when AVP-923 was added to paroxetine (G1), the exposure of quinidine are higher by 47% as shown by CSS_{min}.
- Adding AVP-923 to paroxetine seemed to exhibit relatively similar exposure of quinidine when compared to AVP-923 alone.

Adverse Events

Incidence of adverse events in both groups is summarized below.

Table 12.2.2-1. Incidence of Treatment-Emergent Adverse Events by System Organ Class and Treatment for Group 1

	Treatment at Onset of Adverse Event	
	Paroxetine 20 mg qd (N=14)	Paroxetine 20 mg qd + AVP-923 30 mg bid (N=14)
Any System Organ Class		
Any Event	11 (78.6%)	9 (64.3%)

Table 12.2.2-2. Incidence of Treatment-Emergent Adverse Events by System Organ Class and Treatment for Group 2

	Treatment at Onset of Adverse Event	
	AVP-923 30 mg bid (N=13)	AVP-923 30 mg bid+ Paroxetine 20 mg qd (N=12)
Any System Organ Class		
Any Event	4 (30.8%)	10 (83.3%)

- Adding AVP-923 to paroxetine didn't show increase of incidence of adverse events (64%) when compared to paroxetine alone (78%).
- Adding paroxetine to AVP-923 significantly increase the incidence of adverse events (83%) when compared to AVP-923 alone (30%).

The intensity of the treatment-emerged adverse events in both groups is summarized below.

Table 12.2.3-1. Maximum Intensity of Treatment-Emergent Adverse Events by Treatment and System Organ Class for Group 1

System Order Class/ Preferred Term	Maximum Intensity	Treatment at Onset of Adverse Event	
		Paroxetine 20 mg qd N=14	Paroxetine 20 mg qd + AVP-923 30 mg bid N=14
Any System Organ Class			
Any Event	Mild	9 (64.3%)	5 (35.7%)
	Moderate	2 (14.3%)	3 (21.4%)
	Severe	0 (0.0%)	1 (7.1%)

Table 12.2.3-2. Maximum Intensity of Treatment-Emergent Adverse Events by Treatment and System Organ Class for Group 2

System Order Class/ Preferred Term	Maximum Intensity	Treatment at Onset of Adverse Event	
		AVP-923 30 mg bid N=13	AVP-923 30 mg bid + Paroxetine 20 mg qd N=12
Any System Organ Class			
Any Event	Mild	4 (30.8%)	4 (33.3%)
	Moderate	0 (0.0%)	4 (33.3%)
	Severe	0 (0.0%)	2 (16.7%)

- In both groups, the co-administration of paroxetine and AVP-923 was associated with an increased incidence of moderate and severe AEs compared to the administration of paroxetine or AVP-923 alone.
- A higher incidence and severity of AEs was observed in subjects who had paroxetine added to a regimen of AVP-923, compared those subjects who had a reversed order of co-administration.

Subjects discontinued from the study are listed in the table below.

**Appendix 16.2.1.1
Subjects Discontinued from the Study**

Group	PID (Sex/Age)	Date of Discontinuation	Date & Time of First Dose	No. of Days in the study	Reason for Withdrawal
1	9010 (F/55)	13JUL2006	25JUN06:08:45	18	Adverse Event or Serious Adverse Event
2	9021 (F/28)	07JUL2006	25JUN06:10:15	1	Withdrawal of Consent
2	9039 (F/24)	13JUL2006	25JUN06:09:55	18	Adverse Event or Serious Adverse Event
2	9055 (M/25)	11JUL2006	25JUN06:10:10	16	Adverse Event or Serious Adverse Event

- Three out of four subjects who discontinued from the study were due to severe adverse events. Of these 3 subjects, one was in group 1 and two were in group 2.
- The one severe AE in Group 1 occurred when AVP-923 was added to paroxetine: it consisted of non-cardiac chest pains and was deemed to be probably related to the study drugs. This AE was likely an acid-related disorder and consistent with dyspepsia, a known side-effect of paroxetine.
- The two severe AEs were reported in Group 2 following the addition of paroxetine to AVP-923. They consisted of psychomotor activity (probably related to the study drugs) and mood swings (highly probably related to the study drugs).

Conclusions:

- The addition of AVP-923 to steady state levels of paroxetine resulted in increased steady state levels of paroxetine in healthy adult volunteers.
- The addition of paroxetine to steady state levels of AVP-923 resulted in increased steady state levels of dextromethorphan and quinidine in healthy adult volunteers while the steady state levels of dextrophan were found to be decreased following coadministration of paroxetine.
- Paroxetine gave rise to an increased incidence and severity of AEs, compared to AVP-923 alone.
- The co-administration of paroxetine and AVP-923 led to an increased incidence of moderate and severe AEs, compared to the administration of either paroxetine or AVP-923 alone. A higher incidence and severity of AEs was observed in subjects who had paroxetine added to a regimen of AVP-923, compared those subjects who had a reversed order of co-administration.
- There may be an impact of the co-administration of paroxetine and AVP-923 on AE emergence and severity. It may therefore be advisable to warn patients of potential interactions between these two drugs.

**Study 06-AVR-122: A Multiple-Dose Pharmacokinetic Drug Interaction Study
Between AVP-923 and Memantine in Healthy Adult Subjects**

Memantine is not metabolized by CYP2D6 and does not modulate CYP2D6 metabolism; however, it is possible that Q may inhibit memantine excretion, and in addition, both DM and memantine are antagonists of the *N*-methyl-D-aspartate (NMDA) receptor, concomitant use of DM and memantine could theoretically result in an additive effect at NMDA receptors and potentially an increased incidence of adverse events.

A brief overview of some essential components of the study design is given below:

Study Design	open-label, randomized, parallel-group study		
Study Population	52 randomized subjects (Group 1 [n=23] and Group 2 [n=29]) 34 completed the study (Group 1 [n=17] and Group 2 [n=17])		
	Group 1 N=23	Group 2 N=29	Total N=52
Age (years)			
N	23	29	52
Arithmetic Mean (SD)	33.9 (9.69)	37.9 (9.47)	36.1 (9.68)
Median	33.0	37.0	36.0
Range	20 - 54	19 - 55	19 - 55
Gender			
N	23	29	52
Male	15 (65.2%)	24 (82.8%)	39 (75.0%)
Female	8 (34.8%)	5 (17.2%)	13 (25.0%)
Race			
N	23	29	52
White	7 (30.4%)	12 (41.4%)	19 (36.5%)
Asian	4 (17.4%)	6 (20.7%)	10 (19.2%)
Black or of African Descent	5 (21.7%)	4 (13.8%)	9 (17.3%)
Hispanic or Latino	5 (21.7%)	6 (20.7%)	11 (21.2%)
Other	2 (8.7%)	1 (3.4%)	3 (5.8%)
Height (cm)			
N	23	29	52
Arithmetic Mean (SD)	172.28 (10.272)	172.19 (8.911)	172.23 (9.440)
Median	174.00	172.00	174.00
Range	151.0 - 187.0	157.0 - 188.0	151.0 - 188.0
Weight (kg)			
N	23	29	52
Arithmetic Mean (SD)	76.93 (9.522)	76.10 (9.100)	76.47 (9.206)
Median	79.80	76.30	76.80
Range	54.9 - 92.5	55.2 - 96.0	54.9 - 96.0
BMI (kg/m ²)			
N	23	29	52
Arithmetic Mean (SD)	25.93 (2.557)	25.65 (2.250)	25.77 (2.371)
Median	25.50	25.80	25.65
Range	21.5 - 30.0	21.0 - 29.4	21.0 - 30.0
Phenotype			
N	23	28	51
INTERMEDIATE METABOLIZER	1 (4.3%)	0 (0.0%)	1 (2.0%)
EXTENSIVE METABOLIZER	19 (82.6%)	27 (96.4%)	46 (90.2%)
ULTRA-RAPID METABOLIZER	3 (13.0%)	1 (3.6%)	4 (7.8%)
	Note: Percentage is calculated based on the number of subjects randomized per group as the denominator.		
Dosage and Administration	Group 1 (memantine + AVP-923) Memantine was titrated to a dose of 10 mg/twice daily (q12h).		

	<p>Week 1, single dose of 5 mg; Week 2, two daily doses of 5 mg; Week 3, one daily dose of 5 mg and one daily dose of 10 mg; and Week 4, two daily doses of 10 mg for 11 days, Subsequently, in addition to the two daily doses of 10 mg memantine, AVP-923 30 mg (30 mg DM/30 mg Q) was administered twice daily (q12h) for 8 days.</p> <p>Group 2 (AVP-923 + memantine) AVP-923 30 mg (30 mg DM/30 mg Q) was administered twice daily for 8 days. While continuing to administer AVP-923, memantine was titrated up to 20 mg/day as indicated for Group 1. Once the target dose of memantine was reached, subjects took both memantine and AVP-923 for an additional 11 days.</p> <p>Subjects were required to fast (abstain from food) for approximately 8 hours prior to dosing (on days requiring post-dose PK sampling) or 2 hours prior to dosing (on all other study days) until approximately 1 hour post dosing (and post second dose administration, if applicable). 125 mL of non-carbonated water was taken during each study drug administration.</p> <p style="text-align: right;"><u>Lot No.</u></p> <p>AVP-923 capsules(30 mgDM+30mg Q): Lot PD108A-001; Expiry 01 May 2008 Memantine (Ebixa®, Lundbeck Canada Inc.) (10 mg Tablets? 5 mg?): Lot 503711; Expiry 31 March 2007</p> <p><u>Diet:</u> Water was not permitted from 2 hours pre-dose (first dose administration) until 1 hour post-dose (postsecond dose administration, if applicable).</p> <p>Subjects was prohibited from the following foods and/or beverages for at least 2 weeks prior to the first dose administration until final discharge: grapefruit juice/products, foods containing poppy seeds, Seville oranges and/or products (including supplements containing <i>Citrus aurantium</i> or “bitter orange”), apple or orange juice, vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), charbroiled meats, caffeine containing beverages and foods (e.g., coffee, Cola-products, chocolate), and/or drinks or foods containing quinine (e.g., tonic water).</p> <p>Alcohol was prohibited for 2 weeks prior to dosing until study completion.</p> <p><u>Exclusion criteria for concomitant drugs:</u></p> <ul style="list-style-type: none">• any drugs or substances known to be strong inhibitors or inducers of cytochrome P450 enzymes within 30 days of the first dose.• prescription drugs (except oral contraceptives or sex hormone replacement therapy) within 14 days of the first dose and for the duration of the study.
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	<ul style="list-style-type: none"> monoamine oxidase inhibitors, thioridazine, pimozone, serotonin-precursors (such as L-tryptophan, oxitriptan) and other serotonergic drugs (triptans, lithium, tramadol, St. John's Wort, most tricyclic antidepressants), or neuroleptics/antipsychotics within 21 days of the first dose. Use of NMDA antagonists, L-dopa, dopaminergic agonists, anticholinergics, and amantadine within 21 days of the first dose. barbiturates, neuroleptics, anticonvulsants, dantrolene, or baclofen within 21 days of the first dose. 								
Sampling: Plasma	<p>AVP-923: at pre-dose, 1, 2, 3, 4, 5, 6, 8, and 12 hours post-dose Memantine: at pre-dose, 2, 4, 6, 8, 10, and 12 hours post-dose</p> <p>Trough levels: Group 1: At predose (0 hour), and on the mornings of Days 2, 5, 8, 11, 14, 17, 20, 23, 26, and 29 to 31 to assess trough memantine levels and on Days 37 to 39 to determine levels of trough AVP-923. Group 2: At predose (0 hour), and on the mornings of Days 2, 5 to 7, 10, 13, 16, 19, 22, 25, and 28 to assess trough AVP-923 levels and Days 10, 13, 16, 19, 22, 25, 28, and 37 to 39 to determine levels of trough memantine.</p>								
Pharmacodynamics	<p>Group 1: CRT, DA, Postural Stability, VAS for Nausea, VAS for Dizziness, BDI-II, BAI, and LSEQ were taken on Days 8, 15, 22, 33, and 36 at 2, 4, and 6 hours post-administration one (Days 8, 15, and 22) or post-administration two (Days 33 and 36). Group 2: CRT, DA, Postural Stability, VAS for Nausea, VAS for Dizziness, BDI-II, BAI, and LSEQ were taken on Days 9, 15, 22, and 36 at 2, 4, and 6 hours post-administration two.</p>								
Analysis (Plasma)	<p><u>Method</u> LC-MS/MS <u>Lower Limits of Quantitation</u></p> <table> <thead> <tr> <th></th> <th><u>Plasma</u></th> </tr> </thead> <tbody> <tr> <td>Dextromethorphan</td> <td>0.200 ng/mL</td> </tr> <tr> <td>Dextrorphan</td> <td>2.50 ng/mL</td> </tr> <tr> <td>Quinidine</td> <td>0.05 µg/mL</td> </tr> </tbody> </table> <p><u>Dextromethorphan:</u> Linear range : 0.200-200 ng/mL in plasma (heparin) Inter-day Precision (%CV for Quality Controls) : < 7.9% Inter-day accuracy: -2.7 % to 3.3% Short term Stability: 27 hours in propylene tubes at ambient temperature under white light</p> <p><u>Dextrorphan:</u> Linear range : 2.50-2500 ng/mL in plasma (heparin) Inter-day Precision (%CV for Quality Controls) : < 5.0% Inter-day accuracy: -3.2 % to - 2.0% Short term Stability: 27 hours in propylene tubes at ambient temperature under white light</p>		<u>Plasma</u>	Dextromethorphan	0.200 ng/mL	Dextrorphan	2.50 ng/mL	Quinidine	0.05 µg/mL
	<u>Plasma</u>								
Dextromethorphan	0.200 ng/mL								
Dextrorphan	2.50 ng/mL								
Quinidine	0.05 µg/mL								

	<p><u>Quinidine:</u> Linear range : 0.05-10 µg/mL in plasma (heparin) Inter-day Precision (%CV for Quality Controls) : < 7.0% Inter-day accuracy: -8.7 % to -2.0% Short term Stability: 24.5 hours at ambient temperature</p> <p>HPLC <u>Lower Limits of Quantitation</u></p> <p style="text-align: center;"><u>Plasma</u></p> <p>Memantine 0.10 ng/mL</p> <p><u>Memantine:</u> Linear range : 0.10-30 ng/mL in plasma (EDTA) Inter-day Precision (%CV for Quality Controls) : < 8.8% Inter-day accuracy: -0.5 % to 2.8 % Short term Stability: 24.5 hours at room temperature</p>
PK Assessment (Primary endpoints)	<p>90% confidence intervals of</p> <ul style="list-style-type: none"> • Memantine AUC_{0-12h} on Day 32 (memantine alone) and Day 40 (memantine with AVP-923) • AVP-923 AUC_{0-12h} on Day 8 (DM, DX, and Q; AVP-923 alone) and Day 40 (DM, DX, and Q; AVP-923 with memantine). <p>Memantine and AVP-923: CSS_{max}, CSS_{min}, T_{max}, and t_{1/2}</p>
PD Assessment (Secondary endpoints)	<p>CRT: test of psychomotor function DA: simultaneous manual tracking and visual target detection tasks Postural Stability: assessment of stability VAS for Nausea: assessment of nausea VAS for Dizziness: assessment of dizziness BDI-II: assessment of depression BAI: assessment of multiple symptoms of anxiety LSEQ: Assessment of sleep quality</p>
Safety Assessment (Primary endpoints)	<p>Vital signs (sitting blood pressure, respiratory rate, pulse rate, oxygen saturation, and oral temperature), 12-lead ECG, Clinical laboratory tests (hematology, clinical chemistry, and urinalysis) and AE assessment</p>

Results:

Pharmacokinetics of Memantine:

The pharmacokinetic parameters of memantine are summarized in the following table:

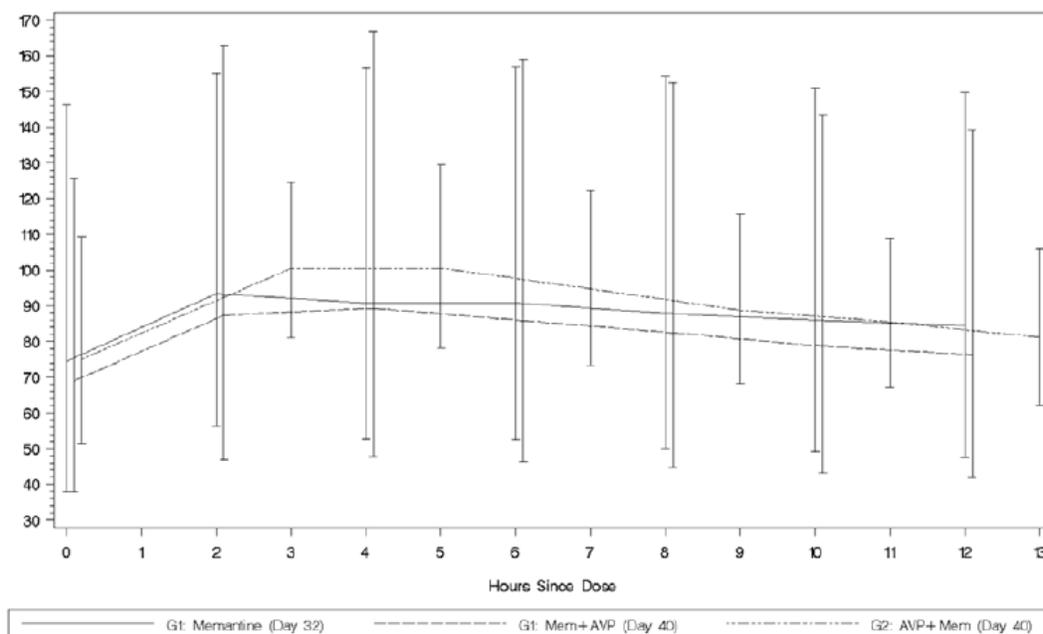
**Table 14.2.2.1 Summary of Steady State Pharmacokinetic Parameters: Memantine (ng/mL)
Evaluable Population**

	Group 1 Day 32 Memantine 10mg bd N=17	Group 1 Day 40 Memantine 10mg bd + AVP-923 30mg bd N=17	Group 2 Day 40 AVP-923 30mg bd + Memantine 10mg bd N=17
AUC(0-12h)			
N	17	17	17
Arithmetic Mean (SD)	1160.536 (360.2074)	1111.633 (391.3005)	1219.512 (282.6213)
Geometric Mean (CV)	1059.023 (59.4%)	993.851 (67.2%)	1186.703 (25.2%)
Median	1184.990	1143.620	1172.440
Range	147.29 - 1717.75	115.52 - 1897.59	592.17 - 1835.90
CSSmax			
N	17	17	17
Arithmetic Mean (SD)	106.412 (32.8256)	102.737 (35.5764)	106.406 (23.7994)
Geometric Mean (CV)	97.813 (55.3%)	91.596 (69.3%)	103.913 (23.0%)
Median	107.000	106.000	106.000
Range	15.80 - 157.00	9.93 - 170.00	60.50 - 165.00
CSSmin			
N	17	17	17
Arithmetic Mean (SD)	81.564 (25.9503)	76.606 (30.0273)	77.094 (22.6733)
Geometric Mean (CV)	72.470 (74.8%)	67.780 (67.7%)	73.129 (38.0%)
Median	82.300	75.400	73.800
Range	6.19 - 123.00	9.00 - 137.00	22.90 - 117.00
Tmax (h)			
N	17	17	17
Minimum	0.0	2.0	3.0
Lower Quartile	2.00	4.00	3.00
Median	4.00	4.00	5.00
Upper Quartile	6.00	4.00	5.00
Maximum	12.0	6.0	9.0
T1/2 (h)			
N	14	16	16
Arithmetic Mean (SD)	39.74 (18.704)	33.44 (15.392)	24.09 (11.726)
Geometric Mean (CV)	36.68 (40.9%)	30.13 (51.3%)	21.85 (47.3%)
Median	33.68	30.66	19.28
Range	22.5 - 91.2	11.5 - 63.6	8.6 - 53.3

Note: Sample timings relative to administration of drug differ from Group 1 to Group 2; hence, direct comparison is not appropriate.

The concentration-time profiles of memantine are shown in the following figure:

In-Text Figure 9. Plasma Concentrations for Memantine (ng/mL)



A summary of pharmacokinetic analysis shown as Estimate of Ratio of Geometric Means and 90 % CI are provided in the table below.

In-Text Table 1. Comparison of Steady State Pharmacokinetic Analysis for Memantine

	Estimate of Ratio of Geometric Means	90% Confidence Interval for Ratio
Group 1: Memantine (Day 40 - Day 32)		
AUC _{0-12h}	0.938	(0.850 - 1.036)
C _{SSmax}	0.936	(0.849 - 1.033)
C _{SSmin}	0.935	(0.826 - 1.059)

- Memantine trough plasma concentration data revealed that steady state levels of memantine were achieved in both groups after the titration period.
- In Group 1, plasma concentrations of memantine (AUC₀₋₁₂, C_{SSmin}, C_{SSmax}) were within the 90% confidence interval [0.8, 1.25] when comparing memantine given alone (Day 32) and co-administration with AVP-923 (Day 40).

Pharmacokinetics of Dextromethorphan:

The pharmacokinetic parameters of dextromethorphan are summarized in the following table:

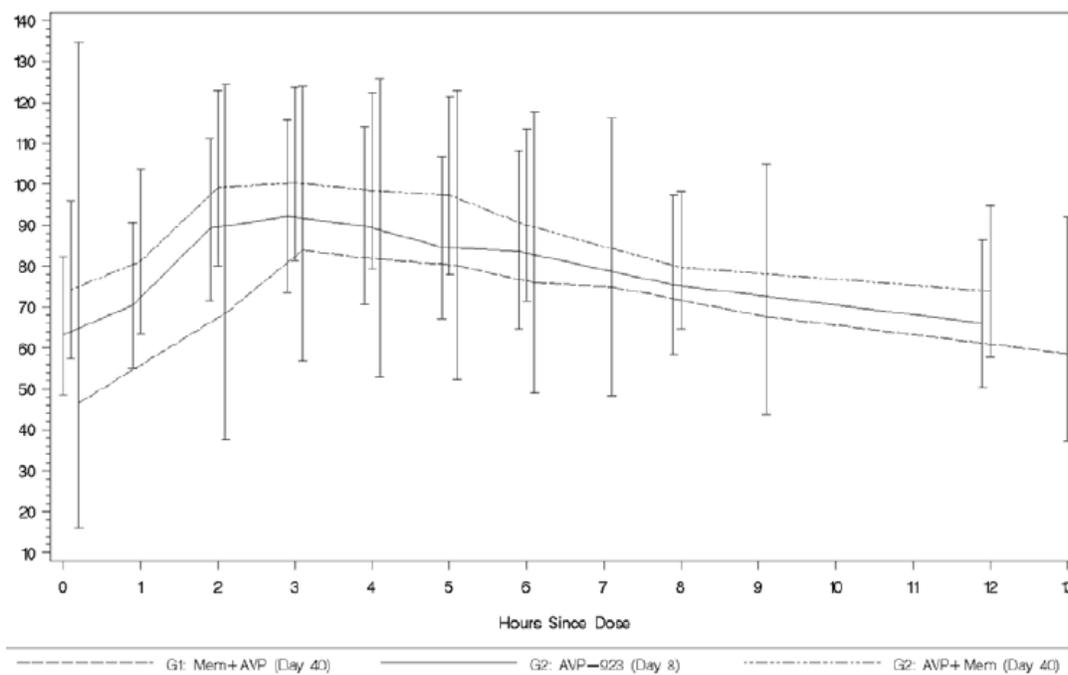
Table 14.2.2.2.1 Summary of Steady State Pharmacokinetic Parameters: AVP-923 Dextromethorphan (ng/mL) Evaluable Population

	Group 1 Day 40 Memantine 10mg bd + AVP-923 30mg bd N=17	Group 2 Day 8 AVP-923 30mg bd N=17	Group 2 Day 40 AVP-923 30mg bd + Memantine 10mg bd N=17
AUC(0-12h)			
N	17	17	17
Arithmetic Mean (SD)	981.7884 (374.65437)	969.2745 (248.74125)	1060.8666 (250.36813)
Geometric Mean (CV)	904.1243 (47.8%)	943.2596 (23.7%)	1036.7522 (21.8%)
Median	900.2430	897.8690	1044.8700
Range	240.384 - 1716.610	615.862 - 1630.000	737.376 - 1801.400
CSSmax			
N	17	17	17
Arithmetic Mean (SD)	94.9471 (33.89855)	98.5882 (24.02407)	108.7941 (24.21599)
Geometric Mean (CV)	88.3351 (44.0%)	96.1681 (22.7%)	106.5301 (21.0%)
Median	92.7000	92.6000	108.0000
Range	26.800 - 151.000	71.900 - 156.000	73.600 - 179.000
CSSmin			
N	17	17	17
Arithmetic Mean (SD)	56.9176 (25.35486)	62.8353 (18.53041)	72.8824 (19.41096)
Geometric Mean (CV)	44.7916 (140.4%)	60.5367 (28.1%)	70.8171 (24.3%)
Median	57.5000	57.4000	70.8000
Range	1.000 - 110.000	40.800 - 106.000	50.100 - 130.000
Tmax (h)			
N	17	17	17
Minimum	3.0	1.0	2.0
Lower Quartile	3.00	2.00	2.00
Median	3.00	3.00	3.00
Upper Quartile	4.00	4.00	4.00
Maximum	7.0	6.0	5.0
T1/2 (h)			
N	17	17	17
Arithmetic Mean (SD)	19.12 (10.233)	20.98 (12.158)	19.44 (6.315)
Geometric Mean (CV)	17.07 (51.3%)	18.59 (50.7%)	18.57 (31.6%)
Median	16.77	16.71	18.46
Range	6.0 - 48.1	9.0 - 51.0	12.5 - 32.4

Note: Sample timings relative to administration of drug differ from Group 1 to Group 2; hence, direct comparison is not appropriate.

The mean concentration-time profiles of dextromethorphan are shown in the following figure:

In-Text Figure 10. Plasma Concentrations for Dextromethorphan (ng/mL)



A summary of pharmacokinetic analysis shown as Estimate of Ratio of Geometric Means and 90 % CI are provided in the table below.

In-Text Table 2. Comparison of Steady State Pharmacokinetic Analysis for Dextromethorphan

	Estimate of Ratio of Geometric Means	90% Confidence Interval for Ratio
Group 2: Dextromethorphan (Day 40 - Day 8)		
AUC _{0-12h}	1.0991	(1.0413 - 1.1601)
C _{SSmax}	1.1077	(1.0579 - 1.1600)
C _{SSmin}	1.1698	(1.0758 - 1.2720)

Data extracted from [Table 14.2.2.3](#)

- DM trough plasma concentrations showed that steady state was achieved in both groups.
- In Group 2, levels of DM (AUC₀₋₁₂ and C_{SSmax}) were within the confidence interval when AVP-923 was administered alone, compared to when it was co-administered with memantine.
- The C_{SSmin} was slightly higher when memantine was added to AVP-923 and fell slightly outside of the upper limit of the 90% confidence interval.

Pharmacokinetics of Dextrophan:

The pharmacokinetic parameters of dextrophan are summarized in the following table:

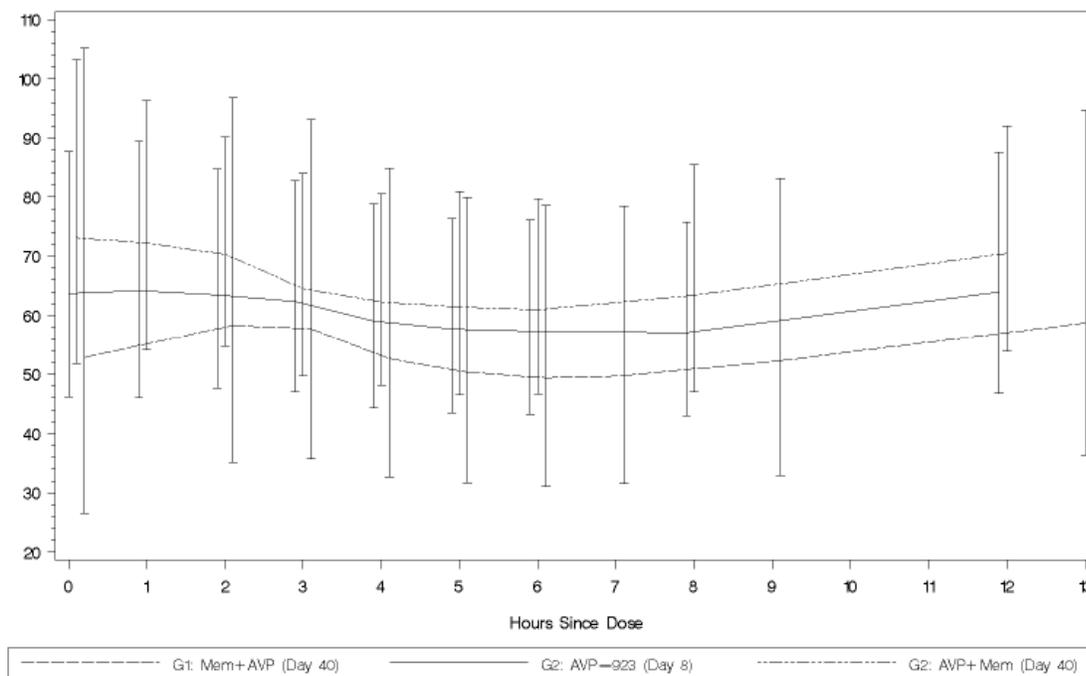
**Table 14.2.2.2.2 Summary of Steady State Pharmacokinetic Parameters: AVP-923 Dextrophan (ng/mL)
Evaluable Population**

	Group 1 Day 40 Memantine 10mg bd + AVP-923 30mg bd N=17	Group 2 Day 8 AVP-923 30mg bd N=17	Group 2 Day 40 AVP-923 30mg bd + Memantine 10mg bd N=17
AUC(0-12h)			
N	17	17	17
Arithmetic Mean (SD)	777.977 (437.1393)	753.259 (213.8171)	818.256 (215.5759)
Geometric Mean (CV)	696.295 (49.2%)	725.370 (29.3%)	791.196 (27.8%)
Median	664.326	763.602	809.233
Range	293.64 - 2214.34	359.43 - 1334.58	400.68 - 1359.08
CSSmax			
N	17	17	17
Arithmetic Mean (SD)	70.971 (36.3348)	72.747 (21.5598)	81.600 (27.5349)
Geometric Mean (CV)	64.511 (45.6%)	69.659 (31.9%)	77.651 (33.1%)
Median	61.100	70.200	74.900
Range	27.60 - 188.00	32.70 - 121.00	39.20 - 153.00
CSSmin			
N	17	17	17
Arithmetic Mean (SD)	51.152 (33.6185)	57.124 (16.8507)	60.753 (15.3225)
Geometric Mean (CV)	42.657 (73.7%)	54.894 (30.0%)	58.909 (26.6%)
Median	44.700	59.100	59.000
Range	6.79 - 160.00	28.50 - 104.00	30.20 - 100.00
Tmax (h)			
N	17	17	17
Minimum	0.0	0.0	0.0
Lower Quartile	2.00	1.00	1.00
Median	3.00	3.00	1.00
Upper Quartile	13.00	12.00	6.00
Maximum	13.0	12.0	12.0
T1/2 (h)			
N	2	4	3
Arithmetic Mean (SD)	25.47 (27.027)	55.03 (17.420)	86.57 (27.015)
Geometric Mean (CV)	16.83 (238.0%)	52.90 (33.7%)	83.94 (30.7%)
Median	25.47	55.59	77.55
Range	6.4 - 44.6	37.2 - 71.8	65.2 - 116.9

Note: Sample timings relative to administration of drug differ from Group 1 to Group 2; hence, direct comparison is not appropriate.

The mean concentration-time profiles of dextrophan are shown in the following figure:

In-Text Figure 11. Plasma Concentrations for Dextrophan (ng/mL)



A summary of pharmacokinetic analysis shown as Estimate of Ratio of Geometric Means and 90 % CI are provided in the table below.

In-Text Table 3. Comparison of Steady State Pharmacokinetic Analysis for Dextrophan

	Estimate of Ratio of Geometric Means	90% Confidence Interval for Ratio
Group 2: Dextrophan (Day 40 - Day 8)		
AUC _{0-12h}	1.091	(1.020 - 1.167)
C _{SSmax}	1.115	(1.026 - 1.211)
C _{SSmin}	1.073	(0.993 - 1.160)

Data extracted from [Table 14.2.2.3](#)

- DX trough plasma concentration showed that steady state was achieved in both groups.
- Plasma concentrations of DX were comparable between AVP-923 administered alone and co-administered with memantine. The pharmacokinetic parameters (AUC₀₋₁₂, C_{SSmax}, and C_{SSmin}) fell within the 90% confidence interval (80-125%).

Pharmacokinetics of Quinidine:

The pharmacokinetic parameters of quinidine are summarized in the following table:

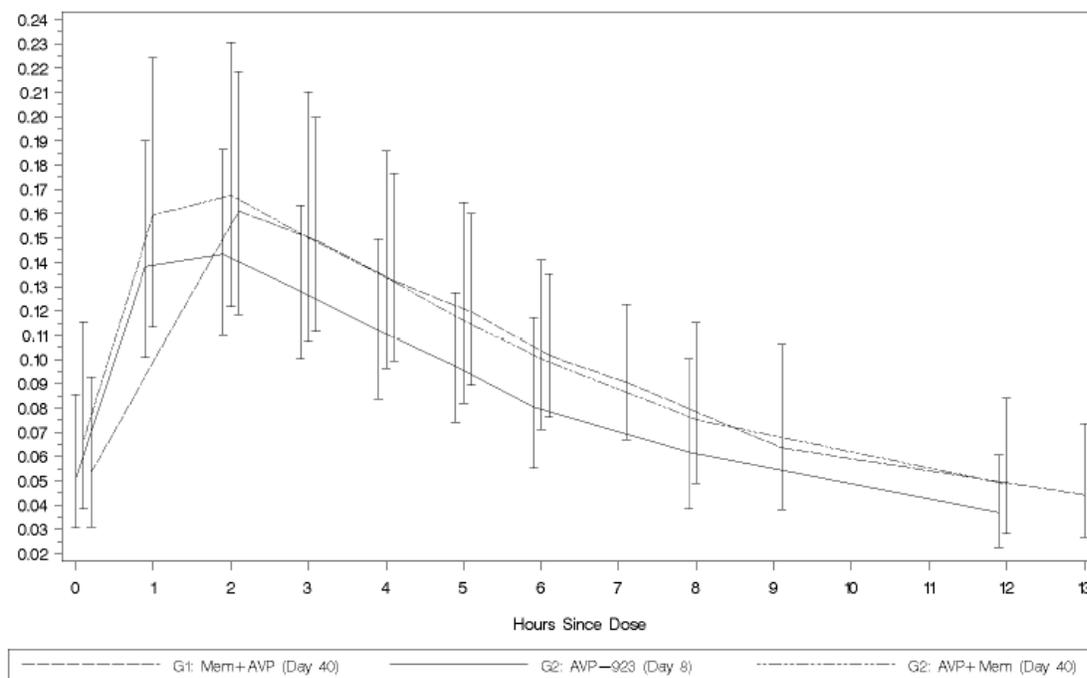
**Table 14.2.2.2.3 Summary of Steady State Pharmacokinetic Parameters: AVP-923 Quinidine ($\mu\text{g/mL}$)
Evaluable Population**

	Group 1 Day 40 Memantine 10mg bd + AVP-923 30mg bd N=17	Group 2 Day 8 AVP-923 30mg bd N=17	Group 2 Day 40 AVP-923 30mg bd + Memantine 10mg bd N=17
AUC(0-12h)			
N	17	17	17
Arithmetic Mean (SD)	1.23107 (0.452180)	1.03430 (0.376155)	1.29167 (0.493467)
Geometric Mean (CV)	1.14810 (41.2%)	0.96824 (39.7%)	1.20773 (39.2%)
Median	1.24868	0.92118	1.18111
Range	0.5847 - 2.1000	0.4450 - 1.6368	0.6224 - 2.3057
CSSmax			
N	17	17	17
Arithmetic Mean (SD)	0.16862 (0.045722)	0.15718 (0.042539)	0.19059 (0.060249)
Geometric Mean (CV)	0.16274 (28.4%)	0.15233 (25.6%)	0.18240 (30.8%)
Median	0.15400	0.13400	0.16600
Range	0.0866 - 0.2500	0.1120 - 0.2600	0.1210 - 0.3100
CSSmin			
N	17	17	17
Arithmetic Mean (SD)	0.03916 (0.034988)	0.02701 (0.034163)	0.04673 (0.038869)
Geometric Mean (CV)	0.04412 (54.1%)	0.03695 (52.7%)	0.04864 (59.1%)
Median	0.05570	0.00000	0.05710
Range	0.0000 - 0.0928	0.0000 - 0.0872	0.0000 - 0.1050
Tmax (h)			
N	17	17	17
Minimum	2.0	1.0	1.0
Lower Quartile	2.00	1.00	1.00
Median	2.00	2.00	1.00
Upper Quartile	2.00	2.00	2.00
Maximum	3.0	3.0	2.0
T1/2 (h)			
N	17	17	17
Arithmetic Mean (SD)	7.29 (1.963)	7.03 (2.104)	6.67 (1.787)
Geometric Mean (CV)	7.02 (29.6%)	6.70 (34.1%)	6.47 (25.0%)
Median	7.55	6.93	6.25
Range	4.1 - 10.9	2.8 - 11.7	4.9 - 11.2

Note: Sample timings relative to administration of drug differ from Group 1 to Group 2; hence, direct comparison is not appropriate.

The mean concentration-time profiles of quinidine are shown in the following figure:

In-Text Figure 12. Plasma Concentrations for Quinidine ($\mu\text{g}/\text{mL}$)



A summary of pharmacokinetic analysis shown as Estimate of Ratio of Geometric Means and 90 % CI are provided in the table below.

In-Text Table 4. Comparison of Steady State Pharmacokinetic Analysis for Quinidine

	Estimate of Ratio of Geometric Means	90% Confidence Interval for Ratio
Group 2: Quinidine (Day 40 - Day 8)		
AUC _{0-12h}	1.24735	(1.15321 - 1.34918)
C _{SSmax}	1.19738	(1.13028 - 1.26847)
C _{SSmin}	1.31638	(1.14508 - 1.51330)

Data extracted from [Table 14.2.2.3](#)

- Q trough plasma concentration showed that steady state was achieved in both groups.
- Plasma concentrations of Q were slightly higher when memantine was added to AVP-923 than AVP-923 was given alone, in all measured parameters (AUC₀₋₁₂, C_{SSmax}, and C_{SSmin}). The sponsor stated that this finding is likely of no clinical importance for the following reasons: 1) Plasma concentrations of Q throughout the study were very low, with many falling under the lower limit of quantification (0.05 $\mu\text{g}/\text{mL}$). Such data were given a value half of the lower limit of quantification, as opposed to zero, due to the logarithmic transformation (i.e., it is impossible to extract a log of zero). Thus, many values were incorrectly estimated. 2) The difference in Q concentrations was small (about 0.03 $\mu\text{g}/\text{mL}$).

Adverse Events

Incidence of adverse events in both groups is summarized below.

In-Text Table 20. Incidence and Frequency of Treatment-Emergent Adverse Events by System Organ Class and Treatment for Group 1

System Organ Class/ Preferred Term	Memantine 5mg od (N=23)	Memantine 5mg bd (N=22)	Memantine 10/5mg (N=20)	Memantine 10mg bd (N=20)	Memantine 10mg bd + AVP-923 30mg bd (N=19)
Any System Organ Class					
Any Event	12 (52.2%) [29]	10 (45.5%) [21]	9 (45.0%) [22]	9 (45.0%) [32]	14 (73.7%) [90]

In-Text Table 21. Incidence of Treatment-Emergent Adverse Events by System Organ Class and Treatment for Group 2

System Organ Class/ Preferred Term	AVP-923 30mg bd (N=28)	AVP-923 30mg bd + Memantine 5mg od (N=23)	AVP-923 30mg bd + Memantine 5mg bd (N=23)	AVP-923 30mg bd + Memantine 10/5mg (N=21)	AVP-923 30mg bd + Memantine 10mg bd (N=20)
Any System Organ Class					
Any Event	25 (89.3%) [121]	15 (65.2%) [29]	12 (52.2%) [22]	12 (57.1%) [22]	14 (70.0%) [31]

- The incidence of AEs was greater when AVP-923 was given alone compared with memantine alone or combination in either order. This finding suggested that the majority of AEs resulted from AVP-923 than from memantine or a drug interaction.
- The incidence of AEs decreased with the duration of AVP-923 treatment in both groups over time following the introduction of AVP-923, suggesting that subjects gradually adjusted to the dose.

The intensity of the treatment-emerged adverse events in both groups is summarized below.

In-Text Table 22. Maximum Intensity of Treatment-Emergent Adverse Events by Treatment and System Organ Class for Group 1

System Organ Class	Maximum Severity	Memantine 5mg od (N=23)	Memantine 5mg bd (N=22)	Memantine 10/5mg (N=20)	Memantine 10mg bd (N=20)	Memantine 10mg bd + AVP-923 30mg bd (N=19)
Any System Organ Class						
Any Event	Mild	5 (21.7%)	9 (40.9%)	4 (20.0%)	4 (20.0%)	7 (36.8%)
	Moderate	7 (30.4%)	1 (4.5%)	5 (25.0%)	5 (25.0%)	6 (31.6%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)

In-Text Table 23. Maximum Intensity of Treatment-Emergent Adverse Events by Treatment and System Organ Class for Group 2

System Organ Class	Maximum Severity	AVP-923	AVP-923	AVP-923	AVP-923
		30mg bd (N=28)	+ Memantine 30mg bd 5mg od (N=23)	+ Memantine 30mg bd 5mg bd (N=23)	+ Memantine 30mg bd 10/5mg (N=21)
Any System Organ Class					
Any Event	Mild	14 (50.0%)	8 (34.8%)	8 (34.8%)	11 (55.0%)
	Moderate	9 (32.1%)	7 (30.4%)	4 (17.4%)	3 (15.0%)
	Severe	2 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

- There were no marked differences between groups in the incidence and severity of AEs when co-administering the two drugs, suggesting that the order of administration (either memantine first or AVP-923 first) did not differentially affect the incidence or severity of AEs.

Withdrawals Due to an Adverse Event

Four (7.7%) subjects withdrew from the study because of AEs. One (4.3%) of these subjects was in Group 1 and the remaining 3 (10.3%) subjects were in Group 2. Subjects discontinued from the study are listed below.

- Subject 9105 (female, Group 1) withdrew from the study due to 9 mild to moderate AEs, after 10 days of receiving memantine (i.e., 2 days after starting the 10 mg dose).
- Subject 9125 (male, Group 2) was on the study drug for 2 days before withdrawing due to severe vomiting (plus 4 mild to moderate AEs).
- Subject 9130 (male, Group 2) experienced 9 AEs; 3 (moderate general weakness, vertigo, and nausea) of these AEs occurred 3 days after the introduction of AVP-923 alone.
- Subject 9204 (female, Group 2) experienced continuous moderate nausea and 2 mild AEs 1 day after beginning AVP-923 alone.

Pharmacodynamics

Most PD measurements revealed no differences between groups as shown by 90% confidence intervals of the following contrasts:

- Group 1: Day 40 (memantine + AVP-923) – Day 32 (memantine only)
- Group 2: Day 40 (AVP-923 + memantine) – Day 8 (AVP-923 only)

These PD markers are listed below.

Motor function measured by CRT, *Attention* measured by DA, *Nausea* measured by VAS, *Depression* measured by the Beck Depression Inventory–II, *Anxiety* measured by the Beck Anxiety Inventory and *Sleep* measured by the Leads Sleep Evaluation Questionnaire showed no differences between groups.

Dizziness: dizziness was greater when AVP-923 was added to memantine than when memantine was given alone (Group 1), as measured by VAS Dizziness at 2 and 4 hours post-dose. No differences were observed at 6 hours post-dose between the treatment conditions.

**Table 14.2.3.28 Comparison of Visual Analog Scales (VAS)
Evaluable Population**

		Estimate of Difference in Means	90% Confidence Interval for Difference
Group 1 (Day 40 - Day 32)			
Summary of VAS for Dizziness	Hour 2	12.3	(1.1 - 23.5)
	Hour 4	11.5	(0.3 - 22.8)
	Hour 6	8.8	(-2.5 - 20.0)
Summary of VAS for Nausea	Hour 2	5.2	(-5.5 - 15.9)
	Hour 4	8.5	(-2.2 - 19.2)
	Hour 6	7.2	(-3.5 - 17.9)
Group 2 (Day 40 - Day 8)			
Summary of VAS for Dizziness	Hour 2	1.2	(-7.5 - 10.0)
	Hour 4	-0.5	(-9.2 - 8.3)
	Hour 6	1.9	(-6.8 - 10.7)
Summary of VAS for Nausea	Hour 2	-2.1	(-10.1 - 5.9)
	Hour 4	-6.8	(-14.8 - 1.2)
	Hour 6	-0.4	(-8.3 - 7.6)

Postural Stability: in general, stability was slightly improved when AVP-923 was added to memantine in comparison to memantine alone but slightly decreased when memantine was added to AVP-923 in comparison to AVP-923 given alone.

In-Text Table 18. Comparison of Postural Stability

		Estimate of Difference in Means	90% Confidence Interval for Difference
Group 1 (Day 40 - Day 32)			
Area of a 95% Confidence Ellipsoid, Eyes Closed (cm sq)	Hour 2	0.845	(-1.878 - 3.568)
	Hour 4	1.048	(-1.675 - 3.771)
	Hour 6	-0.647	(-3.370 - 2.076)
Area of a 95% Confidence Ellipsoid, Eyes Open (cm sq)	Hour 2	-2.059	(-6.356 - 2.239)
	Hour 4	-4.518	(-8.815 - -0.221)
	Hour 6	-3.113	(-7.410 - 1.184)
Average Velocity of the Center-of-Pressure, Eyes Closed (cm/sec)	Hour 2	-0.138	(-0.262 - -0.014)
	Hour 4	-0.133	(-0.256 - -0.009)
	Hour 6	-0.095	(-0.219 - 0.029)
Average Velocity of the Center-of-Pressure, Eyes Open (cm/sec)	Hour 2	0.063	(-0.080 - 0.207)
	Hour 4	-0.020	(-0.164 - 0.124)
	Hour 6	-0.143	(-0.287 - 0.000)
Group 2 (Day 40 - Day 8)			
Area of a 95% Confidence Ellipsoid, Eyes Closed (cm sq)	Hour 2	1.259	(0.204 - 2.314)
	Hour 4	-0.244	(-1.299 - 0.811)
	Hour 6	0.193	(-0.862 - 1.248)
Area of a 95% Confidence Ellipsoid, Eyes Open (cm sq)	Hour 2	0.966	(0.155 - 1.777)
	Hour 4	0.590	(-0.221 - 1.401)
	Hour 6	-0.050	(-0.861 - 0.761)
Average Velocity of the Center-of-Pressure, Eyes Closed (cm/sec)	Hour 2	0.596	(0.260 - 0.933)
	Hour 4	0.042	(-0.295 - 0.378)
	Hour 6	0.056	(-0.280 - 0.393)
Average Velocity of the Center-of-Pressure, Eyes Open (cm/sec)	Hour 2	0.101	(0.032 - 0.171)
	Hour 4	0.061	(-0.008 - 0.131)
	Hour 6	0.025	(-0.045 - 0.094)

Data reproduced from [Table 14.2.3.27](#)

Conclusions:

- The addition of AVP-923 to memantine did not alter the steady state pharmacokinetics of memantine in healthy volunteers.
- The addition of memantine to AVP-923 did not alter the steady state pharmacokinetics of AVP-923 in healthy volunteers.
- The addition of memantine to AVP-923 or that of AVP-923 to memantine did not differentially affect the incidence or severity of AEs, suggesting the absence of drug interaction
- The addition of AVP-923 to memantine did not adversely affect any pharmacodynamic measures and in fact slightly improved some of the pharmacodynamic measures observed, compared to the administration of memantine alone in healthy volunteers.
- The addition of memantine to AVP-923 did not adversely affect pharmacodynamic measures in healthy adult volunteers and slightly improved the performance on some measures, compared to the administration of AVP-923 alone.

Study: AA42125-01: VALIDATION OF AN HPLC METHOD FOR THE DETERMINATION OF QUINIDINE IN HUMAN PLASMA (HEPARIN)

Analysis of human plasma concentrations of quinidine was performed using an HPLC method with mass spectrometric detection.

VALIDATION SUMMARY

Information Requested	Data
Validation Summary	(b) (4) Validation Study AA42125-01
Analyte	Quinidine
Internal Standard (IS)	Quinine
Method Description	Protein precipitation with analysis/detection by HPLC
Limit of Quantitation (ng/mL)	2.00 ng/mL
Average Recovery of Drug (% Mean)	82% at 4.00 ng/mL 87% at 25.0 ng/mL 87% at 200 ng/mL
Average Recovery of IS (% Mean)	87%
Standard Curve Concentrations (ng/mL)	2.00, 4.00, 8.00, 25.0, 75.0, 150, 200, and 250 ng/mL
QC Concentrations (ng/mL)	LLOQ QC, 6.00, 40.0, and 190 ng/mL
QC Intra-batch Precision Range (% CV)	0.5 to 6.4%
QC Intra-batch Accuracy Range (% Bias)	-8.5 to 12.8%
QC Inter-batch Precision Range (% CV)	1.1 to 8.3%
QC Inter-batch Accuracy Range (% Bias)	0.5 to 9.0%
Bench-top Stability (Hrs)	Short-term Stability: 28 hours in polypropylene tubes at ambient temperature under white light
Stock Stability (Days)	917 days at approximately 1000 µg/mL in methanol in a polypropylene container at 5°C
Processed Stability (Hrs)	Post-preparative Stability: 256 hours in amber injection vials at 5°C Processed Sample Integrity: 135 hours in amber injection vials at 5°C
Freeze-thaw Stability (Cycles)	Freeze and Thaw Stability: 6 cycles in polypropylene tubes at -20°C under white light
Long-term Storage Stability (days)	Long-term Stability: 28 days in polypropylene tubes at -20°C
Dilution Integrity	up to 10,000 ng/mL, diluted 100-fold
Selectivity	No significant matrix effect was observed in 9 of 10 human plasma (heparin) lots that were spiked at the concentration of the LLOQ (2.00 ng/mL) and in any of the 10 human plasma (heparin) lots that were spiked at the concentration of the high QC (190 ng/mL) sample

Additional Information			
Matrix (Anticoagulant)		Human Plasma (Heparin)	
Bioanalytical Method (BAM) SOP Number		BAM SOP AA42125-01, v2	
Detector		(b) (4)	
Assay Volume Required		0.400 mL	
Regression Type		Linear (1/concentration)	
Quantitation Method		Peak Height Ratio	
Co-administered Compound Evaluation		Dextrophan (b) (4) Dextromethorphan (b) (4) Hydroquinidine (b) (4)	
Quality Control Samples		Precision (% CV)	Accuracy (% Bias)
Inter-batch	LLOQ	8.3	0.5
	Low	2.8	9.0
	Medium	1.1	7.0
	High	1.1	3.7
Intra-batch (Batch 15) Aliquot Method: Manual Extraction Method: Manual	LLOQ	6.4	-8.5
	Low	1.6	7.2
	Medium	1.3	6.8
	High	0.5	4.2
Intra-batch (Batch 17) Aliquot Method: Manual Extraction Method: Manual	LLOQ	5.1	6.5
	Low	1.2	12.8
	Medium	1.0	7.8
	High	1.2	4.7
Intra-batch (Batch 16) Aliquot Method: Manual Extraction Method: Manual	LLOQ	4.7	3.0
	Low	1.0	7.0
	Medium	0.7	6.8
	High	1.2	3.2
Substock Solution Stability		157 days at 100 µg/mL in (b) (4) in a polypropylene container at 5°C 28 days at 0.0400 µg/mL in (b) (4) in a polypropylene container at 5°C	
Internal Standard Stock Stability		112 days at approximately 1000 µg/mL in methanol in a polypropylene container at 5°C	
Internal Standard Substock Stability		27 days at 40.0 ng/mL in acetonitrile in a polypropylene container at 5°C	
Sample Aliquot Frozen Storage Integrity		samples manually aliquotted at 0.400 mL, stored in 12 x 75 mm glass culture tubes at -20°C prior to extraction	
Batch Size		(b) (4) injections	

4.2 APPENDIX II

ORIGINAL CLINICAL PHARMACOLOGY REVIEW

1.1 Recommendations

We have reviewed the clinical pharmacology and biopharmaceutics information submitted to NDA 21879. The thorough QT study showed a risk of QT prolongation of greater than 10 msec after administration of NEURODEX that could be greater than 19 msec in 5% of the population.

Our PK/PD modeling of the QT prolongation suggests that a lower dose of quinidine (10 or 15 mg) is likely to result in QT prolongation of less than 10 msec in 95% of the population. Therefore, we recommend that the Sponsor conduct a Phase 3 clinical study to evaluate efficacy (and the exposure-response relationship) of a lower dose of quinidine to be given with dextromethorphan.

We recommend that NEURODEX (at the proposed dose or even with a lower quinidine dose) be contraindicated with strong or moderate inhibitors of CYP3A since quinidine is a CYP3A substrate and inhibitors can further increase the quinidine-induced QT prolongation and resultant safety risk.

CYP2D6 poor metabolizers (PMs) or patients chronically taking strong CYP2D6 inhibitors would have dextromethorphan exposure after administration of DM alone that is similar to exposure in extensive metabolizers (EMs) taking NEURODEX. Therefore, CYP2D6 PMs taking NEURODEX or patients chronically taking strong CYP2D6 inhibitors have an unnecessary risk of QT prolongation from quinidine without any benefit from the quinidine component of this combination product. Because of this, with the current dose of NEURODEX, we would suggest that NEURODEX not be used in CYP2D6 PMs and in patients taking strong CYP2D6 inhibitors.

Specific recommendations are as follows:

- 1) The proposed dose of NEURODEX has a risk of QT prolongation of greater than 10 msec. The Sponsor should evaluate in a Phase 3 study whether 10 or 15 mg quinidine/30 mg DM or higher (and consider 0 mg quinidine/30 mg DM in a population of PMs) would provide adequate therapeutic benefit. This dose of quinidine would be expected to result in less QT risk than the proposed dose of 30 mg quinidine.
- 2) NEURODEX should be contraindicated in patients taking strong or moderate inhibitors of CYP3A.
- 3) Because of the unnecessary risk of QT exposure in patients who are CYP2D6 PMs or in patients taking strong CYP2D6 inhibitors, we would recommend the following if NEURODEX were to be approved at the current dose (30 mg quinidine/30 mg dextromethorphan):
 - CYP2D6 genotype testing should be required prior to administration of NEURODEX.
 - Adequate labeling should be written to indicate that the quinidine component of NEURODEX is not necessary for
 - 1) patients who are PMs of drugs metabolized by CYP2D6.
 - 2) patients who are chronically taking strong CYP2D6 inhibitors.
- 4) Satisfactory agreement must be reached between the Sponsor and the Agency regarding labeling (Please refer to **Section 4** of this review)
- 5) The following *in vitro* studies should be conducted preferably prior to approval to be included in labeling. If this NDA is approved this cycle, the *in vitro* studies could be done in Phase 4:
 - Evaluate quinidine as an inhibitor and as an inducer of P450s
 - Evaluate dextromethorphan (DM) as an inhibitor and as an inducer of P450s

The Sponsor should refer to the Draft Guidance for Industry: Drug Interaction studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (<http://www.fda.gov/cder/guidance/6695dft.htm>). The results of these *in vitro* studies would indicate whether further *in vivo* drug interaction studies are needed.

- 6) The Sponsor proposed the following dissolution method and specifications:

Apparatus:	USP Apparatus 1 (Basket)
Medium:	Simulated Gastric Fluid, without enzymes, pH 1.2
Volume:	900 ml
Rotation Speed:	100 rpm
Specification:	
Dextromethorphan:	15 minutes: Q= (b) (4)
Quinidine:	15 minutes: Q= [REDACTED]

1.2 Phase 4 Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

NDA 21-879 has been submitted to support the approval of NEURODEX (30 mg dextromethorphan/30 mg quinidine sulfate) for the treatment of pseudobulbar affect (PBA). The proposed dose is 1 capsule given orally twice daily (every 12 hours). The sole purpose of Q is to inhibit the CYP2D6-mediated metabolism of DM, resulting in increased exposure to DM that is significantly greater than from administration of DM alone.

The following clinical pharmacology studies have been submitted and reviewed:

- 99-AVR-100 Determining Lowest Dose of Q that inhibits CYP2D6
- 99-AVR-101 Single and Multiple Dose PK Study
- 99-AVR-103 Q Interaction with High Dose DM
- 04-AVR-111 Food Effect Study
- 04-AVR-115 Hepatic Impairment Study
- 04-AVR-116 Renal Impairment Study
- 04-AVR-117 Population PK Study
- 05-AVR-119 Thorough QT Study
- 04-AVR-112 Desipramine Interaction Study

In addition, the two pivotal clinical studies (99-AVR-102 and 02-AVR-106) have been reviewed from a PK/PD perspective.

Dissolution Method Development and justification for methods and specifications have been reviewed. In addition, the to-be-marketed formulation differs from the clinical trial formulation in the technical grades of 3 excipients as well as the site of manufacture, and a request for biowaiver has been reviewed.

The key findings with respect to the Clinical Pharmacology and biopharmaceutics of NEURODEX are as follows:

Pharmacokinetics

- Quinidine inhibits the CYP2D6-metabolism of dextromethorphan (DM) to dextrorphan (DX), resulting in an approximate 10-30 fold increase in DM exposure in plasma of extensive CYP2D6 metabolizers compared to when DM is given alone.
- The dose of Q that was selected was based on the urinary DM/DX ratio in Phase 1 studies. The selected dose (30 mg Q) converted 8/8 extensive metabolizers of drugs metabolized by CYP2D6 (EMs) to the poor metabolizer (PM) phenotype. It should be

noted that a 10 mg dose of Q converted 6/7 subjects to PMs. This resulted in a mean 10-fold increase in exposure compared to DM alone. However, a dose-response evaluation for efficacy has not been conducted, and the efficacy of the Q/DM combination that would result in lower exposures has not been thoroughly evaluated.

- A single and multiple dose study of 30 mg Q/30 mg DM has been conducted in healthy volunteers (99-AVR-101). In EMs, mean C_{max} and AUC for DM were approximately 6 to 8-fold greater on Day 8 than on Day 1. There was little change in exposure to DX. In PMs (n=2) there was a 6 to 7-fold increase in DM exposure between Days 8 and 1. DX was formed, with a 2-fold increase in DX C_{max} and a 6-fold increase in DX AUC between Days 8 and 1. DX exposure remained higher in EMs than in PMs throughout the study. At Day 8, DM exposure in the PMs (n=2) was approximately 45% greater than in EMs.
- Mean (%CV) Q C_{max} values in the multiple dose study 99-AVR-101 were 0.16 (23) µg/ml in EMs with similar values in the PMs. However, Q concentrations in the clinical efficacy and safety studies were as high as 2.21 µg/ml in efficacy study 99-AVR-102.
- Exposure to DM (C_{max} or AUC) or Q (C_{max}) was not increased in subjects with mild-moderate renal impairment after NEURODEX administration for 6 days, and an increase in DX exposure was within the range of concentrations observed when DM is given at an OTC dose in the absence of Q. Q AUC increased by approximately 3%. No dosage adjustment is needed for mild-moderate renal impairment. NEURODEX has not been evaluated in severe renal impairment.
- Exposure to Q was not increased in mild to moderate hepatic impairment. Exposure to DM was increased less than 20% in mild to moderate hepatic impairment. There was an increase in common adverse events in subjects with moderate impairment. No dosage adjustment is needed for mild-moderate hepatic impairment, but in moderate impairment patients should be closely evaluated for adverse events. NEURODEX has not been evaluated in severe hepatic impairment.
- Quinidine is a strong inhibitor of CYP2D6. An interaction study showed a 5-6 fold increase in exposure to the sensitive CYP2D6 substrate desipramine after coadministration with NEURODEX.
- Quinidine is a substrate of CYP3A4. The literature shows a 1.6-fold increase in Q C_{max} and a 2.4-fold increase in AUC in the presence of a strong CYP3A inhibitor, itraconazole, *in vivo*.
- A thorough QT study showed QT prolongation consistent with the known effect of Q. At the proposed therapeutic dose the maximal mean placebo-subtracted, baseline-adjusted QTcF was 10.12 msec, and the upper bound of the one-sided 95% CI was 15.05 msec. For a suprathreshold dose (60 mg DM/60 mg Q), the value was 18.81 msec and the upper bound of the one-sided 95% CI for that value was 24.5 msec. (It should be noted that the Q exposure after administration of the suprathreshold doses was less than 1.1 times the highest mean values in healthy volunteers in other Phase 1 studies and did not exceed the maximum quinidine concentration reported in efficacy study 99-AVR-102 that was 2.21 µg/ml).
- A PK/PD model analyzing the relationship between change in QTc interval and changes in plasma quinidine concentration predicted that in 5% of the population the prolongation would be 19 msec after a 30 mg dose and at least 37.8 msec after the 60 mg dose. The model also was used to predict QTc prolongation for doses of 15 and 10 mg of quinidine

that have not been studied clinically, and the prolongation was predicted to be less than 10 msec in 95% of the population.

- BE was demonstrated for AUC and C_{max} for DM and for Q following administration of NEURODEX under fasting conditions or with a high fat meal. NEURODEX can be taken without regard to meals.

Biopharmaceutics

The dissolution profile of the to-be-marketed capsule is similar to that of the clinical trial capsule, and a biowaiver can be granted.

The Sponsor has proposed the following method and specifications:

Apparatus:	USP Apparatus 1 (Basket)
Medium:	Simulated Gastric Fluid, without enzymes, pH 1.2
Volume:	900 ml
Rotation Speed:	100 rpm
Specification:	
Dextromethorphan:	15 minutes: Q= (b) (4)
Quinidine:	15 minutes: Q= (b) (4)

The Office of Clinical Pharmacology finds the proposed dissolution method and specifications acceptable.

Recommendations

- 1) The proposed dose of NEURODEX has a risk of QT prolongation of greater than 10 msec. The Sponsor should evaluate in a Phase 3 study whether 10 or 15 mg quinidine/30 mg DM or higher (and consider 0 mg quinidine/30 mg DM in a population of PMs) would provide adequate therapeutic benefit. This dose of quinidine would be expected to result in less QT risk than the proposed dose of 30 mg quinidine.
- 2) NEURODEX should be contraindicated in patients taking strong or moderate inhibitors of CYP3A.
- 3) Because of the unnecessary risk of QT exposure in patients who are CYP2D6 PMs or in patients taking strong CYP2D6 inhibitors, we would recommend the following if NEURODEX were to be approved at the current dose (30 mg quinidine/30 mg dextromethorphan):
 - CYP2D6 genotype testing should be required prior to administration of NEURODEX.
 - Adequate labeling should be written to indicate that the quinidine component of NEURODEX is not necessary for
 - 1) patients who are PMs of drugs metabolized by CYP2D6.
 - 3) patients who are chronically taking strong CYP2D6 inhibitors.

- 4) Satisfactory agreement must be reached between the Sponsor and the Agency regarding labeling (Please refer to **Section 4** of this review)
- 5) The following *in vitro* studies should be conducted preferably prior to approval to be included in labeling. If this NDA is approved this cycle, the *in vitro* studies could be done in Phase 4:
 - Evaluate quinidine as an inhibitor and as an inducer of P450s
 - Evaluate dextromethorphan (DM) as an inhibitor and as an inducer of P450s

The Sponsor should refer to the Draft Guidance for Industry: Drug Interaction studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (<http://www.fda.gov/cder/guidance/6695dft.htm>). The results of these *in vitro* studies would indicate whether further *in vivo* drug interaction studies are needed.

2 Question-Based Review

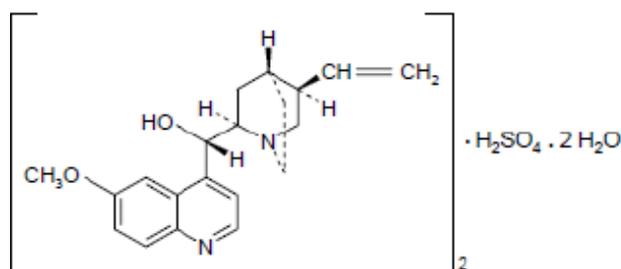
2.1 General Attributes

NEURODEX is a combination of quinidine sulfate (30 mg) and dextromethorphan hydrobromide (HBr) (30 mg). Quinidine sulfate (Q) and dextromethorphan HBr (DM) are currently marketed individually. Q is indicated for reduction of frequency of atrial fibrillation/flutter beginning at doses of 200 mg every 6 hours, conversion of atrial fibrillation/flutter to sinus rhythm beginning at doses of 400 mg every 6 hours, and treatment of *P. falciparum* malaria. DM is an OTC antitussive given in doses of 30 mg every 6 to 8 hours up to 120 mg/day.

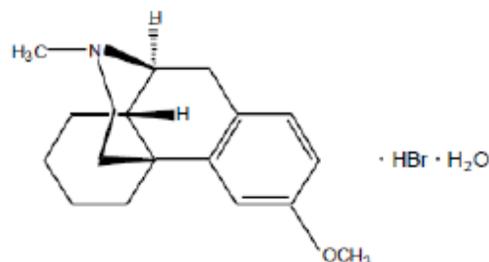
2.1.1 What are the highlights of the chemistry and physical-chemical properties of NEURODEX, and the formulation of the drug product?

Quinidine sulfate has an empirical formula of $C_{40}H_{48}N_4O_4 \cdot H_2SO_4 \cdot 2H_2O$ and is designated as cinchonan-9-ol, 6'-methoxy-(9S)-, sulfate (2:1) dehydrate with a molecular weight of 782.96. Dextromethorphan HBr has an empirical formula of $C_{18}H_{25}NO \cdot HBr \cdot H_2O$ and is designated as morphinan, 3-methoxy-17-methyl-, (9 α , 13 α , 14 α)-, hydrobromide monohydrate with a molecular weight of 370.33. The structures are shown below, as provided by the Sponsor:

Quinidine Sulfate



Dextromethorphan HBr



AVP-923 capsules are hard gelatin immediate release capsules. Each capsule contains 30 mg of DM and 30 mg of Q on an anhydrous basis. The composition of the to-be-marketed NEURODEX (AVP-923) capsules are shown in the table below, as provided by the Sponsor. The to-be-marketed capsules differ from the clinical trials batch C0051001 in the technical grades of three of the excipients: microcrystalline cellulose, lactose, and magnesium stearate, as well as the site of manufacture.

Table 3.2.P.2-9. Composition of AVP-923 Formulation 5

Ingredient	Amount per Capsule	
	mg	%
Dextromethorphan Hydrobromide USP, EP		(b) (4)
Quinidine Sulfate USP, EP		
Croscarmellose Sodium NF, Ph. Eur, JP		
Microcrystalline Cellulose NF, Ph. Eur, JP		
(b) (4)		
Lactose NF (b) (4) NF		
Colloidal Silicon Dioxide NF		
Magnesium Stearate NF (b) (4)		
(b) (4)		

BP = British Pharmacopoeia; EP = European Pharmacopoeia; JP = Japanese Pharmacopoeia; NF = National Formulary; Ph. Eur. = Pharmacopoea Europaeica; USP = United States Pharmacopoeia.

2.1.2 *What is the proposed mechanism of drug action and what is the proposed therapeutic indication?*

The proposed indication for NEURODEX is for the treatment of pseudobulbar affect (PBA) also known, for example, as pathological laughing and crying/weeping, emotional lability, and emotional incontinence. The Sponsor states that PBA occurs in patients with neurodegenerative diseases such as ALS, MS, and Alzheimer's disease or in patients with neuronal damage following stroke or traumatic brain injury. It is postulated that DM, considered the active therapeutic agent, acts by controlling glutamate excitatory activity through modulation as an antagonist of sigma-1 and NMDA receptor activities. The action of Q in this product is to competitively inhibit the metabolism of DM catalyzed by CYP2D6, increasing the plasma concentrations of DM in order to enhance the potential for the desired therapeutic effect.

The literature also suggests that DM blocks serotonin uptake and increases its release, and therefore increases serotonergic tone in the CNS.

2.1.3 *What is the proposed dosage and route of administration?*

The proposed recommended dose for NEURODEX is 1 capsule taken orally twice daily (to be administered once in the evening and a second capsule approximately 12 hours later).

2.2 General Clinical Pharmacology

2.2.1 *What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?*

Clinical pharmacology studies 99-AVR-100 and 00-AVR-103 were designed to determine the lowest dose of Q that inhibits conversion of a given dose of DM to DX based on urinary DM/DX ratios, converting subjects into phenotypic poor metabolizers of drugs metabolized by CYP2D6 (PMs). The dose selected was 30 mg Q/30 mg DM and this dose was given twice daily in the remaining clinical pharmacology and clinical studies.

2.2.2 *What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?*

The primary efficacy endpoint was change from baseline in the CNS-LS score. The CNS-LS questionnaire is a 7-item self-report measure that assesses frequency and severity of PBA, and is validated for use in ALS and in MS. Questions were answered on a 1- to 5-point scale, with 1 indicating a normal response and 5 suggesting an over-reactive response. The range of possible scores is 7-35. Response to treatment was defined as a change from baseline in the total score.

Adverse events to DM include drowsiness, dizziness, and fatigue, and effects consistent with serotonin syndrome have been noted in the literature at higher doses. For quinidine common adverse reactions noted in the labeling (>10%) include diarrhea, nausea, vomiting, and lightheadedness. Heartburn and esophagitis have also been reported. Autoimmune and inflammatory syndromes have been reported. Dose-related prolongation of QTc is a known effect of quinidine. QTc has been monitored in the studies submitted to this NDA. In addition, a thorough QT study was conducted.

2.2.3 *Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

The active moieties for the purposes of the proposed indication are considered to be Q and DM. There are appropriately measured. Please refer to section 2.6 of this review.

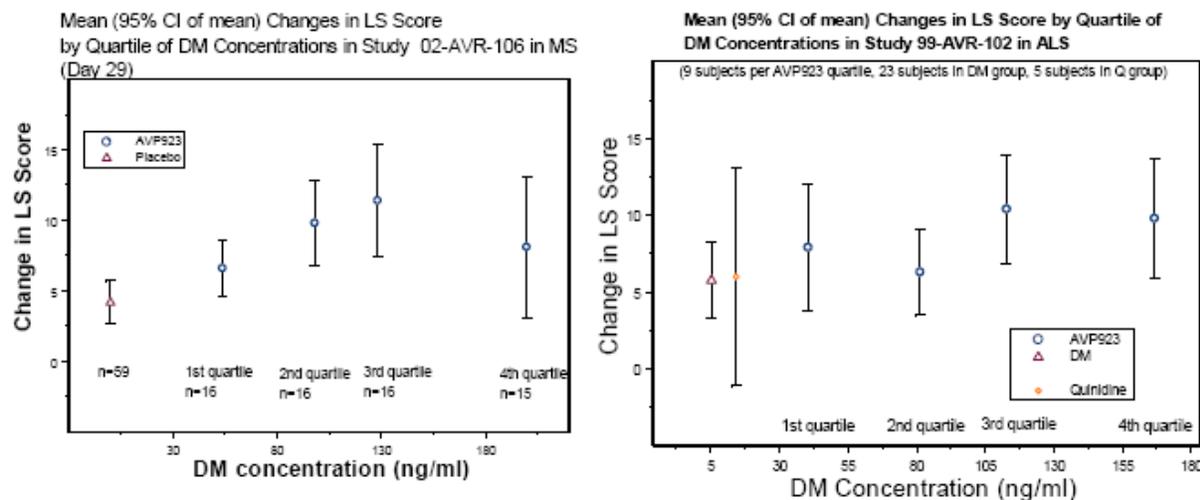
2.2.4 *Exposure –response*

2.2.4.1 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.*

In clinical study 99-AVR-102 comparing AVP-923 to 30 mg DM or 30 mg Q, there was a small but statistically significant decrease in CNS-LS score associated with administration of AVP-923 compared to either DM or Q alone. This was associated with higher plasma concentrations of DM than were observed after DM given alone.

