CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021879Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: October 29, 2010

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 21-879 (Nuedexta; dextromethorphan plus quinidine); SDN 38, dated April 23, 2010 (received April 30, 2010).

Nuedexta™ (formerly Neurodex™, Zenvia™) is a combination drug product intended for the treatment of pseudobulbar affect (PBA) in patients with amyotrophic lateral sclerosis or multiple sclerosis. Nuedexta contains dextromethorphan hydrobromide and quinidine sulfate, two marketed drugs. NDA 21-879 was originally submitted by the sponsor (Avanir Pharmaceuticals) on January 27, 2006 (received January 30, 2006). The nonclinical data provided in support of that application were reviewed by Dr. Kathleen Young (*Pharmacology/Toxicology Review and Evaluation, NDA 21-879, Kathleen Young, Ph.D., October 30, 2006*). An Approvable letter was sent to the sponsor on October 30, 2006, without draft labeling. Deficiencies precluding approval were clinical (both safety and efficacy); however, a number of nonclinical comments were communicated to the sponsor:

- Potential deficiencies (e.g., lack of adequate high dose) in the fertility and early embryonic development, embryofetal development, and pre-and post-natal development studies in rat and the embryofetal development study in rabbit.
- The lack of a chronic toxicology study in non-rodent.
- The need to conduct a juvenile neurotoxicology study in an appropriate animal species to assess the potential for [Nuedexta] to induce apoptotic neurodegeneration during development.
- The ongoing 2-year carcinogenicity study in rat should be submitted as soon as possible.

The sponsor submitted nonclinical data to IND 56954 (dextromethorphan/quinidine for PBA) in response to these comments. These data were reviewed by Dr. D. Charles Thompson (*Preliminary Pharmacology/Toxicology IND Safety Evaluation, IND 56,954, D. Charles Thompson, R.Ph, Ph.D., 5/7/2009*) and comments were sent to the sponsor on 7/22/2009:

- The new nonclinical data adequately justified the high dose used in the original rat fertility and early embryonic development (to implantation) and embryofetal development studies, so those studies would not need to be repeated. However, the pre- and post-natal development study, conducted using a lower high-dose, will need to be repeated using the same high dose used in the original fertility and embryofetal studies. In addition, due to differences in the degree of maternal toxicity between studies, the pre- and post-natal study should include a teratology examination.
- The embryofetal development study in rabbit will need to be repeated.

The sponsor was informed in preliminary responses to a Type C meeting request (sent 11/9/2009; meeting cancelled by the sponsor) that a pre- and post-natal development study in rat and an embryofetal development study in rabbit would be needed, but may be submitted post-approval. However, based on additional information submitted by the sponsor, the repeat pre- and post-natal evaluation would not need to include a teratology evaluation.

In the Complete Response, the sponsor submitted the following nonclinical studies:

- *In vitro* hERG assay of AVP-923 (dextromethorphan [DM]/quinidine [Q]) in HEK293 cells.
- *In vitro* effects of quinidine sulfate on ECG parameters in the rabbit left ventricular wedge preparation.
- *In vivo* 7-day PK study of DM/Q in Beagle dog
- *In vitro* metabolism studies in human liver preparations
- Toxicology
    - 5-week dose-ranging study of DM/Q in Beagle dog
    - 39-week oral toxicity study of DM/Q in Beagle dog
    - 24-month carcinogenicity study of DM/Q in rat

All of these studies, with the exception of the *in vitro* metabolism studies (to be reviewed by the Clinical Pharmacology team), were reviewed by Dr. Thompson (*Pharmacology/Toxicology NDA Review and Evaluation, NDA 21-879, D. Charles Thompson, R.Ph, Ph.D., 10/1/2010*). Based on his review, Dr. Thompson has concluded that the nonclinical studies submitted are adequate to support approval of Nuedexta for the intended indication, with the following nonclinical studies to be conducted as postmarketing requirements (PMRs):

- Juvenile neurotoxicology study in rat.
- Pre- and post-natal development study in rat
- Embryo-fetal development study in rabbits.

Dr. Thompson notes that the sponsor has committed to conducting these studies post-approval, and has suggested time lines for the conduct and submission of these studies.

Comments: I concur with Dr. Thompson's conclusion and recommendations. I would also recommend, as a postmarketing requirement (PMR), a juvenile animal toxicology study in one species (rat) to support the PMR for a pediatric study.

One additional issue needs to be addressed. According to a recent published study (Huang X-P *et al*. *Mole Pharm* 76(4):710-722, 2009, discussed in Elangbam CS *Tox Path* 000:1-12, 2010 online), quinidine has been identified as a $5HT_{2B}$ agonist. According to Huang *et al*. (2009), these are the first data to demonstrate this effect of quinidine. (Huang *et al*. (2009) did not identify dextromethorphan as a $5HT_{2B}$ agonist; the sponsor did not assess either quinidine or dextromethorphan for binding or activity at the $5HT_{2B}$ receptor.)

$5HT_{2B}$ agonist activity is considered a potential cause of drug-induced cardiac valvulopathy. A number of drugs reported to induce valvular heart disease (VHD) in humans, including some that have been removed from the market due to a documented association with VHD (pergolide, fenfluramine, and dexfenfluramine), have been demonstrated to be potent $5HT_{2B}$ agonists (cf. Frachon I *et al*. *PLoS One* 5(4):1-5, 2010; Roth BL *NEJM* 356(1):6-9, 2007; Zanettini R *et al*. *NEJM* 356(1):39-46, 2007). To my knowledge, there have been no published reports of VHD in humans caused by quinidine, although quinidine has been marketed for many years as a Class 1a antiarrhythmic at substantially higher doses. It is possible, however, that treatment may be longer in duration in patients with PBA, and duration of treatment is reported to be an important risk factor for drug-induced VHD (cf. Roth, 2007; Shade *et al*. *NEJM* 356(1):29-38, 2007).

No effects on cardiac valves were observed in the toxicity studies of DM/Q; however, at least in the rodent, histopathological evaluation of cardiac valves is commonly absent. Therefore, the lack of reported valvular effects in the toxicity studies of DM/Q does not rule out the potential for quinidine to induce valvulopathy. Since $5HT_{2B}$ agonist activity has been reported only in a single published study, the sponsor should be given the opportunity to confirm this pharmacodynamic effect, i.e., by conducting studies to assess the *in vitro* binding affinity and functional activity of quinidine at the $5HT_{2B}$ receptor. If these studies confirm that quinine is a $5HT_{2B}$ agonist, an investigative study should be conducted to assess the potential for quinidine to induce cardiac valvulopathy. Depending on the results of these studies, it may also be necessary for a focused examination of cardiac valves to be incorporated into the juvenile animal toxicology study to be conducted post-approval. This issue can be addressed when the juvenile study protocol is submitted for review.

Therefore, I would recommend that studies to investigate the binding affinity and functional activity of quinidine at the $5HT_{2B}$ receptor and, if necessary, a follow-up investigative study to assess the potential for quinidine to induce cardiac valvulopathy be an additional PMR.

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

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/s/

LOIS M FREED
10/29/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	21-879
Supporting document/s:	38
Applicant's letter date:	23 April 2010
CDER stamp date:	30 April 2010
Product:	Zenvia™ (Dextromethorphan/Quinidine; formerly Neurodex™)
Indication:	Treatment of Pseudobulbar Affect occurring in ALS, MS, stroke, and Alzheimer's Disease
Applicant:	Avanir Pharmaceuticals, Inc. 101 Enterprise, Suite 300 Aliso Viejo, CA 92656
Review Division:	Neurology Products, HFD-120
Reviewer:	D. Charles Thompson, R.Ph., Ph.D., D.A.B.T.
Supervisor/Team Leader:	Lois M. Freed, Ph.D.
Division Director:	Russell G. Katz, M.D.
Project Manager:	Susan B. Daugherty, R.N., B.S.N.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 21-879 are owned by Avanir Pharmaceuticals, Inc. or are data for which Avanir Pharmaceuticals, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 21-879 that Avanir Pharmaceuticals, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling.

TABLE OF CONTENTS

1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

The data submitted to date in total provide the necessary support for approval of Zenvia™ from a nonclinical perspective, contingent upon formal agreement to terms of PMRs as noted below.

1.1.2 Additional Non Clinical Recommendations

It is recommended that approval for Zenvia™ be made contingent upon formal agreement by the sponsor to the terms of Post Marketing Requirements (PMR) for submission of protocols for and the conduct of: 1) a juvenile neurotoxicology study in rats; 2) a repeat pre- and post-natal development study in rats; and 3) a repeat embryo-fetal development study in rabbits.

1.1.3 Labeling

It is recommended that relevant findings from studies to date of the developmental/ reproductive toxicity, genetic toxicity, and carcinogenicity of Zenvia™ be incorporated as appropriate into labeling.

1.2 Brief Discussion of Nonclinical Findings

Data in the current Resubmission have addressed outstanding nonclinical issues previously identified in the Approvable Letter as pivotal to support the approval of Zenvia™. Based on findings from a two-year carcinogenicity study in rats, it is concluded "...that there were no biologically significant neoplastic findings for dextromethorphan and quinidine, alone or in combination, under the conditions tested." This finding, coupled with the previous negative carcinogenicity findings in Tg.rasH2 mice and predominantly negative genotoxicity findings, suggests that Zenvia™ possesses negligible carcinogenic potential.

The chronic toxicity of Zenvia™ was further assessed in a non-rodent species via a 39-week repeated oral dose study in dogs. Whereas the central nervous system (CNS), kidneys, and liver had been identified in previous nonclinical studies of the original submission as the main target organs of toxicity, pathology in the liver and kidney was largely unremarkable following chronic treatment in the dog. Rather, it was predominantly CNS-related clinical observations, supported by quinidine-induced effects on the cardiovascular system (ECG), which defined dose-limiting toxicity.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number (Optional)

Dextromethorphan hydrobromide: 6700-34-1 (monohydrate) and 125-69-9 (anhydrous);
Quinidine sulfate: 6591-63-5 (dihydrate) and 50-54-4 (anhydrous)

2.1.2 Generic Name

Dextromethorphan hydrobromide; Quinidine sulfate

2.1.3 Code Name

AVP-923

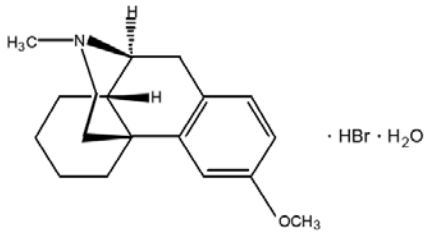
2.1.4 Chemical Name

Dextromethorphan hydrobromide: morphinan, 3-methoxy-17-methyl, (9alpha, 13alpha, 14alpha)-, hydrobromide; quinidine sulfate: (8R, 9S)-6'-Methoxycinchonan-9-ol-Sulfate

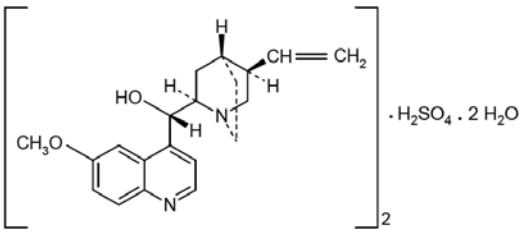
2.1.5 Molecular Formula/Molecular Weight

Dextromethorphan: $C_{18}H_{25}NO.HBr.H_2O$ / Molecular weight: 370.33
Quinidine: $[C_{20}H_{24}N_2O_2]2.H_2SO_4.2H_2O$ / Molecular weight: 782.96

2.1.6 Structure



Dextromethorphan HBr



Quinidine sulfate

2.1.7 Pharmacologic class

Dextromethorphan: d-isomer of codeine analog, levorphanol; noncompetitive NMDA receptor antagonist (N0000020015, NMDA Receptor Antagonists) and antitussive

Quinidine: d-isomer of quinine; CYP450 2D6 inhibitor (N0000000133, Enzyme Inhibitors) and antimalarial, antiarrhythmic (N0000000180, Sodium Channel Interactions; N0000000211, Potassium Channel Interactions; N0000000153, Adrenergic Receptor Interactions)

2.2 Relevant INDs, NDAs, and DMFs

IND 56,954; IND 62, 567

2.3 Clinical Formulation

2.3.1 Drug Formulation

Reproduced below from the sponsor's submission is a tabular summary of the proposed drug product composition. The currently proposed formulation constitutes a change from that proposed in the original NDA submission of 30 January 2006 (see previous P/T review, K. Young, Ph.D., 30 October 2006). Specifically, whereas the previous proposed formulation was for an oral capsule of a single dosage strength (30/30, DM/Q), the current (b) (4) two dosage strengths (20/10 and 30/10, DM/Q). (b) (4) excipients remain the same as do excipient levels, save for lactose monohydrate, (b) (4).

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			(b) (4)
Microcrystalline Cellulose (b) (4)	NF, EP, JP			
Lactose Monohydrate (b) (4)	NF, EP, JP			
Colloidal Silicon Dioxide	NF, EP, JP			
Magnesium Stearate (b) (4)	NF, EP, JP			
(b) (4)				
Total			335	335

EP = European Pharmacopeia; JP = Japanese Pharmacopeia; NF = National Formulary;
USP = United States Pharmacopeia.
* On anhydrous basis.

(b) (4)

2.3.2 Comments on Novel Excipients: N/A

2.3.3 Comments on Impurities/Degradants of Concern

None—no change from original NDA submission (see previous P/T review, K. Young, Ph.D., 30 October 2006).

2.4 Proposed Clinical Population and Dosing Regimen

AVP-923 is proposed for the treatment of pseudobulbar affect (PBA) in patients with neurologic disorders (e.g., ALS, MS, stroke, and Alzheimer's disease). As such, it will be indicated for chronic use in these patients at a daily dosage (b) (4)

2.5 Regulatory Background

NDA 21-879 was originally received by the Agency on 30 January 2006 following development of AVP-923 under IND 56,954 for the treatment of PBA, with a proposed dosing regimen of DM 30 mg/Q 30 mg BID. Based upon review findings that raised "fundamental questions about both the effectiveness and safety of the product", an Approvable Letter was issued on 30 October 2006. Nonclinical comments conveyed in

this letter included the following (see P/T review, K. Young, Ph.D., 30 October 2006 and P/T Supervisory Memorandum, L.M. Freed, Ph.D., 13 November 2006):

> 1. You have not provided sufficient justification for the high doses used in the reproductive toxicology studies in rat (fertility and early embryonic development, embryofetal development, and pre- and post-natal development) and rabbit (embryofetal development). In none of the studies was dose-limiting toxicity observed, and the dose-range finding studies in rat and rabbit do not convincingly establish that higher doses could not have been tolerated....
>
> We recommend that you conduct appropriate dose-range finding studies in rat and rabbit in order to select adequate doses for the definitive studies; the high doses need to produce some degree of maternal or fetal (or offspring) toxicity. If the results of these dose-range finding studies establish that higher dose could not have been tolerated, then repeat studies would not be needed. In the rat, you should consider exploring combination doses between 50/100 and 100/100 mg/kg (dextromethorphan/quinidine).
>
> 2. The chronic toxicity of the combination of dextromethorphan and quinidine was assessed only in rat....We note your commitment to a chronic toxicology study in non-rodent under IND 62,567 (End of Phase 2 meeting minutes, 11/12/03). If this study is ongoing or has been completed, a final study report should be submitted for review. If not, you will need to conduct a chronic study in non-rodent. You have concluded that the dog is an inappropriate animal model; however, you have not provided sufficient data to establish this. If the dog is documented to be an inappropriate species, you should consider another non-rodent species, such as monkey or minipig. Whether or not the chronic nonrodent study will be needed prior to approval will depend on availability of an appropriate non-rodent animal model and an overall evaluation of the nonclinical and clinical data.
>
> 3. You need to conduct a juvenile neurotoxicology study in an appropriate animal species to assess the potential for Zenvia™ to induce apoptotic neurodegeneration during development. In the animal species selected, the timing of dosing during development should cover the vulnerable period in humans (i.e. last trimester through postnatal ages 2- 3). This study may be conducted post-approval. Please propose a time line for conduct of the study and submission of the final study report.
>
> 4. The 2-year carcinogenicity study in rat was not required for the NDA. However, since the study was initiated in mid-2003, it should be completed. The final study report should be submitted as soon as possible.

In response to the Approvable Letter, the sponsor has conducted an additional clinical study (07-AVR-123), as well as continued and/or additional nonclinical testing (see IND 56,954 P/T review, D.C. Thompson, 7 May 2009; Advice Letter to Sponsor, IND 56,954, 22 July 2009; and Preliminary Meeting [Pre-Submission] Comments, NDA 21-879, S.B. Daugherty, 9 November 2009). The present submission, received on 30 April 2010, constitutes the sponsor's Resubmission/Complete Response to Approvable Letter for NDA 21-879.

3 Studies Submitted

3.1 Studies Reviewed

The following study reports were submitted in the original NDA 21-879 submission and have been reviewed (see previous P/T review, K. Young, Ph.D., 30 October 2006):

- A Study of the Pharmacokinetics of Dextromethorphan and Quinidine and the Effect of Quinidine on the Pharmacokinetics of Dextromethorphan Following a Single Oral Administration in Male and Female Sprague-Dawley Rats (Avanir Study No. DMQ-101)
- A Dose-Ranging Study of the Plasma Pharmacokinetics of Dextromethorphan, Dextrorphan, and Quinidine after Oral Dosing in Mice with Combinations of Dextromethorphan and Quinidine (DMQ-116)
- Effects of AVP-923 (Dextromethorphan Hydrobromide and Quinidine Sulfate) on HERG Currents Recorded from Stably Transfected HEK293 Cells (DMQ-130)
- 28-day Repeated Dose Oral Toxicity and Toxicokinetic Study in CByB6F1 Hybrid Mice with a Preliminary Range-Finding Toxicity Study (DMQ-118)
- Dextromethorphan/Quinidine Combination – 2 Week Oral (Gavage) Preliminary Toxicity Study in the Rat (Avanir Study No. DMQ-105)
- Dextromethorphan/Quinidine Combination – 26-Week Oral (Gavage) Toxicity Study in the Rat with a 4 Week Interim Kill and Followed by a 4 Week Treatment-Free Period (DMQ-103)
- Dextromethorphan – Determination of the Maximum Tolerated Dose by the Oral Route (Gavage) in the Beagle Dog (DMQ-102; MDS Pharma Study # 84/002)
- Dextromethorphan Hydrobromide Bacterial Reverse Mutation Test (DMQ-112; (b) (4) AWN/004)
- Quinidine Sulphate Bacterial Reverse Mutation Test (DMQ-109; (b) (4) AWN/001)
- Dextromethorphan Hydrobromide Mouse Micronucleus Test (DMQ-114; (b) (4) AWN/006)
- Quinidine Sulphate Mouse Micronucleus Test (DMQ-111; (b) (4) AWN/003)
- Dextromethorphan Hydrobromide – *In vitro* Mammalian Chromosome Aberration Test in Human Lymphocytes (DMQ-113; (b) (4) AWN/005)
- Quinidine Sulphate – *In vitro* Mammalian Chromosome Aberration Test in Human Lymphocytes (DMQ-110; (b) (4) AWN/002)
- *In vitro* Mammalian Chromosome Aberration Test (Combination of Dextromethorphan Hydrobromide-USP and Quinidine Sulphate-USP 24) (DMQ-115)
- 26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 and CByB6F1 Mice (DMQ-119)
- Dextromethorphan/Quinidine: A 24-Month Oral (Gavage) Carcinogenicity Study in Rats – Month 12 Unaudited Status Report (DMQ-120)
- Dextromethorphan/Quinidine (DMQ): Preliminary (Dose Finding) Study in Rats (DMQ-122)
- Dextromethorphan/Quinidine (DMQ): Preliminary (Dose Finding) Study in Rabbits (DMQ-121)
- Dextromethorphan/Quinidine (DMQ): Study of Fertility and Early Embryonic Development to Implantation in Rats (DMQ-126)

- Dextromethorphan/Quinidine (DMQ): Embryo-Fetal Toxicity Study in Rats (DMQ-124)
- Dextromethorphan/Quinidine (DMQ): Embryo-Fetal Toxicity Study in Rabbits (DMQ-123)
- Dextromethorphan/Quinidine (DMQ): Pre- and Post-Natal Development Study in Rats, Including Maternal Function (DMQ-125)
- An Acute Oral Neurotoxicity Study in Rats with Dextromethorphan and Quinidine (AVP-923) (Avanir Study No. DMQ-106)

The following study reports were received under IND 56,954 on 31 July 2008 and have been reviewed (see P/T review, D.C. Thompson, Ph.D., 7 May 2009):

- Oral (Gavage) Dosage-Range Developmental Toxicity Study of Dextromethorphan/ Quinidine (DMQ) in Rats (DMQ-140)
- Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of Dextromethorphan/Quinidine (DMQ) in Rabbits (DMQ-141)

The following new study reports within the current resubmission have been reviewed:

- Dextromethorphan/Quinidine: A 24-Month Oral (Gavage) Carcinogenicity Study in Rats, Final Report (DMQ-120)
- Effects of AVP-923 on HERG Tail Current Recorded from Stably Transfected HEK293 Cells (DMQ-131)
- Dextromethorphan/Quinidine: 7-Day Oral (Gavage) Pharmacokinetic Study in the Beagle Dog (DMQ-137)
- Dextromethorphan/Quinidine: 5-Week Oral (Gavage) Toxicity Study in the Beagle Dog (DMQ-138)
- Dextromethorphan/Quinidine: 39-Week Oral (Gavage) Toxicity Study in the Beagle Dog Followed by an 8-Week Treatment-Free Period (DMQ-139)
- In Vitro Effects of Quinidine Sulfate on QRS, QT, T_{p-e} and Proarrhythmias in the Rabbit Left Ventricular Wedge Preparation (DMQ-146)

3.2 Studies Not Reviewed: Review of the following studies in the current resubmission is deferred to the Clinical Pharmacology staff.

- GLP In Vitro Assessment of Human Liver Cytochrome P450 Inhibition Potential of Dextromethorphan Hydrobromide (DMQ-142, (b) (4))
- GLP In Vitro Assessment of Human Liver Cytochrome P450 Inhibition Potential of Quinidine Sulfate (DMQ-143, (b) (4))
- GLP In Vitro Assessment of the Induction Potential of Dextromethorphan Hydrobromide in Primary Cultures of Human Hepatocytes (DMQ-144, (b) (4))
- GLP In Vitro Assessment of the Induction Potential of Quinidine Sulfate in Primary Cultures of Human Hepatocytes (DMQ-145, (b) (4))

3.3 Previous Reviews Referenced

- Pharmacology/Toxicology Review, NDA 21-879, Kathleen Young, Ph.D., 30 October 2006
- Pharmacology/Toxicology Supervisory Memorandum, NDA 21-879, Lois M. Freed, Ph.D., 13 November 2006
- Pharmacology/Toxicology Review, IND 56,954, D. Charles Thompson, Ph.D., 7 May 2009
- Carcinogenicity Study Statistical Review, IND 56,954, Steve Thomson, M.S., 28 March 2008

4 Pharmacology

4.3 Safety Pharmacology

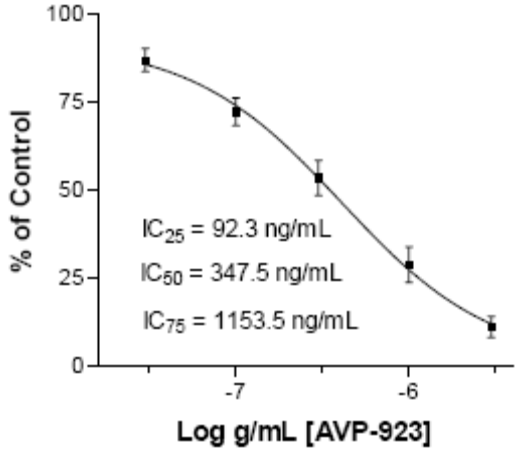
Study title: Effects of AVP-923 on HERG Tail Current Recorded from Stably Transfected HEK293 Cells
Study no.: SPH05-008/Avanir #DMQ-131
Study report location: EDR
Conducting laboratory and location: (b) (4)
Date of study initiation: 5 April 2005
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: AVP-923 (formulated by two components, quinidine sulfate, lot no. 4963, and dextromethorphan hydrobromide, lot no. DM 0302015, 1:1 by weight); positive control, E-4031 (lot no. RLK9302); vehicle, DMSO (lot no. 01843TB).

Summary Description and Conclusions

The effects of AVP-923 (DM/Q, 1:1) on the human ether-a go-go-related gene (HERG)-encoded channel tail current were assessed via whole-cell patch-clamp technique in human embryonic kidney 293 (HEK293) cells stably transfected with HERG complementary DNA (cDNA). AVP-923 solutions were perfused at final concentrations of 10, 30, 100, 300, 1000, and 3000 ng/mL, with a corresponding vehicle (DMSO) concentration of 0.1% (n = 4 cells/each). The reference substance, E-4031, was formulated in bath solution at 100 nM. Results indicate that a statistically significant inhibition in HERG tail current was observed at target concentrations of 100 ng/mL and above ($p \leq 0.01$ versus vehicle), with an estimated IC_{50} value of 347.5 ng/mL (equivalent to a combination of 222.0 nM quinidine sulfate and 469.3 nM

dextromethorphan hydrobromide) (see sponsor's figure reproduced below). Treatment with E-4031 resulted in a mean tail current decrease of 92.5% (n = 2).

Figure 3. Concentration-Response Relationship for the Effects of AVP-923 on HERG Tail Current



The target concentrations of AVP-923 (30, 100, 300, 1000, and 3000 ng/mL) were used to create the concentration-response relationship.

Study title: In Vitro Effects of Quinidine Sulfate on QRS, QT, T_{p-e} and Proarrhythmias in the Rabbit Left Ventricular Wedge Preparation
Study no.: DMQ-146
Study report location: EDR
Conducting laboratory and location: (b) (4)

Report date: 10 November 2008
GLP compliance: No
QA statement: No
Drug, lot #, and % purity: Not reported

Summary Description and Conclusions

The effects of quinidine sulfate on QRS duration, QT interval, T_{p-e} interval and proarrhythmias, including early afterdepolarization (EAD), were assessed in the isolated rabbit left ventricular wedge preparation. Left ventricular transmural wedges were dissected from rabbits (either sex, strain not specified) and incubated in tissue bath (Tyrode's solution) with cyclic electrical stimulation until electrically stable (approximately one hour). Once stable, baseline transmural ECG recordings were taken with a total drug perfusion time of 30 minutes at each concentration (range, 0.015 µM to 1.5 µM) (see sponsor's testing protocol schematic reproduced below). According to the sponsor, "Since one quinidine sulfate (MW: 782.94) generates two quinidine molecules

in the perfusion solution...we will use the concentrations of free quinidine." Under the conditions of this study, the sponsor concludes that "...quinidine has no significant effect on QRS duration in the concentration range tested. However, quinidine produces a concentration-dependent QT and T_{p-e} prolongation at concentrations from 0.1 μM to 3.0 μM. At a concentration of 0.03 μM, quinidine has no effect on QT and T_{p-e} intervals" (see sponsor's representative ECG tracings reproduced below).

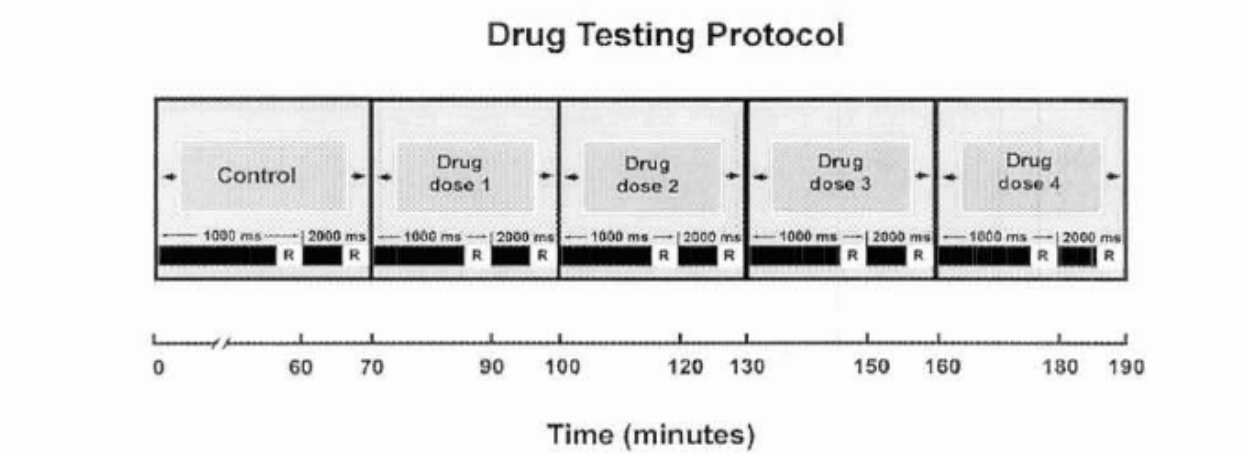


Figure 1. Experimental protocol used to study a test article in the isolated arterially perfused rabbit ventricular preparation. Data were recorded (R) for 30-60 sec before the end of each stimulation period.

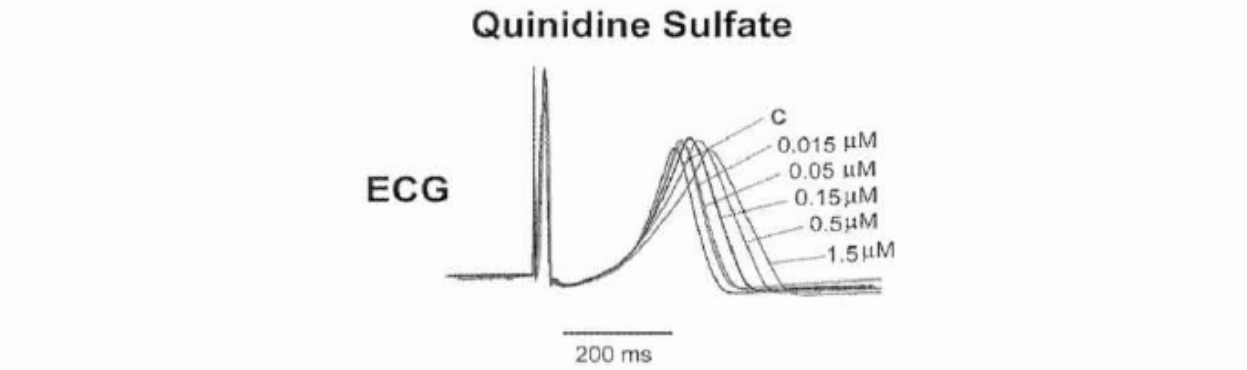


Figure 2. Original ECG tracings recorded from a rabbit left ventricular wedge preparation in control condition and in the presence of quinidine sulfate. The tracings were recorded when the preparation was paced at a BCL of 2000 ms.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study title: Dextromethorphan/Quinidine—7-day oral (gavage) pharmacokinetic study in the beagle dog.
Study no.: AA41165/Avanir #DMQ-137
Study report location: EDR
Conducting laboratory and location: (b) (4)

Date of study initiation: 12 June 2007
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Dextromethorphan HBr, batch #168973, 99.6%; quinidine sulfate, batch #160334, 100.7%

Summary Description and Conclusions

The plasma pharmacokinetics of dextromethorphan (DM), dextrorphan (DX), and quinidine (Q) were assessed in beagle dogs (1/sex) following oral gavage (5 mL/kg) administration for seven days of DM/Q combined at doses of 10/0, 10/2, 10/20, and 10/100 mg/kg/day, respectively. Due to severe clinical signs (e.g., tonic convulsions, posterior paralysis, marked tremors, unsteady gait, vomiting, decreased activity), the animals receiving the high dose of 10/100 mg/kg/day were humanely sacrificed on Day 3 and Day 5 for the female and male, respectively. All other animals survived to scheduled study termination. Blood samples for PK analyses were collected via jugular vein from unanesthetized animals on Day 0 and Day 6 (where possible) before dosing and at 0.5, 1, 2, 4, 6, 8, 10, and 24 hours after dosing. A summary of estimated PK parameters (where calculable) for males and females is provided in the tables below. These data were used by the sponsor to guide determination of appropriate dose levels for the 39-week oral toxicity study in dogs (DMQ-139, reviewed below).

Summary PK Parameter Estimates: Male Dogs (n = 1/dose)

		Dextromethorphan			Dextrorphan			Quinidine		
Day	DM/Q (m/k/d)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	AUC_{0-t} (µg•hr/mL)	C_{max} (µg/mL)	$t_{1/2}$ (hr)
0	10/0	153	49	3.8	1115	326	3.6	-	-	-
	10/2	300	88	3.0	1604	303	-	5.0	1.1	3.4
	10/20	297	92	2.1	502	196	-	32	2.7	4.0
	10/100	127	30	1.7	80	50	-	63	4.8	5.4
6	10/0	229	72	3.0	430	99	-	-	-	-
	10/2	548	186	1.8	341	77	2.9	4.9	1.3	2.4
	10/20	410	134	2.4	-	43	-	21	2.3	4.1
	10/100	375	92	-*	-	-	-	35	6.6	-

*- = Not applicable and/or not calculated

Summary PK Parameter Estimates: Female Dogs (n = 1/dose)

		Dextromethorphan			Dextrorphan			Quinidine		
Day	DM/Q (m/k/d)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	AUC_{0-t} (µg•hr/mL)	C_{max} (µg/mL)	$t_{1/2}$ (hr)
0	10/0	194	48	5.1	1232	319	-	-	-	-
	10/2	155	50	2.5	993	190	5.7	6.6	1.4	2.8
	10/20	192	48	2.3	304	103	-	36	2.4	4.2
	10/100	146	29	3.3	52	31	-	86	4.6	-
6	10/0	463	147	2.0	269	88	-	-	-	-
	10/2	303	99	2.4	204	62	-	7.4	1.7	2.8
	10/20	316	89	1.7	-	29	-	30	2.8	4.2
	10/100	-	-	-	-	-	-	-	-	-

*- = Not applicable and/or not calculated

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: Dextromethorphan/Quinidine - 39-week oral (gavage) toxicity study in the beagle dog followed by an 8-week treatment-free period.

Study no.:	AA41167RE/Avanir #DMQ-139
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	22 October 2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Dextromethorphan HBr, batch #168973, 99.6%; quinidine sulfate, batch #160334, 100.7%

Key Study Findings

- All animals survived to scheduled necropsy. Notable clinical signs, including decreased activity, intermittent/permanent tremors, increased muscle tone, and stiff hind limbs, were observed in HD animals only (both sexes); head shaking was reported in males only at the high dose, but in females at both the mid and high doses.
- At termination of dosing, mean body weight in HD females was decreased approximately 12% versus controls.
- Heart rate was increased notably in HD animals on Days 126/127 after the quinidine dose was doubled to 12 mg/kg/day, which resulted in a decrease in the QT interval (QT_c values were essentially unchanged).

- Mean reticulocyte counts (%) appeared to be decreased in almost all treated groups of both sexes relative to controls.
- A finding of “keratin cyst” (grade 4) was reported in the brain of one (1/4) HD female; it was located in the telencephalon and was characterized as “...focally with cholesterol clefts. Associated with lymphoid cell infiltrate.”
- A apparent dose-responsive focal squamous metaplasia of the larynx/trachea (minimal to moderate) was observed in main study animals; the finding (minimal to slight) remained evident in 1/2 recovery animals from each sex and group.
- Minimal mineralization of the renal papilla was reported in all study animals (both sexes, all dose groups); this finding was still present and unresolved in all recovery animals.
- Minimal sinusoidal histiocytosis was reported in the mesenteric lymph nodes in half or more of all study animals (both sexes, all dose groups, including controls); similarly, pigmented histiocytes (minimal) were reported in the spleens of comparable numbers of males and females from all treated and control groups. These findings, as well, were incompletely resolved in recovery animals.
- TK analyses of plasma drug concentrations (DM/DX/Q) indicate that mean plasma concentrations of DM increased with increasing dose and with repeated administration. Mean systemic exposure to DM was generally higher in females than in males. Half-lives were generally comparable between males and females and increased with increasing dose. Plasma concentrations of DX decreased with repeated DM/Q administration, though values remained relatively constant from Day 84 to Day 267. Mean systemic exposure for DX was generally lower in females than in males. Doubling the Q dose in HD animals on Day 126 did not result in any apparent further decrease in mean systemic exposure of DX, suggesting the enzyme inhibitory effect of Q had plateaued. Mean Q plasma concentrations increased with dose, but appeared to remain relatively constant with repeated dosing. Mean systemic exposure of Q was generally slightly lower in females than in males. The overall net impact of the Day 126 doubling of Q dose to HD animals on systemic exposure to DM and DX is difficult to discern in light of an apparent overall drug accumulation effect.
- Based on observations in HD animals of increased incidence and/or severity of clinical signs, reduction in mean body weight of HD females, the alteration of ECG parameters in HD animals, and an apparent slight increase in the incidence and severity of focal squamous metaplasia of the trachea/larynx in HD animals, the MD of 6/3 mg/kg/day may be considered a NOAEL for chronic oral administration of DM/Q in dogs. At this dose, Day 267 dextromethorphan AUC values were 380 and 372 ng•hr/mL and C_{max} values were 99.4 and 92.2 ng/mL in males and females, respectively. The corresponding quinidine AUC values were 11.1 and 8.51 µg•hr/mL and C_{max} values were 1.88 and 1.52 µg/mL in males and females, respectively.

Methods

Doses:	See sponsor's summary table below, including escalation scheme to definitive doses. Doses were selected based on results of previous studies of 5-week (#AA41166/DMQ-138) and 7-day (#AA41165/DMQ-137) duration.
Frequency of dosing:	Once daily for 39 weeks
Route of administration:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.5% (w/v) Methylcellulose in water
Species/Strain:	Dogs/beagle
Number/Sex/Group:	See sponsor's summary table below
Age:	5-6 months
Weight:	7-10 kg, males; 6-10 kg, females
Satellite groups:	None
Unique study design:	Animals were housed singly in pens during daily procedures and socialized in groups of up to three animals of the same sex and dose group during the night. Animals were provided 300 g/day of pelleted complete commercial diet (Diet 125C, Safe); water was available ad libitum. Due to detection of ascariasis in most animals, all animals were treated with a vermifuge (b (4)) in Week 15.
Deviation from study protocol:	Reported deviations were judged "...not to have affected the outcome or the achievement of the study objectives."

Group	Test item A Dextromethorphan		Test item B Quinidine		Dose volume of formulation	Number of animals	
	Dose level (mg/kg/day)	Dose concentration (mg/mL)	Dose level (mg/kg/day)	Dose concentration (mg/mL)	(mL/kg/day)	Terminal kill(1)	Recovery(2)
1. Control	0	0	0	0	5	4M + 4F	2M + 2F
2. Intermediate dose I	3.0	0.6	1.5	0.3	5	4M + 4F	/
3. Intermediate dose II	6.0	1.2	3.0	0.6	5	4M + 4F	/
4. High dose	12.0	2.4	6.0/12.0(3)	1.2/2.4(3)	5	4M + 4F	2M + 2F

M: males; F: females; /: not applicable.

(1) end of the treatment period (week 39).

(2) end of the treatment-free period (week 47).

(3) Regarding the absence of clinical signs in any group at week 18, the Quinidine dose level was increased from week 19 in group 4 in attempt to increase exposure to Dextromethorphan.

Treatment days	Dose level (mg/kg/day)							
	Group 1		Group 2		Group 3		Group 4	
	D	Q	D	Q	D	Q	D	Q
0 to 6	0	0	3	1.5	3	1.5	3	1.5
7 to 13	0	0	3	1.5	6	3	6	3
14 to week 19	0	0	3	1.5	6	3	12	6
Week 19	0	0	3	1.5	6	3	12	12

Observations and Results

Mortality

Observed twice daily. All animals survived to scheduled necropsy.

Clinical Signs

Assessed daily; detailed physical/behavioral assessments were conducted pretest, weekly for first 4 weeks of treatment, and monthly thereafter. During the dosing phase, decreased activity, intermittent/permanent tremors, increased muscle tone, and stiff hind limbs were observed in HD animals only of both sexes; head shaking was reported in males only at the high dose, but in females at both the MD and HD. Excess salivation (slight to abundant) was observed across all dose groups, but to a greater degree in treated versus control animals. Red skin and mucous membranes were also reported in HD females at a higher incidence than in the control group. All other reported observations occurred with comparable incidence and severity in treated and control groups.

Body Weights

Recorded weekly. Plots of mean body weight versus time for males and females are reproduced below from the sponsor's submission. At termination of dosing, mean body weight in HD females was decreased approximately 12% versus controls.

Figure 1
Mean body weights - Males

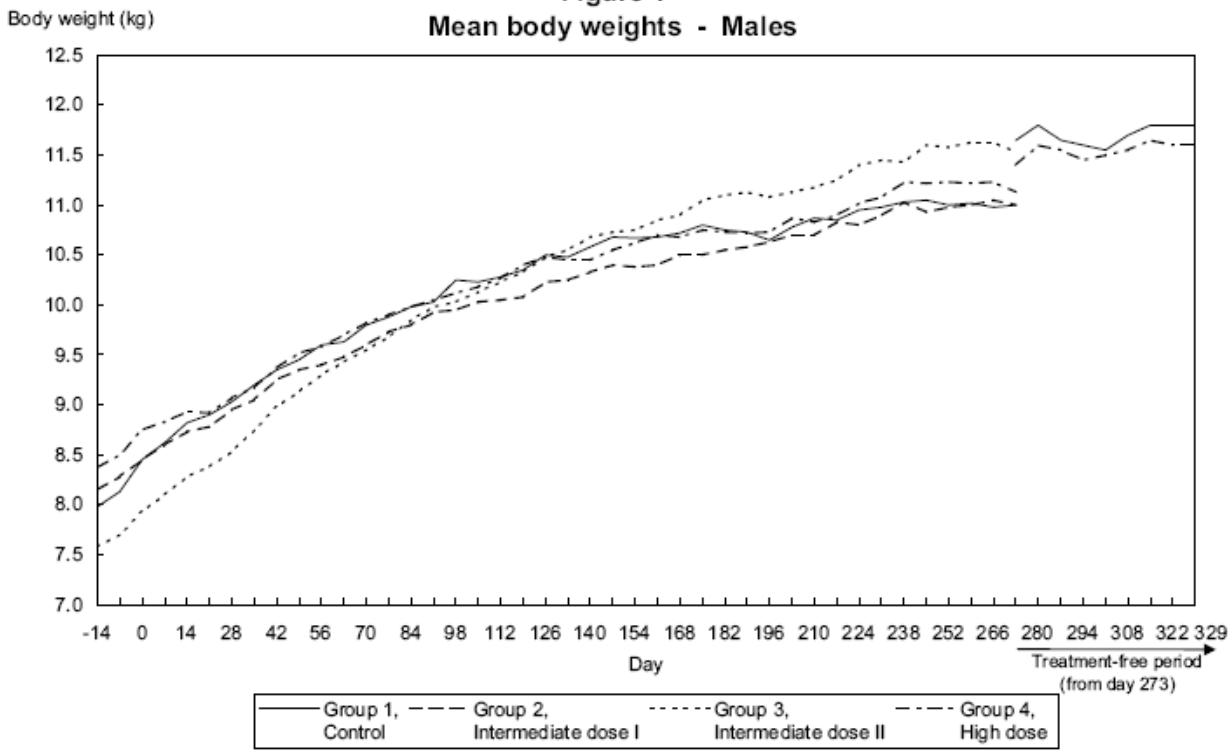
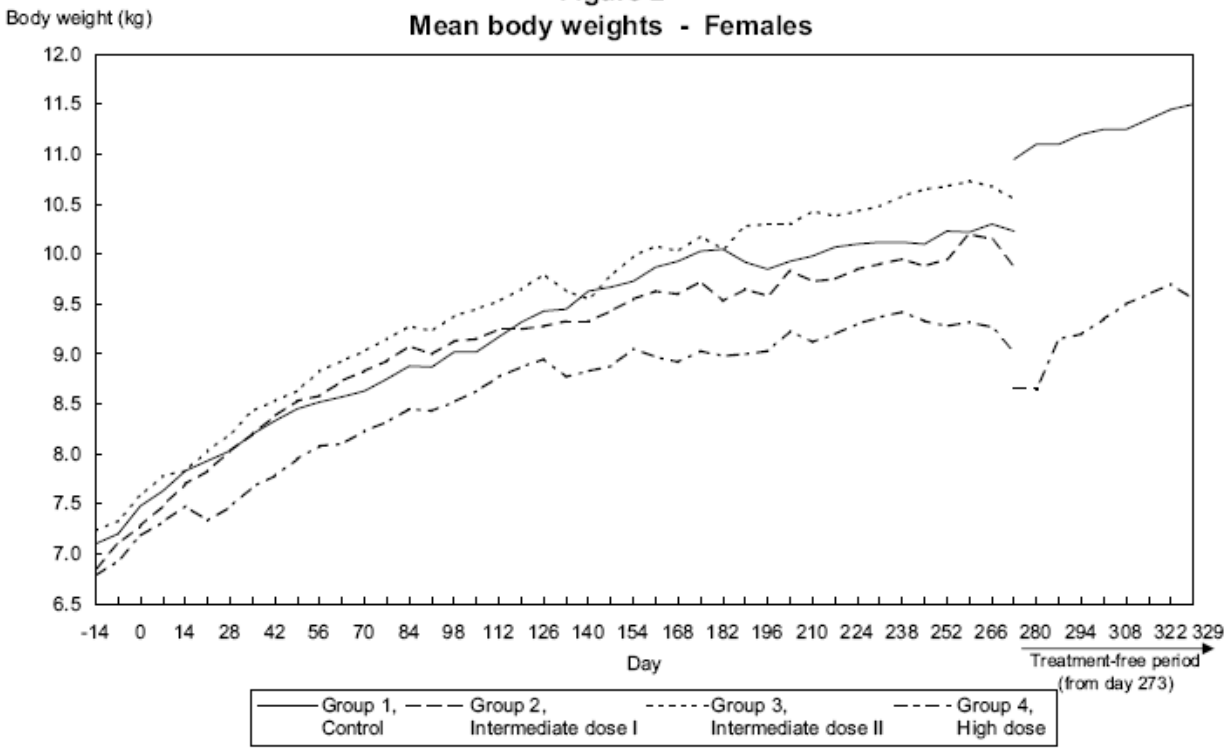


Figure 2
Mean body weights - Females



Feed Consumption

Measured daily. No effect of treatment on food consumption was apparent among male dogs. Among females, mean consumption for Group 2 and 4 animals was slightly decreased versus controls during most of the dosing phase.