In clinical study 02-AVR-106 that compared AVP-923 to placebo, the earliest measurement of CNS-LS score was on Day 15 (the first measurement point), and at that point, subjects receiving AVP-923 had significantly greater decrease in CNS-LS score than subjects receiving placebo. The primary efficacy endpoint was change from baseline in CNS-LS score (using the average of scores on Days 15, 29, 57, and 85) and significantly greater reduction was seen in the AVP-923 group. Secondary endpoints included frequency of episodes of inappropriate laughing and/or crying per week in which a difference was seen between drug and placebo as early as 1 week. This is consistent with the approximate 13 hour half-life of DM in the presence of Q.

The exposure-response relationships for the two pivotal clinical studies are shown in the figures below, plotted by the reviewer based on quartiles of DM concentrations. Although in 02-AVR-106 the figure suggests a relationship between exposure and response, in both studies there was substantially variability in response (consistent with a limited number of subjects in each study).



The Sponsor has not evaluated the effects of withdrawing treatment of PBA with a combination of DM and Q.

2.2.4.1.1 What is the rationale for this combination and what is the rationale for this combination of doses?

The rationale for the combination is that Q is a potent inhibitor of CYP2D6, the enzyme primarily responsible for metabolism of DM to DX. DM is rapidly metabolized by CYP2D6 to DX resulting in DM plasma concentrations of < 10 ng/ml in the absence of Q. When DM at doses of 30-60 mg is given with Q doses of 10-60 mg, there is an approximate 10-30 fold increase in DM exposure (Studies 99-AVR-100 and 00-AVR-103). The Sponsor has selected a dose based on the ability of Q to inhibit CYP2D6 to the extent that it would convert extensive metabolizers of drugs metabolized by CYP2D6 (EMs) to poor metabolizers (PMs). In EMs this results in exposure to DM greater than would be obtained in CYP2D6 extensive metabolizers taking DM alone. Study 99-AVR-100 demonstrated that 8/8 subjects taking 28.8 mg Q with 30 mg DM given every 12 hours were converted to PMs, whereas a lower rate of conversion was seen with lower doses of Q, and higher doses of Q did not produce proportionally higher exposure to DM. At a quinidine dose of 10 mg every 12 hours, 6/7 subjects converted to PMs after 13 doses.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Some adverse events, including nausea, dizziness, somnolence, fatigue, falls, and cramps occurred more frequently in the NEURODEX treatment group than in the DM or Q groups in Pivotal efficacy study 99-AVR-102, suggesting an exposure-response relationship. Onset of adverse reactions in the clinical studies occurred primarily in the first several weeks of drug

2.2.4.3 Does this drug prolong the QT or QTc interval?

NEURODEX resulted in QT prolongation in the thorough QT study, consistent with the known effect of Q. At the proposed therapeutic dose the maximal mean placebo-subtracted, baseline-adjusted QTcF was 10.12 msec, and the upper bound of the one-sided 95% CI was 15.05 msec. For a suprathreshold dose (60 mg DM/60 mg Q), the value was 18.81 msec and the upper bound of the one-sided 95% CI for that value was 24.5 msec. (It should be noted that the Q exposure after administration of the suprathreshold doses was less than 1.1 times the highest mean values in healthy volunteers in other Phase 1 studies such as in normal subjects in the renal impairment study in whom the mean Quinidine concentration was 0.332 µg/ml and did not exceed the maximum quinidine concentration reported in efficacy study 99-AVR-102 that was 2.21 µg/ml).

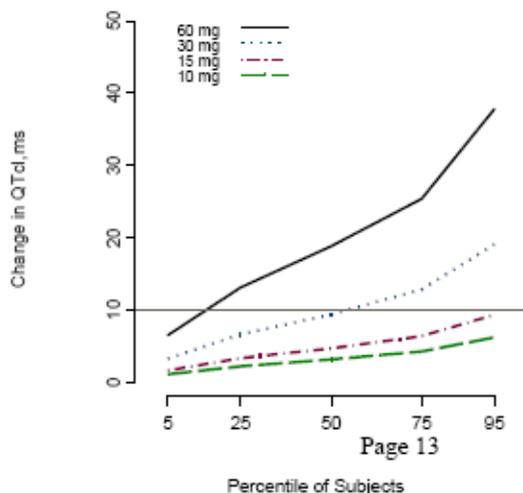
A combined pharmacokinetic and pharmacodynamic model was used to analyze the relationship between change in the QTc interval and changes in plasma concentration of quinidine (Please refer to the QT Pharmacometrics Review in the Appendix). The effect of quinidine on the QTc interval could be explained by a linear pharmacodynamic model with a delayed effect. The equilibration between plasma and effect site had a half-time of 3 hours (BSV of 123%). The median slope was 55.6 msec•mg/l (BSV of 40%). The slope estimate is comparable to literature reports.

The pharmacodynamic model was used to predict QTc prolongation at 4 different dose levels in the population using parametric simulations. For the 60 mg dose, the median change in QTcI interval was 18.8 msec but in 5% of the population the prolongation was at least 37.8 msec. For the 30 mg dose, the predicted median change was 9.3 msec but in 5% of the population the prolongation is predicted to be 19.0 msec.

The pharmacodynamic model was used to predict QTc prolongation for two lower doses of quinidine (15 mg and 10 mg) that have not been studied clinically. For both dose levels, the prolongation was predicted to be less than 10 msec in 95% of the population.

The model predictions are shown in the figure below.

Model Predicted Change in QTc Interval Stratified by Dose Group



2.2.4.4. *Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues? (In some cases it may be possible to combine with 2.2.4.2 and 2.2.4.3)*

The proposed dose and dosing regimen is the same as evaluated in the pivotal clinical studies. The dose of Q was selected based on its ability to result in the PM phenotype, rather than on an exposure response relationship between DM concentration and change in LS score. That relationship has been characterized by the reviewer as shown above. Of note, in Study 99-AVR-100, when 10 mg of Q was given with 30 mg of DM, mean (CV) DM plasma concentrations were approximately 57.1 (30) ng/ml. The unresolved dosing/administration issue is whether the DM exposure after that dose, in the range of the 1st quartile in the exposure-response figure below would be sufficient to balance the risk-benefit ratio, resulting in sufficient exposure to DM to provide efficacy, while minimizing the risk of QT prolongation.

2.2.5 *What are PK characteristics of the drug and its major metabolites?*

2.2.5.1 *What are the single dose and multiple dose PK parameters?*

Single and multiple dose PK parameters of DM, DX, and Q have been evaluated in several studies. Study 99-AVR 101 evaluated PK in 7 EMs and 2PMs for CYP2D6 after single and multiple doses (13 doses) of 30 mg DM and approximately 29 mg Q. The results are shown in the tables below. In EMs, mean C_{max} for DM was approximately 6-fold greater on Day 8 than on Day 1, and mean AUC was approximately 8-fold greater on Day 8 than on Day 1. There was little change in exposure to DX in EMs. In PMs, formation of DX could still be observed. In PMs there was an approximate 6-7-fold increase in DM exposure between Day 1 and 8 as well as a 2-fold increase in DX C_{max} and an approximate 6-fold increase in DX AUC from Day 1 to Day 8. For DM as well as for DX, the elimination half-life in EMs was less than that observed in PMs. Exposure to DX did not substantially change in the EMs between Days 1 and 8, and DX exposure remained higher in the EMs than in the PMs throughout the study.

	PK Parameter	Study Day	EMs	PMs
Dextromethorphan, plasma	T _{max} (hr)	1	6.00 (4.0-11.9)	8.0
		4	4.00 (3.99-8.0)	6.0 (4.0-8.0)
		8	8.0 (2.0-8.0)	5.0 (4.0-6.0)
	C _{max} (ng/ml)	1	15.9 (52)	22.3 (1)
		4	76.7 (20)	105.7 (9)
		8	95.5 (21)	136.2 (2)
	AUC ₀₋₁₂ (ng*hr/ml)	1	133.3 (45)	198.3 (4)
		4	811.7 (19)	1146 (7)
		8	1049.0 (23)	1533 (5)
	T _{1/2} (hr)	8	13.3 (26)	42.0 (11)
	C _{min} (ng/ml) (at end of dosing interval on Day 8)	8	80.0 (21)	117.6 (12)
	C _{avg} (ng/ml)	8	87.5 (23)	128.1 (5)
	% fluctuation	8	18.0 (29)	14.8 (66)

	% swing	8	19.6 (29)	16.7 (71)
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	PK Parameter	Study Day	EMs (n=7)	PMs (n=2)
Dextrophan, plasma	T _{max} (hr)	1	4.0 (4.0-4.01)	3.01 (2.0-4.01)
		4	2.0 (0-4.0)	2.0 (2.0)
		8	48.0 (24.2-48)*	3.0 (2.0-4.0)
	C _{max} (ng/ml)	1	124.86 (43)	19.8 (15)
		4	79.33 (23)	37.0 (0.6)
		8	123.5 (14)	51.45 (8)
	AUC ₀₋₁₂ (ng*hr/ml)	1	933.8 (35)	90.95 (21)
		4	849.2 (21)	365.3 (8)
		8	1001 (15)	530.4 (15)
	t _{1/2} (hr)	8	18.0 (24)	39.3 (13)
	C _{min} (ng/ml) (at end of dosing interval on Day 8)	8	78.2 (15)	36.3 (32)
	C _{avg} (ng/ml)	8	83.4 (15)	44.3 (16)
	% fluctuation	8	55.7 (41)	35.9 (61)
% swing	8	59.7 (43)	47.2 (74)	

The results for the Quinidine plasma PK parameters are shown below. Based on the elimination half-life, an approximate 1.4-fold accumulation of quinidine would be predicted. In fact, in both EMs there is an approximate 1.8-fold increase in C_{max} (2-fold in PMs), and an approximate 2.7-fold increase in AUC in EMs (and 2-fold in PMs).

	PK Parameter	Study Day	EMs	PMs
Quinidine, plasma	T _{max} (hr)	1	1.5 (1.5-2.0)	3.01 (2.0-4.01)
		4	1.53 (1.0-2.0)	1.52 (1.52)
		8	1.99 (1.98-2.0)	1.5 (1.49-1.5)
	C _{max} (µg/ml)	1	0.09 (23)	0.08 (7)
		4	0.15 (20)	0.14 (4)
		8	0.16 (23)	0.16 (12)
	AUC ₀₋₁₂ (µg*hr/ml)	1	0.48 (38)	0.51 (25)
		4	1.198 (18)	0.969 (5)
		8	1.313 (14)	1.074 (2)
	t _{1/2} (hr)	8	7.66 (14)	6.66 (6)
	λ _z (hr ⁻¹)	1	0.0944 (32)	0.0886 (32)
		4	0.103 (16)	0.107 (11)
		8	0.092 (14)	0.104 (6)
	C _{min} (µg/ml) (at end of dosing interval on Day 8)	8	0.06 (14)	0.00
	C _{avg} (µg/ml)	8	0.11 (14)	0.09 (2)
% fluctuation	8	91.2 (20)	184.6 (14)	
% swing	8	157.7 (26)	*NC	

2.2.5.1.1 How do the PK characteristics of AVP-923 compare to the individual components given separately?

Quinidine – Quinidine has not been given alone in any of the Phase I studies in this NDA. In the pivotal clinical study 99-AVR-102, quinidine was taken at a dose of 30 mg twice daily in subjects with ALS with pseudobulbar affect. Blood samples were collected on Day 29 within 8 hours of the last dose of study medication and Q concentrations (mean, %CV) were 0.0796 (86) in EMs (n=21) and were generally within the range of the mean C_{min} and mean C_{max} values after administration of AVP-923 in Phase 1 Study 99-AVR 101 described above. The elimination half-life observed in 99-AVR-101 is in agreement with the 6-8 hour elimination half-life described in the approved quinidine sulfate labeling.

Dextromethorphan – Dextromethorphan when given alone in EMs gave urinary metabolic ratios of DM/DX of approximately 0.01-0.05 in Study 99-AVR-100. When given with 28.8 mg Q, the urinary metabolic ratio became 0.35 after a single dose and 1.42 after dosing every 12 hours for 13 doses. This metabolic ratio indicates conversion to the PM phenotype. Plasma concentration of both DM and DX when DM was given alone at a dose of 30 mg was not evaluated in Phase 1 studies. However in Phase 1 Study 99-AVR-103, a single dose of 45 mg DM in the absence of Q resulted in a mean (%CV) plasma DM concentration of approximately 4.4 (177) ng/ml and a mean (%CV) plasma DX concentration of 545.9 (34) ng/ml, with similar concentrations observed on Day 8 after q 12 h dosing. The DM/DX ratio in the plasma was approximately 0.008. In contrast, a 45 mg DM dose in that study given with 30 mg Q resulted in DM and DX concentrations (on Day 8) of 141.5 (53) ng/ml and 89.1 (29) ng/ml. The DM/DX ratio in the plasma was approximately 1.6 after co-administration. This is consistent with the exposure to DM and to DX seen on Day in Study 99-AVR-101, above, after 8 days of AVP-923 administration every 12 hours where the ratios of DM/DX are approximately 0.13 on Day 1 and 0.77 on Day 8 in EMs.

2.2.5.1.2 Is there a drug interaction between dextromethorphan and quinidine?

Yes. Quinidine inhibits the CYP2D6-mediated metabolism of dextromethorphan. Please refer to section 2.4.2.1.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Based on a population PK analysis, PK was similar in subjects and in patients and for Q was also consistent with what has been reported in the literature. In addition, the range of plasma concentrations of DM, DX, and Q taken within 8 hours of a dose of AVP-923 in patients was consistent with concentrations observed in Phase 1 studies.

2.2.5.3. What are the characteristics of drug absorption? (This may include discussion of transporter or pH effect).

Quinidine: According to the approved quinidine sulfate label ((b) (6)), the absolute bioavailability of quinidine (from quinidine sulfate tablets) is about 70% but varies widely (45-100%). According to that labeling, the less than complete bioavailability is due to first-pass metabolism. Following administration of AVP-923, peak plasma concentrations are reached in approximately 1.5-3 hours.

DM: Following administration of AVP-923, peak plasma concentrations of DM are reached in approximately 4-8 hours.

2.2.5.4. What are the characteristics of drug distribution? (Include protein binding)

Quinidine: According to the approved quinidine labeling, the volume of distribution is 2-3 L/kg in healthy young adults, decreasing to 0.5 L/kg in patients with CHF and increasing to 3-5 L/kg in patients with hepatic cirrhosis. In the present submission, *in vitro* protein binding in human plasma was approximately 80-89%, and was not concentration dependent at concentrations of 30 ng/ml and 350 ng/ml (the upper range for expected concentrations after administration of NEURODEX). This is in agreement with the approved quinidine sulfate labeling that states that fraction bound is 80-88% in adults and older children and lower in pregnant women and infants and neonates. DM and DX did not alter protein binding of quinidine.

Dextromethorphan: In the present submission, *in vitro* protein binding in human plasma was approximately 60-70% and was not concentration dependent at concentrations of approximately 50 ng/ml and 350 ng/ml (the upper range expected after administration of NEURODEX). Quinidine and DX did not alter protein binding of DM.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination? (This may include table with results of mass balance study)

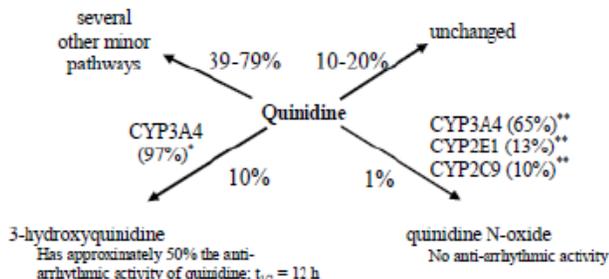
Quinidine: According to the approved quinidine sulfate labeling, most quinidine is metabolized hepatically, mediated by CYP3A4. When urine pH is < 7, 20% of administered quinidine appears unchanged in the urine, and less than 5% is excreted unchanged when the urine is more alkaline. Renal clearance involves glomerular filtration and tubular secretion.

Dextromethorphan is extensively metabolized as outlined in section 2.2.5.6, below. DM and its metabolites are renally eliminated. In a publication by Capon et al, 41% of a dose of DM was recovered in the urine in EMs and 64% in PMs. In EMs this was accounted for by DX (27%), 3-hydroxymorphinan (16%, total including conjugated), and DM (0.2%). In PMs this was accounted for by DM (26%), DX (8%, total), 3-hydroxymorphinan (14%, total), and 3-methoxymorphinan (11%).¹

2.2.5.6 What are the characteristics of drug metabolism? (This may include data on extraction ratio; metabolic scheme; enzymes responsible for metabolism; fractional clearance of drug).

¹ Capon DA, Bochner F, Kerry N, Mikus G, Danz, C, Somogyi AA. Clin Pharmacol Ther 1996; 60:295-307.

Quinidine: The extraction ratio for quinidine is considered to be low to intermediate (0.3-7) in published literature. At least 6 metabolites of quinidine have been identified; 3-hydroxyquinidine (3HQ) and 2'-quinidinone are considered to be the primary metabolites. The 3-HQ metabolite is thought to have the most anti-arrhythmic effects relative to other metabolites and is considered to be at least half as pharmacologically active as quinidine with respect to cardiac effects (based on QTc studies in pre-clinical models), and plasma concentrations can exceed those of quinidine. The elimination half-life of 3-HQ is approximately 12 hours.



Quinidine metabolism is mediated by primarily by CYP3A. The proposed metabolic scheme has been outlined as shown at right (provided by the Sponsor).

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Dextromethorphan:

The figure at left shows the proposed pathways for Phase I metabolism of DM.² Based on the published literature,³ DM is O-demethylated to DX and this reaction is mediated primarily by CYP2D6 but to some extent by CYP2C9.⁴ DM is N-demethylated to 3-methoxymorphinan and this is mediated in part by CYP3A.² DX and 3-methoxymorphinan are further demethylated by CYP3A and by CYP2D6, respectively, to 3-hydroxymorphinan. Dextrorphan and 3-hydroxymorphinan are glucuronidated.⁵

2.2.5.7 What are the characteristics of drug excretion?

Please refer to section 2.2.5.5, above.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Dose linearity was not specifically evaluated in NDA 21-879. However, linearity can be addressed as follows. For **DM**, in comparing 30 mg (Study 99-AVR-101), and 45mg and 60 mg (Study 99-AVR-103) doses of DM in the presence of 30 mg quinidine, there seems to be an approximately proportional increase in DM exposure as shown in the table below.

² Di Marco MP, Edwards DJ, Wainer IW, Ducharme MP. Life Sciences 2002; 71:1149-60

³ Schmider J, Greenblatt DJ, Fogelman SM, von Moltke LL, Shader RI. Biopharm Drug Disposition 1997; 18:227-240.

⁴ Von Moltke LL, Greenblatt DJ, Grassi JM, et al. J Pharm Pharmacol 1998; 50:997-1004.

⁵ Lutz U, Volkel W, Lutz RW, Lutz WK. J Chromatography B 2004; 813:217-225.

Mean (%CV) C_{max} and AUC of DM on Day 8 when given with 30 mg Q

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)

Linearity in Q pharmacokinetics (at the clinically relevant dose of DM) can be addressed by the results of Study 99-AVR-100 that only looked at 2, 4, and 8 hours post dose. C_{max} and AUC based on those time points at steady state are shown in the table below for specific doses of Q. For the 50 and 75 mg doses, a 2-fold and 3-fold increase in dose, respectively, compared to 25 mg, there was an approximate 1.8 and 2.5 fold increase in exposure.

Mean (%CV) C_{max} and AUC of Q on Day 7 when given with 30 mg DM

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 in 99-AVR-100 was calculated on the basis of quinidine sulfate, although the quinidine drug substance contained approximately (b)(4) dihydroquinidine. Therefore the 25 mg Q dosage strength is equivalent to approximately 28.8 mg Q.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

Please refer to the tables in section 2.2.5.1. Following 8 days of twice daily dosing with AVP-923 in EMs the DM AUC and C_{max} were approximately 6- and 8-fold higher, respectively, than on Day 1 and the DX C_{max} and AUC did not change. For PMs the DM C_{max} and AUC were 6- and 7.7-fold higher, respectively, on Day 8 compared to Day 1, and the DX C_{max} and AUC were 2.6 and 5.8-fold higher, respectively. The Quinidine C_{max} and AUC were 1.8 and 2.7-fold greater, respectively, on Day 8 compared to Day 1 in EMs and approximately 2-fold greater, on Day 8 compared to Day 1 in PMs.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Intra-subject variability was not assessed. Inter-subject variability for DM across studies in healthy volunteers in fasted state was approximately 21-40% for C_{max} and AUC. Inter-subject variability for DX across studies was approximately 14-43% for C_{max} and 21-35% for AUC. Inter-subject variability for Q across studies was approximately 23-30% for C_{max} and 14-47% for AUC. Variability could be due to absorption (in the case of DM or Q) as well as variability in metabolism.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

Age – In the pivotal clinical studies there were 18 patients 65 years of age and over. The results of the population PK study (04-AVR-117) suggest that increasing age was associated with an increase in the apparent central volume of distribution for DX. This effect on DX is not likely to impact on efficacy and is not likely to have clinically relevant safety consequences following administration of NEURODEX since it would result in a decrease in exposure. However, an age difference in pharmacodynamic effects has not been evaluated. The effect of age on efficacy was not systematically evaluated.

Gender – Based on the population PK analysis, gender did not affect the PK of DM or DX. The effect of gender as a covariate on Q PK was not evaluated in this submission. However, published literature suggests that in the absence of statistically significant differences in PK parameters for Q and 3-HQ between healthy young men (n=12) and women (n=12), quinidine causes a greater prolongation of cardiac repolarization in women than in men at equivalent serum concentrations after IV administration of quinidine.⁶

Race – The effect of race has not been evaluated. The majority (75%) of the subjects in the PK population were Caucasian. Similarly in the efficacy studies 99-AVR-102 and 02-AVR-106 more than 80% of the subjects were Caucasian.

Weight – IBW affected the PK parameters of DM and DX in the population PK study (04-AVR-117), and PK parameters in that study were adjusted for IBW. This does not affect the clinical use of NEURODEX since trials were done without adjusting for body weight.

Height – Not evaluated.

Disease – Not evaluated in this submission. Congestive heart failure reduces quinidine's apparent volume of distribution and requires a reduction in dosage to prevent toxicity, according to the quinidine labeling.

Genetic Polymorphism – Genetic polymorphisms in CYP2D6 are responsible for altered metabolism of DM. Extensive metabolizers (EMs of CYP2D6) are phenotypically converted to PMs by the dose of Q in AVP-923.

Pregnancy – AVP-923 has not been studied in pregnant women.

Organ Dysfunction –

Renal Impairment – PK of DM, DX, and Q were evaluated in subjects with mild renal impairment (n=6), moderate impairment (n=6), or normal renal function (n=9) in Study 04-

⁶ Benton RE, Sale M, Flockhart DA, Woosley RL. Clin Pharmacol Ther 2000; 67:413-8.

AVR-116 after administration of NEURODEX for 6 days. NEURODEX has not been evaluated in patients with severe renal impairment.

For DM there was a less than 10% decrease in mean C_{max}, AUC, and C_i/F in mild renal impairment, and a decrease of $\leq 12\%$ for those parameters compared to normal renal function. For DX there was a 34% and 23% increase in C_{max} and AUC, respectively in mild renal impairment and an 85% and 93% increase in C_{max} and AUC, respectively, in moderate renal impairment compared to normal renal function (reflecting a 30-58% decrease in renal clearance in moderate impairment). There was also a delay in median t_{max} by 9 hours. Subjects with moderate renal impairment had fewer adverse events than subjects with normal function or mild impairment. The 90% CI for C_{max} and AUC fell outside of the BE interval for both mild and moderate renal impairment (and for both DM and DX). The DX concentrations observed in moderate impairment remain within the range of concentrations when DM is given at an OTC dose in the absence of Q (Study 99-AVR-102).

For Q there was an approximate 30% decrease in mean C_{max} and AUC in mild renal impairment and an approximate 13% decrease in C_{max} and a 3% increase in AUC in moderate renal impairment compared to normal renal function. The 90% CI fell outside of the BE interval for both mild and moderate renal impairment compared to normal function. This decrease is not likely to impact efficacy, since all subjects with mild renal impairment had a poor metabolizer phenotype on Day 7, based on urinary DM/DX ratio. These results are in contrast however to the approved quinidine labeling that states that renal dysfunction causes the elimination of quinidine to be slowed and can lead to toxicity if dosage is not appropriately reduced. However, the approved labeling supports doses of more than 200 mg every 6 hours and that is significantly higher than the Q doses proposed for NEURODEX (30 mg every 12 hours). (For quinidine sulfate the dosing is initiated with 200 mg every six hours, and can be increased if the regimen is well tolerated and if the serum quinidine level is within the laboratory's therapeutic range).

Hepatic impairment – PK of DM, DX, and Q were evaluated in subjects with mild hepatic impairment (n=6), moderate impairment (n=6), or normal hepatic function (n=9) in Study 04-AVR-115. NEURODEX has not been evaluated in patients with severe hepatic impairment.

For DM, protein binding is approximately 60%, and therefore total DM will be considered. There was an approximate 10-13% increase in mean C_{max} and AUC in mild hepatic impairment compared to normal hepatic function. In moderate hepatic impairment there was an approximate 16% increase in C_{max} and AUC compared to normal hepatic function. These values fell outside of the BE interval. There was also a decrease in renal excretion of DM in subjects with moderate hepatic impairment. For DX, C_{max} and AUC increased less than 2% in mild impairment and < 10% in moderate impairment compared to subjects with normal hepatic function.

For Q, total concentrations will be considered rather than unbound parameters since it has a low to intermediate hepatic extraction ratio and fraction unbound > 10%. However, it is noted that in the hepatic impairment study, fraction unbound was approximately 18.8% in normal hepatic function, 21% in mild hepatic impairment, and 31% in moderate hepatic impairment. There was an approximate 3% decrease in C_{max} and a 19% decrease in AUC in mild hepatic impairment and an approximate 23% decrease in C_{max} and a 4% decrease in AUC in moderate hepatic

impairment compared to normal hepatic function. Of note, there was a 26% increase in AUC(u) for Q in moderate hepatic impairment, although there were only 3 subjects for whom sufficient data was evaluable, and therefore may not be reliable. Whether this small increase in free concentration could have resulted in additional inhibition of P-glycoprotein that would have interfered with elimination of DM (a P-gp substrate), resulting in a decrease in renal excretion of DM is unknown. According to the approved labeling of quinidine sulfate, the increased volume of distribution seen in cirrhosis leads to a proportionate increase in elimination half-life. The labeling of quinidine sulfate (that allows for initial doses of 200 mg every 6 hours) states that hepatic dysfunction can lead to quinidine toxicity if dosage is not appropriately reduced.

The most common adverse events (occurring in more than 10% of subjects) occurred more frequently in the subjects with moderate impairment.

2.3.2 Based upon what is known about exposure-response relationships and their variability, and the groups studied, healthy volunteers vs patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly - None.

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

Pediatric patients were not included in the efficacy or Phase 1 studies. The Sponsor plans to defer pediatric studies to Phase 4.

2.3.2.3 Gender – None.

2.3.2.4 Race – None.

2.3.2.5 Renal Impairment – Dosage adjustment not necessary in mild or moderate renal impairment. NEURODEX has not been studied in patients with severe renal impairment.

2.3.2.6 Hepatic Impairment – The small increase in DM exposure (10-16% increase in C_{max} and AUC in mild and moderate hepatic impairment) and the decrease in total Q exposure would not require a dosage adjustment. However, patients with moderate impairment had increased adverse events and the labeling should acknowledge this. The labeling should also state that the use of AVP-923 has not been evaluated in patients with severe hepatic impairment.

2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?

Quinidine is used in the combination to convert CYP2D6 EMs to PMs. In the small number of PM subjects evaluated, there was no substantial difference in PK of DM or DX when given in the presence or absence of quinidine. Given the lack of contribution of Q to the therapeutic

effect in PMs and the risk of QTc prolongation due to Q at the dose used in NEURODEX, there is no need for PMs to receive this combination.

2.3.2.8 What pregnancy and lactation use information is there in the application?

There is no pregnancy and lactation information in humans in this application. Information available in quinidine labeling should be extended to NEURODEX.

A review of dextromethorphan in pregnancy does not suggest that DM is a major teratogen.⁷ Although it has not been studied in lactation, it is recommended that it is probably safe to use during breast feeding.

The approved labeling of quinidine sulfate states that there are no adequate and well-controlled studies in pregnant women and that quinidine should be given to a pregnant woman only if clearly needed. The labeling also states that quinidine is present in human milk at levels slightly lower than those in maternal serum and that administration of quinidine should (if possible) be avoided in lactating women who continue to nurse. The same labeling should be extended to the NEURODEX label.

2.3.2.9 Other human factors that are important to understanding the drug's efficacy and safety

None.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on response?

According to the approved labeling of quinidine sulfate, quinidine's PK are unaffected by cigarette smoking. Effect of these extrinsic factors on DM is unknown, although since CYP1A2 does not contribute to its metabolism, it is unlikely that smoking will have an effect on exposure.

Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

None.

2.4.2 Drug-Drug Interactions

2.4.2.1 Since NEURODEX is a combination of dextromethorphan 30 mg and quinidine sulfate 30 mg has the interaction potential between these drugs been evaluated?

What is the effect of dextromethorphan on quinidine PK?

This has not been evaluated.

⁷ Briggs GG, Freeman RK, Yaffe SJ, eds. Drugs in Pregnancy and Lactation, 6th edition, Lippincott Williams & Wilkins, Philadelphia 2002.

What is the effect of quinidine on dextromethorphan PK?

Quinidine results in a 30- fold increase in DM exposure (C_{max} and AUC) following administration of approximately 30 mg Q and 30 mg DM (Study 99-AVR-100) compared to those values when DM was given alone.

2.4.2.2 Is there an in vitro basis to suspect in vivo drug-drug- interactions?

Yes. Q is a potent inhibitor of CYP2D6 and is a substrate for CYP3A4.

2.4.2.3 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Dextromethorphan is a P450 substrate as described in section 2.2.5.6. The primary pathways involved in its metabolism are CYP2D6, CYP3A, and a small contribution from CYP2C9. CYP2D6 mediates O-demethylation of DM to DX and that is the basis for its combination with quinidine that inhibits CYP2D6 and increases exposure to DM. The difference between CYP2D6 EMs and PMs can be seen in the urinary DM/DX ratio that serves as the phenotype for PMs of drugs metabolized by CYP2D6. In the present submission there was very limited inclusion of PMs in the Phase I studies. In the literature, following a single 30 mg dose of DM, C_{max} was approximately 23 times greater and AUC was approximately 150 x greater in PMs than in EMs, supporting the role for pharmacogenetics.⁸

Since DM is considered to be a sensitive CYP2D6 substrate, increases in DM similar to those seen in PMs vs EMs or in EMs in the presence of quinidine would be expected with other strong inhibitors of CYP2D6.

The Sponsor has not provided information regarding the potential for CYP3A mediated inhibition of dextromethorphan metabolism. Although dextromethorphan has been evaluated as a probe drug for CYP3A-mediated metabolism, the reviewer's search of the literature did not identify any drug interaction studies *in vivo* in humans.

Quinidine is primarily metabolized by CYP3A4 as outlined in section 2.2.5.6. Its metabolism is not known to be influenced by genetics.

2.4.2.4 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Quinidine: As previously discussed, Q is considered to be a specific and potent inhibitor of CYP2D6. In one published study using bufuralol as a substrate, the IC₅₀ of quinidine *in vitro* was reported to be 0.4 μM and another published study reported an IC₅₀ of 0.018 μM using debrisoquine as a substrate. The Sponsor believes, based on a literature review, that *in vitro* studies (discussed in the Sponsor's literature review) do not suggest significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP3A, CYP2B6, or CYP2A6. However, the substrates used in those studies are not the preferred or acceptable substrates identified in the draft guidance and therefore are difficult to interpret. An additional *in vitro* study suggested no inhibition of

⁸ Capon DA, Bochner F, Kerry N, Mikus G, Danz, C, Somogyi AA. Clin Pharmacol Ther 1996; 60:295-307.

CYP2C8.⁹ Branch et al evaluated the effect of Q (200 mg/day) on a cocktail of caffeine, mephenytoin (used as a 2C19 substrate), debrisoquine (2D6), and dapsone (used as a marker of CYP2C9, CYP2E1, CYP3A, and N-acetyltransferase) *in vivo* for 3 and 28 days. Inhibition of debrisoquine metabolism indicative of CYP2D6 inhibition was observed, but no inhibition of other substrates was observed. However, mephenytoin and dapsone are not recognized as suitable *in vivo* substrates in the draft Guidance for Industry on Drug Interaction Studies, and therefore this is not an adequate *in vivo* study.

Quinidine has not been evaluated as an inducer of P450s based on the reviewer's literature search. Several *in vitro* studies have described an "activation" of CYP3A including CYP3A-mediated hydroxylation of warfarin. The clinical relevance of this interaction with CYP3A is unknown (the approved Q labeling refers to quinidine potentiating the anticoagulant effect of warfarin requiring a reduction in dose).

DM has not been evaluated as an inhibitor or inducer of P450s. There is no information in this submission or in the literature.

2.4.2.5 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?
Quinidine is a potent inhibitor of P-gp. The IC₅₀ for inhibition of P-gp in Caco-2 cells is 2.2 μM. Quinidine at antiarrhythmic doses (where usually therapeutic plasma concentrations are 2-6 mg/L or 6.2-18.5 μM) approximately doubles the concentrations of digoxin, a P-gp substrate. The IC₅₀ for P-gp inhibition is less than 10-fold higher than the relevant plasma concentrations of quinidine after administration of NEURODEX (approximately 0.6 μM). The effect of quinidine on P-gp after administration of NEURODEX (30 mg Q twice daily) has not been evaluated.

Quinidine is also considered to be a substrate of P-gp.

Dextromethorphan has not been well characterized regarding its interaction with Pgp.

2.4.2.6 Are there other metabolic/transporter pathways that may be important in the pharmacokinetics of NEURODEX?

Dextrophan and 3-hydroxymorphinan are glucuronidated by UGT as described in section 2.2.5.6.

2.4.2.7 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

No co-administration specified.

2.4.2.8 What other co-medications are likely to be administered to the target patient population?

Study 02-AVR-107 was an open-label safety study in patients with pseudobulbar affect. The primary neurological condition was MS or ALS, and the population also included patients with

⁹ Baldwin SJ, Clarke SE, Chenery RJ. Br J Clin Pharmacol 1999; 48:424-32.

Alzheimer's disease, stroke, traumatic brain injury, and Parkinson's disease. In the study report of the 5/31/06 submission, 506 subjects had been enrolled and treated. Concomitant medications in the treatment phase included strong CYP3A inhibitors (clarithromycin or ketoconazole) in 7 subjects (1.4%) and moderate CYP3A inhibitors (diltiazem, erythromycin, fluconazole, or verapamil) in 25 subjects (4.9%), strong CYP2D6 inhibitors (fluoxetine or paroxetine) in 34 subjects (6.7%), or moderate CYP2D6 inhibitors (terbinafine) in 4 subjects (0.8%), and CYP2D6 substrates in 50 subjects (9.9%) including amitriptyline in 27 subjects (5.3%) and metoprolol in 19 subjects (3.7%), nortriptyline in 2 patients (0.4%), and timolol ophthalmic in 2 patients (0.4%). Of note, clarithromycin and erythromycin prolong the QT interval, as does quinidine. These concomitant medications reflect those in the pivotal clinical studies.

Other commonly used medications included acetaminophen (14.4%), aspirin (18.6%), baclofen (19.2%), ibuprofen (19.2%), beta interferon (13.6%), oxybutynin (10.5%), and riluzole (16%).

2.4.2.9 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Quinidine-mediated inhibition of CYP2D6: Desipramine is a CYP2D6 substrate. Study 04-AVR-112 evaluated the effect of steady state administration of AVP-923 on steady state PK of desipramine (25 mg once daily) in 13 healthy male and female volunteers, 19-42 years of age. There was an approximate 5-fold increase in mean C_{max} and a 6-fold increase in mean AUC for desipramine when given with AVP-923 compared to desipramine alone. There was evidence of increased QT prolongation during co-administration; it is unknown whether this is due to dextromethorphan or quinidine.

Other CYP2D6 inhibitors: *In vivo* interactions that alter CYP2D6-mediated metabolism of DM will not be reviewed here. There are many literature examples of phenotypic conversion of CYP2D6 EMs to PMs in the presence of strong inhibitors. They can be predicted as well from the quinidine-DM interaction. It is relevant to consider that some candidates for AVP-923 are already chronically taking strong CYP2D6 inhibitors such as fluoxetine or paroxetine that would be expected to have a similar effect on DM as does quinidine.

Inhibitors of CYP3A: Watson's approved labeling of Q states that ketoconazole (a strong CYP3A inhibitor) results in increased quinidine concentrations. The Sponsor has reviewed the literature with respect to inhibition of CYP3A-mediated Q metabolism *in vivo*. Itraconazole, a strong CYP3A inhibitor increases Q C_{max} approximately 1.6 fold and increases Q AUC approximately 2.4 fold. Erythromycin, a moderate CYP3A inhibitor increased C_{max} by approximately 39%.

2.4.2.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Quinidine: According to the approved labeling of quinidine sulfate, quinidine has anticholinergic, vasodilating, and negative inotropic actions that may be additive to those of other drugs with these effects and antagonistic to drugs with cholinergic, vasoconstricting, and positive inotropic effects. Quinidine potentiates the actions of depolarizing and nondepolarizing neuromuscular blocking agents.

Quinidine is a Class 1a antiarrhythmic drug and is known to prolong the QT interval. The combined effects of multiple agents that prolong QTc interval has not been evaluated but could be expected to have a greater effect than expected from 1 drug alone.

Dextromethorphan: The literature suggests that DM blocks 5HT reuptake and inhibits its release. Consistent with that, and with published reports of serotonin syndrome in patients taking DM,¹⁰ current warnings on OTC labeling recommend avoiding DM in patients taking MAO inhibitors.

2.4.2.11 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

- Does DM inhibit or induce P450s?
- Does DX inhibit or induce P450s?
- Is DM a substrate or inhibitor of Pgp?
- Does Q inhibit or induce P450s other than CYP2D6?

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved, and represent significant omissions?

- Can Q 10 mg q 12 hours result in enough CYP2D6 inhibition to result in a clinically significant therapeutic effect with less risk of QT prolongation compared to the 30 mg dose?
- Should all candidates for NEURODEX be genotyped for CYP2D6 prior to initiating therapy?
- Should NEURODEX be contraindicated in PMs of CYP2D6?
- Should strong CYP3A inhibitors be contraindicated?
- Should patients chronically taking strong CYP2D6 inhibitors be given NEURODEX?

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS principles), in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

There is insufficient information to determine the BCS class. The solubility has been provided for pH 2.0-7.5, but not for pH 1 for either quinidine or dextromethorphan. Although it is sufficiently soluble at the pH provided, since pH 1 has not been provided, it cannot be determined that either quinidine or dextromethorphan is highly soluble. The absolute BA of quinidine is about 70%, and it cannot be considered to be highly permeable. Permeability data for dextromethorphan has not been provided.

¹⁰ Boyer EW, Shannon M. *New Engl J Med* 2005; 352:1112-20.

2.5.2 *What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?*

This has not been evaluated.

2.5.2.1 *What data support or do not support a waiver of in vivo BE data?*

A biowaiver for the to-be-marketed formulation can be granted. The differences in the clinical trial formulation and the to-be-marketed formulation are due to changes in excipient grade (a Level 2 change in components and composition based on SUPAC IR) and a site change. These changes require a CASE B evaluation of dissolution (a multipoint dissolution profile in the application/compendial medium at 15, 30, 45, 60, and 120 minutes or until an asymptote is reached). In 3 different media, including the proposed dissolution medium, both quinidine and dextromethorphan from either formulation were $\geq 95\%$ dissolved at 15 minutes. Based on the similarity of these profiles and rapid dissolution of either formulation, a biowaiver can be granted.

2.5.2.2 *What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%*

Not applicable.

2.5.2.3 *If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?*

Not applicable.

2.5.3 *What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?*

BE was demonstrated for AUC and C_{max} for DM and for Q following administration of NEURODEX to 18 healthy volunteers under fasting conditions or with a high fat meal in protocol 04-AVR-111. For DM, the median t_{max} was 1 hour later in the fed condition than in the fasted condition. For Q the median t_{max} was 1.5 hours later in the fed condition than in the fasted condition. NEURODEX can be taken without regard to meals.

2.5.4 *When would a fed BE study be appropriate and was one conducted?*

Not required in this case.

2.5.5 *How do the dissolution conditions and specifications assure in vivo performance and quality of the product?*

The Sponsor has provided information to determine the adequacy of the conditions (rotation speed, apparatus, and dissolution media). For both quinidine and dextromethorphan, a mean of more than ^{(b) (4)} was dissolved in 15 minutes.

The Sponsor proposed the following dissolution method and specifications based on the biobatch (C0051001) and the proposed commercial formulation (Batch GZ18M):

Apparatus:	USP Apparatus 1 (Basket)
Medium:	Simulated Gastric Fluid, without enzymes, pH 1.2
Volume:	900 ml
Rotation Speed:	100 rpm
Specification:	
Dextromethorphan:	15 minutes: Q= (b) (4)
Quinidine:	15 minutes: Q= (b) (4)

The Office of Clinical Pharmacology finds the proposed dissolution method and specifications acceptable.

2.5.6 *If different-strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?*

Not applicable.

2.5.7 *If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?*

Not applicable.

2.5.8 *If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?*

Not applicable.

2.5.9 *What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?*

None.

2.6 Analytical Section

2.6.1 *How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?*

Please refer to section 2.6.4.1.

2.6.2 *Which metabolites have been selected for analysis and why?*

Dextromethorphan is considered to be the active moiety and has been measured. DX is also determined in some studies as it is used to determine phenotype in the urine analysis and also provides an exposure comparison in the setting of a "PM" phenotype compared to the "EM" phenotype. None of the quinidine metabolites have been measured.

2.6.3 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Total Q and total DM and DX have been appropriately considered since they are less than 90% protein bound. (In the renal and hepatic impairment studies, free concentrations have also been determined but are not used in the PK considerations).

2.6.4 What bioanalytical methods are used to assess concentrations?

2.6.4.1 What is the range of the standard curve and how does it relate to the requirements for the clinical studies? What curve fitting techniques are used?

Bioanalytical methods are summarized below. The calibration range was adequate to cover the range of plasma concentrations observed in most cases, and otherwise, dilution integrity was shown.

Analyte	Method	Study	Calibration Range	LOQ	Linearity	
DM, plasma	(b) (4) (LC/MS/MS)	99-AVR-102 01-AVR-105 02-AVR-106 02-AVF-107 04-AVR-111 04-AVR-112 04-AVR-115 04-AVR-116	0.2 ng/ml-200 ng/ml	0.2 ng/ml	1/x ² regression, linear	
		(b) (4)	99-AVR-100	0.2-20 ng/ml	0.2	1/x regression, linear
		(b) (4)	99-AVR-101 00-AVR-103	0.2-20 ng/ml	0.2 ng/ml	1/x regression, linear
DX, plasma	(b) (4) (LC/MS/MS)	99-AVR-102 01-AVR-105 02-AVR-106 02-AVF-107 04-AVR-111 04-AVR-112 04-AVR-115 04-AVR-116	2.5-2500 ng/ml	2.5 ng/ml	1/x ² regression, linear	
		(b) (4)	99-AVR-100	25-1000 ng/ml	25 ng/ml	1/x regression, linear
		(b) (4)	99-AVR-101 00-AVR-103	2.5-500 ng/ml	2.5 ng/ml	1/x, regression, linear
DM or DX, urine	(b) (4)	99-AVR-100 99-AVR-101 00-AVR-103 04-AVR-111 04-AVR-112 04-AVR-115 04-AVR-116	0.05-15.0 ug/ml	0.05 ug/ml	1/y regression, linear	
Q, plasma	(b) (4)	All clinical studies	0.05-10.0 ug/ml	0.05 ug/ml	1/x, regression, linear	

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See Section 2.6.4.1 above.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

Selectivity was determined with respect to quinidine and hydroquinidine and internal standard for the urine DM/DX assay, with respect to quinidine, quinine, and hydroquinidine in the quinidine plasma assay, and with respect to DM, DX, and internal standard as well as other DM metabolites in DM/DX plasma assays. Accuracy and precision were within acceptable limits.

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Analyte	Method	Freeze-thaw	In process	Autosampler	Long-term stability
DM/DX, plasma	(b) (4)				
DM or DX, urine					
Q, plasma					

2.6.4.5 What is the QC sample plan?

Duplicate QC standard replicates and 1 calibration curve were run with each batch of study samples analyzed.

4.3 APPENDIX III

CLINICAL PHARMACOLOGY FILING FORM

<i>Office of Clinical Pharmacology and Biopharmaceutics</i> <i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA Number	21-879	Brand Name	Neurodex	
OCPB Division (I, II, III)	DPE-I	Generic Name	Dextromethorphan hydrobromide and quinidine sulfate	
Medical Division	HFD-120	Drug Class	Sigma-1 receptor agonist, uncompetitive NMDA antagonist	
OCPB Reviewer	Sally Usdin Yasuda, MS, PharmD	Indication(s)	Pseudobulbar affect (PBA)	
OCPB Team Leader	Ramana Upoor, PhD	Dosage Form	Capsule containing 30 mg each of dextromethorphan hydrobromide and quinidine sulfate	
		Dosing Regimen	1 capsule bid	
Date of Submission	1/30/06	Route of Administration	Oral	
Estimated Due Date of OCPB Review	6/25/06	Sponsor	Avanir Pharmaceuticals	
PDUFA Due Date	7/30/06	Priority Classification	Priority	
Division Due Date	7/9/06			
<u>Clin. Pharm. and Bioharm. Information</u>				
<p><u>Summary:</u> This NDA is for a combination product comprised of 2 approved drugs, quinidine sulfate (Q) and dextromethorphan hydrobromide (DM) for treatment of pseudobulbar affect in patients with neurological disorders. The submission is supported by 2 pivotal efficacy studies. According to the Sponsor, the primary pharmacologic effect of quinidine in this product is to inhibit the metabolism of DM by CYP2D6, increasing plasma concentrations of DM and enhancing potential for desired pharmacological effect of DM. PK studies have been performed to determine optimal dose of Q to inhibit DM metabolism by CYP2D6. PK studies 100 and 101 evaluate BA of either DM as DM/Q given separately (100) or as DM/Q in a combination (study 101). Study 101 was an extension of Study 100, such that it was a 1-way crossover in a limited number of subjects. These two studies included a limited number of subjects and a limited number of samples (in Study 100). Since this combination is for a new indication and there is data on DM alone as well as the combination DM/Q, a relative BA assessment could be made. BA assessments are based on DM as the Sponsor considers that the therapeutic activity resides with that moiety. Study 102 is a factorial design clinical efficacy study that looks at each component (DM and Q) given separately and given together as the combination product.</p>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	5		Methods not cross-validated
I. Clinical Pharmacology				
Mass balance:	-	-	-	
Isozyme characterization:				
Blood/plasma ratio:		-	-	
Plasma protein binding:	X	1		Study 0-AVR-115

Zenvia (Dextromethorphan/Quinidine) capsules
N21-879

Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2	-	(Study 99-AVR-100 in EMs & 99-AVR-101 in EMs and PMs but with 30 mg DM/25mg Q)
multiple dose:	X	3	-	7 days (Studies 99-AVR-100 , AVR-103, and 99-AVR-101)
Patients-				
single dose:		-	-	
multiple dose:			-	See Pop PK
Dose proportionality -				
fasting / non-fasting single dose:			-	
fasting / non-fasting multiple dose:	X	2	-	Increasing doses of Q (Study 99-AVR-101) Increasing doses of Q with 45 or 60 mg DM (Study 00-AVR-103) Various doses of DM and Q (00-AVR-103)
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-	-		
In-vivo effects of primary drug:	X	1		Desipramine (Study 04-AVR-112)
In-vitro:			-	
Subpopulation studies -				
ethnicity:		-	-	See Pop PK; small size of non-Caucasian population
gender:		-	-	See Pop PK
pediatrics:		-	-	
geriatrics:		-	-	See Pop PK
renal impairment:	X	1	-	Study 04-AVR-116
hepatic impairment:	X	1	-	Study 04-AVR-115
PD:				
Phase 2:	X	1	CNS-93	
Phase 3:	X	2	-	Study 99-AVR-102 evaluated AVP-923 vs 30 mg DM or 30 mg Q 02-AVR-106 evaluated AVP-923 vs placebo
PK/PD:				
Phase 1 and/or 2, proof of concept:			-	
Phase 3 clinical trial:			-	
Population Analyses -				
Data rich:	-	-		
Data sparse:	X	1		Study 04-AVR-117: Age and IBW were significant covariates; Includes Phase I studies as well as Phase III study 99-AVR-102 & 02-AVR-106 & open label ongoing study 02-AVR-107
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	Not done
Relative bioavailability -				Not done
solution as reference:	-	-	-	
alternate formulation as reference:	-	-	-	
Bioequivalence studies -				
traditional design; single / multi dose:	-	-	-	
replicate design; single / multi dose:	-	-	-	

Food-drug interaction studies:	X	1	-	04-AVR-111
Dissolution:	X	1		March 9, Section 3.2.P.2
(IVIVC):	-	-	-	
Bio-waiver request based on BCS	-	-		
BCS class	-			
III. Other CPB Studies				
Genotype/phenotype studies:	X	7	-	PGx in 7 studies
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X			
Total Number of Studies		22		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. None at this time.		
QBR questions (key issues to be considered)		<p>What information is available that contributes to assessment of clinical pharmacology/dose response/exposure-response? This applies to the dose of Q as well as the dose of the combination of Q and DM with respect to exposure, safety, and efficacy. CYP2D6 status is of particular interest.</p> <p>Do CYP2D6 PMs require the quinidine component?</p> <p>Are the bioanalytical methods adequate to assess concentrations?</p> <p>Have the pharmacokinetics been adequately characterized to support safety and efficacy?</p> <p>Has the to-be-marketed product been adequately linked to the clinical trial formulation and has the combination product been adequately linked to the individual components in terms of PK?</p> <p>Is drug metabolism and potential for drug interactions adequately characterized? Have appropriate in vivo drug interaction studies been done?</p> <p>Do the dissolution conditions and specifications assure in vivo performance and quality of the product?</p>		
Other comments or information not included above		<p>Comments to the Project Manager:</p> <p>None.</p>		
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 21-879, HFD-850(Electronic Entry or Lee), HFD-120(Calder), HFD-860 (R. Uppoor, M. Mehta)

4.4 Appendix IV QT Consult Review (consisting of 43 pages) dated 9/17/ has been removed immediately following this page and has been removed as a duplicate copy. The Original review is located in the Other Review section of this NDA approval package.

4.5 APPENDIX V

PHARMACOMETRICS CONSULT

Office of Clinical Pharmacology:
Pharmacometric review

Summary of Findings

Key Review Questions

The purpose of this review is to address the following key questions.

Is there any significant covariate which influences AVP-923 PK?

The sponsor's population PK analysis showed that none of the available covariates of height, weight, BMI, age, race and gender were considered significantly correlated with any of the PK parameters.

The sponsor conducted the population PK analysis to determine the population PK parameters of quinidine (Q) in plasma and dextromethorphan (DM) and its metabolite dextrorphan (DX) in plasma after single and multiple doses of AVP-923 and also to identify covariates on the population PK parameter estimates. The data from studies 07-AVR-123, 07-AVR-125, 08-AVR-126 were included in the analysis and five other studies (99-AVR-100, 99-AVR-101, 04-AVR-111, 04-AVR-115 and 04-AVR-116) were used for an external validation of the model.

The PK of Q was described by a 2 compartment model with first-order absorption and absorption lag time with first-order elimination from the central compartment. The PK of DM and DX was described by using 2 first-order constants of absorption with lag times, the distribution of DM with 2 compartments and the distribution of DX with 1 compartment. The metabolic conversion of DM to DX was described by a sigmoidal inhibition model related to Q concentrations. Furthermore, the first-pass effect in the liver was related to the inhibition model from which the hepatic extraction ratio could be defined.

The covariates investigated for inclusion in the model were age, body mass index (BMI), weight, height, gender and race. The impact of covariates was initially assessed graphically by performing a linear regression on the parameter values vs. covariates (for continuous covariates) or by making box plots for categorical covariates. The sponsor's final model didn't identify any covariate which influences AVP-923 PK in a clinically significant manner.

Recommendations

The Division of Pharmacometrics has reviewed the submission (NDA 21879) and finds it acceptable, provided that satisfactory agreement is reached between the sponsor and the Agency regarding language in the labeling text.

Pertinent regulatory background

This is the re-submission. Zenvia is known as Neurodex or AVP923 in the previous submissions in NDA 21879. Doses studied in the previous submissions were DM 30mg/Q 30mg and FDA issued approvable letter due to both efficacy and safety concerns which included QT prolongation. In this re-submission, (b) (4) Zenvia 20/10 (combination of DM 20mg/Q 10mg) and Zenvia 30/10 (combination of DM 20mg/Q 10mg) indicated for the treatment of pseudobulbar affect (PBA).

The (b) (4) dose schedule is summarized as follows:

- 1) One Zenvia 20/10 or one Zenvia 30/10 capsule administered daily by mouth for 7 days with or without food
- 2) Starting on the eighth day and thereafter, the daily dose should be increased by taking a second capsule of ZENVIA 20/10 or ZENVIA 30/10 capsule by mouth approximately 12 hours after taking the first dose.

Results of Sponsor's Analysis

The sponsor conducted population PK analyses to determine the population PK parameters of quinidine (Q) in plasma and dextromethorphan (DM) and its metabolite dextrorphan (DX) in plasma after single and multiple doses of AVP-923 and also to identify covariates on the population PK parameter estimates.

The data from studies 07-AVR-123, 07-AVR-125, 08-AVR-126 were included in the analysis and five other studies (99-AVR-100, 99-AVR-101, 04-AVR-111, 04-AVR-115 and 04-AVR-116) were used for an external validation of the model. All subjects from studies 07-AVR-125 and 08-AVR-126 were extensive metabolizers. Study 07-AVR-123 included subjects with other genotypes. Of the 24 subjects included in the analysis for this study, two were not EM; subject 109-502 was an intermediate metabolizer (IM); subject 138-503 was an ultra-metabolizer (UM).

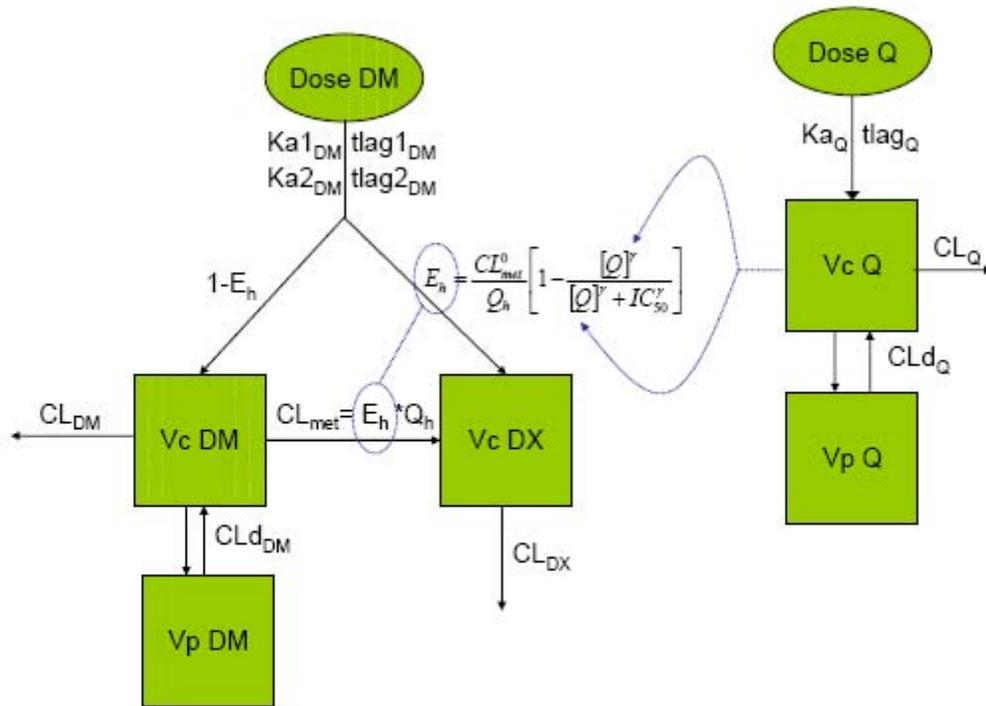
Because data from study 07-AVR-123 were not completely available at the time the analysis started, the model development was based on data from studies 07-AVR-125 and 08-AVR-126. Q data from study 07-AVR-123 were analyzed afterward by including them for a final analysis with the final model. Additional analysis were performed to evaluate the PK of subjects that were not extensive metabolizers in study 07-AVR-123. The metabolic clearance of DM resulting

from fitted parameters for these two subjects along with overall population mean is presented in **Figure 2**.

The PK of Q was described by a 2 compartment model with first-order absorption and absorption lag time with first-order elimination from the central compartment. Q data were first fitted without any DM and DX data. Individual PK parameters resulting from the population PK analysis of Q were then fixed and included in the dataset for DM/DX analysis. Predicted Q concentrations were calculated at each time for each individual using their individual PK parameters.

The PK of DM and DX was described by using 2 first-order constants of absorption with lag times, the distribution of DM with 2 compartments and the distribution of DX with 1 compartment. The metabolic conversion of DM to DX was described by a sigmoidal inhibition model related to Q concentrations. Furthermore, the first-pass effect in the liver was related to the inhibition model from which the hepatic extraction ratio could be defined. Overall structural model description and the parameter estimates are presented in **Figure 1**, **Table 1** and **Table 2**.

Figure 1. Overall PK structural model for Quinidine (Q), Dextromethorphan (DM) and Dextrorphan (DX) in plasma.



Ka=first-order constant of absorption; tlag=absorption lag time; E_h=hepatic extraction ratio; Q_h=hepatic blood flow; CL=systemic clearance; CLd=distribution clearance; Vc=volume of central compartment; Vp=volume of peripheral compartment; CL⁰_{met}=metabolic clearance of DM to DX in the absence of Q; CL_{met}= metabolic clearance of DM to DX; IC₅₀=quinidine concentration at half the maximum inhibition effect; γ =Hill coefficient

Source : The sponsor population PK report “Population Pharmacokinetic meta analysis of zenvia:Modeling of the inhibition by quinidine of the metabolism of dextromethorphan to dextrorphan” page 28.

Table 1. Population PK parameters for Quinidine

Parameters	Mean	Inter-subject variability (%CV)
tlag (h)	0.357	101
Ka (h ⁻¹)	2.32	38.9
CL/F (L/h)	20.7	33.1
Vc/F (L)	173	30.1
CLd (L/h)	3.02	64.9
Vp (L)	33.3	38.7
Intra-subject variability (%CV)		5.81

Source : The sponsor population PK report “Population Pharmacokinetic meta analysis of zenvia:Modeling of the inhibition by quinidine of the metabolism of dextromethorphan to dextrorphan” page 20.

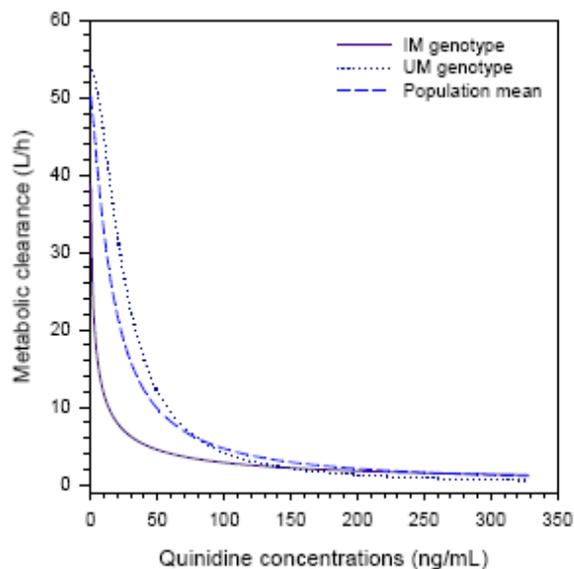
Table 2. Population PK parameters for dextromethorphan (DM) and its metabolite dextrorphan (DX).

	Parameters	Mean	Inter-subject variability (%CV)
Absorption	tlag1 (h)	0.597	38.9
	Ka1 (h ⁻¹)	0.791	57.7
	tlag2 (h)	1.38	22.2
	Ka2 (h ⁻¹)	0.555	47.6
DM	prop1*	1.20	72.8
	CL/F (L/h)	11.7	43.2
	Vc/F (L)	431	31.1
	CLd/F (L/h)	66.4	55.8
	Vp/F (L)	409	32.0
DX	CL/F (L/h)	9.59	14.3
	Vc/F (L)	17.4	31.7
Metabolism	CL _{met} ^D (L/H)	57.5	37.4
	IC50 (mcg/L)	19.3	80.7
	γ	1.21	58.7
DM - Intra-subject variability (%CV)			5.26
DX - Intra-subject variability (%CV)			4.24

*Proportion of the dose being absorption by the Ka1 path = 1/(1+prop1)

Source : The sponsor population PK report “Population Pharmacokinetic meta analysis of zenvia:Modeling of the inhibition by quinidine of the metabolism of dextromethorphan to dextrorphan” page 32.

Figure 2. Predicted metabolic clearance of DM over the observed quinidine concentration range.



Source : The sponsor population PK report “Population Pharmacokinetic meta analysis of zenvia:Modeling of the inhibition by quinidine of the metabolism of dextromethorphan to dextrorphan” page 43.

Once a structural model was selected, covariate analysis was performed to evaluate if some of them could improve the pharmacokinetic model. The covariates investigated for inclusion in the

model were either continuous data (age, body mass index (BMI), weight and height) or categorical data (gender and race). The impact of covariates was initially assessed graphically by performing a linear regression on the parameter values vs. covariates (for continuous covariates) or by making box plots for categorical covariates. None of the available covariates of height, weight, BMI, age, race and gender were considered significantly correlated with any of the PK parameters.

Reviewer's comment:

- *The sponsor's conclusion is consistent with that shown in the original submission.*
- *The sponsor's population PK model is acceptable.*

4.6 APPENDIX VI

GENOMICS GROUP REVIEW

NDA Number	21,879 (SDN 38)
Submission Date	30 Apr 2010
Applicant Name	Avanir Pharmaceuticals
Generic Name	Dextromethorphan and quinidine
Proposed Indication	Pseudobulbar affect (PBA)
Primary Reviewer	Li Zhang, Ph.D.
Secondary Reviewer	Michael A Pacanowski, Pharm.D., M.P.H.

1 Background

NDA 21,879 is a resubmission for dextromethorphan (DM) 20 mg or 30 mg in combination with quinidine (Q) 10 mg (Zenvia) for the treatment of pseudobulbar affect (PBA). This submission is a complete response to the deficiencies outlined in the 30 Oct 2006 Approvable Letter for DM 30 mg/Q 30 mg (Neurodex), in which the FDA recommended to evaluate lower doses of DM and Q secondary to safety concerns. The current submission includes an efficacy and safety trial of a lower dose regimen in patients with multiple sclerosis and amyotrophic lateral sclerosis (Trial 07-AVR-123).

The active moiety of this combination product is DM. Q is administered as an inhibitor of CYP2D6 to boost the concentrations of DM. CYP2D6 poor metabolizers (PMs) ostensibly do not benefit from the CYP2D6 inhibitory properties of Q. *The purpose of this review is to evaluate 1) the risk-benefit profile of administering the modified DM/Q dose regimen in patients who are CYP2D6 PMs and 2) the adequacy of the sponsor's proposed labeling related to CYP2D6 PMs.*

2 Submission Contents Related to Genomics

Trial 07-AVR-123 was a double-blind, randomized, placebo-controlled, multicenter study to assess the safety and efficacy and to determine the PK of two doses of DM/Q (30 mg/10 mg and 20 mg/10 mg) for the treatment of pseudobulbar affect in patients with amyotrophic lateral sclerosis and multiple sclerosis. In 07-AVR-123, blood samples were collected for CYP2D6 genotyping at baseline (Day 1). DNA was collected and analyzed for 290 subjects of the 326 total subjects in the trial.

CYP2D6 genotyping or phenotyping was performed in several other clinical trials that were included in the original NDA submission. Phenotypic or genotypic PMs were generally excluded or not available for analysis in most clinical pharmacology studies (i.e., 99-AVR-101, 00-AVR-103, 07-AVR-125, 05-AVR-119, 08-AVR-126, 04-AVR-112, 06-AVR-122, 04-AVR-116). However, PMs were included in the following efficacy and safety trials: 07-AVR-123, 99-AVR-102, and 02-AVR-106.

Based on the available data, the sponsor has proposed descriptive language related to the influence of CYP2D6 poor metabolism on DM/Q exposure and safety in the *Adverse Reactions* and *Clinical Pharmacology* sections (see section 5.2 of this review for specific label language).

Please see the Office of Clinical Pharmacology review filed on 16 Oct 2006 (Appendix II) for detailed information and recommendation concerning CYP2D6 metabolism and DM/Q administration.

3 Key Questions and Summary of Findings

3.1 Does Q increase DM exposure in CYP2D6 PMs?

The database for DM pharmacokinetics in PMs is small, limiting firm conclusions. PMs that receive DM alone or DM/Q tend to have DM concentrations that are similar to or higher than EMs receiving DM/Q. The DM:DX ratio does not change with multiple dosing of DM/Q suggesting that Q does not further inhibit CYP2D6 metabolism in PMs. A crossover study evaluating changes in DM concentration following addition of Q to DM has not been conducted.

DM is extensively metabolized by CYP2D6 to dextrophan (DX), which is rapidly glucuronidated. Coadministration of Q with DM inhibits the CYP2D6-catalyzed metabolism of DM, increasing plasma concentrations of DM and its desired pharmacological action. According to published studies in EMs, 55% of the DM dose is recovered (as conjugated metabolites) within the first 12 hours, whereas the same cumulative recovery takes 72 hours if Q (100 mg) is coadministered.¹

Approximately 5% to 10% of the Caucasian population has genetically reduced CYP2D6 activity. The incidence of the PM phenotype in Chinese, Black, and Middle Eastern populations is lower (1.9-3.0%). The major null function alleles of CYP2D6 accounting for the PM phenotype in Europeans include but are not limited to *3, *4, *5, *6, and *8. Individuals with intrinsically low or absent CYP2D6 activity have high exposures to DM without coadministration of a CYP2D6 inhibitor. In PMs, only 26% of the DM dose is recovered (as unchanged DM) after 72 hours, suggesting an even greater effect on CYP2D6-mediated metabolism than Q.¹

The original dose of DM 30 mg/Q 30 mg was originally selected based on the ability of Q to convert CYP2D6 (phenotyped) EMs to PMs. Trial 99-AVR-100 demonstrated that 8/8 subjects taking 28.8 mg Q with 30 mg DM every 12 hours were converted to PMs. Q 10 mg converted 6/7 subjects to PMs. A lower rate of conversion was seen with low doses of Q (0 mg, 2.5 mg), but higher doses of Q (25 mg, 50 mg, 75 mg) did not produce proportionally higher exposure to DM. Pharmacometric modeling suggested that Q 10 mg would pose less of a risk for QT-prolongation (see Office of Clinical Pharmacology review filed on 16 Oct 2006).

Trial 99-AVR 101 evaluated DM, DX, and Q PK in 7 EMs and 2PMs for CYP2D6 after single and multiple doses of 30 mg DM and approximately 29 mg Q. The results are of the sponsor's

¹ Schadel, et al. J Clin Psychopharmacol 1995;15.

analysis areshown in the tables below. PMs had higher DM exposure on both Days 1 and 8. In EMs, mean Cmax for DM was approximately 6-fold greater on Day 8 than on Day 1, and mean AUC was approximately 8-fold greater on Day 8 than on Day 1. There was little change in exposure to DX in EMs. In PMs, there was an approximate 6-7-fold increase in DM exposure between Day 1 and 8 as well as a 2-fold increase in DX Cmax and an approximate 6-fold increase in DX AUC from Day 1 to Day 8. For DM as well as for DX, the elimination half-life in EMs was less than that observed in PMs. Exposure to DX did not substantially change in the EMs between Days 1 and 8, and DX exposure remained higher in the EMs than in the PMs throughout the study. *The urinary DM:DX metabolic ratios did not appear to change with Q treatment. Since excretion of both DM and DX increased, but DX excretion increased more than proportionally to DM, the data suggest that Q did not further inhibit DM metabolism to DX in PMs.*

DM and DX pharmacokinetics following single and multiples doses of DM/Q

Compound	Parameter	Day	EM (n=7)		PM (n=2)	
			Mean	SD	Mean	SD
DM	Cmax (ng/mL)	1	15.89	8.22	22.30	0.14
		8	95.50	19.92	136.20	3.25
	AUC(0-12) (ng*hr/mL)	1	133.27	59.86	198.33	6.97
		8	1049.0	243.3	1533.5	80.97
	T _{1/2} (hr)	8	13.13	3.41	41.96	4.47
DX	Cmax (ng/mL)	1	124.86	53.26	10.80	3.39
		8	123.51	17.07	51.45	4.17
	AUC(0-12) (ng*hr/mL)	1	933.83	324.8	90.95	19.08
		4	849.22	181.9	365.27	30.37
	T _{1/2} (hr)	8	1000.5	147.2	530.40	82.39
DM:DX ratio		1	0.268	0.227	1.790	0.493
		8	0.804	0.366	1.859	0.507
		14	0.027*	0.061	2.061	0.115
*n=6						

Source: 99-AVR 101 study report

Plasma concentrations (ng/ml) of DM and DX by CYP2D6 metabolic status following DM 30 mg/Q 10 mg treatment in trial 07-AVR-123 are shown in the table below. *PMs tended to have the highest DM concentrations at the DM 30 mg/ Q 10 mg dose on Day 29, whereas UMs had the lowest.* The findings at Day 57, (b) (4) were generally consistent.

DM and DX plasma concentrations on Day 29 of DM/Q in 07-AVR-123

	DM 30 mg/Q 10 mg				DM 20 mg/Q 10 mg			
	UM (n=1)	EM (n=83)	IM (n=9)	PM (n=4)	UM (n=1)	EM (n=79)	IM (n=9)	PM (n=3)
DM								
Mean (SD)	35 (9.4)	79 (41)	117 (26)	123 (41)	19	50 (27)	62 (55)	79 (27)
95%CI	(28, 42)	(72, 85)	(106, 128)	(58, 188)		(46, 54)	(-6.2, 129)	(-167, 324)
Median	36	70	117	132	19	46	68	79
Range	24, 45	8.6, 280	52, 156	66, 163		6.6, 140	2.0, 127	59, 98

DX								
Mean (SD)	126 (14)	145 (48)	83 (25)	45.3 (27)	109	76 (28)	55 (34)	28 (14)
95%CI	(115, 137)	(137, 152)	(72, 93)	(2.9, 88)		(72, 80)	(12, 98)	(-101, 158)
Median	132	147	83	48	109	72	66	28
Range	109, 145	26, 322	50, 137	10, 75		30, 177	7.3, 98	18, 39

Source: 07-AVR-123 study report

A crossover study evaluating the changes in DM exposure before and after treatment with Q in CYP2D6 PMs has not been conducted. *Data are available for only one parallel arm study of DM monotherapy as compared to DM/Q that included PMs and evaluated pharmacokinetics (99-AVR-102). As shown in the following table, these data demonstrate that PMs have exposures to DM that are similar to PMs receiving DM/Q and EMs receiving DM/Q.*

DM and DX concentrations following administration of DM/Q or DM in EMs and PMs

Genotype		DM/Q*		DM*		DM/Q†		DM†	
		DM	DX	DM	DX	DM	DX	DM	DX
PM	N	3	3	1	1	5	5	2	2
	Mean	132.5	44.7	153	38.831	109.3	38.0	76.5	19.4
	SD	99.9	14.8			78.8	15.8	108.2	27.5
	Median	84.3	48	153	38.831	84.3	38.8	76.5	19.4
	Range	65.7-247.4	28.6-57.6			54.0-47.4	17.3-57.6	0-153.9	0-38.8
EM	N	35	35	23	23	54	54	26	26
	Mean	96.4	89.5	5.2	295.9	77.2	72	8.3	273.3
	SD	46.7	52.3	5	143.2	59.1	53.6	18.2	152.9
	Median	96.3	78.2	4.6	262.3	71.7	70.5	3.8	256.9
	Range	1.1-212.4	8.2/235.3	0.4-15.8	101.1-526.6	0-244.8	0-235.3	0-94.5	0-526.6
* sampled within 8 hours of study medication									
† all samples									

Source: 99-AVR-102 study report

3.2 What is the impact of CYP2D6 genotype on DM/Q efficacy and safety?

The efficacy and safety database for PMs is small. CYP2D6 genotype relationships with efficacy- or safety-related endpoints are inconclusive given the small number of PMs enrolled in trial 07-AVR-123. SAEs, drug-related AEs, and AEs leading to discontinuation in trial 07-AVR-123 do not appear to differ substantially according to CYP2D6 metabolic status in 07-AVR-123 or the pooled PBA safety population. AEs attributable to low-dose Q (10 mg) cannot be adequately isolated since the combination product was administered in nearly all of the studies.

3.2.1 CYP2D6 metabolic effects on DM/Q efficacy

The ITT population of trial 07-AVR-123 consists of 326 subjects, randomized to treatment at a ratio of 1:1:1 as follows: 110 in 30 mg/10 mg group, 107 in the 20 mg/10 mg group, and 109 in the placebo group. Most subjects were Caucasian (75%) or Hispanic (19%), 54% of subjects were female, and the average age was 51 years (range of 25 to 80 years). The primary diagnosis was amyotrophic lateral sclerosis for 60.4% and multiple sclerosis for 39.6%.

The primary efficacy endpoint was the change in number of laughing and/or crying episodes from baseline. Based on the sponsor's analyses, decreases from baseline to Day 84 in laughing

and crying episodes were greater in the DM 30 mg/Q 10 mg group compared to the placebo group (p = 0.0099) and the DM 20 mg/Q 10 mg group compared to the placebo group (p = 0.0048) in the overall population. The decreases from baseline in Center for Neurologic Studies-Lability Scale (CNS-LS) total scores (secondary endpoint) were statistically different between the 30 mg/10 mg group and the placebo group at all study visits (Days 15, 29, 57, and 84), and significant between the 20 mg/10 mg group and the placebo group at Days 57 and 84. Although mean Neuropsychiatric Inventory (NPI) frequency scores decreased in all treatment groups, the decreases (mean change) from baseline to Day 84 were not significantly different between the treatment groups and the placebo group. Mean BDI-II total scores decreased in all treatment groups, and the decrease from baseline to Day 84 was statistically significant between the DM 30 mg/Q 10 mg group and the placebo group. For Pain Rating Scale (PRS), although mean changes in PRS scores decreased in all treatment groups, the decreases were not statistically significant.

The table below shows the changes in the primary and secondary endpoints from baseline to day 84 by CYP2D6 metabolizer group in ITT population. Nonrandomized comparisons of genotype effects within treatment arms were performed using a Generalized Estimating Equation. *Nominally significant genotype effects on efficacy endpoints were identified, although, very few subjects were included in some of the genotype groups (UMs and PMs). Genotype effects for the primary endpoint tended to follow a graded relationship with decreasing metabolic capacity, but this was not directionally consistent in the DM/Q treatment arms.*

Change from baseline in primary and secondary endpoints 07-AVR-123 by CYP2D6 metabolic status

		DM 30mg/Q 10mg			DM 20mg/Q 10mg			Placebo			
		N	Mean	95%CI	N	Mean	95%CI	N	Mean	95%CI	
Laughing/ crying episodes	UM	1	-4.6	...	1	-2.8	...	6	-3.1	-5.30, -0.99	
	EM	71	-4.5	-7.15, -1.81	61	-3	-4.79, -1.16	65	-3.3	-5.29, -1.39	
	IM	8	-2.2	-3.52, -0.81	8	-5.3	-11.4, 0.82	5	-1.5	-2.89, -0.14	
	PM	4	-0.6	-1.73, 0.45	1	-13.7	...	7	-2.4	-7.64, 2.91	
	P		0.031			0.014			0.046		
	P*					0.029					
CNS-LS Total Score	UM	1	-12	...	1	-10	...	7	-4.9	-9.04, -0.67	
	EM	79	-8.1	-9.53, -6.57	74	-8.5	-9.91, -7.12	72	-5.9	-7.17, -4.67	
	IM	9	-10	-12.7, -7.34	8	-8.5	-12.8, -4.24	5	-6	-8.78, -3.22	
	PM	4	-6.8	-10.7, -2.77	2	-1	...	7	-3.9	-8.76, 1.05	
	P		0.073			0.027			0.376		
	P*					0.033					
(b) (4) Frequency Score	UM	1	-2	...	0	3	-2	-6.30, 2.30	
	EM	56	-1.9	-3.02, -0.80	60	-2.9	-4.52, -1.25	47	-1.3	-2.81, 0.17	
	IM	6	-1.8	-2.78, 6.45	6	-2.3	-6.07, 1.40	2	-4	...	
	PM	3	-3	-10.5, 4.45	2	3.5	...	5	-2.8	-6.13, 0.53	
	P		0.104			0.034			0.386		
	P*					0.152					
BDI-II Total Score	UM	1		-7	1	3	...	7	0.4	-4.55, 5.40	
	EM	80	-1.5	-2.66, -0.26	74	-1	-2.25, 0.31	72	-0.6	-1.78, 0.61	
	IM	9	-3.6	-7.42, 0.31	8	-3.1	-5.93, -0.32	5	8.6	-13.8, 31.0	
	PM	4	0.3	-8.11, 8.61	2	1	...	7	-0.3	-5.70, 5.13	
	P		0.016			0.022			0.002		
	P*					<0.01					
PRS (MS only)	UM	0	1	1.2	...	4	1.5	-21.6, 57.3	
	EM	33	-1.2	-2.07, -0.27	30	-0.6	-1.31, 0.10	30	-0.6	-1.73, 0.44	
	IM	3	-1.5	-5.62, 2.67	1	-2.6	...	2	-0.4	...	

	DM 30mg/Q 10mg			DM 20mg/Q 10mg			Placebo		
	N	Mean	95%CI	N	Mean	95%CI	N	Mean	95%CI
PM	2	0.6	...	0	2	-0.9	...
P		0.059			0.108			0.487	
P*					0.102				

P-values are for differences across genotype within treatment arm
P*-values reflect genotype x treatment interaction

Source: Reviewer analysis

3.2.2 CYP2D6 metabolic effects on DM/Q safety

Based on the sponsor's analysis, a total of 941 AEs were reported across the 3 treatment groups in trial 07-AVR-123. The greatest frequency of AEs among DM/Q-treated subjects occurred in the System Organ Class (SOC) of nervous system disorders (26% in DM 20 mg/Q 10 mg; 29% in DM 30 mg/Q 10 mg). Within this SOC, headache was the most frequent AE, occurring in 14% of subjects in both treatment arms. The second most frequent AEs were in the gastrointestinal disorders SOC (22% in DM 20mg/Q 10mg; 25% in DM 30 mg/Q 10 mg). Dizziness, diarrhea, and dry mouth were reported more frequently in both DM/Q treatment groups than in the placebo group; the incidences of dizziness and dry mouth increased with DM dose, whereas the incidence of diarrhea was not related to DM dose. Based on the experience with higher doses of Q used in the treatment of arrhythmias, AEs that may be attributable to Q beyond cardiovascular effects include vomiting, anorexia, headache, and weakness (Integrated Summary of Safety).

As a result of the CYP2D6 genotyping, the total number of CYP2D6 PMs in each treatment arm of the 07-AVR-123 genotyped population was as follows: 4 of 98 in DM 30 mg/Q 10 mg, 3 of 95 in DM 20 mg/Q 10 mg, and 7 of 97 in Placebo group. SAEs, drug-related AEs, and discontinuations due to AEs in 07-AVR-123 are shown according to CYP2D6 metabolic status in the table below. *The number of PMs was very limiting the ability to draw firm conclusions regarding genotypic differences in AE incidence. However, the data suggest that PMs demonstrate AEs at a similar if not greater rate than EMs and IMs.*

DM/Q (combined dose groups) AEs in 07-AVR-123 by CYP2D6 metabolic status

	DM/Q				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)

Source: Reviewer analysis

In terms of SAEs, one PM, in the DM 30 mg/Q 10 mg group (Subject 302-503) experienced syncope on Day 67 that was considered to be moderate in intensity and not related to study drug, but rather concurrent administration of tamsulosin. One subject in the DM 20 mg/Q 10 mg group (Subject 133-501) experienced respiratory failure resulting in death on Day ^(b)₍₆₎ and was considered not related to study drug but rather disease progression. One PM (131-501), also in the DM 20 mg/Q 10 mg group was discontinued due to AEs of decreased appetite and insomnia

of severe intensity and fatigue of moderate intensity on Day 1; these events were considered to be probably related to study drug.

To increase the sample size of PMs available, the pooled safety set of controlled and uncontrolled clinical trials in PBA patients (Pool 2) was reviewed according to CYP2D6 metabolic status. SAEs, drug-related AEs, and discontinuations due to AEs in the pooled safety population are shown in the table below according to CYP2D6 metabolic status. Consistent with the results of 07-AVR-123, AE rates tended to be highest in PMs receiving DM/Q.

DM/Q (combined dose groups) AEs in pooled controlled and uncontrolled PBA trials by CYP2D6 metabolic status

	DM/Q				Placebo			
	UM (n=10)	EM (n=395)	IM (n=27)	PM (n=18)	UM (n=6)	EM (n=105)	IM (n=8)	PM (n=9)
SAE	1 (10.0%)	53 (13.4%)	3 (11.1%)	4 (22.2%)	1 (16.7%)	8 (7.6%)	2 (25.0%)	1 (11.1%)
AE attributed to treatment	6 (60.0%)	198 (50.1%)	9 (33.3%)	13 (72.2%)	2 (33.3%)	35 (33.3%)	3 (37.5%)	3 (33.3%)
Discontinuation due to AE	2 (20.0%)	82 (20.8%)	5 (18.5%)	5 (27.8%)	0 (0)	13 (12.4%)	3 (37.5%)	1 (11.1%)

Source: Reviewer analysis

4 Summary and Conclusions

Plasma concentrations of DM when DM was administered alone were generally highest in PMs; plasma concentrations of DX were generally highest in EMs in the absence of Q. A study has not been conducted that evaluates the effect of adding Q to DM on DM concentrations in a sufficient number of PMs. However, parallel arm trials comparing DM alone and DM/Q indicate that DM concentrations in PMs are similar to those observed in EMs when Q is coadministered. Urinary DM:DX metabolic ratios do not change substantially between single and multiple dosing of DM/Q in PMs whereas they increase in EMs, suggesting that Q is not adding to the level of CYP2D6 inhibition in PMs.

The efficacy and safety database for PMs is small. CYP2D6 genotype relationships with efficacy- and safety-related endpoints are inconclusive given the small number of PMs enrolled in trial 07-AVR-123. SAEs, drug-related AEs, and AEs leading to discontinuation in trial 07-AVR-123 do not appear to differ substantially according to CYP2D6 metabolic status in 07-AVR-123 or the pooled PBA safety population. AEs attributable to low-dose Q (10 mg) cannot be adequately isolated since the combination product was administered in nearly all of the studies

Taken together, few PMs were included in clinical studies DM/Q. Adding Q to DM appears to be of limited utility in PMs from a pharmacokinetic standpoint. The efficacy of DM monotherapy in PMs has not been adequately evaluated. DM/Q treatment effects do not appear to differ in a consistent manner across CYP2D6 metabolic groups. AE rates appeared similar across CYP2D6 metabolic groups receiving DM/Q. Use of DM/Q may expose PMs to an unnecessary risk for QT-prolongation AEs since Q is not adding any benefit. Prescribers should

consider the potential risk for Q-related AEs relative to the benefit of administering the DM/Q combination product (vs. DM alone) in known CYP2D6 PMs.

Labeling language related to genetically mediated CYP2D6 PM should be consistent with recommendations for CYP2D6 inhibitors.

5 Recommendations

The Genomics Group of the Office of Clinical Pharmacology has reviewed NDA 21,879 for DM 20 mg or 30 mg in combination with Q 10 mg for the treatment of pseudobulbar affect. The application is acceptable from the perspective of the Genomics Group. No postmarketing studies are recommended at this time. The sponsor should include labeling that adequately highlights potential risks of Q administration in patients who are PMs.

5.1 Postmarketing commitments/requirements

None.

5.2 Label recommendations

Specific labeling recommendations related to CYP2D6 PMs and use DM/Q are provided in Section 3.0 (Detailed Label Recommendations) of this review document.

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Reviewer, Genomics Group, OCP

Michael Pacanowski, Pharm.D., M.P.H.
Acting Team Leader, Genomics Group, OCP

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/s/

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Clinical Pharmacology/Biopharmaceutics Review Pre-submission Meeting

PRODUCT (Generic Name):	Dextromethorphan/Quinidine (DM/Q) (AVP923)
PRODUCT (Brand Name):	Zenvia TM
DOSAGE FORM:	Gelatin Capsule
DOSAGE STRENGTH:	30/10, 20/10 mg
NDA:	21879
SUBMISSION DATE:	10/16/09
INTERNAL MEETING:	11/3/09
SPONSOR MEETING:	11/18/09 (Cancelled)
SPONSOR:	Avanir Pharmaceuticals
REVIEWER:	Ju-Ping Lai, Ph.D.
TEAM LEADER:	Angela Men, M.D., Ph.D.
OCP DIVISION:	DCP I, HFD 860
OND DIVISION:	HFD 120

OBJECTIVES

In this submission, the sponsor intended to discuss and obtain the Agency's concurrence for their plans of the response to the approvable letter issued on October 30, 2006 for NDA 21879 Zenvia. The sponsor also asked for OCP's concurrence that no additional clinical pharmacology studies are required.

BACKGROUND

Zenvia is a combination product comprised of 2 approved drugs, dextromethorphan (DM) and quinidine (Q) for the treatment of Pseudobulbar Affect (PBA). Q is an inhibitor of CYP2D6 and a substrate of CYP3A4. The primary pharmacologic effect of Q is to inhibit the metabolism of DM by CYP2D6, increasing plasma concentrations of DM and enhancing potential for desired pharmacological effect of DM.

Zenvia is known as Neurodex or AVP923 in the previous submissions in NDA 21879 and IND 56954. Doses studied were 30 mg DM/30 mg Q in the original NDA in 2006. As there are both efficacy and safety concerns, suggestions from different perspectives were provided by the Agency in the approvable letter. From the clinical pharmacology perspective, the potential of drug-drug interactions for CYP2D6 and CYP3A4 and QT prolongation by Q are of the major concerns. OCP conducted PK/PD modeling for QT prolongation and suggested studying lower Q doses. And in addition, *in vitro* studies for evaluating DM and Q as an inducer and as an inhibitor of P450s were asked.

There are several communications between the sponsor and the Agency since then regarding additional plans/studies for the submission. The correspondences are listed in the table below.

October 30, 2006	Approvable Letter for NDA 21,879. (Attachment 1 A)
March 26, 2007	Presubmission Meeting Minutes for February 26, 2007 meeting held to discuss the approvable letter. (Attachment 1 B)
May 24, 2007	Special Protocol Assessment (SPA) Response Letter to IND Amendment SN 0081, dated April 6, 2007 requesting a SPA for protocol 07-AVR-123. (Attachment 1 C)
October 4, 2007	SPA Response Letter to IND amendment SN 0086 dated August 1, 2007 which contained a revised final protocol that addressed FDA's comments contained within the May 24, 2007 Agency SPA response letter. (Attachment 1 D)
July 17, 2009	SPA ADVICE/INFORMATION Letter to the Statistical Analysis Plan (SAP) for protocol 07-AVR-123 submitted in the Special Protocol Assessment (SPA) IND Amendment SN 0100, dated June 19, 2009. (Attachment 1 E)
August 4, 2009	Memorandum Summary Letter for the July 30, 2009 telephone conversation between the Agency and Avanir to discuss the final Statistical Analysis Plan (SAP) for protocol 07-AVR-123. (Attachment 1 F)
September 16, 2009	Type C Meeting Grant Letter dated September 16, 2009 (Attachment 1 G)

Based on the discussions, an additional clinical study (07-AVR-123) assessing the safety and efficacy of a new formulation containing lower doses of DM and Q was submitted as a SPA and would serve as the final definitive trial for approval of Zenvia and would also support a complete response to the approvable letter.

Below listed the comments from OCP for the SPA and revised protocol for reference.

Clinical Pharmacology comments for SPA:

The SSRIs such as fluoxetine and paroxetine (not excluded in the study) are potent inhibitors of CYP2D6 and will not allow for an evaluation of the effect of Q on DM exposure. So similar to inclusion of CYP2D6 poor metabolizers, this population may contribute to safety information but should not be such a large population that it interferes with evaluation of efficacy.

Yes, this (bioavailability) is adequately addressed. However, we have the following comments regarding the protocol with respect to pharmacokinetics. The exclusion for

concomitant medications should be 2 weeks or 5 half-lives, whichever is longer. For example, amiodarone has a mean half-life of 53 days and therefore, 2 weeks is not sufficient. In addition, you have excluded concomitant use of some but not all CYP2D6 inhibitors (SSRIs). You should justify this inconsistency and be aware of the difficulty that including CYP2D6 inhibitors may present. You have not outlined a plan for PK/PD analysis or the use of the Sparse PK samples, or how the results of the pharmacogenomic analysis will be used. This should be included in the protocol.

Clinical Pharmacology comments for the revised protocol of SPA:

We recommend that the genotype information not be combined as you have proposed for the purposes of evaluating PK. Intermediate metabolizers are not typically combined with poor metabolizers, since, by genotype, poor metabolizers lack functional CP2D6. Intermediate metabolizers could be included with extensive metabolizers. However, for the purposes of reporting the data, it would be preferable to report these 2 groups separately, as well as combined. The ultra-rapid metabolizers have multiple copies of CYP2D6, and therefore are not logically combined with extensive metabolizers.

In addition to the genotype information in the PK patients, the genotype for all patients should be reported, and the number (and %) of poor metabolizers (and each of the other groups) in each treatment arm should be provided.

In the current submission, the sponsor summarized 3 *in vivo* drug-drug interaction studies which were submitted previously with desipramine, paroxetine and memantine and new results *in vitro* drug interaction studies. Based on the sponsor, DM didn't inhibit (<20% inhibition) CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 (midazolam) or CYP3A4 (testosterone) in human liver microsomes at 5 μ M. Q didn't inhibit (<30% inhibition) CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, CYP3A4 (midazolam) or CYP3A4 (testosterone) in human liver microsomes at 5 μ M. Q inhibited CYP2D6 with IC50 of less than 0.5 μ M. Neither DM nor Q induced CYP1A2, CYP2B6 or CYP3A4 in human hepatocytes at concentrations up to 4.8 μ M. The sponsor indicated full reports will be submitted in their complete response.

Clinical pharmacology studies to support the approval of Zenvia are listed below.

Study Number	Status	Study Title	Number of Subjects	Number of Subjects Exposed to DM/Q
Phase 1 Pharmacokinetic Studies				
99-AVR-100 ¹	Complete	Clinical Pharmacology Study to Determine the Lowest Dose of Quinidine which Protects Dextromethorphan from Degradation by Cytochrome P450 2D6	46	39
99-AVR-101 ¹	Complete	A Single-Dose and Multiple-Dose Pharmacokinetic Study with a Product Containing Dextromethorphan and Quinidine (AVP-923)	10	10
00-AVR-103 ¹	Complete	A Phase I Drug Interaction Study to Determine the Lowest Dose of Quinidine that Protects Dextromethorphan in Two Dose Levels from Metabolism by Cytochrome P450 2D6	65	48
05-AVR-119 ¹	Complete	Randomized, Double-Blind, Placebo-Controlled, Crossover Study in Healthy Volunteers to Determine the Electrocardiogram Changes Associated with Two Doses of AVP-923 (Neurodex™), with an Open-Label Active Control Arm of Oral Moxifloxacin 4 days on standard dose DM/Q and 4 days on supratherapeutic dose of DM/Q	36	36
07-AVR-125 ³	Complete	<i>Randomized, Double-blind, Placebo-Controlled Pharmacokinetic Evaluation of Various Combinations and Regimens of Dextromethorphan and Quinidine Given for Eight Consecutive Days</i>	79	69
08-AVR-126 ³	Complete	<i>A Double-Blind Randomized Crossover Trial to Define the ECG Effects of AVP-923 (Dextromethorphan/Quinidine) Using a Clinical Dose of 30 mg Dextromethorphan and 10 mg Quinidine Twice Daily Compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women</i>	50	50

Bioavailability/Drug Interaction Studies				
04-AVR-112 ¹	Complete	Drug Interaction Study between AVP-923 (30 mg Dextromethorphan Hydrobromide and 30 mg Quinidine Sulfate) and Desipramine (25 mg Norpramin [®]) in Healthy Adult Subjects (CYP2D6 Extensive Metabolizers)	16	15
04-AVR-111 ¹	Complete	A Randomized, Single-dose, 2-Way Crossover Study to Determine the Effects of Food on the Pharmacokinetics of AVP-923 (30 mg Dextromethorphan Hydrobromide and 30 mg Quinidine Sulfate) in Healthy Volunteers	18	18
04-AVR-115 ¹	Complete	An Open-Label, Multiple-Dose, Multiple-Site, Parallel Group Study to Evaluate the Pharmacokinetics and Safety of AVP-923 (30 mg Dextromethorphan Hydrobromide and 30 mg Quinidine Sulfate) in Patients with Hepatic Impairment and Healthy Volunteers	21	21

04-AVR-116 ¹	Complete	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	21	21
06-AVR-121 ²	Complete	<i>A Multiple-Dose Pharmacokinetic Drug Interaction Study Between AVP-923 and Paroxetine in Healthy Adult Subjects</i>	27	23 completed
06-AVR-122 ²	Complete	<i>A Multiple-Dose Pharmacokinetic Drug Interaction Study Between AVP-923 and Memantine in Healthy Adult Subjects</i>	52	34 completed
07-AVR-123 ³	Complete	<i>A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy and to Determine the Pharmacokinetics of Two Doses of AVP-923 (Dextromethorphan/Quinidine) in the Treatment of Pseudobulbar Affect (PBA) in Patients with Amyotrophic Lateral Sclerosis and Multiple Sclerosis</i>	306 planned 326 enrolled	207 (placebo: 109)
07-AVR-123 ³ OLE	Complete	<i>Open Label Safety Extension of A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy and to Determine the Pharmacokinetics of Two Doses of AVP-923 (Dextromethorphan/Quinidine) in the Treatment of Pseudobulbar Affect (PBA) in Patients with Amyotrophic Lateral Sclerosis and Multiple Sclerosis</i>	N/A	253

SPONSOR'S CLINICAL PHARMACOLOGY QUESTION

One question is asked by the sponsor in the present submission to be addressed by OCP.

Background to Q3

Drug interaction studies have been completed for a tricyclic antidepressant (desipramine), a selective serotonin reuptake inhibitor (paroxetine), and an Alzheimer's disease drug (memantine). In addition, thorough QTc studies including DM 30 mg/Q 10 mg, DM 30 mg/Q 30 mg and DM 60 mg/Q 60 mg with b.i.d. dosing to steady state and formal PK studies in healthy volunteers with different DM/Q formulations and dose regimens as well as studies in special populations have been completed. We have also evaluated the potential for DM and Q to inhibit or induce cytochrome P450 in vitro. Summaries of the in vitro and human investigations are provided in the meeting package. Final study reports for one of the PK studies and for one of the thorough QTc studies have not yet been submitted to FDA. One of the formulations studied in 07-AVR-125 was DM 30 mg/Q 10 mg b.i.d. The synopsis of the final study report is included in Attachment 4. Study 08-AVR-126 is a recently completed thorough QTc study evaluating the new formulation DM 30 mg/Q 10 mg b.i.d. The ECG analysis report for this study is provided in Attachment 5. Complete final study reports will be included in the full response to the approvable letter. In addition, we are providing an integrated analysis of cardiac safety (Attachment 6) for Zenvia including a discussion of its potential to affect the QTc interval. These completed investigations along with substantial clinical pharmacology data contained in the literature and the approved package inserts for the reference listed drugs containing dextromethorphan and quinidine should provide sufficient information for appropriate labeling. We do not intend to perform additional clinical pharmacology studies.

Question 3: Does the Agency agree that no additional clinical pharmacology studies will be required for approval of Zenvia?

Response from OCP: Yes, no additional clinical pharmacology studies will be required.

RECOMMENDATIONS

Since OCP requested studies (*in vitro* drug interaction for the potential of induction/inhibition of P450s by DM and Q) were conducted and will be submitted, no additional clinical pharmacology studies will be required given that the clinical pharmacology comments through the communications were addressed and the clinical pharmacology program was reviewed previously in the original NDA. There are no further studies required except the *in vitro* drug interaction studies.

Sponsor Meeting: Cancelled by the sponsor due to sufficient preliminary responses.

Ju-Ping Lai, Ph.D.
Division of Clinical Pharmacology I

Team Leader: Angela Men, M.D., Ph.D. _____

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21879	GI-1	AVANIR PHARMACEUTICA LS	NEURODEX(DEXTROMETHOR PHAN PLUS QUINIDINE

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

/s/

Ju Ping LAI
11/23/2009

YUXIN MEN
11/23/2009

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-879
Brand Name:	Neurodex
Generic Name:	Dextromethorphan/quinidine
Type of Dosage Form:	Capsules
Strengths:	30 mg dextromethorphan hydrobromide /30 mg quinidine sulfate
Indications:	Pseudobulbar Affect
Type of Submission:	Priority
Sponsor:	Avanir Pharmaceuticals
Submission Date:	12/15/04 4/26/06 3/9/05 5/4/06 5/2/05 5/30/06 6/2/05 6/5/06 9/26/05 6/6/06 10/18/05 6/13/06 11/8/05 6/28/06 11/27/06 7/14/06 2/3/06 8/4/06 2/28/06 8/16/06 3/20/06 9/6/06 3/23/06 10/9/06
OCP Division:	DCP-I
OND Division:	Division of Neurology Drug Products HFD-120
OCP Reviewer:	Sally Usdin Yasuda, MS, PharmD
OCP Team Leader:	Ramana Uppoor, PhD

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1 Executive Summary

1.1 Recommendations

We have reviewed the clinical pharmacology and biopharmaceutics information submitted to NDA 21879. The thorough QT study showed a risk of QT prolongation of greater than 10 msec after administration of NEURODEX that could be greater than 19 msec in 5% of the population.

Our PK/PD modeling of the QT prolongation suggests that a lower dose of quinidine (10 or 15 mg) is likely to result in QT prolongation of less than 10 msec in 95% of the population. Therefore, we recommend that the Sponsor conduct a Phase 3 clinical study to evaluate efficacy (and the exposure-response relationship) of a lower dose of quinidine to be given with dextromethorphan.

We recommend that NEURODEX (at the proposed dose or even with a lower quinidine dose) be contraindicated with strong or moderate inhibitors of CYP3A since quinidine is a CYP3A substrate and inhibitors can further increase the quinidine-induced QT prolongation and resultant safety risk.

CYP2D6 poor metabolizers (PMs) or patients chronically taking strong CYP2D6 inhibitors would have dextromethorphan exposure after administration of DM alone that is similar to exposure in extensive metabolizers (EMs) taking NEURODEX. Therefore, CYP2D6 PMs taking NEURODEX or patients chronically taking strong CYP2D6 inhibitors have an unnecessary risk of QT prolongation from quinidine without any benefit from the quinidine component of this combination product. Because of this, with the current dose of NEURODEX, we would suggest that NEURODEX not be used in CYP2D6 PMs and in patients taking strong CYP2D6 inhibitors.

Specific recommendations are as follows:

- 1) The proposed dose of NEURODEX has a risk of QT prolongation of greater than 10 msec. The Sponsor should evaluate in a Phase 3 study whether 10 or 15 mg quinidine/30 mg DM or higher (and consider 0 mg quinidine/30 mg DM in a population of PMs) would provide adequate therapeutic benefit. This dose of quinidine would be expected to result in less QT risk than the proposed dose of 30 mg quinidine.
- 2) NEURODEX should be contraindicated in patients taking strong or moderate inhibitors of CYP3A.
- 3) Because of the unnecessary risk of QT exposure in patients who are CYP2D6 PMs or in patients taking strong CYP2D6 inhibitors, we would recommend the following if NEURODEX were to be approved at the current dose (30 mg quinidine/30 mg dextromethorphan):
 - CYP2D6 genotype testing should be required prior to administration of NEURODEX.
 - Adequate labeling should be written to indicate that the quinidine component of NEURODEX is not necessary for
 - 1) patients who are PMs of drugs metabolized by CYP2D6.
 - 2) patients who are chronically taking strong CYP2D6 inhibitors.
- 4) Satisfactory agreement must be reached between the Sponsor and the Agency regarding labeling (Please refer to **Section 4** of this review)
- 5) The following *in vitro* studies should be conducted preferably prior to approval to be included in labeling. If this NDA is approved this cycle, the *in vitro* studies could be done in Phase 4:
 - Evaluate quinidine as an inhibitor and as an inducer of P450s
 - Evaluate dextromethorphan (DM) as an inhibitor and as an inducer of P450s

The Sponsor should refer to the Draft Guidance for Industry: Drug Interaction studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (<http://www.fda.gov/cder/guidance/6695dft.htm>). The results of these *in vitro* studies would indicate whether further *in vivo* drug interaction studies are needed.

- 6) The Sponsor proposed the following dissolution method and specifications:

Apparatus:	USP Apparatus 1 (Basket)
Medium:	Simulated Gastric Fluid, without enzymes, pH 1.2
Volume:	900 ml
Rotation Speed:	100 rpm
Specification:	
Dextromethorphan:	15 minutes: Q= (b) (4)
Quinidine:	15 minutes: Q= [REDACTED]

The Office of Clinical Pharmacology finds the proposed dissolution method and specifications acceptable.

1.2 *Phase 4 Commitments*

None.

1.3 *Summary of Clinical Pharmacology and Biopharmaceutics Findings*

NDA 21-879 has been submitted to support the approval of NEURODEX (30 mg dextromethorphan/30 mg quinidine sulfate) for the treatment of pseudobulbar affect (PBA). The proposed dose is 1 capsule given orally twice daily (every 12 hours). The sole purpose of Q is to inhibit the CYP2D6-mediated metabolism of DM, resulting in increased exposure to DM that is significantly greater than from administration of DM alone.

The following clinical pharmacology studies have been submitted and reviewed:

- 99-AVR-100 Determining Lowest Dose of Q that inhibits CYP2D6
- 99-AVR-101 Single and Multiple Dose PK Study
- 99-AVR-103 Q Interaction with High Dose DM
- 04-AVR-111 Food Effect Study
- 04-AVR-115 Hepatic Impairment Study
- 04-AVR-116 Renal Impairment Study
- 04-AVR-117 Population PK Study
- 05-AVR-119 Thorough QT Study
- 04-AVR-112 Desipramine Interaction Study

In addition, the two pivotal clinical studies (99-AVR-102 and 02-AVR-106) have been reviewed from a PK/PD perspective.

Dissolution Method Development and justification for methods and specifications have been reviewed. In addition, the to-be-marketed formulation differs from the clinical trial formulation in the technical grades of 3 excipients as well as the site of manufacture, and a request for biowaiver has been reviewed.

The key findings with respect to the Clinical Pharmacology and biopharmaceutics of NEURODEX are as follows:

Pharmacokinetics

- Quinidine inhibits the CYP2D6-metabolism of dextromethorphan (DM) to dextrophan (DX), resulting in an approximate 10-30 fold increase in DM exposure in plasma of extensive CYP2D6 metabolizers compared to when DM is given alone.
- The dose of Q that was selected was based on the urinary DM/DX ratio in Phase 1 studies. The selected dose (30 mg Q) converted 8/8 extensive metabolizers of drugs metabolized by CYP2D6 (EMs) to the poor metabolizer (PM) phenotype. It should be

noted that a 10 mg dose of Q converted 6/7 subjects to PMs. This resulted in a mean 10-fold increase in exposure compared to DM alone. However, a dose-response evaluation for efficacy has not been conducted, and the efficacy of the Q/DM combination that would result in lower exposures has not been thoroughly evaluated.

- A single and multiple dose study of 30 mg Q/30 mg DM has been conducted in healthy volunteers (99-AVR-101). In EMs, mean C_{max} and AUC for DM were approximately 6 to 8-fold greater on Day 8 than on Day 1. There was little change in exposure to DX. In PMs (n=2) there was a 6 to 7-fold increase in DM exposure between Days 8 and 1. DX was formed, with a 2-fold increase in DX C_{max} and a 6-fold increase in DX AUC between Days 8 and 1. DX exposure remained higher in EMs than in PMs throughout the study. At Day 8, DM exposure in the PMs (n=2) was approximately 45% greater than in EMs.
- Mean (%CV) Q C_{max} values in the multiple dose study 99-AVR-101 were 0.16 (23) µg/ml in EMs with similar values in the PMs. However, Q concentrations in the clinical efficacy and safety studies were as high as 2.21 µg/ml in efficacy study 99-AVR-102.
- Exposure to DM (C_{max} or AUC) or Q (C_{max}) was not increased in subjects with mild-moderate renal impairment after NEURODEX administration for 6 days, and an increase in DX exposure was within the range of concentrations observed when DM is given at an OTC dose in the absence of Q. Q AUC increased by approximately 3%. No dosage adjustment is needed for mild-moderate renal impairment. NEURODEX has not been evaluated in severe renal impairment.
- Exposure to Q was not increased in mild to moderate hepatic impairment. Exposure to DM was increased less than 20% in mild to moderate hepatic impairment. There was an increase in common adverse events in subjects with moderate impairment. No dosage adjustment is needed for mild-moderate hepatic impairment, but in moderate impairment patients should be closely evaluated for adverse events. NEURODEX has not been evaluated in severe hepatic impairment.
- Quinidine is a strong inhibitor of CYP2D6. An interaction study showed a 5-6 fold increase in exposure to the sensitive CYP2D6 substrate desipramine after coadministration with NEURODEX.
- Quinidine is a substrate of CYP3A4. The literature shows a 1.6-fold increase in Q C_{max} and a 2.4-fold increase in AUC in the presence of a strong CYP3A inhibitor, itraconazole, *in vivo*.
- A thorough QT study showed QT prolongation consistent with the known effect of Q. At the proposed therapeutic dose the maximal mean placebo-subtracted, baseline-adjusted QTcF was 10.12 msec, and the upper bound of the one-sided 95% CI was 15.05 msec. For a suprathreshold dose (60 mg DM/60 mg Q), the value was 18.81 msec and the upper bound of the one-sided 95% CI for that value was 24.5 msec. (It should be noted that the Q exposure after administration of the suprathreshold doses was less than 1.1 times the highest mean values in healthy volunteers in other Phase 1 studies and did not exceed the maximum quinidine concentration reported in efficacy study 99-AVR-102 that was 2.21 µg/ml).
- A PK/PD model analyzing the relationship between change in QTc interval and changes in plasma quinidine concentration predicted that in 5% of the population the prolongation would be 19 msec after a 30 mg dose and at least 37.8 msec after the 60 mg dose. The model also was used to predict QTc prolongation for doses of 15 and 10 mg of quinidine

that have not been studied clinically, and the prolongation was predicted to be less than 10 msec in 95% of the population.

- BE was demonstrated for AUC and Cmax for DM and for Q following administration of NEURODEX under fasting conditions or with a high fat meal. NEURODEX can be taken without regard to meals.

Biopharmaceutics

The dissolution profile of the to-be-marketed capsule is similar to that of the clinical trial capsule, and a biowaiver can be granted.

The Sponsor has proposed the following method and specifications:

Apparatus:	USP Apparatus 1 (Basket)
Medium:	Simulated Gastric Fluid, without enzymes, pH 1.2
Volume:	900 ml
Rotation Speed:	100 rpm
Specification:	
Dextromethorphan:	15 minutes: Q= (b) (4)
Quinidine:	15 minutes: Q= (b) (4)

The Office of Clinical Pharmacology finds the proposed dissolution method and specifications acceptable.

Recommendations

- 1) The proposed dose of NEURODEX has a risk of QT prolongation of greater than 10 msec. The Sponsor should evaluate in a Phase 3 study whether 10 or 15 mg quinidine/30 mg DM or higher (and consider 0 mg quinidine/30 mg DM in a population of PMs) would provide adequate therapeutic benefit. This dose of quinidine would be expected to result in less QT risk than the proposed dose of 30 mg quinidine.
- 2) NEURODEX should be contraindicated in patients taking strong or moderate inhibitors of CYP3A.
- 3) Because of the unnecessary risk of QT exposure in patients who are CYP2D6 PMs or in patients taking strong CYP2D6 inhibitors, we would recommend the following if NEURODEX were to be approved at the current dose (30 mg quinidine/30 mg dextromethorphan):
 - CYP2D6 genotype testing should be required prior to administration of NEURODEX.
 - Adequate labeling should be written to indicate that the quinidine component of NEURODEX is not necessary for
 - 1) patients who are PMs of drugs metabolized by CYP2D6.
 - 3) patients who are chronically taking strong CYP2D6 inhibitors.

- 4) Satisfactory agreement must be reached between the Sponsor and the Agency regarding labeling (Please refer to **Section 4** of this review)
- 5) The following *in vitro* studies should be conducted preferably prior to approval to be included in labeling. If this NDA is approved this cycle, the *in vitro* studies could be done in Phase 4:
 - Evaluate quinidine as an inhibitor and as an inducer of P450s
 - Evaluate dextromethorphan (DM) as an inhibitor and as an inducer of P450s

The Sponsor should refer to the Draft Guidance for Industry: Drug Interaction studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (<http://www.fda.gov/cder/guidance/6695dft.htm>). The results of these *in vitro* studies would indicate whether further *in vivo* drug interaction studies are needed.

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CSO/M.Griffis
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/TL Biopharm/R. Uppoor
HFD-860 /DD DCP1/M. Mehta

2 Question-Based Review

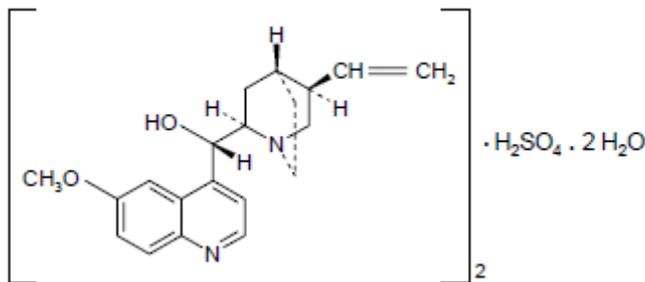
2.1 General Attributes

NEURODEX is a combination of quinidine sulfate (30 mg) and dextromethorphan hydrobromide (HBr) (30 mg). Quinidine sulfate (Q) and dextromethorphan HBr (DM) are currently marketed individually. Q is indicated for reduction of frequency of atrial fibrillation/flutter beginning at doses of 200 mg every 6 hours, conversion of atrial fibrillation/flutter to sinus rhythm beginning at doses of 400 mg every 6 hours, and treatment of *P. falciparum* malaria. DM is an OTC antitussive given in doses of 30 mg every 6 to 8 hours up to 120 mg/day.

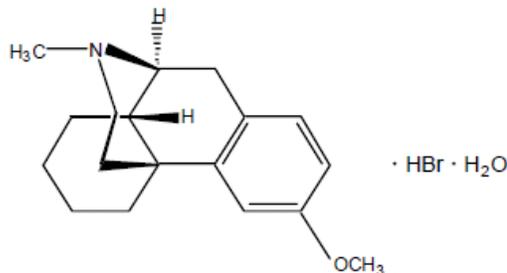
2.1.1 What are the highlights of the chemistry and physical-chemical properties of NEURODEX, and the formulation of the drug product?

Quinidine sulfate has an empirical formula of $C_{40}H_{48}N_4O_4 \cdot H_2SO_4 \cdot 2H_2O$ and is designated as cinchonan-9-ol, 6'-methoxy-(9S)-, sulfate (2:1) dehydrate with a molecular weight of 782.96. Dextromethorphan HBr has an empirical formula of $C_{18}H_{25}NO \cdot HBr \cdot H_2O$ and is designated as morphinan, 3-methoxy-17-methyl-, (9 α , 13 α , 14 α)-, hydrobromide monohydrate with a molecular weight of 370.33. The structures are shown below, as provided by the Sponsor:

Quinidine Sulfate



Dextromethorphan HBr



AVP-923 capsules are hard gelatin immediate release capsules. Each capsule contains 30 mg of DM and 30 mg of Q on an anhydrous basis. The composition of the to-be-marketed NEURODEX (AVP-923) capsules are shown in the table below, as provided by the Sponsor. The to-be-marketed capsules differ from the clinical trials batch C0051001 in the technical grades of three of the excipients: microcrystalline cellulose, lactose, and magnesium stearate, as well as the site of manufacture.

Table 3.2.P.2-9. Composition of AVP-923 Formulation 5

Ingredient	Amount per Capsule	
	mg	%
Dextromethorphan Hydrobromide USP, EP		(b) (4)
Quinidine Sulfate USP, EP		
Croscarmellose Sodium NF, Ph. Eur, JP		
Microcrystalline Cellulose NF, Ph. Eur, JP		
(b) (4)		
Lactose NF (b) (4) NF		
Colloidal Silicon Dioxide NF		
Magnesium Stearate NF (b) (4)		
(b) (4)		

BP = British Pharmacopoeia; EP = European Pharmacopoeia; JP = Japanese Pharmacopoeia; NF = National Formulary; Ph. Eur. = Pharmacopoee Europeenne; USP = United States Pharmacopoeia.

(b) (4)

2.1.2 What is the proposed mechanism of drug action and what is the proposed therapeutic indication?

The proposed indication for NEURODEX is for the treatment of pseudobulbar affect (PBA) also known, for example, as pathological laughing and crying/weeping, emotional lability, and emotional incontinence. The Sponsor states that PBA occurs in patients with neurodegenerative diseases such as ALS, MS, and Alzheimer’s disease or in patients with neuronal damage following stroke or traumatic brain injury. It is postulated that DM, considered the active therapeutic agent, acts by controlling glutamate excitatory activity through modulation as an antagonist of sigma-1 and NMDA receptor activities. The action of Q in this product is to competitively inhibit the metabolism of DM catalyzed by CYP2D6, increasing the plasma concentrations of DM in order to enhance the potential for the desired therapeutic effect.

The literature also suggests that DM blocks serotonin uptake and increases its release, and therefore increases serotonergic tone in the CNS.

2.1.3 What is the proposed dosage and route of administration?

The proposed recommended dose for NEURODEX is 1 capsule taken orally twice daily (to be administered once in the evening and a second capsule approximately 12 hours later).

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Clinical pharmacology studies 99-AVR-100 and 00-AVR-103 were designed to determine the lowest dose of Q that inhibits conversion of a given dose of DM to DX based on urinary DM/DX ratios, converting subjects into phenotypic poor metabolizers of drugs metabolized by CYP2D6 (PMs). The dose selected was 30 mg Q/30 mg DM and this dose was given twice daily in the remaining clinical pharmacology and clinical studies.

2.2.2 *What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?*

The primary efficacy endpoint was change from baseline in the CNS-LS score. The CNS-LS questionnaire is a 7-item self-report measure that assesses frequency and severity of PBA, and is validated for use in ALS and in MS. Questions were answered on a 1- to 5-point scale, with 1 indicating a normal response and 5 suggesting an over-reactive response. The range of possible scores is 7-35. Response to treatment was defined as a change from baseline in the total score.

Adverse events to DM include drowsiness, dizziness, and fatigue, and effects consistent with serotonin syndrome have been noted in the literature at higher doses. For quinidine common adverse reactions noted in the labeling (>10%) include diarrhea, nausea, vomiting, and lightheadedness. Heartburn and esophagitis have also been reported. Autoimmune and inflammatory syndromes have been reported. Dose-related prolongation of QTc is a known effect of quinidine. QTc has been monitored in the studies submitted to this NDA. In addition, a thorough QT study was conducted.

2.2.3 *Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

The active moieties for the purposes of the proposed indication are considered to be Q and DM. There are appropriately measured. Please refer to section 2.6 of this review.

2.2.4 *Exposure –response*

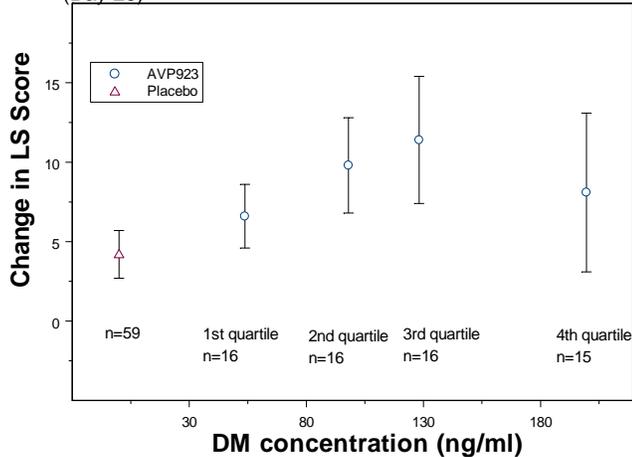
2.2.4.1 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.*

In clinical study 99-AVR-102 comparing AVP-923 to 30 mg DM or 30 mg Q, there was a small but statistically significant decrease in CNS-LS score associated with administration of AVP-923 compared to either DM or Q alone. This was associated with higher plasma concentrations of DM than were observed after DM given alone.

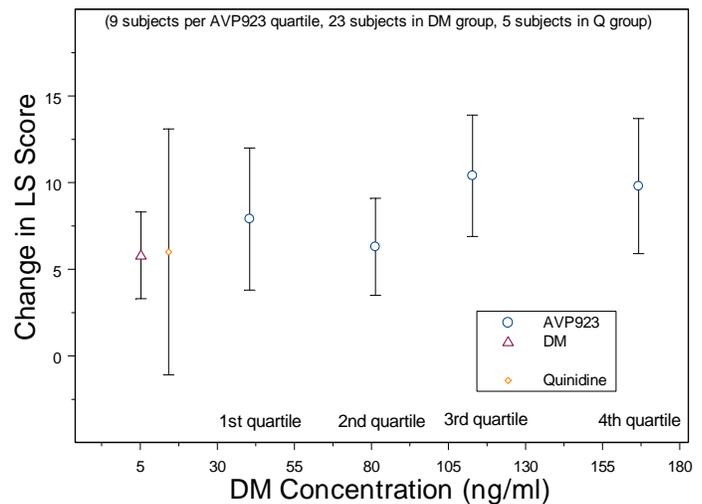
In clinical study 02-AVR-106 that compared AVP-923 to placebo, the earliest measurement of CNS-LS score was on Day 15 (the first measurement point), and at that point, subjects receiving AVP-923 had significantly greater decrease in CNS-LS score than subjects receiving placebo. The primary efficacy endpoint was change from baseline in CNS-LS score (using the average of scores on Days 15, 29, 57, and 85) and significantly greater reduction was seen in the AVP-923 group. Secondary endpoints included frequency of episodes of inappropriate laughing and/or crying per week in which a difference was seen between drug and placebo as early as 1 week. This is consistent with the approximate 13 hour half-life of DM in the presence of Q.

The exposure-response relationships for the two pivotal clinical studies are shown in the figures below, plotted by the reviewer based on quartiles of DM concentrations. Although in 02-AVR-106 the figure suggests a relationship between exposure and response, in both studies there was substantially variability in response (consistent with a limited number of subjects in each study).

Mean (95% CI of mean) Changes in LS Score by Quartile of DM Concentrations in Study 02-AVR-106 in MS (Day 29)



Mean (95% CI of mean) Changes in LS Score by Quartile of DM Concentrations in Study 99-AVR-102 in ALS



The Sponsor has not evaluated the effects of withdrawing treatment of PBA with a combination of DM and Q.

2.2.4.1.1 What is the rationale for this combination and what is the rationale for this combination of doses?

The rationale for the combination is that Q is a potent inhibitor of CYP2D6, the enzyme primarily responsible for metabolism of DM to DX. DM is rapidly metabolized by CYP2D6 to DX resulting in DM plasma concentrations of < 10 ng/ml in the absence of Q. When DM at doses of 30-60 mg is given with Q doses of 10-60 mg, there is an approximate 10-30 fold increase in DM exposure (Studies 99-AVR-100 and 00-AVR-103). The Sponsor has selected a dose based on the ability of Q to inhibit CYP2D6 to the extent that it would convert extensive metabolizers of drugs metabolized by CYP2D6 (EMs) to poor metabolizers (PMs). In EMs this results in exposure to DM greater than would be obtained in CYP2D6 extensive metabolizers taking DM alone. Study 99-AVR-100 demonstrated that 8/8 subjects taking 28.8 mg Q with 30 mg DM given every 12 hours were converted to PMs, whereas a lower rate of conversion was seen with lower doses of Q, and higher doses of Q did not produce proportionally higher exposure to DM. At a quinidine dose of 10 mg every 12 hours, 6/7 subjects converted to PMs after 13 doses.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Some adverse events, including nausea, dizziness, somnolence, fatigue, falls, and cramps occurred more frequently in the NEURODEX treatment group than in the DM or Q groups in Pivotal efficacy study 99-AVR-102, suggesting an exposure-response relationship. Onset of adverse reactions in the clinical studies occurred primarily in the first several weeks of drug

administration, although the cumulative incidence increases throughout the duration of the clinical studies.

2.2.4.3 Does this drug prolong the QT or QTc interval?

NEURODEX resulted in QT prolongation in the thorough QT study, consistent with the known effect of Q. At the proposed therapeutic dose the maximal mean placebo-subtracted, baseline-adjusted QTcF was 10.12 msec, and the upper bound of the one-sided 95% CI was 15.05 msec. For a suprathreshold dose (60 mg DM/60 mg Q), the value was 18.81 msec and the upper bound of the one-sided 95% CI for that value was 24.5 msec. (It should be noted that the Q exposure after administration of the suprathreshold doses was less than 1.1 times the highest mean values in healthy volunteers in other Phase 1 studies such as in normal subjects in the renal impairment study in whom the mean Quinidine concentration was 0.332 µg/ml and did not exceed the maximum quinidine concentration reported in efficacy study 99-AVR-102 that was 2.21 µg/ml).

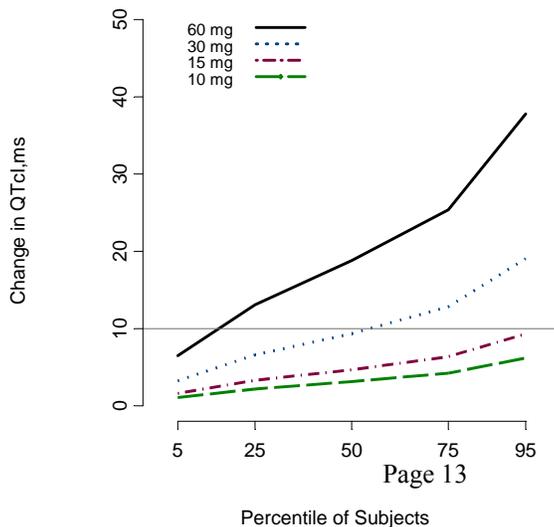
A combined pharmacokinetic and pharmacodynamic model was used to analyze the relationship between change in the QTc interval and changes in plasma concentration of quinidine (Please refer to the QT Pharmacometrics Review in the Appendix). The effect of quinidine on the QTc interval could be explained by a linear pharmacodynamic model with a delayed effect. The equilibration between plasma and effect site had a half-time of 3 hours (BSV of 123%). The median slope was 55.6 msec•mg/l (BSV of 40%). The slope estimate is comparable to literature reports.

The pharmacodynamic model was used to predict QTc prolongation at 4 different dose levels in the population using parametric simulations. For the 60 mg dose, the median change in QTcI interval was 18.8 msec but in 5% of the population the prolongation was at least 37.8 msec. For the 30 mg dose, the predicted median change was 9.3 msec but in 5% of the population the prolongation is predicted to be 19.0 msec.

The pharmacodynamic model was used to predict QTc prolongation for two lower doses of quinidine (15 mg and 10 mg) that have not been studied clinically. For both dose levels, the prolongation was predicted to be less than 10 msec in 95% of the population.

The model predictions are shown in the figure below.

Model Predicted Change in QTc Interval Stratified by Dose Group



2.2.4.4. *Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues? (In some cases it may be possible to combine with 2.2.4.2 and 2.2.4.3)*

The proposed dose and dosing regimen is the same as evaluated in the pivotal clinical studies. The dose of Q was selected based on its ability to result in the PM phenotype, rather than on an exposure response relationship between DM concentration and change in LS score. That relationship has been characterized by the reviewer as shown above. Of note, in Study 99-AVR-100, when 10 mg of Q was given with 30 mg of DM, mean (CV) DM plasma concentrations were approximately 57.1 (30) ng/ml. The unresolved dosing/administration issue is whether the DM exposure after that dose, in the range of the 1st quartile in the exposure-response figure below would be sufficient to balance the risk-benefit ratio, resulting in sufficient exposure to DM to provide efficacy, while minimizing the risk of QT prolongation.

2.2.5 *What are PK characteristics of the drug and its major metabolites?*

2.2.5.1 *What are the single dose and multiple dose PK parameters?*

Single and multiple dose PK parameters of DM, DX, and Q have been evaluated in several studies. Study 99-AVR 101 evaluated PK in 7 EMs and 2PMs for CYP2D6 after single and multiple doses (13 doses) of 30 mg DM and approximately 29 mg Q. The results are shown in the tables below. In EMs, mean C_{max} for DM was approximately 6-fold greater on Day 8 than on Day 1, and mean AUC was approximately 8-fold greater on Day 8 than on Day 1. There was little change in exposure to DX in EMs. In PMs, formation of DX could still be observed. In PMs there was an approximate 6-7-fold increase in DM exposure between Day 1 and 8 as well as a 2-fold increase in DX C_{max} and an approximate 6-fold increase in DX AUC from Day 1 to Day 8. For DM as well as for DX, the elimination half-life in EMs was less than that observed in PMs. Exposure to DX did not substantially change in the EMs between Days 1 and 8, and DX exposure remained higher in the EMs than in the PMs throughout the study.

	PK Parameter	Study Day	EMs	PMs
Dextromethorphan, plasma	T _{max} (hr)	1	6.00 (4.0-11.9)	8.0
		4	4.00 (3.99-8.0)	6.0 (4.0-8.0)
		8	8.0 (2.0-8.0)	5.0 (4.0-6.0)
	C _{max} (ng/ml)	1	15.9 (52)	22.3 (1)
		4	76.7 (20)	105.7 (9)
		8	95.5 (21)	136.2 (2)
	AUC ₀₋₁₂ (ng*hr/ml)	1	133.3 (45)	198.3 (4)
		4	811.7 (19)	1146 (7)
		8	1049.0 (23)	1533 (5)
	T _{1/2} (hr)	8	13.3 (26)	42.0 (11)
C _{min} (ng/ml) (at end of dosing interval on Day 8)	8	80.0 (21)	117.6 (12)	
C _{avg} (ng/ml)	8	87.5 (23)	128.1 (5)	
% fluctuation	8	18.0 (29)	14.8 (66)	

	% swing	8	19.6 (29)	16.7 (71)
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	PK Parameter	Study Day	EMs (n=7)	PMs (n=2)
Dextrorphan, plasma	T _{max} (hr)	1	4.0 (4.0-4.01)	3.01 (2.0-4.01)
		4	2.0 (0-4.0)	2.0 (2.0)
		8	48.0 (24.2-48)*	3.0 (2.0-4.0)
	C _{max} (ng/ml)	1	124.86 (43)	19.8 (15)
		4	79.33 (23)	37.0 (0.6)
		8	123.5 (14)	51.45 (8)
	AUC ₀₋₁₂ (ng*hr/ml)	1	933.8 (35)	90.95 (21)
		4	849.2 (21)	365.3 (8)
		8	1001 (15)	530.4 (15)
	t _{1/2} (hr)	8	18.0 (24)	39.3 (13)
	C _{min} (ng/ml) (at end of dosing interval on Day 8)	8	78.2 (15)	36.3 (32)
	C _{avg} (ng/ml)	8	83.4 (15)	44.3 (16)
	% fluctuation	8	55.7 (41)	35.9 (61)
% swing	8	59.7 (43)	47.2 (74)	

The results for the Quinidine plasma PK parameters are shown below. Based on the elimination half-life, an approximate 1.4-fold accumulation of quinidine would be predicted. In fact, in both EMs there is an approximate 1.8-fold increase in C_{max} (2-fold in PMs), and an approximate 2.7-fold increase in AUC in EMs (and 2-fold in PMs).

	PK Parameter	Study Day	EMs	PMs
Quinidine, plasma	T _{max} (hr)	1	1.5 (1.5-2.0)	3.01 (2.0-4.01)
		4	1.53 (1.0-2.0)	1.52 (1.52)
		8	1.99 (1.98-2.0)	1.5 (1.49-1.5)
	C _{max} (µg/ml)	1	0.09 (23)	0.08 (7)
		4	0.15 (20)	0.14 (4)
		8	0.16 (23)	0.16 (12)
	AUC ₀₋₁₂ (µg*hr/ml)	1	0.48 (38)	0.51 (25)
		4	1.198 (18)	0.969 (5)
		8	1.313 (14)	1.074 (2)
	t _{1/2} (hr)	8	7.66 (14)	6.66 (6)
	λ _z (hr ⁻¹)	1	0.0944 (32)	0.0886 (32)
		4	0.103 (16)	0.107 (11)
		8	0.092 (14)	0.104 (6)
	C _{min} (µg/ml) (at end of dosing interval on Day 8)	8	0.06 (14)	0.00
	C _{avg} (µg/ml)	8	0.11 (14)	0.09 (2)
% fluctuation	8	91.2 (20)	184.6 (14)	
% swing	8	157.7 (26)	*NC	

2.2.5.1.1 How do the PK characteristics of AVP-923 compare to the individual components given separately?

Quinidine – Quinidine has not been given alone in any of the Phase I studies in this NDA. In the pivotal clinical study 99-AVR-102, quinidine was taken at a dose of 30 mg twice daily in subjects with ALS with pseudobulbar affect. Blood samples were collected on Day 29 within 8 hours of the last dose of study medication and Q concentrations (mean, %CV) were 0.0796 (86) in EMs (n=21) and were generally within the range of the mean C_{min} and mean C_{max} values after administration of AVP-923 in Phase 1 Study 99-AVR 101 described above. The elimination half-life observed in 99-AVR-101 is in agreement with the 6-8 hour elimination half-life described in the approved quinidine sulfate labeling.

Dextromethorphan – Dextromethorphan when given alone in EMs gave urinary metabolic ratios of DM/DX of approximately 0.01-0.05 in Study 99-AVR-100. When given with 28.8 mg Q, the urinary metabolic ratio became 0.35 after a single dose and 1.42 after dosing every 12 hours for 13 doses. This metabolic ratio indicates conversion to the PM phenotype. Plasma concentration of both DM and DX when DM was given alone at a dose of 30 mg was not evaluated in Phase 1 studies. However in Phase 1 Study 99-AVR-103, a single dose of 45 mg DM in the absence of Q resulted in a mean (%CV) plasma DM concentration of approximately 4.4 (177) ng/ml and a mean (%CV) plasma DX concentration of 545.9 (34) ng/ml, with similar concentrations observed on Day 8 after q 12 h dosing. The DM/DX ratio in the plasma was approximately 0.008. In contrast, a 45 mg DM dose in that study given with 30 mg Q resulted in DM and DX concentrations (on Day 8) of 141.5 (53) ng/ml and 89.1 (29) ng/ml. The DM/DX ratio in the plasma was approximately 1.6 after co-administration. This is consistent with the exposure to DM and to DX seen on Day in Study 99-AVR-101, above, after 8 days of AVP-923 administration every 12 hours where the ratios of DM/DX are approximately 0.13 on Day 1 and 0.77 on Day 8 in EMs.

2.2.5.1.2 Is there a drug interaction between dextromethorphan and quinidine?

Yes. Quinidine inhibits the CYP2D6-mediated metabolism of dextromethorphan. Please refer to section 2.4.2.1.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Based on a population PK analysis, PK was similar in subjects and in patients and for Q was also consistent with what has been reported in the literature. In addition, the range of plasma concentrations of DM, DX, and Q taken within 8 hours of a dose of AVP-923 in patients was consistent with concentrations observed in Phase 1 studies.

2.2.5.3. What are the characteristics of drug absorption? (This may include discussion of transporter or pH effect).

Quinidine: According to the approved quinidine sulfate label ((b) (4)), the absolute bioavailability of quinidine (from quinidine sulfate tablets) is about 70% but varies widely (45-100%). According to that labeling, the less than complete bioavailability is due to first-pass metabolism. Following administration of AVP-923, peak plasma concentrations are reached in approximately 1.5-3 hours.

DM: Following administration of AVP-923, peak plasma concentrations of DM are reached in approximately 4-8 hours.

2.2.5.4. What are the characteristics of drug distribution? (Include protein binding)

Quinidine: According to the approved quinidine labeling, the volume of distribution is 2-3 L/kg in healthy young adults, decreasing to 0.5 L/kg in patients with CHF and increasing to 3-5 L/kg in patients with hepatic cirrhosis. In the present submission, *in vitro* protein binding in human plasma was approximately 80-89%, and was not concentration dependent at concentrations of 30 ng/ml and 350 ng/ml (the upper range for expected concentrations after administration of NEURODEX). This is in agreement with the approved quinidine sulfate labeling that states that fraction bound is 80-88% in adults and older children and lower in pregnant women and infants and neonates. DM and DX did not alter protein binding of quinidine.

Dextromethorphan: In the present submission, *in vitro* protein binding in human plasma was approximately 60-70% and was not concentration dependent at concentrations of approximately 50 ng/ml and 350 ng/ml (the upper range expected after administration of NEURODEX). Quinidine and DX did not alter protein binding of DM.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination? (This may include table with results of mass balance study)

Quinidine: According to the approved quinidine sulfate labeling, most quinidine is metabolized hepatically, mediated by CYP3A4. When urine pH is < 7, 20% of administered quinidine appears unchanged in the urine, and less than 5% is excreted unchanged when the urine is more alkaline. Renal clearance involves glomerular filtration and tubular secretion.

Dextromethorphan is extensively metabolized as outlined in section 2.2.5.6, below. DM and its metabolites are renally eliminated. In a publication by Capon et al, 41% of a dose of DM was recovered in the urine in EMs and 64% in PMs. In EMs this was accounted for by DX (27%), 3-hydroxymorphinan (16%, total including conjugated), and DM (0.2%). In PMs this was accounted for by DM (26%), DX (8%, total), 3-hydroxymorphinan (14%, total), and 3-methoxymorphinan (11%).¹

2.2.5.6 What are the characteristics of drug metabolism? (This may include data on extraction ratio; metabolic scheme; enzymes responsible for metabolism; fractional clearance of drug).

¹ Capon DA, Bochner F, Kerry N, Mikus G, Danz, C, Somogyi AA. Clin Pharmacol Ther 1996; 60:295-307.

Quinidine: The extraction ratio for quinidine is considered to be low to intermediate (0.3-7) in published literature. At least 6 metabolites of quinidine have been identified; 3-hydroxyquinidine (3HQ) and 2'-quinidinone are considered to be the primary metabolites. The 3-HQ metabolite is thought to have the most anti-arrhythmic effects relative to other metabolites and is considered to be at least half as pharmacologically active as quinidine with respect to cardiac effects (based on QTc studies in pre-clinical models), and plasma concentrations can exceed those of quinidine. The elimination half-life of 3-HQ is approximately 12 hours.

Quinidine metabolism is mediated primarily by CYP3A. The proposed metabolic scheme has been outlined as shown at right (provided by the Sponsor).

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Dextromethorphan:

The figure at left shows the proposed pathways for Phase I metabolism of DM.² Based on the published literature,³ DM is O-demethylated to DX and this reaction is mediated primarily by CYP2D6 but to some extent by CYP2C9.⁴ DM is N-demethylated to 3-methoxymorphinan and this is mediated in part by CYP3A.² DX and 3-methoxymorphinan are further demethylated by CYP3A and by CYP2D6, respectively, to 3-hydroxymorphinan. Dextrophan and 3-hydroxymorphinan are glucuronidated.⁵

2.2.5.7 What are the characteristics of drug excretion?

Please refer to section 2.2.5.5, above.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Dose linearity was not specifically evaluated in NDA 21-879. However, linearity can be addressed as follows. For DM, in comparing 30 mg (Study 99-AVR-101), and 45mg and 60 mg (Study 99-AVR-103) doses of DM in the presence of 30 mg quinidine, there seems to be an approximately proportional increase in DM exposure as shown in the table below.

² Di Marco MP, Edwards DJ, Wainer IW, Ducharme MP. Life Sciences 2002; 71:1149-60

³ Schmider J, Greenblatt DJ, Fogelman SM, von Moltke LL, Shader RI. Biopharm Drug Disposition 1997; 18:227-240.

⁴ Von Moltke LL, Greenblatt DJ, Grassi JM, et al. J Pharm Pharmacol 1998; 50:997-1004.

⁵ Lutz U, Volkel W, Lutz RW, Lutz WK. J Chromatography B 2004; 813:217-225.

Mean (%CV) C_{max} and AUC of DM on Day 8 when given with 30 mg Q

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)

Linearity in Q pharmacokinetics (at the clinically relevant dose of DM) can be addressed by the results of Study 99-AVR-100 that only looked at 2, 4, and 8 hours post dose. C_{max} and AUC based on those time points at steady state are shown in the table below for specific doses of Q. For the 50 and 75 mg doses, a 2-fold and 3-fold increase in dose, respectively, compared to 25 mg, there was an approximate 1.8 and 2.5 fold increase in exposure.

Mean (%CV) C_{max} and AUC of Q on Day 7 when given with 30 mg DM

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 in 99-AVR-100 was calculated on the basis of quinidine sulfate, although the quinidine drug substance contained approximately (b)(4) dihydroquinidine. Therefore the 25 mg Q dosage strength is equivalent to approximately 28.8 mg Q.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

Please refer to the tables in section 2.2.5.1. Following 8 days of twice daily dosing with AVP-923 in EMs the DM AUC and C_{max} were approximately 6- and 8-fold higher, respectively, than on Day 1 and the DX C_{max} and AUC did not change. For PMs the DM C_{max} and AUC were 6- and 7.7-fold higher, respectively, on Day 8 compared to Day 1, and the DX C_{max} and AUC were 2.6 and 5.8-fold higher, respectively. The Quinidine C_{max} and AUC were 1.8 and 2.7-fold greater, respectively, on Day 8 compared to Day 1 in EMs and approximately 2-fold greater, on Day 8 compared to Day 1 in PMs.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Intra-subject variability was not assessed. Inter-subject variability for DM across studies in healthy volunteers in fasted state was approximately 21-40% for C_{max} and AUC. Inter-subject variability for DX across studies was approximately 14-43% for C_{max} and 21-35% for AUC. Inter-subject variability for Q across studies was approximately 23-30% for C_{max} and 14-47% for AUC. Variability could be due to absorption (in the case of DM or Q) as well as variability in metabolism.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

Age – In the pivotal clinical studies there were 18 patients 65 years of age and over. The results of the population PK study (04-AVR-117) suggest that increasing age was associated with an increase in the apparent central volume of distribution for DX. This effect on DX is not likely to impact on efficacy and is not likely to have clinically relevant safety consequences following administration of NEURODEX since it would result in a decrease in exposure. However, an age difference in pharmacodynamic effects has not been evaluated. The effect of age on efficacy was not systematically evaluated.

Gender – Based on the population PK analysis, gender did not affect the PK of DM or DX. The effect of gender as a covariate on Q PK was not evaluated in this submission. However, published literature suggests that in the absence of statistically significant differences in PK parameters for Q and 3-HQ between healthy young men (n=12) and women (n=12), quinidine causes a greater prolongation of cardiac repolarization in women than in men at equivalent serum concentrations after IV administration of quinidine.⁶

Race – The effect of race has not been evaluated. The majority (75%) of the subjects in the PK population were Caucasian. Similarly in the efficacy studies 99-AVR-102 and 02-AVR-106 more than 80% of the subjects were Caucasian.

Weight – IBW affected the PK parameters of DM and DX in the population PK study (04-AVR-117), and PK parameters in that study were adjusted for IBW. This does not affect the clinical use of NEURODEX since trials were done without adjusting for body weight.

Height – Not evaluated.

Disease – Not evaluated in this submission. Congestive heart failure reduces quinidine's apparent volume of distribution and requires a reduction in dosage to prevent toxicity, according to the quinidine labeling.

Genetic Polymorphism – Genetic polymorphisms in CYP2D6 are responsible for altered metabolism of DM. Extensive metabolizers (EMs of CYP2D6) are phenotypically converted to PMs by the dose of Q in AVP-923.

Pregnancy – AVP-923 has not been studied in pregnant women.

Organ Dysfunction –

Renal Impairment – PK of DM, DX, and Q were evaluated in subjects with mild renal impairment (n=6), moderate impairment (n=6), or normal renal function (n=9) in Study 04-

⁶ Benton RE, Sale M, Flockhart DA, Woosley RL. Clin Pharmacol Ther 2000; 67:413-8.

AVR-116 after administration of NEURODEX for 6 days. NEURODEX has not been evaluated in patients with severe renal impairment.

For DM there was a less than 10% decrease in mean C_{max}, AUC, and CI/F in mild renal impairment, and a decrease of $\leq 12\%$ for those parameters compared to normal renal function. For DX there was a 34% and 23% increase in C_{max} and AUC, respectively in mild renal impairment and an 85% and 93% increase in C_{max} and AUC, respectively, in moderate renal impairment compared to normal renal function (reflecting a 30-58% decrease in renal clearance in moderate impairment). There was also a delay in median t_{max} by 9 hours. Subjects with moderate renal impairment had fewer adverse events than subjects with normal function or mild impairment. The 90% CI for C_{max} and AUC fell outside of the BE interval for both mild and moderate renal impairment (and for both DM and DX). The DX concentrations observed in moderate impairment remain within the range of concentrations when DM is given at an OTC dose in the absence of Q (Study 99-AVR-102).

For Q there was an approximate 30% decrease in mean C_{max} and AUC in mild renal impairment and an approximate 13% decrease in C_{max} and a 3% increase in AUC in moderate renal impairment compared to normal renal function. The 90% CI fell outside of the BE interval for both mild and moderate renal impairment compared to normal function. This decrease is not likely to impact efficacy, since all subjects with mild renal impairment had a poor metabolizer phenotype on Day 7, based on urinary DM/DX ratio. These results are in contrast however to the approved quinidine labeling that states that renal dysfunction causes the elimination of quinidine to be slowed and can lead to toxicity if dosage is not appropriately reduced. However, the approved labeling supports doses of more than 200 mg every 6 hours and that is significantly higher than the Q doses proposed for NEURODEX (30 mg every 12 hours). (For quinidine sulfate the dosing is initiated with 200 mg every six hours, and can be increased if the regimen is well tolerated and if the serum quinidine level is within the laboratory's therapeutic range).

Hepatic impairment – PK of DM, DX, and Q were evaluated in subjects with mild hepatic impairment (n=6), moderate impairment (n=6), or normal hepatic function (n=9) in Study 04-AVR-115. NEURODEX has not been evaluated in patients with severe hepatic impairment.

For DM, protein binding is approximately 60%, and therefore total DM will be considered. There was an approximate 10-13% increase in mean C_{max} and AUC in mild hepatic impairment compared to normal hepatic function. In moderate hepatic impairment there was an approximate 16% increase in C_{max} and AUC compared to normal hepatic function. These values fell outside of the BE interval. There was also a decrease in renal excretion of DM in subjects with moderate hepatic impairment. For DX, C_{max} and AUC increased less than 2% in mild impairment and < 10% in moderate impairment compared to subjects with normal hepatic function.