Ophthalmoscopy

Performed pretest and in Weeks 13, 26, 39, and 47. No treatment-related effects were reported.

ECG

Performed pretest and in Weeks 1, 2, 3, 13, and 39 before and at 1 hour after dosing, plus in Week 19 for Group 4 animals (at time of increase in quinidine dose) and Week 47 for all Recovery animals (QT_c correction via Fridericia's formula). No treatment-related effects on blood pressure were apparent. Heart rate did not appear to be affected in the LD and MD groups, but was increased notably in HD animals on Days 126/127 after the quinidine dose was increased to 12 mg/kg/day, which resulted in a decrease in the QT interval (QT_c values were essentially unchanged). No other treatment-related effects on ECG parameters were apparent. Selected parameter values are summarized in the tables below.

Heart Rate (beats/min) (mean ± SD)

Group/ Sex (n)	Day 0 (before)	Day 85 (+1 hr)	Day 126 (before)	Day 126 (+1 hr)	Day 127 (before)	Day 127 (+1 hr)	Day 266 (+1 hr)	Day 323 (n = 2)
1M (6)	113 ± 8	88 ± 17					97 ± 26	85 ± 21
2M (4)	138 ± 26	98 ± 13					100 ± 8	
3M (4)	145 ± 46	118 ± 33					120 ± 42	
4M (6)	120 ± 13	103 ± 16	92 ± 17	115 ± 21	82 ± 12	120 ± 22	107 ± 16	105 ± 21
1F (6)	115 ± 24	103 ± 15					105 ± 12	100 ± 14
2F (4)	122 ± 35	110 ± 12					115 ± 21	
3F (4)	120 ± 12	105 ± 19					102 ± 17	
4F (6)	125 ± 27	115 ± 14	105 ± 18	138 ± 23	108 ± 8	147 ± 19	115 ± 16	105 ± 21

QT Interval (ms) (mean ± SD)

Group/ Sex (n)	Day 0 (before)	Day 85 (+1 hr)	Day 126 (before)	Day 126 (+1 hr)	Day 127 (before)	Day 127 (+1 hr)	Day 266 (+1 hr)	Day 323 (n = 2)
1M (6)	231 ± 9	234 ± 13					230 ± 21	232 ± 7
2M (4)	222 ± 14	236 ± 12					233 ± 7	
3M (4)	208 ± 13	223 ± 23					227 ± 29	
4M (6)	218 ± 6	235 ± 20	233 ± 16	227 ± 18	239 ± 12	215 ± 18	237 ± 11	217 ± 14
1F (6)	227 ± 19	229 ± 6					229 ± 5	222 ± 2
2F (4)	223 ± 18	229 ± 10					230 ± 22	
3F (4)	219 ± 10	234 ± 19					222 ± 27	
4F (6)	213 ± 10	221 ± 10	223 ± 11	207 ± 15	228 ± 7	206 ± 12	224 ± 9	214 ± 19

QT_c Interval (beats/min) (mean ± SD)

Group/ Sex (n)	Day 0 (before)	Day 85 (+1 hr)	Day 126 (before)	Day 126 (+1 hr)	Day 127 (before)	Day 127 (+1 hr)	Day 266 (+1 hr)	Day 323 (n = 2)
1M (6)	288 ± 12	266 ± 9					270 ± 15	267 ± 1
2M (4)	289 ± 7	281 ± 18					279 ± 9	
3M (4)	276 ± 23	276 ± 12					277 ± 11	
4M (6)	276 ± 9	282 ± 13	272 ± 14	281 ± 10	272 ± 12	270 ± 10	283 ± 10	254 ± 16
1F (6)	284 ± 11	268 ± 14					276 ± 16	266 ± 9
2F (4)	278 ± 15	290 ± 30					286 ± 15	
3F (4)	289 ± 6	283 ± 10					268 ± 30	
4F (6)	283 ± 17	274 ± 10	270 ± 7	276 ± 7	284 ± 9	283 ± 6	287 ± 17	262 ± 5

QRS Complex (ms) (mean ± SD)

Group/ Sex (n)	Day 0 (before)	Day 85 (+1 hr)	Day 126 (before)	Day 126 (+1 hr)	Day 127 (before)	Day 127 (+1 hr)	Day 266 (+1 hr)	Day 323 (n = 2)
1M (6)	76 ± 4	80 ± 9					78 ± 3	82 ± 2
2M (4)	76 ± 4	78 ± 3					72 ± 8	
3M (4)	76 ± 5	75 ± 4					76 ± 4	
4M (6)	74 ± 4	79 ± 5	76 ± 4	78 ± 8	78 ± 3	76 ± 6	77 ± 4	78 ± 2
1F (6)	80 ± 1	78 ± 2					80 ± 3	80 ± 0
2F (4)	77 ± 7	80 ± 7					78 ± 9	
3F (4)	82 ± 4	76 ± 6					82 ± 4	
4F (6)	75 ± 5	75 ± 2	78 ± 4	73 ± 7	78 ± 6	73 ± 5	80 ± 12	78 ± 12

Hematology

Performed pretest and in Weeks 13, 26, 39 and 47. Although there was considerable variability in the data, mean reticulocyte counts (%) appeared to be decreased in almost all treated groups of both sexes relative to controls (see sponsor's summary tables reproduced below). In addition, mean APTT values (seconds) in HD females were statistically elevated versus controls on Days 84 (↑10%) and 267 (↑10%), although values in control animals did vary by over 15% during the study. The remaining findings were unremarkable.

Reticulocyte (Percentage)

Group	Sex		Day numbers relative to Start Date -12	84	175	267	322
1	m	Mean	1.42	0.80	0.70	0.73	0.70
		S.D.	0.33	0.37	0.36	0.35	0.14
		N	6	6	6	6	2
2	m	Mean	1.83	0.58	0.45	0.45	.
		S.D.	0.56	0.17	0.17	0.17	.
		N	4	4	4	4	0
3	m	Mean	2.10*	0.58	0.50	0.48	.
		S.D.	0.42	0.34	0.26	0.24	.
		N	4	4	4	4	0
4	m	Mean	1.32	0.40*	0.35*	0.45	1.00
		S.D.	0.35	0.27	0.14	0.21	0.14
		N	6	6	6	6	2

Reticulocyte (Percentage)

Group	Sex		Day numbers relative to Start Date -12	84	175	267	322
1	f	Mean	1.35	0.72	1.05	0.43	0.65
		S.D.	0.52	0.28	0.48	0.15	0.49
		N	6	6	6	6	2
2	f	Mean	0.93	0.45*	0.33**	0.30	.
		S.D.	0.15	0.13	0.13	0.12	.
		N	4	4	4	4	0
3	f	Mean	1.20	0.48*	0.40**	0.48	.
		S.D.	0.22	0.22	0.14	0.21	.
		N	4	4	4	4	0
4	f	Mean	0.95	0.33**	0.18**	0.22*	0.95
		S.D.	0.20	0.08	0.04	0.13	0.35
		N	6	6	6	6	2

Clinical Chemistry

Performed pretest and in Weeks 13, 26, 39 and 47. A number of differences between treated and control values for clinical chemistry parameters were noted to have attained statistical significance. However, due to the sporadic nature of the observations, the low magnitude of the differences, the lack of a dose response, and/or the inherent variability of the data, the toxicological significance of these differences was considered to be negligible.

Urinalysis

Performed pretest and in Weeks 13, 26, 39 and 47 (16-hr collection in metabolism cages). No treatment-related effects were apparent.

Gross Pathology

Week 40 (Terminal sacrifice) and Week 48 (Recovery sacrifice). A uterine mass ("homogeneous, solid") was reported in one female each from Groups 2 and 3. Otherwise, reported gross necropsy findings were unremarkable.

Organ Weights

The following organs were weighed at necropsy for all animals: adrenal glands, brain, epididymides, heart, kidneys, liver, ovaries, pituitary gland, prostate, spleen, testes, thymus, thyroids/parathyroids, and uterus. No effects of treatment on organ weights were evident.

Histopathology

Adequate Battery: Yes

Peer Review: Yes, by "P. Fant"; with extent of review described as follows: "Larynx from all terminal and recovery animals and all tissues from male no. 513 from group 1 and male nos. 539 and 542 and female nos. 546 and 548 from group 4."

Histological Findings

A finding of "keratin cyst" (grade 4) was reported in the brain of one (1/4) HD female (#547). The lesion was described as being located in the telencephalon and characterized as "...focally with cholesterol clefts. Associated with lymphoid cell infiltrate." Intimal thickening (grade 2) was noted in the right-sided coronary vessel(s) of a single HD female (#546) "with minimal perivascular lymphoid cell infiltrate". Minimal mineralization of the renal papilla was reported in all study animals (both sexes, all dose groups); this finding was still present and unresolved in all recovery animals. Minimal sinusoidal histiocytosis was reported in the mesenteric lymph nodes in half or more of all study animals (both sexes, all dose groups); similarly, pigmented histiocytes (minimal) were reported in the spleens of comparable numbers of males and females from all groups. These findings, as well, were incompletely resolved in recovery animals. Glandular dilatation of the prostate (minimal to slight) was observed in all main study males except for one HD animal, while atrophy of the gland was reported in 4/4 Group 2 males (3 minimal; 1 slight) and 1/4 Group 3 males (slight) with no incidence in control animals. However, in recovery animals, both males in each of the control and HD groups exhibited prostatic atrophy (minimal to moderate). In addition, certain notable observations in the larynx and pituitary gland are summarized in the sponsor's tables reproduced below. All other reported microscopic findings in main study animals were unremarkable. At recovery, the focal squamous metaplasia of the trachea (minimal to slight) remained

evident in 1/2 animals from each sex and group. Mixed cell aggregates in the liver (minimal), while present only in control and lower dose animals of the main study, was observed in 1/2 HDM and 2/2 HDF, along with 1/2 control females. All other findings, except as noted above, were unremarkable.

DOSE GROUP:	1		2		3		4	
SEX :	M	F	M	F	M	F	M	F
NO.ANIMALS:	4	4	4	4	4	4	4	4
LARYNX :	4	4	4	4	4	4	4	4
- Lymphoid follicles :	1	-	2	-	2	-	1	-
Grade 1:	1	-	2	-	2	-	1	-
- Mixed cell infiltr. :	1	-	-	-	-	-	-	-
Grade 1:	1	-	-	-	-	-	-	-
- Trach:foc.squam.met.:	-	2	3	3	3	3	4	4
Grade 1:	-	2	2	2	1	2	3	1
Grade 2:	-	-	1	-	2	1	-	3
Grade 3:	-	-	-	1	-	-	1	-
PITUITARY GLAND :	4	4	4	4	4	4	4	4
- Cyst(s) :	-	2	3	2	1	1	-	1
Grade 1:	-	1	-	1	-	-	-	-
Grade 2:	-	1	-	-	1	-	-	-
Grade 3:	-	-	3	1	-	1	-	1

Special Evaluation: None

Toxicokinetics

Blood samples were collected via jugular vein for TK analyses in Weeks 1, 2, 3, 13, 19, 26, 39, and 47 at before and 0.5, 1, 2, 6, 8, and 12 hours after dosing during the dosing period. Selected plasma TK parameter estimates for dextromethorphan, dextrorphan, and quinidine are summarized in the tables below. The results indicate that mean plasma concentrations of DM increased with increasing dose and with repeated once daily administration. Mean systemic exposure to DM was generally higher in females than in males. Half-lives were generally comparable between males and females and increased with increasing dose.

Plasma concentrations of dextrorphan (DX) decreased with repeated DM/Q administration, though values remained relatively constant from Day 84 to Day 267. Mean systemic exposure of DX was generally lower in females than in males, except on day 267. The increase in Q dose from 6 to 12 mg/kg/day in HD animals on Day 126 did not result in any apparent further decrease in mean systemic exposure of DX.

Mean Q plasma concentrations increased with dose, but remained relatively constant with repeated dosing. Mean systemic exposure of Q was generally slightly lower in females than in males.

Dextromethorphan: Mean Plasma TK Parameters

Day	DM/Q Dose (mg/kg/day)	Sex	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	Half-life (hr)
84	3/1.5	M	44.4	14.8	NC
		F	90.3	27.6	1.88*
	6/3	M	162	38.0	2.51
		F	219	57.3	2.19
	12/6	M	469	105	2.63
		F	419	107	2.77
175	3/1.5	M	71.2	19.0	NC
		F	85.5	24.0	1.87*
	6/3	M	273	60.2	1.92
		F	377	84.2	2.29
	12/12	M	646	146	2.30
		F	636	148	2.31
267	3/1.5	M	105	26.5	1.78*
		F	141	39.7	1.76
	6/3	M	380	99.4	2.34
		F	372	92.2	2.93
	12/12	M	856	186	3.17
		F	1079	240	2.74

*Only one value available for calculation of the mean
NC = not calculated

Dextrorphan: Mean Plasma TK Parameters

Day	DM/Q Dose (mg/kg/day)	Sex	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	Half-life (hr)
84	3/1.5	M	77.1	49.5	N/C
		F	77.4	48.7	“”
	6/3	M	142	58.6	“”
		F	75.2	51.8	“”
	12/6	M	257	80.6	“”
		F	151	72.4	“”
175	3/1.5	M	67.1	48.8	“”
		F	55.6	39.1	“”
	6/3	M	172	62.9	“”
		F	149	58.0	“”
	12/12	M	350	76.6	“”
		F	236	71.9	“”
267	3/1.5	M	37.6	43.6	“”
		F	63.8	45.7	“”
	6/3	M	140	65.6	“”
		F	127	61.4	“”
	12/12	M	260	78.3	“”
		F	375	82.1	“”

*Only one value available for calculation of the mean
NC = not calculated

Quinidine: Mean Plasma TK Parameters

Day	DM/Q Dose (mg/kg/day)	Sex	AUC_{0-t} (µg•hr/mL)	C_{max} (µg/mL)	Half-life (hr)
84	3/1.5	M	4.06	0.91	2.87
		F	4.45	0.98	2.84
	6/3	M	9.27	1.57	4.31
		F	7.94	1.31	3.86
	12/6	M	14.2	2.17	4.14
		F	12.1	1.89	4.10
175	3/1.5	M	4.45	0.91	3.12*
		F	5.08	1.08	3.27
	6/3	M	10.4	1.67	3.80
		F	8.51	1.35	4.40
	12/12	M	25.8	3.09	5.54
		F	22.9	2.92	5.32
267	3/1.5	M	4.59	0.94	3.73
		F	5.72	1.22	3.03
	6/3	M	11.1	1.88	4.10
		F	8.51	1.52	4.26
	12/12	M	28.7	3.49	6.27
		F	23.8	2.86	6.39

*Only one value available for calculation of the mean

Based on the TK parameter findings summarized above, the following table summarizes the changes in AUC values (percent and direction) from Day 84 to Day 267 of the study, which brackets, as noted above, the change on Day 126 in the quinidine dose administered to HD animals from 6 to 12 mg/kg/day. The same changes are also shown for MD animals, for which the quinidine dose remained constant throughout the noted

study period. The increase in quinidine AUC values of HDM and HDF between Day 84 and Day 175 appeared to be roughly proportional to the 100% increase in quinidine dose that occurred beginning on Day 126. However, it is difficult to discern the net impact of this increased quinidine dose on systemic exposure to dextromethorphan and to dextrorphan in light of what appeared to be an overall drug accumulation effect. For example, both DM and DX appeared to increase from Day 84 to Day 175 not only in HD animals, but also in MD animals, for which the quinidine dose remained constant.

Change in Estimated AUC Values
(direction and percentage change between noted sampling days)

		Dextromethorphan		Dextrorphan		Quinidine	
Group	**Study Day Transition**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
High Dose	84 > 175	↑38	↑52	↑36	↑56	↑82	↑89
	175 > 267	↑33	↑70	↓26	↑59	↑11	↑4
Mid Dose	84 > 175	↑69	↑72	↑21	↑98	↑12	↑7
	175 > 267	↑39	↓1	↓19	↓15	↑7	NC

Stability and Homogeneity

Confirmation that stability and homogeneity of test article suspensions were within stated specifications (±15% of theoretical values) under relevant study conditions, with very few stated exceptions, was provided in the sponsor's report.

Study title: Dextromethorphan/Quinidine - 5-week oral (gavage) toxicity study in the beagle dog

Study no.:	AA41166/Avanir #DMQ-138
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	26 July 2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Dextromethorphan HBr, batch #168973, 99.6%; quinidine sulfate, batch #160334, 100.7%

Key Study Findings

- Severe clinical signs in Group 4 animals at a top initial dose of 30/20 (DM/Q, mg/kg/day) on Day 7 (including tonic convulsions, paresis, and tremors) necessitated a 7-day stop-dose/wash-out period; dosing resumed at a lower maximum DM/Q dose of 12/12 mg/kg/day beginning on Day 19 and continuing for 28 consecutive days.

- Group 4 animals lost weight between Days 0 and 7, but subsequently gained weight at approximately the same rate as did lower dose groups.
- All animals survived to scheduled necropsy, which was Day 35 for animals in Groups 1 to 3 and Day 47 for Group 4 animals. There were no reported treatment-related effects on hematology, clinical chemistry, or urinalysis parameters. Microscopic histopathology was not assessed.
- Based on the noted findings under the conditions of this study, the sponsor concluded that the top dose for the 39-week oral toxicity study in dogs should be 12/12 mg/kg/day of DM/Q. At this dose, Day 46 plasma dextromethorphan AUC values were 410 and 369 ng•hr/mL and C_{max} values were 102 and 82 ng/mL in males and females, respectively. The corresponding quinidine AUC values were 40 and 40 µg•hr/mL and the C_{max} values were 4.3 and 4.1 µg/mL in males and females, respectively.

Methods

Doses:	See sponsor's summary table below, including escalation scheme to definitive doses.
Frequency of dosing:	Once daily for 5 weeks (see dose escalation schemes reproduced below)
Route of administration:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.5% (w/v) Methylcellulose in water
Species/Strain:	Dogs/beagle
Number/Sex/Group:	See sponsor's summary table below
Age:	5 months at dosing initiation
Weight:	7-9 kg, males; 6-9 kg, females
Satellite groups:	None
Unique study design:	Animals were housed singly in pens during daily procedures and socialized in groups of two animals of the same sex and dose group during the night. Animals were provided 300 g/day of pelleted complete commercial diet (Diet 125C3, Safe); water was available ad libitum.
Deviation from study protocol:	Reported deviations were judged "...not to have affected the outcome or the achievement of the study objectives."

Sponsor's Experimental Design Summary

Group	Test item A Dextromethorphan		Test item B Quinidine		Dose volume of formulation (mL/kg/day)	Number of animals	
	Dose level (mg/kg/day)	Dose concentration (mg/mL)	Dose level (mg/kg/day)	Dose concentration (mg/mL)		Males	Females
1. Control	0	0	0	0	5	2	2
2. Intermediate dose I	6	1.2	4	0.8	5	2	2
3. Intermediate dose II	12	2.4	8	1.6	5	2	2
4. High dose	30 12	6 2.4	20 12	4 2.4	5	2	2

Sponsor's Dose Escalation Scheme (Groups 1-3)

Treatment days	Dose level (mg/kg/day)					
	Group 1		Group 2		Group 3	
	D	Q	D	Q	D	Q
0 to 6	0	0	3	4	6	8
7 to 35	0	0	6	4	12	8

Sponsor's Dose Escalation Scheme (Group 4)

Treatment days	Dose level (mg/kg/day)	
	Dextromethorphan	Quinidine
0 and 1	6	20
2 and 3	12	20
4 to 6	20	20
7	30	20
8 to 14	Wash-out period	
15 to 18	6	12
19 to 46	12	12

Summary Description and Conclusions

Following a dose escalation phase of approximately seven days, groups of beagle dogs (2/sex/dose group) were administered a combination of dextromethorphan/quinidine via oral gavage for 28 days at doses of 0 (vehicle), 6/4, 12/8, and 12/12 (DM/Q, mg/kg/day), respectively. Severe clinical signs in Group 4 animals at a top initial dose of 30/20 on Day 7 (including tonic convulsions, paresis, and tremors; see sponsor's summary tables reproduced below) necessitated a 7-day stop-dose/wash-out period, with resumption of dosing at a lower dose on Day 15.

Summary of Clinical Observations (Groups 2 and 3)

Treatment days	Dose level (mg/kg/day)					
	Group 2			Group 3		
	D	Q	Clinical Observations after treatment	D	Q	Clinical Observations after treatment
0 to 6	3	4	D0: abdomen and ear redness in 2/2M and 2/2F D5: slight decreased activity and slight tremors after treatment (2/2 F)	6	8	D0: abdomen and/or ear redness (to purple) in 2/2M and 2/2F ears and mouth swelling (1/2F) D5: slight decreased activity and slight tremors after treatment (1/2M and 2/2F). Poor hindlimbs coordination after treatment (1/2F)
7 to 35	6	4	Decreased activity sporadically Slight liquid feces sporadically Slight food vomit (1/2 F)	12	8	Decreased activity (variable intensity), sporadically Paresis (D7 in 1/2M) Lame/limping (1/2 M) Abnormal vocalization and bars biting (1/2 F)

Summary of Clinical Observations (Group 4)

Treatment days	Dose level (mg/kg/day)		Clinical Observations (after treatment)
	D	Q	
0 and 1	6	20	D0: Ear redness in 1/2M and 2/2F, abdomen redness in 1/2F Slight food vomit 1/2F
2 and 3	12	20	D2: Ear swelling in 2/2M
4 to 6	20	20	D4: tremors and unsteady gait (all animals), slow movements and decreased activity (all animals), loss of balance (2/2F), abnormal movement of the head (1/2M), increased muscle tone (1/2M), paresis (1/2 M) D5: decreased activity (all animals), slight tremors (2/2M and 1/2F), paresis (all animals), loss of balance (1/2F) D6: unsteady gait (1/2 M and 2/2F), slow movements (1/2M and 1/2F), decreased activity (1/2M)
7	30	20	Paresis and subdued behaviour (all animals), decreased activity (2/2 F), tonic convulsions and loss of balance (1/2M and 2/2F), tremors (1/2M), unsteady gait (1/2F)
8 to 14	Wash-out period		D8: unsteady gait (all animals), decreased activity (2/2M and 1/2F), tremors (1/2F), abnormal movements of the head (1/2M) D9: abnormal vocalisation and bars biting (1/2F)
15 to 18	6	12	D16: slight decreased activity and unsteady gait (1/2M) D17: unsteady gait (1/2M) D18: right hindlimb limping (1/2M)
19 to 46	12	12	D19 and D20: liquid feces and red traces in feces (2/2 M) D19 to D31: right hindlimb limping (1/2 M) D40: liquid feces (2/2 F) D46: forelimbs limping with pain and abnormal vocalisation (1/2 F)

Subsequently, clinical signs in Group 4 animals were comparable in type and severity to those of Group 3 animals. Body weight curves for males and females are also reproduced below, which indicate Group 4 animals lost weight between Days 0 and 7, but subsequently gained weight at approximately the same rate as did lower dose groups. There were no reported treatment-related effects on hematology, clinical chemistry, or urinalysis parameters. All animals survived to scheduled necropsy, which was Day 35 for animals in Groups 1 to 3 and Day 47 for Group 4 animals. Microscopic histopathology evaluation was not conducted. Based on the noted findings under the conditions of this study, the sponsor concluded that "...the maximum dose of quinidine tolerable by the animals in this study is greater than or equal to 12 mg/kg/day and less than 20 mg/kg/day when associated with a dose of 12 mg/kg/day of dextromethorphan." The sponsor had previously concluded, based on findings from an earlier dog study with dextromethorphan only (DMQ-102; submitted and reviewed in the original NDA

submission), that 13.4 mg/kg/day was a "...MTD for D alone" and these data, in combination, were used in defining maximum doses for the subsequent 39-week dog study (DMQ-139, reviewed above). Selected TK parameter values from sampling at termination of the current study are summarized in the table below. These data suggest that plasma exposure to DM following a DM/Q dose of 12/12 mg/kg/day was no greater than, and perhaps less than, that following a dose of 12/8 mg/kg/day.

Figure 1
Mean body weights - Males

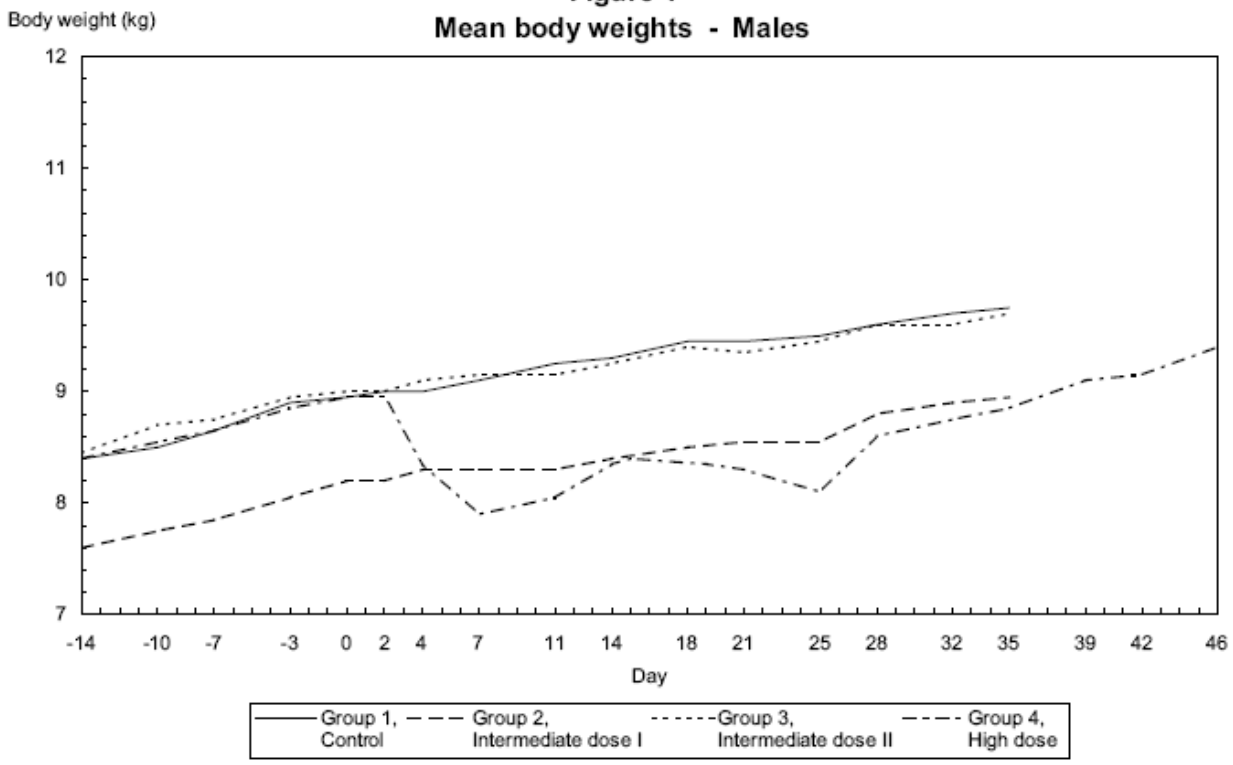
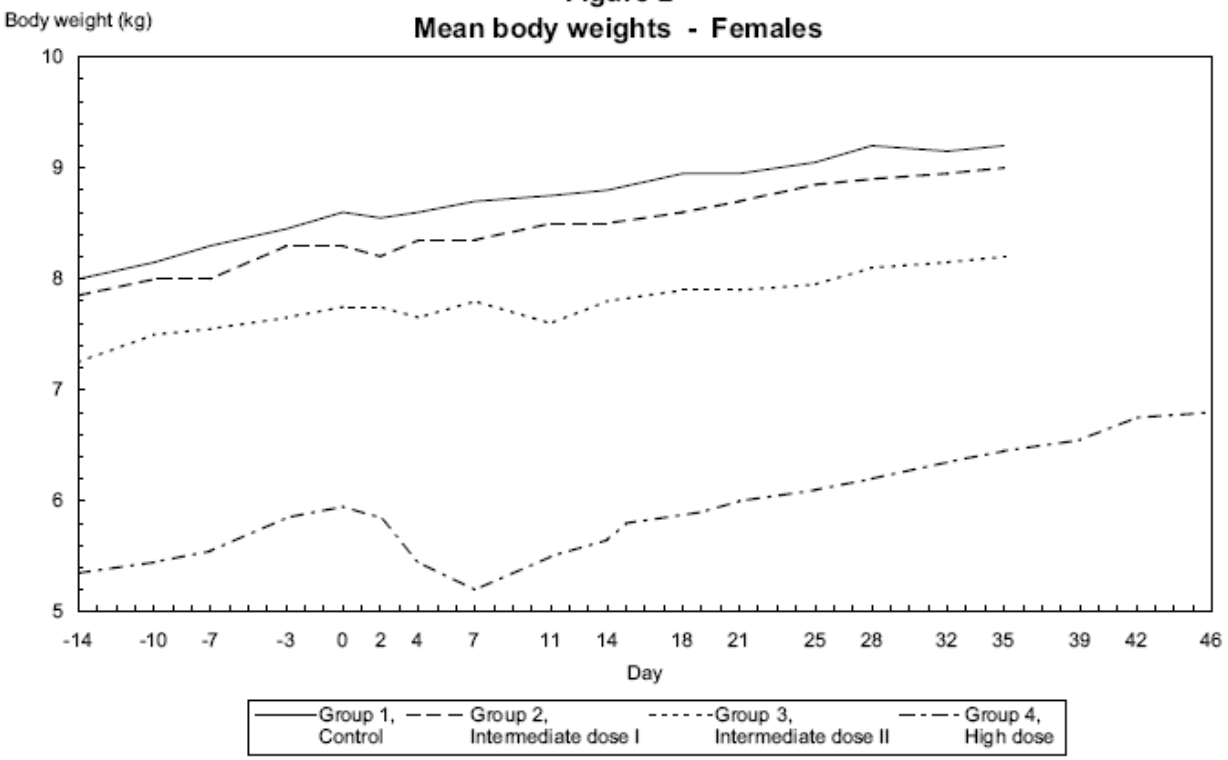


Figure 2
Mean body weights - Females



Mean Terminal Plasma TK Parameters (DM/Q)*

Dextromethorphan					
Study Day	**DM/Q Dose (mg/kg/day)**	**Sex**	**AUC_{0-t} (ng•hr/mL)**	**C_{max} (ng/mL)**	**Half-life (hr)**
33	6/4	M	136	41	1.4
		F	180	44	1.6
33	12/8	M	533	128	3.8
		F	491	126	2.1
46	12/12	M	410	102	2.6
		F	369	82	3.1
Quinidine					
Study Day	**DM/Q Dose (mg/kg/day)**	**Sex**	**AUC_{0-t} (µg•hr/mL)**	**C_{max} (µg/mL)**	**Half-life (hr)**
33	6/4	M	5.0	1.1	2.4
		F	8.5	1.4	3.0
33	12/8	M	15	1.7	5.0
		F	8.4	1.3	3.3
46	12/12	M	40	4.3	5.2
		F	40	4.1	4.0

*Dextrorphan parameters not calculated in most instances due to insufficient samples with quantifiable drug levels

8 Carcinogenicity

Study title: Dextromethorphan/Quinidine: A 24-Month Oral (Gavage) Carcinogenicity Study in Rats

Study no.:	DMQ-120 (03-2801)
Study report location:	Electronic (EDR)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	10 July 2003
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	DM, lot DM0302015, 99.6% purity; Q, lot 4963, 100.8% purity
CAC concurrence:	Yes (ECAC meeting minutes, 12 June 2003)

Key Study Findings

- The incidences of benign adenomas and of adenomas plus carcinomas in the pars distalis of the pituitary were statistically significantly increased between Group 4 (50/100, DM/Q) males and females compared to controls. Comparisons of Group 4 versus Group 5 (50/0, DM/Q) and of Group 6 (0/100, DM/Q) versus controls also attained statistical significance in the males, but not in females. No other neoplastic findings attained statistical significance.
- Survival was decreased in all treated groups relative to controls and the study was terminated after 23 months due to excessive mortality.
- Cage sores/lesions were observed on the paws of a number of treated and control animals and were attributed as the cause for humane sacrifice of many of these animals.
- Mean body weights in Group 4 males were significantly decreased relative to those of control animals throughout most of the study (-14% at Week 78); body weights of other treated groups of both sexes did not differ meaningfully from controls.
- An increased incidence of gross lung discoloration was apparent in treated animals versus controls.
- Notable non-neoplastic findings were confined largely to the following: chronic abscesses/pyogranulomas, which appeared to be associated with bacterial colonies consistent with Staphylococcal infections (Botryomycosis); apparent dose-related increases in severity of alveolar macrophages observed in the lungs of all study animals; an increased incidence of histiocytic infiltration in lymph node tissue of drug-treated animals as compared to controls; accumulation of brown pigment (positive for lipofuscin) in the centrilobular hepatocytes of female rats only and of intralumenal pigment (positive for bile pigments) most prominently in male rats; and an absence of any apparent dose-related increase in cellular hyperplasia in the pars distalis of the pituitary gland.

- TK analyses suggest that exposure of female and male rats to dextromethorphan increased with increasing doses of dextromethorphan and, generally, in a greater than or approximately equal to dose proportional fashion. Dextrorphan exposure also increased with increasing doses of dextromethorphan. The data appear to confirm that quinidine treatment increased systemic exposure to dextromethorphan. It is also evident that systemic dextromethorphan exposure was generally less in males than that in females, while dextrorphan exposure was approximately equal between the sexes.

Adequacy of Carcinogenicity Study

The 24-month carcinogenicity study on dextromethorphan in combination with quinidine in Crl:CD (SD)IGS BR rats used an adequate number of animals and parameters evaluated. The doses were based on the results of a 26-week dose range-finding toxicity study in male and female Ico:OFA.SD ((b) (4)) Sprague Dawley rats, in which dextromethorphan hydrobromide (DM) at 5, 20, and 50 mg/kg/day in combination with quinidine sulfate (Q) at 100 mg/kg/day were administered by oral gavage. Based on increased organ weight and tissue histopathology findings in liver and kidney at all doses, 50 mg/kg/d dextromethorphan and 100 mg/kg/day quinidine were considered to be the maximum tolerated doses (MTDs). Agency concurrence for the study protocol, including the use of the Sprague Dawley rat model and the dosing regimen, was provided (ECAC meeting, 12 June 2003). Toxicokinetic analyses confirmed that animals were exposed to dextromethorphan, dextrorphan, and quinidine at Weeks 1, 4, 13 and 26. MTD values were confirmed in the carcinogenicity study by decreased body weight (HD males) and decreased survival in all drug-treated groups versus controls.

Appropriateness of Test Models

The Crl:CD_(SD)IGS BR VAF/Plus_ strain is an appropriate model for this study, because historical data are available for this strain in the proposed testing facility, and the strain shows good long-term survival and few spontaneously occurring tumors. The proposed route of administration (oral) is the intended route of clinical exposure. The study design for testing the drugs dextromethorphan and quinidine separately and in combination is appropriate.

Evaluation of Tumor Findings

Statistical analysis with adjustment for time of death (Peto analysis, at 0.01 level for common tumors) were performed by both the sponsor and CDER's Office of Biostatistics, though pair-wise comparisons evaluated were not uniformly the same between the two analyses. The two analyses were alike in indicating that a statistically significant increase in the adjusted incidence of benign adenomas and also the incidence of adenomas plus carcinomas was apparent in the pars distalis of the pituitary between Group 4 (50/100, DM/Q) males and females versus controls. The analyses also found comparisons of Group 4 versus Group 5 (50/0, DM/Q) males and of Group 6 (0/100, DM/Q) versus controls to be statistically significant; neither of the latter

comparisons was significant in females. The analyses suggest that tumors developed earlier in the specified treatment groups than in the control groups, given that the absolute numbers of pituitary neoplasms were comparable for all groups and the incidences in Group 4 males and females and Group 6 females were actually lower than in the respective control groups. There was no apparent increase in pituitary neoplasms in animals of either sex treated with dextromethorphan alone. The data also suggest that the statistical significance of the combined adenomas and carcinomas was primarily a function of the statistical significance from comparisons with the adenomas alone, since the incidences of carcinomas were very low and were comparable across the treatment groups.

Methods

Doses:	See sponsor's summary table below
Frequency of dosing:	Once daily for up to 23 months (see further discussion under Mortality section below)
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	1% Methylcellulose in water
Basis of dose selection:	MTD (see ECAC meeting minutes of 12 June 2003)
Species/Strain:	Rat, Albino VAF/Plus® Sprague-Dawley – derived (CD®) Crl:CD (SD)IGS BR ((b) (4))
Number/Sex/Group:	See sponsor's summary table below
Age:	Approximately 6 weeks at initiation of dosing
Animal housing:	Individually in elevated, stainless steel, wire mesh cages or in solid bottom plastic "shoe-box" cages
Paradigm for dietary restriction:	None; water and Certified Rodent Diet No. 5002 available ad libitum
Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	See sponsor's summary table below
Deviation from study protocol:	No protocol deviations that compromised the validity or integrity of the study were reported.

	Daily Doses[a]					Number of Animals							
	Dose (mg/kg)		Volume (mL/kg)	Concentration (mg/mL)		Main		Toxicokinetic[b]		Necropsy (Termination)		Microscopic Pathology	
Group	DM	Q		DM	Q	M	F	M	F	M	F	M	F
1	0	0	5	0	0	60	60	9	9	31	28	60	60
2	5	100	5	1	20	60	60	9	9	14	18	60	60
3	20	100	5	4	20	60	60	9	9	10	12	60	60
4	50	100	5	10	20	60	60	9	9	9	14	60	60
5	50	0	5	10	0	60	60	9	9	24	19	60	60
6	0	100	5	0	20	60	60	9	9	14	17	60	60

[a]Doses represent active ingredient.

[b]Samples were collected for toxicokinetic analysis on 4 occasions during the first 26 weeks of treatment (on the day of the first dose and at the end of 4, 13 and 26 weeks). Animals were euthanized, without necropsy examination, after the final blood collection.

DM – Dextromethorphan Q – Quinidine

M = Male F = Female

mg/kg = milligrams of test article per kilogram of body weight
mL/kg = milliliters of test/control article formulation per kilogram of body weight
mg/mL = milligrams of test article per milliliter of vehicle

Observations and Results

2.6.7.10 *(A)* Carcinogenicity

Report Title: Dextromethorphan/Quinidine: A 24-Month Oral (Gavage) Carcinogenicity Study in Rats

Test Articles: Dextromethorphan/Quinidine (DM/Q)

Species/Strain: Albino Rats (Outbred) VAF/Plus® Crl: CD (SD) ICS BR
Initial Age: Approx. 6 weeks
Date of First Dose: 10 July 2003

Duration of Dosing: 23 months

Method of Administration: Oral gavage
Vehicle/Formulation: Aqueous 1% methylcellulose
Treatment of Controls: One vehicle treated group

Study No.: 03-2801

Location in CTD: Vol. Page

GLP Compliance: Part 58 of 21 CFR (FDA Good Laboratory Practice Regulations)

Basis for High Dose Selection: The highest dose (50/100 mg/kg/day of DM/Q) is considered to be the maximum dose of the combination that will be tolerated for 2 years. This is based on results of short-term studies (1 to 14 days) that indicated that this dose combination represents an approximate maximum tolerated dose (MTD) level for rats, and that higher doses would not be tolerated. Two hundred (200) mg/kg/day of DM (with no Q) produced severe CNS toxicity after a single dose, including mortality, as did 100 mg/kg/day of DM in the presence of CYP2D1 inhibitory levels of Q. The ratio of Q to DM is higher than the 1:1 ratio used in humans because the action of Q on DM in rats is less efficient than in humans. Based on previous studies, a dose of 100 mg/kg/day of Q was considered appropriate for this study.
Special Features: This study included satellite groups (9/sex/dose group) for toxicokinetic measurements.

Daily Dose (mg/kg/day)	**0 (Untreated)**		**5/100 (DM/Q)**		**20/100 (DM/Q)**		**50/100 (DM/Q)**		**50 (DM)**		**100 (Q)**	
Gender	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Toxicokinetics: $AUC_{0\text{-}24h}$ (ng•h/mL)												
Dextromethorphan												
Week 1 (first dose)	0	0	14.7	61.6	229	373	411	1390	289	605	-	-
Week 4	0	0	65.1	207	396	879	1360	2400	309	1480	-	-
Week 13	0	0	110	138	581	615	1610	3860	557	1990	-	-
Week 26	0	0	191	201	815	1000	1980	2610	880	2870	-	-
Dextrorphan												
Week 1 (first dose)	0	0	2780	3050	8670	8600	20700	18300	16900	18200	-	-
Week 4	0	0	4600	3670	11500	12400	27800	29200	15300	31200	-	-
Week 13	0	0	4390	4410	15600	14000	38200	42600	23000	28500	-	-
Week 26	0	0	5130	4220	15800	14500	28500	24500	34200	33000	-	-
Quinidine												
Week 1 (first dose)	0	0	9290	15300	11300	13000	11800	13700	-	-	9380	14600
Week 4	0	0	26700	41700	25400	37900	27500	28800	-	-	23000	28800
Week 13	0	0	37900	40500	37200	32300	27800	33600	-	-	32900	34000
Week 26	0	0	50600	50700	45000	50500	47900	38500	-	-	55700	44900

2.6.7.10 *(A)* Carcinogenicity **Study No. (Continued):** 03-2801

Daily Dose (mg/kg/day)	0 (Untreated)		5/100 (DM/Q)		20/100 (DM/Q)		50/100 (DM/Q)		50 (DM)		100 (Q)	
Gender	M	F	M	F	M	F	M	F	M	F	M	F
Number of Animals												
At Start	60	60	60	60	60	60	60	60	60	60	60	60
Preterm Deaths[a]	28	32	46	40	49	47	51	46	33	38	46	40
Terminal Sacrifice	31	28	14	19	10	12	9	14	24	19	14	17
Survival (%)[a]	53	47	23	31	17	20	15	23	42	33	23	30
Number Evaluated	60	60	60	60	60	60	60	60	60	60	60	60
Noteworthy Findings												
Decreased Body Weight Gain	-	-	-	-	-	-	+	-	-	-	-	-
Histopathology												
Neoplasms – Overall Incidence												
Total primary neoplasms	72	127	73	121	68	117	54	97	62	98	80	102
Animals with one or more	51	56	52	55	47	57	39	50	42	53	51	49
Neoplasm – Pituitary Adenoma	34	45	39[b]	49[b]	40[b]	52[b]	32[b]	43[b]	30	43	44[b]	40
Non-neoplastic Findings												
Chronic abscesses/ pyogranulomas (Skin and other with bacterial colonies)	1	-	4	-	6	1	14	2	19	1	1	-
Increased severity of alveolar macrophages (Lung)	-	-	+	-	+	+	+	+	+	-	-	+
Increased sinusoidal histiocytes (Mesenteric Lymph Node)	7	8	13	18	16	21	22	20	23	15	16	19
Histiocytic granulomas (Lymph Nodes)	3	2	12	15	18	17	15	13	8	6	23	11
Hepatocellular pigment (Liver)	-	0	-	20	-	19	-	16	-	0	-	12
Bile duct pigment (Liver)	0	-	14	0	30	-	26	-	0	-	19	-

[a]Excludes accidental deaths.
[b]Significantly different from control when tumor prevalence was corrected for early mortality using the Peto method of statistical analysis.
+ Effect present - No effect

Page 11

Mortality

Observed twice daily. Survival was decreased in all treated groups relative to controls and the study was terminated after 23 months due to excessive mortality. In addition, based on guidance communicated to the sponsor (see IND 56,954 communication, issue date 19 Nov 2004), dosing was terminated prior to terminal sacrifice in several groups, the earliest being Group 4 males (dosing terminated after 82 weeks; see sponsor's study date summary reproduced below). Also reproduced below from the sponsor's submission is a tabular summary of mortality and cause of death data, followed by several tables generated by this reviewer that further characterize study mortality, including deaths judged to have been accidental by the sponsor. As noted, deaths judged to be accidental by the sponsor have been excluded from the sponsor's mortality calculations. Based upon the fact that survival through 78 weeks on study had fallen below 50% only in Group 3 and 4 males and, except in these same two groups, survival was still at 35% or higher after 91 weeks on study (≥60% in controls), it would appear that overall survival for this study would be considered adequate according to Agency guidance.[1] At the end of this section are the Kaplan-Meier survival curves for male and female rats, respectively, as reproduced directly from the CDER statistical reviewer's review (S. Thomson, issued 28 March 2008).