For Q, total concentrations will be considered rather than unbound parameters since it has a low to intermediate hepatic extraction ratio and fraction unbound > 10%. However, it is noted that in the hepatic impairment study, fraction unbound was approximately 18.8% in normal hepatic function, 21% in mild hepatic impairment, and 31% in moderate hepatic impairment. There was an approximate 3% decrease in C_{max} and a 19% decrease in AUC in mild hepatic impairment and an approximate 23% decrease in C_{max} and a 4% decrease in AUC in moderate hepatic

impairment compared to normal hepatic function. Of note, there was a 26% increase in AUC(u) for Q in moderate hepatic impairment, although there were only 3 subjects for whom sufficient data was evaluable, and therefore may not be reliable. Whether this small increase in free concentration could have resulted in additional inhibition of P-glycoprotein that would have interfered with elimination of DM (a P-gp substrate), resulting in a decrease in renal excretion of DM is unknown. According to the approved labeling of quinidine sulfate, the increased volume of distribution seen in cirrhosis leads to a proportionate increase in elimination half-life. The labeling of quinidine sulfate (that allows for initial doses of 200 mg every 6 hours) states that hepatic dysfunction can lead to quinidine toxicity if dosage is not appropriately reduced.

The most common adverse events (occurring in more than 10% of subjects) occurred more frequently in the subjects with moderate impairment.

2.3.2 Based upon what is known about exposure-response relationships and their variability, and the groups studied, healthy volunteers vs patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly - None.

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

Pediatric patients were not included in the efficacy or Phase 1 studies. The Sponsor plans to defer pediatric studies to Phase 4.

2.3.2.3 Gender – None.

2.3.2.4 Race – None.

2.3.2.5 Renal Impairment – Dosage adjustment not necessary in mild or moderate renal impairment. NEURODEX has not been studied in patients with severe renal impairment.

2.3.2.6 Hepatic Impairment – The small increase in DM exposure (10-16% increase in C_{max} and AUC in mild and moderate hepatic impairment) and the decrease in total Q exposure would not require a dosage adjustment. However, patients with moderate impairment had increased adverse events and the labeling should acknowledge this. The labeling should also state that the use of AVP-923 has not been evaluated in patients with severe hepatic impairment.

2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?

Quinidine is used in the combination to convert CYP2D6 EMs to PMs. In the small number of PM subjects evaluated, there was no substantial difference in PK of DM or DX when given in the presence or absence of quinidine. Given the lack of contribution of Q to the therapeutic

effect in PMs and the risk of QTc prolongation due to Q at the dose used in NEURODEX, there is no need for PMs to receive this combination.

2.3.2.8 What pregnancy and lactation use information is there in the application?

There is no pregnancy and lactation information in humans in this application. Information available in quinidine labeling should be extended to NEURODEX.

A review of dextromethorphan in pregnancy does not suggest that DM is a major teratogen.⁷ Although it has not been studied in lactation, it is recommended that it is probably safe to use during breast feeding.

The approved labeling of quinidine sulfate states that there are no adequate and well-controlled studies in pregnant women and that quinidine should be given to a pregnant woman only if clearly needed. The labeling also states that quinidine is present in human milk at levels slightly lower than those in maternal serum and that administration of quinidine should (if possible) be avoided in lactating women who continue to nurse. The same labeling should be extended to the NEURODEX label.

2.3.2.9 Other human factors that are important to understanding the drug's efficacy and safety

None.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on response?

According to the approved labeling of quinidine sulfate, quinidine's PK are unaffected by cigarette smoking. Effect of these extrinsic factors on DM is unknown, although since CYP1A2 does not contribute to its metabolism, it is unlikely that smoking will have an effect on exposure.

Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

None.

2.4.2 Drug-Drug Interactions

2.4.2.1 Since NEURODEX is a combination of dextromethorphan 30 mg and quinidine sulfate 30 mg has the interaction potential between these drugs been evaluated?

What is the effect of dextromethorphan on quinidine PK?

This has not been evaluated.

⁷ Briggs GG, Freeman RK, Yaffe SJ, eds. Drugs in Pregnancy and Lactation, 6th edition, Lippincott Williams & Wilkins, Philadelphia 2002.

What is the effect of quinidine on dextromethorphan PK?

Quinidine results in a 30- fold increase in DM exposure (C_{max} and AUC) following administration of approximately 30 mg Q and 30 mg DM (Study 99-AVR-100) compared to those values when DM was given alone.

2.4.2.2 *Is there an in vitro basis to suspect in vivo drug-drug- interactions?*

Yes. Q is a potent inhibitor of CYP2D6 and is a substrate for CYP3A4.

2.4.2.3 *Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?*

Dextromethorphan is a P450 substrate as described in section 2.2.5.6. The primary pathways involved in its metabolism are CYP2D6, CYP3A, and a small contribution from CYP2C9. CYP2D6 mediates O-demethylation of DM to DX and that is the basis for its combination with quinidine that inhibits CYP2D6 and increases exposure to DM. The difference between CYP2D6 EMs and PMs can be seen in the urinary DM/DX ratio that serves as the phenotype for PMs of drugs metabolized by CYP2D6. In the present submission there was very limited inclusion of PMs in the Phase I studies. In the literature, following a single 30 mg dose of DM, C_{max} was approximately 23 times greater and AUC was approximately 150 x greater in PMs than in EMs, supporting the role for pharmacogenetics.⁸

Since DM is considered to be a sensitive CYP2D6 substrate, increases in DM similar to those seen in PMs vs EMs or in EMs in the presence of quinidine would be expected with other strong inhibitors of CYP2D6.

The Sponsor has not provided information regarding the potential for CYP3A mediated inhibition of dextromethorphan metabolism. Although dextromethorphan has been evaluated as a probe drug for CYP3A-mediated metabolism, the reviewer's search of the literature did not identify any drug interaction studies *in vivo* in humans.

Quinidine is primarily metabolized by CYP3A4 as outlined in section 2.2.5.6. Its metabolism is not known to be influenced by genetics.

2.4.2.4 *Is the drug an inhibitor and/or an inducer of CYP enzymes?*

Quinidine: As previously discussed, Q is considered to be a specific and potent inhibitor of CYP2D6. In one published study using bufuralol as a substrate, the IC₅₀ of quinidine *in vitro* was reported to be 0.4 μM and another published study reported an IC₅₀ of 0.018 μM using debrisoquine as a substrate. The Sponsor believes, based on a literature review, that *in vitro* studies (discussed in the Sponsor's literature review) do not suggest significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP3A, CYP2B6, or CYP2A6. However, the substrates used in those studies are not the preferred or acceptable substrates identified in the draft guidance and therefore are difficult to interpret. An additional *in vitro* study suggested no inhibition of

⁸ Capon DA, Bochner F, Kerry N, Mikus G, Danz, C, Somogyi AA. Clin Pharmacol Ther 1996; 60:295-307.

CYP2C8.⁹ Branch et al evaluated the effect of Q (200 mg/day) on a cocktail of caffeine, mephenytoin (used as a 2C19 substrate), debrisoquine (2D6), and dapsone (used as a marker of CYP2C9, CYP2E1, CYP3A, and N-acetyltransferase) *in vivo* for 3 and 28 days. Inhibition of debrisoquine metabolism indicative of CYP2D6 inhibition was observed, but no inhibition of other substrates was observed. However, mephenytoin and dapsone are not recognized as suitable *in vivo* substrates in the draft Guidance for Industry on Drug Interaction Studies, and therefore this is not an adequate *in vivo* study.

Quinidine has not been evaluated as an inducer of P450s based on the reviewer's literature search. Several *in vitro* studies have described an "activation" of CYP3A including CYP3A-mediated hydroxylation of warfarin. The clinical relevance of this interaction with CYP3A is unknown (the approved Q labeling refers to quinidine potentiating the anticoagulant effect of warfarin requiring a reduction in dose).

DM has not been evaluated as an inhibitor or inducer of P450s. There is no information in this submission or in the literature.

2.4.2.5 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?
Quinidine is a potent inhibitor of P-gp. The IC₅₀ for inhibition of P-gp in Caco-2 cells is 2.2 μM. Quinidine at antiarrhythmic doses (where usually therapeutic plasma concentrations are 2-6 mg/L or 6.2-18.5 μM) approximately doubles the concentrations of digoxin, a P-gp substrate. The IC₅₀ for P-gp inhibition is less than 10-fold higher than the relevant plasma concentrations of quinidine after administration of NEURODEX (approximately 0.6 μM). The effect of quinidine on P-gp after administration of NEURODEX (30 mg Q twice daily) has not been evaluated.

Quinidine is also considered to be a substrate of P-gp.

Dextromethorphan has not been well characterized regarding its interaction with Pgp.

2.4.2.6 Are there other metabolic/transporter pathways that may be important in the pharmacokinetics of NEURODEX?

Dextrophan and 3-hydroxymorphinan are glucuronidated by UGT as described in section 2.2.5.6.

2.4.2.7 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

No co-administration specified.

2.4.2.8 What other co-medications are likely to be administered to the target patient population?

Study 02-AVR-107 was an open-label safety study in patients with pseudobulbar affect. The primary neurological condition was MS or ALS, and the population also included patients with

⁹ Baldwin SJ, Clarke SE, Chenery RJ. Br J Clin Pharmacol 1999; 48:424-32.

Alzheimer's disease, stroke, traumatic brain injury, and Parkinson's disease. In the study report of the 5/31/06 submission, 506 subjects had been enrolled and treated. Concomitant medications in the treatment phase included strong CYP3A inhibitors (clarithromycin or ketoconazole) in 7 subjects (1.4%) and moderate CYP3A inhibitors (diltiazem, erythromycin, fluconazole, or verapamil) in 25 subjects (4.9%), strong CYP2D6 inhibitors (fluoxetine or paroxetine) in 34 subjects (6.7%), or moderate CYP2D6 inhibitors (terbinafine) in 4 subjects (0.8%), and CYP2D6 substrates in 50 subjects (9.9%) including amitriptyline in 27 subjects (5.3%) and metoprolol in 19 subjects (3.7%), nortriptyline in 2 patients (0.4%), and timolol ophthalmic in 2 patients (0.4%). Of note, clarithromycin and erythromycin prolong the QT interval, as does quinidine. These concomitant medications reflect those in the pivotal clinical studies.

Other commonly used medications included acetaminophen (14.4%), aspirin (18.6%), baclofen (19.2%), ibuprofen (19.2%), beta interferon (13.6%), oxybutynin (10.5%), and riluzole (16%).

2.4.2.9 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Quinidine-mediated inhibition of CYP2D6: Desipramine is a CYP2D6 substrate. Study 04-AVR-112 evaluated the effect of steady state administration of AVP-923 on steady state PK of desipramine (25 mg once daily) in 13 healthy male and female volunteers, 19-42 years of age. There was an approximate 5-fold increase in mean C_{max} and a 6-fold increase in mean AUC for desipramine when given with AVP-923 compared to desipramine alone. There was evidence of increased QT prolongation during co-administration; it is unknown whether this is due to dextromethorphan or quinidine.

Other CYP2D6 inhibitors: *In vivo* interactions that alter CYP2D6-mediated metabolism of DM will not be reviewed here. There are many literature examples of phenotypic conversion of CYP2D6 EMs to PMs in the presence of strong inhibitors. They can be predicted as well from the quinidine-DM interaction. It is relevant to consider that some candidates for AVP-923 are already chronically taking strong CYP2D6 inhibitors such as fluoxetine or paroxetine that would be expected to have a similar effect on DM as does quinidine.

Inhibitors of CYP3A: Watson's approved labeling of Q states that ketoconazole (a strong CYP3A inhibitor) results in increased quinidine concentrations. The Sponsor has reviewed the literature with respect to inhibition of CYP3A-mediated Q metabolism *in vivo*. Itraconazole, a strong CYP3A inhibitor increases Q C_{max} approximately 1.6 fold and increases Q AUC approximately 2.4 fold. Erythromycin, a moderate CYP3A inhibitor increased C_{max} by approximately 39%.

2.4.2.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Quinidine: According to the approved labeling of quinidine sulfate, quinidine has anticholinergic, vasodilating, and negative inotropic actions that may be additive to those of other drugs with these effects and antagonistic to drugs with cholinergic, vasoconstricting, and positive inotropic effects. Quinidine potentiates the actions of depolarizing and nondepolarizing neuromuscular blocking agents.

Quinidine is a Class 1a antiarrhythmic drug and is known to prolong the QT interval. The combined effects of multiple agents that prolong QTc interval has not been evaluated but could be expected to have a greater effect than expected from 1 drug alone.

Dextromethorphan: The literature suggests that DM blocks 5HT reuptake and inhibits its release. Consistent with that, and with published reports of serotonin syndrome in patients taking DM,¹⁰ current warnings on OTC labeling recommend avoiding DM in patients taking MAO inhibitors.

2.4.2.11 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

- Does DM inhibit or induce P450s?
- Does DX inhibit or induce P450s?
- Is DM a substrate or inhibitor of Pgp?
- Does Q inhibit or induce P450s other than CYP2D6?

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved, and represent significant omissions?

- Can Q 10 mg q 12 hours result in enough CYP2D6 inhibition to result in a clinically significant therapeutic effect with less risk of QT prolongation compared to the 30 mg dose?
- Should all candidates for NEURODEX be genotyped for CYP2D6 prior to initiating therapy?
- Should NEURODEX be contraindicated in PMs of CYP2D6?
- Should strong CYP3A inhibitors be contraindicated?
- Should patients chronically taking strong CYP2D6 inhibitors be given NEURODEX?

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS principles), in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

There is insufficient information to determine the BCS class. The solubility has been provided for pH 2.0-7.5, but not for pH 1 for either quinidine or dextromethorphan. Although it is sufficiently soluble at the pH provided, since pH 1 has not been provided, it cannot be determined that either quinidine or dextromethorphan is highly soluble. The absolute BA of quinidine is about 70%, and it cannot be considered to be highly permeable. Permeability data for dextromethorphan has not been provided.

¹⁰ Boyer EW, Shannon M. New Engl J Med 2005; 352:1112-20.

2.5.2 *What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?*

This has not been evaluated.

2.5.2.1 *What data support or do not support a waiver of in vivo BE data?*

A biowaiver for the to-be-marketed formulation can be granted. The differences in the clinical trial formulation and the to-be-marketed formulation are due to changes in excipient grade (a Level 2 change in components and composition based on SUPAC IR) and a site change. These changes require a CASE B evaluation of dissolution (a multipoint dissolution profile in the application/compendial medium at 15, 30, 45, 60, and 120 minutes or until an asymptote is reached). In 3 different media, including the proposed dissolution medium, both quinidine and dextromethorphan from either formulation were (b) (4) dissolved at 15 minutes. Based on the similarity of these profiles and rapid dissolution of either formulation, a biowaiver can be granted.

2.5.2.2 *What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%*

Not applicable.

2.5.2.3 *If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?*

Not applicable.

2.5.3 *What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?*

BE was demonstrated for AUC and Cmax for DM and for Q following administration of NEURODEX to 18 healthy volunteers under fasting conditions or with a high fat meal in protocol 04-AVR-111. For DM, the median tmax was 1 hour later in the fed condition than in the fasted condition. For Q the median tmax was 1.5 hours later in the fed condition than in the fasted condition. NEURODEX can be taken without regard to meals.

2.5.4 *When would a fed BE study be appropriate and was one conducted?*

Not required in this case.

2.5.5 *How do the dissolution conditions and specifications assure in vivo performance and quality of the product?*

The Sponsor has provided information to determine the adequacy of the conditions (rotation speed, apparatus, and dissolution media). For both quinidine and dextromethorphan, a mean of more than (b) (4) was dissolved in 15 minutes.

The Sponsor proposed the following dissolution method and specifications based on the biobatch (C0051001) and the proposed commercial formulation (Batch GZ18M):

Apparatus: USP Apparatus 1 (Basket)
Medium: Simulated Gastric Fluid, without enzymes, pH 1.2
Volume: 900 ml
Rotation Speed: 100 rpm
Specification:
Dextromethorphan: 15 minutes: Q= (b) (4)
Quinidine: 15 minutes: Q=

The Office of Clinical Pharmacology finds the proposed dissolution method and specifications acceptable.

2.5.6 *If different-strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?*

Not applicable.

2.5.7 *If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?*

Not applicable.

2.5.8 *If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?*

Not applicable.

2.5.9 *What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?*

None.

2.6 Analytical Section

2.6.1 *How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?*

Please refer to section 2.6.4.1.

2.6.2 *Which metabolites have been selected for analysis and why?*

Dextromethorphan is considered to be the active moiety and has been measured. DX is also determined in some studies as it is used to determine phenotype in the urine analysis and also provides an exposure comparison in the setting of a “PM” phenotype compared to the “EM” phenotype. None of the quinidine metabolites have been measured.

2.6.3 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Total Q and total DM and DX have been appropriately considered since they are less than 90% protein bound. (In the renal and hepatic impairment studies, free concentrations have also been determined but are not used in the PK considerations).

2.6.4 What bioanalytical methods are used to assess concentrations?

2.6.4.1 What is the range of the standard curve and how does it relate to the requirements for the clinical studies? What curve fitting techniques are used?

Bioanalytical methods are summarized below. The calibration range was adequate to cover the range of plasma concentrations observed in most cases, and otherwise, dilution integrity was shown.

Analyte	Method	Study	Calibration Range	LOQ	Linearity
DM, plasma	(b) (4) [REDACTED] (LC/MS/MS)	99-AVR-102 01-AVR-105 02-AVR-106 02-AVF-107 04-AVR-111 04-AVR-112 04-AVR-115 04-AVR-116	0.2 ng/ml-200 ng/ml	0.2 ng/ml	1/x ² regression, linear
	(b) (4) [REDACTED]	99-AVR-100	0.2-20 ng/ml	0.2	1/x regression, linear
	(b) (4) [REDACTED]	99-AVR-101 00-AVR-103	0.2-20 ng/ml	0.2 ng/ml	1/x regression, linear
DX, plasma	(b) (4) [REDACTED] (LC/MS/MS)	99-AVR-102 01-AVR-105 02-AVR-106 02-AVF-107 04-AVR-111 04-AVR-112 04-AVR-115 04-AVR-116	2.5-2500 ng/ml	2.5 ng/ml	1/x ² regression, linear
	(b) (4) [REDACTED]	99-AVR-100	25-1000 ng/ml	25 ng/ml	1/x regression, linear
	(b) (4) [REDACTED]	99-AVR-101 00-AVR-103	2.5-500 ng/ml	2.5 ng/ml	1/x, regression, linear
DM or DX, urine	(b) (4) [REDACTED]	99-AVR-100 99-AVR-101 00-AVR-103 04-AVR-111 04-AVR-112 04-AVR-115 04-AVR-116	0.05-15.0 ug/ml	0.05 ug/ml	1/y regression, linear
Q, plasma	(b) (4) [REDACTED]	All clinical studies	0.05-10.0 ug/ml	0.05 ug/ml	1/x, regression, linear

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See Section 2.6.4.1 above.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

Selectivity was determined with respect to quinidine and hydroquinidine and internal standard for the urine DM/DX assay, with respect to quinidine, quinine, and hydroquinidine in the quinidine plasma assay, and with respect to DM, DX, and internal standard as well as other DM metabolites in DM/DX plasma assays. Accuracy and precision were within acceptable limits.

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Analyte	Method	Freeze-thaw	In process	Autosampler	Long-term stability
DM/DX, plasma	(b) (4) (LC/MS/MS)	6 cycles	31 hours at room temperature	183 hours	101 weeks at -20° C
	(b) (4)	3 cycles	22.5 hrs at room temperature	42 hours	5 days to 22 months at -20° C
	(b) (4)	6 cycles	22.5 hrs at room temperature	113 hours (reinjection reproducibility)	22 months at -20° C
DM or DX, urine	(b) (4)	3 cycles	6 hours (benchtop)	48 hours at room temperature	34 months at -20° C
Q, plasma	(b) (4)	6 cycles	24.5 hours at room temperature	47 hours	129 weeks at -20° C

2.6.4.5 What is the QC sample plan?

Duplicate QC standard replicates and 1 calibration curve were run with each batch of study samples analyzed.

3 Detailed labeling recommendations

Please refer to Appendix 4.1 for OCP labeling recommendations.

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

4.2.1 BIOANALYTICAL METHOD FOR DM AND DX IN HUMAN URINE

Bioanalytical Method (12730) for Dextromethorphan and Dextrorphan in Human Urine in NDA 21-879

Analysis of urine concentrations of dextromethorphan (DM) and dextrorphan (DX) was performed using HPLC/ (b) (4)

Standard operating procedures (SOPs) were in place.

Selectivity, Accuracy, Precision, and Recovery

Selectivity was with respect to unextracted quinidine and hydroquinidine. (b) (4)

Ranges of the calibrations curves, LOQ for each analyte, and nominal values for the QC samples are shown in Table 1 below.

Table 1. Summary of standard curves and QC samples for method validation for DM and DX

Analyte	Range of Calibration Curve	LOQ	QC Samples
DM or DX	0.05 µg/ml 0.1 µg/ml 0.25 µg/ml 0.75 µg/ml 2. µg/ml 7.5 µg/ml 12.0 µg/ml 15.0 µg/ml	0.05 µg/ml	0.150 µg/ml 1.0 µg/ml 12.0 µg/ml

A calibration curve consisted of 8 non-zero standards run in singlicate. In addition, the SOP for the method specified inclusion of a blank and a zero sample for each analytical run. Six sets of calibration curves were performed. Linearity was established for each analyte ($r > 0.998$, linear weighted $1/y$ regression analysis where $y = \text{ratio of compound}$

peak height/area to internal standard peak height/area). The accuracy and precision for each nonzero standard ranged from -10.1 to 5.2% and from 1.9 to 7.0%, respectively, and are therefore acceptable.

Accuracy and precision were analyzed on one assay day for 6 replicates of each of the 3 quality control (QC) concentrations listed above. The intra-day accuracy and precision ranged from -7.3 to 5.0% and from 1.7% to 5.5%, respectively. Six sets of QC samples (run in duplicate) were used to determine inter-assay accuracy and precision that ranged from -5.3% to 2.0% and from 2.6% to 4.2% (as calculated by reviewer), respectively. These values are acceptable.

Stability

Stability of DM and DX at low, medium, and high quality control concentrations in urine was demonstrated as follows. (High QC was 10 or 12 µg/ml in these studies). Freeze-thaw stability was demonstrated after three freeze/thaw cycles. In-process stability was demonstrated for 6 hours at room temperature. Autosampler stability of extracted samples was demonstrated for approximately 48 hours at room temperature. Long term stability was demonstrated for 34 months at -20° C. Processed spiked samples were stable for 72 hours at 2-8° C. Stability of solutions of standards was not described. (However, there is no reason to believe that this would be different than the QC samples).

In conclusion, the bioanalytical method used for analysis of plasma samples in the clinical studies in NDA 21-617 is considered adequately documented and validated.

4.2.2 BIOANALYTICAL METHOD FOR NON-HYDROLYZED DM AND DX IN PLASMA

Bioanalytical HPLC Method (12730-2.01) for Determination of Non-Hydrolyzed DM and DX in Human Plasma in NDA 21-879

Analysis of plasma concentrations of non-hydrolyzed DM and DX was performed using an HPLC (b) (4)

[Redacted]

Standard operating procedures (SOPs) were in place.

Selectivity, Accuracy, Precision, and Recovery

Selectivity was demonstrated with respect to DM, DX and (b) (4)

Ranges of the calibration curves, LOQ, and nominal values for the QC samples are shown in Table 1 below.

Table 1. Summary of standard curves and QC samples for method validation for DM & DX

Analyte	Range of Calibration Curve	LOQ	QC Samples
DM	0.2 ng/ml 0.5 ng/ml 1.0 ng/ml 2.0 ng/ml 5.0 ng/ml 10 ng/ml 18 ng/ml 20 ng/ml	0.2 ng/ml	0.6 ng/ml 3.5 ng/ml 15 ng/ml
DX	25 ng/ml 50 ng/ml 100 ng/ml 200 ng/ml 400 ng/ml 500 ng/ml 850 ng/ml 1000 ng/ml	25 ng/ml	75 ng/ml 350 ng/ml 750 ng/ml

A calibration curve consisted of 8 non-zero standards run in singlicate. Five sets of calibration curves were performed. Linearity was established ($r > 0.997$, linear weighted $1/x$ regression analysis where $x = \text{conc}$). For DM the accuracy and precision for each nonzero standard ranged from -6.3 to 4.9% and from 1.5 to 2.9%, respectively, and are

therefore acceptable. For DX the accuracy and precision ranged from -3.8% to 2.7% and from 1.5% to 4.2%, respectively and are acceptable.

For DM, accuracy and precision were analyzed on one assay day for 6 replicates of each of the 3 quality control (QC) concentrations listed above. The intra-day accuracy and precision ranged from 6.8 to 8.5% and from 1.4% to 4.0%, respectively. Five sets of QC samples (run with 6 samples per set) were used to determine inter-assay accuracy and precision that ranged from 4.8% to 8.3% and from 3.4% to 5.6%, respectively. These values are acceptable.

For DX, accuracy and precision were analyzed on one assay day for 6 replicates of each of the 3 quality control (QC) concentrations listed above. The intra-day accuracy and precision ranged from 3.0 to 3.7% and from 1.0% to 1.5%, respectively. Five sets of QC samples (run with 6 samples per set) were used to determine inter-assay accuracy and precision that ranged from 1.2% to 1.8% and from 3.7% to 4.1%, respectively. These values are acceptable.

Stability

Stability of DM and DX at low, medium, and high quality control concentrations was demonstrated as follows. Freeze-thaw stability in plasma was demonstrated after three freeze/thaw cycles. In-process stability was demonstrated in human plasma for 22.5 hours at room temperature. Autosampler stability of extracted samples was demonstrated for approximately 36 hours at room temperature. Reinjection stability was shown 42 hours after the original injection. Long term stability in plasma was demonstrated for 5 days at -20° C. (During the analysis for Study 99-AVR-100, long-term stability for DX was demonstrated for 22 months. At 22 months the DM was 85% of the initial analysis.) Processed spiked samples were stable for 66.5 hours at 2-8° C. Stability of solutions of standards was not described. (However, there is no reason to believe that this would be different than the QC samples). Dilution integrity was shown for a 10-fold dilution of dextromethorphan and of dextropropriofen.

Recovery of DM was 96.5% and for internal standard ((b)(4)) was 86.2%. Recovery for DX was 93.3%.

In conclusion, the bioanalytical method used for analysis of DM and DX in non-hydrolyzed plasma samples by HPLC in the clinical studies in NDA 21-879 is considered adequately documented and validated.

4.2.3 BIOANALYTICAL METHOD FOR HYDROLYZED DM AND DX IN PLASMA

Bioanalytical HPLC Method (12730-3.01) for Determination of Hydrolyzed DM and DX in Human Plasma in NDA 21-879

Analysis of plasma concentrations of hydrolyzed DM and DX was performed using an HPLC method (b) (4)

[Redacted]

Standard operating procedures (SOPs) were in place.

Selectivity, Accuracy, Precision, and Recovery

Selectivity was demonstrated with respect to DM, DX and (b) (4)

[Redacted]

Ranges of the calibrations curves, LOQ, and nominal values for the QC samples are shown in Table 1 below for each analyte.

Table 1. Summary of standard curves and QC samples for method validation for DM and DX

Analyte	Range of Calibration Curve	LOQ	QC Samples
DM	0.2 ng/ml 0.5 ng/ml 1.0 ng/ml 2.0 ng/ml 5.0 ng/ml 10 ng/ml 18 ng/ml 20 ng/ml	0.2 ng/ml	0.6 ng/ml 3.5 ng/ml 15 ng/ml
DX	2.5 ng/ml 5.0 ng/ml 10.0 ng/ml 25.0 ng/ml 50.0 ng/ml 100 ng/ml 200 ng/ml 400 ng/ml 500 ng/ml	2.5 ng/ml	7.5 ng/ml 75 ng/ml 350 ng/ml

A calibration curve included 8 non-zero standards for DM and 9 non-zero standards for DX run in singlicate. Five sets of calibration curves were performed. Linearity was

established ($r > 0.997$, linear weighted $1/x$ regression analysis where $x = \text{conc}$). The accuracy and precision for each nonzero standard for DM ranged from -6.4 to 13.1% and from 2.5 to 6.1%, respectively, and are therefore acceptable. The accuracy and precision for each nonzero standard for DX ranged from -1.8 to 2.0% and from 0.2 to 4.5%, respectively, and are therefore acceptable.

Accuracy and precision were analyzed on one assay day for 4 replicates of each of the 3 quality control (QC) concentrations listed above. For DM the intra-day accuracy and precision ranged from 2.7 % to 12.8% and from 0.5% to 2.3%, respectively. For DX the intra-day accuracy and precision ranged from 2.6% to 5.3% and from 0.7% to 1.5%, respectively. Five sets of QC samples (run with 4 samples per set) were used to determine inter-assay accuracy and precision that ranged from -0.6% to 12.1% and from 4.1% to 7.5%, respectively for DM and from 2.0% to 5.7% and from 1.6% to 2.0%, respectively for DX. These values are acceptable.

Stability

Stability of DM and DX at low, medium, and high quality control concentrations was demonstrated as follows. Freeze-thaw stability in plasma was demonstrated after six freeze/thaw cycles. In-process stability was demonstrated in human plasma for 22.5 or 28 hours at room temperature of DX at QC 7.5 ng/ml and was otherwise determined in method HL 12730_2.01. Processed samples were stable for 289 hours at 2-8° C. Stability of solutions of standards was not described. Autosampler stability of extracted samples was not directly addressed. However, reinjection reproducibility was shown for reinjection at 113 hours after the original injection. Long term stability in plasma had been demonstrated for 22 months at -20° C (85-87% for DM and 96% for DX) in the analysis of samples using 12730_2.01 in 99-AVR-001.

Recovery of DM was 88%, of DX was 90%, and of internal standard ((b)(4)) was 88%.

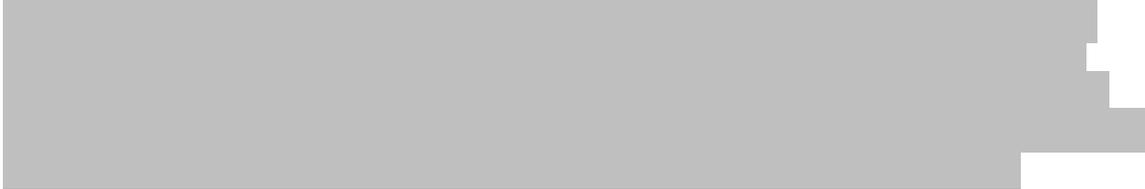
Dilution integrity was shown for a 10-fold dilution of dextromethorphan and of dextrophan in the same method that used (b)(4) as internal standard (12730-2.01).

In conclusion, the bioanalytical method used for analysis of DM and DX in hydrolyzed plasma samples by HPLC in the clinical studies in NDA 21-879 is considered adequately documented and validated.

4.2.4 BIOANALYTICAL METHOD (LLC-MS/MS) FOR DM AND DX IN PLASMA

Bioanalytical LC-MS/MS Method (26267) for Determination of Hydrolyzed DM and DX in Human Plasma in NDA 21-879

Analysis of plasma concentrations of hydrolyzed DM and DX was performed using an LC-MS/MS method. Following enzymatic hydrolysis with β -glucuronidase, DM, DX and the internal standards (b) (4)



Standard operating procedures (SOPs) were in place for sample preparation, the analytical procedure, for acceptance of the bioanalytical run.

Selectivity, Accuracy, Precision, and Recovery

Selectivity was demonstrated against (b) (4)

Ranges of the calibrations curves, LOQ, and nominal values for the QC samples are shown in Table 1 below.

Table 1. Summary of standard curves and QC samples for method validation for DM & DX

Analyte	Range of Calibration Curve	LOQ	QC Samples
DM	0.2 ng/ml 0.5 ng/ml 1.0 ng/ml 2.0 ng/ml 10 ng/ml 20 ng/ml 40 ng/ml 100 ng/ml 175 ng/ml 200 ng/ml	0.2 ng/ml	0.6 ng/ml 15 ng/ml 150 ng/ml
DX	2.5 ng/ml 5.0 ng/ml 25 ng/ml 50ng/ml 200 mg/ml 500 ng/ml 1000 ng/ml 1500 ng/ml	2.5 ng/ml	7.5 ng/ml 250 ng/ml 1875 ng/ml

	2000 ng/ml		
	2500 ng/ml		

A calibration curve consisted of 10 non-zero standards run in singlicate. Six sets of calibration curves were performed. Linearity was established ($r > 0.997$, linear weighted $1/x^2$ regression analysis where $x = \text{conc}$). For DM the accuracy and precision for each nonzero standard ranged from -9.0 to 5.1% and from 1.7 to 9.0%, respectively, and are therefore acceptable. For DX the accuracy and precision ranged from -5.0% to 3.3% and from 1.3% to 6.0%, respectively and are acceptable.

For DM, accuracy and precision were analyzed on one assay day for 6 replicates of each of the 3 quality control (QC) concentrations listed above. The intra-day accuracy and precision ranged from 0 to 2.9% and from 4.1% to 4.6%, respectively. Six sets of QC samples (run with 6 or 12 samples per set) were used to determine inter-assay accuracy and precision that ranged from 2.7% to 4.0% and from 3.9% to 6.2%, respectively. These values are acceptable.

For DX, accuracy and precision were analyzed on one assay day for 6 replicates of each of the 3 quality control (QC) concentrations listed above. The intra-day accuracy and precision ranged from 3.0 to 3.7% and from 1.0% to 1.5%, respectively. Five sets of QC samples (run with 6 or 12 samples per set) were used to determine inter-assay accuracy and precision that ranged from -0.4% to 2.5% and from 5.0% to 6.1%, respectively. These values are acceptable.

Stability

Stability of DM and DX at low, medium, and high quality control concentrations was demonstrated as follows. Freeze-thaw stability in plasma was demonstrated after six freeze/thaw cycles. In-process stability was demonstrated in human plasma for 31 hours at room temperature. Long term stability in plasma (>96%) was demonstrated for 47 days at -20°C (and in the assay report for Study 04-AVR-115 long term stability has been shown for 101 weeks). Autosampler stability was not evaluated although re-injection stability was shown 183 hours after the original injection. Processed spiked samples were stable for 199 hours at $2-8^\circ \text{C}$. Stability of solutions of standards was not described although had previously been determined. Dilution integrity was demonstrated for 10-fold and 100-fold dilution factors for dextromethorphan and for dextrorphan.

Recovery was as follows:

DM	85-101%
DX	89-102%
d_3 -DM	91%
d_3 -DX	92%

In conclusion, the LC-MS/MS bioanalytical method used for analysis of DM and DX in hydrolyzed plasma samples by HPLC in the clinical studies in NDA 21-879 is considered adequately documented and validated.

4.2.5 BIOANALYTICAL METHOD FOR QUINIDINE IN PLASMA

Bioanalytical Method for Determination of Quinidine in Human Plasma in NDA 21-879 (Method 22004-1)

Analysis of plasma concentrations of quinidine was performed using an HPLC method with mass spectrometric detection. Aliquots of plasma are combined with internal standard (quinine) and extracted from plasma by protein precipitation with acetonitrile. The supernatants were diluted with water before injection onto the HPLC column. The method was developed and performed at (b) (4)

Standard operating procedures (SOPs) were in place for sample preparation, the analytical procedure, for acceptance of the bioanalytical run (acceptance of calibration standards and quality control (QC) samples).

Selectivity, Accuracy, Precision, and Recovery

Selectivity was addressed using 6 lots of blank control (b) (4) plasma in which no significant interference at the retention time of quinidine was observed with respect to quinidine, quinine, or hydroquinidine which is present in commercial sources of quinidine.

Ranges of the calibrations curves, LOQ for each analyte, and nominal values for the QC samples are shown in Table 1 below.

Table 1. Summary of standard curves and QC samples for method validation for Q

Analyte	Range of Calibration Curve	LOQ	QC Samples
Quinidine	0.05 µg /ml 0.1 µg /ml 0.2 µg /ml 0.75 µg /ml 2.0 µg /ml 5.0 µg /ml 8.0 µg /ml 10.0 µg /ml	0.05 µg/ml	0.15 µg /ml 1.5 µg /ml 7.5 µg /ml

A calibration curve included 8 non-zero standards run in singlicate. Seven sets of calibration curves were performed. Linearity was established ($r > 0.998$, linear weighted $1/x$ regression analysis where $x = \text{conc}$). The accuracy and precision for each nonzero standard ranged from -1.9 to 2.0% and from 0.6 to 3.9%, respectively, and are therefore acceptable.

Accuracy and precision were analyzed on one assay day for 6 replicates of each of the 3 quality control (QC) concentrations listed above. The intra-day accuracy and precision ranged from 2.0 to 2.7% and from 0.5% to 1.9%, respectively. Seven sets of QC

samples (run with 6 samples per set) were used to determine inter-assay accuracy and precision that ranged from 1.1% to 4.0% and from 1.9% to 2.5%, respectively. These values are acceptable.

Stability

Stability of quinidine at low, medium, and high quality control concentrations was demonstrated as follows. Freeze-thaw stability in plasma was demonstrated after six freeze/thaw cycles. In-process stability was demonstrated in human plasma for 24.5 hours at room temperature. Stability of processed samples was demonstrated at 2-8° C for at least 74 hours. Autosampler stability of extracted samples was addressed by reinjection reproducibility. Reinjection reproducibility was shown for reinjection at least 47 hours after the original injection. Long term stability in plasma was demonstrated for 129 weeks at -20° C. Stability of solutions of quinidine stock solution was shown for 131 weeks at 5° C. Dilution Integrity was shown for 10-fold and 20-fold dilution.

Recovery of quinidine was 88% and for internal standard was 93%.

In conclusion, the bioanalytical method used for analysis of quinidine in plasma samples in the clinical studies in NDA 21-879 is considered adequately documented and validated.

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4.2.7 DETERMINATION OF QUINIDINE DOSE

CLINICAL PHARMACOLOGY STUDY TO DETERMINE THE LOWEST DOSE OF QUINIDINE WHICH PROTECTS DEXTROMETHORPHAN FROM DEGRADATION BY CYTOCHROME P4502D6

Study Investigators and Site:



Protocol Number: 99-AVR-100

Note: The Sponsor states that the amount of Q used in 99-AVR-100 was calculated on the basis of quinidine sulfate, although the quinidine drug substance contained approximately (b) (4) dihydroquinidine. Therefore the 25 mg Q dosage strength is equivalent to approximately 28.8 mg Q.

OBJECTIVES:

1. To determine the lowest dose of quinidine (Q) which inhibits the conversion of dextromethorphan (DM) to dextrophan (DX)
2. To chronicle the occurrence of side effects during administration of dextromethorphan/quinidine

FORMULATIONS:

Table 1. Products used in 99-AVR-100

	Use in Study	Lot Number	Date of Manufacture (Dates of Study)
Dextromethorphan hydrobromide (HBr) 30 mg capsules (b) (4)	Phenotyping & Quinidine Dose Determination Part A	981203-1	12/3/98 (4/4/99-4/19/99)
Dextromethorphan HBr 30 mg/Quinidine Sulfate 2.5 mg capsules (b) (4)	Quinidine Dose Determination Part B	981210-2	12/14/98 (4/4/99-4/19/99)
Dextromethorphan HBr 30 mg/Quinidine Sulfate 10 mg capsules (b) (4)	Quinidine Dose Determination Part C	981214-1	12/14/98 (4/4/99-4/19/99)
Dextromethorphan HBr 30 mg/Quinidine Sulfate 25 mg capsules (b) (4)	Quinidine Dose Determination Part D	981215-1	12/15/98 (4/4/99-4/19/99)
Dextromethorphan HBr 30 mg/Quinidine Sulfate 50 mg capsules (b) (4)	Quinidine Dose Determination	981216-1	12/17/98 (4/4/99-4/19/99)

Part E			
Dextromethorphan HBr 30 mg/Quinidine Sulfate 75 mg capsules	Quinidine Dose Determination	981217-1	12/17/98 (4/4/99-4/19/99)
(b) (4)	Part F		

The Sponsor states that the expiration dates were not available.

STUDY DESIGN:

Part 1 was an open-label single-dose study in which subjects who met entry criteria received a single 30 mg dose of dextromethorphan HBr with 240 ml of tap water for phenotyping. Subjects were to empty their bladders and have a 5 ml blood sample drawn for measurement of plasma DM and DX before dosing (pre-dose sample). Subjects were to remain at the clinic for 8 hours post dose for additional blood samples (2, 4, and 8 hours post-dose) and urine collection (up to 12 hours post-dose).

Part 2 was an open-label, randomized, multiple dose quinidine dose-ranging study in subjects identified as dextromethorphan (CYP2D6) extensive metabolizers (EM) in Part 1. By convention, a DM/DX urinary ratio of 0.3 or greater defines a poor metabolizer. Subjects were to be ranked by their DM/DX metabolic ratio and then randomized in blocks of 6 for assignment to treatment groups (A through F as shown above) following a washout-period of at least 2 days after Part 1. Subjects received an evening dose on Day 1, doses at 12 hour intervals for the next 6 days, and a final morning dose on Day 8. Subjects self-medicated on Day 2 (PM), Day 3 (AM), Day 4 (PM), Days 5 and 6 (AM and PM) and Day 7 (AM). All other doses were administered in the clinic. All subjects were instructed to dose themselves and were queried about their compliance and asked to provide a log documenting medication usage. After administration of the first, fifth, and thirteenth dose, urine was collected for 12 hours for determination of DM and DX. A blood sample was drawn for determination of plasma DM and DX before the fourteenth (last) dose (pre-dose sample). Following the last dose, blood was collected for determination of plasma DM, DX, and quinidine at 2, 4, and 8 hours post-dose. Plasma and aliquots of urine samples were stored frozen at -20° C until analyzed.

Inclusion criteria included healthy males or females, 18 years of age or older with normal resting ECG and hematologic, hepatic, and renal function, and no clinically significant deviations from standard laboratory tests (CBC, SMA-12, and urinalysis). Exclusion criteria included known sensitivity to Q or opiates and subjects who had taken medication within the last 14 days. Concomitant medications were not allowed except for oral contraceptives. Subjects were required to refrain from eating or drinking grapefruit products while participating in the study.

ASSAY:

Urine DM and DX

Table 2. Performance of Analytical Method for 99-AVR-100 for Urine DM and DX

Analyte	Method	Calibration Standards (µg/ml)	Linearity	LOQ (µg/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
DM	HPLC/ Fluorescence Detection	0.05-15.0 µg/ml	r > 0.999	0.05	0.15	5.47	1.07
					1.0	3.6	-2.29
					12.0	3.77	-3.06
DX	HPLC/ Fluorescence Detection	0.05-15.0 µg/ml	r > 0.999	0.05	0.15	3.53	1.93
					1.0	3.28	-0.98
					12.0	4.51	-2.39

One calibration curve with 8 non-zero standards and duplicate QC samples were analyzed with each batch of study samples for Study 99-AVR-100 for detection of DM and DX in urine. For the calibration curves, a weighted (1/conc) linear regression was used. Study samples were stored at -20° C. Samples were analyzed within approximately 1 month from the beginning of sample collection; this is within the period for which the samples are stable at -20° C. All of the calibration standards were within 15% of the nominal value (20% for LOQ). All of the QC samples were within 15% of their respective nominal values. The performance of the assay is considered acceptable.

Plasma DM and DX

Table 3. Performance of Analytical Method for 99-AVR-100 for Plasma DM and for Plasma Q

Analyte	Method	Calibration Standards (µg/ml)	Linearity	LOQ	QC	Inter-assay CV (%)	Inter-assay Accuracy (%)
DM	HPLC/ Fluorescence Detection	0.2-20.0 ng/ml	r > 0.998	(ng/ml)	(ng/ml)		
				0.02	0.6	3.03	10.0
					3.5	2.29	-2.29
				15	2.18	-2.33	
Q	HPLC	0.05-10.0 µg/ml	r>0.999	µg/ml	µg/ml		
				0.05	0.15	3.45	-3.33
					1.5	2.15	-3.8
				7.5	1.10	-3.97	

On analysis of the data it was determined that all DX concentrations were < 25 ng/ml. It was determined that DX is primarily conjugated, and that the assay only determines the unconjugated form. Therefore, only DM results were reported in plasma.

DM

In the present analytical report, stability of at least 22 months is reported, although for DM the mean at 22 months was 85% of the initial analysis (96% for DX). Subsequent validation of an LC-MS/MS method ((b) (4) 27267_1) showed DM stability in frozen plasma for 47 days at -20° C (>100% of control). Samples were analyzed within approximately 25 days from the beginning of the study collection. Although the method was originally validated for (b) (4) as internal standard, the present assay used (b) (4) as internal standard. One calibration curve (with 8 nonzero standards) and duplicate QC samples were analyzed with each batch of study samples for Study 99-AVR-100 for detection of DM and DX in plasma. For DM all but 1 of the calibration standards were within 15% of the nominal value (20% for LOQ). For DM at least 4 out of 6 QC samples in each run were within 15% of their respective nominal values. In addition, a dilution factor of 50 was demonstrated to be acceptable. The performance of the assay is considered acceptable.

Quinidine

Samples were analyzed within the time that they are stable. One calibration curve with 8 nonzero standards and duplicate or triplicate QC samples were analyzed with each batch of study samples for detection of Q in plasma. For Q all of the QC samples in each run and all of the calibration standards were within 15% of their respective nominal values.

RESULTS:

Demographics

In Part 1, 50 subjects were dosed with dextromethorphan (25 female and 25 male). Forty-six subjects enrolled in Part 2 (24 female, 22 male). However 1 subject (subject 23, 86 y.o. female) discontinued because she could not tolerate the AEs from DM/Q, and 45 subjects completed. Demographics of the subjects completing the study are shown in the table below.

Table 4. Demographics of Subjects Completing Study AVR-100

	Mean Age (Range)	Weight (mean ± SD)	2D6 Phenotype	Race
Study Part 1	51 (20-86)	74.5 ± 12.6 kg (n=50)	46 EM	Asian 2
		81.6 ± 10.7 kg (male)	4 PM	Black 3
		67.9± 10.6 kg (female)		Caucasian 39
Study Part 2	50 (20-84)	74.5 ± 12.3 kg (n=45)	45 EMs	Hispanic 5
		81.1 ± 10.1 kg (male)		American Indian 1
		68.3± 11.0 kg (female)		Asian 3
				Black 2
				Caucasian 36
				Hispanic 4

Concomitant medications included ibuprofen, aspirin, and acetaminophen; these are not known to interact with CYP2D6.

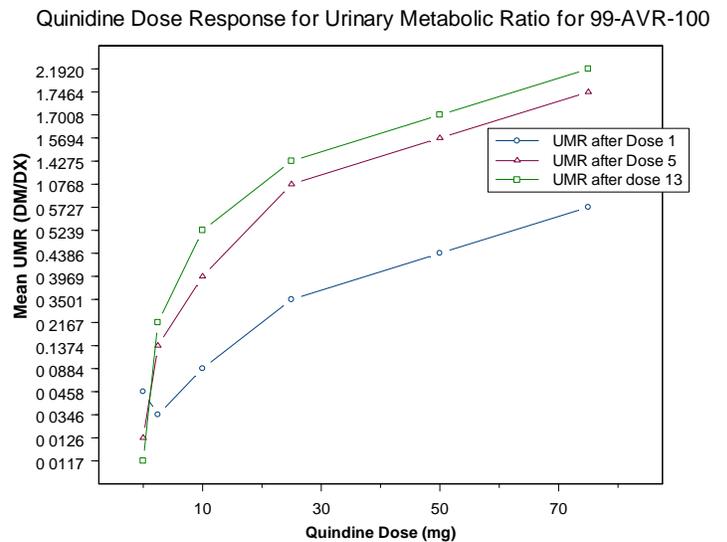
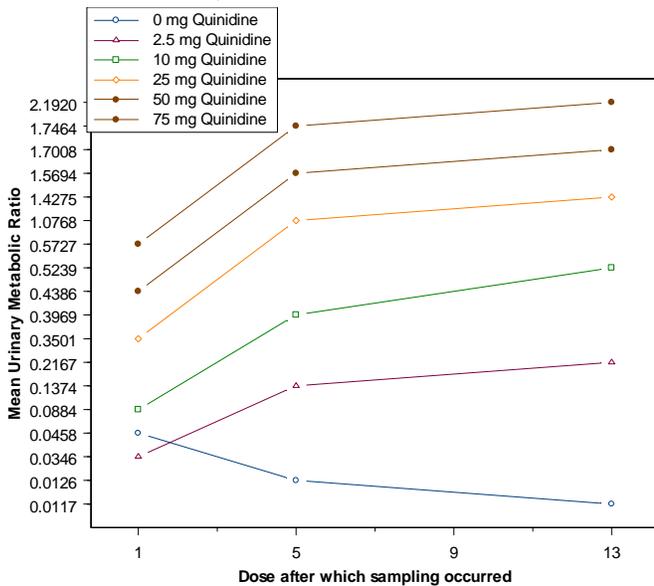
Baseline Phenotype

In Part 1, 4 subjects were identified as poor metabolizers (PMs) of DM. Maximum observed plasma DM concentrations after the single dose ranged from 11.7 to 18.8 ng/ml in the PMs. For the subjects identified as EMs, the metabolic ratios ranged from 0-0.133. Maximum observed plasma DM concentrations after the single dose ranged from 0.21 to 7.63 ng/ml in the EMs. (*Of note*, ultrarapid metabolizers (URM) are generally characterized with a urinary metabolic ratio for DM to DX that is < 0.003. Thirty-one of the 48 EMs that enrolled in Part 2 (64%) had ratios < 0.003, according to data provided by the Sponsor. This is higher than generally observed (up to 10% in Caucasians and 29% in black Ethiopians)). Three subjects enrolled in part 2 did not have baseline urine DM/DX ratios; on Dose 1 of Part 2 all three were considered to be EMs (and 2 meet the definition of URM).

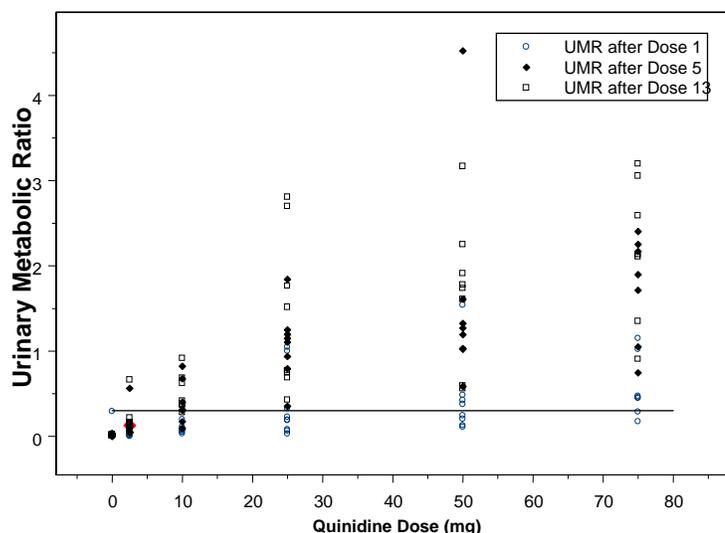
Quinidine/Dextromethorphan Pharmacokinetic Results

In Part 2, subject 22 received Treatment A for 5 days and Treatment F for the remainder of the study. The results for this subject have been included in the analysis.

The results of the urinary metabolic ratio, used to determine CYP2D6 phenotype after concomitant administration of Quinidine and dextromethorphan, are shown in the figures below (as plotted by reviewer). Means represent arithmetic mean (as calculated by reviewer).



Urinary Metabolic Ratio for 99-AVR-100



The figure at left, shows the range of metabolic ratios for a given quinidine dose, and after 1, 5, or 13 doses. The solid line represents the metabolic ratio for discriminating between CYP2D6 EMs and PMs.

Table 5. Urinary Metabolic Ratio (DM/DX, arithmetic mean) After Specified Doses (Study 99-AVR-100)

Quinidine Dosage (mg)	Dose 1 (% CV)	Dose 5 (% CV)	Dose 13 (% CV)
0	0.05 (218)	0.01 (105)	0.01 (65)
2.5	0.03 (115)	0.14 (128)	0.22 (93)
10	0.09 (61)	0.40 (66)	0.52 (43)
25	0.35 (112)	1.08 (39)	1.42 (65)
50	0.44 (106)	1.6 (78)	1.7 (49)
75	0.57 (64)	1.75 (36)	2.19 (39)

Table 6. Number of Subjects Converted to PM Phenotype in 99-AVR-100 (as provided by Sponsor)

Quinidine Dose	Number Converted (UMR \geq 0.3) / Total Number		
	Dose 1	Dose 5	Dose 13
0	0/7	0/7	0/7
2.5	0/8	1/8	1/7

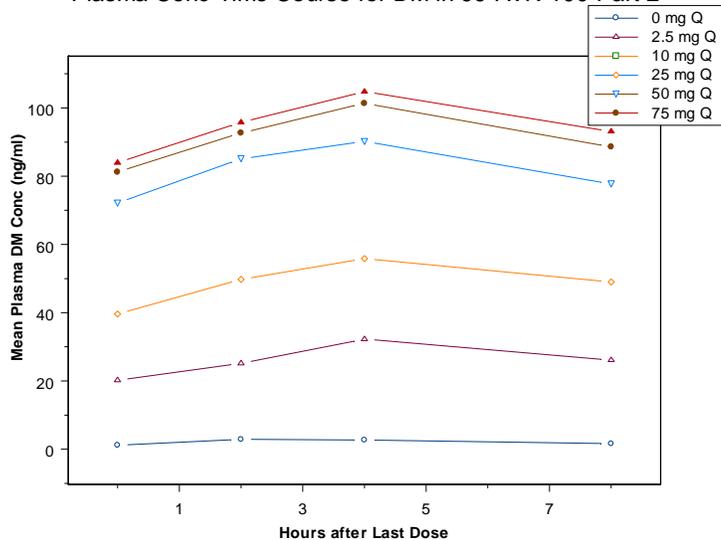
10	0/7	5/7	6/7
25	2/8	8/8	8/8
50	4/8	8/8	8/8
75	5/8	7/7	7/7

The 25 mg quinidine dose was the lowest dose at which all subjects converted to the PM phenotype. Large variability is observed in the UMR, especially at the lower doses of quinidine. There is an increase in UMR with increasing quinidine doses. The sponsor has performed ANOVA for UMR followed by the Tukey test and reports that after Dose 1, the 50 mg dose was significantly different from the 0 and 2.5 mg doses, and the 75 mg quinidine dose was significantly different from doses up to 10 mg. After the 5th dose and after the 13th dose, the 25 mg quinidine dose was significantly different from the 0 and 2.5 mg doses, and the 50 and 75 mg doses were significantly different from the lowest 3 doses. The UMR with the quinidine 25 mg dose was not statistically significantly different from either the 10 mg dose or the 50 and 75 mg doses at any time point.

Dextromethorphan Plasma Concentrations

Mean DM plasma concentrations are shown in the figure at right (as plotted by reviewer). The Sponsor has expressed the results of the DM plasma concentrations as C_{max} and AUC₀₋₈. The plasma concentration time course represents only limited samples and doesn't truly reflect the C_{max}. However, the table below allows for some comparison of the range of plasma concentrations and variability. The results in the table below are expressed as arithmetic mean (%CV).

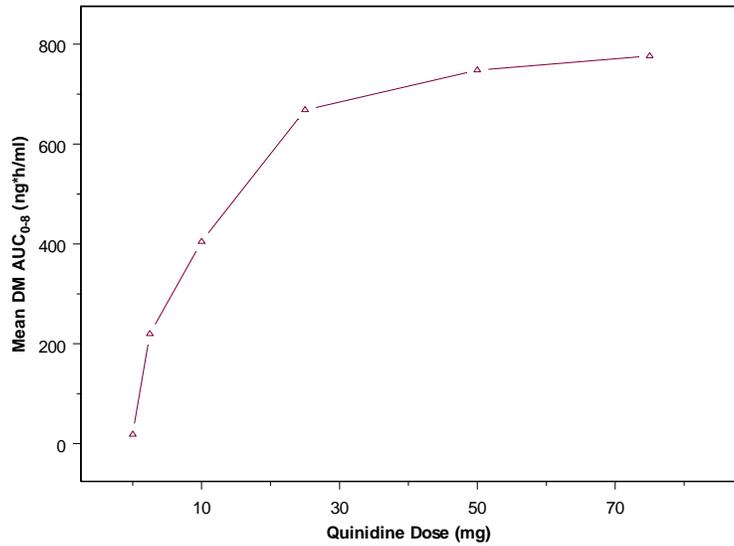
Plasma Conc-Time Course for DM in 99-AVR-100 Part 2



	Quinidine Dose (mg)					
	0	2.5	10	25	50	75
C_{max} (ng/ml)	3.1 (92)	32.2 (73)	57.1 (30)	91.4 (21)	101.8 (26)	105.2 (20)
AUC₀₋₈ (ng*hr/ml)	18.3 (97)	219.5 (78)	404.8 (30)	668.4 (22)	747.9 (28)	776.2 (19)

The results in the table above, and expressed in the figure at right, show that Q doses of 2.5-26 mg result in an approximate 10-35-fold increase in DM exposure compared to DM given alone. However, with quinidine doses of 2-3 fold greater than 25 mg, the increase in mean DM in plasma was less than approximately 15%.

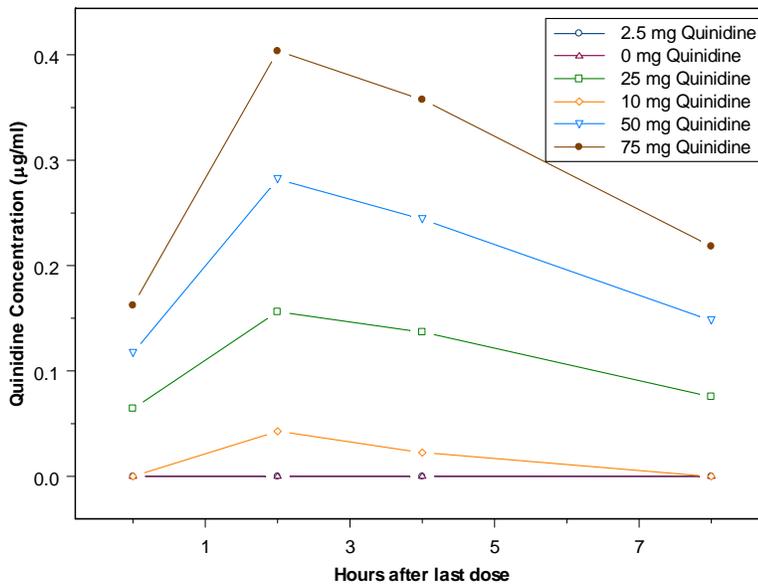
Quinidine Dose vs DM Exposure in 99-AVR-100 Part 2



PK results for quinidine by dose level (on the last day of dosing) are shown in the table below, as calculated by the Reviewer, and mean plasma concentrations at the time points evaluated are shown in the figure at right. For the PK parameters, results are shown as arithmetic mean (%CV), except for T_{max} that shows median and range. For the 2.5 mg dose, the plasma concentrations were generally below the limit of quantitation.

Quinidine Dose	T _{max} (hrs)	C _{max} (ug/ml)	AUC last (ug*hr/ml)	AUC inf (ug*hr/ml)	t 1/2 (hrs)
10 mg	2.0 (2.0-4.0)	0.04 (69)	.09 (90)	ND	ND
25 mg	2.0 (2.0-4.0)	0.16 (31)	0.92 (40)	1.85 (24)	6.1 (13)
50 mg	2.0 (2.0-4.0)	0.29 (35)	1.71 (30)	2.87 (38)	5.7 (20)
75 mg	2.0 (2.0-4.0)	0.41 (12)	2.48 (11)	4.49 (16)	6.5 (20)

ND=not determined



Safety

During Part 1 of the study (30 mg DM), one AE (headache) was reported. In Part 2, there were 150 AEs experienced by 74 of the subjects. There was 1 serious AE in which a subject (86 y.o. female) experienced protracted vomiting after 4 doses of DM 30 mg/Q 75 mg. She was discontinued from the study. Two days later she went to an emergency room and was admitted to the hospital with dehydration and continued vomiting. On the third day of hospitalization she was noted to have a firm bloated abdomen; ultrasound and CT revealed mechanical bowel obstruction. She aspirated and coded and suffered myocardial damage and died. The remained of the AEs were classified as mild (96%) or moderate. The most frequently reported AEs included headache, loose stool, lightheadedness, dizziness, and nausea. There were more AEs reported in the DM/Q groups than in the DM/0mg quinidine group. A clear difference between the Q dose groups in terms of adverse events was not apparent.

CONCLUSIONS:

This study demonstrated that repeated doses of quinidine 25 mg (28.8 mg) given every 12 hours with 30 mg dextromethorphan converted 8/8 CYP2D6 phenotypic extensive metabolizers (EMs) to poor metabolizers (PMs) as defined by a urinary dextromethorphan/dextrorphan ratio of ≥ 0.3 .

Dextromethorphan plasma concentrations increased less than approximately 15% with 2-3 fold increases in quinidine doses greater than 25 mg (28.8 mg).

There were more AEs reported in the DM/Q groups than in the DM/0mg quinidine group. A clear difference between the Q dose groups in terms of adverse events was not apparent.

4.2.8 SINGLE AND MULTIPLE DOSE PK STUDY

A SINGLE-DOSE AND MULTIPLE DOSE PHARMACOKINETIC STUDY WITH A PRODUCT CONTAINING DEXTROMETHORPHAN AND QUINIDINE (AVP-923)

Study Investigators and Site:

(b) (4)

Protocol Number: 99-AVR-101

OBJECTIVES:

1. To determine PK parameters of dextromethorphan (DM) after single and multiple doses of AVP-923
2. To determine differences in PK parameters in extensive metabolizers (EMs) and poor metabolizers (PMs)
3. To chronicle occurrence of side effects during administration of AVP-923.

FORMULATIONS:

Table 1. Product used in 99-AVR-101

	Lot Number	Date of Manufacture (Dates of Study)
Dextromethorphan 30 mg (as 31.5 mg DX hydrobromide monohydrate)/quinidine sulfate 25 mg	981215-1	12/15/98 (5/9/99-5/24/99)
(b) (4)		

Note: The Sponsor stated that the amount of Q used in 99-AVR-100 (same lot number as in the present study) was calculated on the basis of quinidine sulfate, although the quinidine drug substance contained approximately (b) (4) dihydroquinidine. Therefore the 25 mg Q dosage strength is equivalent to approximately 28.8 mg Q.

STUDY DESIGN:

This was an open-label, single and multiple-dose study that was an extension of study 99-AVR-100. After a washout period of at least 2 weeks following conclusion of 99-AVR-100, 8 subjects identified in 99-AVR-100 as EMs and 2 subjects identified as PMs were enrolled in the study (n=10). PMs had urinary metabolic ratios for DM/DX > 0.3. The Sponsor states that sample size was chosen based on practical limitations and not any statistical consideration.

Inclusion criteria included healthy males or females, 18 years of age or older with normal resting ECG and hematologic, hepatic, and renal function, and no clinically significant

deviations from standard laboratory tests (CBC, SMA-12, and urinalysis). Exclusion criteria included known sensitivity to quinidine (Q) or opiates and subjects who had taken medication within the last 14 days. Concomitant medications were not allowed except for oral contraceptives. Subjects were not to consume any alcohol for 24 hours prior to and during the study. OTC medications were prohibited 3 days prior to dosing and during the study. Prescription medications were not allowed 14 days prior to dosing and during the study.

Subjects checked into the clinic 15 hours before their first dose. Following overnight fast, subjects were dosed on Day 1 and remained confined to the clinic until post-dose (AM) on Day 5. Subjects were dosed every 12 hours with AVP-923 for 1 week with an additional dose administered on Day 9. Doses were to be taken with 240 ml of water. Subjects fasted 2 hours before and 4 hours after dosing. A light meal was allowed 4 hours after each dose. Subjects returned to the clinic prior to the PM dosing on Day 7 and remained in house for 12 hours following the AM dose on Day 8.

Blood samples were collected on Days 1 and 4 at pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours post dose. On Day 2, samples were collected prior to dosing and 2 hours after the AM dosing. On Day 8 samples were collected prior to the AM dosing and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 48, and 72, 96, 120, and 168 hours after the dosing. A 12-hour urine collection for urinary metabolic ratio (DM/DX) was performed on Days 1 and 8 and Days 9-14. Samples were stored frozen at -20 °C. Blood and urine samples were analyzed for dextromethorphan and dextrorphan. Plasma samples were analyzed for quinidine.

Twelve-lead ECGs were recorded prior to dosing and Day 8 at 3 hours post-dose.

ASSAY:
Urine DM and DX

Table 2. Performance of Analytical Method for 99-AVR-101 for Urine DM and DX

Analyte	Method	Calibration Standards (µg/ml)	Linearity	LOQ (µg/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
DM	HPLC/ Fluorescence Detection	0.05-15.0 µg/ml	r > 0.998	0.05	0.15	0.88	5.73
					1.0	4.64	1.35
					12.0	3.59	1.62
DX	HPLC/ Fluorescence Detection	0.05-15.0 µg/ml	r > 0.999	0.05	0.15	1.82	2.47
					1.0	2.74	2.95
					12.0	2.44	1.98

(b) (4) was the internal standard. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for Study 99-AVR-101 for detection of DM and DX in urine. For the calibration curves, a weighted (1/conc) linear regression was used. Study samples were stored at -20° C. Samples were analyzed within less than 1 month from the beginning of sample collection; this is within the period for which the samples are stable at -20° C. All of the calibration standards were within 15% of the

nominal value. All of the QC samples were within 15% of their respective nominal values. The performance of the assay is considered acceptable.

Plasma DM and DX and Q

Table 3. Performance of Analytical Method for 99-AVR-101 for Plasma DM and for Plasma Q

Analyte	Method	Calibration Standards	Linearity	LOQ	QC	Inter-assay CV (%)	Inter-assay Accuracy (%)
DM	HPLC/ Fluorescence Detection	0.2 -20.0 ng/ml	r > 0.999	(ng/ml)	(ng/ml)		
				0.02	0.6	7.35	13.33
					3.5	3.89	2.86
				15	2.53	0.13	
DX		2.5 -500.0 ng/ml	r > 0.999	(ng/ml)	(ng/ml)		
				2.5	7.5	3.43	1.07
					75	2.15	5.83
				350	2.31	0.04	
Q	HPLC	0.05 -10.0 µg/ml	r>0.999	µg/ml	µg/ml		
				0.05	0.15	6.00	0.00
					1.5	4.16	-3.80
				7.5	3.53	-5.52	

The assays for DM and DX in plasma were performed after enzymatic hydrolysis.

DM

In the analytical report for Study 100, stability of at least 22 months was reported, although for DM the mean at 22 months was 85% of the initial analysis (96% for DX). Subsequent validation of an LC-MS/MS method (b)(4) 27267_1) showed DM stability in frozen plasma for 47 days at -20° C (>100% of control). Samples were analyzed within approximately 49 days from the beginning of the study collection. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for Study 99-AVR-101 for detection of DM and DX in plasma. For DM and DX all of the calibration standards were within 15% of the nominal value. For DX all QC samples in each run and for DM at least 5 out of 6 QC samples in each run were within 15% of their respective nominal values. The performance of the assay is considered acceptable.

Quinidine

Samples were analyzed within the time that they are stable. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for detection of Q in plasma. For Q all of the QC samples in each run and all of the calibration standards were within 15% of their respective nominal values.

RESULTS:

Demographics

A total of 10 subjects entered the trial and nine subjects completed the trial. One subject (subject #3) was dropped due to sensitivity to codeine. Demographics of the 9 subjects eligible for PK evaluation are shown in the table below.

Table 4. Demographics of Subjects Completing Study 99-AVR-101

Mean Age (Range)	Weight (mean ± SD)	2D6 Phenotype	Race
51 (36-61)	69 ± 6.4 kg (n=9)	7 EM 2 PM	Asian 1 Caucasian 7 Hispanic 1
	73 ± 5.1 kg (5 males)		
	64 ± 4.6 kg (4 females)		

The 2 PMs were a Caucasian female and a Caucasian male, 40 and 59 years old, respectively.

Pharmacokinetics

The dextromethorphan, dextrorphan, and quinidine plasma concentrations are shown below for each study day. The data show EMs and PMs separately. Data shown are mean (% CV) except for t_{max} that is median (range).

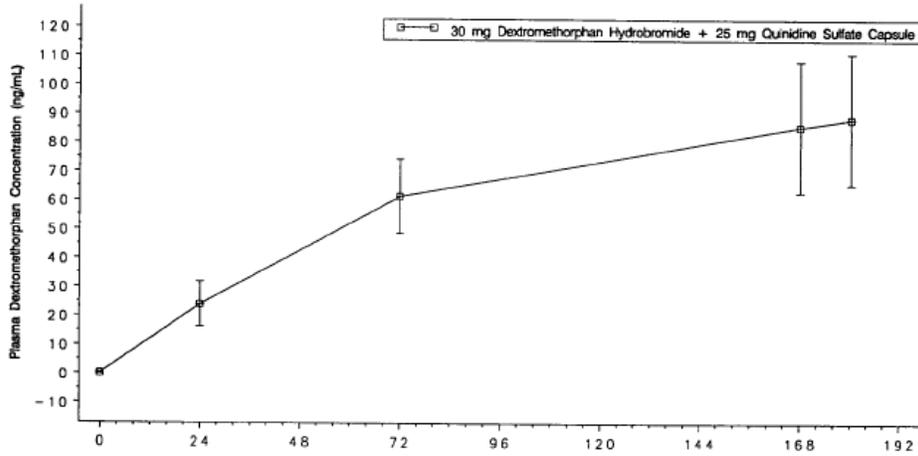
	PK Parameter	Study Day	EMs	PMs
Dextromethorphan	T _{max} (hr)	1	6.00 (4.0-11.9)	8.0
		4	4.00 (3.99-8.0)	6.0 (4.0-8.0)
		8	8.0 (2.0-8.0)	5.0 (4.0-6.0)
	C _{max} (ng/ml)	1	15.9 (52)	22.3 (1)
		4	76.7 (20)	105.7 (9)
		8	95.5 (21)	136.2 (2)
	AUC ₀₋₁₂ (ng*hr/ml)	1	133.3 (45)	198.3 (4)
		4	811.7 (19)	1146 (7)
		8	1049.0 (23)	1533 (5)
	T _{1/2} (hr)	8	13.3 (26)	42.0 (11)
	C _{min} (ng/ml) (at end of dosing interval on Day 8)	8	80.0 (21)	117.6 (12)
	C _{avg} (ng/ml)	8	87.5 (23)	128.1 (5)
	% fluctuation	8	18.0 (29)	14.8 (66)
% swing	8	19.6 (29)	16.7 (71)	

Of note, subject 43 (EM) had a half-life calculated to be 150 hours and this value was not included in the mean calculations. That subject had measurable concentrations after dosing on Day 8 for up to 336 hours at which point his concentrations were 19.4 ng/ml (all other EMs had < 0.5 ng/ml at that time and the PMs had 6.5 and 11.0 ng/ml at that time).

The C_{max} for dextromethorphan in EMs was approximately 6-fold higher on Day 8 compared to Day 1, and the AUC was approximately 7.9-fold higher on Day 8 compared to Day 1. Similar results were observed in the PMs. While taking quinidine, exposure in PMs was approximately 40-50% greater than exposure in the EMs, with a longer elimination half-life in the 2 PMs than in the EMs. However, both EMs and PMs continued to accumulate dextromethorphan throughout the dosing period. This is also shown in the figure below (combined EMs and PMs) showing trough dextromethorphan concentrations through the 9 days of the study. Dextromethorphan began to approach

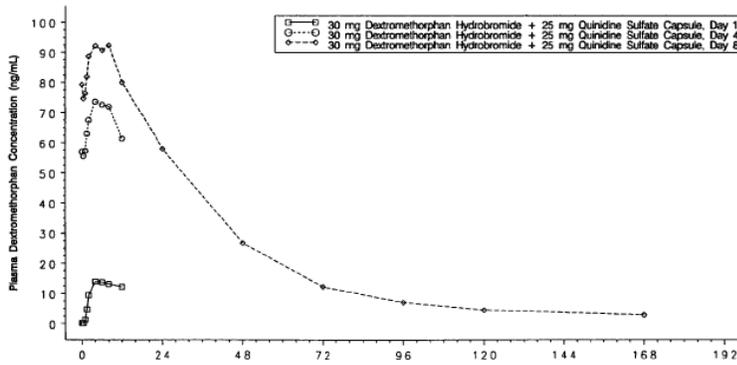
steady state after Day 3, reflecting the long half-life of dextromethorphan dosed concomitantly with quinidine, and the long elimination half-life of DM in PMs.

Mean (S.D.) Trough Plasma Dextromethorphan Concentrations Versus Time
Linear Scale

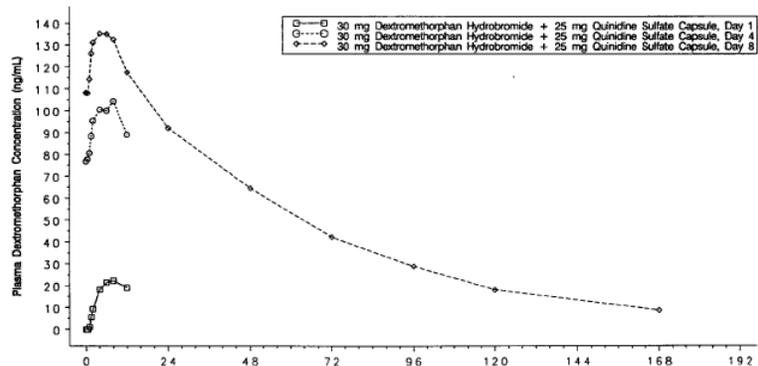


The mean plasma concentration vs time curves for EMs and PMs for dextromethorphan on Days 1, 4, and 8 are shown in the figures below.

Mean Plasma Dextromethorphan Concentrations Versus Time for Extensive Metabolizers
Linear Scale



Mean Plasma Dextromethorphan Concentrations Versus Time for Poor Metabolizers
Linear Scale



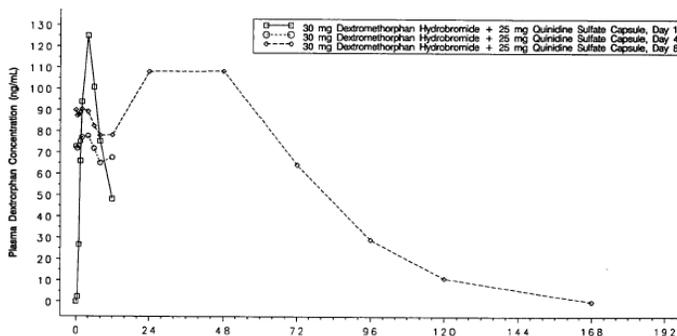
Dextrorphan PK parameters are shown in the table below. Dextrorphan exposure in PMs was approximately 90% less than in EMs on Day 1 and approximately 50% less on Days 4 and 8. Dextrorphan formation from dextromethorphan is a marker of CYP2D6 activity. Since dextrorphan is present in both EMs and PMs on quinidine, these results support an alternate pathway of formation for dextrorphan. It is noted that exposure to DX in EMs is relatively stable from Days 1 to 8, and in the PMs exposure increases. This reflects the long elimination half-life resulting in accumulation of DX, even as its formation is inhibited by Q or by absence of CYP2D6 in PMs.

	PK Parameter	Study Day	EMs (n=7)	PMs (n=2)
Dextrorphan	T _{max} (hr)	1	4.0 (4.0-4.01)	3.01 (2.0-4.01)
		4	2.0 (0-4.0)	2.0 (2.0)
		8	48.0 (24.2-48)*	3.0 (2.0-4.0)
	C _{max} (ng/ml)	1	124.86 (43)	19.8 (15)
		4	79.33 (23)	37.0 (0.6)
		8	123.5 (14)	51.45 (8)
	AUC ₀₋₁₂ (ng*hr/ml)	1	933.8 (35)	90.95 (21)
		4	849.2 (21)	365.3 (8)
		8	1001 (15)	530.4 (15)
	t _{1/2} (hr)	8	18.0 (24)	39.3 (13)
C _{min} (ng/ml) (at end of dosing interval on Day 8)	8	78.2 (15)	36.3 (32)	
C _{avg} (ng/ml)	8	83.4 (15)	44.3 (16)	
% fluctuation	8	55.7 (41)	35.9 (61)	
% swing	8	59.7 (43)	47.2 (74)	

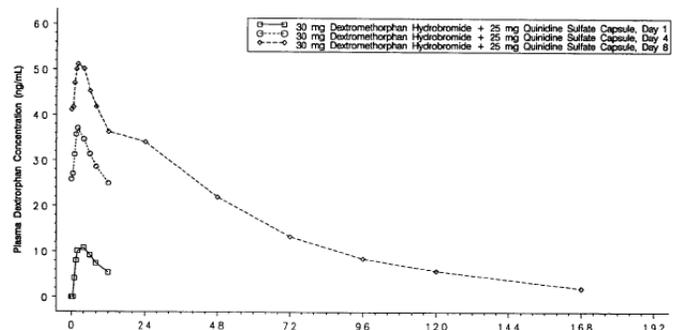
*All subjects received a final dose on Day 9, so that the a t_{max} of 24.2 hours reflects the plasma concentration after the Day 9 dose (24 hours after the Day 8 dose), and a t_{max} of 48 hours reflects the 24 hour time point after the Day 9 dose).

The dextrorphan plasma concentration time course curves in EMs and in PMs on Days 1, 4, and 8 are shown in the figures below.

Mean Plasma Dextrorphan Concentrations Versus Time for Extensive Metabolizers
Linear Scale



Mean Plasma Dextrorphan Concentrations Versus Time for Poor Metabolizers
Linear Scale

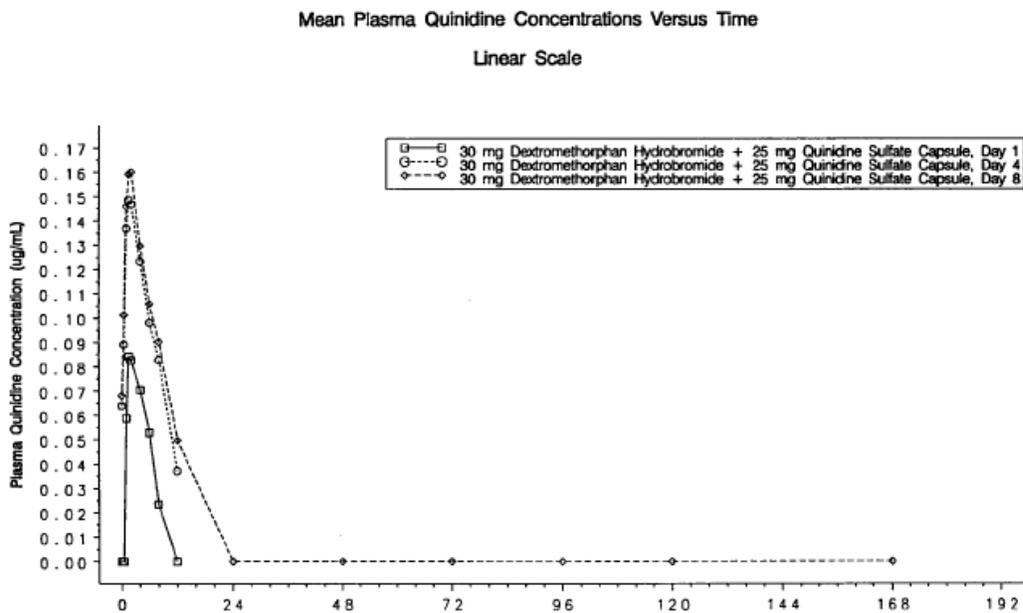


Quinidine pharmacokinetic parameters in EMs and PMs are shown in the table below. The PK parameters were similar in EMs and in PMs.

	PK Parameter	Study Day	EMs	PMs
Quinidine	Tmax (hr)	1	1.5 (1.5-2.0)	3.01 (2.0-4.01)
		4	1.53 (1.0-2.0)	1.52 (1.52)
		8	1.99 (1.98-2.0)	1.5 (1.49-1.5)
	Cmax (µg/ml)	1	0.09 (23)	0.08 (7)
		4	0.15 (20)	0.14 (4)
		8	0.16 (23)	0.16 (12)
	AUC0-12 (µg*hr/ml)	1	0.48 (38)	0.51 (25)
		4	1.198 (18)	0.969 (5)
		8	1.313 (14)	1.074 (2)
	t ½ (hr)	8	7.66 (14)	6.66 (6)
	λz (hr ⁻¹)	1	0.0944 (32)	0.0886 (32)
		4	0.103 (16)	0.107 (11)
8		0.092 (14)	0.104 (6)	
	C _{min} (µg/ml) (at end of dosing interval on Day 8)	8	0.06 (14)	0.00
	C _{avg} (µg/ml)	8	0.11 (14)	0.09 (2)
	% fluctuation	8	91.2 (20)	184.6 (14)
	% swing	8	157.7 (26)	*NC

*NC = not calculated since C_{min}=0.

Median Tmax was 1.5 hours later in PMs than in EMS. C_{max}, AUC, and half-life did not appear to differ substantially. Any comparisons need to be considered in light of the small number of PMs included in the study. Based on the elimination half-life, an approximate 1.4-fold accumulation of quinidine would be predicted. In fact, in both EMs there is an approximate 1.8-fold increase in C_{max} (2-fold in PMs), and an approximate 2.7-fold increase in AUC in EMs (and 2-fold in PMs).



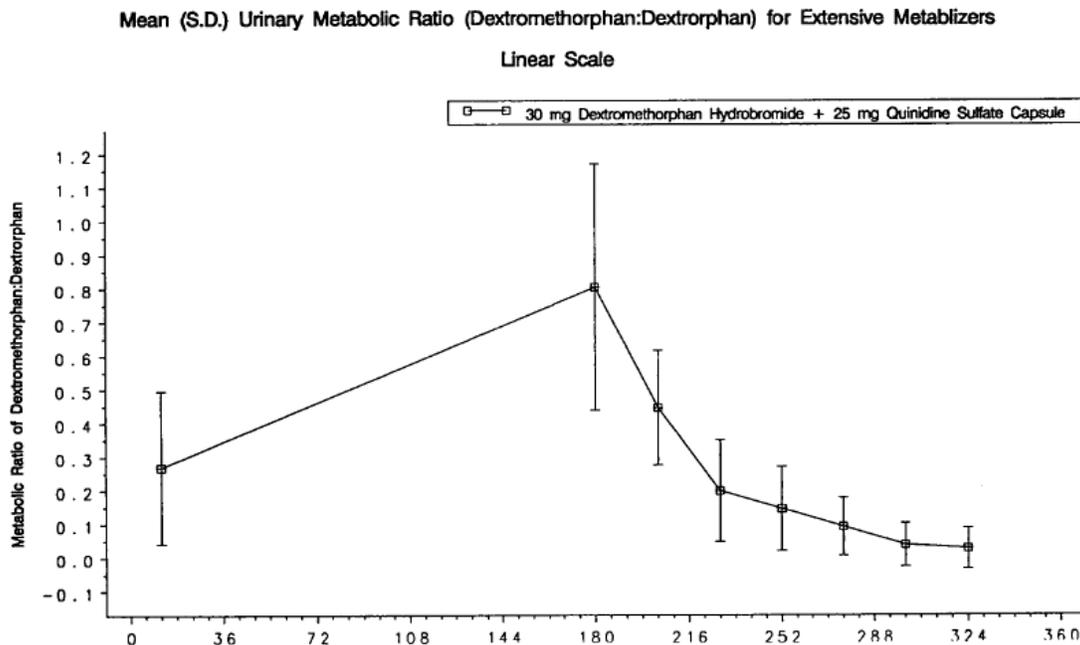
The mean plasma quinidine concentration time course curves for Days 1, 4, and 8 are shown

at left (combined EMs and PMs).

Urinary Metabolic Ratios of DM:DX

By Day 8, the mean urinary metabolic ratios of DM:DX for EMs was indicative of the poor metabolizer phenotype and this reverted to the EM phenotype by Day 10 (after quinidine had been discontinued for 1 day). In contrast, the phenotype for PMs remained that of a PM (DM:DX > 0.3) throughout the course of the study.

For the EMs, 3 out of the 7 subjects had urinary ratios of the PM phenotype (>0.3) on Day 1 of dosing. By Day 8, all subjects expressed the PM phenotype. In 5 of the 7 EMs this phenotype was maintained on the last day of dosing (Day 9), on which only 1 dose was given in 5 of the 7 EMs. By Day 10, 5 of the original EMs expressed an EM phenotype, and by Day 12, all of the original EMs expressed an EM phenotype. The 2 original PMs expressed the PM phenotype throughout the study. The results for the EMs are shown in the figure below, as provided by the Sponsor, where the X-axis represents hours after the first dose on Day 1 (such that the 2nd point occurs on Day 8).



Safety

Adverse events (AEs) were reported by 50% of the EM group and 50% of the PM group. There were 16 treatment-emergent adverse events reported by 5 of the 10 subjects that were dosed (4/8 EMs and 1 out of the 2 PMs). Fifteen AEs were considered mild and

one was considered moderate in severity. All resolved without treatment. No serious AEs occurred and no deaths were reported. Adverse events included asthenia (verbatim terms “weak”, “tired”), diarrhea, anorexia, nausea, vomiting, anxiety, depersonalization, insomnia, and somnolence.

There was no pre-dose or post-dose QTc value that was greater than 450 msec and no change in QTc interval of > 30 msec (as measured at 3 hours post-dose on Day 8). The largest positive change in QTc interval was 16 msec, and the mean change was -8 msec. Two subjects had a > 5 msec change as follows:

Subject	Change in QTc	Quinidine Conc (µg/ml) at 2 hours	Quinidine Conc (µg/ml) at 4 hours
17	14 msec	0.169	0.138
145	16 msec	0.145	0.117

CONCLUSIONS:

The C_{max} for dextromethorphan in EMs was approximately 6-fold higher on Day 8 of DM/Q administration compared to Day 1, and the AUC was approximately 7.9-fold higher on Day 8 compared to Day 1. Similar accumulation was observed in the PMs, although DM exposure in the PMs (n=2) was approximately 40-50% greater than in the EMs (n=7).

DX exposure was approximately 90% and 50% lower in PMs than in EMs on Days 1 and 8, respectively. The absence of CYP2D6 or its inhibition by quinidine does not eliminate the formation of DX.

Quinidine exposure was similar in EMs (n=7) and PMs (n=2). Quinidine accumulation was observed in both EMs and PMs. However, the small number of PMs included in the study does not allow for definitive determinations of PK or safety in the PM population. Quinidine accumulation was observed in both EMs and PMs.

4.2.9 QUINIDINE INTERACTION WITH HIGH DOSE DM (99-AVR-103)

A PHASE I DRUG INTERACTION STUDY TO DETERMINE THE LOWEST DOSE OF QUINIDINE THAT PROTECTS DEXTROMETHORPHAN IN TWO DOSE LEVELS FROM METABOLISM BY CYTOCHROME P450 2D6

Study Investigators and Site:



Protocol Number: 99-AVR-103

OBJECTIVES:

1. Determine the lowest dose of quinidine (Q) that effectively inhibits the conversion of 45 mg dextromethorphan (DM) to dextrorphan (DX) and the lowest dose of Q that effectively inhibits the conversion of 60 mg DM to DX
2. Chronicle the occurrence of side effects during administration of dextromethorphan/quinidine

FORMULATIONS:

Table 1. Products used in 99-AVR-103

	Use in Study	Lot Number
Dextromethorphan HBr 60 mg/Quinidine Sulfate 0 mg capsules	Treatment A (n=7)	N01004F
Dextromethorphan HBr 60 mg/Quinidine Sulfate 30 mg capsules	Treatment B (n=4)	N02002F
Dextromethorphan HBr 60 mg/Quinidine Sulfate 45 mg capsules	Treatment C (n=3)	N02003F
Dextromethorphan HBr 60 mg/Quinidine Sulfate 60 mg capsules	Treatment D (n=6)	N02004F
Dextromethorphan HBr 45 mg/Quinidine Sulfate 0 mg capsules	Treatment E (n=8)	N01003F
Dextromethorphan HBr 45 mg/Quinidine Sulfate 30 mg capsules	Treatment F (n=7)	N01006F

capsules	Dextromethorphan HBr 45 mg/Quinidine Sulfate 45 mg	Treatment G (n=7)	N01007F
capsules	Dextromethorphan HBr 45 mg/Quinidine Sulfate 60 mg	Treatment H (n=5)	N01008F
capsules			

Dextromethorphan HBr capsules, 30 mg (Lot M11007F) were used for phenotyping. All of the capsules were manufactured by Avanir Pharmaceuticals, and received from (b) (4) on 2/13/01 and 2/21/01. The expiration date was not provided. The study was conducted from Feb 23, 2001 to March 24, 2001.

STUDY DESIGN:

This was a Phase I, open-label, parallel-group, multiple-dose, single-center, safety and PK study. Part 1 was a phenotyping screening study in which subjects ingested 30 mg dextromethorphan after emptying their bladders. All urine was collected over the next 12 hours and analyzed for DM and DX to determine the DM/DX ratio. Extensive metabolizers (EMs) were identified as having a DM/DX ratio of < 0.3. Poor metabolizers (PMs) had a DM/DX ratio > 0.3.

Following a wash-out period of at least 2 days, 65 subjects identified as EMs in Part 1 were assigned to the 8 dose groups (A through H) identified above, with 8 subjects per group except Group E that included 9 subjects. Dosing began with an AM dose on Day 1 in which all subjects received a capsule containing DM (at the assigned dose level) only as a baseline measure, after which all urine was collected for 12 hours. Dosing with the assigned medication began with the evening dose on Day 1 and continued at 12 hour intervals for the next 6 days, with a final AM dose on Day 8. After administration of the 2nd, 6th, and 14th doses urine was collected for 12 hours. Subjects had a blood sample collected for measurement of plasma DM and DX prior to the last dose and additional samples were collected at 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours post-dose for determination of plasma DM, DX, and quinidine. An ECG was performed 1-4 hours post-dose on Day 1, Day 4, and Day 8.

Inclusion criteria included healthy males or females, 18-60 years of age, identified as extensive metabolizers (EMs) of dextromethorphan. Exclusion criteria included known sensitivity to Q or opiates and subjects who had taken medication within the last 14 days. Concomitant medications were not allowed except for oral contraceptives. There was no restriction regarding grapefruit products.

ASSAY:

Urine DM and DX

Table 2. Performance of Analytical Method for 99-AVR-103 (Method 12730) for Urine DM and DX

Analyte	Method	Calibration Standards (µg/ml)	Linearity	LOQ (µg/ml)	QC (ng/ml)	Inter-assay CV	Inter-assay Accuracy (%)
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							(%)
DM	HPLC/	0.05-15.0	r > 0.996	0.05	0.15	4.9	-4.67
	Fluorescence	µg/ml			1.0	4.28	0.4
	Detection				12.0	4.51	-5.3
DX	HPLC/	0.05-15.0	r > 0.996	0.05	0.15	6.58	1.33
	Fluorescence	µg/ml			1.0	5.54	4.7
	Detection				12.0	3.39	-3.57

One calibration curve and duplicate QC samples were analyzed with each batch of study samples for Study 99-AVR-103 for detection of DM and DX in urine. Study samples were stored at -20° C and were analyzed within the period for which the samples are stable at -20° C. The performance of the assay is considered acceptable. The Study report states that at the direction of the Principal Scientist, for screen samples all results with dextrophan concentrations > 15 ng/ml were reported without being diluted.

Plasma DM and DX

Plasma DM and DX were determined using Method 12730_3.01 for hydrolyzed samples.

Table 3. Performance of Analytical Method for 99-AVR-103 for Plasma DM, DX, and for Plasma Q

Analyte	Method	Calibration Standards (µg/ml)	Linearity	LOQ	QC	Inter-assay CV (%)	Inter-assay Accuracy (%)
DM	HPLC/Fluorescence Detection	0.2 -20.0 ng/ml	r > 0.995	0.2 ng/ml	(ng/ml)		
					0.6	8.62	0.5
					3.5	7.9	-2.03
					15	7.74	1.83
DX	HPLC/Fluorescence Detection	2.5 -500 ng/ml	r > 0.995	2.5 ng/ml	(ng/ml)		
					7.5	8.49	-7.69
					75	10.02	-5.78
					350	8.35	-3.12
Q	HPLC	0.05-10.0 µg/ml	r>0.995	µg/ml	µg/ml		
				0.05	0.15	3.22	1.47
					1.5	2.96	-2.85
					7.5	2.48	-4.47

DM and DX

Samples were extracted and analyzed within 4 months for DM and for DX. This is within period for which stability has been demonstrated (although for DM more than 100% stability was shown for 47 days, the mean at 22 months was 85% of the initial analysis (96% for DX)). One calibration curve and duplicate QC samples were analyzed with each batch of study samples for Study 99-AVR-103 for detection of DM and DX in plasma. Cmax plasma concentrations for dextromethorphan were as high as 399.8 ng/ml and the Sponsor diluted samples at specific time points 10-fold. (Dilution integrity was shown using the same method but with a different internal standard). The performance of the assay is considered acceptable.

Quinidine

Samples were analyzed within the time that they are stable. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for detection of Q in plasma. The performance of the assay is considered acceptable.

RESULTS:

Demographics

Sixty-five subjects were enrolled in the study. One subject (subject 32) was dropped due to a personal reason and was replaced by subject 132. Seventeen subjects were dropped due to adverse events. (Please see safety section of this review). A total of 47 subjects completed the study and were included in the PK analysis. Demographics of subjects completing the study are shown in the table below.

Table 4. Demographics of Subjects Completing Study 99-AVR-103

DM Dose	Mean Age (Range)	Weight (mean \pm SD)	Race
45 mg DM	30 (19-60)	75.8 \pm 14.4 kg (n=27)	Black 1
			Caucasian 26
60 mg DM	27 (19-47)	82.6 \pm 13.2 kg (male; n=16)	
		66.0 \pm 9.6.0 kg (female; n=11)	
		76.8 \pm 12.7 kg (n=20)	Caucasian 20
		86.1 \pm 6.3 kg (male; n=9)	
		69.1 \pm 11.5 kg (female; n=11)	

Of note, ultrarapid metabolizers (URM) are generally characterized with a urinary metabolic ratio for DM to DX that is < 0.003 . Thirty of the 47 EMs (64%) that completed the PK portion of the study had ratios < 0.003 , according to data provided by the Sponsor. **Note:** This is higher than generally observed (up to 10% in Caucasians and 29% in black Ethiopians).

Dextromethorphan and Dextrorphan Plasma Concentrations

Mean plasma concentrations of DM in the present study exceed those observed following the proposed dose of 30 mg DM/30 mg Q (Study 99-AVR-101). (In that study, C_{max} on Day 8 was approximately 95 ng/ml). Dextromethorphan was greater in the presence of quinidine than when given alone (approximately 24-33-fold for C_{max} and 37-46 fold for AUC). For either the 45 mg or 60 mg doses of dextromethorphan, increasing quinidine dose above 30 mg daily did not result in further increases in dextromethorphan exposure. These results are shown in the tables below.

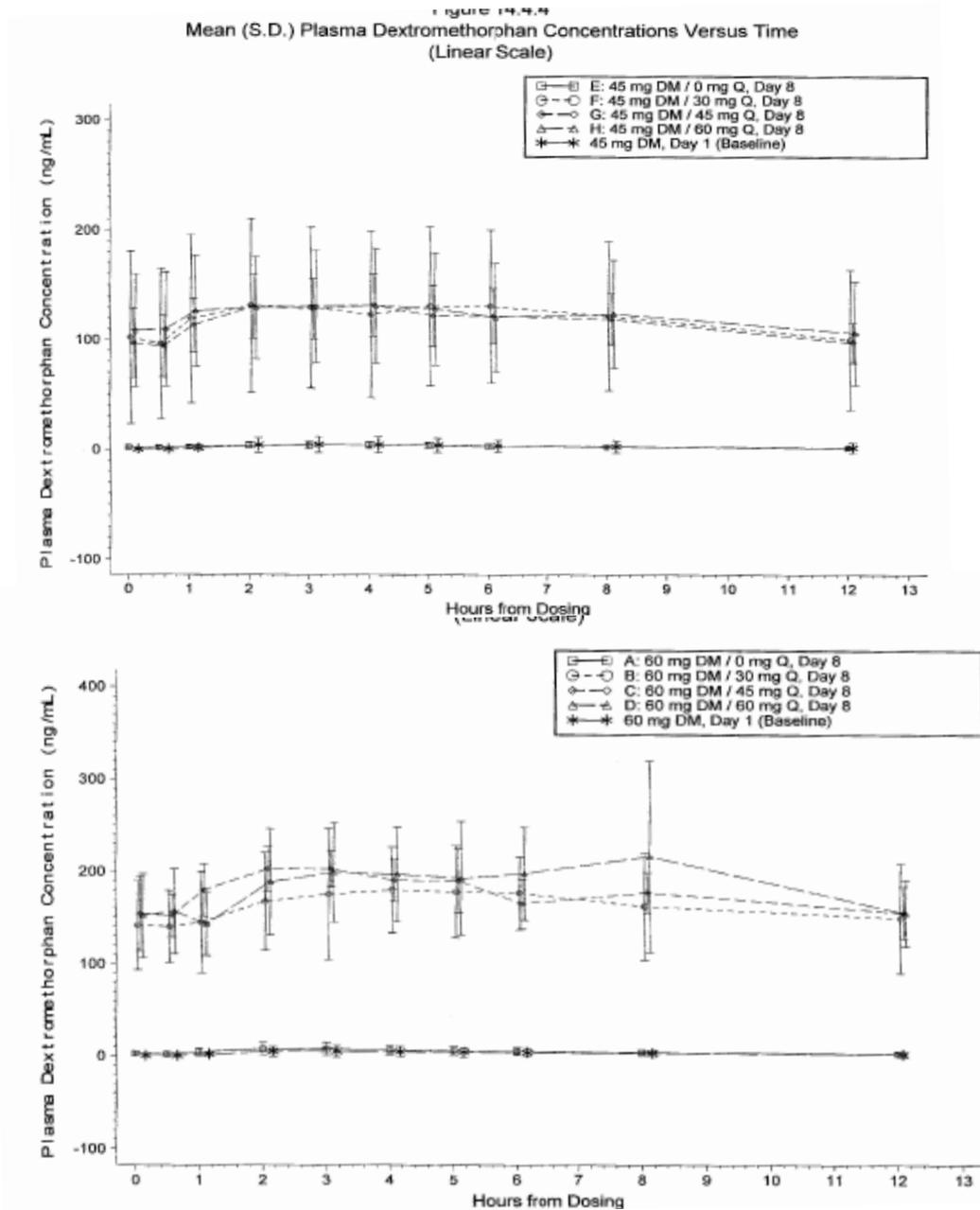
Summary Parameters of the Plasma DM PK in Study 99-AVR-103

DM Dose	Study Day	PK Parameter	Quinidine Dose			
			0 mg	30 mg	45 mg	60 mg
45 mg	1*	C _{max} (ng/ml)	4.4 (177)			
		T _{max} (hr)	3.0 (2.0-5.03)			
		AUC ₀₋₁₂ (ng*hr/ml)	33.0 (202)			
	8	C _{max} (ng/ml)	4.2 (71)	141.5 (53)	138.9 (26)	136.1 (37)
		T _{max} (hr)	3.1 (3.0-	5.0 (2.0-	3.05	4.0 (0.999-

			4.0)	6.0)	(0.998-6.0)	6.0)
		AUC ₀₋₁₂ (ng*hr/ml)	31.46 (75)	1438 (59)	1403 (20)	1464 (40)
60 mg	1*	C _{max} (ng/ml)	3.7 (99)			
		T _{max} (hr)	3.0 (1.0-5.0)			
		AUC ₀₋₁₂ (ng*hr/ml)	23.3 (106)			
	8	C _{max} (ng/ml)	7.7 (91)	191.8 (24)	204.8 (11)	231.9 (42)
		T _{max} (hr)	2.0 (2.0-3.0)	3.0 (2.0-6.0)	3.0 (3.0-5.02)	5.5 (3.0-8.01)
		AUC ₀₋₁₂ (ng*hr/ml)	52.3 (89)	1963 (31)	2121 (13)	2252 (31)

* Day 1 parameters reflect those of all subjects receiving the dose on Day 1

The plasma concentration time course curves for the 45 mg and 60 mg doses of dextromethorphan following specific doses of quinidine are shown in the figures below, as provided by the Sponsor.

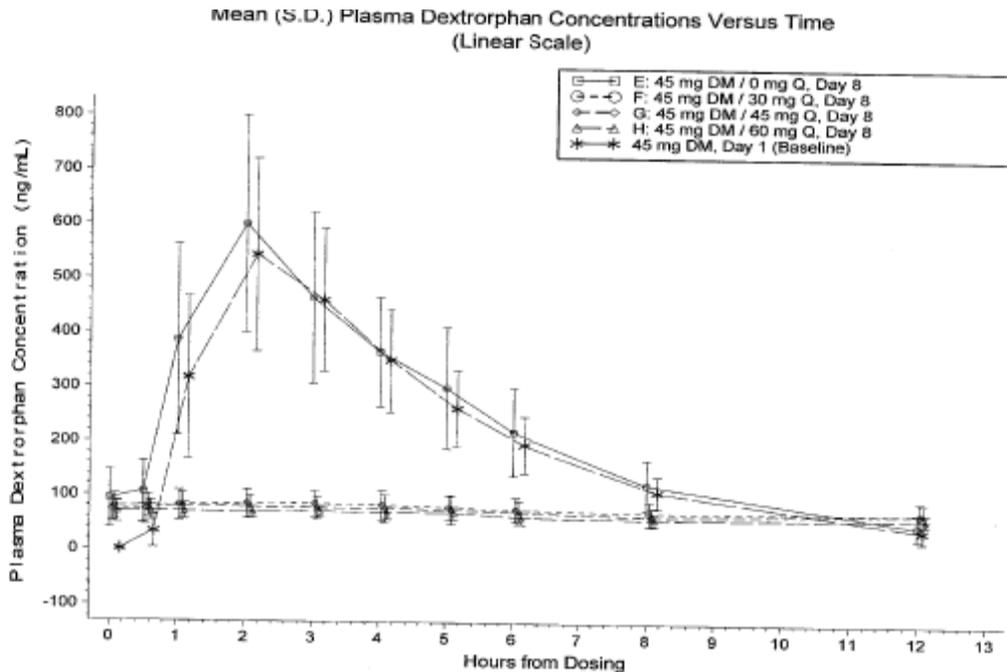


Dextrophan exposure in plasma was higher in the absence of quinidine than when given with quinidine (approximately 4-7-fold for C_{max} and 2-3- fold for AUC when given with 30 mg quinidine). For either the 45 mg or 60 mg doses of dextromethorphan, increasing the quinidine concentration above 30 mg daily did not result in further decreases in dextrophan exposure. These results can be seen in the tables below.

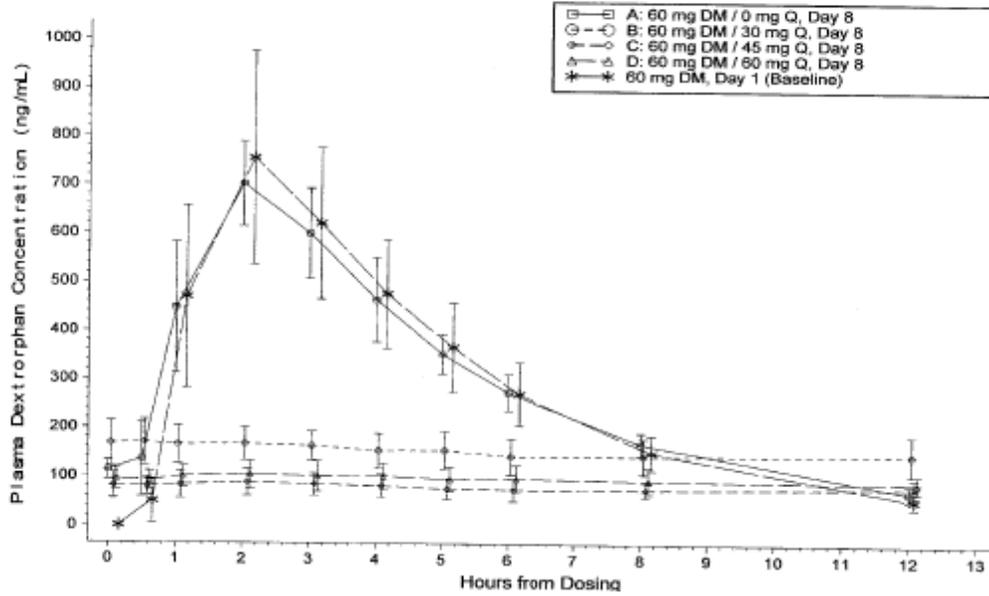
Summary Parameters of the Plasma Dextrophan PK in Study 99-AVR-103

DM Dose	Study Day	PK Parameter	Quinidine Dose			
			0 mg	30 mg	45 mg	60 mg
45 mg	1	C _{max} (ng/ml)	545.9 (34)			
		T _{max} (hr)	2.0 (2.0-3.0)			
		AUC ₀₋₁₂ (ng*hr/ml)	2535 (26)			
	8	C _{max} (ng/ml)	599.2 (33)	89.1 (29)	86.8 (27)	77.7 (20)
		T _{max} (hr)	2.0 (2.0-2.03)	3.0 (0.0-4.0)	0.5 (0.0-3.0)	1.0 (0.0-3.0)
		AUC ₀₋₁₂ (ng*hr/ml)	2898 (31)	920.7 (30)	874.1 (27)	782.6 (17)
60 mg	1	C _{max} (ng/ml)	733.4 (20)			
		T _{max} (hr)	2.00 (2.0-3.01)			
		AUC ₀₋₁₂ (ng*hr/ml)	3446 (16)			
	8	C _{max} (ng/ml)	709.6 (13)	176.7 (23)	90.1 (27)	110.8 (25)
		T _{max} (hr)	2.0 (2.0-3.0)	1.8 (0-3.0)	2.01 (2.0-12.0)	2.5 (1.0-12.0)
		AUC ₀₋₁₂ (ng*hr/ml)	3608 (11)	1830 (24)	958.0 (26)	1157 (24)

* Day 1 parameters reflect those of all subjects receiving the dose on Day 1



Mean (S.D.) Plasma Dextrophan Concentrations Versus Time
(Linear Scale)



Quinidine Pharmacokinetics

Maximum plasma quinidine concentrations (maximum C_{max}) on Day 8 were as follows:

	45 mg DM	60 mg DM
30 mg Quinidine	0.384 µg/ml	0.21 µg/ml
45 mg Quinidine	0.49 µg/ml	0.2961 µg/ml
60 mg Quinidine	0.4169 µg/ml	0.59 µg/ml

These C_{max} values are less than the “usually therapeutic range” of quinidine when given as an antiarrhythmic drug (2-6 ng/ml).

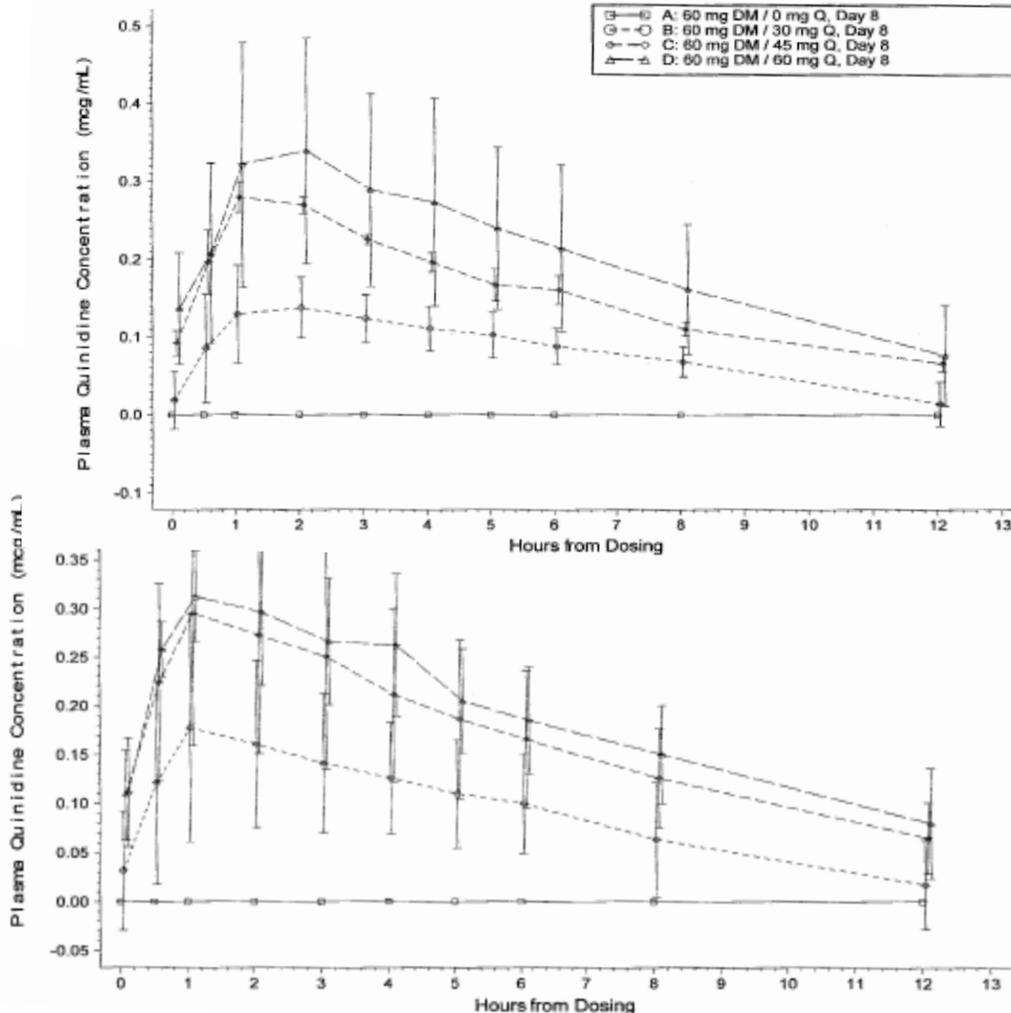
Mean (%C V) for Plasma Quinidine PK Parameters (on Study Day 8)

DM Dose	PK Parameter	Quinidine Dose		
		30 mg	45 mg	60 mg
45 mg	C _{max} (ug/ml)	0.18 (61)	0.30 (42)	0.33 (19)
	T _{max} (hr) ^a	1.00 (0.999-3.0)	1.00 (0.501-2.00)	1.00 (0.999-4.0)
	AUC ₀₋₁₂ (ug*hr/ml)	1.11 (67)	2.04 (13)	2.31 (28)
60 mg	C _{max} (ug/ml)	0.145 (34)	0.28 (7)	0.35 (42)
	T _{max} (hr) ^a	2.01 (1.01-4.0)	1.01 (1.0-2.0)	2.0 (1.03-2.00)
	AUC ₀₋₁₂ (ug*hr/ml)	0.980 (35)	1.9 (5)	2.5 (49)

^amedian (range)

The effect of DM on quinidine PK cannot be determined since quinidine is not given in the absence of DM. Similarly, determining linearity of quinidine PK is confounded by potential effects of DM on exposure. However it is noted that for a 2-fold increase in quinidine dose in the presence of 60 mg DM, the increase in C_{max} and AUC are approximately 2.4-fold and 2.6-fold, respectively.

Mean (S.D.) Plasma Quinidine Concentrations versus time (Linear Scale)



Urinary Excretion of Dextromethorphan

Data regarding urinary excretion of DM and DX has been provided by the Sponsor but will not be reviewed here as it does not add to the consideration of PK after NEURODEX administration.

Safety

There were 279 adverse events experienced by 48 of the 65 subjects dosed during the trial (75%); these occurred in 21 of 33 subjects following the 45 mg DM treatments and 27 of 32 subjects dosed with the 60 mg DM treatments. Seventeen subjects were discontinued from the study due to adverse events, although all of the adverse events were considered by the Sponsor to be mild or moderate in severity. Dizziness, nausea, somnolence, headache, fatigue, feeling jittery, tremor, and mild dyspepsia were the most common adverse events and occurred in more than 10% of subjects for 60 mg. The most common adverse events in the 45 mg group were dizziness, headache, nausea, and loose stools and occurred in more than 10% of subjects for 45 mg DM. Discontinuations were due to dizziness, vomiting, vomiting, feeling jittery, tremor, feeling abnormal, euphoric mood, loose stools, tinnitus, disorientation and somnolence, paresthesia, and disturbance in attention.

Following the 60 mg DM dose, there was no post-dose QTc measurement that was > 450 msec, although change from baseline of > 30 msec (but < 60 msec) was observed at all doses of Q. For the 45 mg dose of DM given with 60 mg Q, at QTc of > 500 msec was observed on Day 8 (within 4 hours after the dose; mean QTc was 418 during this time), and the largest change from baseline was 155 msec on that day. Change from baseline of 30-60 msec was observed also on Days 1 and 4.

CONCLUSIONS:

This study has only been partially reviewed, with consideration of data that could contribute to the pharmacokinetic information pertinent to the dose that will be given.

Coadministration of dextromethorphan (either 45 mg or 60 mg) with 60 mg quinidine does not provide greater exposure to dextromethorphan (or lesser exposure to dextrophan) than does coadministration with lower doses of quinidine (30mg or 45 mg).

An effect of DM on quinidine exposure cannot be determined since quinidine was not given alone in the present study.

QTc prolongation was observed in the present study. The quinidine Cmax values are less than the “usually therapeutic range” of quinidine when given as an antiarrhythmic drug (2-6 ng/ml). It should be noted, however that according to the quinidine labeling, serum quinidine concentrations were “subtherapeutic” in approximately 50% of cases of patients developing torsades de pointes, and that quinidine appears to have the highest risk of torsades at low concentrations.

4.2.10 FOOD EFFECT STUDY 04-AVR-111

A RANDOMIZED, SINGLE-DOSE, 2-WAY CROSSOVER STUDY TO DETERMINE THE EFFECTS OF FOOD ON THE PHARMACOKINETICS OF AVP-923 (30 MG OF DEXTROMETHORPHAN HYDROBROMIDE AND 30 MG OF QUINIDINE SULFATE) IN HEALTHY ADULT VOLUNTEERS

Study Investigators and Site:



Protocol Number: 04-AVR-111

OBJECTIVES:

Determine the effect of food on the PK of AVP-923 (dextromethorphan, total dextrophan and quinidine).

FORMULATIONS:

Table 1. Product used in 04-AVR-111

	Lot Number	Date of Manufacture (Dates of study)
AVP-923 capsules (30 mg DM/30 mg Q) (b) (4)	C0051B002	10/17/2002 (1/31/04-5/4/04)

According to the Stability Study Report provided in the present submission, the test product appears to be stable for at least 36 months at room temperature.

STUDY DESIGN:

This was a Phase I, open-label, randomized, single-dose, 2-way crossover study. Subjects reported to the clinic on the evening prior to each dosing (Day -1) and had an overnight fast of at least 10 hours. On Day 1 of each period (January 31, 2004 and Feb 7, 2004) the subjects randomized to Treatment A were in a fasted state when they received a single oral dose of AVP-923. Subjects randomized to Treatment B received a high-fat breakfast as per the FDA guidance at 9AM in Period 1 and at 8:30 AM in period 2. The high-fat breakfast was served 30 minutes prior to dosing and was consumed within 30 minutes. Water was restricted 1 hour pre-dose until 1 hour post-dose. On Day 1 and Day 2, there was a standardized meal schedule beginning with lunch on Day 1. In each period subjects were confined to the clinic for at least 10 hours before dosing until after the 36 hour blood draw. Periods 1 and 2 were separated by a 7 day washout period.

Blood samples were collected during each study period at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, and 48 hours post-dose for analysis of DM, DX, and quinidine in plasma. Plasma samples were frozen at -20° C until assayed.

ECG measurements (12-lead ECG) were made at screening and at approximately 0, 2, 6, and 12 hours post-dose.

Urine samples were also collected at pre-dose, 0-12, 12-24, and 24-36 hours post-dose for analysis of DM and DX, with the intention of establishing CYP2D6 phenotype. However, since quinidine inhibits CYP2D6, the Sponsor determined that this would not be appropriate and performed post-hoc genotyping. As subjects can convert to the PM phenotype as early as Dose 1 (see Study 99-AVR-100) the phenotype data will not be used here. Subjects were asked to return to the clinic in April 2004 to provide a blood sample to be used for CYP2D6 genotyping. Twelve of the 18 subjects in the study provided this additional sample.

Inclusion criteria included healthy males or females, 19-55 years of age. Subjects were to be non-smokers (for at least 3 months). Females of childbearing potential could use hormonal contraceptives. Exclusion criteria included history of hypersensitivity or idiosyncratic reaction or DM or Q or related drugs, QTc interval > 450 msec, use of any drugs or substances known to be strong inhibitors of CYP enzymes within 10 days prior to the first dose, or strong inducers of CYP enzymes within 30 days prior to the first dose. No medication (including OTC) or herbal products were permitted for 7 days prior to the first dose, during sample collection, or during the washout period. This did not include vitamins and hormonal contraceptives. Foods and beverages containing the following

substances were prohibited as indicated: xanthines (24 hours before dosing and throughout the period of sample collection), alcohol (48 hours before dosing and throughout the period of sample collection), and grapefruit (10 days before dosing and throughout the period of sample collection).

ASSAY:

Plasma DM and DX

Table 3. Performance of Analytical Method for 04-AVR-111 for Plasma DM, DX, and for Plasma Q

Analyte	Method	Calibration Standards (µg/ml)	Linearity	LOQ	QC	Inter-assay CV (%)	Inter-assay Accuracy (%)
DM	LC-MS/MS Method 26267	0.2 -200 ng/ml	r > 0.998	0.2 ng/ml	(ng/ml)		
					0.6	6.32	0.17
					15	1.7	2.69
DX	LC-MS/MS Method 26267	2.5 -2500 ng/ml	r > 0.998	2.5 ng/ml	(ng/ml)		
					7.5	2.79	2.09
					250	3.07	7.31
Q	HPLC	0.05-10.0 µg/ml	r>0.998	0.05 µg/ml	µg/ml		
					0.15	5.9	0.6
					1.5	2.73	3.57
					7.5	3.04	2.27

DM and DX

Samples were extracted and analyzed within period for which stability has been demonstrated. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for Study 04-AVR-111 for detection of DM and DX in plasma. For DX, the 5 ng/ml calibration standard was not used for regression in any batch. The performance of the assay is considered acceptable.

Quinidine

Samples were analyzed within the time that they are stable. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for detection of Q in plasma. The performance of the assay is considered acceptable.

RESULTS:

Demographics

Eighteen subjects were enrolled and completed the study. Demographics of those subjects completing the study are shown in the table below.

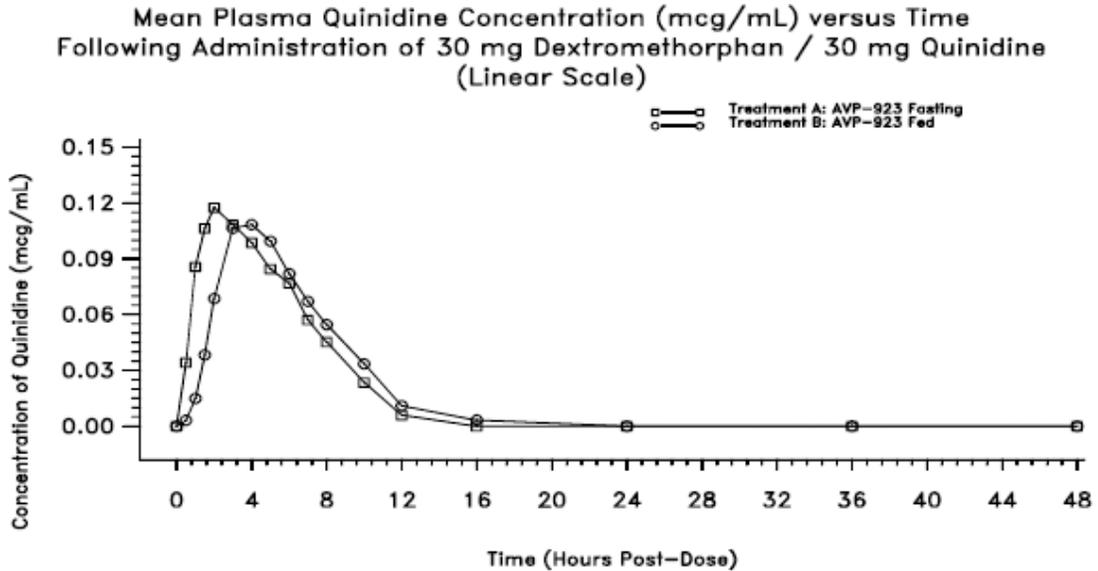
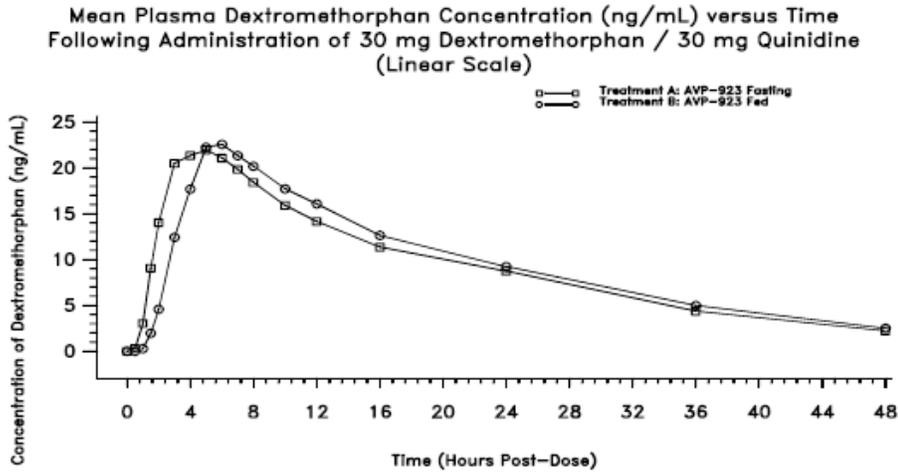
Table 4. Demographics of Subjects Completing Study 04-AVR-111

Mean Age (Range)	Weight (mean ± SD)	Race
27 (19-53)	73.9 ± 10.9 kg (n=27)	Caucasian 18
	79.5 ± 7.0 kg (male; n=11)	
	62.5 ± 6.9 kg (female; n=7)	

The only concomitant medications taken were aspirin in 1 subject (during Treatment B) and oral contraceptives in 1 subject during both periods and at screening.

Dextromethorphan and Dextrorphan Plasma Concentrations

The mean plasma concentration time course from each treatment for dextromethorphan (DM) or for Quinidine (Q) fed or fasted are shown in the figures below, as provided by the Sponsor.



PK parameters were determined using noncompartmental analysis. The pertinent PK parameters for DM and for Q from fed and fasting periods are shown in the table below. (Note: 12 subjects were genotyped for CYP2D6 and were either wt/wt/ or *4/wt. There were no subjects who were phenotyped prior to dosing with NEURODEX. Four subjects were phenotyped (with the NEURODEX dose) and reported to be extensive metabolizers. Two subjects (#9 and #14) were neither genotyped nor phenotyped. The PK data includes all 18 subjects and is considered without regard to the known EM subset). In study 99-AVR-101 that included 2 PMs as well as EMs, the EMs had an approximate 5-fold greater C_{max} and 10-fold greater AUC for DX than did the EMs after a single dose. Such a difference was not discernable in Subjects 9 and 14. In addition, Subjects 9 and 14 had half-lives for DM of approximately 10-12 hours; therefore they were not outliers with respect to DM PK either).

Table 5. Pharmacokinetic parameters (arithmetic mean) for DM and for Q in 04-AVR-111

	Fed TREATMENT B (% CV) n=18	Fasted TREATMENT A (% CV) n=18
DM		
t _{max} (h) ^a	6.0 (4.0-8.0)	5.0 (2.0-7.0)
C _{max} (ng/mL)	23.2 (23)	23.3 (25)
AUC _{0-t} (ng*h/mL)	454.8 (36)	442.7 (40)
AUC _{0-∞} (ng*h/mL)	516.3 (46)	491.9 (48)
λz (hr ⁻¹)	0.0603 (32)	0.0635 (29)
t _{1/2} (h)	12.6 (34)	11.9 (33)
Q		
t _{max} (h) ^a	3.5 (1.5-5.0)	2.0 (1.0-4.0)
C _{max} (μg/mL)	0.117 (34)	0.131 (30)
AUC _{0-t} (μg*h/mL)	0.680 (59)	0.707 (47)
AUC _{0-∞} (μg*h/mL)	1.144 (39)	1.171 (28)
λz (hr ⁻¹)	0.144 (30)	0.138 (26)
t _{1/2} (h)	5.2 (30)	5.3 (21)

^a median (range)

For DM, the median t_{max} was 1 hour later in the fed condition than in the fasted condition. For Q the median t_{max} was 1.5 hr later in the fed condition than in the fast condition.

The bioavailability comparisons for fed vs fasted for NEURODEX are shown in the Table below. The 90% CI for both C_{max} and AUC fell within the BE interval for both DM and for Q.

Table 6. Bioavailability Ratios for NEURODEX Fed and Fasting in Study 04-AVR-111

	Geometric Mean		Ratio of Geometric Means	90% CI for the Ratio of Geometric Means
	Fasted (REFERENCE)	Fed (TEST)		
DM				
C _{max} (ng/ml)	22.6	22.7	1.00	(0.96, 1.04)
AUC _{0-t} (ng*h/ml)	410.5	427.7	1.04	(0.98, 1.11)
AUC _{0-∞} (ng*h/mL)	445.6	403.5	1.06	(1.00, 1.13)
Q				
C _{max} (µg/ml)	0.125	0.111	0.89	(0.80, 0.98)
AUC _{0-t} (µg*h/ml)	0.626	0.575	0.92	(0.83, 1.02)
AUC _{0-∞} (µg*h/mL)	1.128	1.072	0.95	(0.86, 1.04)

Other PK analyses

The Sponsor has also compared DX pharmacokinetic parameters under fed and fasted conditions. Since the food effect study is generally conducted to determine performance of a product in the presence of a high fat meal, the primary measure should generally be the parent compound. However, for completeness, the DX parameters are presented below, as provided by the Sponsor.

Table 5. Pharmacokinetic parameters (arithmetic mean) for DX in 04-AVR-111

	Fed TREATMENT B (% CV) n=18	Fasted TREATMENT A (% CV) n=18
DX		
t _{max} (h) ^a	5.0 (4.0-10.0)	4.0 (2.0-5.0)
C _{max} (ng/mL)	63.6 (38)	81.7 (45)
AUC _{0-t} (ng*h/mL)	1350.9 (21)	1446.8 (19)
AUC _{0-∞} (ng*h/mL)	1792.5 (20)	1841.9 (21)
λ _z (hr ⁻¹)	0.04023 (50)	0.04417 (40)
t _{1/2} (h)	20.9 (41)	19.1 (52)

Safety

Seven subjects reported 13 treatment emergent adverse events. Of these, 9 occurred under fasting conditions and 4 occurred under fed conditions. Two adverse events were judged to be related to study treatment. All adverse events were considered to be mild or moderate in severity. The Sponsor reports no deaths, serious adverse events, or other significant adverse events in the study. Safety has not been reviewed in detail by OCP.

The most frequently reported adverse events (reported by more than 10% of subjects) were headache and dizziness reported by 5 (28%) and 2 (11%) of subjects, respectively.

One subject had a QTc of 490 msec that was recorded 11.8 hours after the study drug was administered (at the 10 hour time point and later that subject's Q concentration was not detectable). Three subjects had QTc change from screening of >30 msec and 3 had changes of greater than 60 msec. There was only a single screening determination for each subject.

CONCLUSIONS:

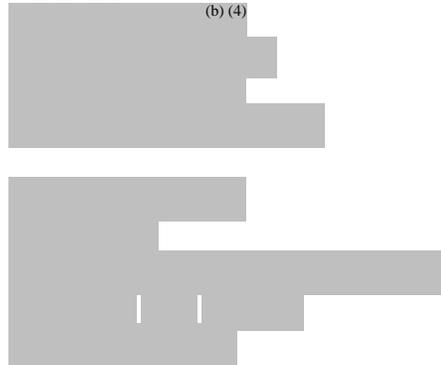
Administration of NEURODEX to healthy volunteers under fasting conditions and with a high fat meal demonstrated no clinically significant effect on C_{max} or AUC of either DM or Q, and an approximate 1-1.5 hr delay in t_{max}. NEURODEX can be taken without regard to meals.

4.2.11 HEPATIC IMPAIRMENT STUDY (O4-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 OF QUINIDINE SULFATE) IN PATIENTS WITH HEPATIC IMPAIRMENT AND HEALTHY VOLUNTEERS

Study Investigators and Site:

(b) (4)



Protocol Number: 04-AVR-115

OBJECTIVE:

The primary objective was to determine and compare the PK at steady state of AVP-923 in healthy volunteers and in patients with mild and moderate hepatic impairment.

The secondary objective was to compare the safety profile at steady-state of AVP-923 in healthy volunteers and in patients with mild and moderate hepatic impairment.

FORMULATIONS:

Table 1. Product used in 04-AVR-115

	Lot Number	Date of Manufacture (Dates of study) or else put exp date
AVP-923 capsules (30 mg DM/30 mg Q)	C0051B001	10/17/2002 (4/6/04-5/27/04)
(b) (4)		

According to the Stability Study Report provided in the present submission, the test product (packaged from lot number C0051001) appears to be stable for at least 36 months at room temperature.

STUDY DESIGN:

This was an open-label, multiple dose, parallel group study. Screening evaluations including CYP2D6 genotype analysis were performed within 28 days prior to the first

dose. CYP2D6 alleles to be evaluated were *3, *4, *7, *8, and *6 as well as *5 and 2XN. Each subject was administered a single oral dose of AVP-923 with 240 ml of water twice daily for 6 consecutive days (Days 1-6) and once in the morning on Day 7. The morning doses were administered between 7 and 9AM, and the afternoon doses were given 12 hours later.

Blood samples were collected in heparinized tubes 30 minutes prior to study drug administration before the initial dose on Day 1, pre-dose on Days 6 and 7 (for pre-dose C_{min} determination) and at the following times after the last dose on Day 7: 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hours. Additional blood samples were taken to measure the unbound fraction of plasma concentrations of analytes at 4 and 12 hours post-dose on Day 7. Urine samples were collected prior to the initial dose on Day 1 and over a collection interval of 0-12 hours after dosing following the last dose on Day 7. Plasma and urine samples were stored at -20° C until analysis.

Safety assessments including 12-lead ECG were performed at Screening, on Day -1, before drug administration and approximately within 20 minutes of the scheduled blood draws at 2, 6, and 12 hours following the 1st dose on Day 1, at 2 and 6 hours following the 13th dose on Day 7, as well as at the end of the 12-hour PK sample on Day 7.

Inclusion criteria for the healthy subjects group included healthy males or females, 18-75 years of age. Subjects could be smokers or nonsmokers. Subjects were matched to hepatic impairment subjects by age, weight, and gender at each site. Subjects were to be medically healthy with clinically normal laboratory profiles and ECGs. Males were required to use barrier contraception during the study and for at least 1 month after the study. Females of child bearing potential were required to use acceptable birth control that could include hormonal contraceptives. Patients in the mild or moderate impaired hepatic function groups were required to meet criteria for the healthy subjects except they must have had medical history, physical findings, ECG, laboratory values and other evidence consistent with a diagnosis of hepatic impairment, must have had mild or moderate hepatic impairment based on Child-Pugh Classification System or hepatic impairment was determined by liver biopsy or liver/spleen scan, must have had evidence of stable hepatic impairment, and if on medications for treatment of liver disease, the patients must have been taking the medications at a stable dose for at least 14 days prior to the first dosing date and continue at that same dose for the duration of the study. These drugs were held between 8 hours before and 4 hours after the dose on Day 7. (**Note:** For the Child-Pugh Score, INR was used instead of prothrombin time, with a scoring system of 1 point for < 1.7, and 2 points for 1.7-2.5. Other published Child Pugh classification systems using the INR generally use a cut-off of 1.7-2.3 for 2 points. However in the subjects included in this study, there were no INR values greater than 2.3. Therefore, this difference does not affect the scoring). Exclusion criteria included subjects with QTc > 470 for females and > 450 msec for males, LFT > 1.5 ULN, use of drugs or substances known to be strong inducers of CYP enzymes within 30 days prior to the first dose, or strong inhibitors within < 10 days prior to the first dose.

Specific drugs were also excluded (other than CYP inhibitors and inducers) that included substrates of CYPs as well as other types of medications. Medications containing dextromethorphan or quinidine were not permitted and the following foods and beverages were prohibited as indicated: xanthines (24 hours before dosing and throughout the study), alcohol (48 hours before dosing and throughout the study), and grapefruit (10 days before dosing and throughout the study). Excluded medications also included OTC and herbal products for 7 days prior to the first dose and throughout the study.

ASSAY:

Plasma DM and DX and Q

Table 2. Performance of Analytical Method for 04-AVR-112 for Plasma DM, DX, and for Plasma Q

Analyte	Method	Calibration Standards (µg/ml)	Linearity	LOQ	QC	Inter-assay CV (%)	Inter-assay Accuracy (%)
DM	LC-MS/MS Method 26267	0.2 -200 ng/ml	r > 0.997	0.2 ng/ml	(ng/ml)		
					0.6	5.06	-7.83
					15	4.29	3.01
DX	LC-MS/MS Method 26267	2.5 -2500 ng/ml	r > 0.998	2.5 ng/ml	(ng/ml)		
					7.5	4.158	2.37
					250	5.54	4.46
Q	HPLC	0.05-10.0 µg/ml	r>0.996	0.05 µg/ml	µg/ml		
					0.15	3.01	-7.00
					1.5	1.85	-5.47
					7.5	1.56	-2.93

For DM and DX in plasma, the method was validated with long term stability demonstrated for 101 weeks at -20° C and samples were analyzed within the time period for which they are stable. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for Study 04-AVR-115 for detection of DM and DX in plasma. The performance of the assay is considered acceptable.

For Q in plasma the method was validated with long term stability demonstrated for 129 weeks at -20° C. The samples were analyzed within the period for which they are stable. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for detection of Q in plasma. The performance of the assay is considered acceptable.

DM and DX in Urine

Table 3. Performance of Analytical Method for 04-AVR-115 for Urine DM and DX

Analyte	Method	Calibration Standards (µg/ml)	Linearity	LOQ	QC	Inter-assay CV (%)	Inter-assay Accuracy (%)
DM	HPLC Method 12730	0.05-15 µg/ml	r > 0.999	0.05 µg/ml	(µg/ml)		
					0.15	1.58	-2.93
					1.0	3.74	-6.54
					12.0	1.24	-7.25

DX	HPLC	0.05-15	$r > 0.999$	0.05	($\mu\text{g/ml}$)	*	2.27
	Method	$\mu\text{g/ml}$		$\mu\text{g/ml}$	0.15		-2.18
	12730				1.0		-5.12
					12.0		

*Only 1 batch was analyzed.

For DM and DX in urine, samples were analyzed within the time for which they have been shown to be stable. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for detection of DM and DX in plasma (only 1 batch of DX was required). The performance of the assay is considered acceptable.

Urine Q was not determined.

Protein Binding

Plasma samples were evaluated for dextromethorphan protein binding using the method described under project AA19370-01 (please refer to individual study report for details of the method).

RESULTS:

Demographics

Twenty-one subjects were enrolled in the study and all 21 subjects completed the study. The demographics of the subjects are shown in the table below, as provided by the Sponsor. The subjects are generally similarly distributed across groups, although it is noted that 1 subject with normal function was an ultra-rapid metabolizer and 1 subject with moderate impairment was a poor metabolizer as determined by genotype.

Table 3. Demographics in subjects in Study 04-AVR-115 (as provided by Sponsor)

Attribute	Hepatic Function			Overall (N=21) Mean \pm SD or N (%)
	Normal Function (N=9)	Mild Impairment (N=6)	Moderate Impairment (N=6)	
	Mean \pm SD or N (%)	Mean \pm SD or N (%)	Mean \pm SD or N (%)	
Age at First Dose (years)	50.7 \pm 3.2	55.0 \pm 5.4	51.7 \pm 6.2	52.2 \pm 4.9
Weight (kg)	82.4 \pm 10.4	88.7 \pm 11.6	84.3 \pm 16.6	84.8 \pm 12.4
Gender				
Male	5 (55.6%)	3 (50.0%)	3 (50.0%)	11 (52.4%)
Female	4 (44.4%)	3 (50.0%)	3 (50.0%)	10 (47.6%)
Race				
Caucasian	3 (33.3%)	1 (16.7%)	2 (33.3%)	6 (28.6%)
Black	2 (22.2%)	3 (50.0%)	1 (16.7%)	6 (28.6%)
Hispanic	4 (44.4%)	2 (33.3%)	2 (33.3%)	8 (38.1%)
Asian/Pacific Islander	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (4.8%)
Phenotype				
Extensive Metabolizer	8 (88.9%)	6 (100.0%)	5 (83.3%)	19 (90.5%)
Ultra-Rapid Metabolizer	1 (11.1%)	0 (0.0%)	0 (0.0%)	1 (4.8%)
Poor Metabolizer	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (4.8%)
Genotype				
(b) (4)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (4.8%)
	4 (44.4%)	2 (33.3%)	0 (0.0%)	6 (28.6%)
	0 (0.0%)	2 (33.3%)	1 (16.7%)	3 (14.3%)
	1 (11.1%)	0 (0.0%)	0 (0.0%)	1 (4.8%)
	4 (44.4%)	2 (33.3%)	4 (66.7%)	10 (47.6%)

Concomitant medications taking during the study included insulin, urosodial, lotensin, ipratropium/albuterol, fluticasone/salmeterol, chondroitin, glucosamine, milk thistle, albuterol, lactulose, clonidine, spironolactone, folic acid, potassium, furosemide, atenolol, and felodipine. None of these are expected to interfere with metabolism or elimination of quinidine or dextromethorphan.

Steady State Analysis

The Sponsor performed a steady state analysis on the ln-transformed pre-dose concentrations at the -24, -12, and 0- hour and the ln-transformed post-dose 12-hour concentration using an ANOVA and Helmert contrasts with each time point compared to the mean of subsequent time points. It could be concluded that dextromethorphan and dextrophan had reached steady state. For quinidine in the mild hepatic impairment group steady state was not statistically concluded for the last time point, although no (mean) accumulation was observed.

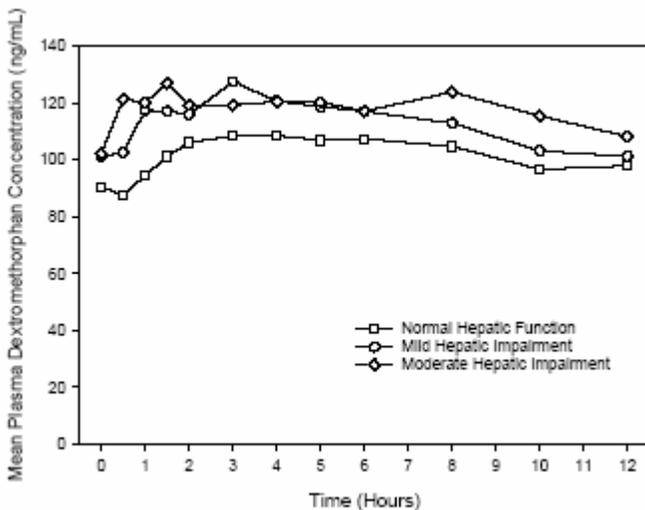
Protein Binding

Protein binding results (fu) are shown in the table below.

	Mean % fu (%CV)	
	DM	Q
Normal Hepatic Function	30.61 (11)	18.8 (20)
Mild Hepatic Impairment	34.98 (11)	21.4 (24)
Moderate Hepatic Impairment	37.22 (17)	30.9 (33)

There was a 14% increase in fu from normal to mild and a 22% increase from normal to moderate for DM. For Q there was a 13% increase in fu from normal to mild and a 64% increase from normal to moderate for quinidine.

The mean baseline albumin levels in patients with normal hepatic, mild and moderate hepatic function were 4.31, 4.23, and 3.88 g/dL, respectively.

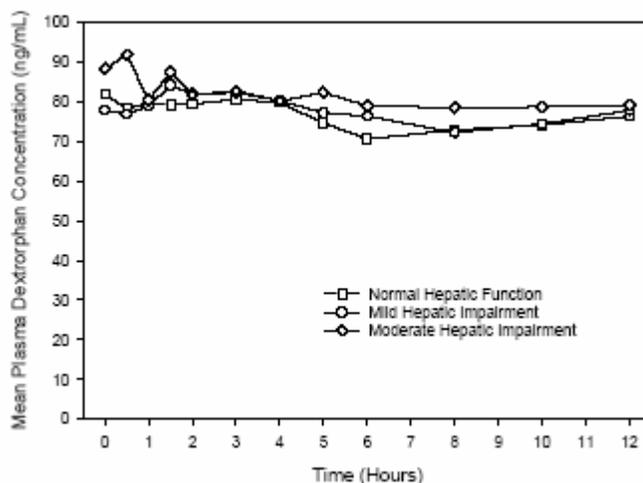


Dextromethorphan and Dextrophan Plasma Concentrations

Mean plasma concentrations for DM and DX on Day 7 are shown in the figures below (as provided by the Sponsor) for patients with normal hepatic function, and mild or moderate impairment.

Pharmacokinetic parameters were determined using noncompartmental analysis. The pertinent pharmacokinetic parameters for DM and DX in plasma are shown below.

Table 5. Pharmacokinetic parameters (arithmetic mean) for DM and for DX in plasma in 04-AVR-115



	Normal Hepatic Function (% CV) n = 9	Mild Hepatic Impairment (% CV) n = 6	Moderate Hepatic Impairment (% CV) n = 6
DM			
t_{max} (h) ^a	3.0 (1.5-12)	3.5 (2.0-6.0)	2.25 (0.5-8.0)
C_{max} (ng/mL)	115.5 (28)	130.5 (26)	134.1 (50)
AUC_{0-t} (ng*h/mL)	1228.9 (30)	1356.3 (23)	1421.2 (47)
Cl/F (L/hr)	20.3 (29)	17.9 (25)	18.5 (34)
C_{min} (ng/ml)	97.9 (34)	101.2 (21)	108.2 (51)
Degree of Fluctuation (%)	18.2 (76)	24.6 (70)	21.1 (39)
Swing (%)	20.3 (83)	29.3 (80)	24.0 (47)
$C_{max(u)}$ (ng/ml)	35.1 (26)	45.0 (24)	50.9 (61)
$AUC_{0-t(u)}$ (ng*h/ml)	372.3 (27)	468.9 (21)	538.0 (56)
$Cl_{(u)}/F$ (L/h)	66.4 (28)	50.9 (18)	51.5 (40)
$C_{min(u)}$ (ng/ml)	29.5 (30)	35.0 (19)	41.2 (62)
DX			
t_{max} (h) ^a	3.0 (0.0-10.0)	2.5 (1.03-12.0)	1.0 (0.5-12.0)
C_{max} (ng/mL)	87.8 (24)	89.4 (23)	96.4 (40)
AUC_{0-t} (ng*h/mL)	909.5 (25)	925.9 (25)	970.2 (42)
Cl/F (L/hr)	ND	ND	ND
C_{min} (ng/ml)	76.3 (26)	77.8 (27)	79.1 (51)
Degree of Fluctuation (%)	14.8 (32)	15.8 (111)	26.3 (92)
Swing (%)	14.9 (34)	17.7 (120)	32.3 (99)

^a median (range)

ND=not determined

For **DM**, there was an approximate 10-13% increase in mean C_{max} and AUC_{0-t} (and an 11% decrease in Cl/F) in mild hepatic impairment and an approximate 26-28% increase in C_{max(u)} and AUC_{0-t(u)} (and 23% decrease in Cl/F) compared to normal hepatic function. In moderate hepatic impairment there was an approximate 16% increase in C_{max} and AUC_{0-t} (and 9% decrease in Cl/F), and an approximate 45% increase in C_{max(u)} and AUC_{0-t(u)} (and 91% decrease in Cl/F) compared to normal hepatic function. For **DX**, the differences in C_{max} and AUC were < 2% in the mild hepatic impairment group and < 10% in moderate hepatic impairment compared to normal hepatic function.

The bioavailability comparisons for **DM** and **DX** in normal hepatic function compared to mild or moderate hepatic impairment are shown in the Table below. The 90% CI for both C_{max} and AUC (total and unbound) fell outside of the BE interval for comparisons of either mild or moderate hepatic impairment to normal hepatic function. For **DX**, since the differences were so small, this is most likely due to variability in the small number of subjects evaluated.