2.2.3. DOSING INITIATION

Carginogenicity Study: 10 July 2003 (Experimental Start Date)

Toxicokinetic Study: 7 August 2003

2.2.4. DOSING TERMINATION

	Males	Females
Group 1	8 June 2005	8 June 2005
Group 2	22 May 2005	8 June 2005
Group 3	31 May 2005	29 April 2005
Group 4	3 February 2005	8 May 2005
Group 5	8 June 2005	8 June 2005
Group 6	8 June 2005	8 June 2005

2.2.5. TERMINAL SACRIFICE

31 May, 1, 2, 3, 6, and 9 June 2005

[1] Guidance for Industry Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals, FDA/CDER, 2001 [DRAFT]

Table 3.3-1
Mortality and Cause of Death Summary

	Males						Females					
	mg/kg/day (DM/Q)						mg/kg/day (DM/Q)					
Dose Level:	0/0	5/100	20/100	50/100	50/0	0/100	0/0	5/100	20/100	50/100	50/0	0/100
Group	1	2	3	4	5	6	1	2	3	4	5	6
Total No.	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Potential Survivors[a]	59	60	59	60	57	60	60	58	59	60	57	57
No. Preterm Deaths[a]	28	46	49	51	33	46[b]	32[b]	40	47[b]	46[b]	38	40
No. Survivors	31	14	10	9	24	14	28	18	12	14	19	17
Diff. from Control	-	**	**	**	-	*	-	*	**	**	-	*
Diff. from Group 4	-	na	na	-	**	*	-	na	na	-	-	-
Percent Mortality[a]	**47**	**77**	**83**	**85**	**58**	**77**	**53**	**69**	**80**	**77**	**67**	**70**
Cause of Death (Preterm Deaths)												
Accidental	1	0	1	0	3	0	0	2	1	0	3	3
Undetermined	2	6	5	11	2	6	0	2	1	4	2	5
Pituitary Neoplasm	14	25	25	19	10	27	11	28	32	26	17	24
Mammary Neoplasm	0	1	0	0	0	0	12	7	6	6	12	8
Chronic Nephropathy	2	6	3	2	3	4	0	0	0	0	0	1
Other	10	8	16	19	18	9	9	3	8	10	7	2

[a]Accidental deaths are not included in potential survivors, no. of preterm deaths or percent mortality

[b]Minor difference from numbers used in mortality analysis (See Table 10)

DM - Dextromethorphan Q – Quinidine

Significantly different * $p < 0.05$ ** $p \leq 0.001$ na – not analyzed

Animal Termination Summary

	Type of Death*				
Group/Sex	**Terminal Sac**	**Moribund Sac**	**Humane Sac**	**Found Dead**	**Accidental**
1/M	31	17	8	3	1
2/F	28	12	17	2	0
2/M	14	20	8	18	0
2/F	18	20	7	13	2
3/M	10	20	10	19	1
3/F	12	26	12	9	1
4/M	9	17	9	25	0
4/F	14	22	13	11	0
5/M	24	17	8	8	3
5/F	19	12	14	12	3
6/M	14	26	7	13	0
6/F	17	18	11	11	3

*Extracted from sponsor's submission, Appendix B, pgs. 993-1016

Accidental Deaths Details

Group No.	Animal No./Sex	Death Week/Day	Death Details: Pathology Report Probable COD, plus Relevant Clinical Observations and/or Necropsy Findings
1	1076/M	82/568	“Intubation Error”; slight lung congestion, slight acute mucosal inflammation of trachea/larynx
2	2564/F	14/92	“Nasoturbinal Bone Fracture”; moderate snout bone fracture; moderate multifocal lung hemorrhages; moderate nasal mucosa hemorrhage, erosion, and acute inflammation
2	2586/F	66/457	“Intubation Error”; moderate lung congestion and slight multifocal hemorrhages/hematocysts/acute inflammation; moderate trachea/larynx mucosal erosion with inflammatory cells/debris in lumen
3	3058/M	33/226	“Nasoturbinal Bone Fracture”; severe red discolored snout; moderate edema and hemorrhage of nasal turbinate soft tissue
3	3548/F	23/158	“Nasoturbinal Bone Fracture”; severe red snout with bone fracture; moderate lung edema and slight multifocal hemorrhages/inflammation
5	5036/M	50/344	“Intubation Error”; moderate lung congestion with moderate acute inflammation; foreign material in bronchiolar lumen
5	5070/M	41/283	“Intubation Error”; perforated distal esophagus/”on bronchi site”; slight lung congestion
5	5084/M	8/53	“Intubation Error”; perforated distal esophagus; minimal multifocal lung hemorrhages/hematocysts
5	5541/F	20/133	“Nasoturbinal Bone Fracture”; moderate nose/turbinates bone fracture with moderate nasal mucosa hemorrhage
5	5570/F	41/286	“Nasoturbinal Bone Fracture”; severely swollen snout, moderate left snout bone fracture with moderate nasal mucosa hemorrhage and inflammatory cells/debris in nasal lumen
5	5579/F	17/113	“Intubation Error”; trachea/larynx with slight edema, mucosal erosion, and inflammation, and moderate inflammatory cells/debris in lumen
6	6545/F	6/40	“Intubation Error”; perforated distal esophagus; slight abnormal thick red fluid in thoracic cavity
6	6551/F	20/136	“Intubation Error”; severe perforated proximal esophagus; moderate lung congestion
6	6578/F	62/433	“Intubation Error”; moderate abnormal thin red fluid in thoracic cavity; perforated proximal esophagus; severe red discoloration of all lung lobes with moderate congestion

Deaths and Survival Percentages Summary

	Weeks 1-50		Weeks 51-78		Weeks 79-91		Weeks 92-98		Weeks 99-101	
Group/Sex	**Deaths**	**Cum%Surv**	**Deaths**	**Cum%Surv**	**Deaths**	**Cum%Surv**	**Deaths**	**Cum%Surv**	**Deaths**	**%SurvTS**
1M	2	96.7%	9	81.7%	13	60.0%	5	51.7%	31	51.7%
2M	3	95.0%	24	55.0%	12	35.0%	7	23.3%	14	23.3%
3M	8	86.7%	23	48.3%	14	25.0%	5	16.7%	10	16.7%
4M	15	75.0%	26	31.7%	7	20.0%	3	15.0%	9	15.0%
5M	10	83.3%	12	63.3%	11	45.0%	3	40.0%	24	40.0%
6M	6	90.0%	18	60.0%	14	36.7%	6	26.7%	16	23.3%
1F	3	95.0%	8	81.7%	12	61.7%	8	48.3%	29	46.7%
2F	5	91.7%	16	65.0%	18	35.0%	3	30.0%	18	30.0%
3F	7	88.3%	22	51.7%	10	35.0%	8	21.7%	13	20.0%
4F	11	81.7%	16	55.0%	12	35.0%	6	25.0%	15	23.3%
5F	9	85.0%	14	61.7%	11	43.3%	7	31.7%	19	31.7%
6F	10	83.3%	17	55.0%	9	40.0%	7	28.3%	17	28.3%

Figure A.1.1 Kaplan-Meier Survival Curves for Male Rats

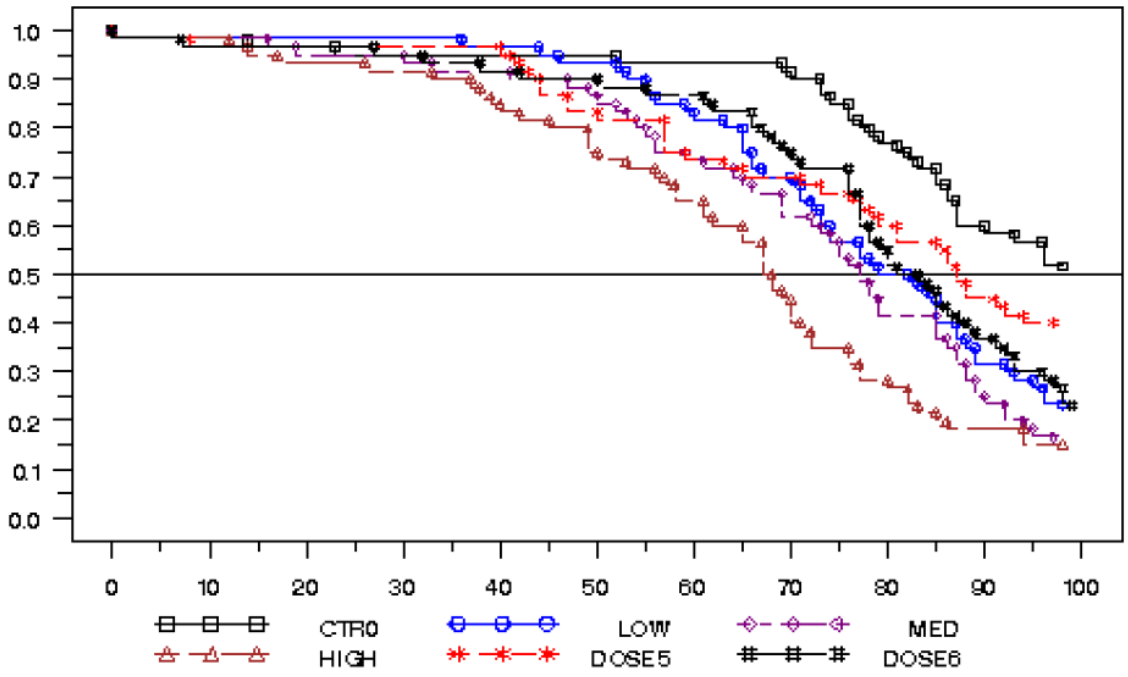
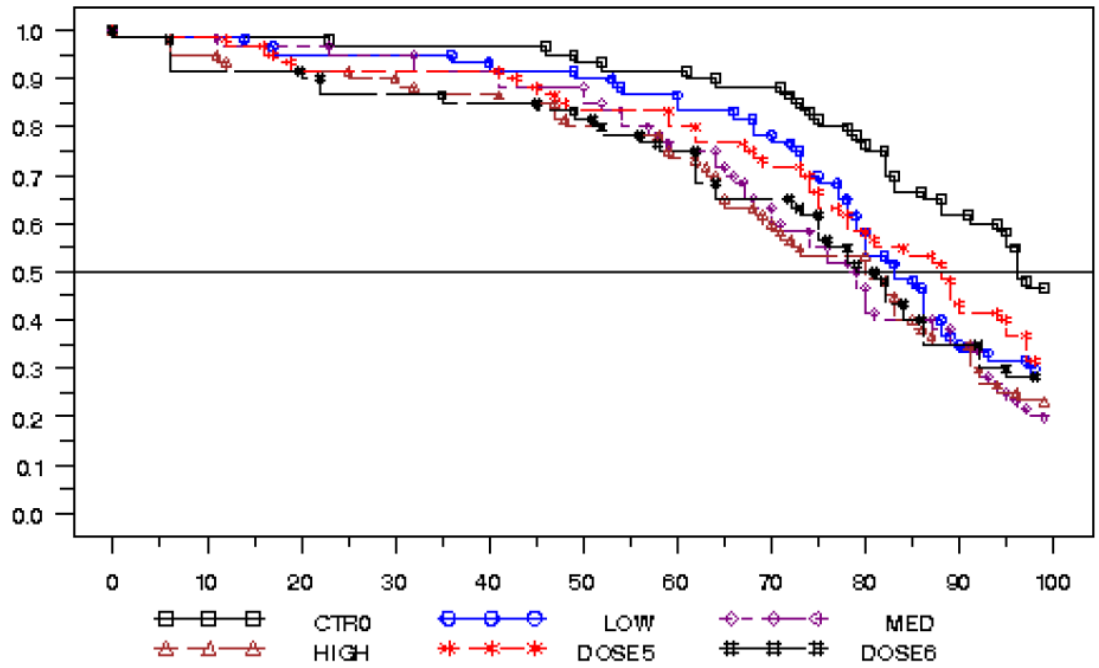


Figure A.1.2 Kaplan-Meier Survival Curves for Female Rats



Clinical Signs

Observed at baseline and then daily on study with physical exams weekly. Post-dosing salivation was observed in a high fraction of treated animals throughout most of the study, which was tentatively attributed by the sponsor to the bitter taste of quinidine. Cage sores/lesions were observed on the paws of a number of treated and control animals and were determined to be the cause for humane sacrifice of many of these animals. The number of animals with masses observed clinically while on study was greater among females than males and the incidences revealed no apparent dose-responsiveness to treatment, as summarized in the table below. Particularly among the males, many of these masses were correlated at necropsy with findings of abscesses/ pyogranulomas (see Histopathology below).

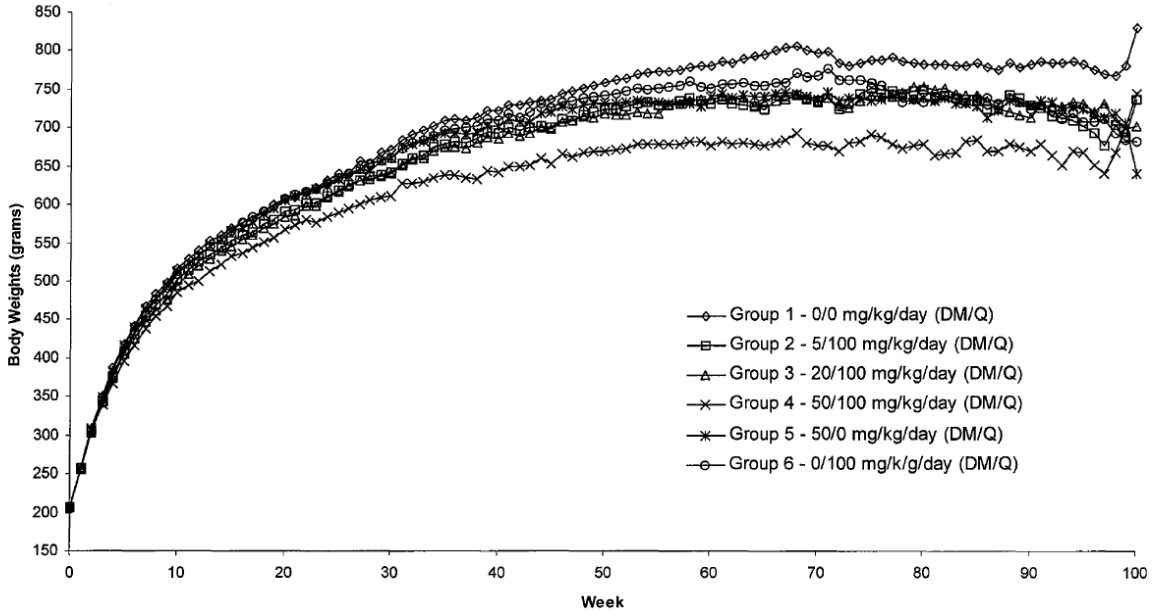
Incidence of Masses

	Group Number					
Sex	**1**	**2**	**3**	**4**	**5**	**6**
Males	22	31	26	38	39	20
Females	48	40	39	33	34	37

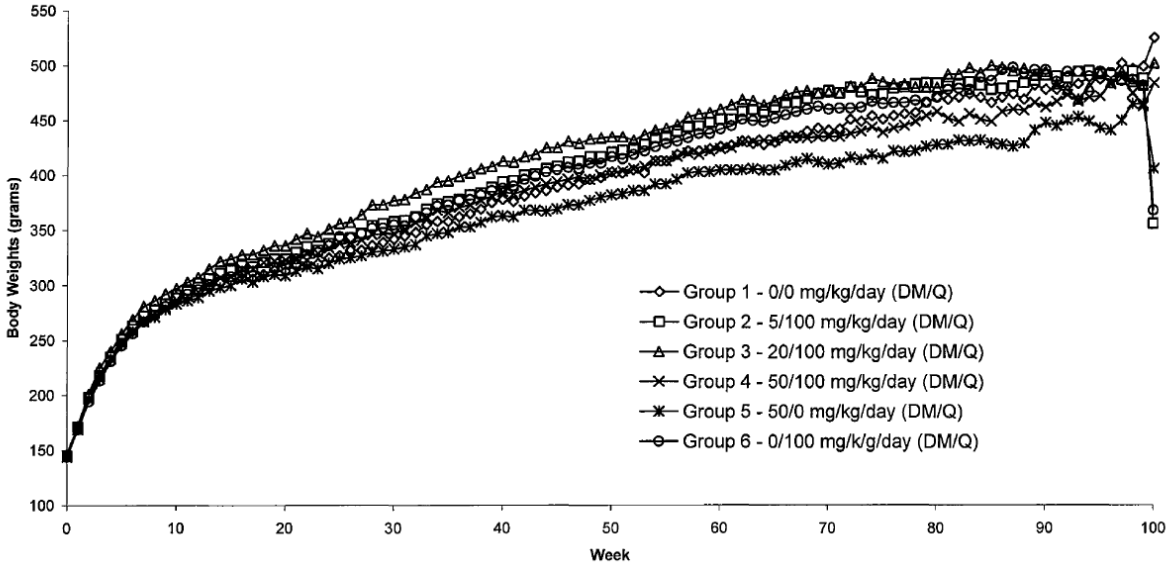
Body Weights

Recorded pretest and then weekly. Body weight curves from the sponsor's submission are reproduced below. A tabular summary of selected mean body weight values is provided for further perspective following the figures. It is evident that mean body weights among Group 4 males were significantly decreased relative to those of control animals throughout most of the study (-14% at Week 78); body weights of other treated groups of both sexes did not differ meaningfully from controls.

Males	Mean Body Weights (grams)	Figure 1



Females	Mean Body Weights (grams)	Figure 2



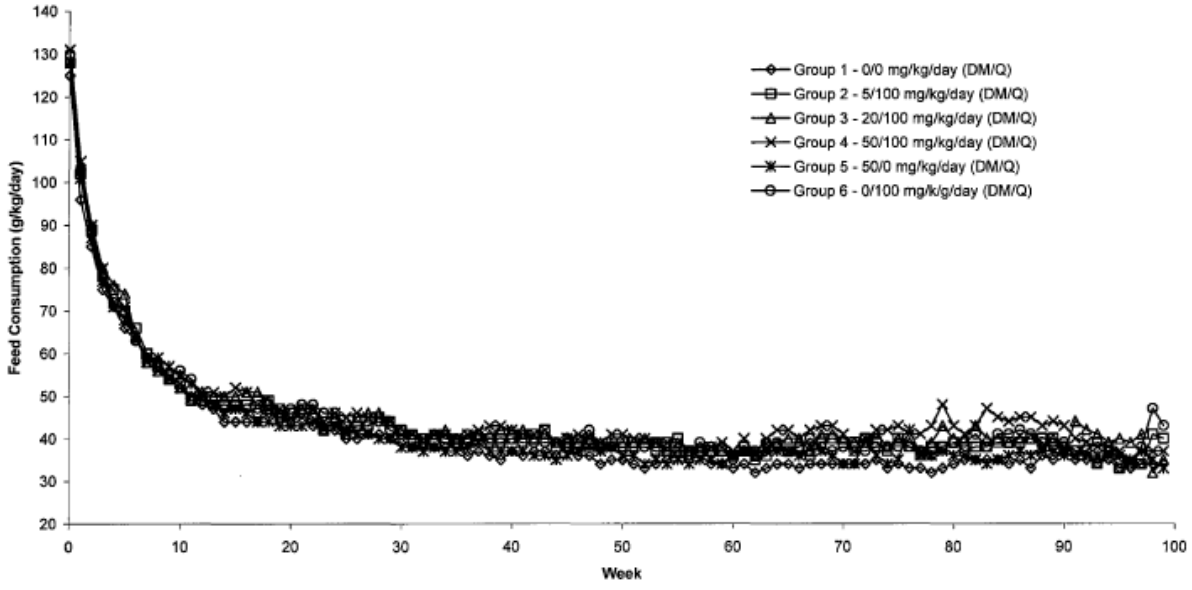
Selected Mean Body Weights (g)
(mean ± SD, n)

Sex/Week	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Males						
Week 0	206 ± 13.8 (60)	207 ± 10.9 (60)	207 ± 13.9 (60)	206 ± 13.1 (60)	206 ± 12.1 (60)	204 ± 12.7 (60)
Week 26	641 ± 63.0 (58)	625 ± 65.0 (60)	624 ± 64.1 (58)	594 ± 60.7 (56)	637 ± 65.4 (59)	641 ± 61.4 (59)
Week 52	764 ± 88.9 (58)	727 ± 82.3 (57)	717 ± 81.4 (51)	674 ± 71.8 (45)	733 ± 83.4 (50)	748 ± 80.3 (54)
Week 78	787 ± 102.4 (49)	744 ± 91.6 (34)	746 ± 75.4 (30)	674 ± 84.4 (19)	738 ± 104.8 (38)	734 ± 78.3 (37)
Females						
Week 0	146 ± 10.2 (60)	145 ± 10.2 (60)	146 ± 11.8 (60)	144 ± 10.6 (60)	145 ± 9.7 (60)	144 ± 10.7 (60)
Week 26	332 ± 40.7 (59)	343 ± 43.5 (58)	357 ± 53.8 (58)	339 ± 40.4 (55)	325 ± 34.6 (56)	343 ± 41.8 (54)
Week 52	405 ± 65.4 (57)	425 ± 81.2 (55)	432 ± 72.1 (51)	406 ± 70.4 (49)	386 ± 53.9 (51)	419 ± 70.3 (49)
Week 78	457 ± 82.5 (49)	483 ± 90.1 (39)	480 ± 66.1 (31)	449 ± 68.7 (33)	422 ± 60.2 (37)	468 ± 88.0 (33)

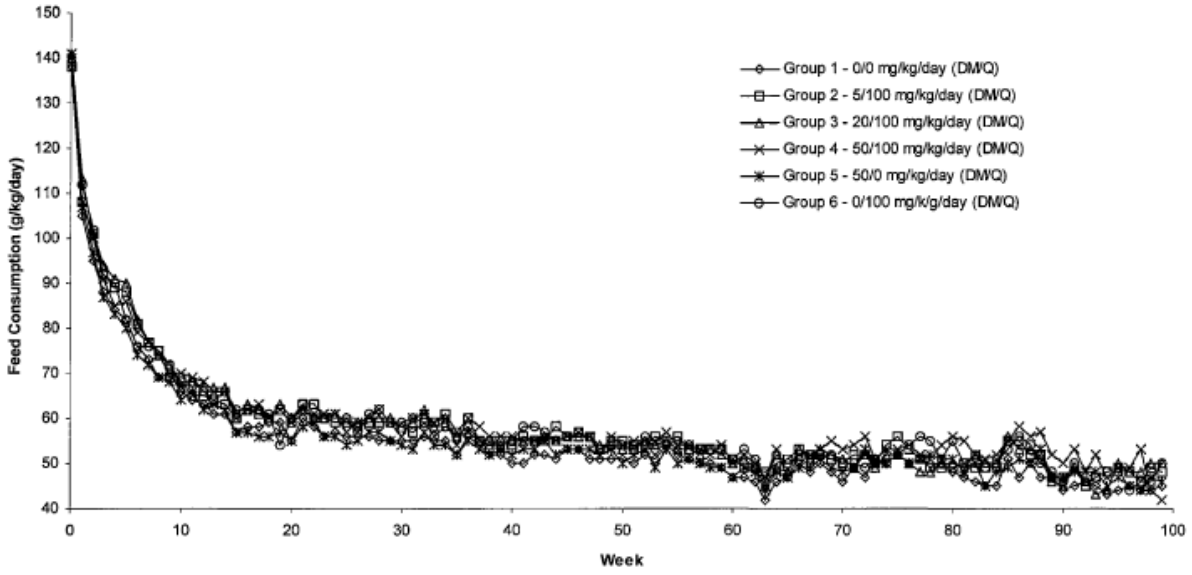
Feed Consumption

Measured at baseline and then weekly. Mean feed consumption among treated animals did not appear to differ significantly from that of control animals. These data are summarized graphically in figures reproduced below from the sponsor's submission.

Males	Mean Feed Consumption (g/kg/day)	Figure 3



Females	Mean Feed Consumption (g/kg/day)	Figure 4



Hematology

Blood collected via orbital sinus at terminal necropsy following overnight fast. Within the limitations of the reduced numbers of animals surviving to terminal necropsy, mean hematological parameters did not appear to differ meaningfully between treated and control animals.

Gross Pathology

Scheduled necropsy on all surviving carcinogenicity animals followed treatment for up to 23 months; complete macroscopic examinations were performed on these and all animals found dead or sacrificed moribund. A summary of notable gross necropsy observations is provided in the table below, sorted with respect to unscheduled deaths and terminal sacrifices.

Notable Gross Necropsy Observations: Males*

	Group 1 (n)		Group 2 (n)		Group 3 (n)		Group 4 (n)		Group 5 (n)		Group 6 (n)	
Observation	UD (29)	TS (31)	UD (46)	TS (14)	UD (50)	TS (10)	UD (51)	TS (9)	UD (36)	TS (24)	UD (46)	TS (14)
Brain, compressed	14	6	16	2	23	3	15	1	12	2	22	3
Brain, mass	0	0	0	0	0	0	0	0	0	0	0	0
Kidneys, enlarged	0	1	10	1	7	0	5	0	1	0	3	2
Liver, discolored	5	4	9	2	6	3	4	1	7	4	8	3
Liver, mass	0	1	1	3	0	1	2	0	0	1	2	0
Lungs, discolored	2	5	12	4	11	2	17	3	9	2	12	3
Lungs, mass	0	0	0	0	0	0	3	0	6	0	0	0
Pituitary gland, enlarged	0	0	2	0	5	0	2	1	2	3	1	2
Pituitary gland, mass	14	7	24	3	26	3	18	1	10	7	25	3
Skin, abscess	4	1	1	0	1	0	1	0	6	0	1	0
Skin, mass	3	3	1	0	4	3	10	0	6	4	1	1

*UD = unscheduled death; TS = terminal sacrifice

Notable Gross Necropsy Observations: Females*

	Group 1 (n)		Group 2 (n)		Group 3 (n)		Group 4 (n)		Group 5 (n)		Group 6 (n)	
Observation	UD (32)	TS (28)	UD (42)	TS (18)	UD (48)	TS (12)	UD (46)	TS (14)	UD (41)	TS (19)	UD (43)	TS (17)
Brain, compressed	18	10	28	7	30	4	19	5	19	3	24	7
Brain, mass	0	0	0	0	0	0	0	0	1	0	0	1
Kidneys, enlarged	0	0	1	1	3	1	0	0	0	0	2	1
Liver, discolored	4	4	0	3	4	2	3	2	6	6	5	2
Liver, mass	0	0	2	1	0	0	0	0	0	0	0	0
Lungs, discolored	3	1	7	7	9	4	11	5	7	4	9	8
Lungs, mass	2	0	0	0	0	0	0	0	0	1	0	0
Pituitary gland, enlarged	9	7	4	3	3	3	6	3	3	2	2	2
Pituitary gland, mass	19	12	30	12	37	5	25	7	21	9	26	9
Skin, abscess	3	1	1	1	1	2	3	0	2	0	1	1
Skin, mass	10	9	13	8	11	5	7	6	12	8	7	7

*UD = unscheduled death; TS = terminal sacrifice

Histopathology

Reproduced below from the sponsor's submission is a listing of tissues collected into 10% neutral buffered formalin and examined microscopically from all carcinogenicity study animals.

adrenal glands	lungs (with mainstem bronchi)	stomach
aorta (thoracic)	lymph nodes (mesenteric, mediastinal)	testes
bone marrow smear (rib)[a]	mammary gland	thymus
bone (sternum, femur)	nerve (sciatic)	thyroid/parathyroid glands
bone marrow (sternum, femur)[a]	ovaries	trachea
brain (medulla, pons, cerebrum and cerebellum)	pancreas	urinary bladder
epididymides	pituitary gland	uterus (body/horns) with cervix
esophagus	prostate gland	vagina
eyes with optic nerve	salivary glands (submandibular)	Zymbal's gland
Harderian gland	seminal vesicles	tissues with macroscopic findings including tissue masses
heart	skeletal muscle (Biceps femoris)	
kidneys	skin	
lacrimal glands	small intestine (duodenum, ileum, jejunum)	
large intestine (cecum, colon, rectum)	spinal cord (cervical, thoracic, lumbar)	
liver	spleen	

[a]Qualitative examination (no differential count).

Peer Review

Yes, by (b) (4) "A microscopic peer review was performed as follows for this study: All diagnoses were reviewed for pituitary, skin, lungs, lymph nodes (mesenteric and mediastinal), liver and bone marrow from all animals in Groups 1, 4, 5, and 6. All pituitary diagnoses and diagnoses of neoplasms in the skin, lungs, lymph nodes (mesenteric and mediastinal), liver, and bone marrow samples from animals in Groups 2 and 3 were reviewed."

Neoplastic

Reproduced below from the sponsor's submission is a summary of the overall incidence of primary neoplasms observed during the study, indicating the incidences were generally comparable between control- and drug-treated animals.

Table 3.8.2-1
Overall Incidence of Neoplasms

	Males						Females					
Dextromethorphan mg/kg/day	0	5	20	50	50	0	0	5	20	50	50	0
Quinidine mg/kg/day	0	100	100	100	0	100	0	100	100	100	0	100
Number of rats examined	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Total primary neoplasms	72	73	68	54	62	80	127	121	117	97	98	102
Animals with one or more	51	52	47	39	42	51	56	55	57	50	53	49

On the pages that follow is a reviewer-generated tabulation of selected neoplastic findings sorted by tissue. Based on statistical analysis (Peto) conducted by both the sponsor (see sponsor's summary table of pituitary neoplastic findings and laboratory historical control data, reproduced below) and the CDER Office of Biostatistics (see summary table excerpted below from the full statistical review, S. Thomson, issued 28 March 2008), there was a statistically significant increase in neoplasms of the pars distalis of the pituitary gland, both benign adenomas, as well as combined adenomas and carcinomas. Other neoplastic findings were observed either sporadically or with comparable incidence in vehicle- and drug-treated groups. These other neoplastic findings were considered to be incidental to the strain and age of rat. There were no other statistically significant differences in incidence.

Sponsor's Analysis Summary:

Table 3.8.2-2
Incidence of Pituitary (*Pars Distalis*) Adenomas and Carcinomas

	Males						Females					
Group	1	2	3	4	5	6	1	2	3	4	5	6
Dextromethorphan mg/kg/day	0	5	20	50	50	0	0	5	20	50	50	0
Quinidine mg/kg/day	0	100	100	100	0	100	0	100	100	100	0	100
Number of rats examined	**59**	**60**	**59**	**60**	**60**	**59**	**60**	**59**	**59**	**60**	**60**	**60**
No. with adenoma	34	39	40	32	30	44	45	49	52	43	43	40
Incidence (%)	58	65	68	54	50	75	75	83	88	72	72	67
Statistical significance												
vs. Control	-	*	**	**	-	**	-	*	**	*	-	-
vs. Group 4	-	-	-	-	*	-	-	-	-	-	-	-
No. with carcinoma	1	0	1	1	3	0	3	2	1	3	1	3
Total (adenoma + carcinoma)	35	39	41	33	33	44	48	51	53	46	44	43
Statistical significance												
vs. Control	-	*	**	**	-	**	-	*	**	**	-	-
vs. Group 4	-	na	na	-	*	-	-	na	na	-	-	-

Significantly different (with Peto adjustment) *p<0.01, **p≤0.001, na-not analyzed, - no statistical significance

Table 3.8.2-3
Historical Control Incidence of Pituitary (*Pars Distalis*) Adenomas

Source		Number	Mean %	Range (%)
[redacted] (b) (4) (6 studies)	Males	198/465	43%	22-58%
	Females	306/468	65%	52-78%
[redacted] (b) (4) (30-31 studies)	Males	1002/3128	47%	1-70%
	Females	1662/2343	71%	26-93%

CDER Statistical Reviewer Analysis Summary:

Table 2. Potentially Statistically Significant Neoplasms in Rats[#]

	Incidence: Ctrl	Low	Med	High	Dose5	Dose6	p-values: Trend	Hi vs 6/
				Hi vs 5	Hi vs C	5 vs C		6 vs C
Male Rats								
Pituitary gland								
B-PARS DISTALIS-ADENOMA	34	39	40	32	30	44	0.3595	0.4555
				0.0022*	<0.0001*		0.3756	<0.0001*
Pars Dist. Adenoma,Carcinoma	35	39	41	33	33	44	0.2643*	0.3626*
				0.0055*	<0.0001*		0.2079	<0.0001*
Female Rats								
Pituitary gland								
B-PARS DISTALIS-ADENOMA	45	49	52	43	43	40	0.2159	0.2203
				0.0563	0.0014*		0.1069	0.0201
Pars Dist. Adenoma,Carcinoma	48	51	53	46	44	43	0.1990	0.2269
				0.0141	0.0006*		0.2274	0.0151

[#] Analyzed using SAS PROC MULTTEST.
* Statistically significant comparison at a rough 0.10 (10%) level or more

Summary of Potentially Noteworthy Neoplastic Findings from Microscopic Analyses (Incidence)

	Males						Females					
Tissue/Observation	**Vehicle**	**5/100***	**20/100***	**50/100***	**50/0***	**0/100***	**Vehicle**	**5/100**	**20/100**	**50/100**	**50/0**	**0/100**
Adrenal Glands (n)	60	60	60	60	60	60	60	60	58	60	60	60
-B-Cortex, adenoma	0	1	0	1	0	1	0	1	2	2	1	1
-B-Medulla, benign neoplasm	2	4	2	3	3	4	1	2	2	1	0	2
-M-Cortex, carcinoma	0	0	0	1	0	0	1	1	2	0	0	0
-M-Medulla, malignant neoplasm	0	0	0	1	0	0	0	0	0	0	1	1
Brain (n)	60	60	60	59	60	60	60	60	59	60	60	59
-M-Mixed glioma	0	1	0	0	2	0	0	0	0	0	0	1
Kidneys (n)	60	60	60	60	60	60	60	60	59	60	60	60
-M-Nephroblastoma	0	0	0	0	0	0	0	0	0	0	2	0
-M-Mesenchymal tumor	0	0	0	0	0	1	0	0	0	0	0	0
Liver (n)	60	60	60	60	60	60	60	60	59	60	60	60
-B-Hepatocellular adenoma	2	4	2	2	0	0	2	4	3	2	0	1
-M-Hepatocellular carcinoma	1	2	1	0	1	1	0	1	1	0	0	0
-M-Hemangiosarcoma	0	0	0	0	1	0	0	0	0	0	0	0
Lymph/Retic System (n)	60	60	60	60	60	60	60	60	60	60	60	60
-M-Histiocytic sarcoma	1	2	0	1	2	0	0	0	1	0	1	0
-M-Malignant lymphoma	0	1	1	0	1	0	0	0	0	0	0	0
-M-Granulocytic leukemia	0	1	0	0	0	0	0	2	0	0	0	0
Mammary (other) (n)	1	3	2	0	1	1	36	29	22	17	24	20
-B-Fibroadenoma	0	1	0	0	0	0	16	16	12	14	13	13
-M-Adenocarcinoma	0	0	0	0	0	0	19	10	7	2	13	6
Mammary-protocol (n)	46	47	48	46	49	43	59	60	58	59	59	60
-B-Fibroadenoma	0	0	1	0	0	0	6	7	3	7	5	5

	Males						Females					
Tissue/Observation	**Vehicle**	**5/100***	**20/100***	**50/100***	**50/0***	**0/100***	**Vehicle**	**5/100**	**20/100**	**50/100**	**50/0**	**0/100**
-M-Adenocarcinoma	0	0	0	0	0	0	7	2	4	4	3	3
Pancreas (n)	60	60	60	60	59	60	60	60	59	60	60	60
-B-Islet cell adenoma	1	3	1	1	2	7	1	2	4	0	0	2
-M-Islet cell carcinoma	1	1	3	1	0	2	1	1	3	1	1	0
Parathyroid (n)	47	47	48	50	53	52	52	48	50	52	51	51
-B-Adenoma	2	3	2	1	1	2	2	1	0	1	0	1
Pituitary Gland (n)	59	60	59	60	60	59	60	59	59	60	60	60
-B-Pars distalis, adenoma	33	39	40	32	30	44	45	49	52	43	43	40
-M-Pars distalis, carcinoma	2	0	1	1	3	0	3	2	1	3	1	3
Prostate (n)	60	59	60	60	60	60	-	-	-	-	-	-
-B-Adenoma	0	0	0	0	1	1	-	-	-	-	-	-
Skin (other) (n)	15	12	17	15	25	11	34	28	25	24	27	27
-B-Keratoacanthoma	3	2	3	2	4	1	0	0	0	2	1	2
-B-Squamous cell papilloma	0	0	0	0	1	2	0	0	0	0	0	0
-B-Fibroma	1	0	1	0	0	0	0	0	0	0	0	0
-M-Fibrosarcoma	1	2	1	0	1	2	5	0	1	1	1	1
Skin, protocol (n)	59	60	60	59	60	60	59	60	59	59	59	60
-M-Fibrosarcoma	0	0	0	0	0	1	1	0	0	0	0	1
Testes (n)	60	60	60	60	60	60	-	-	-	-	-	-
-B-Interstitial cell tumor	1	0	1	0	0	2	-	-	-	-	-	-
Thymus (n)	59	59	58	59	58	58	59	58	58	60	59	60
-B-Benign thymoma	1	0	0	1	0	0	0	1	0	1	0	0
-M-Malignant thymoma	0	0	1	0	0	0	0	0	0	0	0	0
Thyroid Gland (n)	60	60	59	60	60	60	60	59	59	60	60	60
-B-Follicular cell adenoma	1	1	0	0	1	2	1	0	1	1	0	1
-B-C-cell adenoma	4	3	4	2	2	4	2	4	5	3	2	2
-M-Follicular cell carcinoma	0	0	1	0	0	0	0	0	0	0	1	0
-M-C-cell carcinoma	0	0	0	0	0	0	2	0	0	0	0	0

	Males						Females					
Tissue/Observation	**Vehicle**	**5/100***	**20/100***	**50/100***	**50/0***	**0/100***	**Vehicle**	**5/100**	**20/100**	**50/100**	**50/0**	**0/100**
Uterus (n)	-	-	-	-	-	-	60	60	59	60	60	60
-B-Endometrial stromal polyp	-	-	-	-	-	-	2	2	4	3	0	5
-M-Squamous cell carcinoma	-	-	-	-	-	-	0	0	0	1	0	0
-M-Endometrial stromal sarcoma	-	-	-	-	-	-	0	0	0	0	1	0
-M-Fibrosarcoma	-	-	-	-	-	-	0	0	1	1	0	0
Vagina (n)	-	-	-	-	-	-	60	60	59	59	60	60
-M-Fibrosarcoma	-	-	-	-	-	-	0	1	0	0	0	0

*Dose = mg/kg/day, DM/Q

Non Neoplastic

On the pages that follow is a reviewer-generated tabulation of selected non-neoplastic findings sorted by tissue. Certain aspects of these findings are further elaborated upon by selected summary tables reproduced below from the sponsor's submission. These include a summary of tissues with chronic abscesses/pyogranulomas, which appeared to be associated with bacterial colonies consistent with Staphylococcal infections (Botryomycosis). The findings in male rats suggested a relationship to dextromethorphan dose and generally varied in severity from minimal to marked. The sponsor acknowledges that literature reports of such infections in laboratory rats are uncommon and that they have no explanation for the apparent association between dextromethorphan administration and incidence of the infections in male rats. The sponsor does note that "there was no evidence of immunological compromise in the lymphoid tissues or in the circulating white blood cell count of the dextromethorphan-treated groups of animals and no evidence of susceptibility of these animals to any other type of infection."

Table 3.8.2-3
Incidence of Chronic Abscesses/Pyogranulomas

	Males						Females					
Dextromethorphan mg/kg/day	0	5	20	50	50	0	0	5	20	50	50	0
Quinidine mg/kg/day	0	100	100	100	0	100	0	100	100	100	0	100
Number of animals examined	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Chronic abscesses/pyogranulomas with bacterial colonies [a]	1	4	6	14	19	1	0	0	1	2	1	0

[a] incidence represents the number of rats with a lesion in one or more tissues

Alveolar macrophages were observed in the lungs of all study animals, but the severity of the finding, particularly in male rats, suggested a potential relationship to quinidine dose either with or without dextromethorphan.

Table 3.8.2-4
Incidence and Severity of Alveolar Macrophages in the Lungs

	Males						Females					
Dextromethorphan mg/kg/day	0	5	20	50	50	0	0	5	20	50	50	0
Quinidine mg/kg/day	0	100	100	100	0	100	0	100	100	100	0	100
Number of lungs examined	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Alveolar macrophages												
minimal	42	38	33	36	41	37	51	40	39	42	50	37
slight	17	17	19	19	15	20	9	18	15	13	9	16
moderate	1	5	8	4	4	2	0	1	6	5	1	6
marked	0	0	0	1	0	1	0	1	0	0	0	1
total	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**

An increased incidence of histiocytic infiltration was observed in lymph node tissue of drug-treated animals as compared to controls, although it is uncertain whether it was the dextromethorphan or the quinidine, or the combination, that was driving the apparent effects.

Table 3.8.2-5
Incidence of Test Article-Related Changes in Lymph Nodes

	Males						Females					
Dextromethorphan mg/kg/day	0	5	20	50	50	0	0	5	20	50	50	0
Quinidine mg/kg/day	0	100	100	100	0	100	0	100	100	100	0	100
Mesenteric Lymph Node												
Number of nodes examined	60	60	60	60	60	59	59	60	59	60	60	60
Sinusoidal histiocytosis	7	13	16	22	23	16	8	18	21	20	15	19
Histiocytic granulomas	3	12	18	15	8	24	2	15	17	13	6	11
Mediastinal Lymph Node												
Number of nodes examined	60	59	59	60	59	59	60	59	60	59	60	60
Sinusoidal histiocytosis	6	12	13	12	8	7	4	10	12	15	9	8

In the liver, an accumulation of brown pigment (positive for lipofuscin) was noted in the centrilobular hepatocytes of female rats only, whereas intralumenal pigment (positive for bile pigments) was observed more prominently in male rats.

Table 3.8.2-6
Incidence of Test Article-Related Changes in the Liver

	Males						Females					
Dextromethorphan mg/kg/day	0	5	20	50	50	0	0	5	20	50	50	0
Quinidine mg/kg/day	0	100	100	100	0	100	0	100	100	100	0	100
Number of livers examined	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**59**	**60**	**60**	**60**
Hepatocellular brown pigment (central lobular)	0	0	0	0	0	0	0	20	19	16	0	12
Bile ducts: luminal billiary pigment	0	14	30	26	0	19	0	2	6	9	0	0

In addition, cellular hyperplasia in the pars distalis of the pituitary gland appeared to be present with comparable incidence across treated and control animals. Otherwise, non-neoplastic microscopic findings appeared either sporadically or with incidences that were comparable among vehicle- and drug-treated animals.