Table 6. Bioavailability Ratios for DM and DX in plasma Study 04-AVR-115

	Geometric Mean			Ratio of Geometric Means and 95% CI of the Ratio	
	Normal Hepatic Function n = 9	Mild Hepatic Impairment n = 6	Moderate Hepatic Impairment n = 6	Mild vs Normal	Moderate vs Normal
DM					
C _{max} (ng/ml)	112	127	123	1.13 (0.84-1.53)	1.11 (0.82-1.49)
AUC _{0-t} (ng*h/ml)	1182	1325	1321	1.12 (0.84-1.49)	1.12 (0.84-1.49)
C _{max(u)} (ng/ml)	34	44	45.4	1.30 (0.95-1.77)	1.34 (0.98-1.82)
AUC _{0-t(u)} (ng*h/ml)	360	461	486	1.28 (0.95-1.72)	1.35 (1.00-1.82)
DX					
C _{max} (ng/ml)	85.0	87.6	85.9	1.03 (0.72-1.46)	1.01 (0.71-1.44)
AUC _{0-t} (ng*h/ml)	884	904	859	1.02 (0.72-1.46)	0.97 (0.68-1.38)

DM and DX in Urine

Pharmacokinetic parameters for **DM** and **DX** in the urine are shown in the table below.

Table 7. Pharmacokinetic parameters (arithmetic mean) for DM and for DX in urine in 04-AVR-115

	Normal Hepatic Function (% CV) n = 9	Mild Hepatic Impairment (% CV) n = 6	Moderate Hepatic Impairment (% CV) n = 6
DM			
Ae ₀₋₁₂ (µg)	3715 (60)	5101 (33)	2606 (64)
Cl _R (L/hr)	3.0 (61)	3.8 (26)	2.2 (59)
Cl _{R(u)} (L/hr)	10.2 (67)	10.9 (24)	6.0 (60)
fe ₀₋₁₂ (%)	16.1 (60)	22.1 (33)	11.3 (64)
DX			
Ae ₀₋₁₂ (µg)	3752 (41)	4718 (40)	4221 (49)
Cl _{R/F_m} (L/hr)	4.27 (42)	5.03 (20)	4.90 (57)

Cl_R was approximately 11-20% that of Cl/F . For DM, urinary excretion parameters in patients with moderate hepatic impairment were unexpectedly lower than those observed in subjects with normal hepatic function, although the mean creatinine clearance values were similar (96 ml/min in normal vs 112 ml/min in moderate).

Of note, 4 subjects did not convert to CYP2D6 poor metabolizers by phenotype, with the DM/DX ratio remaining < 0.3 . This included 1 subject with normal hepatic function (ratio of 0.13) and 3 subjects with moderate hepatic impairment (0.26, 0.11, and 0.28, respectively). This could potentially be explained by the decrease in urinary excretion parameters in the moderate impairment group, as the urinary excretion parameters for the 3 subjects who remained extensive metabolizers by phenotype were only approximately 4-60% of those values in the other 3 subjects in that group who did become poor metabolizers.

Quinidine in Plasma

The mean quinidine plasma concentration time course curves for normal hepatic function and mild and moderate hepatic impairment on Day 7 are shown in the figure below (as provided by the Sponsor) and PK parameters are shown in the table below.

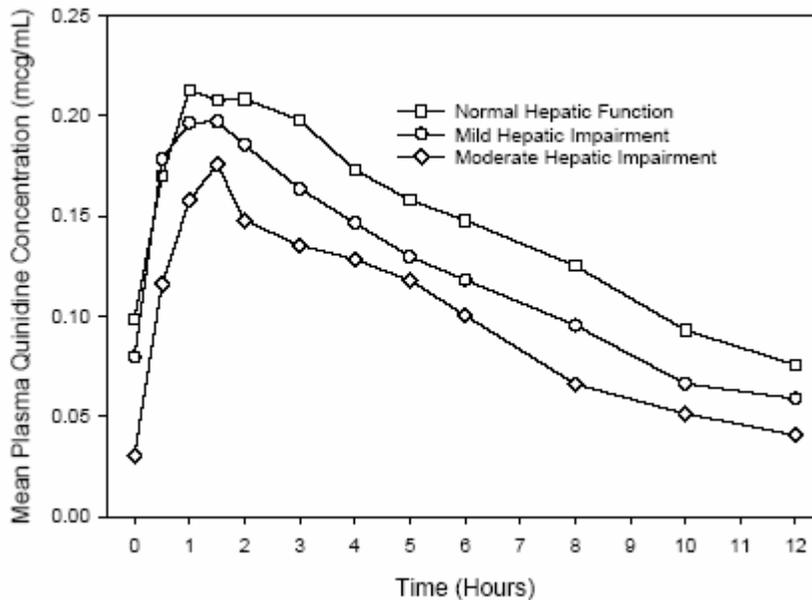


Table 8. Pharmacokinetic parameters (arithmetic mean) for Q in plasma in 04-AVR-115

	Normal Hepatic Function (% CV) n = 9	Mild Hepatic Impairment (% CV) n = 6	Moderate Hepatic Impairment (% CV) n = 6
Q			
t _{max} (h) ^a	1.5 (0.5-3.0)	1.0 (0.5-2.0)	0.79 (0.5-1.5)
C _{max} (µg/mL)	0.236 (25)	0.229 (26)	0.18 (55)
AUC _{0-t} (µg*h/mL)	1.877 (28) (n=7)	1.516 (23) (n=5)	1.809 (22) (n=3)
Cl/F (L/hr)	14.98 (30) (n=7)	18.1 (26) (n=5)	14.85 (19) (n=3)
C _{min} (µg/ml)	0.097 (33) (n=7)	0.07 (20) (n=5)	0.08 (25) (n=3)
Degree of Fluctuation (%)	96.6 (20) (n=7)	135.6 (22) (n=5)	118.9 (7.6) (n=3)
Swing (%)	160.3 (29) (n=7)	244.8 (27) (n=5)	221.5 (5.6) (n=3)
C _{max(u)} (µg/ml)	0.04341 (21)	0.048 (27)	0.0496 (41)
AUC _{0-t(u)} (µg*h/ml)	0.3523 (20) (n=7)	0.294 (22) (n=5)	0.443 (40) (n=3)
Cl _(u) /F (L/h)	76.44 (18) (n=7)	92.8 (25) (n=5)	64.6 (33) (n=3)
C _{min(u)} (µg/ml)	0.018 (26) (n=7)	0.0137 (23) (n=5)	0.0198 (39) (n=3)

^a median (range)

AUC, C_{min}, Cl/F, Degree of Fluctuation, and Swing could not be calculated for some patients due to undetectable concentrations at the end of the dosing interval.

The three moderate impairment subjects who failed to convert to poor metabolizers were not clearly distinguishable from the other moderate impairment subjects in their Q PK parameters.

For Q, there was an approximate 3% decrease in mean C_{max} and a 19% decrease in AUC_{0-t} (and a 21% increase in Cl/F) in mild hepatic impairment and an approximate 10% increase in C_{max(u)} and a 16% decrease in AUC_{0-t(u)} (and 21% increase in Cl_(u)/F) compared to normal hepatic function. In moderate hepatic impairment there was an approximate 23% decrease in C_{max} and a 4% decrease in AUC_{0-t} (and a 1% decrease in Cl/F), and an approximate 14% increase in C_{max(u)} and a 26% increase in AUC_{0-t(u)} (and a 15% decrease in Cl_(u)/F) compared to normal hepatic function.

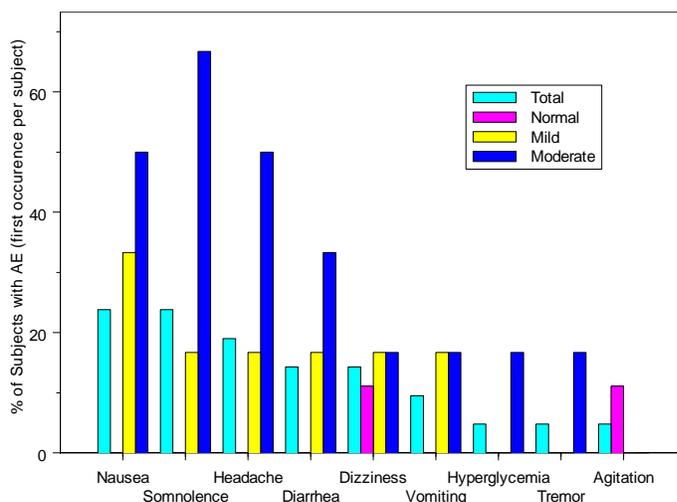
The bioavailability of Q in normal hepatic function compared to mild or moderate hepatic impairment is shown in the Table below. The 90% CI for both C_{max} and AUC (total and unbound) fell outside of the BE interval for comparisons of either mild or moderate hepatic impairment to normal hepatic function. For some parameters, since the differences were so small, this is most likely due to variability in the small number of subjects evaluated and for whom data could be evaluated. The decrease in Q exposure observed in moderate hepatic impairment is not likely to be clinically significant (with respect to the ability to inhibit CYP2D6), since the C_{max} is similar to and AUC is higher than that obtained with the 25 mg dose in Study 99-AVR-100, and that was determined to be the optimal dose.

Table 6. Bioavailability Ratios for Q in plasma Study 04-AVR-115

	Geometric Mean			Ratio of Geometric Means and 95% CI of the Ratio	
	Normal Hepatic Function	Mild Hepatic Impairment	Moderate Hepatic Impairment	Mild vs Normal	Moderate vs Normal
	C_{max} (ng/ml)	0.229	0.223	0.160	0.97 (0.70-1.35)
AUC_{0-t} (ng*h/ml)	1.81	1.48	1.78	0.82 (0.62-1.08)	0.98 (0.71-1.36)
$C_{max(u)}$ (ng/ml)	0.0425	0.0465	0.0468	1.10 (0.85-1.41)	1.10 (0.86-1.42)
$AUC_{0-t(u)}$ (ng*h/ml)	0.347	0.288	0.422	0.83 (0.64-1.07)	1.22 (0.90-1.64)

Safety

The Sponsor has reported that there were no severe or serious adverse events (AEs) reported during this study. A total of 35 AEs were reported. Thirty-one of the 35 were considered possibly, probably, or likely related to study drug, and all AEs were of mild or moderate severity. The most common AEs (occurring in > 10% of subjects) were somnolence, headache, nausea and diarrhea as shown by hepatic impairment group in the figure below. These occurred to a greater extent in the subjects with moderate hepatic impairment. In addition, 1 subject in the mild impairment group developed sinus tachycardia that was ongoing at the end of the study and was considered to be unrelated to study medication and resolved within 2 months of completing the study.



ECG intervals were evaluated at specific time points. The mean change from baseline in QTc was not greater than 12.0 msec in any group at any measured time point. Nine subjects (3 normal, 2 mild, 4 moderate) had QTc values > 450 msec (but less than 480). Five subjects (1 normal, 2 mild, 2 moderate) had change in QTc of >30 msec (and < 60 msec).

CONCLUSIONS:

Note: The hepatic extraction ratio for quinidine has been reported to be low (0.27)¹¹ to intermediate (0.3-0.7)¹² and it is not extensively protein bound ($f_u > 10\%$). The hepatic extraction ratio for DM is high (>0.7)¹³, although it is not extensively protein bound ($f_u > 10\%$). Therefore, the conclusions will primarily consider the PK parameters for total quinidine or dextromethorphan concentrations.

1. Following steady state administration of NEURODEX, dextromethorphan C_{max} and AUC increased approximately 10-13% in subjects with mild hepatic impairment and approximately 16% in subjects with moderate hepatic impairment, compared to subjects with normal hepatic function.
2. Following steady state administration of NEURODEX, dextromethorphan C_{max} and AUC increased less than 2% in mild hepatic impairment and $< 10\%$ in moderate hepatic impairment compared to subjects with normal hepatic function.
3. Following steady state administration of NEURODEX, quinidine C_{max} and AUC *decreased* 3% and 19%, respectively in subjects with mild hepatic impairment and approximately 23% and 4%, respectively in subjects with moderate hepatic impairment, compared to subjects with normal hepatic function.
4. Although exposure to total Q decreased in moderate hepatic impairment, there was a 14% increase in C_{max}(u) and a 26% increase in AUC_{0-t}(u) compared to normal hepatic function. Whether this small increase in free concentration could have resulted in additional inhibition of P-glycoprotein that would have interfered with elimination of DM (a P-gp substrate), resulting in a decrease in renal excretion of DM is unknown.
5. The most common AEs (occurring in $> 10\%$ of subjects) were somnolence, headache, nausea and diarrhea as shown by hepatic impairment group in the figure below. These occurred to a greater extent in the subjects with moderate hepatic impairment.
6. Based on the PK results above, no dosage adjustment is required in patients with mild and moderate hepatic impairment. The PK after administration of NEURODEX has not been studied in severe hepatic impairment, and it should be used with caution in that population.

¹¹ Applied Biopharmaceutics and Pharmacokinetics, 4th edition, 1999. Chapter 13, p. 380. (L Shargel and A.B.C. Yu, eds.)

¹² Clinical Pharmacokinetics, 3rd edition, 1995. Chapter 11, p. 163 (M. Rowland and T. Tozer, eds).

¹³ Vuppugalla R, Mehvar R. Drug Metab Dispos 2006 (April 18; Epub).

4.2.12 RENAL IMPAIRMENT STUDY (O4-AVR-116)

AN OPEN-LABEL, MULTIPLE-DOSE, MULTIPLE-SITE, PARALLEL GROUP STUDY TO EVALUATE THE PHARMACOKINETICS AND SAFETY PROFILE OF AVP-923 (30 MG OF DEXTROMETHORPHAN HYDROBROMIDE AND 30 MG OF QUINIDINE SULFATE) IN PATIENTS WITH VARIOUS STAGES OF RENAL INSUFFICIENCY AND HEALTHY ADULT VOLUNTEERS

Study Investigators and Site:

(b) (4) [Redacted]

Protocol Number: 04-AVR-116

OBJECTIVE:

The primary objective was to determine and compare the PK at steady state of AVP-923 in healthy volunteers and in patients with mild and moderate renal impairment.

The secondary objective was to compare the safety profile at steady-state of AVP-923 in healthy volunteers and in patients with mild and moderate renal impairment.

FORMULATIONS:

Table 1. Product used in 04-AVR-116

	Lot Number	Date of Manufacture (Dates of study) or else put exp date
AVP-923 capsules (30 mg DM/30 mg Q) (b) (4)	C0051B001	10/17/02 (4/5/04-6/10/04)

According to the Stability Study Report provided in the present submission, the test product (packaged from lot number C0051001) appears to be stable for at least 36 months at room temperature.

STUDY DESIGN:

This was an open-label, multiple dose, parallel group study. Screening evaluations including CYP2D6 genotype analysis were performed within 28 days prior to the first dose. CYP2D6 alleles evaluated were *3, *4, *7, *8, and *6 as well as *5 and 2XN. Each subject was administered a single oral dose of AVP-923 with 240 ml of water twice daily for 6 consecutive days (Days 1-6) and once in the morning on Day 7. The morning doses were administered between 7 and 9AM, and the afternoon doses were given 12 hours later.

Blood samples were collected in (b) (4) tubes 30 minutes prior to study drug administration before the initial dose on Day 1, pre-dose on Days 6 and 7 (for pre-dose C_{min} determination) and at the following times after the last dose on Day 7: 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hours. Additional blood samples were taken to measure the unbound fraction of plasma concentrations of analytes at 4 and 12 hours post-dose on Day 7. Urine samples were collected prior to the initial dose on Day 1 and over a collection interval of 0-12 hours after dosing following the last dose on Day 7. Plasma and urine samples were stored at -20° C until analysis.

Safety assessments including 12-lead ECG were performed at Screening, on Day -1, before drug administration and approximately within 20 minutes of the scheduled blood draws at 2, 6, and 12 hours following the 1st dose on Day 1, at 2 and 6 hours following the 13th dose on Day 7, as well as at the end of the 12-hour PK sample on Day 7.

Inclusion criteria for the healthy subjects (normal renal function) group included healthy males or females, 18-75 years of age, with creatinine clearance ≥ 80 ml/min. Subjects could be smokers or nonsmokers. Subjects were to be $\pm 10\%$ of the mean age of the renal failure population included in the study and be $\pm 20\%$ of the average weight of the impaired renal subjects. Subjects were to be medically healthy with clinically normal laboratory profiles and ECGs. Males were required to use barrier contraception during the study and for at least 1 month after the study. Females of child bearing potential were required to use acceptable birth control that could include hormonal contraceptives. Patients in the impaired renal function groups were required to meet criteria for the healthy subjects except they must have had medical history, physical findings, ECG, laboratory values and other evidence consistent with a diagnosis of renal impairment, must have had mild or moderate renal impairment (CrCl 50-80 ml/min for mild and 30-49 ml/min for moderate), evidence of stable renal impairment, stable diabetes (if they have diabetes mellitus) as determined by HbA1c and on a stable insulin/oral hypoglycemic regimen, and if on medications for treatment of renal disease, the patients must have been taking the medications at a stable dose for at least 14 days prior to the first dosing date and continue at that same dose for the duration of the study. These drugs were held between 8 hours before and 4 hours after the dose on Day 7. **Exclusion** criteria included subjects with QTc > 470 for females and > 450 msec for males, LFT > 1.5 ULN, use of drugs or substances known to be strong inducers of CYP enzymes within 30 days prior to the first dose, or strong inhibitors within < 10 days prior to the first dose.

Subjects were housed for at least 24 hours on 2 different sessions, within 21 days prior to dosing, for urine collection for determination of creatinine clearance. Five subjects with normal renal function at 1 site did not have urine collected, but the creatinine clearance was determined via Cockcroft-Gault for those subjects.

Specific drugs were also excluded (other than CYP inhibitors and inducers) that included substrates of CYPs as well as other types of medications. Medications containing dextromethorphan or quinidine were not permitted and the following foods and beverages were prohibited as indicated: xanthines (24 hours before dosing and throughout the

study), alcohol (48 hours before dosing and throughout the study), and grapefruit (10 days before dosing and throughout the study). Excluded medications also included OTC and herbal products for 7 days prior to the first dose and throughout the study.

ASSAY:

Plasma DM and DX and Q

Table 2. Performance of Analytical Method for 04-AVR-116 for Plasma DM, DX, and for Plasma Q

Analyte	Method	Calibration Standards (µg/ml)	Linearity	LOQ	QC	Inter-assay CV (%)	Inter-assay Accuracy (%)
DM	LC-MS/MS Method 26267	0.2 -200 ng/ml	r > 0.998	0.2 ng/ml	(ng/ml)		
					0.6	7.11	-3.83
					15	3.69	1.77
DX	LC-MS/MS Method 26267	2.5 -2500 ng/ml	r > 0.998	2.5 ng/ml	(ng/ml)		
					7.5	4.12	2.69
					250	4.55	6.56
Q	HPLC	0.05-10.0 µg/ml	r>0.993	0.05 µg/ml	(µg/ml)		
					0.15	3.5	-4.8
					1.5	7.36	-5.61
					7.5	6.04	-4.89

For DM and DX in plasma, the method was validated with long term stability demonstrated for 101 weeks at -20° C and samples were analyzed within the time period for which they are stable. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for Study 04-AVR-116 for detection of DM and DX in plasma. The performance of the assay is considered acceptable.

For Q in plasma the method was validated with long term stability demonstrated for 129 weeks at -20° C. The samples were analyzed within the period for which they are stable. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for detection of Q in plasma. The performance of the assay is considered acceptable.

DM and DX in Urine

Table 3. Performance of Analytical Method for 04-AVR-116 for Urine DM and DX

Analyte	Method	Calibration Standards (µg/ml)	Linearity	LOQ	QC	Inter-assay CV (%)	Inter-assay Accuracy (%)
DM	HPLC Method 12730	0.05-15 µg/ml	r > 0.999	0.05 µg/ml	(µg/ml)		
					0.15	2.21	-6.33
					1.0	3.86	-3.87
DX	HPLC Method 12730	0.05-15 µg/ml	r > 0.999	0.05 µg/ml	(µg/ml)		
					0.15	1.91	-2.13
					1.0	3.11	-2.65
					12.0	1.57	-3.02

For DM and DX in urine, samples were analyzed within the time for which they have been shown to be stable (that is 34 months). One calibration curve and duplicate QC samples were analyzed with each batch of study samples for detection of DM and DX in plasma (only 1 batch of DX was required). The performance of the assay is considered acceptable.

Urine Q was not determined.

Protein Binding

Plasma samples were evaluated for dextromethorphan protein binding using the method described under project AA19370-01 and for quinidine under AA19369-01 (please refer to individual study report for details of the method).

RESULTS:

Demographics

Twenty-one subjects were enrolled in the study and all 21 subjects completed the study. The demographics of the subjects are shown in the table below, as provided by the Sponsor. The age range was 46-73 years. The subjects are generally similarly distributed across groups, although the moderately impaired patients were heavier on average compared to the other subjects, although still within the pre-defined weight range. Note: the “phenotype” reflects the predicted CYP2D6 phenotype based on the CYP2D6 genotype.

Table 3. Demographics in subjects in Study 04-AVR-116 (as provided by Sponsor)

Attribute	Renal Function			Overall (N=21) Mean ± SD or N (%)
	Normal Function (N=9)	Mild Impairment (N=6)	Moderate Impairment (N=6)	
	Mean ± SD or N (%)	Mean ± SD or N (%)	Mean ± SD or N (%)	
Age at First Dose (years)	59.4 ± 5.7	61.2 ± 6.8	61.7 ± 9.9	60.6 ± 7.1
Weight (kg)	77.6 ± 5.9	71.7 ± 7.7	90.8 ± 15.3	79.7 ± 12.1
Gender				
Male	4 (44.4%)	4 (66.7%)	3 (50.0%)	11 (52.4%)
Female	5 (55.6%)	2 (33.3%)	3 (50.0%)	10 (47.6%)
Race				
Caucasian	5 (55.6%)	3 (50.0%)	3 (50.0%)	11 (52.4%)
Black	1 (11.1%)	1 (16.7%)	2 (33.3%)	4 (19.0%)
Hispanic	3 (33.3%)	2 (33.3%)	1 (16.7%)	6 (28.6%)
Phenotype				
Extensive Metabolizer	8 (88.9%)	5 (83.3%)	6 (100.0%)	19 (90.5%)
Ultra-Rapid Metabolizer	1 (11.1%)	1 (16.7%)	0 (0.0%)	2 (9.5%)
Genotype				
(b) (4)	5 (55.6%)	2 (33.3%)	1 (16.7%)	8 (38.1%)
	1 (11.1%)	1 (16.7%)	0 (0.0%)	2 (9.5%)
	3 (33.3%)	3 (50.0%)	5 (83.3%)	11 (52.4%)

The mean creatinine clearance by group is shown in the table below, as calculated by Sponsor.

Table 4. Renal function in subjects in 04-AVR-116

	Renal Function			Overall (n=21)
	Normal Function (n=9)	Mild Impairment (n=6)	Moderate Impairment (n=6)	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Creatinine Clearance	87.5 ± 5.3	64.6 ± 8.9	37.0 ± 3.4	66.5 ± 22.2

Concomitant medications taken during the study included insulin, acetaminophen, insulin, fosinopril, metoprolol, simvastatin, aspirin, furosemide, amlodipine, lisinopril, TUMS, prazosin, allopurinol, enalapril, valdecoxib, colchicine, atorvastatin, benazepril, glipizide, and captopril.

Steady State Analysis

The Sponsor performed steady state analysis on ln-transformed pre-dose concentrations at the -24, -12, and 0- hour and the ln-transformed post-dose 12-hour concentration using ANOVA and Helmert contrasts with each time point compared to the mean of subsequent time points. It could be concluded that dextromethorphan and dextrorphan had reached steady state. For quinidine steady state could be concluded, (however, for the normal subjects it could not be statistically concluded at the last 2 time points although accumulation was not observed).

Protein Binding

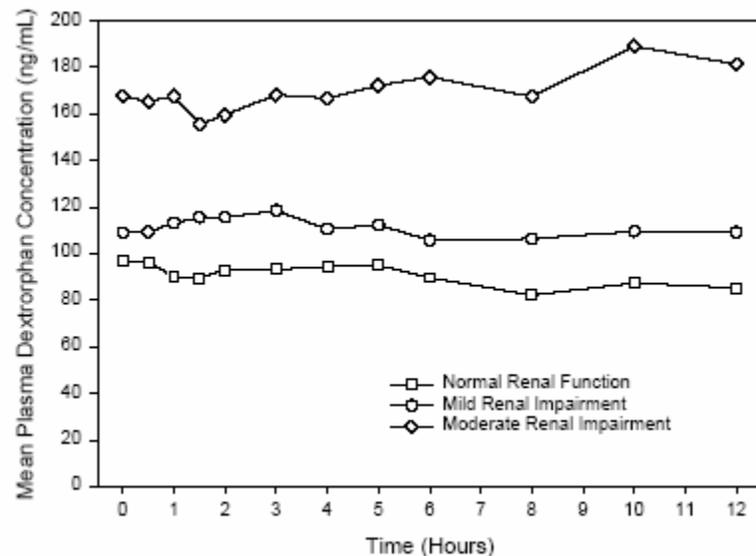
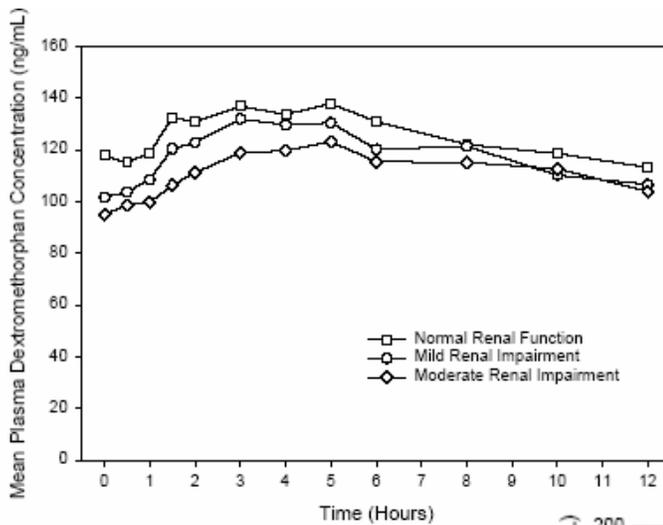
Protein binding results (fu) are shown in the table below.

	Mean % fu (%CV)	
	DM	Q
Normal Renal Function	35.3 (8)	16.6 (14)
Mild Renal Impairment	34.6 (41)	17.2 (17)
Moderate Renal Impairment	34.6 (18)	15.7 (19)

The fu in normal renal function is in agreement with that previously reported in healthy subjects (e.g. Study 04-AVR-115). There was less than a 5% difference in fu in normal renal function vs renal impairment for either DM or Q.

Dextromethorphan and Dextrorphan Plasma Concentrations

Mean plasma concentrations for DM and DX on Day 7 are shown in the figures below (as provided by the Sponsor) for patients with normal renal function, and mild or moderate impairment.



PK parameters were determined using noncompartmental analysis. The pertinent PK parameters for DM and DX in plasma are shown below.

Table 5. Pharmacokinetic parameters (arithmetic mean) for DM and for DX in plasma in 04-AVR-116

	Normal Renal Function (% CV) n = 9	Mild Renal Impairment (% CV) n = 6	Moderate Renal Impairment (% CV) n = 6
DM			
t_{max} (h) ^a	3.0 (1.5-6.0)	3.5 (1.5-5.0)	4.0 (1.5-10.0)
C_{max} (ng/mL)	148.4 (29)	139.1 (36)	131.3 (9)
AUC_{0-t} (ng*h/mL)	1512.2 (29)	1427.9 (40)	1355.6 (13)

Cl/F (L/hr)	17.1 (43)	18.4 (38)	17.2 (12)
C _{min} (ng/ml)	113.3 (39)	106.8 (45)	104.0 (19)
Degree of Fluctuation (%)	29.1 (46)	29.5 (39)	25.1 (82)
Swing (%)	33.9 (56)	34.1 (45)	31.1 (108)
C _{max(u)} (ng/ml)	52.7 (32)	48.3 (37)	46.0 (26)
AUC _{0-t(u)} (ng*h/ml)	538.2 (32)	492.6 (38)	471.9 (27)
Cl _(u) /F (L/h)	49.19 (49)	55.1 (50)	51.3 (21)
C _{min(u)} (ng/ml)	40.4 (37)	36.6 (41)	36.0 (29)
DX			
t _{max} (h) ^a	2.0 (0.0-10)	2.5 (0.0-10.0)	11.0 (4.0-12.0)
C _{max} (ng/mL)	105.7 (61)	142.0 (37)	195.2 (43)
AUC _{0-t} (ng*h/mL)	1072.8 (55)	1323.9 (44)	2071.3 (37)
Cl/F (L/hr)	ND	ND	ND
C _{min} (ng/ml)	85.3 (51)	109.1 (54)	181.3 (45)
Degree of Fluctuation (%)	19.2 (79)	40.3 (154)	7.2 (176)
Swing (%)	20.6 (79)	48.6 (158)	8.1 (183)

^a median (range)

ND=not determined

For DM, there was an approximate 6-7% decrease in mean C_{max} and AUC_{0-t} (and an approximate 8% increase in Cl/F) in mild renal impairment and an approximate 8% decrease in C_{max(u)} and AUC_{0-t(u)} (and 12% increase in Cl_u/F) compared to normal renal function. In moderate renal impairment there was an approximate 10-11% decrease in C_{max} and AUC_{0-t} (and <1 % increase in Cl/F), and an approximate 12% decrease in C_{max(u)} and AUC_{0-t(u)} (and 4% increase in Cl_u/F) compared to normal renal function.

For DX, the median t_{max} was approximately 9 hours later in moderate renal impairment than in either normal renal function or mild renal impairment. The C_{max} and AUC_{0-t} were 34% and 23% greater, respectively, in mild renal impairment compared to normal renal function. In moderate renal impairment the C_{max} and AUC_{0-t} were 85% and 93% greater, respectively, compared to normal renal function. In addition, the DM/DX ratio for both C_{max} and AUC in plasma for both C_{max} and AUC changed from approximately 0.7 in normal renal function, to approximately 1 in mild renal impairment to approximately 1.5 in moderate renal impairment. (The DX concentrations observed in moderate impairment remain within the range of concentrations when DM is given at an OTC dose in the absence of Q (Study 99-AVR-102)).

The bioavailability comparisons for DM and DX in normal renal function compared to mild or moderate renal impairment are shown in the Table below. The 90% CI for both C_{max} and AUC (total and unbound) fell outside of the BE interval for comparisons of either mild or moderate renal impairment to normal renal function. For DM, since the differences were so small, this is most likely due to variability in the small number of subjects evaluated.

Table 6. Bioavailability Ratios for DM and DX in plasma Study 04-AVR-116

Geometric Mean	Ratio of Geometric Means and 95% CI of the Ratio
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	Normal Renal Function n = 9	Mild Renal Impairment n = 6	Moderate Renal Impairment n = 6	Mild vs Normal	Moderate vs Normal
DM					
C _{max} (ng/ml)	141	132	131	0.94 (0.70-1.25)	0.93 (0.70-1.24)
AUC _{0-t} (ng*h/ml)	1441	1339	1346	0.93 (0.69-1.24)	0.94 (0.70-1.25)
C _{max(u)} (ng/ml)	49.6	45.0	44.7	0.91 (0.64-1.28)	0.93 (0.70-1.24)
AUC _{0-t(u)} (ng*h/ml)	508	458	460	0.90 (0.64-1.27)	0.91 (0.64-1.27)
DX					
C _{max} (ng/ml)	88.5	131	181	1.48 (0.88-2.47)	2.05 (1.22-3.43)
AUC _{0-t} (ng*h/ml)	907	1203	1962	1.33 (0.81-2.19)	2.16 (1.31-3.56)

DM and DX in Urine

Pharmacokinetic parameters for DM and DX in the urine are shown in the table below.

Table 7. Pharmacokinetic parameters (arithmetic mean) for DM and for DX in urine in 04-AVR-116

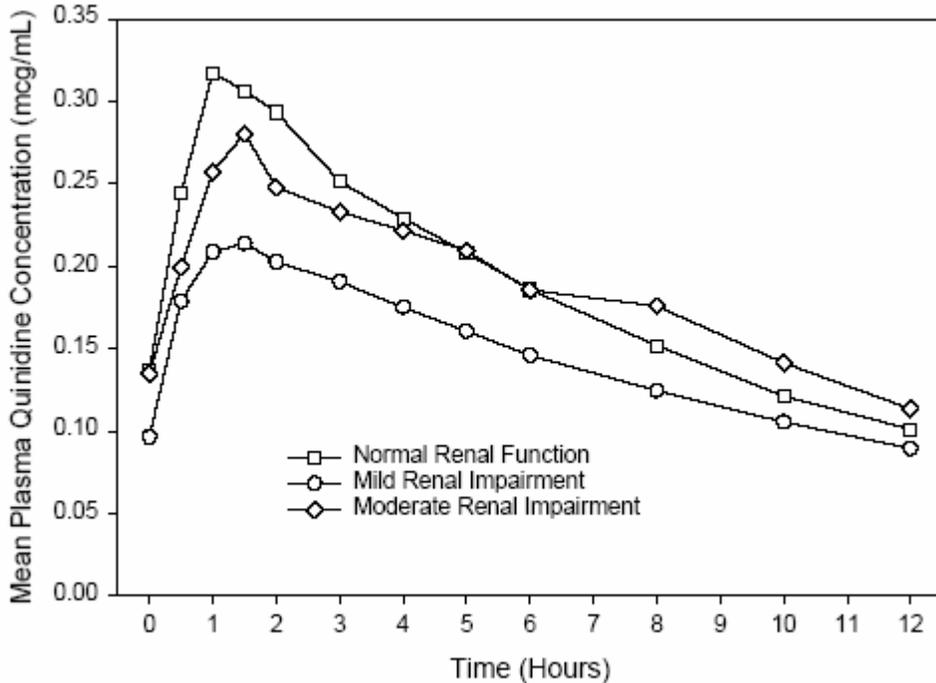
	Normal Renal Function (% CV) n = 9	Mild Renal Impairment (% CV) n = 6	Moderate Renal Impairment (% CV) n = 6
DM			
Ae ₀₋₁₂ (µg)	3866.7 (44)	4126.5 (21)	2234.0 (51)
Cl _R (L/hr)	2.6 (39)	3.1 (26)	1.6 (54)
Cl _{R(u)} (L/hr)	7.5 (41)	9.2 (29)	5.0 (59)
fe ₀₋₁₂ (%)	16.7 (44)	17.9 (21)	9.7 (51)
DX			
Ae ₀₋₁₂ (µg)	3527.7 (56)	4568.8 (56)	2442.2 (59)
Cl _R /F _m (L/hr)	3.3 (27)	3.4 (31)	1.4 (65)

Cl_R of DM was approximately 15-17 % that of Cl/F for normal and mild renal impairment and approximately 29% of Cl/F for moderate renal impairment. For DM and DX, urinary excretion parameters in patients with mild renal impairment were approximately 7-30% greater than those observed in subjects with normal renal function. In patients with moderate renal impairment, those values were approximately 30-58% lower than in patients with normal renal function.

All subjects with normal renal function and mild renal impairment had a poor metabolizer phenotype on Day 7 based on the urinary DM/DX ratio. One subject (#010003) with moderate renal impairment did not have a calculable ratio as he had no detectable DM or DX in his urine; the remainder of subjects with moderate renal impairment had a poor metabolizer phenotype on Day 7. The plasma concentrations of DM in that subject were not distinguishable from those of the other subjects with renal impairment, although his DX C_{max} was approximately 1.7 fold greater than the mean for

that group. CrCl in that subject was 39 ml/min, a value that was greater than the mean for the moderate impairment group.

Quinidine in Plasma



The mean quinidine plasma concentration time course curves for normal renal function and mild and moderate renal

impairment on Day 7 are shown in the figure at left (as provided by the Sponsor) and PK parameters are shown in the table below.

Table 8. Pharmacokinetic parameters (arithmetic mean) for Q in plasma in 04-AVR-116

	Normal Renal Function (% CV) n = 9	Mild Renal Impairment (% CV) n = 6	Moderate Renal Impairment (% CV) n = 6
Q			
t _{max} (h) ^a	1.0 (0.5-2.0)	1.25 (0.5-3.0)	1.5 (1.0-1.5)
C _{max} (µg/mL)	0.332 (36)	0.227 (15)	0.286 (35)
AUC _{0-t} (µg*h/mL)	2.444 (38) (n=8)	1.77 (16)	2.502 (24) (n=5)
Cl/F (L/hr)	11.92 (33) (n=8)	15.1 (17)	11.03 (28) (n=5)
C _{min} (µg/ml)	0.114 (49) (n=8)	0.08923 (21)	0.136 (32) (n=5)
Degree of Fluctuation (%)	123.0 (15) (n=8)	94.1 (19)	84.9 (36) (n=5)
Swing (%)	232.2 (24) (n=8)	161.23 (32)	138.1 (51) (n=5)
C _{max(u)} (µg/ml)	0.0545 (29)	0.039 (17)	0.043 (30)
AUC _{0-t(u)} (µg*h/ml)	0.4025 (29) (n=7)	0.305 (21)	0.377 (32) (n=5)
Cl _(u) /F (L/h)	69.8 (30) (n=7)	90.3 (29)	74.7 (29) (n=5)
C _{min(u)} (µg/ml)	0.0188 (39) (n=7)	0.0156 (30)	0.021 (44) (n=5)

^a median (range)

AUC, C_{min}, Cl/F, Degree of Fluctuation, and Swing could not be calculated for some patients due to undetectable concentrations at the end of the dosing interval.

For Q, there was an approximate 30% decrease in mean C_{max} and AUC_{0-t} (and a 27% increase in Cl/F) in mild renal impairment and an approximate 24-28% decrease in C_{max(u)} and AUC_{0-t(u)} (and a 29% increase in Cl_(u) /F) compared to normal renal function. In moderate renal impairment there was an approximate 13% decrease in C_{max} and a 3% increase in AUC_{0-t} (and a 7% decrease in Cl/F), and an approximate 21% decrease in C_{max(u)} and a 6% decrease in AUC_{0-t(u)} (and a 7% increase in Cl_(u) /F) compared to normal renal function.

The bioavailability of Q in normal renal function compared to mild or moderate renal impairment is shown in the Table below. The 90% CI for both C_{max} and AUC (total and unbound) fell outside of the BE interval for comparisons of either mild or moderate renal impairment to normal renal function. For some parameters, since the differences were so small, this is most likely due to variability in the small number of subjects evaluated.

Table 6. Bioavailability Ratios for Q in plasma Study 04-AVR-116

	Geometric Mean			Ratio of Geometric Means and 95% CI of the Ratio	
	Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment	Mild vs Normal	Moderate vs Normal
C _{max} (µg/mL)	0.313	0.225	0.271	0.72 (0.53-0.97)	0.87 (0.64-1.17)
AUC _{0-t} (µg *h/ml)	2.31	1.75	2.44	0.76 (0.58-0.99)	1.06 (0.80-1.40)
C _{max(u)} (µg /ml)	0.0521	0.0382	0.0417	0.74 (0.56-0.97)	0.80 (0.61-1.05)
AUC _{0-t(u)} (µg *h/ml)	0.388	0.298	0.363	0.77 (0.58-1.01)	0.93 (0.70-1.25)

Safety

The Sponsor states that there were no severe or serious adverse events (AEs) or deaths reported during this study. A total of 17 AEs were reported during the study, 14 in the normal group, 3 in the mild renal impairment group, and none in the moderate renal impairment group. All AEs were of mild or moderate severity. The most common AEs were somnolence, nausea and vomiting (in the same subject), and diarrhea. Syncope was reported in 1 subject with normal renal function.

ECG intervals were evaluated from specific time points. The mean change from baseline in QTc was not greater than 13.6 msec in any group at any measured time point. There were 4 QTc values > 450 msec (but less than 480). Two of those values were at baseline in patients with mild renal impairment. There were 8 values (in 7 subjects) of change in QTc of > 30 msec (but < 60 msec). Four of those subjects had moderate impairment, 1 was a subject with mild renal impairment, and 2 were subjects with normal renal function.

CONCLUSIONS:

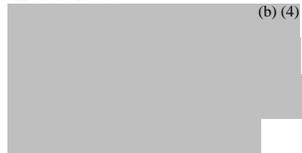
Note: Neither quinidine nor dextromethorphan are extensively protein bound ($f_u > 10\%$), and the f_u did not change in mild or moderate renal impairment relative to that in subjects with normal renal function. Therefore, the conclusions will only consider the PK parameters for total quinidine or dextromethorphan concentrations.

1. Following steady state administration of NEURODEX, dextromethorphan C_{max} and AUC decreased approximately 6-7% in subjects with mild renal impairment and approximately 10-11% in subjects with moderate renal impairment, compared to subjects with normal renal function.
2. Following steady state administration of NEURODEX, the median dextrophan t_{max} was approximately 9 hours later in moderate renal impairment than in normal renal function or mild impairment. Dextrophan C_{max} and AUC increased 34% and 23%, respectively in mild renal impairment and 85% and 93%, respectively, in moderate renal impairment compared to subjects with normal renal function. However, these concentrations remain within the range of concentrations observed when dextromethorphan (at a 30 mg OTC dose) is given in the absence of Q (e.g. study 99-AVR-102). In addition, subjects with moderate renal impairment had fewer adverse events than the subjects in the normal renal function or mild impairment groups. Therefore, these results should not preclude administration of NEURODEX in subjects with mild or moderate renal impairment.
3. Following steady state administration of NEURODEX, quinidine C_{max} and AUC *decreased* approximately 30% in subjects with mild renal impairment. C_{max} decreased approximately 13% and AUC increased 3%, respectively, in subjects with moderate renal impairment, compared to subjects with normal renal function. This decrease in Q C_{max} is not likely to be clinically relevant, since all subjects with mild renal impairment had a poor metabolizer phenotype on Day 7, based on the urinary DM/DX ratio.
4. Based on the PK results above, no dosage adjustment is required in patients with mild and moderate renal impairment. The PK after administration of NEURODEX has not been studied in severe renal impairment, and it should be used with caution in that population.

4.2.13 DESIPRAMINE DRUG INTERACTION STUDY (04-AVR-112)

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)

Study Investigators and Site:



Protocol Number: 04-AVR-112

OBJECTIVE:

Determine the impact of multiple administrations of AVP-923 on the steady state PK of desipramine in healthy humans.

FORMULATIONS:

Table 1. Product used in 04-AVR-112

	Lot Number	Date of Manufacture (Dates of study)
AVP-923 capsules (30 mg DM/30 mg Q) (b) (4)	C0051B001	10/17/2002 (2/28/04-3/17/04)
Desipramine hydrochloride, 25 mg (Norpramine) (b) (4)	3025971	Exp. Date 1/05 (2/28/04-3/17/04)

Batch C0051B001 is from bulk batch C0051001 that had a stability for 36 months at room temperature.

STUDY DESIGN:

This was a Phase I, sequential treatment study. Subjects who had satisfied the screening evaluation were admitted to the study center the evening prior to Day 1. On the morning of Day 1, subjects received an oral dose (25 mg) of desipramine administered q 24 hours with 240 mL of water once daily for 16 days. On Day 8 an oral dose of AVP-923 was administered q 12 h for 9 days (Days 8-16). Standardized meals were served at pre-specified times. Water was restricted from 1 hour pre-dose until 1 hour post-dose. On Day 7 and Day 16 A.M, food was restricted 10 hours pre-dose until 4 hours post-dose. For the evening dose on Day 16, food was restricted from 3 hours pre-dose until 3 hours post-dose. Subjects were to remain ambulatory or seated upright for the first 4 hours after drug administration on Day 1 and Days 7-16.

On Days 7 and 16, blood samples were collected before dosing and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 24 hours after the morning dosing. Sampling for DM/Q was for only 12 hours after the morning dose on Day 16. Blood samples were also collected before morning dosing on Days 5, 6, 14, and 15 for Cmin determinations (only on Days 14 and 15 for DM/Q). Blood samples were collected and processed under fluorescent lighting at room temperature. Plasma samples were frozen at (b) (4) for analysis.

On Days 7 and 16, urine samples were collected before the morning dosing and over the following collection intervals: 0-4, 4-8, 8-12, and 12-24 hours after the morning dose in case they might be assayed afterwards for exploratory purposes.

Safety monitoring included vital signs and ECG monitoring. Twelve-lead ECGs were evaluated on Day 1 prior to dosing and at approximately 3, 6, and 12 hours post-dose. On Days 7 and 9-16, 12-lead ECGs were evaluated each morning prior to dosing and at approximately 6 hours post dose. On Day 8, 12 lead ECGs were evaluated prior to dosing and at approximately 2 and 6 hours post-dose.

Inclusion criteria included healthy males or females, 19-55 years of age. Subjects were to be extensive metabolizers of CYP2D6 as determined by genotype analysis. Subjects were to be non-smokers (for at least 3 months). Females of childbearing potential could use hormonal contraceptives. Exclusion criteria QTc interval > 450 msec for males or > 470 msec for females, use of any drugs or substances known to be strong inhibitors of CYP enzymes within 10 days prior to the first dose, or strong inducers of CYP enzymes within 30 days prior to the first dose, and subjects who were identified as CYP2D6 poor metabolizers. No medication (including OTC) or herbal products were permitted for 7 days prior to the first dose, during sample collection, or during drug administration. This did not include vitamins and hormonal contraceptives. Foods and beverages containing the following substances were prohibited as indicated: xanthines (24 hours before dosing and throughout the study), alcohol (48 hours before dosing and throughout the study), and grapefruit (10 days before dosing and throughout the study).

ASSAY:

Plasma Desipramine and 2-hydroxydesipramine

Table 2. Performance of Analytical Method for 04-AVR-112 for Plasma Desipramine and 2-Hydroxydesipramine

Analyte	Method	Calibration Standards (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
Desipramine	LC-MS/MS	0.5-200	r > 0.998	0.5 ng/ml	1.5	8.42	-2.6
					7.5	10.19	-4.73
					15.0	7.95	-6.39
					150.0	10.13	-8.23
2-hydroxy-desipramine	LC-MS/MS	0.5-200	r > 0.998	0.5 ng/ml	1.5	10.7	7.13
					7.5	13.12	0.71
					15.0	8.11	1.46
					150.0	9.51	1.27

Stability of frozen samples at -20° C was demonstrated in the method validation for 73 days. In the present study, the samples were stored at -80° C, and analyzed within this period of time. QC samples were stored with the clinical samples and remained stable at -80° C over this time. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for Study 04-AVR-112 for detection of desipramine and 2-hydroxydesipramine in plasma. A weighted (1/x²) linear regression was used for the standard curve. The performance of the assay is considered acceptable.

Plasma DM and DX and Q

Table 3. Performance of Analytical Method for 04-AVR-112 for Plasma DM, DX, and for Plasma Q

Analyte	Method	Calibration Standards (µg/ml)	Linearity	LOQ	QC	Inter-assay CV (%)	Inter-assay Accuracy (%)
DM	LC-MS/MS Method	0.2 -200 ng/ml	r > 0.998	0.2 ng/ml	(ng/ml) 0.6	4.58	-1.83

	26267				15	3.32	1.29
					150	2.21	0.6
DX	LC-MS/MS Method 26267	2.5 -2500 ng/ml	r > 0.999	2.5 ng/ml	(ng/ml) 7.5 250 1875	2.42 2.23 3.46	-1.79 3.57 -1.14
Q	HPLC	0.05-10.0 µg /ml	r>0.995	0.05 µg/ml	µg/ml 0.15 1.5 7.5	6.3 4.51 4.27	-12.13 -6.37 -8.14

DM and DX

The method was validated with long term stability demonstrated for 47 days at -20° C. The samples were stored here for < 47 days at -80 ° C, and the samples were stored with QC samples in a freezer set at -80 ° C, with QC samples demonstrating stability throughout the study. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for Study 04-AVR-112 for detection of DM and DX in plasma. The performance of the assay is considered acceptable.

Quinidine

The method was validated with long term stability demonstrated for 129 weeks at -20° C. The samples were stored here for approximately 4 weeks at -80 ° C, and the samples were stored with QC samples in a freezer set at -80 ° C, with QC samples demonstrating stability throughout the study. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for detection of Q in plasma. The performance of the assay is considered acceptable.

RESULTS:

Demographics

Sixteen subjects were enrolled in the study and 13 subjects completed the study. (Subject 3 was withdrawn due to bacteria in urine on Day 7; subject 4 was withdrawn on Day 13 because of an adverse event of abnormal heart rhythm; subject 5 vomited soon after dosing and was removed from the statistical and PK analyses). Demographics of those subjects completing the study are shown in the table below.

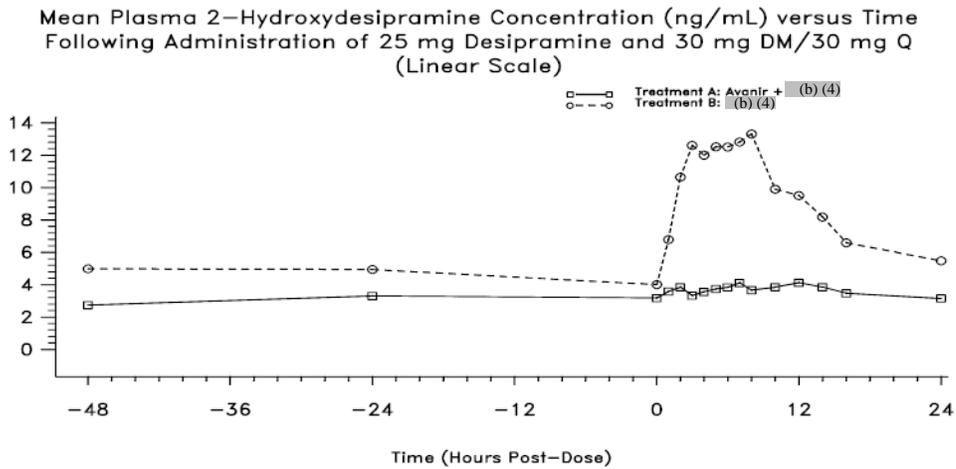
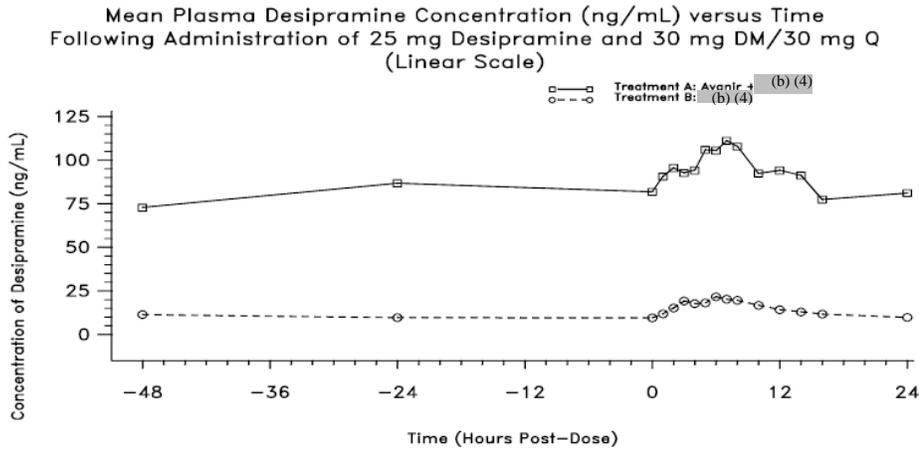
Table 4. Demographics of Subjects Completing Study 04-AVR-112

Mean Age (Range)	Weight (mean ± SD)	Race
27 (19-42)	67.3 ± 9.0 kg (n=13)	Caucasian 1 Hispanic 11
	71.0 ± 8.4 kg (male; n=9)	Asian 1
	58.9± 0.5 kg (female; n=4)	

The only concomitant medications taken during the study were oral contraceptives in 2 subjects.

Dextromethorphan and Dextrophan Plasma Concentrations

The mean plasma concentration time course from each treatment for desipramine and for 2-hydroxydesipramine in the presence (AVP-923 + (b) (4)) or absence (b) (4) of AVP-923 on Days 16 and 7, respectively are shown in the figures below, as provided by the Sponsor.



Pharmacokinetic parameters were determined using noncompartmental analysis. The pertinent pharmacokinetic parameters for desipramine and 2-hydroxydesipramine during each treatment period (Days 7 and 16) are shown in the table below.

Table 5. Pharmacokinetic parameters (arithmetic mean) for Desipramine and for 2-hydroxydesipramine in 04-AVR-112

	Desipramine (% CV) n=13	Desipramine + AVP-923 (% CV) n=13
Desipramine		
t_{max} (h) ^a	6.0 (3.0-8.0)	7.0 (4.0-12.0)
C_{max} (ng/mL)	22.2 (72)	121.2 (28)
AUC_{0-t} (ng*h/mL)	344.2 (83)	2164.8 (27)
C_{min} (ng/ml)	9.8 (9.9)	81.1 (24)

2-Hydroxydesipramine		
t _{max} (h) ^a	5.0 (2.0-10.0)	7.0 (2.0-14.0)
C _{max} (µg/mL)	16.4 (52)	4.8 (35)
AUC _{0-t} (µg*h/mL)	212.35 (40)	86.84 (33)
C _{min} (ng/ml)	5.5 (55)	3.2 (37)

^a median (range)

The Sponsor has conducted steady state analysis and found that desipramine, but not 2-hydroxy-desipramine, was at steady state at Day 7. For Day 16, steady state was concluded for 2-hydroxydesipramine, and although statistically could not be concluded for desipramine it appears to have reached relatively stable concentrations.

For desipramine the (arithmetic) mean C_{max} was approximately 5-fold higher when desipramine was given with AVP-923 than when it was given alone, and the range was approximately 2.7-18-fold. Similarly, mean AUC was approximately 6.3 fold higher when given together than when desipramine was given alone, and the range was approximately 2.7-25-fold.

2-Hydroxydesipramine exposure decreased in the presence of AVP-923. The ratio of the mean C_{max} in the absence to the presence of AVP-923 was approximately 0.3, with a range from approximately 0.16 to 0.67. For mean AUC the ratio was approximately 0.4 with a range of 0.21-0.81.

The bioavailability comparisons for desipramine and for 2-hydroxydesipramine in the presence of AVP-923 vs desipramine alone are shown in the Table below. The 90% CI for both C_{max} and AUC fell outside of the BE interval for both desipramine and 2-hydroxydesipramine.

Table 6. Bioavailability Ratios for Desipramine alone or with AVP-923 in Study 04-AVR-112

	Geometric Mean		Ratio of Geometric Means	90% CI for the Ratio of Geometric Means
	DESIPRAMINE (REFERENCE)	DESIPRAMINE + AVP-923 (TEST)		
Desipramine				
C _{max} (ng/ml)	17.6	117.0	6.65	(494-896%)
AUC _{0-t} (ng*h/ml)	256.8	2093.2	8.15	(571-1164%)

2-hydroxydesipramine	14.8	4.5	0.30	(24.6-37.4%)
C_{max} (µg/ml)	198	82.0	0.41	(33.2-51.6%)
AUC_{0-t} (µg*h/ml)				

Other PK analyses

Selected PK parameters for DM, DX and Q from Day 16 are shown in the table below. The Sponsor has concluded based on C_{min} concentrations that quinidine was at steady state. Steady state could not be concluded statistically for DM or DX, although there was < 9% variation from 1 time to the following.

Table 6. Pharmacokinetic parameters (arithmetic mean) for DM, DX, and Q in 04-AVR-112

	AVP-923 + DESIPRAMINE (% CV) n=13
DM	
t _{max} (h) ^a	2.0 (1.0-7.0)
C _{max} (ng/mL)	156.7 (38)
AUC _{0-t} (ng*h/mL)	1638.0 (40)
DX	
t _{max} (h) ^a	1.0 (0.0-12.0)
C _{max} (µg/mL)	82.1 (30)
AUC _{0-t} (µg*h/mL)	843.1 (28)
Quinidine	
t _{max} (h) ^a	1.0 (1.0-3.0)
C _{max} (µg/mL)	0.24 (27)
AUC _{0-t} (µg*h/mL)	1.38 (37)

^a median (range)

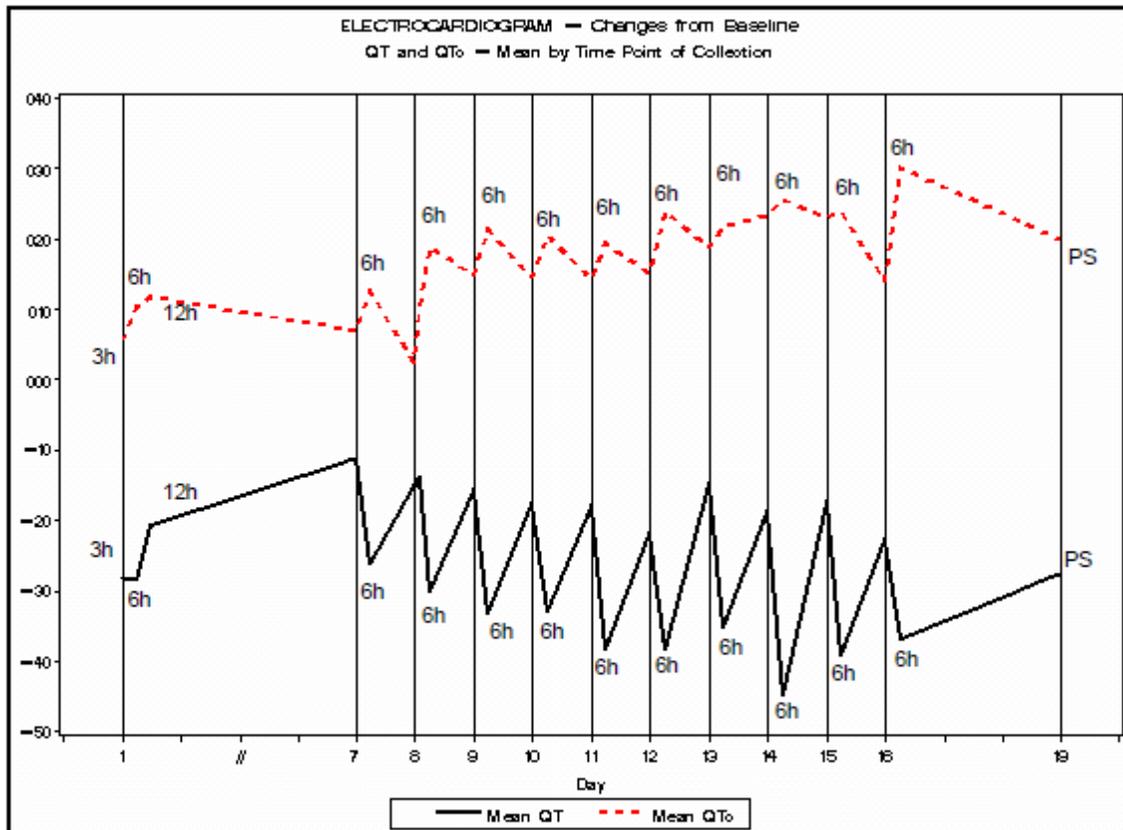
Safety

A total of 109 adverse events occurred during the study. Seven subjects (44%) reported at least one adverse event after dosing with desipramine only and 15 subjects (100%) reported at least 1 adverse event after co-administration of desipramine with AVP-923. The most frequently reported adverse events (> 10% of subjects) included headache, dizziness, somnolence, nausea, fatigue, blurred vision, tachycardia, dry mouth, asthenia, decreased appetite, dysgeusia, insomnia, and dysuria in subjects taking desipramine with AVP-923, and somnolence and fatigue in subjects taking desipramine alone.

Four subjects experienced cardiac related adverse events (tachycardia, palpitations, and arrhythmia). Subject 4 experienced arrhythmia that was characterized as bigeminy with borderline QTc prior to dosing on Day 13 and was removed from the study.

Based on the information provided in the study report, there was 1 QTc value > 450 with desipramine alone and 21 QTc values > 450 (but < 480 msec) during combined treatment with desipramine and AVP-923. The maximum change from baseline QTc reported was 35 msec with desipramine alone and was 75 msec with the combined

treatment, and 7 subjects had change in QTc > 30 msec. Mean pre-dose and 6 hour QTc intervals and change from baseline increased over the duration of the study and in particular when the combination was given. The mean change from baseline is shown in the figure below. Quinidine concentrations are only available from Day 16 and mean Cmax was 2.4 µg/ml as shown in the table above.



Pre-dose values are at the point of intersection on each study day.
PS = post study; 3h = 3 hours postdose; 6h = 6 hours postdose; 12h = 12 hours postdose*

*Hours postdose are approximate.

CONCLUSIONS:

1. The steady state concentration of desipramine was greater when desipramine was given with Quinidine/Dextromethorphan than when given with alone. There was an approximate 5-fold increase in mean Cmax and a 6-fold increase in mean AUC. Exposure to 2-hydroxydesipramine when desipramine was given with

quinidine/Dextromethorphan was approximately 30-40% that of when desipramine was given alone.

2. Abnormal ECG findings including QT prolongation were observed and have been referred to the cardio-renal division as a consult from the clinical division.

4.2.14 THOROUGH QT STUDY (05-AVR-119)

A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED CROSSOVER STUDY IN HEALTHY VOLUNTEERS TO DETERMINE THE ELECTROCARDIOGRAM CHANGES ASSOCIATED WITH 2 DOSES OF AVP-923 (NEURODEX) WITH AN OPEN-LABEL ACTIVE CONTROL ARM OF ORAL MOXIFLOXACIN

Study Investigator and Site:

(b) (4)

Protocol Number: 05-AVR-119

Note: Please refer to the IRT/TQT team review for the definitive review and discussion of the ECG/safety aspects of this study.

OBJECTIVE:

To determine the potential of AVP-923 to cause cardiac repolarization abnormalities by evaluation of primary and secondary endpoints.

FORMULATIONS:

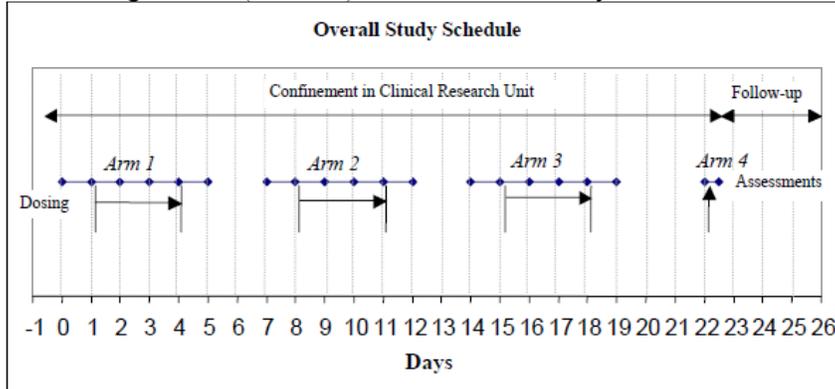
Table 1. Product used in 05-AVR-119

	Lot Number	Date of Manufacture (Dates of study)
AVP-923 capsules (30 mg DM/30 mg Q) (b) (4)	PD-108A-001	Not reported. (10/6/05-11/18/05)
Moxifloxacin 400 mg tablets (AVELOX)	5400JVV	Exp date 8/07 (10/6/05-11/18/05)

STUDY DESIGN:

This was a randomized, placebo-controlled, crossover study with 3 double-blind treatment arms (2 dose levels of AVP-923 and placebo) and an open-label treatment arm with positive control (moxifloxacin). Subjects were confined to the clinical site for the entire treatment period. Subjects were randomized to 1 of 6 sequences of the standard, suprathreshold, and placebo arms for the first 3 double blind treatments (ARMS 1-3). All subjects were to receive the positive control as the fourth arm open label. Twelve-lead continuous digital ECG recordings were used to acquire the definitive study data. Plasma for quantitation of DM, DX and Q levels was obtained. The first 3 treatment arms were 4 days (7 doses) in length, separated by 3 days with no treatment. The standard dose of AVP-923 was 30 mg DM/30 mg Q given twice daily for 7 doses given under fasting conditions. The suprathreshold dose was AVP-923 given as 2 oral

capsules each of 30 mg DM/30mg Q twice daily for 7 doses. The oral moxifloxacin was given as a single dose (ARM 4) . The overall study schedule is shown below.



Blood samples were collected and analyzed for DM, DX, and Q at baseline and first dose at 60 and 30 minutes pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10, 14, 22, and 48 hours post-dose on Days 4, 11, and 18 (multiple dose administration). ECGs were extracted from Holter monitors at the same time as ECG assessments on double-blind treatment days 4, 11, and 18 as well as on Study Days 0, 7, and 14. For the moxifloxacin positive control arm, ECG monitoring was done at pre-dose and at 1, 2, and 3 hours post-dose.

Inclusion criteria included male and female subjects aged 18-60 years inclusive, with a normal screening ECG (or considered not clinically significant), QTcB less than or equal to 450 msec, and regular use of hormonal birth control for women of childbearing potential. Exclusion criteria included family history of long QT or family members with unexplained syncope or premature sudden death, medication other than contraceptives within the last 14 days, or subject was determined to be a poor metabolizer by assessment of CYP2D6 genotype.

ASSAY:

Plasma DM and DX and Q

Table 3. Performance of Analytical Method for 05-AVR-119 for Plasma DM, DX, and for Plasma Q

Analyte	Method	Calibration Standards (µg/ml)	Linearity	LOQ	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
DM	LC-MS/MS Method 26267	0.2 -200 ng/ml	r > 0.992	0.2 ng/ml	(ng/ml)		
					0.6	5.0	2.0
					15	3.3	8.0
DX	LC-MS/MS Method 26267	2.5 -2500 ng/ml	r > 0.998	2.5 ng/ml	(ng/ml)		
					7.5	2.5	-3.3
					250	1.7	-0.4
					1880	1.7	-3.2
Q	HPLC	0.05-10.0 µg/ml	r>0.995	0.05 µg/ml	µg/ml		
					0.15	5.7	-2.0
					1.5	2.2	-8.0
					7.5	2.4	-5.6

DM and DX

The samples were analyzed within the time for which they are stable. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for Study 05-AVR-119 for detection of DM and DX in plasma. The performance of the assay is considered acceptable.

Quinidine

The samples were analyzed within the time for which they are stable. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for detection of Q in plasma. The performance of the assay is considered acceptable.

RESULTS:

Demographics

Thirty-six subjects were enrolled in the study and 33 subjects completed the total study. Three (male) subjects were withdrawn for inappropriate behavior. (Subject #5 only received placebo. Subject #15 received standard, suprathereapeutic, and most of the placebo dosing, and subject #21 received suprathereapeutic, placebo, and most of the standard dosing). Demographics of the 35 subjects who received active drug are shown in the table below.

Demographics of Subjects Completing Study 05-AVR-119

Mean Age (Range)	Weight (mean \pm SD)	Race
40 (19-55)	75.8 \pm 11.6 kg (n=35) 80.1 \pm 9.5 kg (male; n=26) 63.3 \pm 7.1 kg (female; n=9)	Black 11 Caucasian 8 Arabic 1 Other (Hispanic, Latin American, Mexican Descent, Peruvian, Portuguese /Caribbean) 15

Dextromethorphan, Dextrorphan, and Quinidine PK Parameters

The following table shows selected PK parameters for DM, DX, and Q at steady state, based on the data provided by the Sponsor. Data are shown as mean (%CV) except for tmax that is shown as median (range).

Analyte	PK Parameter	Standard Dose (n=34)	Suprathereapeutic Dose (n=35)
DM	Cmax (ng/ml)	88.53 (26)	211.46 (23)
	Tmax (hr)	3.0 (2.0-5.0)	3.0 (2.0-5.0)
	AUC τ (ng*hr/ml)	889 (27)	2064 (22)
	t _{1/2} (hr)	16.5 (22)	17.7 (21)
	Ke (hr ⁻¹)	0.0441 (24)	0.0408 (22)
	Cmin (ng/ml)	45.1 (40)	109 (28.5)
DX	Cmax (ng/ml)	86.6 (27)	136 (33)
	Tmax (hr)	22 (0-22.4)	22.3 (2.33-22.5)
	AUC τ (ng*hr/ml)	706 (28)	1047 (27)
	Cmin (ng/ml)	54.0 (28)	79.3 (28)
Q	Cmax (μ g/ml)	0.177 (28)	0.355 (29)
	Tmax (hr)	2.33 (2.33-3.33)	2.33 (2.33-3.33)

	AUC _τ (μg*hr/ml)	1.32 (32)	2.53 (31)
	t _{1/2} (hr)	8.21 (27)	7.45 (23)
	Ke (hr ⁻¹)	0.0908 (29)	0.0982 (25)
	C _{min} (μg/ml)	0.00695 (282)	0.0352 (98)

The mean plasma concentration curves for DM and for Q at standard and supratherapeutic doses are shown below (as provided by the Sponsor).

Figure 14.2.1.1.1 Mean Plasma Dextromethorphan Concentration versus Time Profile in the Normal Scale (Page 1 of 1)

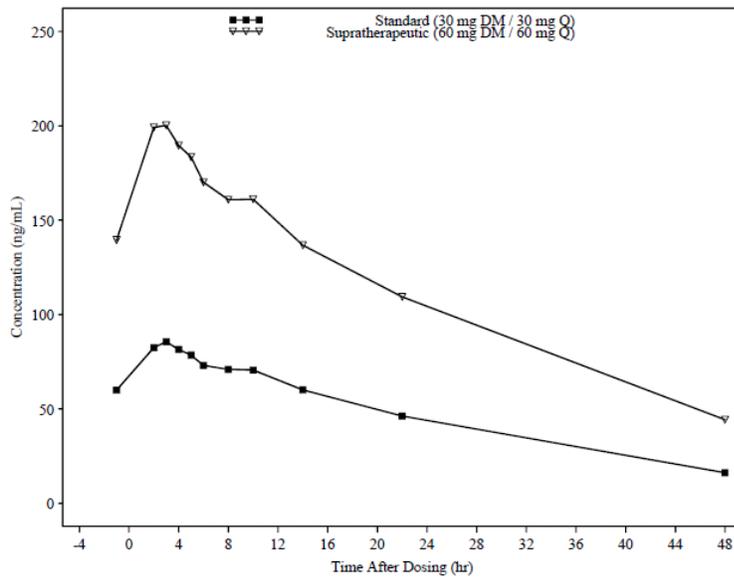
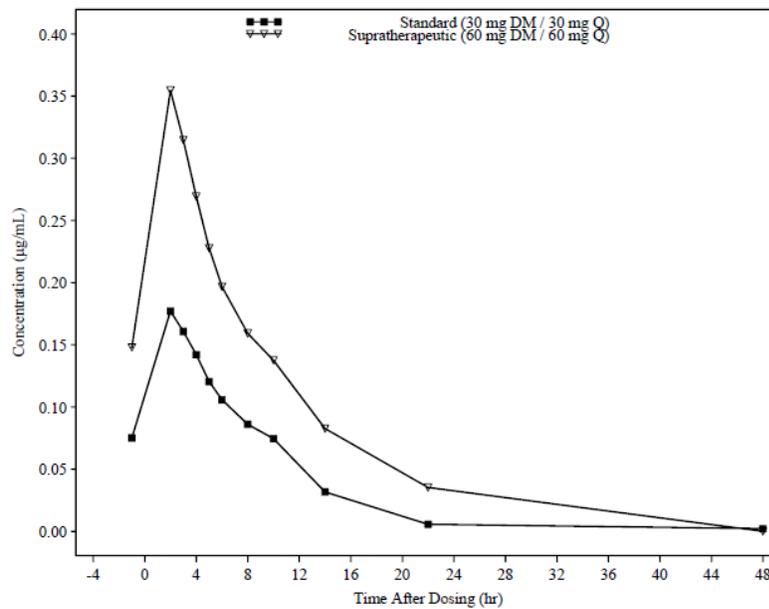


Figure 14.2.1.1.3 Mean Plasma Quinidine Concentration versus Time Profile in the Normal Scale (Page 1 of 1)



The Sponsor notes a greater than dose proportional increase in Cmax and AUC for DM with an increase in dose, without a change in half-life. The DM exposure (Cmax and AUC) following administration of the standard dose for 4 days is comparable to that seen after 4 days of this dose of DM and Q in Study 99-AVR-101. However, it is less than the DM exposure observed by Day 7 or 8 in healthy subjects in the other Phase I studies (04-AVR-115, 04-AVR-115, 99AVR-101). The mean Cmax and AUC following the suprathereapeutic dose are approximately 1.4-times the highest mean Cmax observed in other healthy volunteer studies, the highest being observed study 04-AVR-116 with mean Cmax of 148.4 ng/ml and AUC0-12 of 1512 ng*hr/ml.

For Q, the mean Cmax and AUC from the Suprathereapeutic dose do not substantially exceed the highest mean values observed in healthy volunteers receiving the proposed dose (Cmax of 0.332 µg/ml and AUC of 2.44 µg*hr/ml in healthy subjects in 04-AVR-116).

Placebo subjects had measurable concentrations of DM, DX and Q, based on raw PK data provided by the Sponsor. DM was detectable in 5 subjects post-dose (placebo). Subject #1 had detectable concentrations throughout the 48 hour collection period, the highest being 0.919 ng/ml. Subject 28 also had detectable concentrations throughout the 48 hour collection period, the highest post dose level of which was 0.422. Subjects 11, 20, 21, and 35 had detectable concentrations at various time points after dosing (placebo). Twenty-four subjects had detectable concentrations in the baseline measurements (60 minutes and 30 minutes prior to the first dose of the placebo period), the highest concentration being 28.3 ng/ml. DX was detectable in 3 subjects post-dose (placebo). Subject #1 had detectable concentrations throughout the 48 hour collection period (the highest concentration was 7.7 ng/ml and occurred at 2 hours). Two other subjects (#11 and 35) had detectable concentrations at 8 and 4 hours post-dose respectively. In addition, DX was detectable in 22 subjects at the baseline measurements (in the placebo period) in concentrations up to 93.4 ng/ml. For quinidine, 2 subjects (#11 and #35) detectable Q concentrations in the placebo arm of 0.104 and 0.123 µg/ml and these occurred at 8 hours and 4 hours after the dose of placebo, respectively. There were no detectable baseline pre-dose (placebo) Q concentrations.

QT evaluation

Note: *for a thorough review of the QT evaluation from this study, please refer to the IRT/TOT review.*

The maximum mean, paired, placebo-subtracted dQTcF values are summarized in the table below, as provided by the Sponsor. For the Suprathereapeutic dose, dQTcF was 18.81 msec and the upper bound of the one-sided 95% CI was 24.5 msec. For the Standard treatment, the dQTcF was 10.12 msec and the upper bound of the 95% CI was

15.05 msec. The moxifloxacin result (positive control) confirmed the sensitivity of the assay.

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

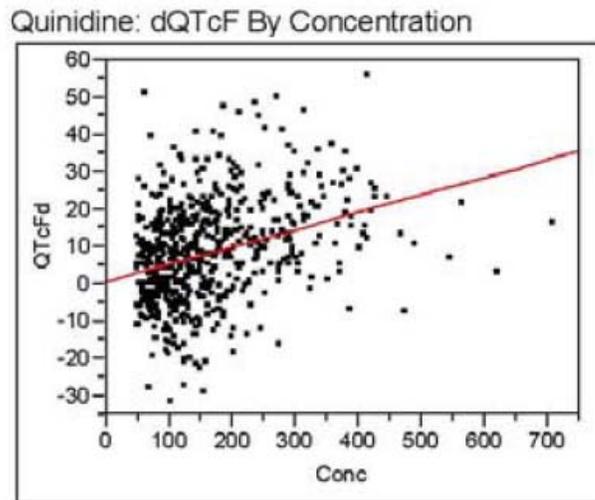
Categorical analysis for QTcF showed the following:

	Placebo	Standard	Supratherapeutic	Moxifloxacin
QTcF>450 msec	0	0	2	0
QTcF>480 msec	0	0	0	0
QTcF>500 msec	0	0	0	0
Δ QTcF >30 msec	3	14	3	25
Δ QTcF >60 msec	0	0	0	0

No subject exceeded QTcF of > 480 msec or a change in QTcF from baseline of >60 msec.

PK/PD Analyses

The following figures show the relationship between QTcF as and Q concentration (slope 46.61, intercept 0.36, Prob > F < 0.0001). The 3-hydroxy metabolite of quinidine has not been measured, and it is recognized to be active (as measured by QTc prolongation).



The Sponsor also has provided the QTcF in relationship to DM and DX (not shown here, please refer to the Sponsor’s submission). Although the Sponsor suggests that a relationship is also seen between DM and DX concentrations and QTcF, this is not an independent relationship since the concentrations are related to the concentration of Q.

Safety

There were 88 adverse events reported by 23 subjects: 15 reported following standard dosing, 47 reported following suprathreshold dosing, 3 reported following positive control, and 23 reported following placebo. All of the adverse events were considered to be mild. Sixty-six treatment related adverse events were reported, and the most frequently reported were dizziness, headache, and nausea.

CONCLUSIONS:

Note: for a thorough review of the QT evaluation from this study, please refer to the IRT/TQT review.

AVP-923 given either at standard doses (the proposed therapeutic dose) or “suprathreshold doses” resulted in a positive study in which QT prolongation of > 10 msec could not be ruled out.

The placebo arms showed detectable plasma concentrations of DM and DX as well as Q, although the latter appeared to be at spurious time points. The Sponsor has not addressed this. It could be due to inadequate washout due to the long half-life of DM in the presence of quinidine. This finding complicates the interpretation of the ECG results. However, if subjects truly had exposures to any of these moieties in concentrations that could affect the QT interval, then in their absence the QT changes that were observed would have been even larger.

The quinidine exposure did not substantially exceed the highest mean values observed in healthy volunteers receiving the proposed dose of AVP-923 (less than 1.1 times the highest mean values in healthy volunteers in other Phase I studies). In addition, the concentration did not exceed the maximum quinidine concentration reported in the efficacy study 99-AVR-102 that was 0.4770 µg/ml. This is despite the suprathreshold dose being 2 times the standard dose. Thus, the quinidine exposure does not cover the expected range when AVP-923 is in clinical use. However, since even at lower exposures QT prolongation was observed, QT prolongation in clinical use of AVP-923 cannot be ruled out.

4.2.15 POPULATION PK STUDY (04-AVR-117)

POPULATION PHARMACOKINETIC ANALYSIS OF AVP-923 IN HEALTHY SUBJECTS AND IN PATIENT POPULATIONS

Study Investigators and Site: (b) (4)

Protocol Number: 04-AVR-117

OBJECTIVES:

Determine the population PK parameters of quinidine (Q) in plasma and dextromethorphan (DM) and its metabolite dextrorphan (DX) in plasma and urine after single and multiple doses of AVP-923 (combination product of DM and quinidine).

Identify the impact of demographic covariates on the population PK parameter estimates.

Determine population PK parameters of these same analytes in patient populations.

STUDY DESIGN:

Data from the following 9 studies were analyzed:

- 99-AVR-100 (BA)
- 99-AVR-101 (BA)
- 00-AVR-103 (BA)
- 04-AVR-111 (Food Effect)
- 04-AVR-115 (Hepatic Impairment)
- 04-AVR-116 (Renal Impairment)
- 99-AVR-102 (Efficacy Study)
- 02-AVR-106 (Efficacy Study)
- 02-AVR-107 (Open-Label Safety Assessment)

There were 53 healthy subjects in the six Phase I studies and 117 patients in the Efficacy and Safety studies.

Demographics are shown in the table below, as provided by the Sponsor. Only subjects receiving 30 mg DM with 25 mg or 30 mg of Q were included in the population PK analysis. For subjects whose phenotype was not determined, the Sponsor assigned an extensive metabolizer status for purposes of analysis.

Table 3.10:1 Summary Demographics of Subjects used in the Population PK Analysis

	Subject Demographics	Mean (CV%)	Median (Range)
ALL (N = 170, 70 Men and 100 Women)	Age (years)	48.9 (27.6%)	51.0 (19 - 82)
	Body Weight (kg)	76.4 (20.5%)	75.0 (41.4 - 136)
	Height (cm)	168.2 (5.67%)	167.6 (145 - 190)
Healthy Subjects (Rich) (N=53, 30 Men and 23 Women) (2 PM and 51 EM)	Age (years)	45.3 (35.1%)	52 (19 - 69)
	Body Weight (kg)	75.9 (14.1%)	75.3 (55.8 - 104.1)
	Height (cm)	170.1 (5.45%)	170 (150 - 189)
Other Patients (Sparse) ^a (N=117, 40 Men and 77 Women) (1 PM and 116 EM)	Age (years)	50.5 (23.7%)	51 (25 - 82)
	Ideal Body Weight (kg)	60.6 (16.7%)	57.8 (38.6 - 84.0)
	Height (cm)	167.2 (5.71%)	165.6 (145 - 190)

^aOnly patients who were included in the quinidine, dextromethorphan and dextrorphan analyses are presented.

Blood samples for the efficacy and safety studies were collected as follows. Study 99-AVR-102 compared safety, efficacy, and tolerance of AVP-923 taken twice daily relative to DM 30 mg and relative to Q 30 mg taken twice daily for 28 days in ALS patients with PBA. During the final visit (between Days 26 and 32) one blood sample for PK analysis was collected. Study 02-AVR-106 was a placebo-controlled study to evaluate safety, tolerance and efficacy of AVP-923 twice daily for 85 days (12 weeks) in MS patients with PBA. On Day 29 and during the final clinical visit (between Days 82 and 88) one blood sample was collected for PK analysis. Study 02-AVR-107 was an open label study in which patients who were diagnosed with PBA associated with any etiology were enrolled. Patients who completed 02-AVR-106 were eligible to participate after their last treatment day. Twice daily treatment with AVP-923 followed a 1-week run-in period where patients were asked to take 1 capsule daily in the evening. Safety assessments were collected up to week 52. One blood sample was collected for PK analysis was collected during week 34. Only samples with known relationship to time of drug administration were used.

Compartmental analyses were performed using a two-stage approach. Multiple compartmental models were constructed and their ability to fit plasma Q and plasma and urinary DM and DX were evaluated. The best compartmental model was identified and the relevant PK parameters were then utilized as prior estimates for the population PK analysis. Covariates for DM and DX PK that were investigated included age, gender, body weight, ideal body weight, genotype, height, phenotype, and race.

RESULTS:

A 1-compartment model was used to describe quinidine PK. The model and the parameter estimates are shown below.

Figure 7:1 Final Compartmental Model for Quinidine Plasma Data

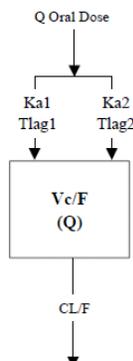


Table 10.1:1 Population PK Parameters of Quinidine (n=65)

Parameters	Mean (CV%)	Median (Range)
%Ka ₁ (%)	45.7 (28.3%)	75.7 (3.11 - 66.6)
Tlag ₁ (h)	0.134 (72.7%)	0.107 (0.00196 - 0.595)
Ka ₁ (h ⁻¹)	0.119 (53.1%)	0.111 (0.0000999 - 0.291)
%Ka ₂ (%) (1- %Ka ₁)	54.3 (23.8%)	53.3 (33.4 - 96.9)
Tlag ₂ (h)	0.705 (29.1%)	0.701 (0.266 - 1.40)
Ka ₂ (h ⁻¹)	0.0790 (37.0%)	0.0771 (0.00590 - 0.149)
CL/F (L/h)	20.0 (32.2%)	19.4 (7.05 - 39.1)
Vc/F (L)	3.64 (64.7%)	3.60 (0.000535 - 10.1)
Residual Variability (%)		12.8%

Ka₁ and Ka₂: first-order rate constant of absorption, Tlag₁ and Tlag₂: absorption lag times for Ka₁ and Ka₂, respectively, CL/F: apparent oral clearance, Vc/F: apparent central volume of distribution.

A 2-compartment model was used to describe plasma and urinary concentrations of DM and of DX. The model also included a CYP2D6 inhibitory E_{max} effect as a function of Q concentration (preventing biotransformation of DM to DX as well as inhibiting renal clearance of DX and of DM presumably by P-gp inhibition). IBW affect all PK parameters and PK parameters were adjusted for IBW. Significant covariates included in the model were 1) ideal body weight and 2) age on the apparent central volume of distribution of DX (there was an increase in Vc/F of DX associated with increasing age). Cl_T was unaffected by age. Gender did not affect the PK of DM or DX. Since 40/53 subjects were Caucasian, the effect of race could not be determined.

The model and the parameters for DM (and the inhibitory effect of Q) and for DX (and the inhibitory effect of Q) are shown below.

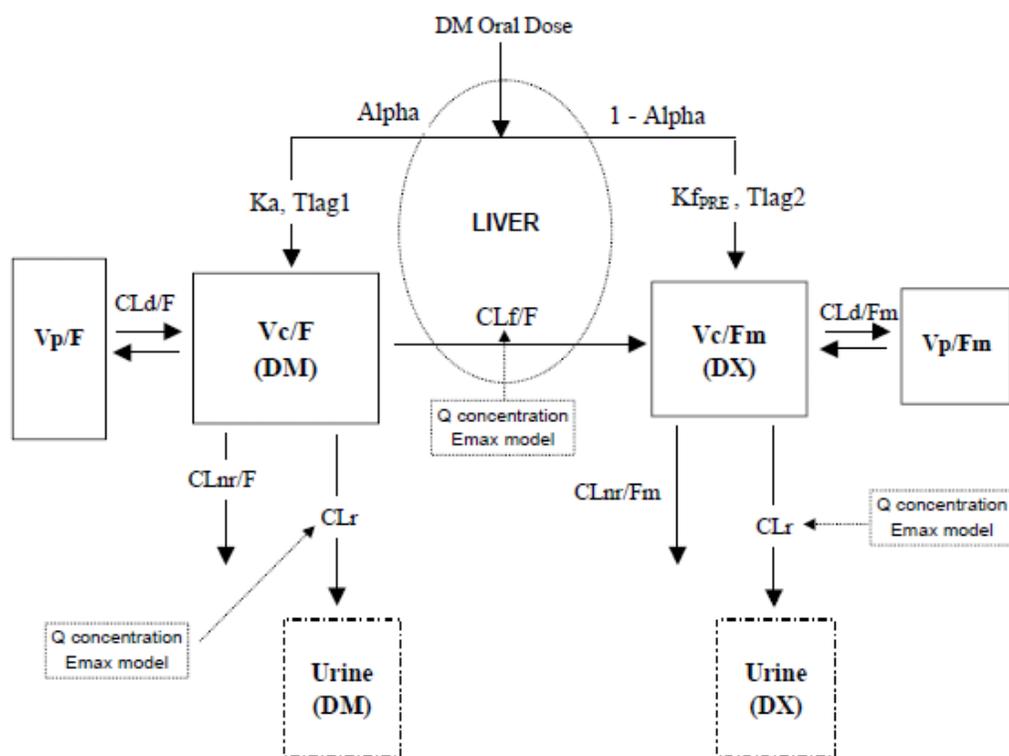


Table 10.2:1 Pharmacokinetic Parameters of DM for Extensive Metabolizers

Parameters	Mean (CV%)	Median (Range)
Alpha	0.766 (27.7%)	0.773 (0.252 - 1.00)
Ka (h ⁻¹)	0.506 (60.4%)	0.422 (0.0554 - 1.42)
Tlag (h)	0.712 (74.9%)	0.872 (0.00000982 - 2.32)
CLf/F (L/h/kg)	1.04 (79.3%)	0.868 (0.0842 - 3.98)
CLr (L/h/kg)	0.103 (90.7%)	0.0626 (0.0107 - 0.382)
CL _r /F (CLnr/F + CLr + CLf/F) (L/h/kg)	1.15 (68.7%)	0.974 (0.180 - 4.02)
Vo/F (L/kg)	9.11 (44.1%)	8.92 (0.875 - 18.5)
Vss/F (L/kg)	21.3 (41.4%)	19.2 (2.33 - 42.4)
Residual variability for plasma data (%)		12.9 %
Residual variability for urine data (%)		45.2 %

Alpha: Fraction of dose undergoing systemic transformation from DM to DX; Ka: first-order rate constant of absorption, Tlag: absorption lag time, CLf/F: formation clearance, CLr: renal clearance, CLF: total clearance, Vo/F: apparent central volume of distribution, Vss/F: apparent total volume of distribution.

Table 10.2:2 Inhibitory Effect of Quinidine on the CL_f/F and CL_r of DM in Extensive Metabolizers

Parameters	Mean (CV%)	Median (Range)
CL_f/F (L/h/kg)		
CL _f /F initial (L/h/kg)	1.04 (79.3%)	0.868 (0.0842 - 3.98)
CL _f /F inhibited (L/h/kg)	0.262 (161%)	0.132 (0.00995 - 2.73)
Emax on CL _f /F (%)	74.6 (23.3%)	77.0 (25.4 - 98.5)
IC ₅₀ on CYP2D6 (ng/mL)	15.5 (108%)	10.1 (0.188 - 99.1)
Q _{threshold} (ng/mL)	1.70 (98.7%)	1.40 (0.000000254 - 9.16)
CL_r (L/h/kg)		
CL _r (L/h/kg) initial	0.103 (90.7%)	0.0626 (0.0107 - 0.382)
CL _r (L/h/kg) inhibited	0.0358 (89.4%)	0.0271 (0.000365 - 0.149)
Emax on P-gp (%)	59.9 (40.7%)	65.6 (0.00940 - 99.3)
IC ₅₀ on P-gp (ng/mL)	37727 (197.6%)	19490 (83.0 - 417000)

CL_f/F: systemic formation clearance of DX from DM, Emax: maximum inhibitory effect of quinidine on CYP2D6 activity or P-gp activity, IC₅₀: inhibitory concentration of quinidine on CYP2D6 activity or P-gp activity, Q_{threshold}: threshold concentration of quinidine, CL_r: renal clearance.

Table 10.3:1 Pharmacokinetic Parameters of DX and Age for Extensive Metabolizers

Parameters	Mean (CV%)	Median (Range)
1 - Alpha		
K _{f_{pre}} (h ⁻¹)	0.234 (90.8%)	0.227 (0.0 - 0.748)
K _{f_{sys}} (h ⁻¹)	0.197 (100.4%)	0.128 (0.00111 - 0.772)
CL _{nr} /F _m (L/h/kg)	0.162 (59.5%)	0.171 (0.000548 - 0.368)
CL _r (L/h/kg)	0.0805 (53.7%)	0.0719 (0.0149 - 0.272)
CL _r /F _m (CL _{nr} /F _m + CL _r) (L/h/kg)	0.243 (37.8%)	0.245 (0.0655 - 0.480)
VolF_m (L/kg) = Intercept_{VolF_m} + (Slope_{VolF_m} × Δ Age)		
Intercept _{VolF_m}	0.646 (87.4%)	0.532 (0.0000368 - 2.72)
Slope _{VolF_m}	0.0298 (125.5%)	0.0240 (0.000000123 - 0.257)
Residual variability for plasma data (%)		11.4 %
Residual variability for urine data (%)		24.5%

1-Alpha: Fraction of DM dose undergoing pre-systemic transformation to DX, K_{f_{pre}}: metabolite rate constant of presystemic formation, K_{f_{sys}}: metabolite rate constant of systemic formation, CL_r: metabolite renal clearance, CL_{nr}/F_m: non-renal clearance, VolF_m: metabolite apparent central volume of distribution.

Table 10.3:2 Inhibitory Effect of Quinidine on CL_r of DX in Extensive Metabolizers

Parameters	Mean (CV%)	Median (Range)
CL_r (L/h/kg)		
CL _r initial (L/h/kg)	0.0805 (53.7%)	0.0719 (0.0149 - 0.272)
CL _r inhibited (L/h/kg)	0.0306 (86.2%)	0.0241 (0.000600 - 0.0866)
Emax on P-gp (%)	59.9 (40.7%)	65.6 (0.00940 - 99.3)
IC ₅₀ on P-gp (ng/mL)	37727 (197.6%)	19490 (83.0 - 417000)

Emax: maximum inhibitory effect of quinidine on CYP2D6 activity or P-gp activity, IC₅₀: inhibitory concentration of quinidine on CYP2D6 activity or P-gp activity, CL_r: renal clearance.

Observe

d vs predicted plasma concentrations for Q, DM, and DX in the healthy volunteers (data rich) were well fitted, although urinary concentrations of DM and DX were difficult to fit (please refer to Sponsor's study report). The observed vs predicted plasma concentrations for Q, DM, and DX in patients (sparse data) are shown in the figures below, as provided by the Sponsor.

Figure 10.4:2 Quality of Fit: Observed vs Fitted Plasma Concentrations of Q for Patients With Sparse Data

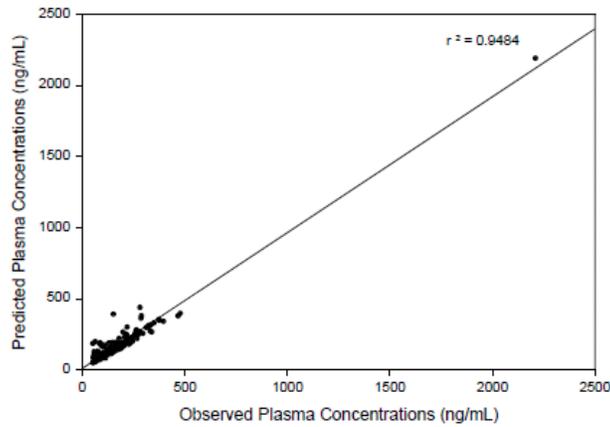


Figure 10.4:6 Quality of Fit: Observed vs Fitted Plasma Concentrations of DX for Patients With Sparse Data

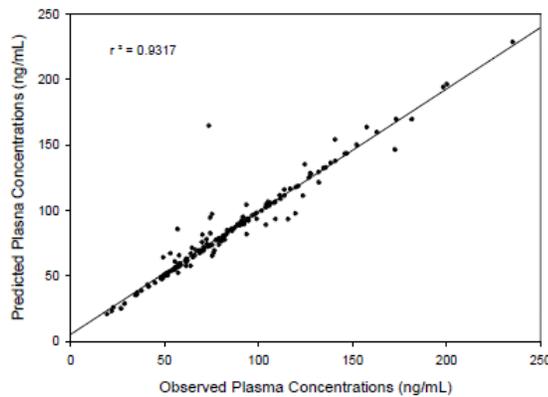
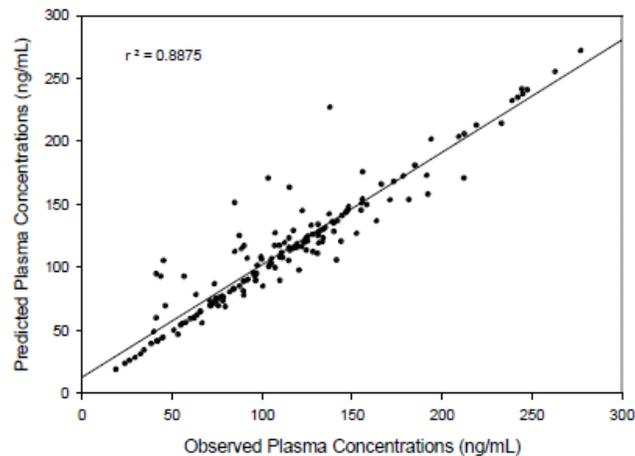


Figure 10.4:4 Quality of Fit: Observed vs Fitted Plasma Concentrations of DM for Patients With Sparse Data



Volume of distribution was similar for subjects and patients for Q, DM, and DX. Values calculated for total clearance are shown in the table below. For Q, Cl in subjects was consistent with values previously published in the literature. Although the Q clearance in patients appears to be lower than that in subjects, it is also consistent with clearance reported in the literature that has great variability (e.g. 1.49-7.15 ml/min/kg).¹⁴ For DX the total clearance appears to be comparable in subjects and in patients, and for DM, the total clearance, although greater in subjects, shows 2-fold greater variability.

		Healthy Subjects (Rich Data)	Patients (Sparse Data)
		Mean (% CV)	Mean (% CV)
Quinidine	Cl/F (L/h)	20.0 (32.2)	13.2 (42.4)
DM	Cl_T/F (l/h/kg)	1.15 (68.7)	0.811 (33.7)
DX	Cl_T/F_m (l/h/kg)	0.243 (37.8)	0.317 (31.0)

Note: the values for healthy subjects for DM and DX reflect data in CYP2D6 EMs only.

CONCLUSIONS AND CONSEQUENCES FOR LABELING

A model has been developed to describe concentrations of Q, DM, and DX.

- Age affected volume of distribution of DX.
- There is no apparent affect on gender on PK.
- The effect of race could not be determined.

PK parameters were similar in subjects and in patients.

Based on these results the Sponsor has proposed the following labeling:



RECOMMENDATIONS:

The proposed labeling based on the findings of the population PK study is generally acceptable.

¹⁴ Ueda CT et al. Clin Pharmacol Ther 1976; 19:30-6.

4.2.16 CLINICAL 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

Study Investigators and Site:

There were 17 centers and 17 investigators participating in the study.

Protocol Number: 99-AVR-102

Note: this study is being reviewed from only the PK/PD perspective

OBJECTIVE:

The objectives were to compare and evaluate efficacy, safety, and tolerance of a combination of 30 mg DM and 30 mg quinidine sulfate (AVP-923) taken twice daily relative to 30 mg DM and to 30 mg Q taken individually in a population of amyotrophic lateral sclerosis (ALS) subjects with pseudobulbar affect.

FORMULATIONS:

Table 1. Product used in 99-AVR-102

	Lot Number	Date of Manufacture (Dates of study)
AVP-923 capsules (30 mg DM/30 mg Q) (b) (4)	M11009F	11/11/00 (1/11/01-4/30/02)
DM 30 mg (b) (4)	M11007F	11/9/00 (1/11/01-4/30/02)
Q 30 mg (b) (4)	M11018F	11/28/00 (1/11/01-4/30/02)

STUDY DESIGN:

This was a multicenter, randomized, double-blind, controlled, parallel group study. All study drugs were self-administered orally every 12 hours for 28 days. The study included a Screening Visit and 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 morning of Day 26 and the morning of Day 32. Subjects were randomized to 1 of 3 treatment groups to receive AVP-923, 30 mg DM, or 30 mg Q. Subjects received a diary in which they recorded the data and time each dose was taken, the number of laughing/crying episodes experienced, and any AEs that had occurred since the last visit. Diary cards were collected on Day 15 and at study completion. Subjects completed the CNS-LS questionnaire and visual analog scales assessing quality of life (QOL) and quality of relationships (QOR) every 2 weeks during the treatment period, and the Hamilton Rating Scale for Depression was

administered at Screening and on Day 29. Safety was evaluated on Day 15 and 29 by examining AEs, results of physical examinations, vital signs, clinical laboratory values, and resting ECGs. Blood samples were collected for DM, D, and Q quantitation on Day 29. The primary efficacy variable was the CNS-LS score.

Inclusion criteria included males or females, 18-80 years of age inclusive, with a confirmed diagnosis of ALS or probable ALS, a clinical history of pseudobulbar affect, and a CNS-LS score on Day 1 of ≥ 13 . Subjects had normal hematologic, hepatic, and renal function, and an ECG with no evidence of heart block, QT prolongation, sinus bradycardia or history of sick sinus syndrome, ventricular tachycardia, multifocal ventricular ectopic beats, or frequent unifocal ventricular ectopic beats. Females were to practice an established method of birth control that could include hormonal contraception. Exclusion criteria included history of ventricular tachycardia or torsades de points, known sensitivity to Q or opiates, use of antidepressants, history of psychiatric disturbance, hypotension, or history of postural syncope. A list of concomitant medications that were not allowed included amantadine, amitriptyline, desipramine, imipramine, nortriptyline, or any antidepressant medication or any MAO inhibitor, aspirin, captopril, cimetidine, dextromethorphan, digoxin, diltiazem, erythromycin, fluoxetine, itraconazole, ketoconazole, quinidine, quinine, and verapamil. (The washout period for fluoxetine was 2 weeks).

ASSAY:

Plasma DM and DX and Q

Table 3. Performance of Analytical Method for 99-AVR-102 for Plasma DM, DX, and for Plasma Q

Analyte	Method	Calibration Standards ($\mu\text{g/ml}$)	Linearity	LOQ	QC	Inter-assay CV (%)	Inter-assay Accuracy (%)
DM	LC-MS/MS Method 26267	0.2 -200 ng/ml	$r > 0.997$	0.2 ng/ml	(ng/ml)		
					0.6	5.87	2.17
					15	4.83	6.67
DX	LC-MS/MS Method 26267	2.5 -2500 ng/ml	$r > 0.997$	2.5 ng/ml	(ng/ml)		
					7.5	3.23	-4.12
					250	3.9	0.81
Q	HPLC Method 22004_1	0.05-10.0 $\mu\text{g/ml}$	$r > 0.996$	0.05 $\mu\text{g/ml}$	$\mu\text{g/ml}$		
					0.15	1.37	-2.67
					1.5	0.96	-2.73
					7.5	0.67	-4.11

DM and DX

The method has been validated with long term stability demonstrated for 101 weeks at -20° C (during analysis for a different study) and the samples were analyzed within the time for which they are stable. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for Study 99-AVR-102 for detection of DM and DX in plasma. The performance of the assay is considered acceptable.

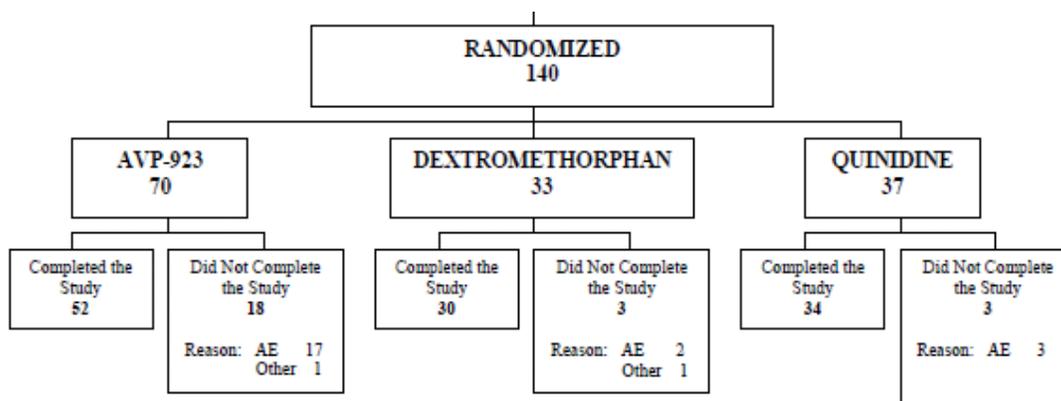
Quinidine

The method was validated with long term stability demonstrated for 129 weeks at -20° C, and the samples were analyzed within the time for which they are stable. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for detection of Q in plasma. The performance of the assay is considered acceptable.

RESULTS:

Demographics

There were 140 subjects randomized into the study. Subject disposition is shown in the figure below, as provided by the Sponsor.



The ITT population consists of all randomized subjects who are not “poor metabolizers” of CYP2D6. The Safety population was all randomized subjects. The Efficacy Evaluable population was all subjects in the ITT population who were protocol adherent (requirement includes taking 80% of their scheduled doses).

There was no statistically significant difference between treatment groups in baseline CNS-LS score (the primary efficacy endpoint) in the ITT population. The mean (SD) CNS-LS scores at baseline were 20.06 (5.46), 21.40 (6.17), and 22.26 (5.22) for the AVP-923, DM, and Q treatment groups, respectively. Other demographics characteristics of the ITT population are shown in the table below, as provided by Sponsor.

Category	AVP-923 (N=65)	DM (N=30)	Q (N=34)	P-values ^a	
				AVP-923 vs DM	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.

Concomitant medications taken during the study included amiodarone, verapamil, and clarithromycin (CYP3A inhibitors), and CYP2D6 substrates amitriptyline, metoprolol, timolol, and acetaminophen with codeine.

CYP2D6 Genotype

The predicted CYP2D6 phenotype based on the CYP2D6 genotype characteristics of the ITT population are shown in the table below, as provided by the Sponsor. CYP2D6 was analyzed for the *3, *4, *5, *6, *7, *8, *10, *17, and *2XN alleles.

Table 19. Genotype at Screening – Safety Population (N=140)

Genotype	AVP-923	DM	Q
	(N=70) n (%)	(N=33) n (%)	(N=37) n (%)
Poor metabolizer	5 (7.2)	3 (9.1)	3 (8.1)
Extensive metabolizer	61 (88.4)	30 (90.9)	32 (86.5)
Ultrarapid metabolizer	3 (4.3)	0 (0.0)	2 (5.4)

Dextromethorphan, Dextrophan, and Quinidine Plasma Concentrations

The following table (provided by the Sponsor) shows plasma concentrations of DM and DX in the Safety population (EMs) in subjects whose time of blood collection was within 8 hours of the time of their last dose of study medication.

Table 20. Concentration (ng/mL) of DM and DX in Plasma of Extensive Metabolizers^a – Safety Population (N=140)

Statistics	AVP-923 N=70		DM N=33		P-values ^b	
	DM	DX	DM	DX	DM	DX
n	35	35	23	23		
Mean	96.37	89.46	5.18	295.92	< 0.0001	< 0.0001
Std Dev	46.71	52.25	4.97	143.21		
Median	96.26	78.24	4.55	262.35		
Min/Max	1.07/212.40	8.17/235.27	0.35/15.81	101.07/526.65		

^a Only those subjects whose time of blood collection was within 8 hours of the time of their last dose of study medication were included in this table.

^b P-value from ANOVA with adjustment for treatment.

The Q concentrations from each treatment (at any time point of blood collection) are shown below.

Analyte	Treatment Group					
	AVP-923 Mean (% CV)		DM Mean (% CV)		Q Mean (% CV)	
Q (µg/ml)	0.1446 (198)	n=61	0.0256 (451)	n=28	0.0756 (95)	n=33
	(range 0-2.21 µg/ml)				(range 0-0.2 µg/ml)	

DM plasma concentrations for AVP-923 were in the range of steady state concentrations in Study 04-AVR-112 (AVP-923 plus Desipramine) in which the C_{max} (determined by the same assay as used in the present study) was approximately 156 ng/ml.

Note: There was not a concomitant medication that appeared to contain dextromethorphan and it is not clear what could result in detectable DM or DX concentrations in subjects receiving only Q.

Q concentrations were generally in the range observed in Phase I studies, except for 1 subject taking AVP-023 that had a quinidine concentration of 2.21 µg/ml. That subject did not appear to be taking concomitant medications that would be expected to interfere with metabolism of quinidine. That patient was taking glycopyrrolate and whether that interacts with elimination or P450-mediated metabolism has not been evaluated.

PK/PD Analyses

The primary efficacy endpoint was change from baseline in CNS-LS (Center for Neurologic Study-Lability Scale) score. This is a 7-item self report measure. The range of possible scores is 7-35. The highest scores show the most lability. The primary analysis was based on improvement in CNS-LS score where individual improvement was measured as the difference between baseline scores and the average of Day 15 and Day 29 scores. Those results are shown in the table below, as provided by the Sponsor. There was a statistically significant difference between the AVP-923 group scores and either the DM group ($P < 0.005$) or the Q group ($p = 0.0004$) according to the data provided by the Sponsor.

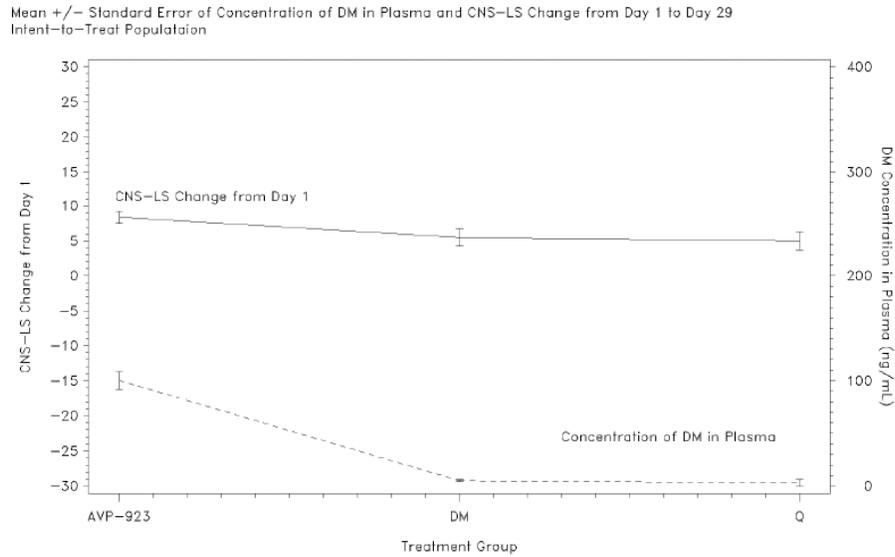
Table 9. Mean Change in CNS-LS Scores^a – ITT Population (N=129)

Change in Score	AVP-923 (N=65)	DM (N=30)	Q (N=34)
n	61	30	34
Mean	-7.39	-5.12	-4.91
Std Dev	5.37	5.56	5.56
Median	-6.50	-4.50	-4.25
Min/Max	-24.00/0.0	-25.00/2.0	-21.00/2.0

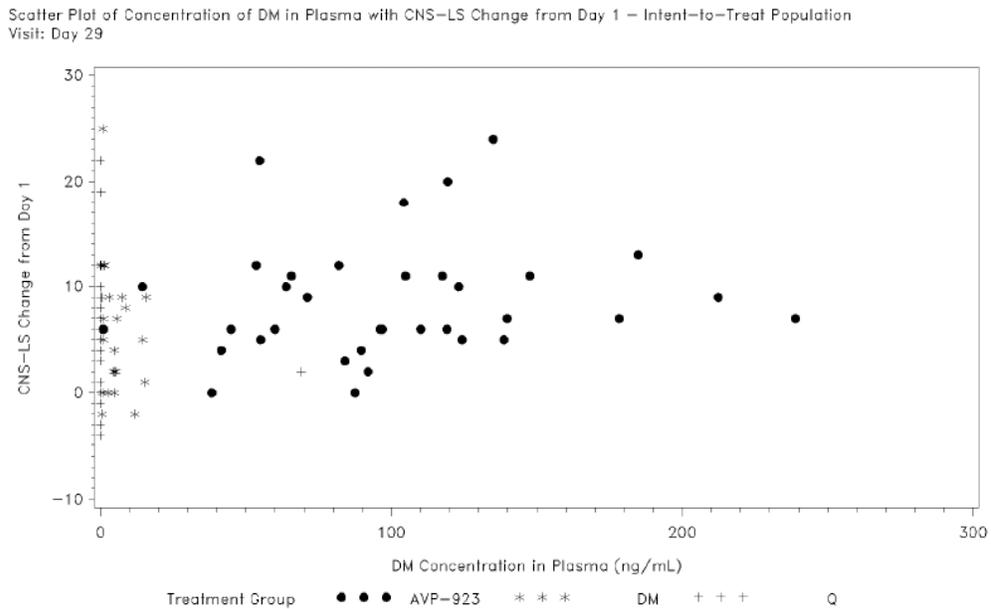
^a Change in CNS-LS scores was defined as the mean of scores on Day 15 and Day 29 minus the baseline (Day 1) score.

Cross-reference: Section 6, Table 7.1

The relationship between mean DM plasma concentration, treatment, and the primary efficacy endpoint (CNS-LS Score) for Day 29 (the day that PK samples were obtained) in the ITT population (all subjects excluding PMs) is shown below.

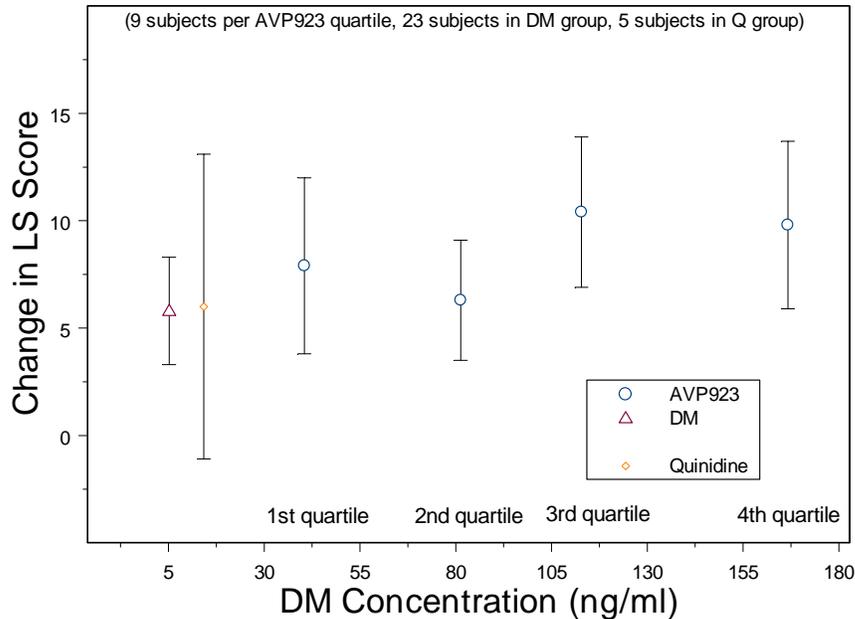


The figure below shows the relationship between change in CNS-LS score from baseline to Day 29 and individual values for DM concentration at steady state (Day 29) in each treatment group, as provided by the Sponsor.



The figure below, as plotted by the reviewer, shows CNS-LS change from baseline in relationship to quartiles of DM exposure.

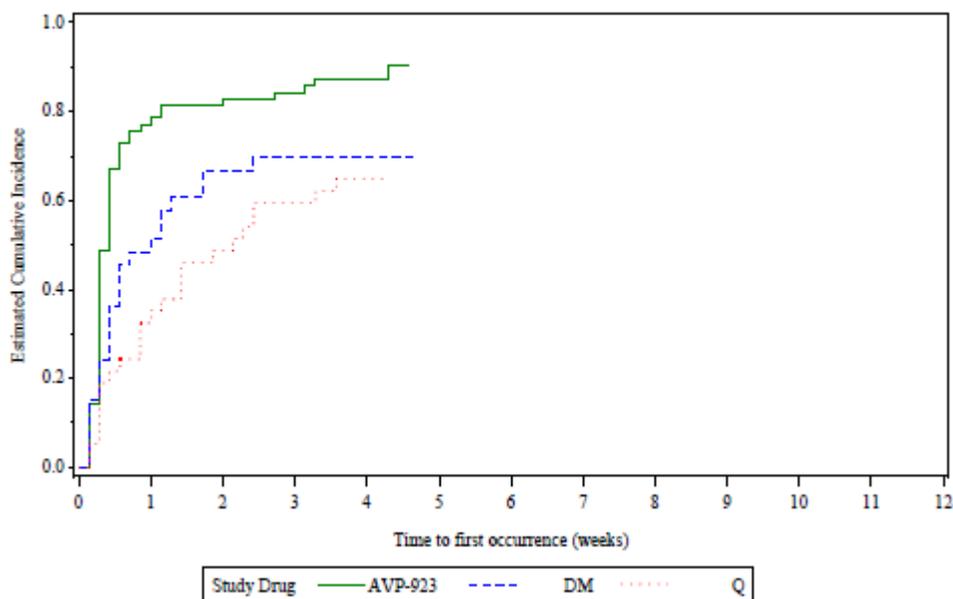
Mean (95% CI of mean) Changes in LS Score by Quartile of DM Concentrations in Study 99-AVR-102 in ALS



The PK/PD evaluations show higher steady state plasma concentrations of DM in subjects receiving AVP-923 than in subjects receiving DM alone and are suggestive of an exposure-response relationship that is related to DM exposure. However, the lack of clear demonstration of this relationship may be due to the small number of subjects in each group.

Safety

The most common adverse events in the AVP-923 group were nausea (32.9%), dizziness (20%), and somnolence (12.9%) and they occurred more frequently in the AVP-923 group than in either of their other 2 groups. In particular, % of subjects with nausea was approximately 4x that in the DM or Q groups, and somnolence was 4x that in the DM group (and not reported at all in the Q group). The % of subjects with dizziness was slightly greater in the AVP-923 group than in the DM group (1.3X) and approximately 7.4x the % in the Q group. Other adverse events included anorexia, constipation, falls, joint stiffness, muscle cramps, increased sweating, and vomiting that occurred more frequently in AVP023 than after DM or Q. The time of reporting of these adverse events from the beginning of the study is shown in the figure below. It is observed that although most of the AVP923 adverse events were reported within approximately the first few weeks of study drug administration, the cumulative incidence increased throughout the study.

Figure 16.1.1 Estimated Cumulative Incidence of any Adverse Event
Study: 99-AVR-102(ALS)

Discontinuation from Study: Twenty-two subjects withdrew from the study due to adverse events: 17 in the AVP-923 group, 2 in the DM group, and 3 in the Q group. The 17 subjects in the AVP-923 group experienced 50 adverse events. All except 4 of those were mild or moderate. The events included severe headache in 1 subject, severe nausea and severe vomiting in 1 subject, and severe respiratory failure resulting in death in 1 subject. The latter was not considered by the Sponsor to be related to study medication. The most prominent adverse events (dizziness, nausea, and somnolence) did not appear to be associated with discontinuation in most cases.

QT evaluation

According to data presented in the ISS, there were 2 subjects in 99-AVR-102 who were outliers with respect to QTc. One subject taking DM alone had a ≥ 60 msec increase in QTc. One subject taking AVP-923 had a QTcF of 434 ms (baseline 447 msec) and a QTcB of 451 msec (baseline 451 msec).

CONCLUSIONS:

- The small but statistically significant decrease in CNS-LS score was associated with administration of AVP-923 and with higher Day 29 DM plasma concentrations than were observed after DM or Q alone.
- Dizziness, nausea, and somnolence/sedation were the most common adverse events and occurred more frequently in the AVP-923 group than in the DM or Q groups. They occurred primarily within the first week of dosing (although nausea occurred throughout the study).

4.2.17 CLINICAL 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

Study Investigators and Site:

(b) (4)

Protocol Number: 02-AVR-106

Note: this study is being reviewed from only the PK/PD perspective

OBJECTIVE:

The objectives were to evaluate safety, tolerance, and efficacy of AVP-923 compared with placebo for the treatment of pseudobulbar affect over a 12-week period in a population of subjects with multiple sclerosis.

FORMULATIONS:

Table 1. Product used in 02-AVR-106

	Lot Number	Date of Manufacture (Dates of study) or else put exp date
AVP-923 capsules (30 mg DM/30 mg Q) (b) (4)	C0051001	October 17, 2002 (12/10/02-6/22/04)
Placebo	C0050001	(12/10/02-6/22/04)

According to the Stability Study Report provided in the present submission, the test product appears to be stable for at least 36 months at room temperature.

STUDY DESIGN:

This was a multicenter, randomized, double-blind, placebo-controlled study. Eligible subjects were randomized to receive study medication (placebo or AVP-923) twice daily for 85 days. Subjects were instructed to keep a diary of the time the doses were taken, as well as a log of any AEs experienced. Subjects were assessed by completing the CNS-LS self report measure of pseudobulbar affect on Days 1, 15, 29, 57, and 85. QOL and pain were also rated, in addition to AEs and vital signs. ECGs were obtained at Screening, Day 29, and Day 85. Blood samples for quantitation of DM, DX and Q were collected on Days 29 and 85.

Inclusion criteria included males or females, 18-68 years of age inclusive, with a confirmed diagnosis of MS or probable MS, a clinical history of pseudobulbar affect, and a CNS-LS score at baseline of ≥ 13 . Subjects had normal hematologic, hepatic, and renal function, and an ECG with no evidence of heart block, QT prolongation, sinus bradycardia or history of sick sinus syndrome, ventricular tachycardia, multifocal ventricular ectopic beats, or frequent unifocal ventricular ectopic beats. Females were to practice an established method of birth control that could include hormonal contraception. Exclusion criteria included history of ventricular tachycardia or torsades de points, known sensitivity to Q or opiates, use of antidepressants, history of psychiatric disturbance, hypotension, history of postural syncope, or any history of unexplained syncope. A list of concomitant medications that were not allowed included some CYP3A4 inhibitors, carbonic anhydrase inhibitors, some CYP3A substrates, some CYP2D6 substrates, and sodium bicarbonate.

ASSAY:

Plasma DM and DX and Q

Table 3. Performance of Analytical Method for 02-AVR-106 for Plasma DM, DX, and for Plasma Q

Analyte	Method	Calibration Standards ($\mu\text{g/ml}$)	Linearity	LOQ	QC	Inter-assay CV (%)	Inter-assay Accuracy (%)
DM	LC-MS/MS Method 26267	0.2 -200 ng/ml	$r > 0.998$	0.2 ng/ml	(ng/ml)		
					0.6	9.8	2.00
					15	3.59	2.38
DX	LC-MS/MS Method 26267	2.5 -2500 ng/ml	$r > 0.998$	2.5 ng/ml	(ng/ml)		
					7.5	8.47	4.57
					250	3.38	5.86
Q	HPLC	0.05-10.0 $\mu\text{g/ml}$	$r > 0.995$	0.05 $\mu\text{g/ml}$	($\mu\text{g/ml}$)		
					0.15	4.82	-4.47
					1.5	5.19	-4.09
					7.5	5.61	-2.01

DM and DX

The method was validated with long term stability demonstrated for 101 weeks at -20°C . One calibration curve and duplicate QC samples were analyzed with each batch of study samples for Study 02-AVR-106 for detection of DM and DX in plasma. The performance of the assay is considered acceptable.

Quinidine

The method was validated with long term stability demonstrated for 129 weeks at -20°C , and the samples were analyzed within the time for which they are stable. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for detection of Q in plasma. The performance of the assay is considered acceptable.

RESULTS:

Demographics

There were 150 subjects randomized into the study (n=76 for AVP-923 and n=74 for placebo). Twenty-one subjects discontinued AVP-923 and 21 subjects discontinued placebo. Reasons for discontinuation were given as “adverse events” (AEs) in 4 AVP-923 subjects and in 5 placebo subjects, and “refused medication due to AE” in 7 AVP subjects and in 3 placebo subjects.

The mean years with multiple sclerosis was 10.3 in the AVP-923 group and 9.6 in the placebo group. The mean number of weekly episodes of pathological laughing and/or crying was 14.1 in the AVP-923 group and 17.3 in the placebo group. Other demographics characteristics of the ITT population are shown in the table below.

Table 4. Demographics of the ITT population in 02-AVR-106

Treatment Group	Mean Age (Range)	Weight (mean ± SD)	Race
AVP-923	46.3 (25-68)	76.5 ± 17.8 kg (n=74)	Caucasian 68
		89.3 ± 19.4 kg (male; n=14)	Black 5
		73.6 ± 16.2 kg (female; n=60)	Hispanic 2
Placebo	43.7 (21-71)	69.82 ± 17.3 kg (n=74)	Asian 1
			Caucasian 68
			Black 5
		76.5 ± 14.1 kg (male; n=12)	Hispanic 1
	68.5 ± 17.6 kg (female; n=62)	Asian 0	

Concomitant medications taken during the study included acetazolamide (a carbonic anhydrase inhibitor), alprazolam, citalopram, diltiazem, oxycodone, Robitussin-DM, and Tussin DM, each in 1 subject. Paroxetine was used in 8 AVP-923 subjects and 17 placebo subjects.

Based on patient diary, treatment compliance was high and similar between treatment groups.

CYP2D6 Genotype

The predicted CYP2D6 phenotype based on the CYP2D6 genotype characteristics of the ITT population are shown in the table below, as provided by the Sponsor. Genotype was not determined for all subjects.

Table 31. Number (%) of Subjects with Predicted Phenotype at Day 1 — ITT Population

Predicted Phenotype	AVP-923 (N=76)	Placebo (N=74)	Total (N=150)
Total with phenotype data available	50 (100.0)	53 (100.0)	103 (100.0)
Poor	1 (2.0)	2 (3.8)	3 (2.9)
Intermediate	0 (0.0)	1 (1.9)	1 (1.0)
Extensive	48 (96.0)	50 (94.3)	98 (95.1)
Ultra-rapid	1 (2.0)	0 (0.0)	1 (1.0)

Dextromethorphan, Dextropropion, and Quinidine Plasma Concentrations

Plasma Concentrations (mean, % CV) of DM, DX, and Q in subjects taking AVP-923

	DM (ng/ml)	DX (ng/ml)	Q (µg/ml)
Day 29 n=60	114.6 (49)	82.2 (38)	0.1621 (59)
Day 85 n=43	114.7 (42)	78.6 (43)	0.1684 (62)

Note that not all subjects had concentrations available. The mean concentrations were relatively stable over the course of the study.

The poor metabolizer (PM) had higher DM concentrations than the means in the extensive metabolizers (EMs), although the concentration was in the range measured in the EMs. The PM had a lower DX concentrations than any measurable concentrations reported for the EMs. For Q, the PM had a concentration in the range of the EMs on Day 29, but on Day 85 was approximately 30% lower than the mean. As this DM concentration had also decreased from Day 29 values (84.8 ng/ml on Day 85 vs 128.3 ng/ml on Day 29), it is likely that the sample timing differed in relation to dose.

PK/PD Analyses

CNS-LS scores at either screening or Day 1 were not statistically significantly different between the AVP-923 and Placebo groups in the ITT population. The primary efficacy endpoint was change from baseline in CNS-LS score (Baseline CNS-LS minus the mean of the scores on Day 15, 29, 57, and 85). Subjects who received AVP-923 had a significantly greater reduction in adjusted mean values for CNS-LS (least squares means computed from a regression model for an individual with a CNS-LS of 20 at baseline and the average of center effects) ($p < 0.0001$) in the ITT population. The results are shown in the figure below, as provided by the Sponsor. It is also noted that as early as Day 15, there was a statistically significantly greater improvement in subjects taking AVP-923 compared to placebo.

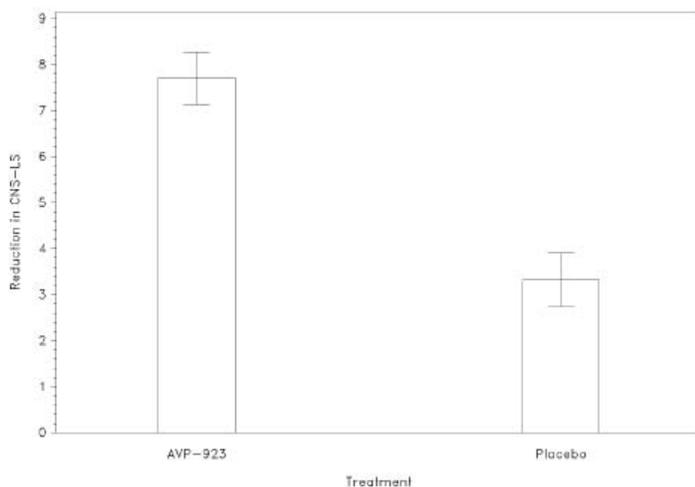
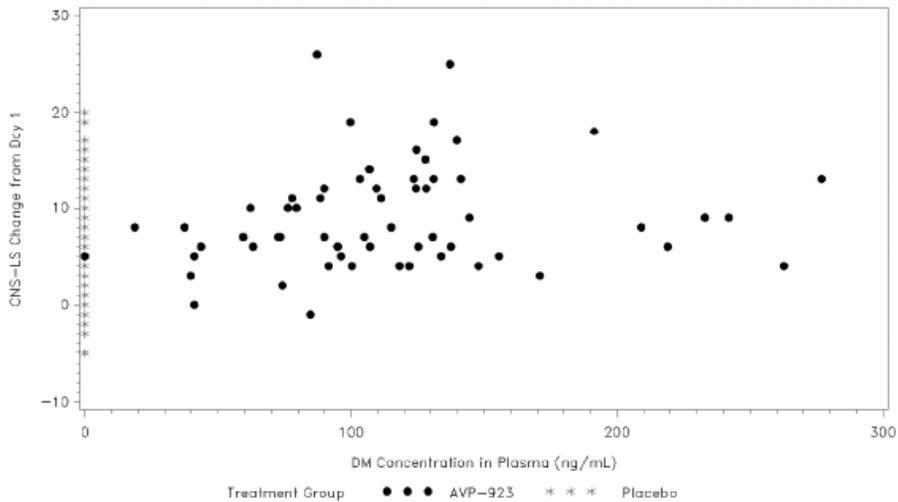


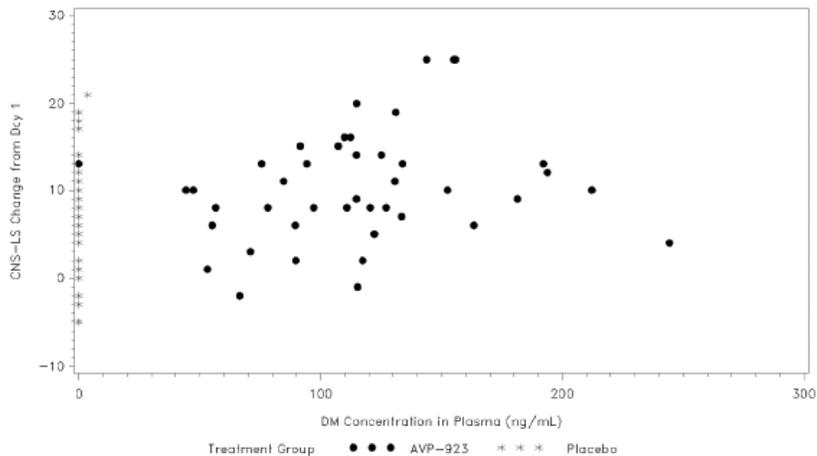
Figure 2. Adjusted Mean Reduction in CNS-LS Score — ITT Population

The figures below, as provided by the Sponsor, show the relationship between change from baseline CNS-LS and plasma dextromethorphan concentrations on Days 29 and 85. The correlation coefficients are -0.5041 (p value < 0.0001) and - 0.4169 (P value < 0.0001), for Days 29 and 85, respectively using all phenotypes and both treatment groups combined. For subjects receiving only AVP-923, for EMs there was a significant correlation on Day 29 but not on Day 28. There was no significant correlation at Day 29 or Day 85 for all phenotypes combined for subjects receiving only AVP-923.

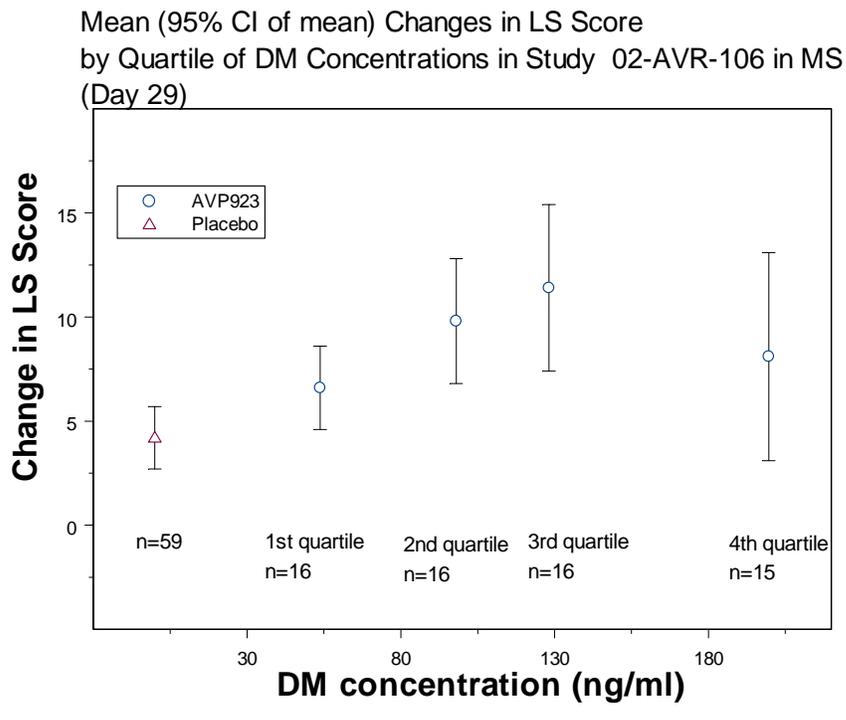
Scatter Plot of Concentration of DM in Plasma with CNS-LS Change from Day 1 – Intent-to-Treat Population
Visit: Day 29



Scatter Plot of Concentration of DM in Plasma with CNS-LS Change from Day 1 – Intent-to-Treat Population
Visit: Day 85



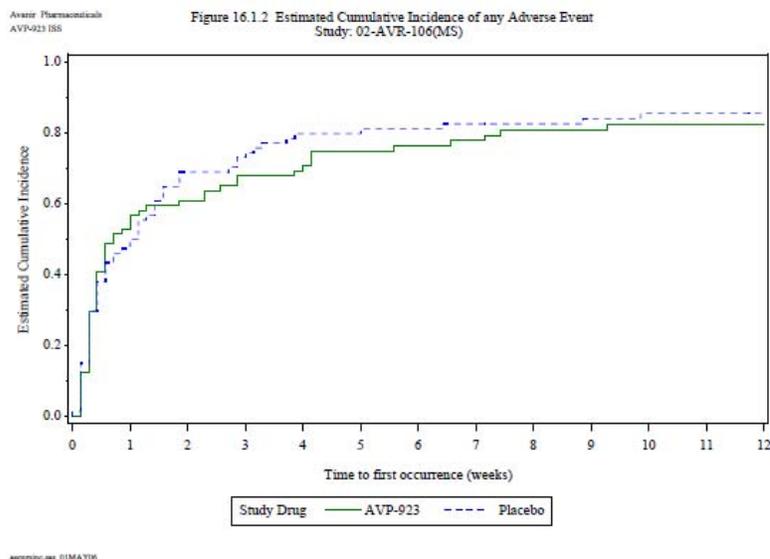
The figure below, as plotted by the reviewer, shows the mean (95% CI of the mean) for changes in CNS-LS score by quartile of DM concentrations in this study as measured at Day 29. For comparison, placebo has been included (all of the placebo DM concentrations were reported as 0 ng/ml). These results show substantial overlap in outcome measure between the different quartiles. The results suggest that there may be a concentration-response effect. However, this could be more definitively shown with a larger study.



Safety

There were no deaths reported. There were 62 AVP-923 subjects and 63 placebo subjects with adverse events. The most common adverse events (reported by $\geq 5\%$ of subjects in the ITT population) that were greater in AVP-923 than placebo included dizziness (26.3% of AVP subjects and 9.5% of placebo), nausea (22.4 of AVP subjects and 14.9% of placebo), and weakness (in 10.5% of AVP and 5.4% of placebo). The median duration of nausea, dizziness, and fatigue in the AVP-923 group was 1.5 days, 1.0 days, and 1.5 days, respectively.

Although it appears from the ISS that adverse events, including nausea, dizziness, headache, fatigue, and falls occur primarily in the first several weeks, they continue throughout the duration of the study. The figure below showing estimated cumulative incidence of adverse events was provided by the Sponsor in the 120-day safety update.



QT evaluation

ECG evaluation did not show $QT_{cF} > 450$ in the subjects treated with AVP-923. The mean QT_{cF} prolongation was 11.0 msec for AVP-923 and 6.2 msec for placebo. There were 7 measurements for change in $QT_{cF} > 30$ msec and one value that was 60.5 msec for AVP-923. (For placebo there were 7 measurements with a change in $QT_{cF} > 30$). All of these changes in the AVP-923 group were in females. Quinidine concentrations corresponding to the changes in $QT_{cF} > 30$ msec ranged from 0.0865 to 0.3953 $\mu\text{g/ml}$. (The maximum quinidine concentration observed in this study was 0.4770 $\mu\text{g/ml}$). There were 2 QT determinations made at unscheduled visits, and there were no quinidine concentrations available at those time points. It should be noted that ECG determinations were not necessarily performed at T_{max} .

CONCLUSIONS:

Plasma concentrations of DM, DX, and Q are consistent with exposures in the Phase I studies.

Some Q concentrations were > 2 -fold higher than the mean, with concentrations up to 0.4770 $\mu\text{g/ml}$.

There is some correlation between DM exposure and response. However, the variability was large. A larger patient sample could more definitively characterize the exposure-response relationship.

4.2.18 IN VITRO DEXTROMETHORPHAN PROTEIN BINDING

THE *IN VITRO* BINDING OF DEXTROMETHORPHAN TO HUMAN PLASMA (HEPARIN) PROTEINS

Study Investigators and Site:

(b) (4)

Protocol Number: AA-19370-01

OBJECTIVES:

The objective of the study was to assess binding of dextromethorphan (DM) in human plasma over a concentration range of 50-350 ng/ml (bracketing the 4 and 12 hour time points observed in Study 04-AVR-111) and to assess the effect of quinidine and dextrophan (DX) on DM protein binding.

TEST COMPOUNDS:

Quinidine (b) (4)
Dextrophan tartrate (b) (4)
Dextromethorphan HBr (USP)
³H-dextromethorphan ,85 Ci/mmol (b) (4)

METHODS:

Human plasma from 3 donors was collected and pooled. Blank plasma samples were determined in human plasma using the following test sets:

Dextromethorphan Concentration	Quinidine Concentration	Dextrophan Concentration
50.0 ng/mL	0 ng/mL	0 ng/mL
350 ng/mL	0 ng/mL	0 ng/mL
50.0 ng/mL	350 ng/mL	130 ng/mL

n ≥ 3 for each test

Samples of fortified plasma, pre-warmed to 37° C were added to sample reservoirs and centrifuged at 1800 x g for 30- minutes. A fixed volume of the resulting ultrafiltrate was added to scintillation cocktail and counted, as was the unfiltered fortified sample. Blank ultrafiltrate was prepared by processing blank plasma through centrifugal filter devices and was used to test non-specific binding (and was found to be 5-7%). Samples and the resulting ultrafiltrate samples were counted for total and free quinidine, respectively.

In addition, equilibrium dialysis was performed in which samples of fortified plasma, pre-warmed to 37° C, were added to the donor side of dialysis cells. To the receptor side, Krebs physiological buffer was added. Dialysis cells were placed in a water bath at 37° C and rotated at 30 rpm for a designated time. Plasma and buffer were removed from each cell, and an aliquot counted.

The % bound was calculated as

$$100 * \frac{(total - free)}{total}$$

RESULTS:

It was determined that equilibrium was obtained at 2 hours in the equilibrium dialysis method. A comparison of results of the equilibrium dialysis method and the ultrafiltrate method were similar. The results are summarized in the table below (as provided by the Sponsor).

50.0 ng/mL Dextromethorphan			Batch ID	Method Type
% NSB	% Bound	% Free		
14.9	63.4	36.6	DEQ_T01	Equilibrium Dialysis 2 hr
12.1	61.3	38.7	DEQ_T02	Equilibrium Dialysis 2 hr
27.8	60.1	39.9	DEQ_T03	Equilibrium Dialysis 2 hr
20.7	64.0	36.0	DEX_T01	Ultrafiltration
23.1	Not run	Not run	DEX_T02	Ultrafiltration (NSB test)
26.1	63.2	36.8	DEX_T03	Ultrafiltration
350 ng/mL Dextromethorphan				
% NSB	% Bound	% Free		
17.6	64.1	35.9	DEQ_T01	Equilibrium Dialysis 2 hr
14.0	58.8	41.2	DEQ_T02	Equilibrium Dialysis 2 hr
25.9	60.7	39.3	DEQ_T03	Equilibrium Dialysis 2 hr
20.7	63.0	37.0	DEX_T01	Ultrafiltration
26.1	64.6	35.4	DEX_T03	Ultrafiltration
50.0 Dextromethorphan + 350 Quinidine and 130 Dextrorphan ng/mL				
% NSB	% Bound	% Free		
22.8	62.4	37.6	DEQ_T03	Equilibrium Dialysis 2 hr
20.7	62.8	37.2	DEX_T01	Ultrafiltration
26.1	63.7	36.3	DEX_T03	Ultrafiltration

CONCLUSIONS and COMMENTS:

1. Protein binding of DM was not concentration dependent at concentrations of approximately 50 ng/ml and 350 ng/ml. The latter concentration represents an upper range for expected concentrations after administration of NEURODEX. DM was approximately 60% bound to human plasma proteins.
2. The presence of quinidine and DX did not alter protein binding of DM.

4.2.19

IN VITRO QUINIDINE PROTEIN BINDING STUDY

THE *IN VITRO* BINDING OF QUINIDINE TO HUMAN PLASMA (HEPARIN) PROTEINS

Study Investigators and Site:

(b) (4)

Protocol Number: AA-19369-01

OBJECTIVES:

The objective of the study was to assess binding of quinidine in human plasma over a concentration range of 30.0-350 ng/ml (bracketing the 4 and 12 hour time points observed in Study 04-AVR-111) and to assess the effect of dextromethorphan (DM) and dextrorphan (DX) on quinidine protein binding.

TEST COMPOUNDS:

Quinidine (b) (4)

Dextrorphan tartrate (b) (4)

Dextromethorphan HBr (USP)

³H-quinidine ,20 Ci/mmol (b) (4)

METHODS:

Human plasma from 3 donors was collected and pooled. Blank plasma samples were determined in human plasma using the following test sets:

Quinidine Concentration	Dextromethorphan Concentration	Dextrorphan Concentration
30.0 ng/mL	0 ng/mL	0 ng/mL
350 ng/mL	0 ng/mL	0 ng/mL
30.0 ng/mL	300 ng/mL	130 ng/mL

n ≥ 3 for each test

Samples of fortified plasma, pre-warmed to 37° C were added to sample reservoirs and centrifuged at 1800 x g for 30- minutes. A fixed volume of the resulting ultrafiltrate was

added to scintillation cocktail and counted, as was the unfiltered fortified sample. Blank ultrafiltrate was prepared by processing blank plasma through centrifugal filter devices and was used to test non-specific binding (and was found to be 5-7%). Samples and the resulting ultrafiltrate samples were counted for total and free quinidine, respectively.

The % bound was calculated as

$$100 * \frac{(total - free)}{total}$$

RESULTS:

The following table (as provided by the Sponsor) summarizes the results.

30.0 ng/mL Quinidine			Batch ID
% NSB	% Bound	% Free	
5.0	89.0	11.0	QUI_T02
7.0	89.1	10.9	QUI_T03
350 ng/mL Quinidine			
% NSB	% Bound	% Free	
5.0	89.8	10.2	QUI_T02
7.0	87.8	12.2	QUI_T03
30.0 ng/mL Quinidine + 300 ng/mL Dextromethorphan and 130 ng/mL Dextrorphan			
% NSB	% Bound	% Free	
5.0	88.4	11.6	QUI_T02
7.0	88.9	11.1	QUI_T03

CONCLUSIONS and COMMENTS:

1. Protein binding of Quinidine was not concentration dependent at concentrations of approximately 30 ng/ml and 350 ng/ml. The latter concentration represents an upper range for expected concentrations after administration of NEURODEX. Quinidine was approximately 89% protein bound.
2. DM and DX did not alter protein binding of Quinidine.

4.2.20 AVP-923 DISSOLUTION METHOD DEVELOPMENT

(b) (4)



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Proposed Dissolution Method and Specifications

The Sponsor has proposed the following dissolution method and specifications:

Apparatus: USP Apparatus 1 (Basket)
Medium: Simulated Gastric Fluid, without enzymes, pH 1.2
Volume: 900 ml
Rotation Speed: 100 rpm
Specification: Q = ^{(b) (4)} in 15 minutes for both DM and for Q

RECOMMENDATION:

The Office of Clinical Pharmacology finds the proposed dissolution method and specifications acceptable.

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Recommendation:

The Office of Clinical Pharmacology recommends the to-be-marketed formulation is similar to the clinical trials formulation based on adequate *in vitro* dissolution documentation. A biowaiver for the to-be-marketed formulation can be granted.

4.2.22 OCP Pharmacogenomics Review

Genomics Review for NDA 21, 879

Shashi Amur

October 4, 2006

In this submission, a combination of dextromethorphan (DM) and quinidine has been used to increase the DM concentration in plasma to enhance the therapeutic value of DM.

This review is focused on the genotyping of subjects for several CYP2D6 alleles(*3, *4, *5, *6, *7, *8, *10, *17 and *2XN) to determine the predicted phenotypes. The choice of the alleles is satisfactory, since the selected alleles covers the major genotypes of CYP2D6. The protocols employed in the genotype reports were examined and some questions about sample type, sample collection, DNA isolation and storage, additional information on the PCR procedures were conveyed to the sponsor. The sponsor sent back the requested information. The procedures used for the DNA isolation and PCR are acceptable.