Summary of Notable Non-Neoplastic Findings from Microscopic Analyses (Incidence)

	Males						Females					
Tissue/Observation	**Vehicle**	**5/100***	**20/100***	**50/100***	**50/0***	**0/100***	**Vehicle**	**5/100**	**20/100**	**50/100**	**50/0**	**0/100**
Adrenal Glands (n)	60	60	60	60	60	60	60	60	58	60	60	60
-Congestion (mostly slight to moderate)	19	21	23	21	16	25	31	34	31	30	33	30
-Cortex, sinusoidal ectasia/hemorrhages/ hematocysts (mostly moderate to slight)	8	3	7	6	4	3	48	46	40	40	47	39
-Cortex, zona fasiculata, vacuolated (mostly minimal to slight)	20	17	13	9	18	15	0	5	3	1	0	6
-Cortex, zona fasiculata, cell alteration/degeneration (mostly slight to moderate)	8	5	7	7	8	6	22	30	27	22	17	20
-Cortex, zona fasiculata, hypertrophy /hyperplasia (mostly slight)	17	21	16	12	20	17	10	13	11	12	12	10
Brain (n)	60	60	60	59	60	60	60	60	59	60	60	59
-Congestion (mostly slight)	4	8	8	9	6	4	1	3	4	1	6	4
-Cerebrum-hypothalamic area/ cerebellum, compressed (mostly slight to moderate)	21	26	28	19	19	27	31	36	43	26	24	31
-Ventricles, dilated (mostly slight to moderate)	19	23	23	16	13	20	27	31	30	26	24	27
Extremity (n)	16	19	18	18	7	27	7	13	13	13	2	17
-Chronic ulcerative/ pododermatitis (mostly moderate to marked)	15	16	18	18	5	25	7	13	12	12	2	17
-Osseous hyperplasia	1	8	5	1	0	14	3	1	2	3	0	3

	Males						Females					
Tissue/Observation	**Vehicle**	**5/100***	**20/100***	**50/100***	**50/0***	**0/100***	**Vehicle**	**5/100**	**20/100**	**50/100**	**50/0**	**0/100**
(mostly moderate to slight)												
Eyes (n)	60	60	60	58	60	60	60	60	60	58	60	59
-Congestion (mostly slight)	1	4	2	4	3	2	0	6	1	0	1	3
-Cornea, neovascularized (slight to moderate)	1	2	1	1	2	3	0	0	0	1	0	0
-Cornea, acute/ subacute inflammation (mostly slight to moderate)	2	2	1	1	2	2	0	0	0	1	0	0
-Anterior chamber, eosinophilic material/ free erythrocytes/ inflammatory cells/ cell debris (minimal to marked)	3	1	3	1	7	4	3	0	1	3	1	0
-Lens, degeneration (slight to marked)	0	2	0	1	5	1	1	0	0	2	0	1
-Retina, degeneration/ atrophy (slight to marked)	2	1	2	1	5	1	5	2	0	3	1	3
Harderian Gland (n)	59	60	59	59	60	60	60	60	59	60	60	60
-Congestion (mostly slight)	2	4	11	9	7	4	1	7	6	8	7	7
-Necrosis (minimal to marked)	9	5	3	2	9	7	3	4	5	7	10	4
Heart (n)	60	60	60	60	60	60	59	60	60	60	60	60
-Ventricle, dilated (slight to moderate)	0	5	1	0	1	2	0	0	0	1	0	0
-Myocardium, myocardiopathy (minimal to moderate)	25	26	27	14	24	17	15	20	12	12	14	15
Kidneys (n)	60	60	60	60	60	60	60	60	59	60	60	60
-Congestion (slight to moderate)	16	25	27	32	19	22	12	23	20	24	19	19

	Males						Females					
Tissue/Observation	**Vehicle**	**5/100***	**20/100***	**50/100***	**50/0***	**0/100***	**Vehicle**	**5/100**	**20/100**	**50/100**	**50/0**	**0/100**
-Cortex, proximal convoluted tubular epithelium, hyaline droplets (minimal to slight)	1	1	0	2	3	2	0	0	0	0	0	0
-Cortex/cortico-medullary junction, mineral deposits (minimal to moderate)	0	9	9	8	1	8	5	5	6	6	2	5
-Cortex/medulla, tubular epithelium/ reticuloendothelial cells, brown pigment (mostly minimal to slight)	2	8	5	1	2	7	0	6	4	4	2	3
-Urothelial/ suburothelial mineral deposits (minimal to moderate)	8	6	4	2	8	10	48	40	38	27	36	27
-Urothelium, hyperplasia (minimal to moderate)	8	14	10	5	12	9	24	17	20	12	19	15
-Subacute/chronic interstitial inflammation /chronic nephropathy (minimal to marked)	40	41	38	32	38	42	5	11	14	12	4	12
-Necrosis/acute-subacute inflammation (slight to marked)	0	0	2	1	2	0	0	0	0	0	0	0
Lacrimal Gland (n)	59	60	59	59	60	60	60	60	59	60	60	60
-Congestion (mostly slight)	4	7	10	9	8	10	0	1	0	4	4	2
-Acinar cells, cyto-/ keratomegaly (mostly slight)	54	57	49	48	51	53	0	0	0	0	0	0
-Lymphoid cell aggregate(s) (mostly minimal to slight)	40	41	35	26	35	34	5	11	13	9	5	15

	Males						Females					
Tissue/Observation	**Vehicle**	**5/100***	**20/100***	**50/100***	**50/0***	**0/100***	**Vehicle**	**5/100**	**20/100**	**50/100**	**50/0**	**0/100**
-Harderian gland alteration (with/without brown pigment) (mostly minimal to moderate)	24	40	30	31	28	36	1	2	2	1	0	0
Liver (n)	60	60	60	60	60	60	60	60	59	60	60	60
-Congestion (slight to moderate)	21	25	32	30	21	29	13	28	24	22	18	18
-Extramedullary hematopoiesis (mostly minimal to slight)	50	30	30	37	49	32	49	41	40	39	46	47
-Hepatocellular vacuolation (periportal) (minimal to marked)	17	6	10	12	10	7	24	11	18	20	21	10
-Hepatocellular vacuolation (non-zonal) (minimal to moderate)	14	12	21	21	15	11	9	21	21	23	4	12
-Hepatocellular cytoplasm, brown pigment (central lobular) (minimal to moderate)	0	0	0	0	0	0	0	20	19	16	0	12
-Hepatocellular hypertrophy/ hyperplasia (regenerative) (minimal to slight)	0	0	1	0	0	0	0	0	0	0	0	1
-Hepatocellular necrosis (central lobular) (minimal to moderate)	2	1	1	0	0	0	0	0	0	0	0	0
-Hepatocellular necrosis (patchy) (mostly minimal to moderate)	2	8	9	2	6	4	3	0	6	3	1	1
-Bile ducts, lumen, biliary pigment	0	14	30	26	0	19	0	2	6	9	0	0

	Males						Females					
Tissue/Observation	**Vehicle**	**5/100***	**20/100***	**50/100***	**50/0***	**0/100***	**Vehicle**	**5/100**	**20/100**	**50/100**	**50/0**	**0/100**
(minimal to moderate)												
-Bile duct(s), dilated/ cyst (minimal to moderate)	0	2	2	0	2	1	0	3	5	1	1	1
Lungs (n)	60	60	60	60	60	60	60	60	60	60	60	60
-Alveolar/ intraalveolar macrophages (mostly minimal to moderate)	60	60	60	60	60	60	60	60	60	60	60	60
-Congestion (slight to moderate)	26	34	40	40	29	45	18	26	27	20	23	20
-Arteries, medial hypertrophy (mostly slight)	5	8	8	9	8	8	2	1	1	0	3	3
-Chronic abscess(es)/ pyogranuloma(s), bacterial colonies consistent with Staph infection (botryomyocosis) (slight to marked)	0	0	2	4	11	0	0	0	0	1	1	0
-Subacute (chronic active)/chronic inflammation (mostly minimal to moderate)	20	18	17	15	22	12	10	9	11	9	10	13
Lymph Node, Mediastinal (n)	60	59	59	60	59	59	60	59	60	59	60	60
-Congestion (mostly slight to moderate)	15	20	20	22	8	18	9	14	9	9	10	14
-Histiocytes, brown pigment (mostly minimal to moderate)	29	28	32	33	28	32	40	45	50	44	44	45
-Sinusoidal histiocytosis (mostly slight to moderate)	6	12	13	12	8	7	4	10	12	15	9	8
-Lymphoid cell hyperplasia (mostly slight to moderate)	5	3	4	7	9	4	9	7	9	10	11	8

	Males						Females					
Tissue/Observation	**Vehicle**	**5/100***	**20/100***	**50/100***	**50/0***	**0/100***	**Vehicle**	**5/100**	**20/100**	**50/100**	**50/0**	**0/100**
-Plasma cell hyperplasia (minimal to marked)	45	39	37	43	42	43	54	45	46	43	48	45
Lymph Node, Mesenteric (n)	60	60	60	60	60	60	59	60	59	60	60	60
-Congestion (minimal to moderate)	10	12	13	16	6	9	8	9	3	9	8	9
-Histiocytes, brown pigment (mostly minimal to moderate)	54	57	55	49	49	54	50	55	56	54	54	53
-Sinusoidal histiocytosis (slight to moderate)	7	13	16	22	23	16	8	18	21	20	15	19
-Lymphoid cell hyperplasia (mostly slight to moderate)	12	17	10	15	7	18	19	19	21	20	14	22
-Plasma cell hyperplasia (slight to moderate)	31	28	23	26	29	28	39	32	31	30	36	32
-Histiocytic granuloma(s) (mostly minimal to moderate)	3	12	18	15	8	24	2	15	17	13	6	11
Lymph Node, other (n)	13	12	11	18	13	6	19	17	19	17	10	14
-Histiocytes, brown pigment (minimal to moderate)	0	1	4	2	0	1	2	3	2	2	2	1
-Plasma cell hyperplasia (slight to marked)	6	1	0	8	5	3	13	5	12	6	5	5
-Lymphoid cell hyperplasia (mostly slight to moderate)	3	3	2	1	1	0	3	1	1	1	2	0
Mammary-protocol (n)	46	47	48	46	49	43	59	60	58	59	59	60
-Histiocytic proliferation/brown pigment (minimal to moderate)	0	0	0	0	1	1	1	2	2	3	1	6

	Males						Females					
Tissue/Observation	**Vehicle**	**5/100***	**20/100***	**50/100***	**50/0***	**0/100***	**Vehicle**	**5/100**	**20/100**	**50/100**	**50/0**	**0/100**
Marrow, Femoral (n)	59	60	59	59	60	59	59	59	57	59	60	57
-Congestion (mostly slight to moderate)	9	19	19	17	14	11	13	24	7	21	17	8
-Hypercellular (slight to marked)	13	8	9	15	17	8	26	26	21	25	23	23
Marrow, Sternal (n)	59	60	60	59	60	60	60	60	60	60	60	59
-Congestion (mostly slight to moderate)	16	21	19	17	14	10	11	23	6	17	14	6
Nasopharynx (n)	56	56	55	57	55	53	56	57	57	56	54	56
-Lumen, inflammatory cells/cell debris (minimal to moderate)	3	5	9	7	1	3	3	4	6	5	5	5
-Mucosa, epithelium-squamous/squamoid, metaplasia/ hyperkeratosis (mostly minimal to slight)	0	0	1	6	2	0	0	0	0	6	0	2
Pancreas (n)	60	60	60	60	59	60	60	60	59	60	60	60
-Acinar cell atrophy (minimal to moderate)	5	9	7	4	9	10	7	10	6	10	5	2
-Islet cell hyperplasia (minimal to moderate)	14	18	17	16	15	19	24	26	30	29	29	32
-Hepatocellular metaplasia (minimal)	0	0	0	0	1	1	0	1	0	0	0	1
Parathyroid (n)	47	47	48	50	53	52	52	48	50	52	51	51
-Hyperplasia (minimal to moderate)	6	8	11	7	8	11	9	2	2	1	4	2
Pituitary Gland (n)	59	60	59	60	60	59	60	59	59	60	60	60
-Congestion (mostly slight to moderate)	3	5	8	14	13	6	1	2	1	5	3	7
-Pars distalis, cyst(s) (minimal to moderate)	2	1	3	3	0	3	2	7	3	1	5	3
-Pars distalis, hyperplasia (minimal to moderate)	6	7	5	6	8	7	8	5	2	6	7	5
-Pars intermedia, cyst(s) (minimal to	4	6	2	9	4	7	4	6	2	2	1	4

	Males						Females					
Tissue/Observation	**Vehicle**	**5/100***	**20/100***	**50/100***	**50/0***	**0/100***	**Vehicle**	**5/100**	**20/100**	**50/100**	**50/0**	**0/100**
moderate)												
Prostate (n)	60	59	60	60	60	60	-	-	-	-	-	-
-Atrophy (mostly moderate)	0	0	2	2	4	1	-	-	-	-	-	-
Rectum/Low Colon (n)	60	60	60	60	60	60	60	60	59	60	60	60
-Lumen, nematodes	9	3	5	2	5	3	6	6	3	3	4	4
Skin (other) (n)	15	12	17	15	25	11	34	28	25	24	27	27
-Chronic abscess(es)/ pyogranuloma(s), bacterial colonies, consistent with Staph infection (botryomyocosis) (mostly slight to marked)	1	1	5	10	11	0	0	0	0	1	0	0
Skin, protocol (n)	59	60	60	59	60	60	59	60	59	59	59	60
-Squamous cell hyperplasia/ hyperkeratosis (slight to moderate)	0	0	0	0	0	2	0	0	1	1	0	0
Spleen (n)	60	60	60	60	60	60	60	60	59	60	60	60
-Extramedullary hematopoiesis (mostly slight to marked)	59	57	59	60	59	60	60	59	59	60	60	59
-Reticuloendothelial cells, brown pigment (minimal to marked)	59	55	59	60	55	60	59	58	58	60	57	60
-Lymphoid cell depletion/atrophy (slight to moderate)	0	0	4	4	4	5	0	3	1	5	5	3
-Lymphoid cell/ follicular hyperplasia (slight to moderate)	0	2	1	2	5	1	1	0	3	1	1	2
Stomach (n)	60	60	60	60	60	60	60	60	59	60	60	60
-Forestomach, squamous cell hyperplasia/	4	2	5	2	2	5	4	1	1	0	1	0

	Males						Females					
Tissue/Observation	**Vehicle**	**5/100***	**20/100***	**50/100***	**50/0***	**0/100***	**Vehicle**	**5/100**	**20/100**	**50/100**	**50/0**	**0/100**
hyperkeratosis (mostly slight to moderate)												
-Glandular mucosa, glands dilated (minimal to moderate)	32	41	35	33	33	39	34	48	47	44	29	39
Thymus (n)	59	59	58	59	58	58	59	58	58	60	59	60
-Congestion (mostly slight to moderate)	13	12	16	24	9	15	10	14	13	14	12	15
-Cyst(s) (minimal to moderate)	2	6	1	0	4	2	23	29	28	26	27	24
-Epithelial hyperplasia (mostly minimal to moderate)	3	5	4	4	4	2	16	22	25	19	19	19
Thyroid Gland (n)	60	60	59	60	60	60	60	59	59	60	60	60
-Congestion (mostly slight to moderate)	11	21	19	21	13	17	1	15	16	16	13	15
-Follicles, follicular cell hypertrophy/ hyperplasia (slight to moderate)	3	6	3	6	10	1	2	2	2	3	2	3
-Follicular cyst(s) (minimal to moderate)	0	4	3	2	2	3	0	1	1	2	2	3
Urinary Bladder (n)	60	60	60	59	60	60	60	60	59	60	60	60
-Congestion (slight to moderate)	0	0	3	1	2	1	0	4	0	0	0	0
-Distended (mostly slight to moderate)	1	8	5	8	9	5	1	0	2	5	1	7
-Lumen, eosinophilic material/free erythrocytes (mostly minimal to moderate)	6	8	3	4	1	10	0	0	0	0	0	1
Uterus (n)	-	-	-	-	-	-	60	60	59	60	60	60
-Congestion (slight to moderate)	-	-	-	-	-	-	1	4	2	7	3	3
-Endometrium, epithelium/glands, squamous/squamoid	-	-	-	-	-	-	3	4	3	4	5	8

	Males						Females					
Tissue/Observation	**Vehicle**	**5/100***	**20/100***	**50/100***	**50/0***	**0/100***	**Vehicle**	**5/100**	**20/100**	**50/100**	**50/0**	**0/100**
metaplasia (minimal to moderate)												
-Endometrium, hyperplasia, cystic/ polypoid (mostly slight to moderate)	-	-	-	-	-	-	2	2	3	5	2	3
Vagina (n)	-	-	-	-	-	-	60	60	59	59	60	60
-Congestion (slight to moderate)	-	-	-	-	-	-	0	4	2	3	1	4
-Mucosa, epithelium, squamous cell hyperplasia (minimal to moderate)	-	-	-	-	-	-	40	35	27	47	44	40

*Dose = mg/kg/day, DM/Q

Toxicokinetics

Blood was collected via orbital sinus from TK animals (3/sex/dose group/sample time) on Day 1 and Weeks 4, 13, and 26; sample collection times were pre-dosing and at 1, 3, 6, 12, and 24 hours post-dosing (i.e., each TK animal was sampled at two different time points per collection day). Animals were euthanized and discarded without necropsy after the final sampling time. Reproduced below from the sponsor's submission is a tabular summary of estimated TK parameters. These results suggest that exposure of female and male rats to dextromethorphan increased with increasing doses of dextromethorphan and, generally, in a greater than or approximately equal to dose proportional fashion. Dextrorphan exposure also increased with increasing doses of dextromethorphan. The data appear to confirm that quinidine treatment increased systemic exposure to dextromethorphan. It is also evident that systemic dextromethorphan exposure was generally less in males than that in females, while dextrorphan exposure was approximately equal between the sexes.

Table 3.2-1
Summary of Toxicokinetic Data

		Dextromethorphan				Dextrorphan				Quinidine			
		$AUC_{0\text{-}24h}$ (ng·h/mL)		C_{max} (ng/mL)		$AUC_{0\text{-}24h}$ (ng·h/mL)		C_{max} (ng/mL)		$AUC_{0\text{-}24h}$ (ng·h/mL)		C_{max} (ng/mL)	
Week	Dose (DM/Q) (mg/kg/day)	M	F	M	F	M	F	M	F	M	F	M	F
1[a]	5/100	14.7	61.6	3.24	6.69	2780	3050	206	231	9290	15300	1070	1090
	20/100	229	373	49.3	73.8	8670	8600	539	480	11300	13000	936	1510
	50/100	411	1390	50.4	266	20700	18300	1260	1270	11800	13700	928	1480
	50/0	289	605	83.9	239	16900	18200	1220	1040	-	-	-	-
	0/100	-	-	-	-	-	-	-	-	9380	14600	1330	1410
4	5/100	65.1	207	5.73	25.2	4600	3670	251	299	26700	41700	2410	3750
	20/100	396	879	55.2	159	11500	12400	643	835	25400	37900	2610	4080
	50/100	1360	2400	139	333	27800	29200	1560	1600	27500	28800	2000	2490
	50/0	309	1480	67.6	441	15300	31200	772	1850	-	-	-	-
	0/100	-	-	-	-	-	-	-	-	23000	28800	2290	2890
13	5/100	110	138	12.3	21.5	4390	4410	232	246	37900	40500	3390	4180
	20/100	581	615	67.1	104	15600	14000	845	1100	37200	32300	2770	3010
	50/100	1610	3860	147	501	38200	42600	2130	2370	27800	33600	2000	2740
	50/0	557	1990	142	727	23000	28500	1520	1780	-	-	-	-
	0/100	-	-	-	-	-	-	-	-	32900	34000	2380	3400
26	5/100	191	201	14.8	34.8	5130	4220	269	216	50600	50700	3710	7430
	20/100	815	1000	81.9	106	15800	14500	787	912	45000	50500	3520	5070
	50/100	1980	2610	203	281	28500	24500	1770	1390	47900	38500	3480	3120
	50/0	880	2870	213	1130	34200	33000	2130	2090	-	-	-	-
	0/100	-	-	-	-	-	-	-	-	55700	44900	4700	4880

[a]Day of first dose.
DM – Dextromethorphan; Q – Quinidine M – Males F - Females

Stability and Homogeneity

Characterization of test article homogeneity, stability, and concentration were performed by the Testing Facility. Analyses of preliminary mixes confirmed that study test article preparation procedures produced homogeneous mixtures and that the test article was stable in the vehicle for at least 14 days when refrigerated and for 28 days when frozen (≤ -20°C). Dosing solution analyses conducted during Weeks 1, 2, 3, and 4 and approximately every 3 months thereafter during the treatment period confirmed that administered test article concentrations were within ±10% of nominal.

11 Integrated Summary and Safety Evaluation

Zenvia™ (AVP-923) is a combination product formulation of two marketed drugs, dextromethorphan hydrobromide and quinidine sulfate, that is proposed for the treatment of pseudobulbar affect (PBA) in patients with neurologic disorders, such as ALS, MS, stroke, and Alzheimer's disease. The (b) (4) dosing regimen will involve chronic use in these patients (b) (4) . This proposed dosage level constitutes a reduction from the dosage of DM 30 mg/Q 30 mg/day b.i.d. that was proposed in the original NDA 21-879 submission of 30 January 2006, a reduction based on findings from an additional clinical trial (07-AVR-123) conducted in response to clinical review team recommendations (see Approvable Letter, issued 30 October 2006).

As described in the Pharmacology/Toxicology Review supporting that Approvable Letter, the nonclinical issues that needed to be addressed in NDA 21-879 were described as follows:

> "The pharmacology and toxicology of the individual marketed drugs, dextromethorphan hydrobromide (DM) and quinidine sulfate (Q) have been previously studied and are well documented. The nonclinical studies conducted for this submission, focused primarily on the potential interactive effects on toxicity when given in combination, on chronic toxicity to support the safety of chronic administration for the indication of treatment of pseudobulbar affect, and on genetic and reproductive toxicology and carcinogenicity of the proposed drug combination" (P/T review, K. Young, Ph.D., 30 October 2006).

On the basis of review and evaluation of the nonclinical data contained in the original 30 January 2006 submission, NDA 21-879 was "...considered to be approvable from a non-clinical perspective taking into consideration the severity of the indication in the proposed patient population..." The review of all nonclinical data contained in the original NDA 21-879 submission are incorporated herein by reference (see P/T review, K. Young, Ph.D., 30 October 2006). Outstanding nonclinical issues to be addressed

were communicated to the sponsor in the Approvable Letter (30 October 2006) and are summarized below.

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

With respect to the first of these outstanding issues, the current Resubmission contains a commitment from the sponsor to conduct a juvenile neurotoxicology study in rats, with a proposed timing of three months post-approval for submission of a protocol for Division review.

In response to the second noted issue, the sponsor submitted the results of repeated developmental/reproductive toxicity dose range-finding studies in rats (DMQ-140) and rabbits (DMQ-141) on 31 July 2008 (SDN-111) and these data have been reviewed separately (see IND 56,954 P/T Review, D. Charles Thompson, Ph.D., issue date 7 May 2009). This review concluded that the pre- and post-natal development study in rats and also the embryo-fetal development study in rabbits need to be repeated, both using a high dose of 50 mg/kg/day dextromethorphan in combination with 100 mg/kg/day quinidine. The substance of these conclusions and recommendations, including the fact that both repeat studies may be conducted post-approval, were conveyed to the sponsor in an Advice Letter (IND 56,954; issue date 22 July 2009) and also in Preliminary Comments to a Type-C Pre-NDA meeting (NDA 21-879, issue date 9 November 2009). The sponsor has committed in the current Resubmission to the conduct of both repeat studies. They propose to combine the juvenile neurotoxicology study noted above with the pre-/post-natal development study under a single protocol with a timing of three months post-approval for protocol submission and a commitment to submit the final study report by 30 months after Division review of the study protocol. The sponsor proposes to submit a final report for the repeated embryo-fetal development study in rabbits by 36 months post-approval. As recommended previously by Dr. Young, relevant findings from developmental/ reproductive toxicity testing completed by the sponsor to date (i.e., studies DMQ-121, DMQ-122, DMQ-123, DMQ-124, DMQ-125, DMQ-126, DMQ-140, and DMQ-141) should be included in labeling for Zenvia™ as appropriate.

The sponsor has submitted as requested the final report for the 2-year carcinogenicity study in rats (DMQ-120). The protocol for this study had previously been reviewed by the Agency and concurrence attained (ECAC meeting, 12 June 2003). Guidance was also conveyed to the sponsor with respect to suspension of dosing and early termination of the study in the presence of decreased survival (see IND 56,954 communication, issue date 19 November 2004). Overall, the study appears to have been adequate from a regulatory perspective.

Results of study DMQ-120 indicate that survival was decreased in all treated groups relative to controls. As a result, dosing was terminated prematurely in several groups (the earliest—at 82 weeks—in Group 4 males) and the study as a whole was terminated after 23 months due to excessive mortality. Mean body weights among Group 4 (50/100, DM/Q, mg/kg/day) males were significantly decreased relative to those of control animals throughout most of the study (-14% at Week 78); body weights of other treated groups of both sexes did not differ meaningfully from controls. TK analyses suggest that exposure of female and male rats to dextromethorphan increased with increasing doses of dextromethorphan and, generally, in a greater than or approximately equal to dose-proportional fashion. Dextrorphan exposure also increased with increasing doses of dextromethorphan. The data appear to confirm that quinidine treatment increased systemic exposure to dextromethorphan. It is also evident that systemic dextromethorphan exposure was generally less in males than that in females, while dextrorphan exposure was approximately equal between the sexes. As a point of reference, mean Week 26 $AUC_{0\text{-}24h}$ values for animals (male and female combined) in Group 4 (50/100 mg/kg/day, DM/Q) were as follows: 2295, 26,500, and 43,200 ng•hr/mL for dextromethorphan, dextrorphan, and quinidine, respectively (see table at the end of this section for a comparison of safety margins relative to plasma exposures observed clinically).

Statistical analysis of neoplastic findings with adjustment for time of death (Peto analysis, at 0.01 level for common tumors) were performed by both the sponsor and FDA, though pair-wise comparisons evaluated were not uniformly the same between the two analyses. The two analyses were alike in indicating that a statistically significant increase in the adjusted incidence of benign adenomas and also the incidence of adenomas plus carcinomas was apparent in the pars distalis of the pituitary between Group 4 (50/100, DM/Q) males and females versus controls. The analyses also found comparisons of Group 4 versus Group 5 (50/0, DM/Q) males and of Group 6 (0/100, DM/Q) versus controls to be statistically significant; neither of the latter comparisons was significant in females. The analyses suggest that tumors developed earlier in the specified treatment groups than in the control groups, given that the absolute numbers of pituitary neoplasms were comparable for all groups and the incidences in Group 4 males and females and Group 6 females were actually lower than in the respective control groups. There was no apparent increase in pituitary neoplasms in animals of either sex treated with dextromethorphan alone. The data also suggest that the statistical significance of the combined adenomas and carcinomas was primarily a function of the statistical significance from comparisons with the adenomas alone, since the incidences of carcinomas were very low and were comparable across the treatment

groups. No other neoplastic findings attained statistical significance. Non-neoplastic findings in the study were largely unremarkable, save for a lack of any apparent dose-related increase in cellular hyperplasia in the pars distalis of the pituitary gland. A review of study findings by the Executive CAC (ECAC meeting minutes, 24 August 2010) concluded that the study was adequate and "...that there were no biologically significant neoplastic findings for dextromethorphan and quinidine, alone or in combination, under the conditions tested." As recommended previously by Dr. Young, relevant findings from carcinogenicity testing conducted by the sponsor (i.e., studies DMQ-119 and DMQ-120) should be included in labeling for Zenvia™ as appropriate.

In response to the final outstanding nonclinical issue, the sponsor submitted the results of a chronic (39-week) oral toxicity study with Zenvia™ in beagle dogs, along with the results of 1- and 5-week dose range-finding studies. In the definitive 39-week study, all animals survived to scheduled necropsy. Notable clinical signs observed only in HD (12/12, DM/Q, mg/kg/day) animals of both sexes included decreased activity, intermittent/permanent tremors, increased muscle tone, and stiff hind limbs; head shaking was reported in HD males only, but in both HD and MD females. Mean body weight in HD females was decreased approximately 12% versus controls at dosing termination. No treatment-related effects were apparent in ophthalmoscopic, clinical chemistry, urinalysis, gross pathology, or organ weight findings. Mean reticulocyte counts (%) was the most notably altered hematology parameter, appearing to be decreased (40-80%) in almost all treated groups of both sexes relative to controls. ECG evaluations indicated a notably increased heart rate in HD animals on Days 126/127 after the quinidine dose was doubled to 12 mg/kg/day, which resulted in a decrease in the QT interval (QT_c values remained essentially unchanged). Histopathology findings were largely unremarkable, save for an apparent dose-responsive focal squamous metaplasia of the larynx/trachea (minimal to moderate) in main study animals; the finding was incompletely resolved in recovery animals.

TK analyses of plasma drug concentrations (DM/DX/Q) indicate that mean plasma concentrations of DM increased with increasing dose and with repeated administration. Mean systemic exposure to DM was generally higher in females than in males. Half-lives were generally comparable between males and females and increased with increasing dose. Plasma concentrations of DX decreased with repeated DM/Q administration, though values remained relatively constant from Day 84 to Day 267. Mean systemic exposure of DX was generally lower in females than in males. Doubling the Q dose in HD animals on Day 126 did not result in any apparent further decrease in mean systemic exposure of DX. Mean Q plasma concentrations increased with dose, but appeared to remain relatively constant with repeated dosing. Mean systemic exposure of Q was generally slightly lower in females than in males. The overall net impact of the Day 126 doubling of Q dose to HD animals on systemic exposure to DM and DX is difficult to discern in light of an apparent overall drug accumulation effect.

Based on observations in HD animals of increased incidence and/or severity of clinical signs, reduction in mean body weight of HD females, the alteration of ECG parameters in HD animals, and an apparent slight increase in the incidence and severity of focal

squamous metaplasia of the trachea/larynx in HD animals, the mid dose of 6/3 mg/kg/day may be considered a NOAEL for chronic oral administration of DM/Q in dogs. At this dose, Day 267 dextromethorphan AUC values were 380 and 372 ng•hr/mL and C_{max} values were 99.4 and 92.2 ng/mL in males and females, respectively. The corresponding quinidine AUC values were 11.1 and 8.51 µg•hr/mL and C_{max} values were 1.88 and 1.52 µg/mL in males and females, respectively (see table at the end of this section for a comparison of safety margins relative to plasma exposures observed clinically).

In conclusion, with the current Resubmission the sponsor has submitted—or committed to submit post-approval—data to address nonclinical issues previously identified as pivotal to support the approval of Zenvia™. Regarding carcinogenicity, analyses of findings from the two-year study in rats (DMQ-120) concluded "...that there were no biologically significant neoplastic findings for dextromethorphan and quinidine, alone or in combination, under the conditions tested." This finding, coupled with the previous negative carcinogenicity findings in Tg.rasH2 mice and the predominantly negative genotoxicity findings cited in Dr. Young's review of the original NDA submission, suggests that Zenvia™ possesses negligible carcinogenic potential.

As was also described by Dr. Young in her earlier review, "the main target organs of toxicity in the nonclinical studies...were the central nervous system (CNS), kidneys, and liver." By comparison, the findings noted above in the chronic (39-week) toxicity study in dogs indicate pathology in the liver and kidney was largely unremarkable. Rather, it was predominantly CNS-related clinical observations, supported by quinidine-induced effects on the cardiovascular system (ECG), which defined dose-limiting toxicity in the dog. The focal squamous metaplasia observed in the trachea/larynx was not a finding that had previously been noted by Dr. Young and its relationship, if any, to drug treatment is not entirely clear. However, the incidence and severity of the finding was only slightly increased over background and, as noted by the sponsor, it did appear to be associated to some degree with excessive salivation in the treated animals. The sponsor suggests this may be related to the epithelial irritancy of quinidine, as well as to an aversion to its bitter taste. Otherwise, the chronic toxicity findings following oral administration of Zenvia™ to dogs for 39 weeks were unremarkable. Evidence of significant chronic toxicity and/or non-neoplastic findings in the two-year rat carcinogenicity study was similarly unremarkable. Summarized in the table below is a comparison of plasma exposure levels (AUC values) attained in the rat carcinogenicity and dog chronic toxicity studies described above versus those derived from the most recent clinical trial (07-AVR-123) in ALS and MS patients at the reduced dosages of DM/Q, 30/10 and 20/10.

Thus, the nonclinical data submitted to date in total provide the necessary support for approval of Zenvia™, taking into consideration the severity of the indication in the proposed patient population. From a nonclinical perspective, therefore, it is recommended that Zenvia™ be approved with inclusion of Post Marketing Requirements (PMR) as noted above. Definitive timing for the sponsor's submission of study protocols and final study reports for the required juvenile neurotoxicology study in rats, the pre-

and post-natal development study in rats, and the embryo-fetal development study in rabbits will be addressed and communicated via separate PMR memoranda.

				AUC (ng•hr/mL)		
Species	**Sex**	**DM/Q Dose**	**Sampling Time**	**DM**	**DX**	**Q**
Dog	M	12/12 mg/kg/day (HD)	Day 267	856	260	28,700
	F	"	"	1079	375	23,800
Dog	M	12/6 mg/kg/day (No Clinical Signs)	Day 84	469	257	14,200
	F	"	"	419	151	12,100
Dog	M	6/3 mg/kg/day (NOAEL)	Day 267	380	140	11,100
	F	"	"	372	127	8510
Rat	M	50/100 mg/kg/day (HD)	Week 26	1980	28,500	47,900
	F	"	"	2610	24,500	38,500
Human	M	30/10 mg BID	Day 29	670	1295	376
	F	"	"	1118	1481	536
	M	20/10 mg BID	Day 29	377	764	345
	F	"	"	730	779	457

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/s/

DONALD C THOMPSON
10/01/2010

LOIS M FREED
10/01/2010

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: November 13, 2006

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 21-879 (Zenvia™; dextromethorphan plus quinidine)

Zenvia™ (formerly Neurodex™) is a combination drug product intended for the treatment of pseudobulbar affect (PBA) in patients with various neurological disorders. Zenvia™ contains two marketed drugs, dextromethorphan hydrobromide and quinidine sulfate, and was developed under IND 56,954 for PBA. Zenvia™ (b) (4) in the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP).

Dextromethorphan is considered to be the active component of Zenvia™. Quinidine is present to increase systemic exposure to dextromethorphan by inhibiting its metabolism by cytochrome P450 2D6. A full battery of nonclinical studies was not required for Zenvia™ since both dextromethorphan and quinidine are marketed drugs. The following nonclinical studies were conducted:

- PK (acute-dose combination in mouse, rat, dog)
- In vitro hERG assay (dextromethorphan and quinidine alone and in combination)
- Toxicology (oral)
  - Acute in rat (combination)
  - 14-day dose-ranging in rat (combination)
  - 26-week (4-week interim sacrifice) + 4 week recovery in rat (combination)
  - Dose-ranging in dog (dextromethorphan alone)
- Reproductive Toxicology (oral)
  - Dose-ranging studies in rat and rabbit (combination)
  - Fertility and early embryonic development in rat (combination)
  - Embryofetal development in rat and rabbit (combination)
  - Prenatal and postnatal development (including maternal function) in rat (dextromethorphan and quinidine alone and in combination)
- Carcinogenicity (dextromethorphan and quinidine alone and in combination)
  - 28-day oral dose-ranging in CByB6F1 hybrid mouse

26-week oral study in Tg.rasH2 and CByB6F1 mice
2-year oral study in rats (ongoing): results of 1-year in-life observations

Genotoxicity

In vitro Ames (2 studies: dextromethorphan and quinidine alone)
In vitro chromosomal aberration in human lymphocytes (3 studies: dextromethorphan and quinidine alone and in combination)
In vivo mouse micronucleus (2 studies: dextromethorphan and quinidine alone)

The nonclinical data submitted in support of an NDA for Zenvia™ have been reviewed in detail by Kathleen Young, Ph.D. Based on this review, Dr. Young has concluded that the NDA is "approvable from a non-clinical perspective", but recommends that the following nonclinical studies be conducted post-approval.

1. repeat reproductive toxicology studies (i.e., fertility and early embryonic development in rat, embryofetal development in rat and rabbit, and pre- and post-natal development in rat) using doses up to "maternal MTD levels".

2. a juvenile neurotoxicology study (in an appropriate animal species) to assess the potential for Zenvia™ to induce apoptotic neurodegeneration during development.

In addition, Dr. Young notes that the study report for the 2-year carcinogenicity study in rats (not required prior to approval, but initiated in mid-2003) should be submitted for review "as soon as possible".

Nonclinical issues

Reproductive Toxicology

Dr. Young has recommended that the entire reproductive toxicology battery of studies be repeated post approval (using doses up to a maternal MTD). Dr. Young notes the lack of clear dose-limiting effects at the high doses used in the definitive studies and the inadequacy of the dose-range finding studies to establish maternal MTDs.

Rat: the high dose combination was 50 mg/kg dextromethorphan/100 mg/kg quinidine in the fertility and early embryonic development and embryofetal development studies, and was 30 mg/kg dextromethorphan/100 mg/kg quinidine in the pre- and post-natal development study.

In the fertility study, there were no dose-related deaths or effects on body weight or food consumption; the only clinical sign was salivation. There were also no apparent drug-related effects on any of the reproductive parameters assessed. In the embryofetal development study, drug-related effects at the high dose consisted of salivation and slight decreases in body weight gain (5%) and food consumption. However, salivation, lasting for 1 hr post dose, was observed at all doses and the effect on food consumption was observed only during the first few days of dosing. Reduced fetal body weights and

delayed ossification were observed at the high dose; however, there was no effect on the number of fetuses or litters available for evaluation at the high dose. In the pre- and postnatal development study, no drug-related effects were noted at the high dose; salivation, lasting 1-2 hours, was observed at all doses. Pup deaths were observed on PNDs 1-4; however, the incidences were not clearly dose-related (affected pups: 8, 15, 40, and 26 pups at 0/0, 5/100, 15/100, and 30/100 mg/kg dextromethorphan/quinidine, respectively; affected litters: 5, 11, 13, and 15 litters, respectively).

The dose-range finding study was conducted at doses of 0/0, 0/100, 50/100, and 100/100 (dextromethorphan [mg/kg]/quinidine [mg/kg]). No deaths occurred during the 14-day study (only 3-day for the high dose combination). According to the study report, clinical signs at the high dose consisted of "…reduced activity/lethargy and/or moderate ataxia, with slight piloerection, approximately five hours after dosing on the third day of treatment". The report further notes that "These signs were more evident among the females, two of which seemed to have some degree of hypothermia." However, none of these clinical signs was documented in the individual animal line listings. Regarding body weight, the report states that "There was essentially no effect of treatment on body weight" and "no meaningful effect on feed consumption…" Since the high dose combination was administered for only 3 days and there is no documentation of dose-limiting toxicity, there are no adequate data in rat that clearly establish a maximum tolerated dose.

It is also of note that toxicokinetic data in the embryofetal development study are inconsistent with those from either the 6-month chronic study or the pre- and post-natal development study. A direct comparison can only be made to the 6-month study; in that study, the plasma levels of dextromethorphan and dextrorphan were 0.45 and 22 times, respectively, the levels obtained in the embryofetal study (data provided on page 4).

Rabbit: in the definitive study, the doses of dextromethorphan (mg/kg)/quinidine (mg/kg) were initially 0/0, 5/100, 15/100, and 50/100; however, the high dose was decreased to 30/60 on GD 11-19 and the quinidine dose was lowered to 60 in all treated groups on GD 18-19 (i.e., 0/0, 5/60, 15/60, 30/60) due to "maternal toxicity". Additional animals (10/group) were added to the study due to "loss of fetuses during processing"; these animals received the lower doses during GD 6-19. Maternal toxicity was apparently characterized by a decrease in body weight gain and reduced food consumption in one-third of high-dose dams. However, prior to the decrease in dose on GD 11, the effect on mean body weight gain appeared stable at ≈70% of controls (on GD 6-10), and mean body weight was ≈97-98% of controls.

In the dose-range finding study, treatment groups were as follows: 0/0, 50 mg/kg quinidine alone, 100 mg/kg quidine alone, and the combination of dextromethorphan (mg/kg)/quinidine (mg/kg) at 50/100 and 100/100. The duration of dosing ranged from 3 to 10 days. Animals initially receiving 50 mg/kg quinidine alone were switched, following a 19-day washout period, to the high-dose combination for 6 daily doses. There were no drug-related deaths or effects on body weight. The only clinical sign reported, i.e., increased respiratory rate, was observed in the high-dose combination group for 1

hour post dose on Day 2 in all animals, and on Days 4 and 6 in 2 of 3 animals. Reduced food consumption (60%) was reported in the high-dose combination group after 3 daily doses.

Overall, the data from the dose-range finding study and the definitive embryofetal development study are inadequate to establish a maximum tolerated dose in rabbit. This is of particular concern since there was a dose-related increase in malformations (all skeletal) in terms of affected fetuses (5, 7, 12, and 15 fetuses) and litters (5, 6, 10, and 11 litters) at 0/0, 5/60, 15/60, and 30/60 dextromethorphan (mg/kg)/quinidine (mg/kg), respectively. In addition, plasma levels of dextromethorphan (in combination with quinidine) achieved in this study were markedly lower (<0.1 times based on AUC) than anticipated in humans at the recommended daily dose of Zenvia™ (60 mg dextromethorphan/60 mg quinidine).

STUDY	SPECIES	DOSE (mg/kg)	SAMPLE TIME	DEXTROMETHORPHAN		DEXTRORPHAN	
				C_{max} (ng/mL)	AUC (ng*hr/mL)	C_{max} (ng/mL)	AUC (ng*hr/mL)
6-month[#]	rat	50/100	Day 182	598	4220	2445	41161
fertility	rat	no TK data					
embryofetal	rat	50/100	GD 17	870	9410	139	1870
	rabbit	30/60	GD 6	33.9	130	7580	40300
		50/100		79.1	183[$]	5590	17500[$]
		30/60	GD 19	70.1	383	6830	35400
pre/postnatal	rat	50/0	GD6	576	2520	1120	18700
			GD 17	1540	4760	1490	18600
		30/100	GD6	187	1220	905	12300
			GD17	409	2960	942	17500
			PND 16	158	1480	1420	18400
99-AVR-101[*]	human	30/30	Day 8	95.5 (EM) 136.2 (PM)	1049.0 (EM) 1533 (PM)	123.5 (EM) 51.45 (PM)	1001 (EM) 530.4 (PM)
99-AVR-103[*]	human (EM)	45/0	Day 8	4.2	31.46	599.2	2898
		45/30		141.5	1438	89.1	920.7

[#]$AUC_{(0\text{-}24\ hr)}$ [$]$AUC_{(0\text{-}4\ hr)}$ [*]$AUC_{(0\text{-}12\ hr)}$ [for human, the plasma $AUC_{(0\text{-}24\ hr)}$ is estimated by multiplying table values by 2.]

Conclusion: I agree that the sponsor has not provided adequate justification for the high doses of the combination used in the definitive reproductive toxicology studies in either rat or rabbit. Although I also agree that these studies may be submitted post approval, I would recommend that they be conducted in a timely manner. The sponsor should commit to a time line for conduct of the study and submission of a final study report for each study. If the sponsor has additional data that would establish, for each study, that higher doses could not have been tolerated, those data should be submitted for review.

Neurotoxicology

Dr. Young has recommended that a juvenile neurotoxicology study be conducted to assess "The potential for "Neurodex™-induced apoptotic neuronal degeneration in the human fetus and human infant…" I concur with this recommendation since, as Dr. Young notes, dextromethorphan is an NMDA receptor antagonist, and other NMDA receptor antagonists (e.g., MK-801 and ketamine) have been shown to induce apoptotic

neurodegeneration in the developing brain (Ikonomidou C et al. *Science* 283: 70-75, 1999; Olney JW et al. *Environ Health Persp Suppl* 108(S3): 383-388, 2000; Scallet AC et al. *Toxicol Sci* 81:364-370, 2004).

The potential for induction of apoptotic lesions is not adequate addressed in the standard battery of reproductive toxicology studies. In the rat, the vulnerable period has been demonstrated to be between postnatal days 7 and 10-14 (cf. Olney JW et al., 2000). In humans, this corresponds to a period from the beginning of the last trimester through the "first several years postnatally"… (Dobbing J, Sands J. *Early Hum Dev* 3:79-84, 1979, as cited by Olney et al., 2000). Thus, in utero exposure in humans could result in adverse effect on the fetus. In none of the animal studies comprising the standard battery is the fetus or pup directly dosed during the vulnerable period in the animal species. Therefore, a directed study is animals is needed to address the potential for Zenvia™ to induce apoptotic neurodegeneration in the developing human.

Dr. Young notes that this study should be conducted phase 4. Considering the indication, I agree that it does not need to be conducted prior to approval. However, I would recommend that the sponsor initiate the study in a timely manner since the intended patient populations do include women of childbearing potential. The sponsor should commit to a time line for conduct of the study and submission of a final study report.