4.2.23 QT PHARMACOMETRICS CONSULT

NDA:	21-879
Compound:	NEURODEX (30 mg dextromethorphan and 30 mg quinidine)
Sponsor:	Avanir Pharmaceuticals
PM Reviewer:	Christine Garnett
PM Team Leader:	Joga Gobburu

EXECUTIVE SUMMARY

A thorough QT study was conducted to assess the effects of two doses of NEURODEX on cardiac repolarization. A suprathreshold dose (60 mg dextromethorphan and 60 mg quinidine) caused QTcF prolongation. The maximal mean change in placebo- and baseline-corrected QTcF was 18.81 ms, and the upper bound of the one-sided 95% CI was 24.50 ms. The time of maximum mean change was 6 h post dose. The therapeutic dose (30 mg dextromethorphan and 30 mg quinidine) also caused QTc prolongation. The maximal mean change in placebo- and baseline-corrected QTcF was 10.12 ms, and the upper bound of the one-sided 95% CI was 15.05 ms. The time of maximum mean change was 5 h post dose. These effects are assumed to be caused by both quinidine and its metabolites.

A combined pharmacokinetic and pharmacodynamic model was used to analyze the relationship between change in the QTc interval and changes in plasma concentration of quinidine. The effect of quinidine on the QTc interval could be explained by a linear pharmacodynamic model with a delayed effect. The equilibration between plasma and effect site had a half-time of 3 hours (BSV of 123%). The median slope was 55.6 ms/mg/l (BSV of 40%). The slope estimate is comparable to literature reports.

The pharmacodynamic model was used to predict QTc prolongation at 4 different dose levels in the population using parametric simulations. For the 60 mg dose, the median change in QTcI interval was 18.8 ms but in 5% of the population the prolongation was at least 37.8 ms. For the 30 mg dose, the median change was 9.3 ms but in 5% of the population the prolongation was 19.0 ms.

The pharmacodynamic model was used to predict QTc prolongation for two lower doses of quinidine (15 mg and 10 mg) that have not been studied clinically. For both dose levels, the prolongation was predicted to be less than 10 ms in 95% of the population.

Recommendations

1. A 15 mg dose of quinidine would result in a risk of QT prolongation that is predicted to be lower than 10 ms in 95% of subjects. The results do not address whether a 15 mg dose of quinidine will sufficiently inhibit CYP2D6 in order to achieve therapeutic concentrations of dextromethorphan.
2. Labeling Statement:
Dose and plasma concentration-related increases in the QTc interval and in some subjects T-wave abnormalities have been observed. These effects are believed to be caused by quinidine and its metabolites. The relationship between the change in QTc and quinidine plasma concentrations is linear with a mean slope of 56 ms per mg/L quinidine. With repeat dosing, the mean effect on QTc of NEURODEX is approximately 10 ms. However, in 5% of the population the prolongation of QTc is 19 ms.

BACKGROUND

Avanir Pharmaceuticals is developing a combination product of quinidine sulfate (30 mg) and dextromethorphan HBr (30 mg) for the treatment of pseudobulbar affect, an involuntary emotional expression.

Preclinical studies have shown that both quinidine and dextromethorphan have a concentration-dependent inhibitory effect on hERG current in transfected HEK293 cells. The estimated IC50 value was 367 ng/ml (469 nM) for quinidine and 6592 ng/ml (17800 nM) for dextromethorphan when each compound was tested alone. When tested together, the IC50 value was 465 ng/ml (297 nM for quinidine and 629 nM for dextromethorphan). This indicates that quinidine is responsible for hERG inhibition and not dextromethorphan (personal communication, John Koerner).

The thorough QT/QTc study was a three-arm, randomized, placebo-controlled, double-blind crossover design and an additional open-label arm for a positive control (moxifloxacin) in 36 healthy volunteers. Subjects received two doses of NEURODEX (30 mg and 60 mg) twice daily for 7 doses.

A summary of PK parameters is presented in Table 1. There was a greater than proportional increase in dextromethorphan and its metabolite dextrorphan with repeat dosing of 30 mg and 60 mg twice daily for 7 doses. Peak concentrations occurred anytime during the dosing interval. In contrast, quinidine increased proportionally with dose. Peak quinidine concentrations occurred between 2 to 3 hours after dosing.

Table 1. Summary of Pharmacokinetic Parameters

Analyte	Dose	Mean ± SD for Cmax and AUC Median (Range) for Tmax		
		Cmax (ng/ml)	Tmax (h)	AUC tau (ng•h/ml)
Dextromethorphan	30 mg	88.5±23.3	3.33(2.33 – 5.33)	889±238
	60 mg	211±49.2	3.33 (2.33 – 5.33)	2064±455
Dextrorphan	30 mg	86.6±23.1	22.3 (0 – 22.4)	706 ± 199
	60 mg	136±44.7	22.3 (2.33 – 22.5)	1047±287
Quinidine	30 mg	0.177±0.05 µg/ml	2.33 (2.33 – 3.33)	1.32±0.42 µg•h/ml
	60 mg	0.355±0.102 µg/ml	2.33 (2.33 – 3.33)	2.53±0.78 µg•h/ml

A suprathreshold dose (60 mg dextromethorphan and 60 mg quinidine) caused QTcF prolongation. The maximal mean change in placebo- and baseline-corrected QTcF was 18.81 ms, and the upper bound of the one-sided 95% CI was 24.50 ms. The time of maximum mean change was 6 h post dose.

The therapeutic dose (30 mg dextromethorphan and 30 mg quinidine) also caused QTcF prolongation. The maximal mean change in placebo- and baseline-corrected QTcF was 10.12 ms, and the upper bound of the one-sided 95% CI was 15.05 ms. The time of maximum mean change was 5 h post dose.

The Sponsor noted that a regression of change in QTcF as a function of concentration of dextromethorphan, dextrorphan, and quinidine showed a strong relationship for each of the compounds, showing a slope that is highly statistically different from zero.

The specific aim of the modeling and simulation analyses was to determine the dose of quinidine that would yield a QT/QTc prolongation of less than 10 ms in 95% of subjects. Our assumption was QT/QTc prolongation is due to quinidine at its metabolites.

OBJECTIVES

1. To develop a PKPD model which describes the time course of quinidine effects on the QT/QTc interval using data collected in a thorough QT study; and
2. To predict risk of QT/QTc prolongation at lower doses of NEURODEX.

METHODS

DATA

Source data for these analyses were obtained from the EDR, \\CDSESUB1\EVSPROD\NDA021879\:

- DM.xpt (6/26/2006 submission)
- Supratherapeuticassembled.xpt (7/28/2006 submission)
- standardassembled.xpt (7/28/2006 submission)

PHARMACOKINETIC MODEL

Plasma concentrations of quinidine were fit to a 2-compartment model. Model parameters were assumed to be log-normally distributed. A constant coefficient of variation model was used for residual error.

The pharmacokinetics of quinidine has been previously described (1).

PHARMACODYNAMIC MODEL

A linear model was used to describe the relationship between plasma quinidine concentrations and the change in the QTc interval. Two models were assessed: one model assumed a direct effect between plasma concentrations ($E = \text{slope} \cdot C_p + \text{intercept}$), and the other model assumed a delayed effect ($E = \text{slope} \cdot C_e + \text{intercept}$). Model parameters were assumed to be normally distributed. An additive residual error model was used.

The PD endpoints were change in the QTcI interval from placebo (∂QTcI) and change in the baseline-corrected QTcI interval from placebo ($\partial\partial\text{QTcI}$). This was computed by subtracting the QTcI interval on placebo from the QTcI interval on treatment at corresponding time points.

A linear pharmacodynamic model to describe the relationship between quinidine plasma concentrations and the QT interval at higher doses of quinidine has been previously described (3–5).

NONLINEAR MIXED EFFECT MODEL

PKPD model parameters were estimated simultaneously using nonlinear mixed effects modeling approach as implemented using the NONMEM (version V) using first-order conditional estimation method.

SIMULATIONS

To predict QTc prolongation in the population, \log_e -transformed C_{max} and slope values were sampled from a normal distribution, where the mean was the population value of the parameter and variance was the between-subject variability. A predictive check was performed by comparing the simulated distribution of parameters to the observed distribution using overlaid histograms and QQ plots.

QTc prolongation was computed by multiplying the C_{max} and slope values and the 5th, 25th, 50th, 75th, and 95th percentiles were reported.

RESULTS

QT/QTc DATA

Individual plots of quinidine concentrations and change in QTcI interval are presented in Figure 6. These plots show that peak QT/QTc prolongation can occur over the entire dosing interval and did not correspond to the observed T_{max} for quinidine. The sponsor did not analyze blood samples for concentrations of quinidine metabolites which have an effect on the QT/QTc interval (1).

PKPD MODEL

All results are presented for the change in the QTcI interval from placebo (∂ QTcI) as the PD measurement. The baseline- and placebo-corrected QTcI interval ($\partial\partial$ QTcI) introduced more variability in the data. The PKPD model parameters for $\partial\partial$ QTcI are presented in [Table 6](#).

Quinidine plasma concentration and the change in QTcI interval data were simultaneously fit to the PKPD model. Model parameters are shown in Table 1 for the direct effect model and Table 2 for the delayed effect model. Goodness-of-fit plots are shown in Figure 1 for the PK model, in Figure 2 for the direct effect PKPD model, and in Figure 3 for the delayed effect PKPD model.

The 2-compartment pharmacokinetic model described the quinidine concentration data (Figure 1). Model parameters are comparable to what have been previously reported.

Including the effect compartment in the model decreased the objective function value by 8 points ($p < 0.01$, assuming chi-squared distribution with 1 degree of freedom), increased the estimate of the slope parameter from 42.8 ms•mg/l to 55.6 ms•mg/l, and reduced the between-subject variability in the slope estimate from 60.3% to 37.9%. The intercept for both models was poorly estimated. Fixing the intercept to zero increased the objection function value by greater than 10 points and it was, therefore, retained in the model.

The median half-time for the time delay was 3 hours with a between-subject variability of 123%. This predicts that the QT interval will reach its equilibrium value 12 hours after dosing. The distribution of individual subject's half-time values are shown in Figure 4. These values are higher than what has been previously reported by Holford et al; when a single dose of 4 mg/kg quinidine (oral and IV) was administered alone to healthy volunteers the half time was estimated to be 8 minutes. Possible explanations for the difference are the timing of pharmacokinetic samples (sampling times were not frequent enough around Tmax to pick up an 8 minute delay) and the high variability in the QTcI data (standard deviation for the residual error of 10 ms). Furthermore, there are conflicting reports in the literature describing the activity of the metabolites of quinidine. At steady state there could be accumulation of metabolites that prolongs the QT interval. The sponsor did not analyze the blood samples for metabolites and, therefore, the time course is not known.

The slope estimates were comparable to values reported in the literature (Table 4). With the delayed effect model, population estimate for the slope was 55.6 ms/mg/l (95% CI: 35.6, 75.6) compared to 33.5 ms/mg/l when quinidine was administered alone (3). For the direct effect model, the population estimate for slope was 42.8 ms/mg/l (95% CI: 31.7, 64.5) compared to an average of 35.7 ms/mg/l for women and men (4), 40.1 mg/mg/l for a single dose (400 mg), and 72.2 ms/mg/l at steady state quinidine concentrations (200 mg q6h) (5).

In contrast to literature reports of greater quinidine-induced QTc interval prolongation in females (5, 6), differences in slope estimates for males and females could not be detected.

Table 2. Simultaneous PKPD Model Parameters: Direct Effect Relationship between Plasma Quinidine Concentrations and Change in the QTcI Interval

Parameter	Mean	RSE%	Between Subject Variability
Ka, h-1	0.965	4.0	--
Ke, h-1	0.198	3.3	9.1%
K23, h-1	0.446	5.6	--
K32, h-1	0.399	4.9	--
V2, L	112	5.7	24.8%
Slope, ms/mg/l	42.8	19.4	25.8 ms (60.3%)
Intercept, ms	4.29	43.1	7.18 ms (167%)
PK Residual error, %	12%	11.1	--
PD Residual error, SD	10.8 ms	12.7	--
OFV = -176.7, Subjects = 34, Observations = 1210			

Table 3. Simultaneous PKPD Model Parameters: Delayed Effect Relationship between Plasma Quinidine Concentrations and Change in the QTcI Interval

Parameter	Mean	RSE%	Between Subject Variability
Ka, h-1	1.29	115	--
Ke, h-1	0.148	5.1	8.99%
K23, h-1	0.192	13.3	--
K32, h-1	0.324	5.6	--
V2, L	137	7.8	24.4%
Keo, h-1	0.228	41.0	123%
Slope, ms/mg/l	55.6	17.6	21.1 ms (37.9%)
Intercept, ms	1.17	176	6.37 ms (544%)
PK Residual error, %	12%		--
PD Residual error, SD	10.6 ms		--

OFV = -184.9, Subjects = 34, Observations = 1210

Figure 1. Individual Predicted vs. Observed Quinidine Plasma Concentrations

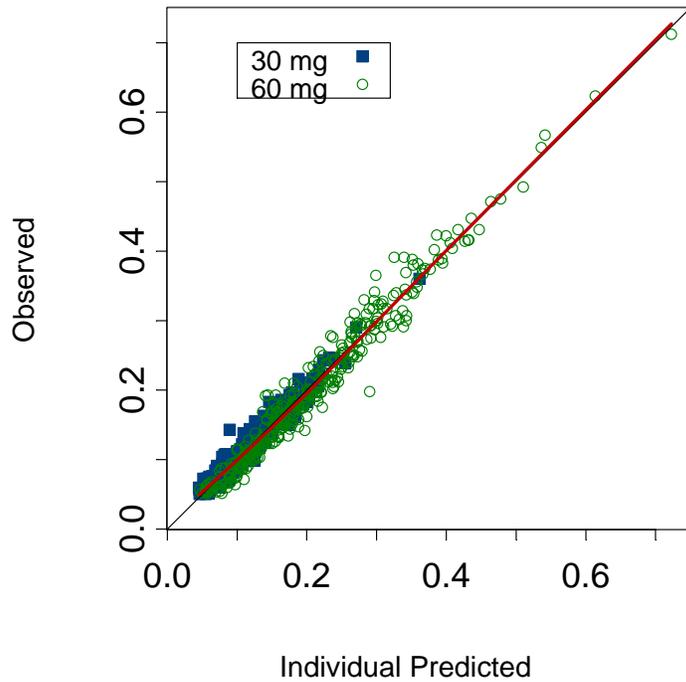


Figure 2. Goodness-of-Fit Plot for the Direct Effect Model

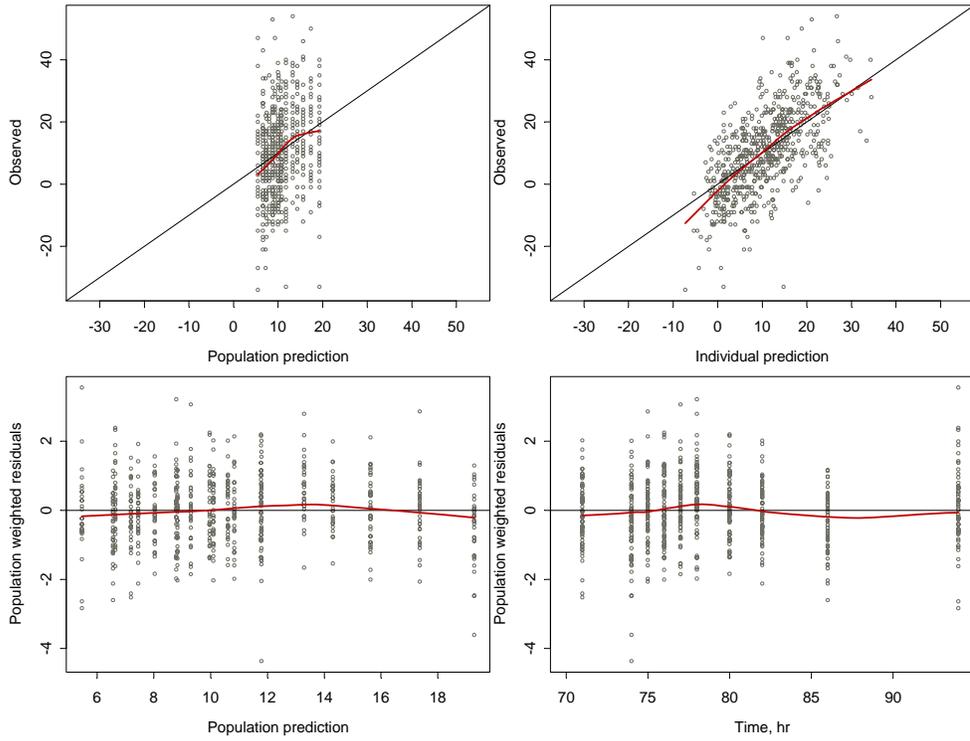


Figure 3. Goodness-of-Fit Plot for the Delayed Effect Model

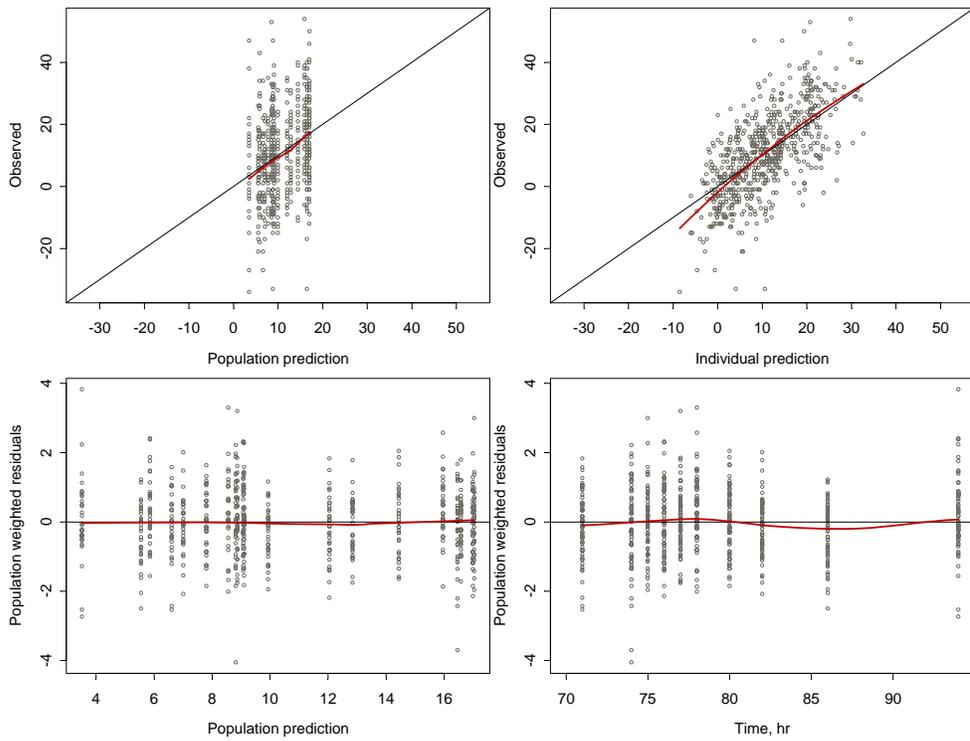


Figure 4. Distribution of equilibration half-time values

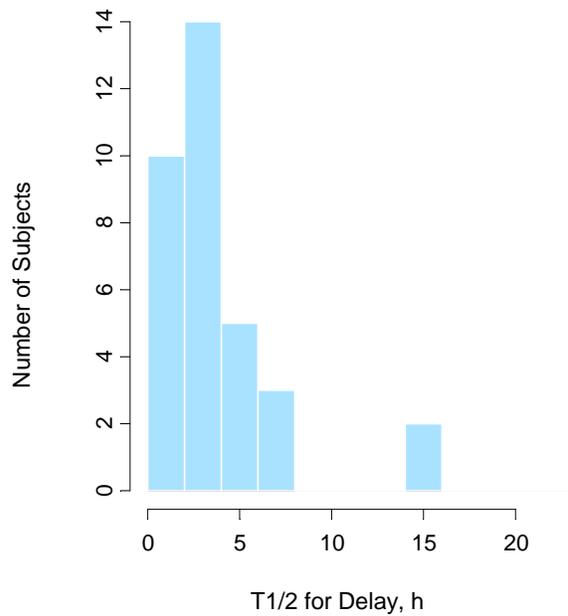


Table 4. Mean Slope and 95% Confidence Intervals for Neurodex for the Delayed and Direct Effect Models Compared to the Mean Slope for Quinidine Alone as Reported in the Literature.

Model	Mean (95% CI) Slope ¹ (ms/mg/l)	Literature Value (Mean±SE) ² (ms/mg/l)	Reference
Delayed Effect	55.6 (35.6, 75.6)	33.5±2.0 (single dose)	Holford et al. (3)
Direct Effect	42.8 (31.7, 64.5)	42.2±3.4 (women)	Benton et al. (4)
		29.3±2.6 (men)	Wooding-Scott et al. (5)
		40.1 (single dose)	
		72.2 (steady state)	

¹Calculated using population PKPD approach where fixed and random effects are simultaneously modeled
²Calculated using standard two-stage approach

QT Risk Predictions

The model-based predicted mean and 90% confidence interval for the change in QTcI for each dose group is presented in Table 5. There is good agreement between the results of the delayed effect model and the E14 metric. The direct effect model slightly under-predicted the mean change in QTcI interval.

Table 5. Mean Maximum and 90% Confidence Intervals for the Change in QTcI Interval by Neurodex Dose: Model Predictions vs. E14 Metric

Neurodex Dose	Mean (90% Confidence Interval)		
	Direct Effect ¹	Delayed Effect ²	E14/Max Mean
30 mg	7.66 (5.21, 10.1)	10.2 (6.95, 13.0)	10.2 (5.32, 15.1) ³
60 mg	15.2 (10.4, 20.1)	19.8 (13.8, 25.8)	18.1 (12.6, 24.5) ⁴

1. Slope Estimate: 42.8 (29.1, 56.4)
2. Slope Estimate: 55.6 (38.8, 72.4)
3. Max mean change occurred at 6 h post dose
4. Max mean change occurred at 5 h post dose

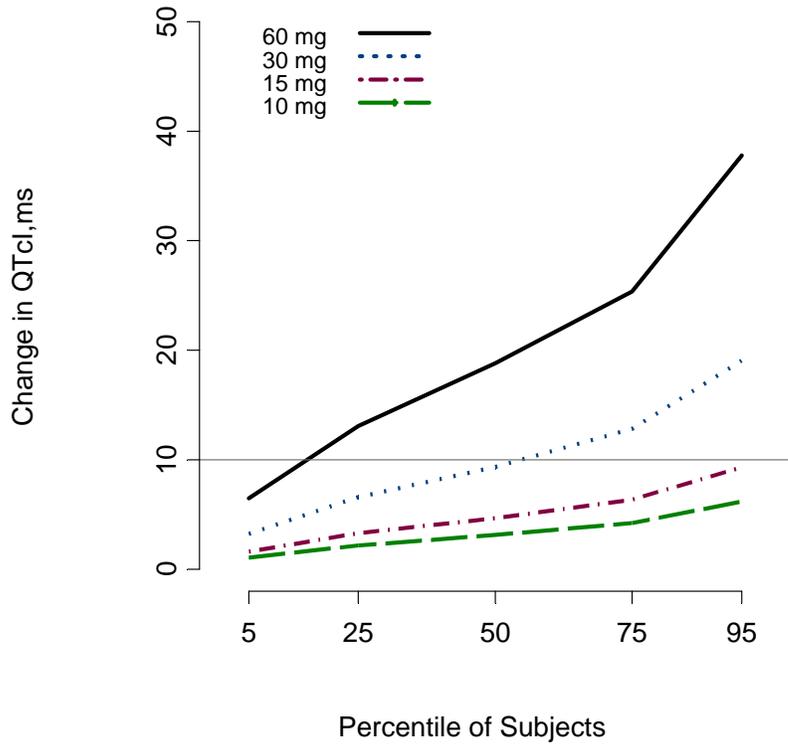
Since NEURODEX increases the QT/QTc interval it is important to not only report mean effects but also to describe the risk of QT/QTc prolongation in the population. The delayed effect model was used for simulations since the slope estimate was greater than the direct effect model and would represent a more conservative estimate of QTc prolongation. The distribution of simulated values was derived by multiplying the distribution of quinidine C_{max} values for the 30 and 60 mg dose groups by the distribution of individual slope values. Evaluation of individual post hoc values

Values for C_{max} were sampled from a log-normal distribution with a mean of 0.179 and 0.356 µg/ml and a standard deviation of 0.05 and 0.10 µg/ml for the 30 and 60 mg dose groups, respectively. Values for slope were sampled from a normal distribution with a mean of 55.6 ms/mg/l and a standard deviation of 21.1 ms/mg/l. A visual check of the distributions for slope and C_{max} are shown in Figure 9 and Figure 10.

The predicted change in the QTcI interval is summarized in Figure 5. For the 60 mg dose, the median change in QTcI interval is 18.8 ms but in 5% of the population the prolongation is at least 37.8 ms. For the 30 mg dose, the median change is 9.3 ms but in 5% of the population the prolongation is 19.0 ms.

Predictions were also made for two lower doses (15 mg and 10 mg) of quinidine that has not been studied clinically. For both doses, the prolongation is predicted to be less than 10 ms in 95% of the population.

Figure 5. Model Predicted Change in QTc Interval Stratified by Dose Group

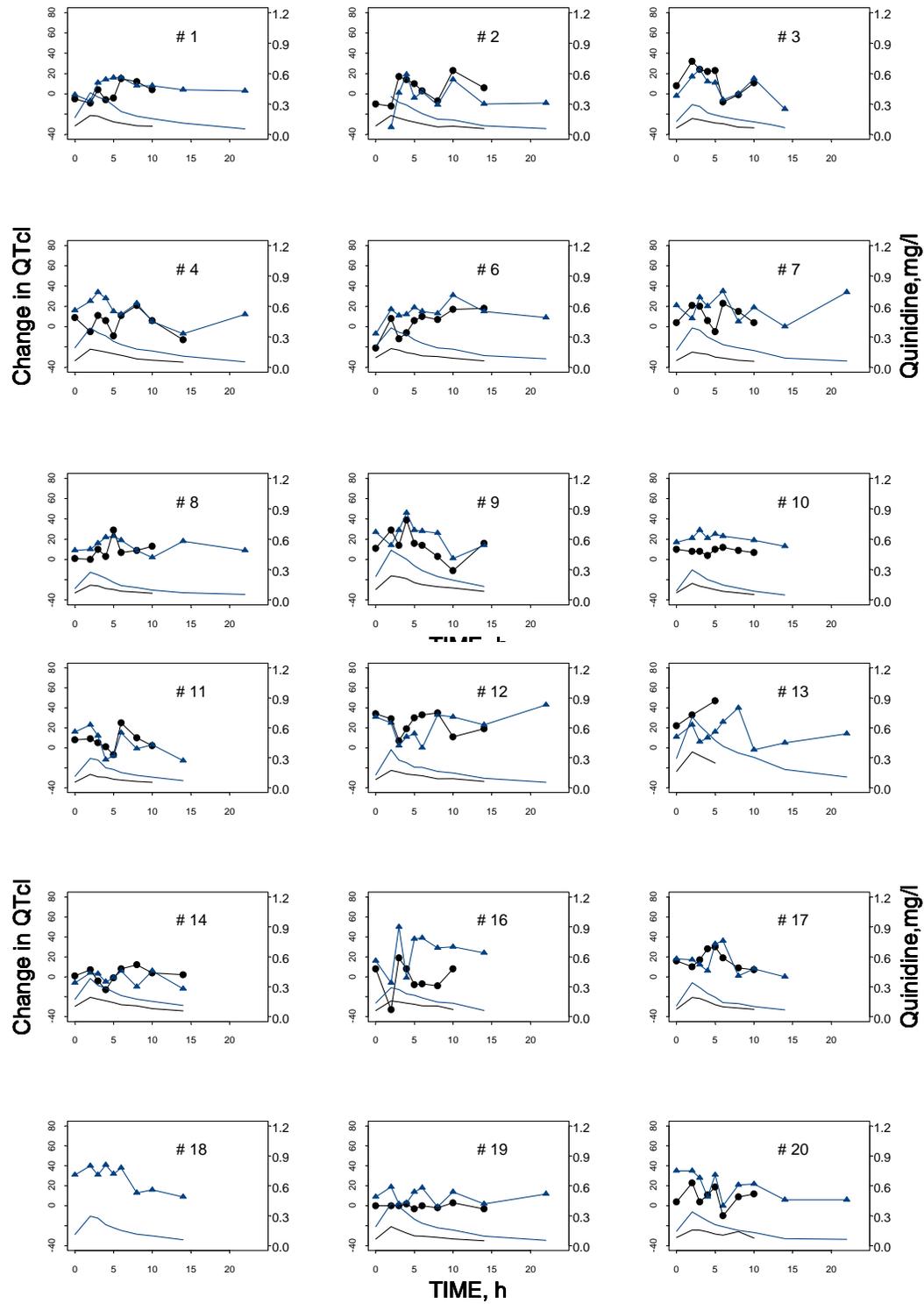


Appendices

Table 6. PKPD Model Parameters: PD Endpoint is Change from Placebo and Baseline in QTcI

Parameter	Mean	RSE%	Between Subject Variability
Ka, h-1	1.72	334	--
Ke, h-1	0.149	5.1	8.87%
K23, h-1	0.194	13.1	24.7%
K32, h-1	0.326	5.5	--
V2, L	137	8.0	--
Keo, h-1	0.197	39.5	154%
Slope, ms/ mg/l	58	26.4	39.1 ms
Intercept, ms	1.06	293	9.34 ms
PK Residual error, %	12.1%	10.6	--
PD Residual error, SD	14.7 ms	11.9	--

Figure 6. Time course of individual quinidine concentrations and change in QTcI interval (30 mg dose shown in blue and 60 mg dose shown in black)



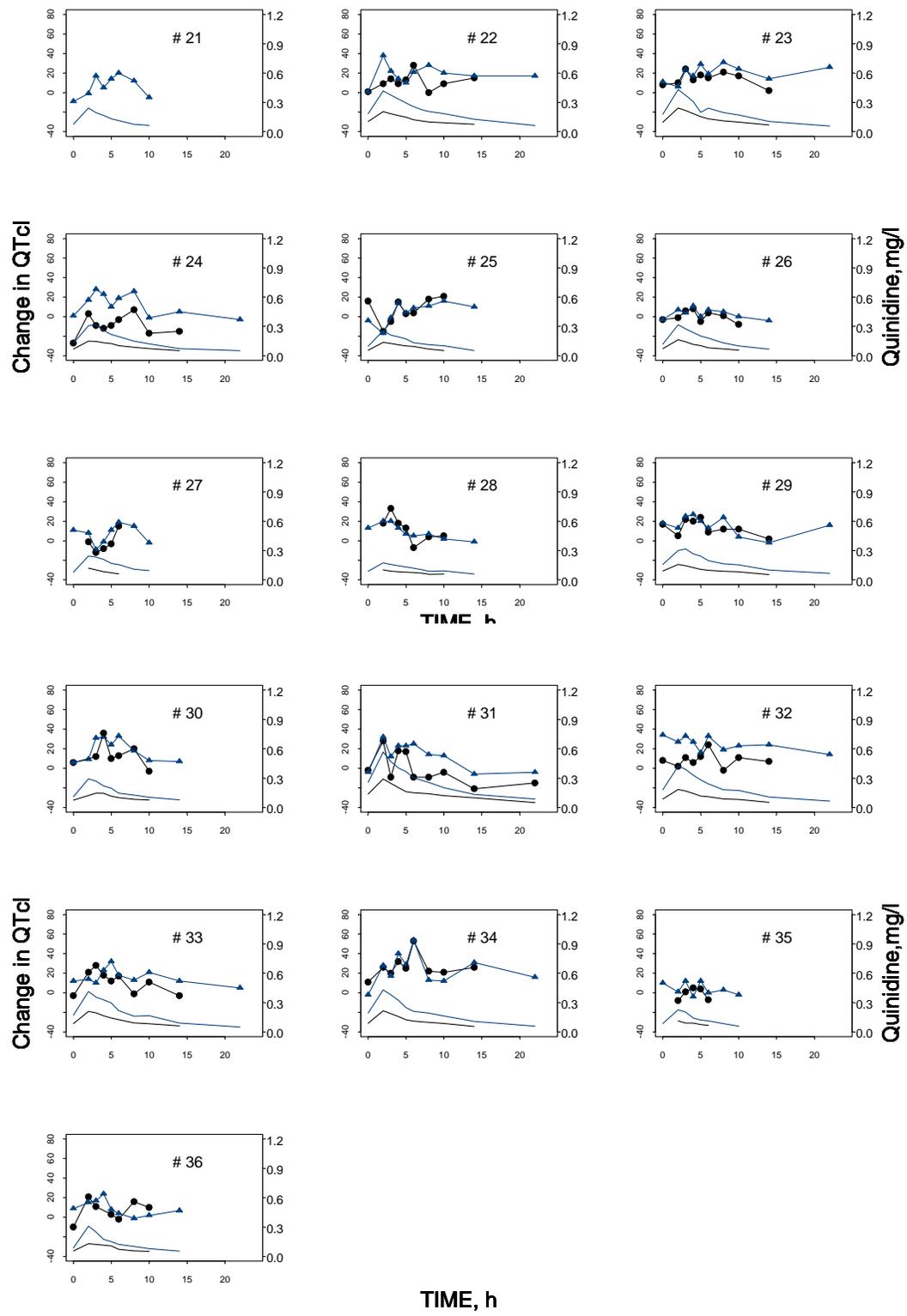
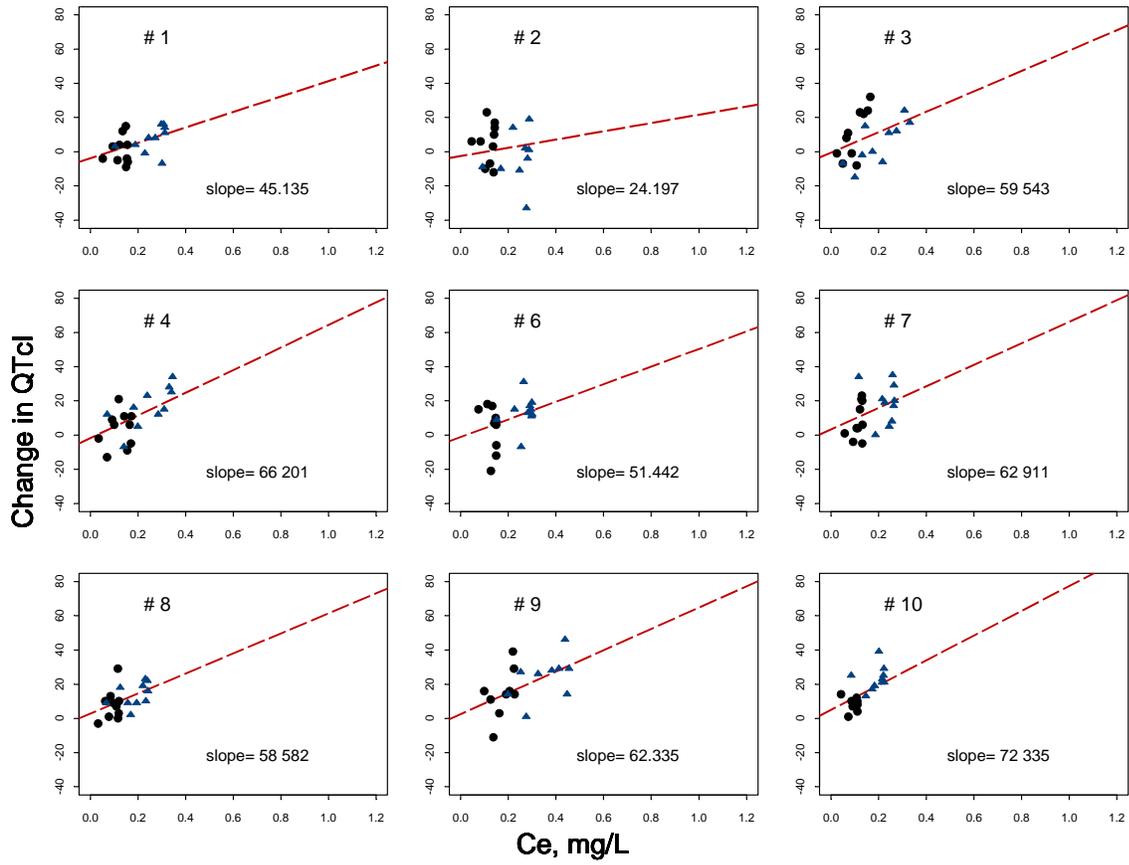
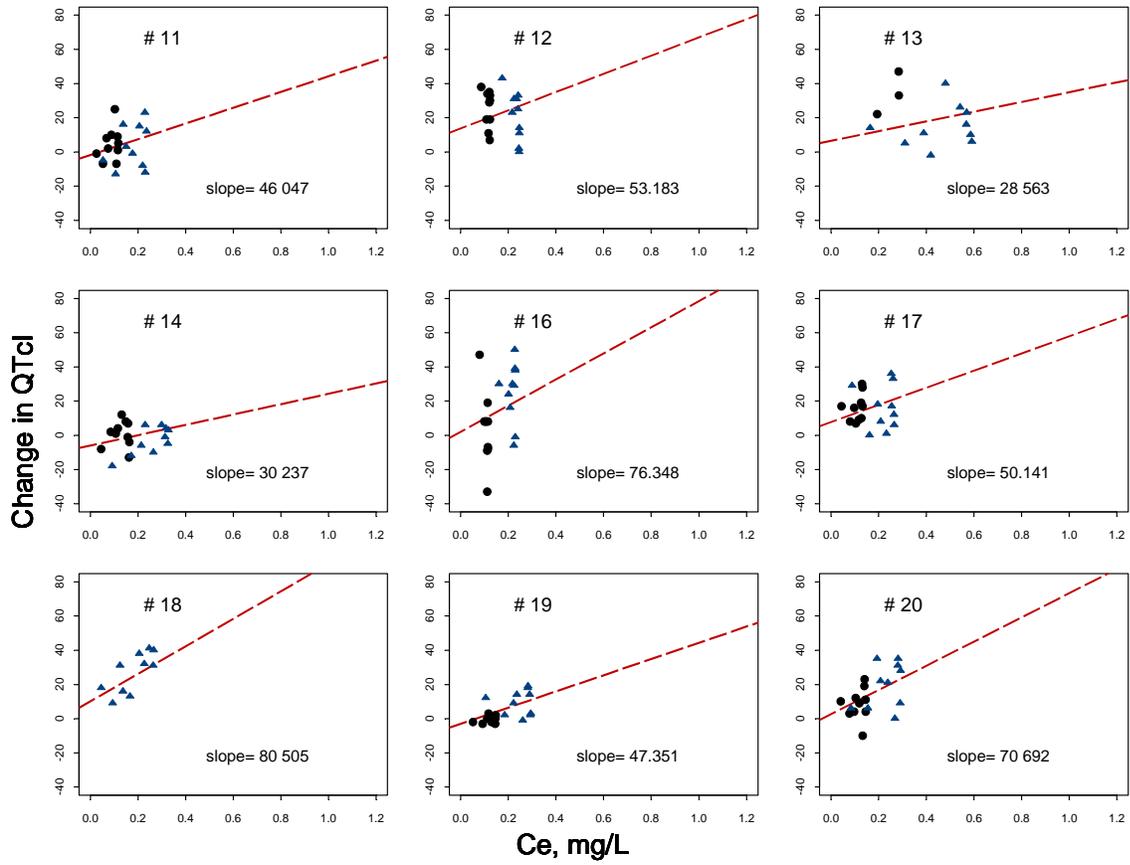


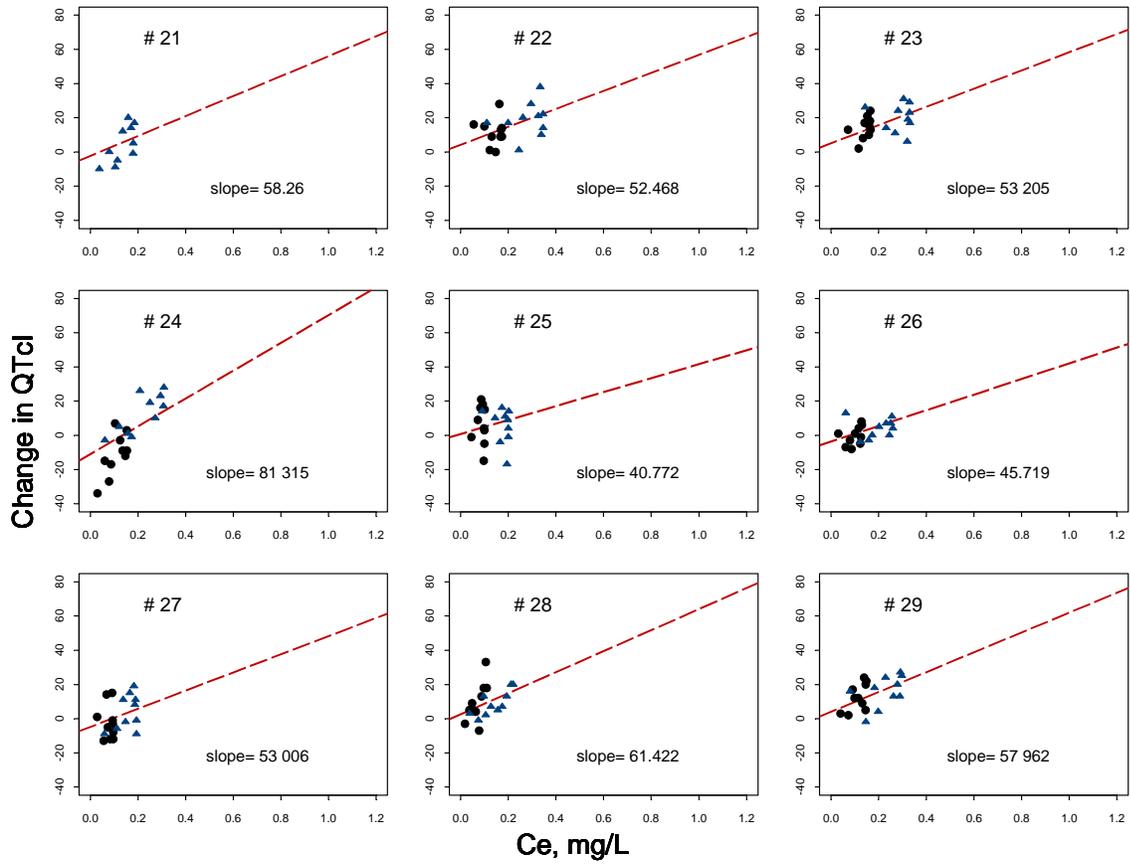
Figure 7. Relationship between quinidine effect site concentrations and change in QTcI stratified by subject (30 mg dose shown in blue and 60 mg dose shown in black)



**NDA 21,879
NEURODEX**



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**NDA 21,879
NEURODEX**

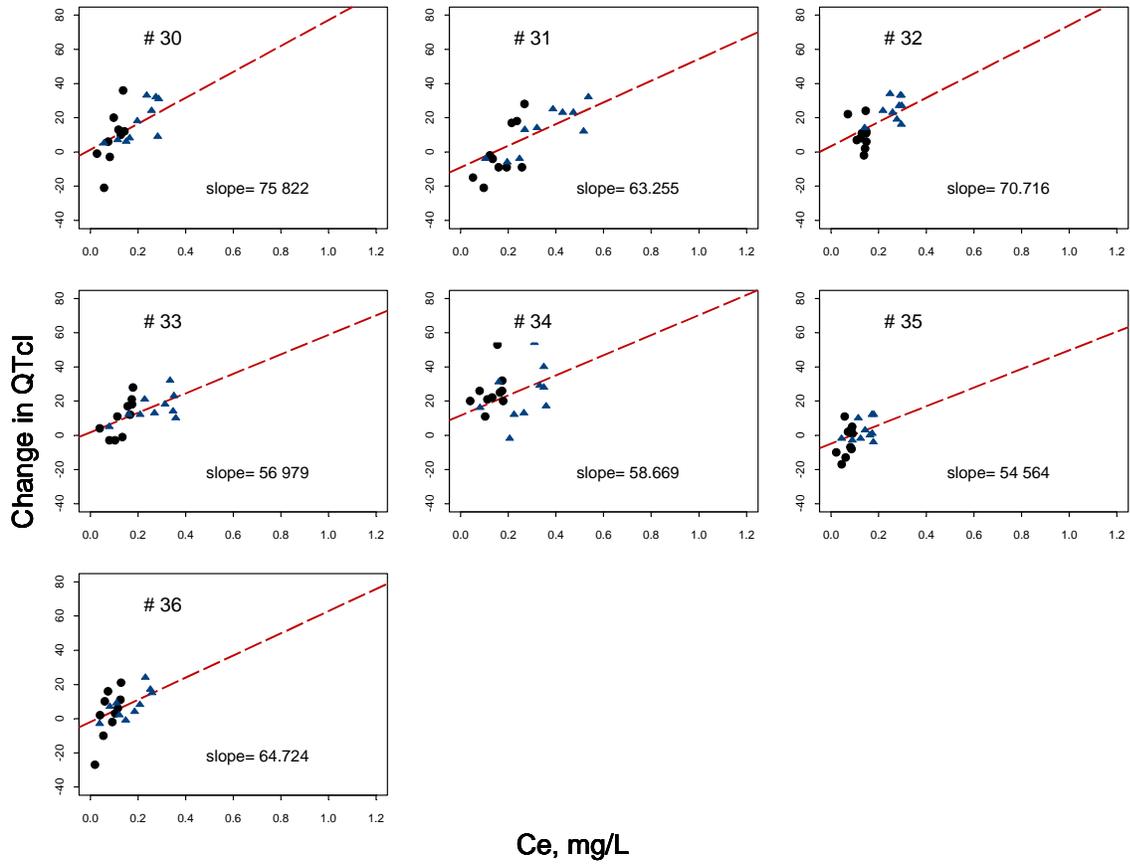


Figure 8. QQ Plot of Effect Site and Plasma Concentrations of Quinidine

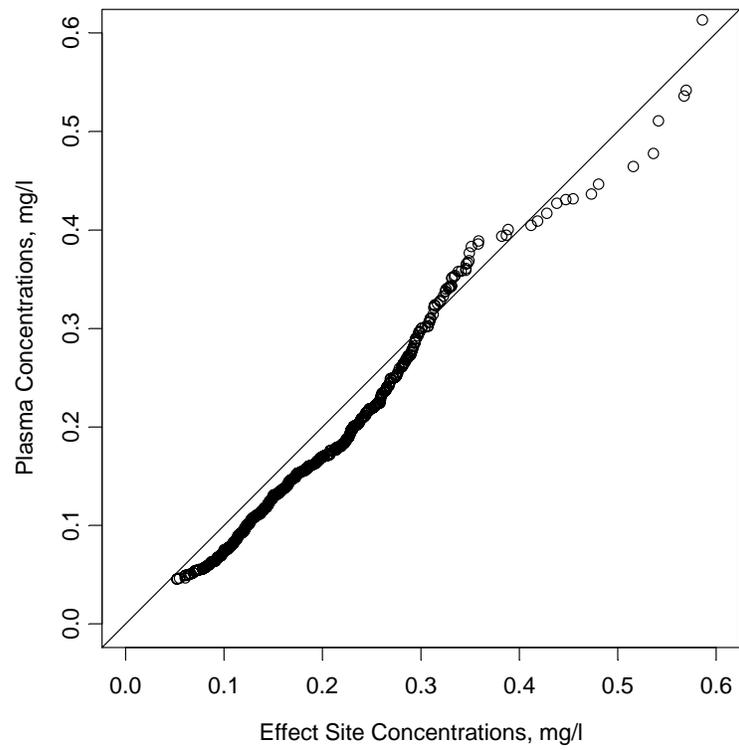


Figure 9. Predictive Check of Simulation Model: Distribution of Slope Values (Note: Observed = distribution of IPRE slope values)

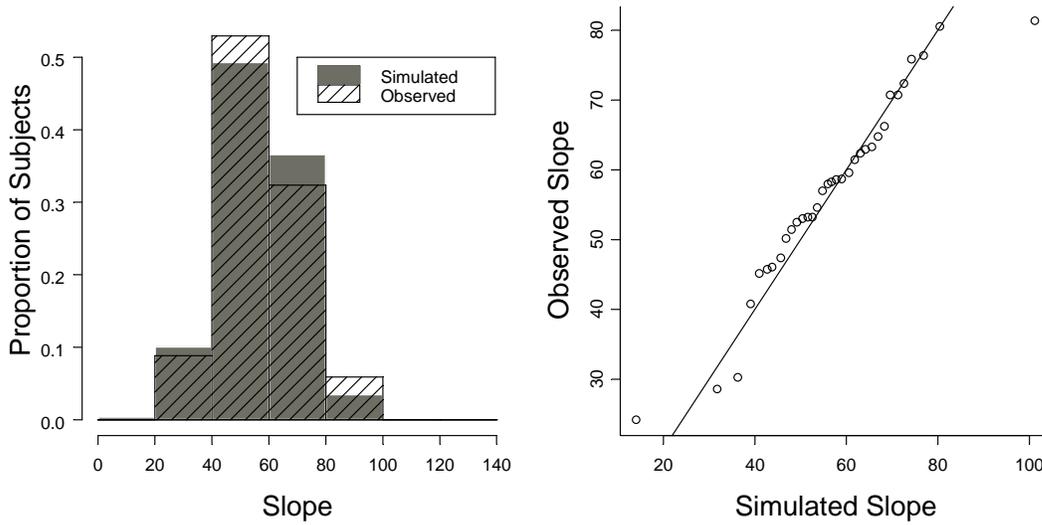
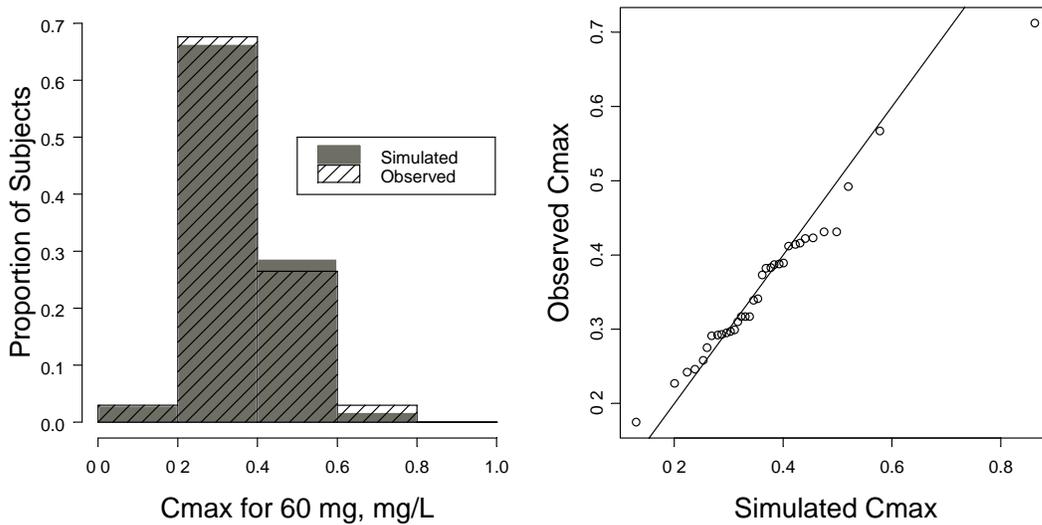


Figure 10. Predictive Check of Simulation Model: Distribution of Cmax Values



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REFERENCES

- (1) Guentert TW, Holford NH, Coates PE, Upton RA, Riegelman S. Quinidine pharmacokinetics in man: choice of a disposition model and absolute bioavailability studies. *J Pharmacokinet Biopharm.* 7, 315-30 (1979).
- (2) Kavanagh KM, Wyse DG, Mitchell LB, Gilhooly T, Gillis AM, Duff HJ. Contribution of quinidine metabolites to electrophysiologic responses in human subjects. *Clin Pharmacol Ther.* 46, 352-8 (1989).
- (3) Holford NH, Coates PE, Guentert TW, Riegelman S, Sheiner LB. The effect of quinidine and its metabolites on the electrocardiogram and systolic time intervals: concentration--effect relationships. *Br J Clin Pharmacol.* 11, 187-95 (1981).
- (4) Benton RE, Sale M, Flockhart DA, Woosley RL. Greater quinidine-induced QTc interval prolongation in women. *Clin Pharmacol Ther.* 67, 413-8 (2000).
- (5) Wooding-Scott RA, Smalley J, Visco J, Slaughter RL. The pharmacokinetics and pharmacodynamics of quinidine and 3-hydroxyquinidine. *Br J Clin Pharmacol.* 26, 415-21 (1988).
- (6) El-Eraky H, Thomas SHL. Effects of sex on the pharmacokinetics and pharmacodynamic properties of quinidine. *Br J Clin Pharmacol.* 56, 198-204 (2002).

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	21-879	Brand Name	Neurodex	
OCPB Division (I, II, III)	DPE-I	Generic Name	Dextromethorphan hydrobromide and quinidine sulfate	
Medical Division	HFD-120	Drug Class	Sigma-1 receptor agonist, uncompetitive NMDA antagonist	
OCPB Reviewer	Sally Usdin Yasuda, MS, PharmD	Indication(s)	Pseudobulbar affect (PBA)	
OCPB Team Leader	Ramana Uppoor, PhD	Dosage Form	Capsule containing 30 mg each of dextromethorphan hydrobromide and quinidine sulfate	
		Dosing Regimen	1 capsule bid	
Date of Submission	1/30/06	Route of Administration	Oral	
Estimated Due Date of OCPB Review	9/25/06	Sponsor	Avanir Pharmaceuticals	
PDUFA Due Date	10/30/06	Priority Classification	Priority	
Division Due Date	10/9/06			
Clin. Pharm. and Biopharm. Information				
<p><u>Summary:</u> This NDA is for a combination product comprised of 2 approved drugs, quinidine sulfate (Q) and dextromethorphan hydrobromide (DM) for treatment of pseudobulbar affect in patients with neurological disorders. The submission is supported by 2 pivotal efficacy studies. According to the Sponsor, the primary pharmacologic effect of quinidine in this product is to inhibit the metabolism of DM by CYP2D6, increasing plasma concentrations of DM and enhancing potential for desired pharmacological effect of DM. PK studies have been performed to determine optimal dose of Q to inhibit DM metabolism by CYP2D6. PK studies 100 and 101 evaluate BA of either DM as DM/Q given separately (100) or as DM/Q in a combination (study 101). Study 101 was an extension of Study 100, such that it was a 1-way crossover in a limited number of subjects. These two studies included a limited number of subjects and a limited number of samples (in Study 100). Since this combination is for a new indication and there is data on DM alone as well as the combination DM/Q, a relative BA assessment could be made. BA assessments are based on DM as the Sponsor considers that the therapeutic activity resides with that moiety. Study 102 is a factorial design clinical efficacy study that looks at each component (DM and Q) given separately and given together as the combination product.</p>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	5	6	Methods not cross-validated
I. Clinical Pharmacology				
Mass balance:	-	-	-	
Isozyme characterization:				

NDA 21,879
NEURODEX

Blood/plasma ratio:		-	-	
Plasma protein binding:	X	1	2	Study 0-AVR-115
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2	2	(Study 99-AVR-100 in EMs & 99-AVR-101 in EMs and PMs but with 30 mg DM/25mg Q)
multiple dose:	X	3	3	7 days (Studies 99-AVR-100 , AVR-103, and 99-AVR-101)
Patients-				
single dose:		-	-	
multiple dose:			-	See Pop PK
Dose proportionality -				
fasting / non-fasting single dose:			-	
fasting / non-fasting multiple dose:	X	2	2	Increasing doses of Q (Study 99-AVR-101) Increasing doses of Q with 45 or 60 mg DM (Study 00-AVR-103) Various doses of DM and Q (00-AVR-103)
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-	-		
In-vivo effects of primary drug:	X	1	1	Desipramine (Study 04-AVR-112)
In-vitro:			-	
Subpopulation studies -				
ethnicity:		-	-	See Pop PK; small size of non-Caucasian population
gender:		-	-	See Pop PK
pediatrics:		-	-	
geriatrics:		-	-	See Pop PK
renal impairment:	X	1	1	Study 04-AVR-116
hepatic impairment:	X	1	1	Study 04-AVR-115
PD:				
Phase 2:	X	1	Not reviewed	CNS-93
Phase 3:	X	2	2	Study 99-AVR-102 evaluated AVP-923 vs 30 mg DM or 30 mg Q 02-AVR-106 evaluated AVP-923 vs placebo
PK/PD:				
Phase 1 and/or 2, proof of concept:			-	
Phase 3 clinical trial:			-	
Population Analyses -				
Data rich:	-	-		
Data sparse:	X	1	1	Study 04-AVR-117: Age and IBW were significant covariates; Includes Phase I studies as well as Phase III study 99-AVR-102 & 02-AVR-106 & open label ongoing study 02-AVR-107
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	Not done
Relative bioavailability -				Not done
solution as reference:	-	-	-	
alternate formulation as reference:	-	-	-	
Bioequivalence studies -				
traditional design; single / multi dose:	-	-		
replicate design; single / multi dose:	-	-	-	
Food-drug interaction studies:	X	1	1	04-AVR-111

NDA 21,879
NEURODEX

Dissolution:	X	1	2	Dissolution method and biowaiver request
(IVIVC):	-	-	-	
Bio-waiver request based on BCS	-	-		
BCS class	-			
III. Other CPB Studies				
Genotype/phenotype studies:	X	7	-	PGx in 7 studies (reviewed by Genomics)
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X			
Thorough QT study		1	1	Submission resulted in extension of review clock
Total Number of Studies		22	25	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. None at this time.		
QBR questions (key issues to be considered)	<p>What information is available that contributes to assessment of clinical pharmacology/dose response/exposure-response? This applies to the dose of Q as well as the dose of the combination of Q and DM with respect to exposure, safety, and efficacy. CYP2D6 status is of particular interest.</p> <p>Do CYP2D6 PMs require the quinidine component?</p> <p>Are the bioanalytical methods adequate to assess concentrations?</p> <p>Have the pharmacokinetics been adequately characterized to support safety and efficacy?</p> <p>Has the to-be-marketed product been adequately linked to the clinical trial formulation and has the combination product been adequately linked to the individual components in terms of PK?</p> <p>Is drug metabolism and potential for drug interactions adequately characterized? Have appropriate in vivo drug interaction studies been done?</p> <p>Do the dissolution conditions and specifications assure in vivo performance and quality of the product?</p>			
Other comments or information not included above	Comments to the Project Manager: None.			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

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Sally Yasuda

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allowed for this be signed in DFS without
him in an email to S. Yasuda on
10/16/06.

Christine Garnett

10/16/2006 03:13:55 PM

PHARMACOLOGIST

Shashi Amur

10/16/2006 05:03:43 PM

INTERDISCIPLINARY

Felix Frueh

10/16/2006 05:12:09 PM

BIOPHARMACEUTICS

Ramana S. Uppoor

10/16/2006 06:33:18 PM

BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-879	Brand Name	Neurodex
OCPB Division (I, II, III)	DPE-I	Generic Name	Dextromethorphan hydrobromide and quinidine sulfate
Medical Division	HFD-120	Drug Class	Sigma-1 receptor agonist, uncompetitive NMDA antagonist
OCPB Reviewer	Sally Usdin Yasuda, MS, PharmD	Indication(s)	Pseudobulbar affect (PBA)
OCPB Team Leader	Ramana Uppoor, PhD	Dosage Form	Capsule containing 30 mg each of dextromethorphan hydrobromide and quinidine sulfate
		Dosing Regimen	1 capsule bid
Date of Submission	1/30/06	Route of Administration	Oral
Estimated Due Date of OCPB Review	6/25/06	Sponsor	Avanir Pharmaceuticals
PDUFA Due Date	7/30/06	Priority Classification	Priority
Division Due Date	7/9/06		

Clin. Pharm. and Biopharm. Information

Summary: This NDA is for a combination product comprised of 2 approved drugs, quinidine sulfate (Q) and dextromethorphan hydrobromide (DM) for treatment of pseudobulbar affect in patients with neurological disorders. The submission is supported by 2 pivotal efficacy studies. According to the Sponsor, the primary pharmacologic effect of quinidine in this product is to inhibit the metabolism of DM by CYP2D6, increasing plasma concentrations of DM and enhancing potential for desired pharmacological effect of DM. PK studies have been performed to determine optimal dose of Q to inhibit DM metabolism by CYP2D6. PK studies 100 and 101 evaluate BA of either DM as DM/Q given separately (100) or as DM/Q in a combination (study 101). Study 101 was an extension of Study 100, such that it was a 1-way crossover in a limited number of subjects. These two studies included a limited number of subjects and a limited number of samples (in Study 100). Since this combination is for a new indication and there is data on DM alone as well as the combination DM/Q, a relative BA assessment could be made. BA assessments are based on DM as the Sponsor considers that the therapeutic activity resides with that moiety. Study 102 is a factorial design clinical efficacy study that looks at each component (DM and Q) given separately and given together as the combination product.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	5		Methods not cross-validated
I. Clinical Pharmacology				
Mass balance:	-	-	-	
Isozyme characterization:			-	
Blood/plasma ratio:		-	-	
Plasma protein binding:	X	1		Study 0-AVR-115

Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2	-	(Study 99-AVR-100 in EMs & 99-AVR-101 in EMs and PMs but with 30 mg DM/25mg Q)
multiple dose:	X	3	-	7 days (Studies 99-AVR-100 , AVR-103, and 99-AVR-101)
Patients-				
single dose:		-	-	
multiple dose:			-	See Pop PK
Dose proportionality -				
fasting / non-fasting single dose:			-	
fasting / non-fasting multiple dose:	X	2	-	Increasing doses of Q (Study 99-AVR-101) Increasing doses of Q with 45 or 60 mg DM (Study 00-AVR-103) Various doses of DM and Q (00-AVR-103)
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-	-		
In-vivo effects of primary drug:	X	1		Desipramine (Study 04-AVR-112)
In-vitro:			-	
Subpopulation studies -				
ethnicity:		-	-	See Pop PK; small size of non-Caucasian population
gender:		-	-	See Pop PK
pediatrics:		-	-	
geriatrics:		-	-	See Pop PK
renal impairment:	X	1	-	Study 04-AVR-116
hepatic impairment:	X	1	-	Study 04-AVR-115
PD:				
Phase 2:	X	1	CNS-93	
Phase 3:	X	2	-	Study 99-AVR-102 evaluated AVP-923 vs 30 mg DM or 30 mg Q 02-AVR-106 evaluated AVP-923 vs placebo
PK/PD:				
Phase 1 and/or 2, proof of concept:			-	
Phase 3 clinical trial:			-	
Population Analyses -				
Data rich:	-	-		
Data sparse:	X	1		Study 04-AVR-117: Age and IBW were significant covariates; Includes Phase I studies as well as Phase III study 99-AVR-102 & 02-AVR-106 & open label ongoing study 02-AVR-107
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	Not done
Relative bioavailability -				Not done
solution as reference:	-	-	-	
alternate formulation as reference:	-	-	-	
Bioequivalence studies -				
traditional design; single / multi dose:	-	-		
replicate design; single / multi dose:	-	-	-	

Food-drug interaction studies:	X	1	-	04-AVR-111
Dissolution:	X	1		March 9, Section 3.2.P.2
(IVIVC):	-	-	-	
Bio-waiver request based on BCS	-	-		
BCS class	-			
III. Other CPB Studies				
Genotype/phenotype studies:	X	7	-	PGx in 7 studies
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X			
Total Number of Studies		22		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. None at this time.		
QBR questions (key issues to be considered)	<p>What information is available that contributes to assessment of clinical pharmacology/dose response/exposure-response? This applies to the dose of Q as well as the dose of the combination of Q and DM with respect to exposure, safety, and efficacy. CYP2D6 status is of particular interest.</p> <p>Do CYP2D6 PMs require the quinidine component?</p> <p>Are the bioanalytical methods adequate to assess concentrations?</p> <p>Have the pharmacokinetics been adequately characterized to support safety and efficacy?</p> <p>Has the to-be-marketed product been adequately linked to the clinical trial formulation and has the combination product been adequately linked to the individual components in terms of PK?</p> <p>Is drug metabolism and potential for drug interactions adequately characterized? Have appropriate in vivo drug interaction studies been done?</p> <p>Do the dissolution conditions and specifications assure in vivo performance and quality of the product?</p>			
Other comments or information not included above	<p style="color: red;">Comments to the Project Manager:</p> <p>None.</p>			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

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this page is the manifestation of the electronic signature.**

/s/

Sally Yasuda
10/13/2006 10:46:56 AM
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Ramana S. Uppoor
10/13/2006 10:56:25 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-879	Brand Name	Neurodex
OCPB Division (I, II, III)	DPE-I	Generic Name	Dextromethorphan hydrobromide and quinidine sulfate
Medical Division	HFD-120	Drug Class	Sigma-1 receptor agonist, uncompetitive NMDA antagonist
OCPB Reviewer	Sally Usdin Yasuda, MS, PharmD	Indication(s)	Pseudobulbar affect (PBA)
OCPB Team Leader	Ramana Uppoor, PhD	Dosage Form	Capsule containing 30 mg each of dextromethorphan hydrobromide and quinidine sulfate
		Dosing Regimen	1 capsule bid
Date of Submission	June 29, 2005	Route of Administration	Oral
Estimated Due Date of OCPB Review	11/15/2005	Sponsor	Avanir Pharmaceuticals
PDUFA Due Date	12/29/2005	Priority Classification	Priority
Division Due Date	11/29/2005		

Clin. Pharm. and Biopharm. Information

Summary: This NDA is for a combination product comprised of 2 approved drugs, quinidine sulfate (Q) and dextromethorphan hydrobromide (DM) for treatment of pseudobulbar affect in patients with neurological disorders. The submission is supported by 2 pivotal efficacy studies. According to the Sponsor, the primary pharmacologic effect of quinidine in this product is to inhibit the metabolism of DM by CYP2D6, increasing plasma concentrations of DM and enhancing potential for desired pharmacological effect of DM. PK studies have been performed to determine optimal dose of Q to inhibit DM metabolism by CYP2D6. PK studies 100 and 101 evaluate BA of either DM as DM/Q given separately (100) or as DM/Q in a combination (study 101). Study 101 was an extension of Study 100, such that it was a 1-way crossover in a limited number of subjects. These two studies included a limited number of subjects and a limited number of samples (in Study 100). Since this combination is for a new indication and there is data on DM alone as well as the combination DM/Q, a relative BA assessment could be made. BA assessments are based on DM as the Sponsor considers that the therapeutic activity resides with that moiety. Study 102 is a factorial design clinical efficacy study that looks at each component (DM and Q) given separately and given together as the combination product.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			It is very difficult to find reports in this submission in multiple pieces. I have not found an overall table of contents
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	5		Methods not cross-validated
I. Clinical Pharmacology				
Mass balance:	-	-	-	
Isozyme characterization:			-	
Blood/plasma ratio:		-	-	

Plasma protein binding:	X	1		Study 0-AVR-115
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2	-	(Study 99-AVR-100 in EMs & 99-AVR-101 in EMs and PMs but with 30 mg DM/25mg Q)
multiple dose:	X	3	-	7 days (Studies 99-AVR-100 , AVR-103, and 99-AVR-101)
Patients-				
single dose:		-	-	
multiple dose:			-	See Pop PK
Dose proportionality -				
fasting / non-fasting single dose:			-	
fasting / non-fasting multiple dose:	X	2	-	Increasing doses of Q (Study 99-AVR-101) Increasing doses of Q with 45 or 60 mg DM (Study 00-AVR-103) Various doses of DM and Q (00-AVR-103)
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-	-		
In-vivo effects of primary drug:	X	1		Desipramine (Study 04-AVR-112)
In-vitro:			-	
Subpopulation studies -				
ethnicity:		-	-	See Pop PK; small size of non-Caucasian population
gender:		-	-	See Pop PK
pediatrics:		-	-	
geriatrics:		-	-	See Pop PK
renal impairment:	X	1	-	Study 04-AVR-116
hepatic impairment:	X	1	-	Study 04-AVR-115
PD:				
Phase 2:	X	1	CNS-93	
Phase 3:	X	2	-	Study 99-AVR-102 evaluated AVP-923 vs 30 mg DM or 30 mg Q 02-AVR-106 evaluated AVP-923 vs placebo
PK/PD:				
Phase 1 and/or 2, proof of concept:			-	
Phase 3 clinical trial:			-	
Population Analyses -				
Data rich:	-	-		
Data sparse:	X	1		Study 04-AVR-117: Age and IBW were significant covariates; Includes Phase I studies as well as Phase III study 99-AVR-102 & 02-AVR-106 & open label ongoing study 02-AVR-107
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	Not done
Relative bioavailability -				Not done
solution as reference:	-	-	-	
alternate formulation as reference:	-	-	-	
Bioequivalence studies -				
traditional design; single / multi dose:	-	-		
replicate design; single / multi dose:	-	-	-	

Food-drug interaction studies:	X	1	-	04-AVR-111
Dissolution:	X	1		March 9, Section 3.2.P.2
(IVIVC):	-	-	-	
Bio-waiver request based on BCS	-	-		
BCS class	-			
III. Other CPB Studies				
Genotype/phenotype studies:	X	7	-	PGx in 7 studies; reports for 3 of the studies were not included
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X			
Total Number of Studies		22		

Filability and QBR comments			
	"X" if yes	Comments	
Application filable ?	X	<p style="color: red;">Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?</p>	
Comments sent to firm ?		<p style="color: red;">Comments have been sent to firm (or attachment included). FDA letter date if applicable.</p> <p style="color: red;">Please forward to sponsor :</p> <ol style="list-style-type: none"> 1) Please provide electronic data sets with the demographic information (including CYP2D6 phenotype and urinary metabolic ratio as well as genotype, as available). 2) Please confirm the source of the data for the DM plasma concentrations in 99-AVR-100. Was it the hydrolyzed or non-hydrolyzed method? 3) The data from Part 1 of 99-AVR-100 has not been provided. Provide the urine and plasma data by subject (including urine metabolic ratio) from Part 1 of 99-AVR-100 as an electronic data set. Please also indicate which subjects completed Part 2 of the study and Study 101, and to which treatment they were randomized (and their respective study numbers for Studies 100 and 101). 4) Please provide the raw data supporting the solubility results including description of test methods and information on analytical method and composition of the buffer solution, and data for the test results including mean, standard deviation, and coefficient of variation, as well as a graphic representation of mean pH-solubility profile. 5) Please specifically state the temperature, volume of media, and other details of the dissolution method development studies and explicitly state your proposed method and specifications. Please also provide dissolution data from the method development studies– this should include raw data and figures representing the means in each media and for both the DX and Q components for each lot. The dissolution data should be based on the labeled amount only (rather than corrected). 6) Please provide the study reports and results for genotype studies for 04-AVR-111, 02-AVR-106, and 01-AVR-105 7) Please provide dates of manufacture for study drug for 99-AVR-100 8) Please provide the brief methods and SOP for each of the analytical methods for the Clin Pharm/Biopharm studies. The material submitted provides insufficient detail about the method. 	

<p>QBR questions (key issues to be considered)</p>	<p>What information is available that contributes to assessment of clinical pharmacology/dose response/exposure-response? This applies to the dose of Q as well as the dose of the combination of Q and DM with respect to exposure, safety, and efficacy. CYP2D6 status is of particular interest.</p> <p>Do CYP2D6 PMs require the quinidine component?</p> <p>Are the bioanalytical methods adequate to assess concentrations?</p> <p>Have the pharmacokinetics been adequately characterized to support safety and efficacy?</p> <p>Has the to-be-marketed product been adequately linked to the clinical trial formulation and has the combination product been adequately linked to the individual components in terms of PK?</p> <p>Is drug metabolism and potential for drug interactions adequately characterized? Have appropriate in vivo drug interaction studies been done?</p> <p>Do the dissolution conditions and specifications assure in vivo performance and quality of the product?</p>
<p>Other comments or information not included above</p>	<p>Comments to the Project Manager:</p> <p>Please ask the Sponsor to provide the information requested above (Comments to Firm) by the end of August</p>
<p>Primary reviewer Signature and Date</p>	
<p>Secondary reviewer Signature and Date</p>	

CC: NDA 21-879, HFD-850(Electronic Entry or Lee), HFD-120(Calder), HFD-860 (R. Uppoor, N.A.M. Rahman, M. Mehta)

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

/s/

Sally Yasuda
8/17/2005 02:13:38 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
8/19/2005 10:22:10 AM
BIOPHARMACEUTICS