Chronic toxicology

The one notable omission in the sponsor's nonclinical data is the lack of general toxicity data in nonrodent. The initial clinical trial was allowed to proceed with no nonclinical data. However, the sponsor was informed that nonclinical studies would be required for the NDA due to the lack of data on dextromethorphan and quinidine, either alone or in combination (teleconference, 7/21/99). In response, the sponsor proposed to conduct the following studies: safety pharmacology studies, a chronic (9-month) toxicity study in dog, and the standard battery of reproductive toxicology and genetic toxicology studies (IND 56,964 serial #021, N4/27/01). The sponsor's selection of species for the chronic toxicity study was based on the dog having CYP 2D6 activity most similar to humans (as compared to rat and African Green monkey). While the Division concurred with the sponsor's general plan, the sponsor was informed that the selection of species for the chronic study should ensure adequate systemic exposure in animals to parent compound and major human circulating metabolites. Subsequently, the sponsor was also informed that carcinogenicity studies in two species would be required. Therefore, with a chronic study in nonrodent, chronic toxicity would have been assessed in both rodent (in the 2-year carcinogenicity study) and nonrodent.

At some point, the sponsor changed the plan to conduct the chronic study in dog. In the annual report dated 4/3/02, the sponsor stated that "Due to the high sensitivity of dogs to DM and the variability in response, it was concluded that dogs are not an appropriate species for the conduct of chronic toxicology". The annual report does not appear to have provided data to support this conclusion.

In a meeting held on 5/17/04, the Division agreed that the sponsor's nonclinical program, which included a chronic (6-month) toxicity study in rat, was sufficient to support a marketing application.

As previously noted, Zenvia™ is also being investigated for treatment of neuropathic pain in diabetic patients (IND 62,567, in DAARP). In an End-of-Phase 2 meeting, DAARP informed the sponsor that the increased sensitivity of the dog to the combination of dextromethorphan and quinidine would need to be addressed and that a chronic toxicity study in nonrodent would be needed to support long-term clinical trials. The minutes of that meeting (12/9/03) state that the sponsor "will commit" to submitting a chronic non-rodent toxicity study. Based on recent communications with pharmacologists in DAARP, a chronic nonrodent study has not been submitted, but it is still being required.

It is my opinion that a chronic toxicity study in nonrodent is needed to support the safety of Zenvia™, based on the fact that (a) the potential for toxicity after prolonged exposure has not be adequately assessed for either dextromethorphan or quinidine, that (b) plasma levels of dextromethorphan are markedly higher in extensive metabolizers, and that (c) dextromethorphan is not currently approved for chronic use. Although Zenvia™ may not result in plasma levels of dextromethorphan higher than those observed in poor metabolizers given dextromethorphan alone, it is expected to result in those high levels in all patients chronically.

To date, the sponsor has not provided data to document that dog is not an appropriate species, nor has the sponsor addressed the possibility that another nonrodent species would be an appropriate animal model for assessing the chronic toxicity of the combination of dextromethorphan and quinidine. The sponsor needs to address this issue prior to approval. A decision as to whether or not a chronic toxicity study in nonrodent would be needed, either prior to approval or post-approval, will be based on review of the sponsor's response and all available clinical and nonclinical data.

Labeling: Labeling issues are deferred at this time.

Information to be relayed to the sponsor

1. You have not provided sufficient justification for the high doses used in the reproductive toxicology studies in rat (fertility and early embryonic development, embryofetal development, and pre- and post-natal development) and rabbit (embryofetal development). In none of the studies was dose-limiting toxicity observed, and the dose-range finding studies in rat and rabbit do not convincingly establish that higher doses could not have been tolerated.

Regarding the rat studies, the highest combination dose tested in the fertility and early embryonic development and embryofetal development studies (50 mg/kg dextromethorphan/100 mg/kg quinidine) was associated only with salivation and a small decrease (5%) in body weight gain (embryofetal development study only). In the dose-range finding study, the high dose (100 mg/kg dextromethorphan/100 mg/kg quinidine)

was only administered for three days, apparently due to clinical signs (reduced activity, ataxia, piloerection) on Day 3, although these findings were not documented in the individual line listings. The highest combination dose tested in the pre- and post-natal study (30 mg/kg dextromethorphan/100 mg/kg quinidine) resulted in no maternal toxicity. There were several instances of total litter loss at the high dose; however, it is not clear that they were drug-related or dose-limiting.

Interpretation of the results of the embryofetal development study in rabbit was complicated by the lowering of doses at different periods during gestation and the addition of animals that received the lower doses for the full dosing period. (The latter was apparently necessary due to technical problems, i.e., the loss of fetuses during processing.) The doses were lowered from the initial high dose (50 mg/kg dextromethorphan/100 mg/kg quinidine) in response to body weight effects that we do not consider sufficient to warrant such action. In the dose-range finding study in rabbits, the highest combination dose administered (100 mg/kg dextromethorphan/100 mg/kg quinidine) was not adequately evaluated (being given for only 6 days), and was associated only with a sporadic increase in respiration rate and a decrease in food consumption that was not accompanied by an effect on body weight.

The adequacy of the embryofetal studies are of particular concern considering the increase in total malformations (all skeletal) in the rabbit study and the skeletal effects observed in the rat study.

We recommend that you conduct appropriate dose-range finding studies in rat and rabbit in order to select adequate doses for the definitive studies; the high doses need to produce some degree of maternal or fetal (or offspring) toxicity. If the results of these dose-range finding studies establish that higher dose could not have been tolerated, then repeat studies would not be needed. In the rat, you should consider exploring combination doses between 50/100 and 100/100 mg/kg (dextromethorphan/quinidine).

2. The chronic toxicity of the combination of dextromethorphan and quinidine was assessed only in rat. We agreed to the assessment of chronic toxicity in a single animal species; however, this was based, at least in part, on the fact that chronic toxicity would be assessed in rodent in the 2-year rat carcinogenicity study. Therefore, ideally the single chronic toxicity study would have been conducted in non-rodent. In fact, you originally proposed to conduct a chronic toxicity study in dog.

Dextromethorphan is currently approved for short-term use (e.g., temporary relief of cough due to colds), whereas Zenvia™ is intended for chronic administration. In addition, plasma levels of dextromethorphan are increased up to 40-fold following administration of Zenvia™ compared to dextromethorphan alone. Since the maximum recommended dose of dextromethorphan in OTC products (120 mg/day) is only two times the recommended daily dose of Zenvia™, it is clear that systemic exposure to dextromethorphan will substantially exceed the exposure for which there is previous human experience, at least in patients who are CYP2D6 extensive metabolizers (EMs).

We note your commitment to a chronic toxicology study in non-rodent under IND 62,567 (End of Phase 2 meeting minutes, 11/12/03). If this study is ongoing or has been completed, a final study report should be submitted for review. If not, you will need to conduct a chronic study in non-rodent. You have concluded that the dog is an inappropriate animal model; however, you have not provided sufficient data to establish this. If the dog is documented to be an inappropriate species, you should consider another non-rodent species, such as monkey or minipig. Whether or not the chronic non-rodent study will be needed prior to approval will depend on availability of an appropriate non-rodent animal model and an overall evaluation of the nonclinical and clinical data.

3. You need to conduct a juvenile neurotoxicology study in an appropriate animal species to assess the potential for Zenvia™ to induce apoptotic neurodegeneration during development. In the animal species selected, the timing of dosing during development should cover the vulnerable period in humans (i.e. last trimester through postnatal ages 2-3). This study may be conducted post-approval. Please propose a time line for conduct of the study and submission of the final study report.

4. The 2-year carcinogenicity study in rat was not required for the NDA. However, since the study was initiated in mid-2003, it should be completed. The final study report should be submitted as soon as possible.

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

/s/

Lois Freed
11/13/2006 10:22:01 AM
PHARMACOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

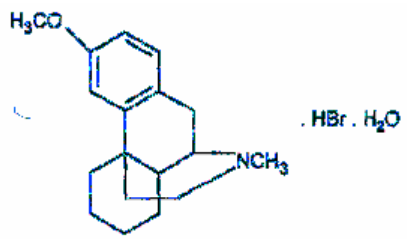
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

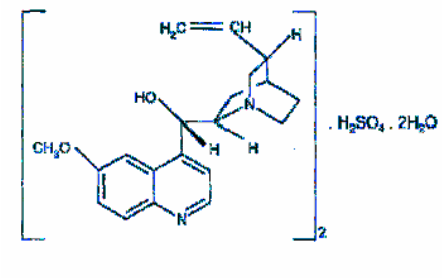
NDA number: 21-879
Serial Number: 000
Date Received by Center: December 15, 2004
Sponsor: Avanir Pharmaceuticals
Manufacturer for drug substance: Dextromethorphan hydrobromide: (b) (4) ; Quinidine sulfate: (b) (4)

Pharmacology and Toxicology Reviewer name: Kathleen Young, Ph.D.
Pharmacology and Toxicology Supervisor: Lois Freed, Ph.D.
Division Director: Russell G. Katz, M.D.
Project Manager: Melina Griffis
Division name: Division of Neurology Products
HFD #: 120
Review completion date: October 30, 2006

Drug: **Trade name**: Neurodex™
Generic name: Dextromethorphan hydrobromide; Quinidine sulfate
Code name: APV-923
Chemical name: Dextromethorphan hydrobromide: morphinan, 3-methoxy-17-methyl,(9alpha,13alpha,14alpha)-, hydrobromide; quinidine sulfate: (8R, 9S)-6'-Methoxycinchonan-9-ol-Sulfate
CAS registry number: Dextromethorphan hydrobromide: 6700-34-1 (monohydrate) and 125-69-9 (anhydrous); Quinidine sulfate: 6591-63-5 (dihydrate) and 50-54-4 (anhydrous)
Mole file number: None
Molecular formula/molecular weight:
Dextromethorphan: $C_{18}H_{25}NO.HBr.H_2O$ / Molecular weight: 370.33
Quinidine: $[C_{20}H_{24}N_2O_2]2.H_2SO_4.2H_2O$ / Molecular weight: 782.96

Structure:





Dextromethorphan HBr Quinidine sulfate

Relevant INDs/NDAs/DMFs: IND 56,954; IND 62, 567

Drug class: Dextromethorphan: d-isomer of codeine analog levorphanol, non-competitive NMDA receptor antagonist and antitussive

Quinidine: d-isomer of quinine, CYP450 2D6 inhibitor and antimalarial, antiarrhythmic

Indication: Treatment of pseudobulbar affect occurring in ALS, MS, stroke, and Alzheimer's Disease

Clinical formulation:

Product Features	Ingredient	Function	Amount per Capsule (mg)	Quality Standard
Dosage form: capsule				(b) (4)
Active Ingredients	Dextromethorphan Hydrobromide Monohydrate	Active Ingredient	30.00	USP, EP
	Quinidine Sulfate Dihydrate	Active Ingredient	30.00	USP, EP
Excipients	Croscarmellose sodium NF	(b) (4)		NF, Ph.Eur., JP
	Microcrystalline cellulose NF			NF, Ph.Eur., JP
	Colloidal silicon dioxide NF			NF
	Lactose monohydrate NF			NF
	Magnesium stearate NF			NF

Impurities: The known impurities from the manufacture of the quinidine sulfate component are (b) (4). The known

impurities from the manufacture of dextromethorphan hydrobromide are (b) (4) . The acceptance criteria provided by the sponsor for the known and unknown related substances in the drug product are presented in the following table (reproduced from the original NDA submission):

Table 2.3.P.5-1. AVP-923 Release Tests and Specifications

Test	Procedure Number	Acceptance Criteria
(b) (4)		

The acceptance criteria for the impurity, (b) (4) is at the limit for qualification, of (b) (4) This level is considered to be acceptable based on its presence in the dextromethorphan lot used in the 28-day mouse toxicology, 26-week mouse carcinogenicity, and fertility (rat), embryo-fetal toxicity (rat and rabbit), and pre- and post-natal development studies (b) (4) .

Route of administration: Oral

Proposed use: For chronic use at 30/30 mg dextromethorphan/quinidine b.i.d. (1/1 mg/kg/day, 37/37 mg/m^2/day)

Disclaimer: ***Tabular and graphical information are reproduced from the original submission, unless cited otherwise.***

Studies reviewed within this submission:
A Study of the Pharmacokinetics of Dextromethorphan and Quinidine and the Effect of Quinidine on the Pharmacokinetics of Dextromethorphan Following a Single Oral Administration in Male and Female Sprague-Dawley Rats (Avanir Study No. DMQ-101)

A Dose-Ranging Study of the Plasma Pharmacokinetics of Dextromethorphan, Dextrorphan, and Quinidine after Oral Dosing in Mice with Combinations of Dextromethorphan and Quinidine (DMQ-116)

Effects of AVP-923 (Dextromethorphan Hydrobromide and Quinidine Sulfate) on HERG Currents Recorded from Stably Transfected HEK293 Cells (DMQ-130)

28-day Repeated Dose Oral Toxicity and Toxicokinetic Study in CByB6F1 Hybrid Mice with a Preliminary Range-Finding Toxicity Study (DMQ-118)

Dextromethorphan/Quinidine Combination – 2 Week Oral (Gavage) Preliminary Toxicity Study in the Rat (Avanir Study No. DMQ-105)

Dextromethorphan/Quinidine Combination – 26-Week Oral (Gavage) Toxicity Study in the Rat with a 4 Week Interim Kill and Followed by a 4 Week Treatment-Free Period (DMQ-103)

Dextromethorphan – Determination of the Maximum Tolerated Dose by the Oral Route (Gavage) in the Beagle Dog (DMQ-102; MDS Pharma Study # 84/002)

Dextromethorphan Hydrobromide Bacterial Reverse Mutation Test (DMQ-112; (b) (4) AWN/004)

Quinidine Sulphate Bacterial Reverse Mutation Test (DMQ-109; (b) (4) AWN/001)

Dextromethorphan Hydrobromide Mouse Micronucleus Test (DMQ-114; (b) (4) AWN/006)

Quinidine Sulphate Mouse Micronucleus Test (DMQ-111; (b) (4) AWN/003)

Dextromethorphan Hydrobromide – *In vitro* Mammalian Chromosome Aberration Test in Human Lymphocytes (DMQ-113; (b) (4) AWN/005)

Quinidine Sulphate – *In vitro* Mammalian Chromosome Aberration Test in Human Lymphocytes (DMQ-110; (b) (4) AWN/002)

In vitro Mammalian Chromosome Aberration Test (Combination of Dextromethorphan Hydrobromide-USP and Quinidine Sulphate-USP 24) (DMQ-115)

26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 and CByB6F1 Mice (DMQ-119)

Dextromethorphan/Quinidine: A 24-Month Oral (Gavage) Carcinogenicity Study in Rats – Month 12 Unaudited Status Report (DMQ-120)

Dextromethorphan/Quinidine (DMQ): Preliminary (Dose Finding) Study in Rats (DMQ-122)

Dextromethorphan/Quinidine (DMQ): Preliminary (Dose Finding) Study in Rabbits (DMQ-121)

Dextromethorphan/Quinidine (DMQ): Study of Fertility and Early Embryonic Development to Implantation in Rats (DMQ-126)

Dextromethorphan/Quinidine (DMQ): Embryo-Fetal Toxicity Study in Rats (DMQ-124)

Dextromethorphan/Quinidine (DMQ): Embryo-Fetal Toxicity Study in Rabbits (DMQ-123)

Dextromethorphan/Quinidine (DMQ): Pre- and Post-Natal Development Study in Rats, Including Maternal Function (DMQ-125)

An Acute Oral Neurotoxicity Study in Rats with Dextromethorphan and Quinidine (AVP-923) (Avanir Study No. DMQ-106)

Studies not reviewed within this submission: None

EXECUTIVE SUMMARY

Recommendations

A. Recommendation on Approvability

NDA 21-879 is approvable from a nonclinical perspective, although there are inadequacies in the reproductive toxicity studies to be addressed, taking into consideration the severity of the indication in the proposed patient population. The following nonclinical studies will be needed during Phase 4:

B. Recommendation for Nonclinical Studies

1. The final study report for the 2-year carcinogenicity study in rats, initiated in mid-2003 should be submitted for review and to update the product label, as soon as possible.

2. The reproductive toxicity studies on fertility (DMQ-126), embryo-fetal development (DMQ-124) and pre- and post-natal development (DMQ-125) in rats are considered to be less than adequate, due to insufficient support for dose selection in the range-finding study (DMQ-122) in rats, and on the absence of observable maternal toxicity in the definitive studies that would clearly demonstrate testing at up to the maximum tolerated dose levels (MTD). The results of these studies should be discussed in the product label, presenting the limitations of the study methodologies and with thorough descriptions of the positive study findings. The studies should be repeated as soon as possible during Phase 4, using appropriate criteria for dose selection with a well-designed dose range-finding study. The rats should be dosed at up to the maternal MTD levels as described in the published ICH Guidelines for Industry.

3. The embryo-fetal toxicity study in rabbits (Study DMQ-123) is considered to be inadequate based on insufficient support in the range-finding study (DMQ-121) for dose selection and on the absence of maternal toxicity demonstrating a maximum tolerated dose (MTD). These deficiencies and the observation of considerable embryo-fetal toxicity at extremely low multiples of the proposed clinical dextromethorphan dose should be thoroughly described in the product label. Additionally, the study should be repeated during Phase 4, using appropriate dose selection based on the results of a properly conducted dose range-finding study and using doses at up to a maternal MTD.

4. The potential for Neurodex™-induced apoptotic neuronal degeneration in the human fetus and human infant should be addressed in the product

label and by conducting a Phase 4 juvenile neurotoxicity study in an appropriate animal species during Phase 4.

C. Recommendations on Labeling

Recommendations on labeling will be provided under separate review.

III. Summary of Nonclinical Findings

A. Brief Overview

The pharmacology and toxicology of the marketed drugs, dextromethorphan hydrobromide (DM) and quinidine sulfate (Q) have been extensively studied and are well documented. The nonclinical studies conducted for this submission focused primarily on potential interactive effects when given in combination, on chronic, genetic and reproductive toxicology, and carcinogenicity of the proposed drug combination to support the safety of chronic administration for the indication of treatment of pseudobulbar affect.

Oral dextromethorphan and quinidine absorption was rapid, at 15 minutes to 1 hour across species. When combined, oral quinidine increased systemic dextromethorphan (oral route) exposure ($AUC_{0\text{-}inf}$ and Cmax) and decreased dextrorphan (DX) exposure at all doses tested in mice and rats, with a maximal effect at the dose of 30 mg/kg quinidine in mice that suggested saturation of quinidine inhibitory effects on CYP2D activity in mice. Systemic exposure to both drugs was greater, and to dextrorphan was lower under fasted than under fed conditions in both the males and females. Dextromethorphan is approximately 50%-60% bound to rat plasma proteins *in vitro*.

Dextromethorphan is metabolized by hepatic O-demethylation by CYP2D6 to dextrorphan, and by CYP3A4 and N-demethylation to 3-methoxymorphinan. Minor metabolites (<15% dose) include d-methoxymorphinane and d-hydroxymorphinane. Dextrorphan and 3-methoxymorphinan are demethylated to 3-hydroxymorphinan, which undergoes glucuronidation before excretion. Quinidine is metabolized in rodents and humans by cytochrome P450 (CYP)3A4. Quinidine metabolites include 3-hydroxy-quinidine (10%), 2'-quinidinone (10%), quinidine-N-oxide (1%), quinidine 10,11-dihydroliol (3%), O-desmethyl-quinidine (1%-2%), and 2'-Oxoquinidione. The 3-hydroxy-quinidine, quinidine-N-oxide, and 2'oxoquinidione metabolites are active. Dextromethorphan excretion is predominantly by the renal route, in the form of parent drug (0%-11%) and demethylated, conjugated morphinan compounds (0.1%-100%). Most quinidine elimination is by first pass metabolism, by hepatic CYP3A4 enzyme activity, and approximately 20% quinidine is excreted unchanged in the urine. The plasma half-life values are 1.4-3.9 hours for dextromethorphan, 2.5 hours for dextrorphan, and 3-16 hours for quinidine (mean 6-8 hours). Quinidine clearance is increased with decreasing urinary pH.

The main target organs of toxicity in the nonclinical studies for this submission were the central nervous system (CNS), kidneys, and liver. CNS effects in all species evaluated included depression, hypoactivity, lethargy and ataxia in rats and dogs, attributed to the dextromethorphan component. Quinidine administration, with and without dextromethorphan co-treatment induced dose-related CNS depression in mice. Convulsions were observed with high oral doses of the quinidine component in mice, and high oral doses of dextromethorphan in rats and dogs. The severity of CNS effects of

each component increased when dextromethorphan and quinidine were combined, and the severity and duration of effects increased with treatment duration. Combination with quinidine reduced the dextromethorphan lethal dose, further demonstrating increased severity of acute dextromethorphan toxicity in mice. There were no deaths in the mice by quinidine given alone. Increased dextromethorphan CNS toxicity with quinidine co-treatment was a function of the increased plasma dextromethorphan exposure due to inhibition of its metabolism by quinidine, and the additive effects of toxicity by each drug when combined.

A study on HERG current in transfected HEK293 cells showed concentration-dependent inhibition by the dextromethorphan:quinidine combination, that appeared to be predominantly related to the quinidine component. Renal toxicity observed in the 26-week study in rats was attributed to the quinidine component of the combination product. The observations included increased urinary volume and relative kidney weights with slight tubular dilation and histopathology findings (kidney pelvic or tubular dilation, papillary and cortical mineralization, kidney hyaline droplets, transitional cellular hyperplasia in the kidneys). Hepatotoxicity (increased liver weights and liver enzymes, centrilobular hypertrophy) was observed in the 26-week study in rats. The increases in liver enzymes and liver weights compared to controls were without a relationship to dose combination level, and were therefore attributed to the quinidine component which was given at a constant dose in each treatment group. The histopathology findings were clearly dextromethorphan dose related.

Dextromethorphan treatment alone was negative for mutagenicity in the Ames test, and for clastogenicity *in vivo* in the mouse Micronucleus test and *in vitro* in the mammalian chromosome aberration testing human lymphocytes. However, dextromethorphan increased polyploidy metaphase figures at the highest concentration tested (400 mcg/ml) in human lymphocytes in the presence of S9 mix in the 3-hour treatment, when compared to solvent control levels. Quinidine sulphate alone was negative for mutagenicity in the Ames test, and for clastogenicity *in vivo* in the Mouse Micronucleus test. However, quinidine was equivocal for clastogenicity in the chromosome aberration test in human lymphocytes in the presence of metabolic activation with S9, without a dose-response effect. Dextromethorphan hydrobromide and quinidine sulphate, when combined in a 1:1 concentration ratio was negative for clastogenicity *in vitro*, in the mammalian chromosome aberration test in human peripheral blood lymphocytes at concentrations of up to those limited by cytotoxicity.

There were no statistically significant treatment-related increases in neoplastic lesions in male and female Tg.rasH2 mice given oral gavage doses of up to 100 mg/kg/day dextromethorphan and 100 mg/kg/day quinidine sulfate, given alone and in combination.

There were no treatment-related effects by Neurodex™ in a study on male and female mating and fertility in Sprague Dawley rats. Neurodex™ was not teratogenic in Sprague Dawley rats. Embryo-fetal toxicity was observed at all doses tested (NOAEL <5/100 mg/kg/day DM/Q, approximately 1X and 10X the exposure to DM and Q, respectively, on a mg/m^2 basis) in the rats, and included dextromethorphan dose-related reduced fetal

weights and reduced ossification throughout the skeleton, in the skull, sternum, vertebrae and extremities, suggesting developmental delay attributed to the dextromethorphan component.

The results of the embryo-fetal toxicity study in rabbits showed slight treatment-related increases in total incidences of malformations, including fused sternebrae, gastroschisis with phalangeal fusion, craniofacial abnormalities, diaphragmatic hernia, persistent truncus arteriosus, vertebral fusions, and skeletal ossification effects with incomplete or non-ossification of the sternebrae, hind limb long-bone epiphyses and hyoid (NOAEL = 5/60 mg/kg/day DM/Q, approximately 2X and 19X the exposure to DM and Q, respectively).

In a study on prenatal and postnatal development in rats, there were no effects by dextromethorphan (50 mg/kg/day) or quinidine (100 mg/kg/day) given alone, but the combination product reduced postnatal pup body weight and induced increases in gestation length and pup mortality, and developmental delay with delayed acquisition of the air-righting response and increased spontaneous activity in the pups at all doses studied (NOAEL <5/100 mg/kg/day DM/Q).

The reproductive toxicity studies in rats and rabbits are considered to be less than adequate based on insufficient support for the dose selection in the dose range-finding studies, and the absence of maternal toxicity demonstrating maximum tolerated doses (MTD) in the definitive studies.

No treatment-related neuronal lesions (vacuolation, necrosis, and degeneration in the posterior cingulate and retrosplenial cortices characteristic of the "Olney Lesion"), were observed in adult rats administered dextromethorphan at oral gavage doses from 2-50 mg/kg PO in combination with quinidine at 50 mg/kg PO, when sampled at 6 and 24 hours, and 7 days after dosing (NOAEL = 50/50 mg/kg DM/Q).

B. Pharmacologic Activity

Dextromethorphan is an agonist at the $sigma_1$-opioid receptor and an uncompetitive antagonist at the N-methyl-D-aspartate (NMDA) receptor, with antitussive, analgesic, and anticonvulsant properties. Antagonism of the NMDA receptor decreases glutamate excitatory activity in the central nervous system. Quinidine has been used as an antiarrhythmic agent, to maintain sinus rhythm in atrial fibrillation patients and to prevent ventricular tachycardia, due to its inhibition of sodium and cardiac potassium currents, thus decreasing the Vmax for sodium influx and excitability, conduction velocity, and contractility, and increasing the duration of cardiac call action potentials. Additionally, quinidine and its metabolites dihydroquinidine, 3-hydroxyquinidine, O-desmethylquinidine and quinidine-N-oxide, competitively inhibit the CYP450 enzyme 2D6, responsible for rapid and extensive metabolism of dextromethorphan to dextrorphan.

The rationale for the development of this combination drug product is that reduction of glutamate excitatory activity with dextromethorphan treatment may decrease the pseudobulbar affect, or episodes of inappropriate or pathological emotional outbursts of laughing or crying associated with neurological diseases including stroke, Amyotrophic lateral sclerosis, and Alzheimer's disease. Quinidine sulfate is expected to elevate and prolong systemic dextromethorphan levels by inhibition of its metabolism by CYP2D6 to dextrorphan, thus decreasing the dose required and prolonging the duration of action in the reduction of pseudobulbar affect.

C. Nonclinical Safety Issues Relevant to Clinical Use

Central Nervous System: CNS depression, associated with the oral dextromethorphan component, was observed across species. The effects included uncoordinated movement, hypoactivity, lethargy, and ataxia at doses representing from 5 to 10 times the proposed clinical oral dose of 60/60 mg/d dextromethorphan/quinidine. Tremors and convulsions were observed at extremely high doses representing 16 times in mice (NOAEL = <125 mg/kg oral dextromethorphan, <500 mg/kg oral quinidine), 32 times in rats (NOAEL = 100 mg/kg DM alone, 100 mg/kg Q alone, and 20/50 mg/kg DM/Q), and 5 times in dogs the proposed clinical dose (NOAEL <10 mg/kg DM, not studied in combination with Q in dog).

Hepatotoxicity: Treatment-related hepatotoxicity in rats, suggesting potential adverse Neurodex™ effects on liver in clinical use, was observed in the 4-week and 26-week oral toxicology studies. The results showed dose-related increases in the incidence and severity of increased liver enzymes, absolute and relative liver weights, and centrilobular hypertrophy, at doses representing 1.5 times for dextromethorphan and 3 times for quinidine the proposed clinical dose and above. Treatment-related increases in liver enzymes (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase) were without relationship to dextromethorphan dose, and therefore associated with the quinidine component, at 100 mg in all treated groups (16X the proposed clinical dose on a mg/m^2 basis). The increases in liver weights observed in all treated groups at 4 and 26 weeks of treatment in the males and females, were also without a dose relationship, and persisted after a 4-week recovery period. Centrilobular hypertrophy was observed with a dose-related increase in incidence (dextromethorphan related) in the male and female rats at 4 and 26 weeks, but there were no adverse histopathology findings in the livers of the recovery animals. The severity and incidence of hepatotoxic effects in the rats generally increased with duration of treatment. The NOAEL was not determined in this study (NOAEL <5/100 mg/kg/d DM/Q).

Renal Toxicity: Treatment-related renal toxicity was observed in the 4-week and 26-week repeated oral toxicity studies in rats given vehicle, and DM/Q at 5/100, 20/100, and 50/100 mg/kg/day (NOAEL not determined, <5/100 mg/kg/d DM/Q). The urinalysis evaluation showed increased urinary volume in the males and females, and decreased specific gravity in the females in all treated groups without relationship to dose

throughout the treatment period, suggesting a relationship to quinidine administration. No adverse effects were observed in the urinalysis after the 4-week recovery period. Kidney weights were increased without relationship to dextromethorphan dose level, in all treated female groups at 26 weeks of treatment, but not in the 4-week recovery females. The histopathology examination showed dose-related (suggesting a relationship to dextromethorphan treatment, because quinidine administration was constant at 100 mg/kg/d in all dose groups) increased incidence of kidney pelvic dilation, papillary mineralization, and hyaline droplets in the male rats at 4 weeks and cortical mineralization and tubule dilatation at the high dose, and hyaline droplets at the mid-dose and high dose in the males at 26 weeks. In the female rats, there were no treatment-related histopathology findings in the kidneys at 4 weeks of treatment, but the 26-week evaluation showed transitional cellular hyperplasia and tubular dilatation in the kidneys at the high dextromethorphan dose, suggesting increased risk of renal toxicity with prolonged use in humans.

Pulmonary Toxicity: Formal pulmonary safety pharmacology studies were not conducted for this NDA. However, the results of a study reported in the published literature (Salonen, 1988) on lung mechanics in anesthetized guinea pigs, showed that dextromethorphan significantly increased bronchoconstriction (increased lung resistance and decreased dynamic lung compliance) compared to controls. Irregular respiration was observed in mice given single oral (gavage) dextromethorphan doses representing 10 times the proposed clinical dose (NOAEL not determined, <125 mg/kg), and single dose oral (gavage) quinidine at 40 times the proposed clinical dose (NOAEL not determined, <500 mg/kg), on a mg/m^2 basis. Quinidine overdose in humans has induced respiratory depression or apnea, and pulmonary edema as a consequence of depressed myocardial contractility and acute left ventricular failure. Quinidine-induced pneumonitis during therapeutic use has been reported. Respiratory depression, dyspnea, and exacerbation of asthma have also been reported following acute dextromethorphan overdose

Cardiovascular Toxicity: The potential for Neurodex™-induced delayed cardiac repolarization and cardiac arrhythmias at high plasma drug concentrations was suggested by quinidine concentration-dependent inhibition of the HERG current in transfected HEK293 cells. Anecdotal clinical reports in the published literature described tachyarrhythmia and cardiac arrest after dextromethorphan overdose in children, ECG abnormalities (e.g., notched T waves and U waves in leads I, II, and V2 through V6) after ingestion of 2160 mg dextromethorphan by a 23 year-old male and hypertension in an 18 year-old male after ingesting 500 mg dextromethorphan. However, dextromethorphan alone and in combination with quinidine was not associated with cardiovascular toxicity in the histopathology and clinical pathology examinations in rats dosed for 26 weeks (up to 8 times for dextromethorphan and 16 times for quinidine the proposed clinical dose), in the clinical observations in rats dosed for 1 year (at up to 1.6 times for dextromethorphan and 3.25 times for quinidine the proposed clinical dose), and in the ECG clinical and histopathology examinations in dogs dosed for 42 days at up to 7 times the proposed clinical dextromethorphan dose (mg/m^2 basis). Quinidine is used therapeutically to prevent ventricular tachycardia and maintain sinus rhythm in atrial fibrillation patients, by inhibiting sodium and potassium cardiac currents, decreasing the

Vmax for Na+ influx, and increasing the duration of cardiac cell action potential by blocking K+ channel activity. Quinidine overdose in humans has been associated with life threatening depression of atrial, atrioventricular, and ventricular conduction, dysrhythmias, syncope, hypotension and shock. QT prolongation has been reported with currently recommended clinical quinidine doses for the treatment of malaria. The proposed clinical quinidine dose of 60 mg/day is 10 times to 40 X lower than that used currently for the treatment of dysrhythmias (200-600 mg orally, 3 to 4 times a day, not to exceed 3 to 4 grams daily).

Other: Quinidine is known to be associated with development of thrombocytopenia in clinical use, attributed to platelet surface binding of quinidine resulting in autoantibody production and platelet lysis (Mitchell JA, *et al*., 1990, Drug Safety 5:168-78). There were no effects on platelet levels by Neurodex™ in the clinical pathology evaluations in the repeated dose toxicology studies in mice at quinidine doses of up to 14 times the proposed clinical dose for 26 weeks and in rats at up to 16 times the clinical dose for 2-26 weeks (clinical pathology examinations not conducted in the 1-year interim study in rats and in the 42-day study in dogs).

Genetic Toxicity: The results of the genetic toxicology studies conducted for this NDA showed that dextromethorphan was negative in the Ames test, Micronucleus test *in vivo*, and in the mammalian chromosome aberration test in human lymphocytes *in vitro*. However, dextromethorphan increased polyploidy metaphase figures at the highest concentration used (400 mcg/ml) in human lymphocytes in the presence of metabolic activation with S9. Quinidine sulfate was negative in the Ames test and in the Mouse Micronucleus test *in vivo*, and equivocal for clastogenicity in the chromosome aberration test in human lymphocytes in the presence of S9 and increased the numbers of polyploidy metaphase figures with and without S9. In combination, dextromethorphan and quinidine were negative for clastogenicity *in vitro*, in the mammalian chromosome aberration test in human peripheral blood lymphocytes with and without metabolic activation. The results of the genetic toxicity studies should be clearly described in the product label.

Carcinogenicity: Neurodex was negative for carcinogenic potential in a 26-week assay in Tg.rasH2 mice given oral doses of up to 100 mg/kg/day dextromethorphan with and without 100 mg/kg/day quinidine. The results of the carcinogenicity study in mice should be presented in the product label. A 2-year carcinogenicity study in rats was initiated in mid-2003; the study report should be submitted for Agency review as soon as possible.

Reproductive Toxicity: Neurodex™ had no adverse effects on fertility in male and female rats, and teratogenicity in rats. Neurodex™ was embryotoxic in rats, inducing developmental delay with decreased ossification throughout the skeleton at the highest dose of 50/100 mg/kg/day DM/Q and in some skeletal areas at the low and mid doses of 5/100 and 15/100 mg/kg/day DM/Q. Dose-related fetal malformations, such as fused sternebrae, gastroschisis, phalangeal fusions, craniofacial abnormalities, diaphragmatic hernia, truncus arteriosis, and vertebral fusions, and decreased ossification of sternebrae, incomplete hyoid ossification and unossified epiphysis were observed in rabbits exposed

to maternal Neurodex™ doses of 5/60-30/60 mg/kg/day DM/Q. Evaluation of pre- and post-natal development in rats showed dose-related increased gestation duration, increased pup mortality and decreased pup weights at all oral doses tested (5/100-30/100 mg/kg/day DM/Q), with developmental delay that included delayed acquisition of righting response and increased spontaneous activity in rats given doses of 15/100-30/100 mg/kg/day DM/Q.

The reproductive toxicity studies in rats are considered to be substandard, based on the lack of adequate support for dose selection, and on insufficient maternal toxicity in the definitive studies to demonstrate maternal MTD levels.

Neurotoxicity: Dextromethorphan is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, and therefore, the Sponsor was asked to conduct a special toxicology study to evaluate the potential for inducing microscopic lesions characteristic of the "Olney Lesion" observed in rodents administered several NMDA antagonists (such as MK-801). Oral dextromethorphan at doses from 2-50 mg/kg (up to approximately 6 times the highest recommended clinical dose of 120 mg/day DM, and 12 times the proposed high dose of 60 mg/day on a mg/m^2 basis) in combination with the metabolic inhibitor quinidine, also given orally at 50 mg/kg was negative for induction of vacuolation and necrosis in the retrosplenial and posterior cingulate cortices that would identify the neurotoxic lesion in rats, under the conditions of the study. However, NMDA receptor antagonists have recently come under scrutiny for their association with induction of apoptosis during neuronal development in rat pups in a developmental period corresponding to that during neuronal development in the human fetus. No studies were conducted by the Sponsor to address the potential for apoptotic neurodegeneration by dextromethorphan in juvenile animals.

Drug Interactions: Potential interactive pharmacokinetic and/or pharmacodynamic effects by co-treatment with Neurodex™ and other drugs should be considered. Dextromethorphan is primarily metabolized by hepatic CYP2D6 to dextrorphan. The rationale for co-treatment with quinidine and dextromethorphan in the proposed drug product, is based on quinidine-induced inhibition of CYP2D6 metabolism to increase plasma levels and the duration of action of dextromethorphan modulation of pseudobulbar affect. However, quinidine may also alter the pharmacokinetics of other drugs that are metabolized by CYP2D6. Co-administration of quinidine may potentiate adverse cardiovascular effects, such as QT prolongation, by other potentially cardiotoxic drugs. Sedative effects may be enhanced by co-administration of dextromethorphan and CNS depressant drugs. Potential metabolic and pharmacodynamic interactions with Neurodex™ and drugs used in the treatment of multiple sclerosis, stroke, Alzheimer's disease, Amyotrophic Lateral Sclerosis (ALS), and other conditions for which patients are treated for pseudobulbar affect should also be considered.

Bromism: The potential for development of bromism due to the bromide moiety in dextromethorphan, although possible, is unlikely. Bromism has not, or has only rarely been reported from chronic abuse of currently marketed over-the-counter (OTC)

dextromethorphan hydrobromide products, at higher doses than those proposed for this product. Bromide toxicity is defined by plasma concentrations higher than 20 mmol/L.

Excipients: There are no novel excipients in the proposed drug product, Neurodex™.

Impurities and Degradation Products: The dextromethorphan impurity, (b) (4) is at the limit for qualification, of (b) (4) This level is considered to be acceptable based on its presence in the dextromethorphan lot used in the 28-day mouse toxicology, 26-week mouse carcinogenicity, and fertility (rat), embryo-fetal toxicity (rat and rabbit), and pre- and post-natal development studies (b) (4) in Lot #DM0302015). (b) (4)

TABLE OF CONTENTS – PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY

Brief summary:

Dextromethorphan has agonist activity at the $sigma_1$-opioid receptor and uncompetitive antagonist activity at the N-methyl-D-aspartate (NMDA) receptor, which decreases glutamate excitatory activity in the central nervous system.

Quinidine inhibits sodium and cardiac potassium currents, decreasing the Vmax for sodium influx and excitability, conduction velocity, and contractility, and increasing the duration of cardiac cell action potentials. Also, quinidine and its metabolites dihydroquinidine, 3-hydroxyquinidine, O-desmethylquinidine and quinidine-N-oxide, competitively inhibit the cytochrome P450 enzyme CYP2D6, responsible for metabolism of dextromethorphan.

Primary pharmacodynamics

Mechanism of action: Dextromethorphan inhibits Ca2+ uptake via the NMDA Ca2+ channel in neuronal PC12 cells *in vitro*, with an IC50 of 13 mcg/ml, and showed inhibition of glutamate-induced neurotoxicity *in vivo*. The results of a study on the comparative binding to the sigma-1, serotonin transporter, and the phencyclidine receptors are presented in the following table:

Table 2.6.2.2-1 Comparative K_i values for $Sigma_1$ and SERT

	K_i (nM)		
	$Sigma_1$	SERT	PCP
Dextromethorphan	150	40	NC
Dextrorphan	118	484	606
Memantine	NC	NC	NC
Amitriptyline	287	4.3*	NC
Fluoxetine	282	0.81*	NC

K_i = binding inhibition constant; NC = no competition at 1 µM; PCP = phencyclidine SERT = serotonin transporter

* K_D value from Tatsumi et al., 1997

Dextromethorphan also increases serotonin release by binding $5\text{-}HT_{1B/D}$ receptors (30% at 10 mcM in rat solitary tract nucleus in brain stem slices).

Early clinical studies showed that dextromethorphan decreased pseudobulbar affect, inappropriate or pathological emotional outbursts of laughing and crying, in some patients with amyotrophic lateral sclerosis, stroke, Alzheimer's disease, and multiple sclerosis. When combined with quinidine, plasma levels of dextromethorphan and presumably the pharmacological activity of dextromethorphan is enhanced, while

exposure to dextrorphan is limited. Dextrorphan is pharmacologically active at 4 times the parent drug concentration.

Secondary pharmacodynamics

Dextromethorphan and dextrorphan have antitussive properties related to inhibitory effects in the cough center of the medulla. Analgesic effects of dextromethorphan and dextrorphan are believed to be related to NMDA receptor antagonist and sigma agonist activity, and have been investigated for the treatment of painful diabetic neuropathy. Dextromethorphan may induce pupil dilation without reducing the respiratory rate or producing drowsiness or adverse gastrointestinal effects, and may increase blood pressure. Anticonvulsant activity by dextromethorphan and dextrorphan may be due to antagonism of glutamate activity.

Quinidine is primarily used for antiarrhythmic properties, to maintain sinus rhythm in atrial fibrillation patients and for prevention of ventricular tachycardia, by inhibiting sodium and potassium cardiac currents.

SAFETY PHARMACOLOGY

Neurological effects: No specific studies were conducted, except for the special toxicology study on neurotoxicity in rats, to evaluate the central nervous system (CNS) effects of dextromethorphan (DM) and quinidine (Q) in animals. CNS depression was observed in the acute toxicology studies in mice, rats and dogs. In the mice, hypoactivity or hyperactivity was induced by dextromethorphan at 125-250 mg/kg PO, and hypoactivity and convulsions by quinidine at ≥500 mg/kg PO and ≥700 mg/kg PO, respectively, in the dose range-finding studies for the Mouse Micronucleus Tests (DMQ-114 and DMQ-111). In single dose studies in rats, lethargy and convulsions were observed by oral (gavage) dextromethorphan administration at 100 mg/kg, and dose-related increases in the severity and incidence of lethargy by dextromethorphan (20-100 mg/kg) in combination with quinidine (50-100 mg/kg). The CNS effects in the acute toxicity study on dextromethorphan in dogs were ataxia, hyper-excitability, and tonic-clonic convulsions at the dose of 10 mg/kg PO. Convulsions were also observed in the dogs after repeated oral dextromethorphan dosing at 34.4 mg/kg/day.

CNS effects following dextromethorphan overdose in humans have included drowsiness, dizziness, gastrointestinal disturbance, ataxia, nervousness, hyper-excitability, stupor, hallucinations, paranoia, and coma (at 720 mg/36 hours). Clinical doses as low as 120 mg/day (controlled-release liquid) were reported to increase the frequency of complex partial seizures in 9 adults with epilepsy (Fisher *et al*., 1990). However, few adverse effects were reported at doses of <10 mg/kg dextromethorphan in children and 14 mg/kg/day in adults (960 mg/day). Serotonin agonist activity by dextromethorphan, by increasing serotonergic tone at 5-HT1A receptors and inhibiting the reuptake of serotonin, can result in serotonin syndrome, with hypertension or hypotension, hyperthermia, ventricular arrhythmias, rigidity, myoclonus, agitation, confusion and

coma. CNS effects of quinidine overdose in humans include headache, vertigo, confusion, delirium, coma, seizures (at ≥4 g in an adult), and cinchonism syndrome (headache, lethargy, psychomotor agitation, memory impairment, delirium, and hallucinations, at plasma levels above 5 mcg/ml).

Cardiovascular effects: No *in vivo* animal studies were conducted for this submission, to evaluate the cardiovascular effects of dextromethorphan and quinidine. A study on AVP-923 (Neurodex, dextromethorphan + quinidine) effects on HERG current in transfected HEK293 cells showed concentration-dependent inhibition by AVP-923 (IC50 values were 465.6 ng/mL (297.3 nM quinidine + 628.6 nM dextromethorphan) for AVP-923, 6591.7 ng/mL (17.8 mcM) for dextromethorphan, and 367.3 ng/mL (469.1 nM) for quinidine), suggesting a potential for delayed cardiac repolarization and cardiac arrhythmias by APV-923 at high plasma concentrations. However, quinidine is used therapeutically to prevent ventricular tachycardia and maintain sinus rhythm in atrial fibrillation patients, by inhibiting sodium and potassium cardiac currents, decreasing Vmax for Na+ influx, and increasing duration of cardiac cell action potential by blocking K+ channel activity.

Anecdotal clinical reports on cardiovascular effects of dextromethorphan in the published literature have described tachyarrhythmia and one case of cardiac arrest after overdose in children, ECG abnormalities (notched T waves and U waves in leads I, II, and V2 through V6) after ingestion of 2160 mg by a 23-year old male, and hypertension in an 18-year old male after ingesting 500 mg dextromethorphan.

Observations of acute quinidine-induced cardiovascular toxicity in humans included atrial, atrioventricular, and ventricular conduction depression, ventricular tachycardia and fibrillation, torsade de pointes, syncope, hypotension and shock. ECG recordings after quinidine overdose in humans have shown prolonged QRS, PR, and QT intervals, ST depression and T inversion. Serious cardiovascular toxicity by quinidine was observed in humans at plasma levels above 14 mcg/ml, although QT and QRS prolongation has been observed at levels above 2 mcg/ml.

Study title: ***Effects of AVP-923 (Dextromethorphan Hydrobromide and Quinidine Sulfate) on HERG Currents Recorded from Stably Transfected HEK293 Cells***

Key study findings:

- hERG current in transfected HEK293 cells were inhibited in concentration-dependent manner by AVP-923, dextromethorphan (DM) and quinidine (Q)
- IC50 values were 465.6 ng/mL (297.3 nM Q + 628.6 nM DM) for AVP-923, 6591.7 ng/mL (17.8 mcM) for DM, and 367.3 ng/mL (469.1 nM) for Q
- Inhibition of the hERG cardiac potassium channels suggests potential for delayed cardiac repolarization and cardiac arrhythmias by APV-923 at high plasma concentrations; however, Q is used therapeutically to prevent ventricular tachycardia and maintain sinus rhythm in atrial fibrillation patients, by inhibiting sodium and potassium cardiac currents, decreasing Vmax for Na+ influx, and

increasing duration of cardiac cell action potential by blocking K+ channel activity

Study no.: DMQ-130
Volume # Electronic submission folder m2\4 nonclinical study reports**, page #** 1
Conducting laboratory and location: (b) (4)
Date of study initiation: Report date November 18, 2004
GLP compliance: No
QA report: yes ( ) no (x)
Drug Dextromethorphan hydrobromide USP (DM)**, lot # DM302015, and % purity**: not provided
Drug Quinidine sulfate (Q)**, lot # 4963, and % purity**: not provided

Methods

Doses: DM and Q in a 1:1 ratio (weight): 20, 200, and 1500 ng/ml AVP-923 (20, 200, and 2000 ng/ml Q, and 200, 4000, and 15000 ng/ml DM combined)

Species/strain: Human embryonic kidney (HEK293) cells transfected with human ether-a-go-go gene (hERG) complementary DNA

Route, formulation, volume, and infusion rate: Test articles formulated in 100% dimethylsulfoxide (DMSO) vehicle (final concentration 0.1%), cells perfused as described under Unique study design, below

Unique study design: Activation of hERG current by depolarizing voltage step (b) (4) repeated 10 times at 15 second intervals, and then the test articles were perfused in the bath for 10 minutes, starting at the lowest concentration.

Observations

- hERG current changes were recorded and test article effects determined in 3 cells/concentration, compared to vehicle control (0.1% DMSO, 3 cells) and reference (E-4031 at 100 nM, 2 cells)
- Tail current amplitudes (before and after 10-minute exposures to test article) measured and presented as percent pretreatment control
- IC25, IC50, and IC75 values were determined

Results The concentration-response relationships for AVP-923, dextromethorphan, and quinidine, on the HERG tail currents are presented in the following figures and table (reproduced from the original NDA submission):

Figure 1. Concentration-Response Relationship of AVP-923 on HERG Tail Curren

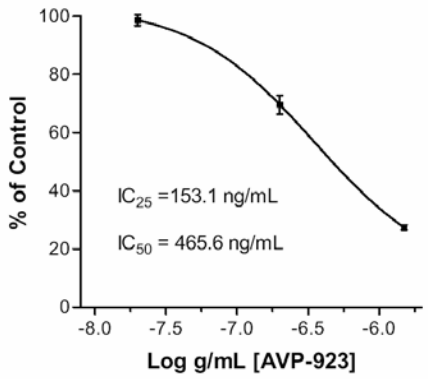


Figure 2. Concentration-Response Relationship of Quinidine Sulfate on HERG Tail Current

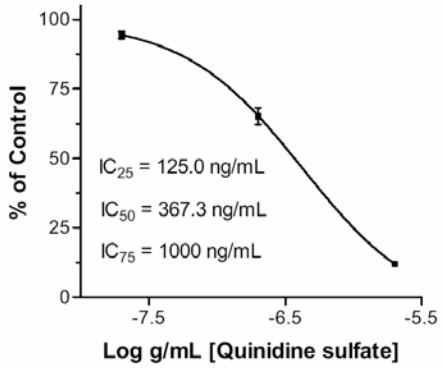


Figure 3. Concentration-Response Relationship of Dextromethorphan Hydrobromide on HERG Tail Current

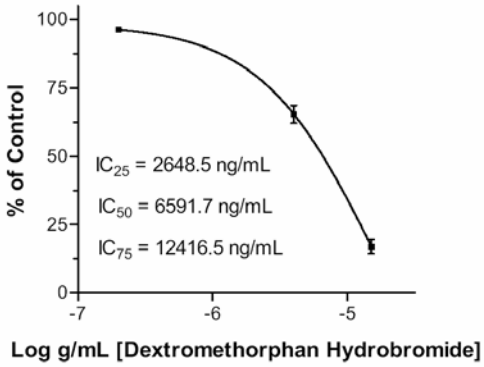


Table 1. Effects of Vehicle (0.1% DMSO), Reference Substance (E-4031), and Test Articles (AVP-923, Dextromethorphan Hydrobromide, and Quinidine Sulfate) on HERG Tail Current

Treatment (Target Concentrations)	Tail Current (% Control)	Tail Current (% Control) Vehicle Corrected Data
0.1% DMSO	88.8 ± 2.8	—
100 nM E-4031	9.2 ± 3.3	—
20 ng/mL AVP-923	87.5 ± 1.7	98.5 ± 1.9
200 ng/mL AVP-923	61.7 ± 2.9**	69.5 ± 3.3
1500 ng/mL AVP-923	24.4 ± 0.8**	27.4 ± 0.9
20 ng/mL Quinidine sulfate	83.8 ± 1.2	94.3 ± 1.3
200 ng/mL Quinidine sulfate	57.9 ± 2.7**	65.2 ± 3.0
2000 ng/mL Quinidine sulfate	10.6 ± 0.6**	12.0 ± 0.7
200 ng/mL Dextromethorphan hydrobromide	85.6 ± 0.2	96.3 ± 0.3
4000 ng/mL Dextromethorphan hydrobromide	58.0 ± 2.8**	65.3 ± 3.2
15000 ng/mL Dextromethorphan hydrobromide	15.1 ± 2.3 **	17.0 ± 2.6

Data are presented as mean ± (SEM) from $n = 3$ for each group with the exception of $n = 2$ in E-4031 group.

— Indicates not applicable

** $p < 0.01$ compared to vehicle group (ANOVA followed by Dunnett's t-test).

The estimated IC values are presented in the following table:

Test Article	IC25	IC50	IC75
AVP-923 (dextromethorphan + quinidine)	153.1 ng/ml (206.7 nM DM + 97.8 nM Q)	465.6 ng/ml (628.6 nM DM + 297.3 nM Q)	Not available
Dextromethorphan alone	2648.5 ng/ml (7. 2 mcM)	6591.7 ng/ml (17.8 mcM)	12416.5 ng/ml (33.5 mcM)
Quinidine alone	125.0 ng/ml (159.7 nM)	367.3 ng/ml (469.1 nM)	1000 ng/ml (1277.2 nM)

HERG tail current inhibited by E-4031 (100 nM) by 91%.

Pulmonary effects: No formal studies were conducted to evaluate respiratory effects of dextromethorphan and quinidine in animals. The results of a study reported in the published literature (Salonen, 1988) on lung mechanics in anesthetized guinea pigs, showed that dextromethorphan significantly increased bronchoconstriction (increased lung resistance and decreased dynamic lung compliance) compared to controls, and induced irreversible bradycardia and hypotension at intravenous doses of 10 and 15 mg/kg.

Quinidine overdose in humans has induced respiratory depression and pulmonary edema.

Renal effects: No formal studies were conducted to evaluate the renal effects of dextromethorphan and quinidine in animals. The results of the 26-week toxicity study in rats showed increased urinary volume and relative kidney weights with slight tubular dilation in the males and females, at oral gavage doses of ≥5/100 mg/kg/day dextromethorphan/quinidine at the 4-week interim evaluation. The kidney weight and microscopic findings were absent at the 26-week evaluations, suggesting a transient nature of the effects.

Chronic dextromethorphan intoxication in humans may induce incontinence, and elevated chloride and low anion gap have been associated with bromism. Oliguria (at 8 g), anuria (at 20 g), and acute renal failure due to shock has been observed after acute quinidine overdose.

Gastrointestinal effects: No formal studies were conducted to evaluate the gastrointestinal effects of dextromethorphan and quinidine in animals.

There are clinical reports of nausea and vomiting with acute and chronic dextromethorphan overdosing. Chronic intoxication may include anorexia and weight loss. Acute quinidine overdose was also associated with nausea, vomiting, and diarrhea.

Abuse liability: Abuse liability studies in animals have not been conducted. Abuse of dextromethorphan has been reported, but no evidence of morphine-like dependence has been found.

Pharmacodynamic drug interactions

Serious adverse events and fatalities have been reported after combined ingestion of dextromethorphan and MAOIs.

PHARMACOKINETICS/TOXICOKINETICS

Brief summary

Oral quinidine increased systemic oral dextromethorphan exposure ($AUC_{0\text{-}inf}$ and Cmax) in a dose-related manner in male and female mice, at all single doses tested (30-120

mg/kg) with maximal effect on dextromethorphan exposure at 30 mg/kg quinidine. This suggests saturation of quinidine inhibitory effects on CYP2D activity in mice at 30-40 mg/kg PO. Consequently, exposure to the metabolite dextrorphan was decreased at all quinidine doses tested. The quinidine $AUC_{0\text{-}inf}$ values increased in a dose-linear manner. Oral absorption was rapid for both dextromethorphan and quinidine. The Tmax for dextromethorphan (15 minutes-1 hour) was not altered by co-administration of quinidine in the males. The Tmax for dextromethorphan decreased to 15-30 minutes in females that received quinidine co-administration. The quinidine Tmax was 15-30 minutes.

Oral quinidine increased systemic exposure to 20 mg/kg oral dextromethorphan ($AUC_{0\text{-}t}$ increased 1.3X, 2.9X, and 4.1X at 2, 20, and 100 mg/kg quinidine, respectively) and 50 mg/kg dextromethorphan (1.5X, 2.5X, and 2.2X at 2, 20, and 50 mg/kg quinidine, respectively) over AUC values for dextromethorphan alone, in Sprague Dawley rats. Exposure to dextromethorphan and to dextrorphan was greater in the females than in the males, and the increase in dextromethorphan exposure induced by quinidine co-administration was lower in the females than in the males. Systemic exposure to dextromethorphan and quinidine was greater, and dextrorphan exposure was lower under fasted than under fed conditions in both the males and females.

In the pharmacokinetic study on dextromethorphan in fasted male Beagle dogs given dextromethorphan in oral capsules at 10 mg/kg, there were insufficient numbers of samples for PK analysis, although plasma sampling showed rapid absorption (15-30 minutes) with Cmax values from 47-2479 ng/ml dextromethorphan and 78-1105 ng/ml dextrorphan.

In humans, oral absorption of dextromethorphan was rapid, with peak plasma levels (Tmax) observed at 2-4 hours after administration. The oral bioavailability of quinidine is 70%-80%. Peak plasma quinidine levels were found at 1-3 hours.

No studies were conducted in animals, to evaluate dextromethorphan and quinidine distribution, for this NDA submission. The dextromethorphan volume of distribution (Vd) in dogs was reported to be 5-6.4 L/kg (b) (4)).

The clinical distribution of dextromethorphan after a fatal overdose (dose unknown) was reported (Kintz and Mangin, 1992) to be 5.09 mg/L in whole blood, 3.29 mg/L in urine, 3.48 mg/L in bile, 10.74 mg/kg of tissue in liver, 2.38 mg/kg of tissue in heart, 4.27 mg/kg of tissue in kidney, and 3.47 mg/kg of tissue in brain. In that report, the distribution of dextrorphan was reported to be 1.20 mg/L in whole blood, 3.09 mg/L in urine, 1.86 mg/L in bile, 4.81 mg/kg of tissue in liver, 1.72 mg/kg of tissue in heart, 2.09 mg/kg of tissue in kidney, and 1.58 mg/kg of tissue in brain (from (b) (4)). The CSF/plasma dextromethorphan ratio has been reported to be 32.8%-80% (Hollander *et al*., 1994, cited in Micromedex, DrugDex Drug Evaluations). In another clinical study (Steinberg *et al*., 1996) in post neurosurgery patients, the brain dextromethorphan concentration was 68X that in serum, and brain dextrorphan concentration was 14X the concentration in serum.

Studies to evaluate dextromethorphan protein binding in animals, were not conducted for this NDA submission. Dextromethorphan is approximately 50%-60% bound to rat plasma proteins *in vitro* at concentrations of 0.5-500 mcM. In humans, quinidine protein binding was approximately 80%-88% in adults and older children, and 50%-70% in pregnant women, infants and neonates, predominantly to alpha-1-acid glycoprotein and albumin. Quinidine protein binding in mice is unknown, and is believed to be comparable in rats to that in humans, based on decreased plasma protein binding of propranolol with quinidine co-administration. The Vd of quinidine is 2-3 L/kg in healthy adults, although the Vd may be reduced in heart failure patients to as low as 0.5 L/kg.

Dextromethorphan is metabolized in humans by hepatic O-demethylation by CYP2D6 to dextrorphan, and by CYP3A4 and N-demethylation to 3-methoxymorphinan. Minor metabolites (<15% dose) include d-methoxymorphinane and d-hydroxymorphinane. Dextrorphan and 3-methoxymorphinan are demethylated to 3-hydroxymorphinan, which undergoes glucuronidation before excretion. Approximately 5%-10% population are poor CPY2D6 metabolizers, with resulting plasma dextromethorphan levels of 10 ng/ml at 4 hours and 5 ng/ml at 24 hours after oral administration at 30 mg. In intermediate metabolizers (approximately 6.8% population), plasma dextromethorphan was 10-20 ng/ml at 4 hours and <5 ng/ml at 24 ours after oral administration of dextromethorphan at 30 mg. The plasma level after an oral dose at 30 mg in extensive metabolizers <5 ng/ml at 4 hours post-dose. Formation of CYP2D6 products are similar in liver microsomes from 12 different mouse strains to those by human liver microsomes, and therefore it is assumed that dextromethorphan metabolism will be similar in mice and humans.

Quinidine is metabolized in rodents and humans by cytochrome P450 (CYP)3A4. Quinidine metabolites include 3-hydroxy-quinidine (10%), 2'-quinidinone (10%), quinidine-N-oxide (1%), quinidine 10,11-dihydroliol (3%), O-desmethyl-quinidine (1%-2%), and 2'-Oxoquinidione. The 3-hydroxy-quinidine, quinidine-N-oxide, and 2'oxoquinidione metabolites are pharmacodynamically active.

According to Hildebrand *et al*, 1989 (cited in Micromedex, MEDITEXT®-Medical Management), 0-11% parent drug dextromethorphan and 0.1%-100% the remainder of the dextromethorphan dose in the form of demethylated, conjugated morphinan compounds is excreted unchanged in urine, the ratio depending on the metabolism phenotype. The plasma half life of dextromethorphan is 1.4-3.9 hours and the half-life of dextrorphan is 2.5 hours after a single oral dextromethorphan dose of 2.5 mg in humans.

In humans, approximately 20% quinidine is excreted unchanged in urine, and clearance is 4.7 ± 1.8 mL/min/kg. Quinidine elimination is predominantly by CYP3A4 enzyme metabolism, and first pass metabolic effect. Quinidine clearance is increased with decreasing urinary pH. The elimination half-life is 3-16 hours (mean 6-8 hours in adults, 3-4 hours in children). The half-life of the major metabolite 3-hydroxy-quinidine is 6.1-10 hours.

Drugs that inhibit dextromethorphan metabolism by interaction with cytochrome P450 CYP2D6 (e.g., quinidine, amiodarone, fluoxetine, paroxetine, propafenone, thioridazine,

etc) can increase dextromethorphan plasma levels to those associated with toxicity. However, this interaction underlies the rationale for this combination product, to increase DM plasma levels by inhibition of metabolism by CYP2D6 enzymes with quinidine co-administration.

Quinidine plasma concentration may be increased by acetazolamide, aluminum hydroxide, amiodarone, cimetidine, sodium bicarbonate, and verapamil, and decreased by diphenoxylate, kaolin-pectin, phenobarbital, phenytoin, and rifampin. Additionally, drugs that inhibit cytochrome P450 enzymes (e.g., metronidazole, ciprofloxacin, and erythromycin) may increase quinidine plasma levels. Reduction of P-glycoprotein-mediated tubular secretion of quinidine (e.g., by itraconazole) may decrease renal clearance and elevate plasma levels to those associated with toxicity in humans.

Study title: ***A study of the pharmacokinetics of dextromethorphan and quinidine and the effect of quinidine on the pharmacokinetics of dextromethorphan following a single oral administration in male and female Sprague-Dawley rats***

Key study findings:

- Deaths were observed after DM administration when given at 200 mg/kg alone, at 20 mg/kg in combination with Q at 100 mg/kg, at 50 mg/kg in combination with Q at 20 mg/kg, and at 100 mg/kg in combination with Q at 50 mg/kg
- The adverse effects attributed to the DM component at 200 mg/kg were lethargy, coma, and convulsions
- Adverse effects of DM (up to 100 mg/kg) in combination with Q (50-100 mg/kg) included decreased locomotor activity, lethargy, severe tremors, and depression
- Dose-related increase in DM exposure (AUC_{0-t}) at the doses of 20, 50, and 100 mg/kg with Q co-administration (for example DM exposure after 20 mg/kg increased from 1.3X – 4.1X compared to DM alone when given with Q at 2, 20 and 100 mg/kg)
- Increase in DM exposure by Q greater in the males than in the females
- However, DM and dextrorphan (DX) AUC_{0-t} and Cmax values higher in females than in males, with Q co-administration.

Study no: Avanir Study No. DMQ-101
Volume # 1**, and page #** 4
Conducting laboratory and location: (b) (4)
Date of study initiation: October 30, 2001
GLP compliance: yes ( ) no (x)
QA report: yes (x) no ( )
Drug Dextromethorphan hydrobromide USP**, lot #** DM 9912074 (MCS 00-377)**, radiolabel** Not applicable**, and % purity** 99.7%
Drug Quinidine sulphate**, lot #**9900130 (MCS 00-376)**, radiolabel** Not applicable**, and % purity** 100.1%
Formulation/vehicle: Test articles in 1% methylcellulose ((b) (4) Lot No. 90K0865) in sterile water ((b) (4), Lot No. 71-057)

Methods (unique aspects)**:** The rats were housed singly in stainless steel cages in a temperature (21°C ± 3°C) and humidity (46% - 69%) controlled animal room with 12 hour light/dark cycle. The rats were fed standard certified commercial laboratory food (Teklad 7012C) *ad libitum* and provided filtered (reverse osmosis and UV sterilized) drinking water *ad libitum*, except that the rats were fasted overnight before dosing. The food was made available 4 hours after dosing.

Dosing:

Species/strain: Sprague Dawley Crl:CD(SD)IGS BR rats ((b) (4))

#/sex/group or time point (main study): 5 males/dose or 3/sex/dose combination (see under Doses in administered units, below)

Satellite groups used for toxicokinetics or recovery: None

Age: 7-8 weeks

Weight: 222-280 g

Doses in administered units: The following dose combinations were administered:

Quinidine (mg/kg)	Dextromethorphan (mg/kg)					
	0	2	20	50	100	200
0	NA	5 males	5 males	5 males	5 males	3 males 3 females
2	5 males	3 males 3 females	3 males 3 females	3 males 3 females	NA	NA
20	5 males	NA	3 males 3 females	3 males 3 females	NA	NA
50	5 males	NA	NA	3 males 3 females	3 males 3 females	NA
100	5 males	NA	3 males 3 females	NA	NA	NA

NA: not administered

Route, form, volume, and infusion rate: Single oral dose by gavage at 5 ml/kg

Observations and times: The rats were observed for 4 hours after dosing for adverse effects. Blood samples (0.4 ml) were obtained from the jugular vein, using lithium heparin as an anticoagulant, at predose and 0.5, 1, 2, 6, 12, and 24 hours after dosing. The limits of detection of the LC/MS/MS procedures were 2.00 ng/ml for dextromethorphan, 25.00 ng/ml for dextrorphan, and 0.110 mcg/ml for quinidine.

Results: There were deaths in 1/5 rats at 50 mg/kg Q, 1/6 rats at 20/100 mg/kg DM/Q, 1/6 rats at 50/20 mg/kg DM/Q, 6/9 rats at 100/50 mg/kg DM/Q, and 1/6 rats at 200 mg/kg DM, and 5/6 rats at 200 mg/kg DM were sacrificed *in extremis* due to the clinical observations. The clinical observations included decreased locomotor activity at 20/100 mg/kg DM/Q, lethargy at 50/20 mg/kg DM/Q, severe tremors, depression, decreased motility, severe swelling in plantar region of hind legs and lethargy at 100/50 mg/kg DM/Q, and lethargy, comatose, and convulsions at 200 mg/kg DM.

The results of the pharmacokinetic analyses are presented in the following tables:

Pharmacokinetic Parameters of Dextromethorphan in Rats Administered Single Oral Doses of Dextromethorphan and Quinidine (Group Means)

Dose DM (mg/kg)	Dose Q (mg/kg)	Sex	AUC_{0-t} (ng.h/ml)	AUC_{0-inf} (ng h/ml)	Tmax (h)	Cmax (ng/ml)	T1/2 (h)
2	0	Males	NC	NC	NC	NC	NC
2	2	Males	1.67	NC	0.67	2.54	NC
		Females	6.50	NC	0.50	6.72	NC
20	0	Males	117.3	128.1	0.80	43.74	1.63
20	2	Males	151.2	173.9	0.50	64.80	4.18
		Females	746.9	799.9	0.83	285.47	4.56
20	20	Males	334.4	351.6	1.00	144.43	1.33
		Females	869.7	884.9	1.33	274.93	1.64
20	100	Males	482.9	536.9	1.68	58.87	5.91
		Females	1792.9	1827.9	1.33	314.39	2.49
50	0	Males	1169.3	1180.3	1.10	435.47	1.83
50	2	Males	1766.2	1781.1	0.83	704.17	1.79
		Females	4299.3	4353.8	1.00	1492.03	2.12
50	20	Males	2969.9	2984.3	0.83	1234.79	1.51
		Females	4051.8	NC	1.67	1695.80	NC
50	50	Males	2630.9	2654.2	0.83	844.84	1.74
		Females	7066.7	7131.9	1.00	1688.23	2.21
100	0	Males	3008.0	3035.4	1.40	836.37	1.82
100	50	Males	4711.8	4739.2	2.00	1010.25	2.26
		Females	NC	NC	NC	NC	NC

DM: dextromethorphan; Q: quinidine; NC: not calculated due to insufficient data

Pharmacokinetic Parameters of Dextrorphan in Rats Administered Single Oral Doses of Dextromethorphan and Quinidine (Group Means)

Dose DM (mg/kg)	Dose Q (mg/kg)	Sex	AUC_{0-t} (ng.h/ml)	AUC_{0-inf} (ng h/ml)	Tmax (h)	Cmax (ng/ml)	T1/2 (h)
2	0	Males	572.1	4675.6	6.00	73.39	56.79
2	2	Males	703.2	1868.2	6.00	79.15	14.4
		Females	928.2	1874.0	4.17	130.82	6.95
20	0	Males	6748.3	8102.6	6.00	443.71	8.25
20	2	Males	7547.1	8680.1	4.33	554.90	7.00
		Females	12976.1	13582.7	6.17	983.43	4.10
20	20	Males	6989.6	8123.3	1.17	765.72	7.80
		Females	14017.6	15222.6	6.33	1036.32	5.47
20	100	Males	5795.5	NC	9.00	317.97	NC
		Females	12143.8	NC	1.00	877.23	NC
50	0	Males	12847.9	28220.4	1.40	1076.20	19.55
50	2	Males	15465.6	17996.4	1.00	1482.34	7.60
		Females	27146.2	34336.4	4.67	2182.18	8.83
50	20	Males	16452.1	21763.0	1.00	1968.55	12.1
		Females	16654.4	NC	1.33	1566.90	NC
50	50	Males	16759.8	NC	1.00	1527.48	NC
		Females	21678.3	NC	2.67	1812.24	NC
100	0	Males	19797.8	35042.2	2.00	2132.28	22.58
100	50	Males	25742.2	NC	2.00	2487.68	NC
		Females	NC	NC	NC	NC	NC

DM: dextromethorphan; Q: quinidine; NC: not calculated due to insufficient data

Pharmacokinetic Parameters of Single Oral Dose Quinidine in Rats (Group Means)

Dose Q (mg/kg)	Sex	AUC_{0-t} (ng.h/ml)	AUC_{0-inf} (ng.h/ml)	Tmax (h)	Cmax (ng/ml)	T1/2 (h)
20	Males	0.0	NC	1.10	0.296	NC
50	Males	6.1	7.6	1.80	1.578	2.38
100	Males	16.2	18.8	1.40	2.21	2.26

Q: quinidine; NC: not calculated due to insufficient data

Summary of individual study findings: Dextromethorphan (DM) exposure (AUC_{0-t}), when administered at 20 mg/kg, was increased 1.3X, 2.9X and 4.1X by quinidine (Q) at 2, 20, and 100 mg/kg, respectively, compared to exposure at 20 mg/kg DM alone. At 50 mg/kg DM, exposure increased 1.5X, 2.5X, and 2.2X by Q co-administration at 2, 20, and 50 mg/kg, respectively. DM exposure, at the dose of 100 mg/kg, increased 1.6X by Q at 100 mg/kg. This effect was greater in the males than in the females. The DM and dextrorphan (DX) AUC_{0-t} and Cmax values were higher in females than in males, with Q co-administration.

Absorption

Dextromethorphan and quinidine are rapidly and extensively absorbed, by the oral route. The time to peak oral dextromethorphan concentration is 2-2.5 hours in humans. There was no effect of food on oral dextromethorphan absorption in clinical testing. Information on oral dextromethorphan bioavailability was not available. Oral quinidine bioavailability is approximately 70%-80%.

Male and female C57BL/6 mice were administered single oral doses of Dextromethorphan and Quinidine in combination, to determine the dose of quinidine required to maximize the exposure to dextromethorphan (Avanir Study No. DMQ-116). The following doses of dextromethorphan/quinidine (mg/kg) were administered in Phase 1: 20/0, 60/0, 200/0; 20/10, 20/20, 20/40, 20/100; 60/30, 60/60, 60/100; 200/50, 200/100. In Phase 2, the following doses of dextromethorphan/quinidine (mg/kg) were administered: 20/0, 60/0; 20/10, 20/20, 20/40; 60/30, 60/60, and 60/120. In Phase 1, there was dose-related mortality in the males (1/3 at 200/50 mg/kg DM/Q, 3/3 at 200/100 mg/kg DM/Q) and females (1/3 at 20/10 mg/kg DM/Q and 3/3 females at all higher dose combinations). In the Phase 2 evaluation, dextromethorphan AUC values were highest at the doses of 40 mg/kg Q in combination with 20 mg/kg DM and 30 mg/kg Q in combination with 60 mg/kg DM. The results of the PK evaluation from Phase 2 are presented in the following tables (reproduced from the original IND submission):

Dextromethorphan Pharmacokinetics in Mice Administered Single Oral Doses of Dextromethorphan and Quinidine in Combination

Dextromethorphan hydrobromide dose (mg/kg)	Quinidine sulphate dose (mg/kg)	Gender	Cmax (ng/ml)	Tmax (h)	$AUC_{0\text{-last}}$ (ng.h/ml)	$AUC_{0\text{-inf}}$ (ng h/ml)	T1/2 (h)
20	0	Male	122.27	0.25	164.4	169.5	1.12
		Female	82.5	1.00	113.1	113.9	0.82
	10	Male	235.3	0.25	217.1	237.5	1.9
		Female	298.0	0.25	201.4	240.7	1.7
	20	Male	358.5	0.25	294.3	303.7	1.3
		Female	144.7	0.50	161.9	191.0	0.66
	40	Male	164.9	0.25	340.2	342.8	1.6
		Female	234.9	0.25	281.1	283.0	0.8
60	0	Male	787.1	0.25	1153.3	1190.1	1.9
		Female	413.9	1.00	821.6	831.0	1.7
	30	Male	1517.5	0.25	1949.1	1991.5	2.1
		Female	1069.7	0.25	1376.7	1383.5	1.7
	60	Male	908.2	0.5	1649.7	1654.7	1.44
		Female	1099.8	0.25	1223.2	1243.5	1.7
	120	Male	1171.3	0.50	1673.4	1787.2	2.4
		Female	591.6	0.25	1184.5	1223.6	2.1

Dextrorphan Pharmacokinetics in Mice Administered Single Oral Doses of Dextromethorphan and Quinidine in Combination

Dextromethorphan hydrobromide dose (mg/kg)	Quinidine sulphate dose (mg/kg)	Gender	Cmax (ng/ml)	Tmax (h)	$AUC_{0\text{-last}}$ (ng.h/ml)	$AUC_{0\text{-inf}}$ (ng h/ml)	T1/2 (h)
20	0	Male	9329	0.50	10836	10937	2.1
		Female	11292	0.50	11883	12056	0.9
	10	Male	10077	0.50	11958	12278	2.7
		Female	10856	0.25	12128	13094	4.3
	20	Male	9960	0.50	11766	12139	2.7
		Female	9861	0.50	10588	10626	1.3
	40	Male	9230	0.25	12156	12468	1.9
		Female	9392	0.25	10943	11160	1.7
60	0	Male	16782	0.25	30037	31839	2.3
		Female	22237	0.25	32219	33642	3.3
	30	Male	13884	0.50	26189	28156	3.6
		Female	19225	0.50	31529	33109	3.5
	60	Male	14530	0.50	24106	25098	3.1
		Female	17120	0.25	24085	25292	2.2
	120	Male	13632	0.50	21129	23970	3.0
		Female	12253	0.25	19933	24604	6.4

Quinidine Pharmacokinetics in Mice Administered Single Oral Doses of Dextromethorphan and Quinidine in Combination

Dextromethorphan hydrobromide dose (mg/kg)	Quinidine sulphate dose (mg/kg)	Gender	Cmax (ng/ml)	Tmax (h)	$AUC_{0\text{-last}}$ (ng.h/ml)	$AUC_{0\text{-inf}}$ (ng h/ml)	T1/2 (h)
20	10	Male	679	0.28	316	372	0.3
		Female	489	0.25	239	312	0.4
	20	Male	863	0.25	748	907	0.7
		Female	750	0.25	625	684	0.5
	40	Male	971	0.25	1235	1614	0.9
		Female	1380	0.25	1373	1670	0.8
60	30	Male	1455	0.25	1762	1842	1.3
		Female	1091	0.25	1009	1184	0.7
	60	Male	1826	0.50	3302	3781	1.8
		Female	2207	0.25	2148	2465	0.7
	120	Male	4265	0.50	7720	8257	2.5
		Female	2690	0.25	5377	5507	1.9

In a single oral dose study in male and female Sprague-Dawley rats (Avanir Study No. DMQ-101), dextromethorphan (DM) exposure ($AUC_{0\text{-t}}$), when administered at 20 mg/kg, was increased 1.3X, 2.9X and 4.1X by quinidine (Q) at 2, 20, and 100 mg/kg, respectively, compared to exposure at 20 mg/kg DM alone. At 50 mg/kg DM, exposure increased 1.5X, 2.5X, and 2.2X by Q co-administration at 2, 20, and 50 mg/kg, respectively. DM exposure, at the dose of 100 mg/kg, was increased 1.6X by Q at 100 mg/kg. This effect was greater in the males than in the females. The DM and dextrorphan (DX) $AUC_{0\text{-t}}$ and Cmax values were higher in females than in males, with Q co-administration.

The effects of food on the pharmacokinetic parameters of dextromethorphan, quinidine, and the dextromethorphan metabolite, dextrorphan, were evaluated in male and female rats given single oral doses of dextromethorphan (50 mg/kg) in combination with quinidine (50 mg/kg) ((b) (4) Study No. 84/015). Exposure to dextromethorphan was higher in female than in male rats under fasted and fed conditions. Feeding decreased the maximum plasma levels of dextromethorphan and quinidine, and decreased exposure (AUC) to both drugs, but increased metabolism of dextromethorphan to dextrorphan. Thus, feeding increased exposure to the metabolite, dextrorphan. The results are presented in the following tables (reproduced, in part, from the original IND submission):

Toxicokinetic Parameters of Dextromethorphan, Dextrorphan, and Quinidine in Male and Female Rats Administered Single Oral Doses of 50 mg/kg Dextromethorphan and 50 mg/kg Quinidine Combined (n=6/sex) under Fasted and Fed Conditions

Alimentary Condition	Sex	Tmax (h)	Cmax (ng/ml)	AUC_t (ng h/ml)	$AUC_{0\text{-inf}}$ (ng.h/ml)	T1/2 (h)	CL/F (L/kg/h)	Varea/F (L/h)
Dextromethorphan								
Fasting	**Male**	0.50	830.4	2719	2732	1.55	18.30	41.01
	Female	2.00	1105.0	4956	5132	2.75	9.74	38.60
Fed	**Male**	1.00	98.5	337	366	3.39	136.70	669.37
	Female	1.00	341.0	1814	NC	NC	NC	NC
Dextrorphan								
Fasting	**Male**	1.00	2278	12443	NC	NC	NC	NC
	Female	2.00	1498	10451	NC	NC	NC	NC
Fed	**Male**	6.00	1726	15284	NC	NC	NC	NC
	Female	6.00	1604	13422	NC	NC	NC	NC
Quinidine								
Fasting	**Male**	2.00	1.743	7.87	NC	NC	NC	NC
	Female	2.00	1.543	8.77	9.14	2,38	5.47	18.81
Fed	**Male**	1.00	0.779	4.67	5.76	5.20	8.68	65.14
	Female	1.00	0.674	3.62	4.48	4.87	11.16	78.38

NC: Not calculated due to insufficient blood sampling times in the terminal elimination phase

The results of the toxicokinetic evaluation in the 26-week toxicity study (b) (4) Study No. 84/014) in male and female rats (n=6/sex/dose) administered oral dextromethorphan at 5, 20, and 50 mg/kg/day in combination with 100 mg/kg/day oral quinidine showed less than dose-proportional increases in dextromethorphan Cmax and AUC, with nonlinear PK indicated by decreased half-life and clearance after repeated dosing. Dextromethorphan exposure was greater in females than in males. There were no changes in quinidine PK parameters as a function of dextromethorphan dose. Accumulation was demonstrated for dextromethorphan, dextrorphan, and quinidine with repeated daily dosing for 26 weeks. The effect of quinidine on dextromethorphan metabolism was not evaluated in this study, as no control group (dextromethorphan alone) was employed. The results of the 26-week TK evaluation in male and female rats are presented below (reproduced from the original IND submission):

Dextromethorphan Pharmacokinetic Parameters in Male and Female Rats Administered Oral Dextromethorphan in Combination with 100 mg/kg/day PO Quinidine for 26 Weeks

Dose DM/Q* (mg/kg/day)	Sex	Tmax (h)	Cmax (ng/ml)	AUC_{0-t} (ng.h/ml)	AUC_{0-24} (ng h/ml)	T1/2 (h)
Day 0						
5/100	**Male**	2.00	17.28	55	64	NC**
	Female	0.25	12.26	113	113	8.63
20/100	**Male**	0.50	84.61	200	216	NC
	Female	1.00	122.12	975	975	NC
50/100	**Male**	0.50	350.75	1852	1852	NC
	Female	1.00	363.28	2623	2623	9.47
Day 27						
5/100	**Male**	2.00	25.64	78	87	NC
	Female	2.00	29.10	147	177	NC
20/100	**Male**	6.01	52.75	429	484	NC
	Female	1.05	390.86	2231	2231	NC
50/100	**Male**	0.51	481.86	2231	2231	2.64
	Female	2.03	495.09	4072	4072	5.52
Day 91						
5/100	**Male**	2.00	19.80	121	132	2.32
	Female	0.25	70.06	364	364	NC
20/100	**Male**	0.52	106.63	393	451	3.32
	Female	1.03	291.98	2355	2355	NC
50/100	**Male**	0.50	521.67	2631	2631	4.09
	Female	2.01	693.45	5129	5129	6.09
Day 182						
5/100	**Male**	0.25	20.22	122	136	2.78
	Female	2.00	33.63	153	213	NC
20/100	**Male**	0.50	132.14	584	616	NC
	Female	1.00	294.95	2573	2573	NC
50/100	**Male**	0.50	546.27	2724	2724	5.04
	Female	2.00	597.81	4220	4220	3.86

*DM = Dextromethorphan hydrobromide; Q = Quinidine sulphate

**Not calculated due to insufficient blood sampling times in the terminal elimination phase

AUC_{0-inf} (ng.h/ml) values on Day 0 were NC and 131 in males and females at 5 mg/kg/d DM, NC in males and females at the mid-dose, and ND and 3237 in males and females at the high dose of 50 mg/kg/day DM in combination with 100 mg/kg/day Q.

Accumulation of Dextromethorphan in Male and Female Rats Administered Oral Dextromethorphan in Combination with 100 mg/kg/day Oral Quinidine for 26 Weeks

Dose Level (mg/kg/day)**	Gender	Accumulation Ratio (%)*		
		Day 27 vs. Day 0	Day 91 vs. Day 0	Day 182 vs. Day 0
5/100	Male	136	207	214
	Female	157	322	188
20/100	Male	225	214	286
	Female	229	241	264
50/100	Male	120	142	147
	Female	155	196	161

*Percent increase in observed AUC0-24 between Days 27, 91, and 182 and Day 0
**Dextromethorphan/Quinidine

Dextrorphan Pharmacokinetic Parameters in Male and Female Rats Administered Oral Dextromethorphan in Combination with 100 mg/kg/day PO Quinidine for 26 Weeks

Dose DM/Q* (mg/kg/day)	Sex	Tmax (h)	Cmax (ng/ml)	AUC_{0-t} (ng h/ml)	AUC_{0-24} (ng.h/ml)	T1/2 (h)
Day 0						
5/100	Male	6.00	335.27	4232	4232	7.56
	Female	0.25	213.66	3080	3080	13.74
20/100	Male	6.00	934.72	13353	13353	10.22
	Female	6.00	702.19	11482	11482	NC
50/100	Male	12.00	2508.88	41302	41302	NC
	Female	1.00	2318.12	25806	25806	NC
Day 27						
5/100	Male	6.01	376.40	5031	5031	15.4
	Female	6.02	366.25	5534	5534	12.0
20/100	Male	6.01	1288.62	24854	24854	16.9
	Female	0.25	1131.04	13743	13743	NC
50/100	Male	11.98	2390.19	47414	47414	NC
	Female	6.00	2202.73	42966	42966	NC
Day 91						
5/100	Male	6.02	510.88	6846	6846	7.36
	Female	0.25	399.81	7985	7985	NC
20/100	Male	12.00	1623.17	30603	30603	NC
	Female	6.02	1005.87	15583	15583	19.10
50/100	Male	0.25	2920.22	49730	49730	32.33
	Female	12.00	2526.95	40892	40892	NC
Day 182						
5/100	Male	6.00	539.60	6624	6624	7.90
	Female	12.02	329.82	6166	6166	NC
20/100	Male	12.04	923.69	20553	20553	NC
	Female	6.00	1187.71	14389	14389	19.70
50/100	Male	0.50	3144.26	54773	54773	12.05
	Female	12.05	2445.05	41161	41161	NC

*DM = Dextromethorphan hydrobromide; Q = Quinidine sulphate
**Not calculated due to insufficient blood sampling times in the terminal elimination phase

AUCinf values (ng.h/ml) for dextrorphan on Day 0 4862 and 4280 ng.h/ml in males and females, respectively at the low DM dose of 5 mg/kg/day, and 17245 ng.h/ml in the males at the mid-dose of 20 mg/kg/day DM in combination with 100 mg/kg/day oral Q. The AUCinf values for the mid-dose females, and the high-dose males and females were not calculated due to insufficient blood sampling times in the terminal elimination phase.

Accumulation of Dextrorphan in Male and Female Rats Administered Oral Dextromethorphan in Combination with 100 mg/kg/day Oral Quinidine for 26 Weeks

Dose Level (mg/kg/day)**	Gender	Accumulation Ratio (%)*		
		Day 27 vs. Day 0	Day 91 vs. Day 0	Day 182 vs. Day 0
5/100	**Male**	119	162	157
	Female	180	259	200
20/100	**Male**	186	229	154
	Female	129	136	125
50/100	**Male**	115	120	133
	Female	166	158	160

*Percent increase in observed AUC_{0-24} between Days 27, 91, and 182 and Day 0
**Dextromethorphan/Quinidine

Quinidine Pharmacokinetic Parameters in Male and Female Rats Administered Oral Dextromethorphan in Combination with 100 mg/kg/day PO Quinidine for 26 Weeks

Dose DM/Q* (mg/kg/day)	Sex	Tmax (h)	Cmax (ng/ml)	AUC_{0-t} (ng h/ml)	AUC_{0-24} (ng h/ml)	T1/2 (h)
Day 0						
5/100	**Male**	2.00	1.56	10.8	11.4	1.74
	Female	6.00	0.69	9.5	9.5	6.18
20/100	**Male**	0.50	1.34	8.7	10.2	5.02
	Female	1.00	1.09	14.0	14.0	5.33
50/100	**Male**	2.00	1.60	14.0	16.8	3.96
	Female	1.00	1.60	13.0	13.0	6.96
Day 27						
5/100	**Male**	2.00	2.57	19.1	23.5	4.83
	Female	1.02	1.86	14.5	18.7	7.94
20/100	**Male**	2.00	2.63	20.8	26.6	6.37
	Female	1.05	2.98	32.5	32.5	2.86
50/100	**Male**	2.01	2.47	28.2	28.2	3.10.2005
	Female	2.03	1.99	25.8	25.8	4.02
Day 91						
5/100	**Male**	6.02	2.80	26.2	33.7	NC
	Female	0.25	3.52	38.1	38.1	6.99
20/100	**Male**	1.03	2.53	21.1	28.8	16.26
	Female	6.02	2.92	40.3	40.3	3.78
50/100	**Male**	6.00	3.36	35.1	35.1	3.08
	Female	2.01	3.56	38.1	38.1	6.38
Day 182						
5/100	**Male**	6.00	3.09	28.9	35.4	NC
	Female	2.00	3.13	26.7	30.7	2.97
20/100	**Male**	6.00	2.83	30.9	30.9	4.24
	Female	1.00	3.03	29.6	44.1	NC
50/100	**Male**	6.00	3.31	38.8	38.8	2.58
	Female	2.00	3.23	36.6	36.6	4.65

*DM = Dextromethorphan hydrobromide; Q = Quinidine sulphate
**Not calculated due to insufficient blood sampling times in the terminal elimination phase

AUC_{0-inf} (ng.h/ml) values on Day 0 were 11.1 and 10.4 in males and females, respectively, at 5 mg/kg/d DM, 10.5 and 14.8, in males and females, respectively, at the mid-dose, and 16.7 and 14.5 in males and females, respectively, at the high dose of 50 mg/kg/day DM in combination with 100 mg/kg/day Q.

Accumulation of Quinidine in Male and Female Rats Administered Oral Dextromethorphan in Combination with 100 mg/kg/day Oral Quinidine for 26 Weeks

Dose Level (mg/kg/day)**	Gender	Accumulation Ratio (%)*		
		Day 27 vs. Day 0	Day 91 vs. Day 0	Day 182 vs. Day 0
5/100	**Male**	206	296	311
	Female	196	400	322
20/100	**Male**	261	282	303
	Female	232	287	315
50/100	**Male**	168	209	231
	Female	199	294	283

*Percent increase in observed AUC_{0-24} between Days 27, 91, and 182 and Day 0
**Dextromethorphan/Quinidine

The toxicokinetic parameters for dextromethorphan and dextrorphan in Beagle dogs administered dextromethorphan at 10 mg/kg by oral gavage are presented in the following table (reproduced from the original NDA submission):

Test Article: Dextromethorphan Hydrobromide and Quinidine Sulfate

Species/Strain: Dog/Beagle	**SamplingTimes Postdose:** 0.25, 0.5, 1, 2, 4, 8, and 24 hours	**Study Reference:** DMQ-100
Initial Age: 1-2 years	**Method of Administration:** Oral (gavage)	**Location in CTD:** Section 2.6.4.3
Date of First Dose: 12 September 2001	**Feeding Conditions:** Fed *ad libitum*	**GLP Compliance:** No
Number of Animals/Sex/Group: 12M	**Dose:** 10 mg/kg DM	**Sample:** Plasma
Number of Animals/Sex/Group/Timepoint: 12M	**Vehicle/Formulation:** Powder within a gelatin capsule	**Assay:** LC-MS/MS for DM and DX
Additional information: All animals either died or were euthanized by 4 hours postdose due to severe clinical signs. No PK analyses were performed.		

Analyte	T_{max} (h)	C_{max}* (ng/mL)	AUC_{0-24} (ng•h/mL)	$AUC_{0-\infty}$ (ng•h/mL)	$t_{1/2}$ (h)
Dextromethorphan	NC	867	NC	NC	NC
Dextrorphan	NC	699	NC	NC	NC

AUC_{0-24} = area under the plasma concentration versus time-curve from time zero to 24 hours postdose; $AUC_{0-\infty}$ = area under the plasma concentration versus time-curve from time zero to infinity; C_{max} = peak plasma concentration; DM = dextromethorphan hydrobromide; DX = dextrorphan; LC-MS/MS = liquid chromatographic tandem mass spectrometric method; NC = not calculated due to lack of data; $t_{1/2}$ = terminal phase half-life; T_{max} = time to peak plasma concentration.
* Values based on highest plasma concentration up to last time point. Some animals may have died before the true C_{max} was attained.

The results of the pharmacokinetic and toxicokinetic evaluations of dextromethorphan and quinidine in human volunteers is presented below, for comparison with the results observed in the nonclinical studies.

The pharmacokinetics of single dose dextromethorphan (30 mg) and quinidine (0, 2.5, 10, 25, 50, and 75 mg) capsules in combination were analyzed in 46 healthy adult male and female volunteers, to determine the lowest dose of quinidine which protects dextromethorphan from degradation by Cytochrome P450 2D6 (Protocol 99-AVR-100). The results are presented in the following tables (reproduced from the original IND submission):

Plasma PK Parameters vs. Quinidine Dose in Human Volunteers

Parameter (DM administered at 30 mg)	Quinidine Dose (mg)					
	0	**2.5**	**10**	**25**	**50**	**75**
DM Cmax (ng/ml)	2.90	35.3	63.7	98.9	110.12	115.71
DM $AUC_{(0-8)}$ (ng.h/ml)	17.8	242.4	451.7	723.7	814.8	851.4
DM Tmax (h)	2.86	4.00	3.71	3.25	3.75	3.71
Q Cmax (mcg/ml)	0	0	0.04	0.16	0.29	0.41

Q $AUC_{(0-8)}$ (mcg.h/ml)	0	0	0.15	0.94	1.71	2.48
Q Tmax (h)	0	0	1.43	2.25	2.25	2.29

Plasma PK Parameters vs. Quinidine Dose in Human Volunteers; Changes from Baseline

Parameter (DM administered at 30 mg)	**Quinidine Dose (mg)**					
	0	**2.5**	**10**	**25**	**50**	**75**
DM Cmax (ng/ml)	1.18	33.8	62.7	96.8	108.2	113.8
DM $AUC_{(0-8)}$ (ng h/ml)	8.4	234.7	445.9	712.6	806.4	841.1
DM Tmax (h)	-1.4	-0.5	-0.29	-0.75	-0.75	-0.57

In another clinical study (00AVR103) to determine the lowest dose of quinidine sulfate that inhibits conversion of dextromethorphan to dextrorphan, 47 volunteers were administered dextromethorphan hydrobromide orally at 45 and 60 mg, in combination with oral quinidine sulfate at 0, 30, 45, and 60 mg. The following results were observed:

Plasma Dextromethorphan PK Parameters vs. Quinidine Dose in Human Volunteers (mean ±S.D.)

Parameter	Day	Quinidine Dose (mg PO)			
		0	**30**	**45**	**60**
45 mg Dextromethorphan Hydrobromide (twice daily)					
Cmax (ng/ml)	**1**	2.3 ± 1.60	9.6 ± 13.91	3.6 ± 5.04	1.7 ± 1.08
	8	4.2 ± 3.01	141.5 ± 74.68	138.9 ± 25.97	136.1 ± 50.59
Tmax (h)	**1**	3.5 ± 0.93	2.9 ± 0.37	3.4 ± 1.40	3.0 ± 1.00
	8	3.4 ± 0.50	4.3 ± 1.70	3.3 ± 1.80	3.6 ± 2.07
$AUC_{(0-12)}$ (ng h/ml)	**1**	15.0 ± 11.36	77.5 ± 120.80	25.5 ± 36.79	10.3 ± 6.98
	8	31.5 ± 23.64	1438.0 ± 842.60	1403.0 ± 283.10	1464.0 ± 588.60
60 mg Dextromethorphan Hydrobromide (twice daily)					
Cmax (ng/ml)	**1**	3.7 ± 3.70	2.1 ± 2.82	3.5 ± 3.19	4.8 ± 4.74
	8	7.7 ± 7.01	191.8 ± 45.48	204.8 ± 22.93	231.9 ± 96.36
Tmax (h)	**1**	2.6 ± 0.96	2.5 ± 0.57	2.4 ± 0.56	3.5 ± 1.05
	8	2.1 ± 0.38	3.5 ± 1.73	3.7 ± 1.17	5.2 ± 1.94
$AUC_{(0-12)}$ (ng h/ml)	**1**	23.2 ± 23.50	12.3 ± 15.93	20.7 ± 17.39	32.2 ± 34.45
	8	52.3 ± 46.72	1963.0 ± 608.50	2121.0 ± 278.50	2252.0 ± 689.30

The pharmacokinetics of single and multiple (8 Day) doses of dextromethorphan (30 mg) and quinidine (25 mg) capsules in combination were analyzed in healthy adult male and female volunteers, to compare pharmacokinetic parameters for extensive metabolizers and poor metabolizers (Protocol 99-AVR-101). The results are presented in the following tables (reproduced from the original IND submission):

Table 11.4.4.2:1 Summary of Plasma Pharmacokinetic Parameters

Compound	Pharmacokinetic Parameter	Day	Metabolizer Type: EM Mean	EM N	EM S.D.	PM Mean	PM N	PM S.D.	All Subjects Mean	All Subjects N	All Subjects S.D.
Dextromethorphan	Cmax (ng/mL)	1	15.89	7	8.22	22.30	2	0.14	17.31	9	7.66
		4	76.69	7	15.28	105.70	2	9.48	83.13	9	18.71
		8	95.50	7	19.92	136.20	2	3.25	104.54	9	24.92
	Tmax (hr)	1	6.85	7	2.78	8.00	2	0.00	7.11	9	2.46
		4	5.42	7	1.90	6.00	2	2.82	5.55	9	1.94
		8	5.99	7	2.58	4.99	2	1.41	5.77	9	2.33
	AUC(0-12) (ng*hr/mL)	1	133.27	7	59.86	198.33	2	6.97	147.73	9	59.30
		4	811.68	7	151.7	1146.4	2	84.43	886.07	9	199.8
		8	1049.0	7	243.3	1533.5	2	80.97	1156.7	9	301.4
	T 1/2el (hr)	8	13.13	6	3.41	41.96	2	4.47	20.33	8	13.76
Dextrorphan	Cmax (ng/mL)	1	124.86	7	53.26	10.80	2	3.39	99.51	9	68.25
		4	79.33	7	18.63	37.05	2	0.21	69.93	9	24.65
		8	123.51	7	17.07	51.45	2	4.17	107.50	9	35.08
	Tmax (hr)	1	4.00	7	0.00	3.00	2	1.42	3.78	9	0.67
		4	2.21	7	1.40	2.00	2	0.00	2.17	9	1.22
		8	41.18	7	11.57	2.99	2	1.41	32.70	9	19.61
	AUC(0-12) (ng*hr/mL)	1	933.83	7	324.8	90.95	2	19.08	746.52	9	466.2
		4	849.22	7	181.9	365.27	2	30.37	741.68	9	265.4
		8	1000.5	7	147.2	530.40	2	82.39	896.04	9	245.1
Quinidine	Cmax (ng/mL)	1	0.09	7	0.02	0.08	2	0.01	0.09	9	0.02
		4	0.15	7	0.03	0.14	2	0.01	0.15	9	0.03
		8	0.16	7	0.04	0.16	2	0.02	0.16	9	0.03
	Tmax (hr)	1	1.71	7	0.27	1.50	2	0.00	1.67	9	0.25
		4	1.65	7	0.37	1.52	2	0.00	1.62	9	0.33
		8	1.99	7	0.01	1.49	2	0.00	1.88	9	0.22
	AUC(0-12) (ng*hr/mL)	1	0.48	7	0.18	0.51	2	0.13	0.49	9	0.17
		4	1.20	7	0.21	0.97	2	0.05	1.15	9	0.21
		8	1.31	7	0.19	1.07	2	0.02	1.26	9	0.19
	T 1/2el (hr)	1	8.11	7	2.95	8.25	2	2.65	8.14	9	2.72
		4	6.86	7	1.11	6.51	2	0.70	6.78	9	1.01
		8	7.66	7	1.09	6.66	2	0.41	7.44	9	1.05

EM = Extensive metabolizer of dextromethorphan, PM = Poor metabolizer.

A randomized single-dose crossover study (04AVR111) was conducted to evaluate effects of food on the pharmacokinetic parameters of oral dextromethorphan (30 mg) and quinidine sulfate (30 mg) measured over 48 hours in 18 healthy adult volunteers. The results (geometric means) are presented in the following table:

Condition	AUC_{0-t}* (ng.h/mL)	AUC_{0-inf} (ng h/mL)	Cmax (ng/ml)	Tmax (h)	Half-life (h)	Kel (l/h)
Dextromethorphan						
Fasting	410.62 ± 42.8	445.71 ± 48.2	22.63 ± 25.1	4.7 ± 27.5	11.9 ± 33.4	0.06 ± 29.0
Fed	427.51 ± 37.9	473.12 ± 44.9	22.72 ± 22.1	5.7 ± 15.6	12.6 ± 34.2	0.06 ± 31.6
Dextrorphan						
Fasting	1420 ± 20.5	1805.6 ± 20.8	74.3 ± 48.1	3.7 ± 24.0	19.1 ± 52.1	0.04 ± 40.4
Fed	1323 ± 21.4	1757.3 ± 21.0	59.2 ± 42.3	5.5 ± 22.7	20.9 ± 41.4	0.04 ± 50.2
Quinidine						
Fasting	0.625 ± 58.5	1.13 ± 28.7	0.12 ± 33.1	2.17± 46.8	5.26 ± 21.2	0.14 ± 25.9
Fed	0.575 ± 68.1	1.07 ± 38.0	0.11 ± 35.7	3.36 ± 30.5	5.23 ± 30.1	0.14 ± 29.6

*Last measurable concentration

The following table presents the plasma pharmacokinetics results of an open-label, multiple-dose, study on dextromethorphan and quinidine given orally at 30 mg each, twice daily for 7 days in healthy adult volunteers and subjects with renal insufficiency (Study 04-AVR-116):

Parameter	Normal Renal Function (n=9)	Mild Renal Impairment (n=6)	Moderate Renal Impairment (n-6)
Dextromethorphan			
AUC_{0-t} (ng h/mL)	1441	1339	1346
Cmax (ng/mL)	141	132	131
Dextrorphan			
AUC_{0-t} (ng h/mL)	907	1203	1962
Cmax (ng/mL)	88.5	131	181
Quinidine			
AUC_{0-t} (ng h/mL)	2.31	1.75	2.44
Cmax (ng/mL)	0.313	0.225	0.271

The pharmacokinetics of dextromethorphan and quinidine were evaluated in patients with hepatic impairment and healthy volunteers given 30 mg each drug, twice daily for 7 days (Study 04-AVR-115). The results are presented in the following table:

Parameter	Normal Hepatic Function (n=9)	Mild Hepatic Impairment (n=6)	Moderate Hepatic Impairment (n-6)
Dextromethorphan			
AUC_{0-t} (ng h/mL)	1182	1325	1321
Cmax (ng/mL)	112	127	123
Dextrorphan			
AUC_{0-t} (ng h/mL)	884	904	859
Cmax (ng/mL)	85.0	87.6	85.9
Quinidine			
AUC_{0-t} (ng h/mL)	1.81	1.48	1.78
Cmax (ng/mL)	0.229	0.223	0.160

Distribution

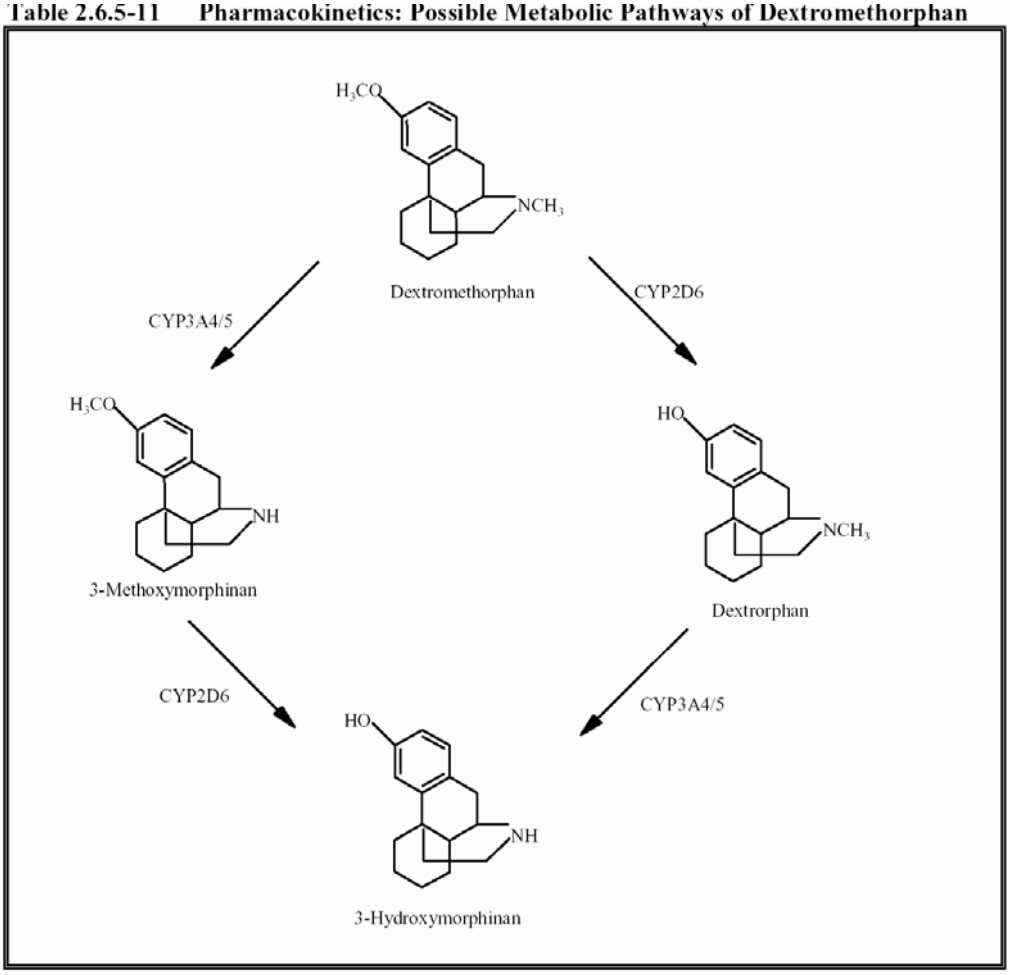
Tissue distribution of dextromethorphan and quinidine were not evaluated in animal studies for this NDA. Dextromethorphan is distributed to whole blood, urine, bile, liver, heart, kidney, brain, and cerebrospinal fluid. The volume of distribution in dog was 5-6.4 L/kg. Measurements of dextromethorphan and dextrorphan levels in several tissues in neurosurgery patients given high doses of dextromethorphan, showed high levels of both parent drug and the primary metabolite in brain (68X serum level and 14X serum level, respectively).

Dextromethorphan is approximately 70% bound, and quinidine is 80%-88% bound to plasma proteins in human adults.

Metabolism

Studies to evaluate dextromethorphan and quinidine metabolism, given alone and in combination, were not conducted for this NDA. The following figure (reproduced from the original NDA submission) presents the possible metabolic pathways of dextromethorphan:

Table 2.6.5-11 Pharmacokinetics: Possible Metabolic Pathways of Dextromethorphan



Approximately 90% human population are "extensive metabolizers" of dextromethorphan, with high CYP2D6 activity. Five percent to 10% are "poor metabolizers", showing slower and less extensive metabolism of dextromethorphan to dextrorphan.

Quinidine is converted in humans to the active metabolites 3-hydroxy-quinidine (10%, active), 2'-quinidinone (10%), quinidine-N-oxide (1%, active), quinidine 10,11-dihydroliol (3%), O-desmethyl-quinidine (1%-2%), and 2'-oxoquinidione (active).

Excretion

Studies to evaluate excretion of dextromethorphan and quinidine were not conducted for this NDA.

Dextromethorphan is excreted unchanged (0%-11% dose) and up to 100% as demethylated, conjugated morphinan compounds in urine. The elimination half-life is 2-4 hours for the parent drug, and 2.5 hours (1.4-3.9 hours) for dextrorphan, after administration of 2.5 mg/kg in a clinical study. Quinidine is excreted unchanged (20% dose) in urine, with clearance 4.7 +/- 1.8 ml/min/kg. Parent drug excretion is increased with decreasing urinary pH. The elimination half-life is 3-16 hours (mean 6-8 hours in adults, 3-4 hours in children). The elimination half life of the metabolite 3-hydroxy-quinidine is 6-10 hours. After co-administration, the elimination half-life is 13 hours for dextromethorphan and 7 hours for quinidine. There were no effects of hepatic and renal impairment on dextromethorphan clearance.

Pharmacokinetic drug interactions

Drugs that inhibit dextromethorphan metabolism by interaction with cytochrome P450 CYP2D6 (e.g., quinidine, amiodarone, fluoxetine, paroxetine, propafenone, thioridazine, etc) can increase dextromethorphan plasma levels to those associated with toxicity. However, this interaction underlies the rationale for this combination product, to increase DM plasma levels by inhibition of metabolism by CYP2D6 enzymes with quinidine co-administration.

Quinidine concentrations may be increased by acetazolamide, aluminum hydroxide, amiodarone, cimetidine, sodium bicarbonate, and verapamil, and decreased by diphenoxylate, kaolin-pectin, phenobarbital, phenytoin, and rifampin. Additionally, drugs that inhibit cytochrome P450 enzymes (e.g., metronidazole, ciprofloxacin, and erythromycin) may increase quinidine plasma levels. Also, reduction of P-glycoprotein-mediated tubular secretion of quinidine (e.g., by itraconazole) may decrease renal clearance and elevate plasma levels to those associated with toxicity in humans.

TOXICOLOGY

Single-dose toxicity

The results of published studies (see Eddy *et al*., 1969 for review) on the acute toxicity of dextromethorphan showed oral LD50 values of 165 mg/kg in the mouse and 350 mg/kg in the rat. In dogs, the minimal lethal dose was 39 mg/kg IV in one study and the LD50 was 10 mg/kg IV and >20 mg/kg SC in another study. Acute dextromethorphan toxicity in animals included pronation, motor impairment, increased muscle tone, tremors, respiratory distress, convulsions, and coma.

The studies reported in the published literature showed quinidine LD50 values of 562 mcmol/kg IP and 535 mg/kg PO in mice. The reported quinidine LD50 values in rats are 23 mg/kg IV and 263 mg/kg PO.

Dose-related mortality was observed in a single dose oral toxicology study in mice (DMQ-116), with deaths in 1/3 males at 200 mg/kg dextromethorphan + 50 mg/kg quinidine within 30 minutes of dosing, and in 3/3 males at 200 mg/kg dextromethorphan + 100 mg/kg quinidine within 120 minutes of dosing. In the female mice, dose-related mortality was observed with deaths in 1/3 females at 20 mg/kg dextromethorphan + 10 mg/kg quinidine, and in all other females at the higher dose combinations, within several hours after dosing.

In a single dose oral toxicology study in rats (DMQ-101) given dextromethorphan and quinidine by oral gavage at doses of 0, 2, 20, 50, 100, and 200 mg/kg dextromethorphan alone, 0, 2, 20, 50, and 100 mg/kg quinidine alone, or both drugs combined at 2/2, 20/2, 20/20, 20/100, 50/2, 50/20, 50/50, and 100/50 mg/kg dextromethorphan/quinidine, 1/3 female rats died and the clinical signs were lethargy and convulsions at the high dose (200 mg/kg dextromethorphan alone). The NOAEL for dextromethorphan alone was 100 mg/kg PO. There were no effects by quinidine alone at doses of 2, 20, 50, and 100 mg/kg P)). When dextromethorphan and quinidine were administered in combination, there were deaths in 1/3 males at 20/100 mg/kg, 1/3 females at 50/20 mg/kg, and 2/3 females and 1/3 males at 100/50 mg/kg. Treatment-related clinical signs were decreased locomotor activity, lethargy, and hindpaw swelling at 20/100, 50/20, and 100/50 mg/kg dextromethorphan/quinidine. The pharmacokinetic analysis showed increased exposure (Cmax and AUC) to dextromethorphan, but no change in exposure to dextrorphan), with quinidine co-administration. Exposure to dextromethorphan and dextrorphan were higher in the females than in the males with quinidine co-administration.

The treatment-related clinical signs in a single dose neurotoxicity and TK study in rats (DMQ-106) were salivation and decreased activity at doses of 2/50-50/50 mg/kg dextromethorphan/quinidine. No neurotoxicity findings indicative of the "Olney Lesion", including vacuolation and necrosis in the posterior cingulate and retrosplenial cortices were observed. The toxicokinetic evaluation showed less than dose proportional increase in dextromethorphan exposure with quinidine co-administration in the females (2/20-50/50 mg/kg dextromethorphan/quinidine) and males (20/50-50/50 mg/kg dextromethorphan/quinidine). The increase in dextrorphan exposure was proportional to dose from 2/50-20/50 mg/kg dextromethorphan/quinidine, but less than dose proportional in females and more than dose proportional in males from 20/50-50/50 mg/kg dextromethorphan/quinidine. Dextromethorphan exposure was higher in females than in males by 1.3X-1.6X at 20/50 and 50/50 mg/kg dextromethorphan/quinidine. quinidine exposure and half-life were higher with dextromethorphan co-administration.

Acute oral dextromethorphan toxicity was evaluated in Beagle dogs given by oral gavage doses of up to 34.3 mg/kg (DMQ-102). There were no spontaneous deaths, but several dogs were sacrificed *in extremis* (1 male and 1 female each at 13.4, 24, and 34.3 mg/kg), due to severe clinical signs of toxicity. Treatment-related weight loss and reduced food

consumption were observed, and the clinical signs were limb stiffness, and abnormal blinking. Higher doses produced weakness, spasmodic head movements, and tremors, and convulsions were observed at the highest dose of 34.3 mg/kg.

In a non-GLP single dose (10 mg/kg) oral toxicity study conducted in 12 Beagle dogs to identify poor and extensive dextromethorphan metabolizers (DMQ-100), the clinical signs of toxicity were central nervous system depression, ataxia, and vomiting during the first hour after dosing, followed by hyper-excitability, muscular rigidity, vomiting and tonic-clonic convulsions after the first post-dose hour. Deaths were observed in 4 dogs at 3 hours after dosing, and all but 2 remaining dogs were euthanized at 4 hours after dosing. The dextromethorphan Cmax was 47.23-2478.65 ng/ml (0.4X-19X the clinical Cmax at the proposed dose of 30/30 mg dextromethorphan/quinidine b.i.d.), and the dextrorphan Cmax was 77.54-1104.9 ng/ml (0.7X-10X the clinical Cmax at the proposed dose of 30/30 mg dextromethorphan/quinidine b.i.d.).

Study title: ***A dose-ranging study of the plasma pharmacokinetics of dextromethorphan, dextrorphan, and quinidine after oral dosing in mice with combinations of dextromethorphan and quinidine***

Key study findings:

- Dose-related mortality in mice, with deaths in 1/3 males at 200/50 mg/kg DM/Q (16X for DM and 4X for Q, the proposed clinical doses of 60 mg/day each DM and Q, on a mg/m^2 basis) within 30 minutes and 3/3 males at 200/100 mg/kg DM/Q (16X for DM and 8X for Q, the proposed clinical doses of 60 mg/day each DM and Q, on a mg/m^2 basis) within 120 minutes of dosing, and in 1/3 females at 20/10 mg/kg DM/Q (1.6X for DM and 1X for Q, the proposed clinical doses on a mg/m^2 basis) and in all females at higher dose combinations within several hours of dosing.

Study no.: DMQ-116
Volume # Electronic submission m2\26-nonclinical study reports**, and page # 1**
Conducting laboratory and location: (b) (4)

Date of study initiation: December 12, 2002
GLP compliance: No
QA report: yes (x) no ( )
Drug Dextromethorphan hydrobromide (DM)**, lot #** Not provided**, and % purity**: Not provided
Drug Quinidine sulfate (Q)**, lot #** Not provided**, and % purity**: Not provided

Methods

Doses: **Phase 1**: DM at 20 mg/kg (with 0, 10, 20, 40, and 100 mg/kg Q), 60 mg/kg (with 0, 30, 60, and 100 mg/kg Q) and 200 mg/kg (with 0, 50, and 100 mg/kg Q); **Phase 2**: DM at 20 mg/kg (with 0, 10, 20, and 40 mg/kg Q), and 60 mg/kg (with 0, 30, 60, and 120 mg/kg Q)

Species/strain: C57BL/6 mice
Number/sex/group or time point (main study): 3/sex/dose
Route, formulation, volume, and infusion rate: test articles dissolved in 1% carboxymethylcellulose (CMC) in distilled water, administered by oral gavage at 10 ml/kg
Satellite groups used for toxicokinetics or recovery: None
Age: 7-20 weeks
Weight: 16-25 g
Unique study design or methodology: Test articles administered in dose-escalation schedule, beginning with DM only groups

Observations

Mortality: For 12 hours after dosing

Toxicokinetics: Performed in Phase 2: Blood samples (500 mcL) from the orbital sinus or vena cava under isoflurane anesthesia at 0.25, 0.5, 1, 2, 6, and 12 hours after dosing

Results:

Mortality: Phase 1: Dose-related mortality in male mice, with deaths in 1/3 males at 200 mg/kg DM + 50 mg/kg Q within 30 minutes of dosing (16X for DM and 4X for Q, the proposed clinical doses of 60 mg/day DM and 60 mg/day Q, on a mg/m^2 basis), and in 3/3 males at 200 mg/kg DM + 100 mg/kg Q (16X for DM and 8X for Q, the proposed clinical doses on a mg/m^2 basis) within 120 minutes of dosing. In the females, dose-related mortality with deaths in 1/3 females at 20 mg/kg DM + 10 mg/kg Q (1.6X for DM and 1X for Q, the proposed clinical doses on a mg/m^2 basis), and in all other females at the higher dose combinations, within several hours after dosing. Phase 2: no deaths.

Toxicokinetics: See under Pharmacokinetics section of review, above (pages 29-30)

Study title: ***A study of the pharmacokinetics of dextromethorphan and quinidine and the effect of quinidine on the pharmacokinetics of dextromethorphan following a single oral administration in male and female Sprague-Dawley rats***

Key study findings:

- Treatment-related mortality at 50/0, 50/20, 100/50, and 200/0 mg/kg DM/Q ($NOAEL_{(mortality)}$ = 20 mg/kg DM alone, 100 mg/kg Q alone, and 20/50 mg/kg DM/Q combined)
- Treatment-related clinical signs were dose-related decreased locomotor activity, lethargy, tremors, depression, and hind leg swelling in the rats given both DM and Q, and coma with convulsions in the rats given 200 mg/kg DM alone (NOAEL = 100 mg/kg Q alone, and 20 mg/kg DM alone and combined with up to 50 mg/kg Q)

Study no.: DMQ-101
Volume # Electronic submission, folder m2\26-nonclinical study reports**, and page #** 1
Conducting laboratory and location: (b) (4)

Date of study initiation: October 30, 2001
GLP compliance: No
QA report: yes (x) no ( )
Drug Dextromethorphan hydrobromide (DM)**, lot #** 00-377 and DM9912074**, and % purity**: Not provided
Drug Quinidine sulfate (Q)**, lot #** 00-376 and 9900130**, and % purity**: Not provided

Methods

Doses: **Phase 1**: DM alone at 0, 2, 20, 50, 100, and 200 mg/kg, or Q alone at 0, 2, 20, 50, and 100 mg/kg; **Phase 2**: DM/Q at 2/2, 20/2, 20/20, 20/100, 50/2, 50/20, 50/50, 100/50, and 200/0 mg/kg
Species/strain: Sprague-Dawley rats
Number/sex/group or time point (main study): 3/sex/dose, or 5 males/dose
Route, formulation, volume, and infusion rate: Test articles dissolved or suspended in 1% methylcellulose in sterile water; administered by oral gavage at 5 ml/kg
Satellite groups used for toxicokinetics or recovery: Satellite animals for brain histology, administered DM at 0, 2, 20, and 50 mg/kg in combination with Q at 0 and 50 mg/kg, sacrificed and perfused at 48 hours after dosing; positive control animals received MK-801 as described in the study review under Special Toxicology Studies, below
Age: 7-8 weeks
Weight: 257-287 g males and 246-291 g females

Observations:

Mortality: For 4 hours after dosing, and daily thereafter
Clinical signs: For 4 hours after dosing, and daily thereafter
Histopathology: Brain histology evaluated in satellite animals, at 48 hours after dosing
Toxicokinetics: Blood samples (0.4 ml) from jugular vein under isoflurane anesthesia at baseline and 0.5, 1, 2, 6, 12, and 24 hours after dosing (Phase II mice)

Results:

Mortality:

1 female at 200 mg/kg DM alone, 1 hour after dosing

3 males and 2 females at 200 mg/kg DM alone sacrificed *in extremis*, due to convulsions, lethargy and coma

1 rat at 50 mg/kg Q alone 12 hours after dosing, cause undetermined

1 female at 50/20 mg/kg DM/Q at 1 hour after dosing, with lethargy

1 male and 2 females at 100/50 mg/kg DM/Q, and their replacements (additional male and 2 females) at 1 hour after dosing, with decreased mobility, lethargy and hind leg swelling

Clinical signs: Decreased locomotor activity 3-4 hours after dosing at 20/100 mg/kg DM/Q, lethargy at 50/20, 50/50, 100/50, and 200/0 mg/kg DM/Q (1-3 hours after dosing), tremors and depression at 100/50 mg/kg DM/Q 1 hour after dosing in 1 animal, swelling in plantar region of hind legs at 1 hour after dosing in 2 animals at 100/50 mg/kg DM/Q, and comatose with convulsions in 5 animals at 1 hour after dosing at 200/0 mg/kg DM/Q.

Histopathology: See review of results, under Special Toxicology Studies, below

Toxicokinetics: See review under Pharmacokinetics Section, above (pages 27-28)

Repeat-dose toxicity

Mouse: Repeated dose toxicity by Neurodex in mice was predominantly due to the dextromethorphan component, and was enhanced by quinidine and by increasing duration of treatment. CB6F1-nonTg.ras H2 mice (5/sex/dose) given dextromethorphan at 0, and 200 mg/kg/day alone, and at 0 and 50-200 mg/kg/day in combination with 50 mg/kg/day quinidine by oral gavage for 5 consecutive days showed mortality at the highest dextromethorphan dose (4 deaths at 200 mg/kg/day dextromethorphan alone and 5 deaths at 200/50 mg/kg/day dextromethorphan/quinidine). The treatment-related clinical signs, noted at the highest dextromethorphan dose (200 mg/kg) with and without quinidine, were ataxia and tremors. There were no adverse effects in male and female Tg.rasH2 mice administered quinidine at 100 mg/kg/day alone and in combination with 100 mg/kg dextromethorphan by oral gavage for 14 days in a dose range-finding toxicology study (DMQ-127) to determine the MTD for a 26-Week carcinogenicity evaluation. However, the results of the 28-day dose range-finding study (DMQ-118) in CB6F1-nonTg ras H2 mice (10/sex/dose, 0, 75, 125, 150, and 175 mg/kg/day dextromethorphan in combination with quinidine at 0 and 50 mg/kg/day by oral gavage) showed deaths in 2 males and 1 female in the mid dose combination groups, 2 males in the high dose combination group, and 1 male given 175 mg/kg/day dextromethorphan alone. Body weights were reduced 9%-10% in the females at 150-175 mg/kg/day dextromethorphan in combination with 50 mg/kg/day quinidine, and body weight gains were reduced in the males (146%) and females (116%) at 175 mg/kg/day dextromethorphan alone, and in the females at 50 mg/kg/day quinidine alone (105%), 150 mg/kg/day dextromethorphan (129%) and 175 mg/kg/day dextromethorphan (140%) with 50 mg/kg/day quinidine. Food consumption was also reduced in these groups. The males showed decreased absolute and relative thymus weights and decreased absolute heart weights, without corresponding microscopic findings, at the higher dose combinations.

Rat: In a 14-day repeated dose preliminary oral toxicity study in Sprague-Dawley rats (n=6/sexdose at 0, 5, 10, 20, and 50 mg/kg/day dextromethorphan in combination with quinidine at 0 and 50 mg/kg/day) (Study # DMQ-105) to find the MTD for evaluation of neurotoxicity, post-dose salivation was observed at all doses from 5/50 to 50/50 mg/kg/day dextromethorphan /quinidine, with a dose-related increase in number of days the sign was observed. Mean relative kidney weights (% body weight) were decreased 11% in the low (10/50 mg/kg/day dextromethorphan /quinidine) and high dose (50/50 mg/kg/day dextromethorphan /quinidine) females. The toxicokinetic analysis showed greater than dose-proportional increases in plasma dextromethorphan, and less than dose-proportional increases in dextrorphan levels, indicating decreased metabolism with quinidine co-administration. Also, dextromethorphan plasma levels were higher and dextrorphan plasma levels were lower in the females than in the males, except for dextrorphan levels at the highest dose combination.

Higher oral gavage doses (0, 50, and 100 mg/kg/day dextromethorphan in combination with 0 and 100 mg/kg/day quinidine) were administered to Sprague Dawley rats (n=6/sex/group) in a 2-week dose-finding study (DMQ-122) to determine the MTD for evaluation of reproductive toxicity. The treatment-related clinical signs of toxicity were salivation in the rats that received quinidine with and without dextromethorphan, and reduced activity, lethargy, ataxia, piloerection, and hypothermia in the high dose combination groups (100/100 mg/kg/day dextromethorphan /quinidine), with greater severity in the females than in the males. Body weight gains were reduced in the high dose combination females. The TK evaluation showed higher systemic exposure to quinidine in the females than in the males (30%-40%), increased quinidine exposure with dextromethorphan co-administration, although no quinidine accumulation over 14 days. The systemic exposure to dextromethorphan increased with quinidine co-administration and was higher (2X) in females than in males, but no accumulation of dextromethorphan over 14 days was observed. Dextrorphan exposure was similar in males and females, but showed accumulation in both sexes over 14 days.

Neurodex™ administration for 4 and 26 weeks (Study # DMQ-103) in male and female Sprague-Dawley rats (n=10/sex/dose in the 4-week evaluation, n=15/sex/dose in the 26-week evaluation, n=6/sex/dose TK evaluation, and n=5/sex/dose in the 4-week recovery evaluation), at doses of 0, 5, 20, and 50 mg/kg/day dextromethorphan in combination with quinidine at 0 and 100 mg/kg/day by oral gavage) resulted in increased treatment-related toxicity compared to the adverse effects observed in the studies of shorter duration. Treatment-related salivation, lasting 45 minutes after dosing, and sporadic increases in food consumption in the treated females from Weeks 3-26 of dosing, were observed. In the clinical chemistry analyses, there were slight treatment-related increases in Ca2+, K+, alkaline phosphatase, and aspartate aminotransferase, and slightly decreased Na+ at all dose combinations compared to controls, without dose-relationships in incidence or severity. Urine volume was increased in the treated males and females, and specific gravity was decreased in the females in all dose groups compared to controls, without a relationship to dose. The lack of dose-response effects in the clinical chemistry and urinalysis results suggested that these effects may be quinidine-related because the dose was kept constant at 100 mg/kg/day across dextromethorphan doses.

Treatment-related organ weight changes in the 26-week study included increased absolute (15%-34%) and relative (12%-29%) liver weights at all doses (without dose-relationship), increased absolute (10%-16%) kidney weights (at all doses without dose-relationship in the treated females), increased absolute (11%-24%) and relative (5%-17%) adrenal gland weights (dose related in the females), and decreased absolute and relative epididymides weights (11%) in the high dose males. The histopathology results showed minimal to slight hypertrophy in the liver, kidney pelvic dilation kidney papillary mineralization and cortical mineralization, kidney hyaline droplets, and inflammation of the prostate in the treated males at week 4, but not after 26 weeks of treatment. In the females, minimal to slight dose-related centrilobular hypertrophy in the liver, transitional cellular hyperplasia in the kidneys, tubular dilatation in the kidneys and colloid decrease in the thyroid glands were observed during Week 4. At the end of the 26-week treatment period, inflammation of the prostate was found in the males given 20 and 50 mg/kg/day dextromethorphan. The treated females showed increased minimal to slight colloid decrease in the thyroids. There were no treatment-related histopathologic abnormalities after the 4-week recovery period.

The results of the 26-week study indicated that the target organs of toxicity of dextromethorphan and quinidine treatment combined were the liver and kidneys in both sexes, the prostate in the males and thyroids in the females. A NOAEL was not identified in this study. The toxicokinetic analysis showed greater than dose-proportional increases in dextromethorphan Cmax and AUC, with a Tmax of 0.5-2 hours across doses. The dextromethorphan AUC was higher in females than in males, but the dextrorphan Cmax and AUC values were similar in males and females. Dextromethorphan dose had no effect on quinidine pharmacokinetic parameters. Increases in the AUC values with repeated dosing indicated accumulation of dextromethorphan, dextrorphan, and quinidine to a similar extent in males and females.

Rabbit: A 10-day oral gavage dose-finding study was conducted in rabbits (Study # DMQ-121, n=3 females/dose, at doses of 0, 50, and 100 mg/kg/day dextromethorphan in combination with 0, 50, and 100 mg/kg/day quinidine) to determine the MTD for a reproductive toxicology evaluation. Treatment-related toxicity was observed at the 100/100 mg/kg/day dextromethorphan /quinidine level, as increased respiration rate for 1 hour and reduced food consumption (60% compared to controls). Quinidine exposure was increased in a dose proportional manner, and was higher with dextromethorphan co-administration than when given alone. The increases in dextromethorphan Cmax and AUC values were greater than dose-proportional with quinidine co-administration, and there was evidence of dextromethorphan accumulation over 10 days, that was reversed after a 24-hour washout period. Dextrorphan exposure was decreased with quinidine co-administration.

Dog: In a repeated oral dose toxicity study in beagle dogs (DMQ-102), dextromethorphan was given alone at 17 sequentially increasing doses from 0.3-34.3 mg/kg/day for up to 42 days (dose increases every 2 days with a washout period on Days 22-29, 2 dogs), 10-24 mg/kg/day for 4 days (2 dogs), or 13.4 mg/kg/day for 14

consecutive days (2 dogs). The dogs were sacrificed *in extremis* after 15 days at 13.4 mg/kg/day, after 4 days at 24 mg/kg/day, and after 12 and 43 days at the 34.3 mg/kg/day dose. The lower dextromethorphan doses produced hot/reddened abdomen and inguinal area, reddish oral/ocular membranes and inner pinna, and nasal discharges. Weight loss and reduced food consumption were observed at 24 mg/kg/day. The clinical signs of toxicity, at oral doses of 27.4 mg/kg and above, were limb stiffness, abnormal blinking, and at higher doses weakness, spasmodic head movements, and tremors. Convulsions were observed at the highest dose of 34.3 mg/kg PO.

Study title: ***28-Day Repeated Dose Oral Toxicity and Toxicokinetic Study in CByB6F1 Hybrid Mice with a Preliminary Range-Finding Toxicity Study***

Key study findings:

- Mortality by DM at 125 mg/kg/day in combination with 50 mg/kg/day Q (1 main study male and 1 TK group male), at 150 mg/kg/day in combination with 50 mg/kg/d Q (1 main study female), and at 175 mg/kg/day with (2 TK males) and without (1 TK male) 50 mg/kg/day
- Body weights reduced in females at 150 (9%) and 175 (10%) mg/kg/day DM + 50 mg/kg/day Q, compared to controls
- Body weight gains reduced 146% in males at 175 mg/kg/day DM alone compared to control weight gain
- Body weight gain was reduced 105%-140% from Days 22-28 in the female mice compared to control gain at
  - 150 mg/kg/day DM + 50 mg/kg/day Q
  - 175 mg/kg/day DM + 50 mg/kg/day Q
  - 175 mg/kg/day DM alone
  - 50 mg/kg/day Q alone.
- Food consumption reduced in males and females from Day 15 to Day 22 compared to controls and overall at end of study in the males compared to baseline, at 150 mg/kg/d DM + 50 mg/kg/day Q, 175 mg/kg/day DM + 50 mg/kg/day Q, and 175 mg/kg/day DM alone.

Study no: (b) (4) Study No. AA74UX-UY.2G3R.02.BTL; Avanir Study No. DMQ-118
Volume # 2**, and page #** 1
Conducting laboratory and location: (b) (4)
Date of study initiation: April 10, 2003
GLP compliance: yes (x) no ( )
QA report: yes (x) no ( )
Drug Dextromethorphan hydrobromide USP**, lot #** DM0302015**, radiolabel** Not applicable**, and % purity %** 99.6%
Drug Quinidine sulphate**, lot #** 4963**, radiolabel** Not applicable**, and % purity** %100.8%

Formulation/vehicle: Test article suspended in 1% methyl cellulose in sterile water for injection

Methods (unique aspects)**:**

Dosing:

Species/strain: CByB6F1-nonTgrasH2 mice

#/sex/group or time point (main study): 5/sex/dose in the 5-day range-finding study, 10/sex/dose in the main study

Satellite groups used for toxicokinetics or recovery: 16/sex/dose in the TK study (except no animals evaluated at 150:50 mg/kg/d DM:Q

Age: 7 weeks

Weight: 21.3-25.7 g males and 18.5-21.4 g females

Oral Gavage Doses in Administered Units: **5-Day Range-Finding Study**:

Group	**1**	**2**	**3**	**4**	**5**	**6**	**7**
DM (mg/kg/day)	0	200	200	100	50	150	0
Q (mg/kg/day)	0	0	50	50	50	50	50

Oral Gavage Doses Administered in the Main (28-Day) Study:

Group	1 Vehicle Control	2 Low Dose Comb.	3 Low-Mid Dose Comb.	4 High-Mid Dose Comb.	5 High Dose Comb.	6 High Dose DM Alone	7 High Dose Q Alone
DM (mg/kg/day)	0	75	125	150	175	175	0
Q (mg/kg/day)	0	50	50	50	50	0	50

Route, form, volume, and infusion rate: Oral by gavage at 10 ml/kg/day

Observations and times:

Mortality: Twice daily

Clinical signs: Daily at 1-2 hours after dosing, with detailed examination on Day 1 and weekly

Body weights: Days 1, 8, 15, 22, and 28 (pre-fasted) and 29 (terminal fasted)

Food consumption: Days 8, 15, 22, and 28

Ophthalmoscopy: Not done

EKG: Not done

Hematology: Retro-orbital sinus bleed on Day 29 after overnight fast

Clinical chemistry: Retro-orbital sinus bleed on Day 29 after overnight fast

Urinalysis: Not done

Gross pathology: Day 29

Organs weighed: Brain, heart, kidneys, liver, lungs, thymus, testes, and ovaries

Histopathology: Adrenal glands, aorta, bone (femur and sternum), bone marrow (femur and sternum), brain, epididymides, esophagus, eyes, gall bladder, gross lesions, Harderian glands, heart, kidneys, large intestine (cecum, colon, rectum), liver, lungs, bronchi, lymph nodes (mesenteric and mandibular), mammary gland with adjacent skin, nasal cavity, ovaries, pancreas, parathyroid glands, pituitary gland, prostate gland, salivary gland, sciatic nerve, seminal vesicles, skeletal muscle (thigh), small intestine (duodenum, jejunum, and ileum), spinal cord

(cervical, thoracic, lumbar), spleen, stomach, testes, thymus, thyroid glands, trachea, urinary bladder, uterus, and vagina
Toxicokinetics: 3 mice/sex/dose/time point at 0 (pre-dose), 1, 2, and 6 hours after dosing on Day 25
Other: None

Results: 5-Day Range-Finding Study

Mortality:

Deaths: **5-Day Range-Finding Study (n=5/sex/group)**

Group	**1**	**2**	**3**	**4**	**5**	**6**	**7**
DM (mg/kg/day)	0	200	200	100	50	150	0
Q (mg/kg/day)	0	0	50	50	50	50	50
Deaths	0	2M + 2F	1M + 3F	0	0	0	0

The females that died in the 200:50 mg/kg DM:Q group showed ataxia and tremors, there were no signs in the males that died.

Clinical signs: Ataxia and tremors in 3/5 females at 200 mg/kg/d DM alone, 2/5 males and 3/5 females at 200 mg/kg/d DM + 50 mg/kg/d Q on Day 1

Body weights and body weight gain: No treatment-related effects

28-Day Toxicity Study (Main Study):

Mortality:

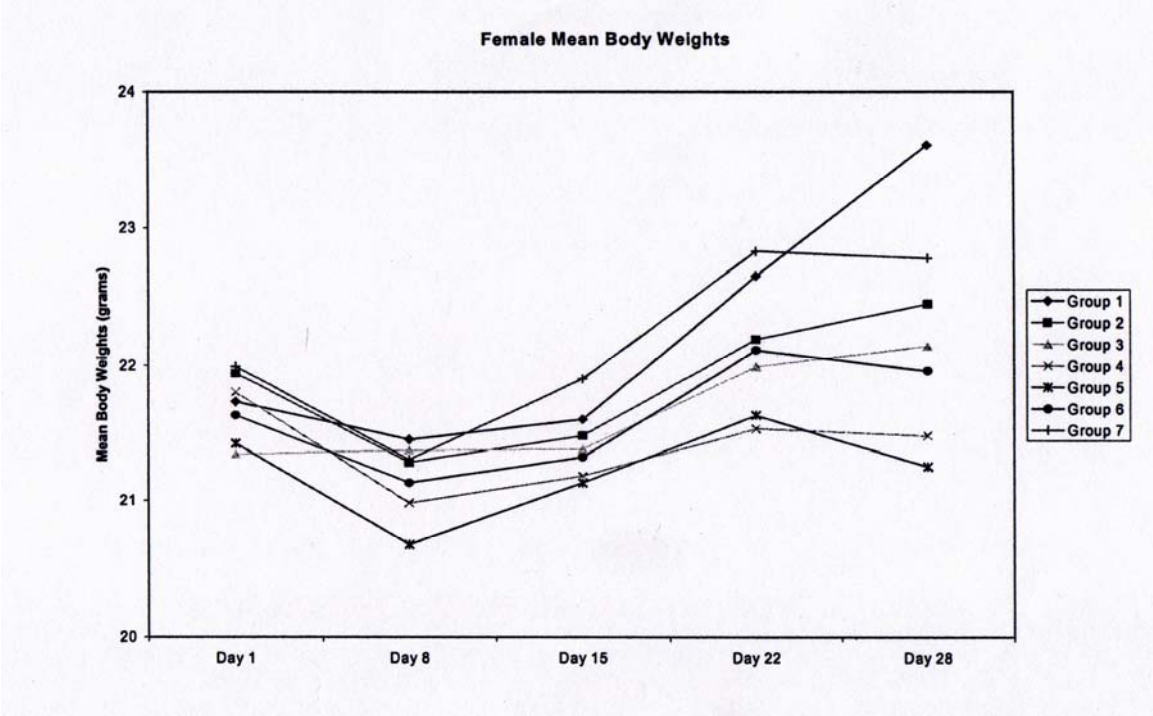
Deaths: Main Study (n=26/sex/group, including 10/sex/group main study animals and 16/sex/group TK animals*)

Group	1 Vehicle Control	2 Low Dose Comb.	3 Mid-Low Dose Comb.	4 Mid-High Dose Comb.	5 High Dose Comb.	6 High Dose DM Alone	7 High Dose Q Alone
DM (mg/kg/day)	0	75	125	150	175	175	0
Q (mg/kg/day)	0	50	50	50	50	0	50
Deaths	0	0	2M	1F	2M	1M	0

*No Group 4 TK evaluation

Clinical signs: No treatment-related effects

Body weights: No treatment-related effects in the males,
Decreased body weights in the females given:
150 mg/kg/d DM + 50 mg/kg/d Q (9%)
175 mg/kg/d DM + 50 mg/kg/d Q (10%)

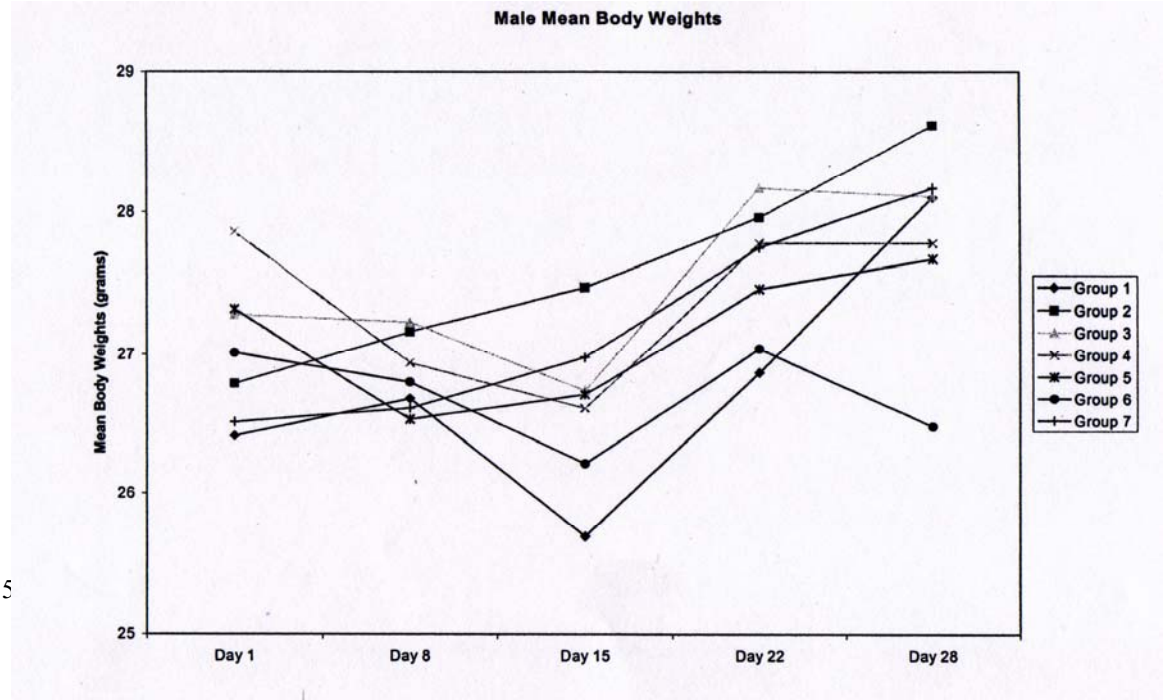


The mean body weights are presented in the following tables (reproduced from the original NDA submission):

Body weight gain: Statistically significant decrease in the males, from Day 22 to Day 28, compared to controls, at 175 mg/kg/d DM alone (146%, overall change at end of study -1.99% from baseline weight compared to 6.4% gain from baseline weight in the controls)

Decreased in the females from Day 22 to Day 28, compared to controls, at:

150 mg/kg/d DM + 50 mg/kg/d Q (129%, overall change at end of study -1.5% from baseline compared to BWG of 8.7% from baseline in controls)



175 mg/kg/d DM + 50 mg/kg/d Q (140%, end of study -0.7%)
175 mg/kg/d DM alone (116%, end of study 1.6%)
50 mg/kg/d Q alone (105%, end of study 3.6%)

Food consumption: Decreased in males, compared to controls, from Day 15 to Day 22 at:

150 mg/kg/d DM + 50 mg/kg/d Q (27%)
175 mg/kg/day DM + 50 mg/kg/d Q (29%)
175 mg/kg/d DM alone (29%)

Total food consumption decreased in the males, compared to controls, at:

150 mg/kg/d DM + 50 mg/kg/d Q (16%)
175 mg/kg/d DM + 50 mg/kg/d Q (18%)
175 mg/kg/d DM alone (19%)

Decreased in the females from Day 22 to Day 28, compared to controls, at:

150 mg/kg/d DM + 50 mg/kg/d Q (27%)
175 mg/kg/d DM + 50 mg/kg/d Q (35.4%)
175 mg/kg/d DM alone (27%)

Hematology and Clinical Chemistry: No treatment-related effects. The statistically significant changes from controls are presented in the following table (reproduced in part from the IND submission:

Hematology and Clinical Chemistry Findings in Mice Administered Dextromethorphan in Combination with Quinidine by Oral Gavage for 28 Days

Laboratory Parameter*	Males (Dose Group**)	% Difference from Control Group	Females (Dose Group**)	% Difference from Control Group
Increased Ca2+	-	-	150:50	5.3%
Decreased Na+	75:50	-1.5%	-	-
Increased Na+	-	-	0:50	2.3%
Increased K+	75:50 125:50 150:50 175:50	11.0% 11.6% 10.1% 10.7%	75:50 - 150:50 175:50	16.7% - 16.2% 15.0%
Increased Cl-	- 125:50 150:50 175:50 175:0 -	- 3.8% 5.1% 4.4% 4.8% -	75:50 125:50 150:50 175:50 175:0 0:50	3.0% 4.1% 4.3% 5.5% 3.7% 3.7%
Decreased TBA	150:50	-16.5%	-	-
Decreased MCHC	0:50	-1.5%	-	-
Decreased MPV (fl)	-	-	150:50 175:0	-5.8% -5.4%
Decreased RDW (%)	75:50 - - - -	-6.0% - - - -	75:50 125:50 150:50 175:50 175:0	-6.8% -4.9% -7.2% -6.0% -5.3%
Decreased RETIC (%)	-	-	125:50 175:50 175:0 0:50	-33.6% -44.5% -37.8% -40.8%
Decreased ABRETI (%)	-	-	125:50 175:50 175:0 0:50	-35.8% -45.2% -40.9% -41.6%

*TBA = Total Bile Acids, MCHC = Mean Corpuscular Hemoglobin Concentration, MPV = Mean Platelet Volume, RDW = Red Cell Distribution of Width, RETIC = Reticulocyte Count, ABRETI = Absolute reticulocytes
**mg/kg/d Dextromethorphan: mg/kg/d Quinidine

The statistically significant changes from control values in the hematology and clinical chemistry evaluation were either within the range of normal physiological reference, showed no dose-response, or were observed in one sex only, and were therefore considered by the Clinical Pathologist to have no relation to treatment.

Organ weights: Decreased absolute thymus weights in males at:
125 mg/kg/d DM + 50 mg/kg/d Q (-21.4%)
150 mg/kg/d DM + 50 mg/kg/d Q (-21.4%)
175 mg/kg/d DM alone (-33.3%)
Decreased relative thymus weights in the males at:
125 mg/kg/d DM + 50 mg/kg/d Q (-20.4%)
150 mg/kg/d DM + 50 mg/kg/d Q (-21.0%)
175 mg/kg/d DM alone (-29.0%)

Decreased absolute heart weights in the males at:
150 mg/kg/d DM + 50 mg/kg/d Q (-10.2%)
175 mg/kg/d DM + 50 mg/kg/d Q (-10.9%)
There were no microscopic findings in the thymus and heart; these changes were considered by the sponsor to have no biological significance
Gross pathology: Clear ovarian cyst in 1 female at 50 mg/kg/d Q alone
Histopathology: No treatment-related effects, no neoplasms
Toxicokinetics: The results of the toxicokinetic analysis are presented in the following table (approximate multiples of the AUC_{0-24} clinical value of 3000 ng.h/ml DM, 10660 ng.h/ml DX, and 2400 ng.h/ml Q, estimated from the clinical AUC_{0-12} values in poor metabolizers at the proposed dose of
30 mg DM/30 mg Q b.i.d.):

Toxicokinetic Parameters in Male and Female Mice Administered Dextromethorphan and Quinidine by Oral Gavage for 28 days

Dose Level DM/Q (mg/kg/d)	Sex	Tmax (h)	Cmax (mcg/ml)	AUC(0-6h) (mcg.h/ml)	AUC(0-24h) (mcg h/ml)	T1/2 (h)
Dextromethorphan						
75:50	Male	0.5	0.91 (7X)	2.51	3.76 (1.3X)	3.0
	Female	0.5	0.71 (5.5X)	1.89	3.05 (1X)	3.5
125:50	Male	0.1	1.15 (9X)	4.29	8.47 (2.8X)	3.4
	Female	1	1.40 (11X)	4.02	6.71 (2.2X)	3.7
175:50	Male	0.5	1.70 (13X)	6.37	14.3 (4.8X)	4.0
	Female	0.5	1.19 (9X)	4.56	9.44 (3X)	NC
175 DM alone	Male	1	1.52 (12X)	4.84	7.47 (2.5X)	3.1
	Female	0.5	1.57 (12X)	4.56	9.01 (3X)	4.6
Dextrorphan						
75:50	Male	0.5	7.33 (67X)	16.0	28.4 (2.7X)	4.4
	Female	0.5	6.37 (58X)	13.9	27.0 (2.5X)	5.8
125:50	Male	0.5	8.62 (78X)	26.7	56.0 (5.3X)	3.8
	Female	0.5	6.56 (60X)	19.0	40.8 (3.8X)	6.1
175:50	Male	0.5	7.47 (68X)	22.7	59.6 (5.6X)	7.7
	Female	0.5	6.01 (55X)	18.9	55.1 (5.2X)	NC
175 DM alone	Male	0.5	7.88 (72X)	25.6	45.4 (4.3X)	4.2
	Female	0.5	8.98 (82X)	25.3	57.7 (5.4X)	7.5
Quinidine*						
75:50	Male	0.5	0.83 (3.5X)	1.80	-	2.3
	Female	0.5	0.62 (2.6X)	1.89	-	2.8
125:50	Male	0.5	0.48 (2X)	1.56	-	4.0
	Female	1	0.54 (2.3X)	1.72	-	2.7
175:50	Male	1	0.34 (1.4X)	1.34	-	NC
	Female	0.5	0.43 (1.8X)	0.55	-	NC
50 Q alone	Male	1	0.82 (3.4X)	1.14	-	NC
	Female	0.5	1.22 (5X)	1.43	-	0.93

DM:Q = mg/kg/d Dextromethorphan hydrobromide : mg/kg/d Quinidine sulfate; NC: not calculated
*AUC(0-tf) for Quinidine, only: time of last quantifiable plasma concentration

Study title: ***Dextromethorphan/quinidine combination – 2 week oral (gavage) preliminary toxicity study in the rat***

Key study findings:

- Post-dose salivation at all doses, from 5/50 to 50/50 mg/kg/day DM/Q, dose-related increase in number of days observed
- Decreased mean relative kidney weights (% body weight) by 11% in low (5/50 mg/kg/day DM/Q) and high dose (50/50 mg/kg/day DM/Q) females
- Greater than dose-proportional increase in plasma DM, and less than dose-proportional increases in DX levels
- DM levels higher, and DX levels were lower in females than in males, except for DX levels at the highest dose combination (50/50 mg/kg DM/Q)
- 50/50 mg/kg DM/Q is well-tolerated in rats and acceptable for the neurotoxicity study

Study no: Avanir Study No. DMQ-105, (b) (4) Study No. 84/013
Volume # 4**, and page #** 1
Conducting laboratory and location: (b) (4)

Date of study initiation: January 21, 2002
GLP compliance: yes (x) no ( )
QA report: yes (x) no ( )
Drug Dextromethorphan hydrobromide USP**, lot #** DM 9912074**, radiolabel** Not applicable**, and % purity** 99.**7%**
Drug Quinidine sulphate**, lot #**9900130**, radiolabel** Not applicable**, and % purity** 100%

Formulation/vehicle: Test article suspended in methylcellulose ((b) (4), Batch 99H1170) and Water for Injection ((b) (4))

Methods (unique aspects)**:** The rats were housed in groups of 3 (toxicokinetic animals) and 5 (main study) in stainless steel cages in a temperature (22°C ± 2°C)and humidity (55% ± 15%) controlled animal room with 12 hour light/dark cycle. The rats were fed Diet A04 C-10 complete rat diet pellets *ad libitum* and provided filtered drinking water *al libitum*, except that the rats were fasted for 16 hours prior to blood sampling and necropsy. The doses were chosen based on the results of a pharmacokinetic study ((b) (4) Study No. 012463) that showed complete inhibition of metabolism of dextromethorphan to dextrorphan by quinidine at 50 mg/kg, and lethality by dextromethorphan at doses greater than 50 mg/kg in combination with quinidine at 50 mg/kg.

Dosing:

Species/strain: Sprague-Dawley Ico-OFA.SD.((b) (4)) rats
#/sex/group or time point (main study): 5/sex/dose including controls
Satellite groups used for toxicokinetics or recovery: 6/sex/dose
Age: 6 weeks
Weight: 167.3-198.4 g males and 131.9-156.6 g females (main study), and 158.7-184.4 g males and 133.9-152.8 g females (toxicokinetic study)

Doses in administered units: 0, 5, 10, 20, 50 mg/kg/day Dextromethorphan and 50 mg/kg/day Quinidine
Route, form, volume, and infusion rate: Oral at 5 ml/kg/day, once daily for 14 days

Observations and times:
Mortality: Twice daily
Clinical signs: Daily before and after dosing
Body weights: Baseline and twice weekly during drug administration
Food consumption: Weekly
Ophthalmoscopy: Not done
EKG: Not done
Hematology: At termination (Treatment Day 14)
Clinical chemistry: At termination (Treatment Day 14)
Urinalysis: Not done
Gross pathology: External surface, orifices, cranial cavity, thoracic and abdominal cavities and organs, carcass, at termination (Treatment Day 14)
Organs weighed: Kidneys and liver, at termination (Treatment Day 14)
Histopathology: Not done
Toxicokinetics: 1 ml blood drawn from the retro-orbital sinus on Dosing Days 1 and 13, at predose, and at 1, 2, 6, 12, and 24 hours after dosing
Other: None

Results:
Mortality: No deaths
Clinical signs: Increased salivation for 30 minutes after dosing at all doses, on days 1-8 at 5/50 mg/kg and 10/50 mg/kg DM/Q, Days 1-11 at 20/50 mg/kg DM/Q, and Days 1-12 at 50/50 mg/kg DM/Q
Body weights: No treatment-related effects
Food consumption: No treatment-related effects
Ophthalmoscopy: Not done
Electrocardiography: Not done
Hematology: No treatment-related effects
Clinical chemistry: No treatment-related effects
Urinalysis: Not done
Organ weights: Decreased mean relative (% body weight) kidney weights in the lower-mid-dose (10/50 mg/kg DM/Q, 11%) and high-dose (50/50 mg/kg DM/Q, 11%) females ($p<0.05$)
Gross pathology: No treatment-related effects
Histopathology: Not done
Toxicokinetics: The results of the toxicokinetic analysis are presented in the following table:

Toxicokinetic Parameters in Male & Female Rats Given Dextromethorphan and Quinidine by Oral Gavage for 2 Weeks

Dose Level DM/Q (mg/kg/d)	Sex	Tmax (h)	Cmax (ng/ml)	AUC_{0-t} (ng h/ml)	AUC_{0-inf} (ng h/ml)	T1/2 (h)	Cl/F (l/h/kg)	Varea/F (l/kg)
Dextromethorphan: Day 0								
5/50	Male	2.0	8.9	36.7	NC	NC	NC	NC
	Female	1.0	20.9	145.4	NC	NC	NC	NC
10/50	Male	1.0	21.1	158.7	NC	NC	NC	NC
	Female	2.0	58.4	460.2	NC	NC	NC	NC
20/50	Male	1.0	79.5	387.8	408.2	3.0	49.00	209.8
	Female	1.0	128.3	564.2	773.8	6.5	25.85	243.9
50/50	Male	1.0	266.2	1514.9	1837.7	4.6	27.21	181.9
	Female	1.0	452.6	2272.8	2277.7	2.5	21.95	80.0
Dextromethorphan: Day 13								
5/50	Male	1.0	5.2	24.1	NC	NC	NC	NC
	Female	1.0	23.3	156.7	162.7	2.0	30.72	87.1
10/50	Male	2.0	12.6	81.3	85.2	2.3	117.43	381.2
	Female	1.0	134.6	553.4)	588.7	3.0	16.99	74.5
20/50	Male	1.0	70.4	276.8	297.1	3.1	67.33	301.5
	Female	1.0	254.4	1413.1	1450.5	4.8	13.79	95.1
50/50	Male	1.0	123.9	929.3	1046.5	3.2	47.78	222.3
	Female	1.0	684.7	3916	3934.4	3.8	12.71	69.3
Dextrorphan: Day 0								
5/50	Male	6.0	338.5	4472.6	4925.3	6.0	-	-
	Female	6.9	428.9	4159.3	4496.4	6.0	-	-
10/50	Male	6.0	857.3	10306.5	NC	NC	-	-
	Female	6.0	506.3	7561.1	NC	NC	-	-
20/50	Male	6.0	1860.1	17858	20380.3	8.3	-	-
	Female	6.0	1042.5	13518.7	14651.7	5.6	-	-
50/50	Male	6.0	3338.7	37728	45627.3	9.6	-	-
	Female	6.0	2195.5	32049	45106	12.5	-	-
Dextrorphan: Day 13								
5/50	Male	6.0	348.7	6166.5	NC	NC	-	-
	Female	6.0	349.8	4515	5435.7	8.7	-	-
10/50	Male	12.0	507.4	9475	NC	NC	-	-
	Female	6.0	713	8801	10346	8.0	-	-
20/50	Male	6.0	1545	19569	24813.1	9.9	-	-
	Female	12.0	920.8	17084	NC	NC	-	-
50/50	Male	6.0	2202.2	33448	44358.2	10.5	-	-
	Female	12.0	1999.7	37145	NC	NC	-	-
Quinidine: Day 0								
5/50	Male	1.0	0.7	2.3	NC	NC	NC	NC
	Female	6.0	0.6	2.8	NC	NC	NC	NC
10/50	Male	1.0	0.7	4.6	NC	NC	NC	NC
	Female	1.0	0.7	4.5	4.7	2.7	10.71	42.3
20/50	Male	1.0	0.7	3.2	NC	NC	NC	NC
	Female	1.0	0.7	4.4	4.6	2.9	10.83	45.6
50/50	Male	2.0	0.7	6.1	NC	NC	NC	NC
	Female	1.0	1. 1	6.6	10.4	8.9	4.81	61.4
Quinidine: Day 13								
5/50	Male	1.0	0.97	5.2	5.4	2.6	9.18	33.9
	Female	6.0	0.99	7.4	NC	NC	NC	NC
10/50	Male	2.0	0.77	7.02	NC	NC	NC	NC
	Female	1.0	1.56	7.9	8.6	3.6	5.83	29.9
20/50	Male	1.0	0.98	7.5	7.9	2.2	6.29	20.2
	Female	2.0	1.43	10.2	NC	NC	NC	NC
50/50	Male	6.0	0.9	7.8	NC	NC	NC	NC
	Female	1.0	1.4	11.3	NC	NC	NC	NC

DM/Q: Dextromethorphan hydrobromide/Quinidine sulfate; NC: not calculated due to insufficient blood sampling times

The increases in peak plasma DM levels (Cmax) and DM exposure (AUC) were greater than proportional to dose at 5/50-50/50 mg/kg DM/Q. The increases in the metabolite dextrorphan (DX) Cmax and AUC values were less than proportional to dose. DM exposure was higher in the females than in the males, and DX exposure was higher in the males than in the females except at the high dose (50/50 mg/kg DM/Q). Increased plasma DX with repeated dosing suggested accumulation.

Summary of individual study findings: In the 14-day repeated dose preliminary oral toxicity study in Sprague-Dawley rats, post-dose salivation was observed at all doses, from 5/50 to 50/50 mg/kg/day dextromethorphan/quinidine (DM/Q), with a dose-related increase in number of days observed. Mean relative kidney weights (% body weight) were decreased 11% in the lower mid-dose and high dose females. There were no other treatment-related effects of DM/Q administration on clinical signs, mortality, body weights, food consumption, hematology, clinical chemistry, and gross pathology. Histopathology was not conducted in this study. The toxicokinetic analysis showed greater than dose-proportional increases in plasma DM, and less than dose-proportional increases in DX levels, indicating decreased metabolism with Q co-administration. Also, DM levels were higher, and the metabolite DX levels were lower in the females than in the males, except for DX levels at the highest dose combination (50/50 mg/kg DM/Q). The results of this study showed that the highest dose combination, 50/50 mg/kg DM/Q is well-tolerated in rats and acceptable for the neurotoxicity study.

Study title: ***Dextromethorphan/Quinidine Combination – 26 week oral (gavage) toxicity study in the rat with a 4 week interim kill and followed by a 4 week treatment-free period***

Key study findings:

- Treatment-related clinical signs: salivation, lasting up to 45 minutes after dosing
- Food consumption increased during some weeks in females
- Clinical chemistry: treatment-related increased Ca (4%-11%), decreased Na (1%-2%) in M & F (all dose groups), increased K (5%-6%) in M (all dose groups, no dose-relationship), increased alkaline phosphatase in M (28%-66%) & F (8%-103%, no dose-relationship), increased aspartate aminotransferase in M (27%-33%, no dose-relationship), increased alanine aminotransferase in M (20%-33%, not significant, week 27) and F (70%-82%, significant, week 14)
- Urinalysis: increased urine volume in M (21%-32%) and F (46%-70%), decreased specific gravity in F (0.3%-1%), all dose groups, throughout study, without relationship to DM dose
- Organ weights: increased absolute (15%-34%) and relative (12%-29%) liver weights in all M & F groups compared to controls, reversible increases in absolute (10%-16%, statistically significant) and relative (non-significant) kidney weights in all F groups

compared to controls, increased absolute (11%-15% in M, 21%-24% in F) and dose-related relative (5%-17% in F) adrenal gland weights in F persisting at HD after recovery (24%), decreased epididymides weights (11% absolute and relative) in HDM, not reversible (16% and 22% absolute and relative, respectively) after 4-week recovery

- Histopathology: In males dose-related centrilobular hypertrophy in liver, kidney pelvic dilation, kidney papillary mineralization and cortical mineralization, kidney hyaline droplets, and inflammation of the prostate, no histopathology abnormalities in recovery males
- Histopathology: In females dose-related centrilobular hypertrophy in the liver, transitional cellular hyperplasia in the kidneys, tubular dilatation in the kidneys, and colloid decrease in the thyroid glands, no abnormalities in recovery females
- Greater than dose-proportional increases in Cmax and AUC values for DM after single and repeated dosing in the males and females
- DM Tmax 0.5-2 hours across doses
- Exposure (AUC) higher in female than male rats
- No effect of dose on DM half-life (approximately 9 hours in the females and 2-5 hours in the males)
- Dextrorphan Cmax and AUC levels similar in males and females
- No effect of DM and Q doses, and repeated dosing compared to single dose on dextrorphan Tmax
- No effects of DM dose and gender on the Q pharmacokinetic parameters
- Increases in AUC values with repeated dosing indicated accumulation of DM, dextrorphan and Q, to a similar extent in the males and females
- Target organs of toxicity liver and kidneys
- NOAEL not determined

Study no: DMQ-103 ((b) (4) study no. 84/014)
Volume # m2 26-nonclinical File Folder in the electronic submission**, and page #** 1
Conducting laboratory and location: (b) (4)
Date of study initiation: March 1, 2002
GLP compliance: Yes
QA report: yes (x) no ( )
Drug Dextromethorphan hydrobromide USP and Quinidine sulfate**, lot #** DM9912074 and 9900131, respectively, **and % purity** 99.7% and 100%, respectively
Formulation/vehicle: 1% methylcellulose (400 centipoise at 2%) in water for injection

Methods (unique aspects)**:**
Dosing:

Species/strain: Ico:OFA.SD ((b) (4)) Sprague-Dawley rats
#/sex/group or time point (main study): 10/sex/dose group in the Week 4 interim evaluation, 15/sex/dose group in the Week 26 evaluation
Satellite groups used for toxicokinetics or recovery: 6/sex/dose group (TK) and 5/sex/group (4-week recovery group)
Age: 6 weeks

Weight: 159-224 g males and 114-149 g females
Doses in administered units:

Group/Treatment	Dose Level (mg/kg/day)		Dose Volume (ml/kg/day)	Dose Concentration (mg/ml)	
	DM	Q		DM	Q
1. Control	0	0	5	0	0
2. Low Dose	5	100	5	1	20
3. Mid-Dose	20	100	5	4	20
4. High Dose	50	100	5	10	20

The doses were selected for the 26-week toxicology study in rats based on the results of a 2-week preliminary toxicity study (DMQ-105) in rats given dextromethorphan at 0, 5, 10, 20, and 50 mg/kg/day in combination with quinidine at 0 and 50 mg/kg/day by oral gavage (n=5/sex/dose group, and 6/sex/dose group for PK evaluation). The results showed a NOAEL of 50/50 mg/kg/day DM/Q.

However, in a dose range-finding study in male and female Sprague-Dawley rats (Study DMQ-122) given dextromethorphan (0, 50, and 100 mg/kg/day) in combination with quinidine (0, and 100 mg/kg/day) by oral gavage for 14 consecutive days, conducted for dose selection in the reproductive toxicity studies in rats, reduced activity, lethargy, ataxia, piloerection, and hypothermia were observed at the high dose combination of 100/100 mg/kg/day DM/Q. Also, decreased body weights were observed in the high dose combination females. These effects were attributed to the dextromethorphan component.

Route, form, volume, and infusion rate: Oral by gavage (5 ml/kg), once daily for 26 weeks

Observations and times:

Clinical signs: 2X daily
Body weights: Weekly for 13 weeks, then weeks 18, 22, 27, and 30 (recovery)
Food consumption: Weekly for 14 weeks, then weeks 18, 22, 26, and 30
Ophthalmoscopy: Baseline and during weeks 4, 26, and 30
EKG: Not done
Hematology: Weeks 4, 13, 26, and 30
Clinical chemistry: Weeks 4, 13, 26, and 30
Urinalysis: Weeks 4, 13, 26, and 30
Gross pathology: All animals that died during the study, low-dose and high dose animals at scheduled 4-week, 26-week and 30-week necropsies
Organs weighed: All animals that died during the study, low-dose and high dose animals at scheduled 4-week, 26-week and 30-week necropsies: thyroid glands, liver, prostate gland, brain, pituitary, adrenal glands, heart, spleen, kidneys, ovaries, testes, epididymides,
Histopathology: All animals that died during the study, all control and high dose animals at scheduled 4-week, 26-week and 30-week necropsies, additionally kidney and liver were examined from low-dose and mid-dose males and females

and heart examined in low-dose and mid-dose females: adrenal gland, aorta, bone marrow (sternum), brain, bronchi, cecum, cervix, colon, duodenum, epididymides, esophagus, eyes, femur, heart, ileum, jejunum, kidneys, knee joint, larynx, liver, lungs, mammary glands, mandibular lymph node, mesenteric lymph node, ovaries, oviducts, pancreas, parathyroid glands, parotid gland, Peyer's patches, pituitary gland, preputial glands, prostate gland, rectum, skin (subcutis), sciatic nerves, seminal vesicles, skeletal muscle, spleen, sternum, stomach, thyroid glands, thymus, trachea, tongue, urinary bladder, ureters, uterus, vagina,
Toxicokinetics: Days 0, 27, 91, and 182 (weeks 1, 3, 13, and 26)
Other: None

Results:

Mortality: No treatment-related deaths; Deaths were observed in 6 males (3 at 5 mg/kg/day DM on Days 2, 59 and 61, 3 at 20 mg/kg/day DM on Days 4, 14, and 134 due to gavage error or unknown causes) and 1 female at 20 mg/kg/day DM on Day 178 due to gavage error, no deaths in the high dose groups
Clinical signs: Treatment-related salivation lasting up to 45 minutes after dosing, and convulsions in 1 female on Day 108 at 5 mg/kg/day DM, 1 female on Days 19, 60, 69, 73, 85, and 94 at 20 mg/kg/day DM, 1 female on Day 154 at 50 mg/kg/day DM, considered not treatment-related by the sponsor
Body weights: No treatment-related effects on body weight and body weight gain (366.6, 407.4, 383.7, and 361.7 g at 0, 5, 20, and 50 mg/kg/day DM, respectively, in the males, and 200.0, 208.5, 214.4, and 206.8 g at 0, 5, 20, and 50 mg/kg/day DM, respectively, in the females)
Food consumption: Increased in treated females compared to controls during some weeks from Week 3 to end of treatment, reversible during recovery
Ophthalmoscopy: No treatment-related effects
Electrocardiography: Not done
Hematology:
-Slight increase (4%-8%) in RBC parameters (RBC, hemoglobin, and packed cell volume) without relationship to dose, in treated males and females compared to controls at occasional time-points
-Decreased (24%-33%) activated partial thromboplastin times in treated males compared to controls during weeks 14 and 27 without dose relationship
-Reversed after recovery period
-Changes not considered treatment-related; lack of dose-relationship, and not found at all time-points or in both sexes
Clinical chemistry:
-Increased Ca2+ in treated males (4%-7% throughout treatment) and females (5%-11%, Weeks 5 and 14) compared to controls
-Decreased Na+ in females at 20-50 mg/kg/day DM (1%-2%, Weeks 5 and 27) and in males at 50 mg/kg/day DM (1.4%, Week 27)
-Increased K+ in treated males compared to controls (5%-6%, Week 27)
-Increased alkaline phosphatase activity in treated males (28%-66%) and females (8%-103%) compared to controls (throughout treatment)

-Increased alanine aminotransferase in treated females (45% at 50 mg/kg/day in Week 5 and 70%-82% at all doses in Week 14)
-Increased aspartate aminotransferase in treated males (27%-33%, Week 27) compared to controls
-Increased urea in treated males compared to controls (13%-19% in Week 14)
-Increased protein (45-9%) and globulin (9%-12%) in treated females compared to controls (Week 14)
-All changes were reversed in recovery period
- The slight increases in Ca and alkaline phosphatase at all dose levels, and decrease in Na at the mid-dose and high dose in Week 27, were considered to be treatment-related (probably Quinidine-related due to lack of a DM dose-response)
Urinalysis: Increased volume in treated males (15%-32% without relationship to DM dose) and females (46%-70%) and decreased specific gravity in treated females (0.3%-1% without relationship to dose) compared to controls (throughout treatment); these changes were not observed after the recovery period

The results of the hematology, clinical chemistry, and urinalysis analyses, showing significant differences from control values, are presented in the following table:

Results of Laboratory Evaluations in Rats Administered Dextromethorphan and Quinidine by Oral Gavage for 26 Weeks

Parameter	0 mg/kg/d DM + 0 mg/kg/d Q	5 mg/kg/d DM + 100 mg/kg/d Q	20 mg/kg/d DM + 100 mg/kg/d Q	50 mg/kg/d DM + 100 mg/kg/d Q
Hematology				
Red Blood Cells (M/mm3)				
Males Week 5	7.97±0.43	8.07±0.42	8.44±0.40 (6%)*	8.39±0.35 (5%)*
Females Week 5	7.38±0.26	7.95±0.21 (8%)**	7.84±0.52 (6%)*	7.89±0.27 (7%)**
Females Week 14	7.93±0.33	8.50±0.26 (7%)**	8.54±0.39 (8%)**	8.26±0.37 (4%)
Females Week 27	7.90±0.37	8.47±0.40 (7%)*	8.55±0.43 (8%)*	8.19±0.69 (4%)
Hemoglobin (g/dL)				
Females Week 5	14.9±0.4	15.9±0.3 (7%)***	15.8±0.7 (6%)**	16.0±0.6 (7%)***
Females Week 14	14.7±0.5	15.7±0.2 (7%)***	15.8±0.7 (7%)**	15.6±0.9 (6%)*
Males Week 31 (recovery)	16.3±0.3	15.9±0.7	16.1±0.5	(15.3±0.6 (6%)*
Packed Cell Volume (%)				
Females Week 5	43.7±1.0	46.3±1.3 (6%)***	45.8±2.1 (5%)*	46.6±1.9 (7%)**
Females Week 14	43.2±1.4	46.4±1.1 (7%)**	46.6±2.2 (8%)**	46.0±1.9 (6%)**
White Blood Cells (k/mm3)				
Males Week 5	7.96±1.01	10.03±1.84 (26%)*	8.95±1.44	9.74±1.64 (22%)*
Eosinophils (k/mm3)				
Males Week 5	0.14±0.07	0.22±0.12	0.12±0.07	0.26±0.12 (86%)*
Basophils (k/mm3)				
Males Week 5	0.09±0.04	0.12±0.02 (33%)*	0.09±0.06	0.14±0.02 (55%)**
Neutrophils (k/mm3)				
Males Week 27	2.29±3.26	1.72±0.35 (25%)*	2.16±1.10 (6%)	2.23±0.70 (3%)*
Reticulocyte count (%)				
Males Week 14	1.7±0.3	2.1±0.4 (23%)*	2.3±0.3 (35%)**	2.1±0.5 (23%)*
Males Week 27	1.4±0.2	1.7±0.3 (21%)*	2.0±0.3 (43%)***	2.0±0.3 (43%)***
Females Week 14	2.1±0.4	2.5±0.4	2.5±0.6	2.8±0.4 (33%)**
Activated partial thromboplastin time (s)				
Females Week 5	17.6±1.9	16.9±2.2	17.6±1.4	15.0±2.7 (15%)*
Males Week 27	27.5±6.7	18.5±3.3 (33%)**	19.6±1.0 (29%)**	18.9±2.5 (31%)***
Males Week 14	29.0±6.3	22.1±3.6 (24%)**	21.6±2.3 (25%)***	21.9±3.3 (24%)**
Large unstained cells (%)				

Females Week 14	0.6±0.2	0.6±0.2	0.8±0.2	0.8±0.2 (33%)*
Platelets (k/mm3)				
Males Week 31 (recovery)	950±157	1168±62 (23%)*	1080±149(14%)	1237±110 (30%)**
Lymphocytes (k/mm3)				
Males Week 31 (recovery)	4.09±0.36	4.77±0.83 (17%)	4.98±0.68 (22%)	5.51±3.9 (35%)**
Clinical Chemistry				
Ca2+ (mg/L)				
Males Week 5	104±4	108±3 (4%)	108±2 (4%)*	108±5 (4%)*
Males Week 14	101±3	107±4 (6%)*	107±5 (6%)**	108±5 (7%)**
Males Week 27	102±2	106±3 (4%)*	107±3 (5%)**	106±3 (5%)*
Females Week 5	101±1	107±4 (6%)**	106±3 (5%)**	106±4 (5%)**
Females Week 14	101±4	110±4 (9%)***	110±5 (9%)***	112±6 (11%)**
Na+ (mEq/L)				
Males Week 27	146±1	144±2	145±1	144±1 (1.4%)**
Females Week 5	143±1	141±2 (1%)*	140±1 (2%)***	141±2 (1%)**
Females Week 27	144±1	142±1	141±1 (2%)**	141±1 (2%)**
K+ (mEq/L)				
Males Week 27	4.7±0.3	5.0±0.2 (6%)**	4.9±0.2 (5%)	5.0±0.2 (6%)*
Cholesterol (g/L)				
Females Week 5	0.84±0.14	1.10±0.21 (31%)**	1.17±0.27 (39%)**	1.13±0.20 (34%)**
Females Week 14	0.81±0.16	1.02±0.17 (26%)*	0.99±0.19 (22%)	1.01±0.19 (25%)*
Alkaline phosphatase (IU/L)				
Males Week 14	225±29	288±101 (28%)	328±68 (46%)**	314±67 (39%)**
Males Week 27	175±18	254±105 (45%)*	291±68 (66%)***	288±59 (65%)***
Females Week 5	373±65	402±79 (8%)	471±92 (26%)*	434±70 (16%)
Females Week 14	176±44	273±50 (55%)**	242±85 (37%)	250±56 (42%)*
Females Week 27	117±32	237±61 (103%)***	188±89 (61%)*	178±65 (52%)*
Alanine aminotransferase (IU/L)				
Males Week 27	30±4	40±19 (33%)	36±8 (20%)	36±8 (20%)
Females Week 5	20±6	24±5 (20%)	26±6 (30%)	29±6 (45%)**
Females Week 14	17±3	29±5 (70%)***	31±7 (82%)***	29±5 (70%)***
Aspartate aminotransferase (IU/L)				
Males Week 27	92±16	122±27 (33%)*	117±20 (27%)*	122±20 (33%)*
Urea (g/L)				
Males Week 14	0.31±0.04	0.35±0.03 (13%)	0.36±0.04 (16%)*	0.37±0.04 (19%)**
Protein (g/L)				
Females Week 14	69±4	75±3 (9%)**	72±5 (4%)	74±4 (7%)*
Globulin (g/L)				
Females Week 14	33±2	37±2 (12%)***	36±3 (9%)*	36±2 (9%)*
Creatinine (mg/L)				
Females Week 31 (recovery)	5.9±0.2	5.9±0.6	6.4±0.4 (8%)	7.1±0.5 (20%)**
Urinalysis				
Volume (ml)				
Males Week 5	13.3±2.6	15.3±3.3 (15%)	16.5±3.5 (24%)	17.6±4.4 (32%)
Males Week 14	15.4±1.4	20.3±3.4 (32%)***	19.7±2.3 (28%)***	18.9±2.8 (23%)**
Males Week 27	15.8±2.2	19.4±2.5 (23%)*	19.1±3.1 (21%)*	19.6±3.2 (24%)*
Females Week 5	9.5±2.4	16.2±3 (70%)***	15.1±4.2 (59%)***	15.6±2.2 (64%)***
Females Week 14	10.4±1.7	17.5±3.8 (68%)***	17.4±2.9 67%)***	16.4±4.4 (58%)**
Females Week 28	11.2±1.7	16.4±4.2 (46%)*	18.6±5.3 (66%)***	16.8±3.5 (50%)**
Specific Gravity				
Females Week 5	1.026±0.005	1.018±0.004(1%)**	1.019±0.004(1%)**	1.019±0.001(1%)***
Females Week 14	1.025±0.002	1.020±0.003(1%)***	1.019±0.003(1%)***	1.020±0.002(1%)***
Females Week 27	1.024±0.002	1.021±0.004 (.3%)*	1.018±0.002(.6%)***	1.020±0.002(.4%)***

*p<0.05; **p<0.01; ***p<0.001

Organ weights:
-Increased absolute (18%-32%) and relative (12%-26%) liver weights in the treated females in Week 4, and increased absolute (15%-27% in males, and 32%-34% in females) and relative (12%-18% in males, and 26%-29% in females) liver weights compared to controls in Week 26, without relationship to dextromethorphan dose; liver weight increases not reversible after 4-week recovery period; appears to be an effect of the quinidine
-Increased absolute (8%-16% in Week 4, 8%-11% in Week 26) kidney weights in treated females without DM dose relationship; no differences observed after recovery period
-Increased absolute (11%-15% in males in Week 26 at low and high doses, 21%-24% in females in Week 26 at mid- and high doses) and relative (24% in females at high dose at 26 weeks and after 4-week recovery) adrenal weights; not reversible in the high dose females
-Decreased absolute and relative epididymides weights in the high dose males at 26 weeks, increased epididymides weights after 4-week recovery
The results of the organ weight measurements are presented in the following table:

Organ Weights in Rats Administered Dextromethorphan and Quinidine by Oral Gavage for 26 Weeks

Organ	0 mg/kg/day	5 mg/kg/day	20 mg/kg/day	50 mg/kg/day
Males				
Liver				
26-week Sacrifice				
Absolute (g)	14.01 ± 1.75	17.77 ± 1.95 (27%)**	16.05 ± 2.40 (15%)*	16.24 ± 2.36 (16%)*
Relative (% BW)	2.71 ± 0.19	3.21 ± 0.25 (18%)**	3.04 ± 0.32 (12%)**	3.16 ± 0.28 (17%)**
4-week Recovery				
Absolute (g)	14.63 ± 2.40	17.91 ± 2.07	16.20 ± 2.82	16.45 ± 1.63
Relative (% BW)	2.57 ± 0.27	2.98 ± 0.236 (16%)*	2.89 ± 0.190	3.04 ± 0.134 (18%)**
Adrenal Glands				
26-week Sacrifice				
Absolute (g)	0.061 ± 0.006	0.070 ± 0.010 (15%)**	0.065 ± 0.007	0.068 ± 0.008 (11%)*
Relative (% BW)	0.012 ± 0.001	0.013 ± 0.002	0.012 ± 0.002	0.013 ± 0.002
Epididymides				
26-week Sacrifice				
Absolute (g)	1.61 ± 0.11	1.60 ± 0.124	1.63 ± 0.099	1.43 ± 0.153 (-11%)*
Relative (% BW)	0.314 ± 0.031	0.291 ± 0.029	0.3113 ± 0.035	0.281 ± 0.037 (-11%)*
4-week Recovery				
Absolute (g)	1.45 ± 0.201	1.58 ± 0.092	1.64 ± 0.151	1.69 ± 0.066 (16%)*
Relative (% BW)	0.258 ± 0.044	0.264 ± 0.021	0.295 ± 0.019	0.314 ± 0.031 (22%)*
Kidneys				
26-week Sacrifice				
Absolute (g)	3.51 ± 0.42	4.25 ± 0.82 (21%)**	3.66 ± 0.39	3.75 ± 0.423
Relative (% BW)	0.68 ± 0.05	0.77 ± 0.16	0.699 ± 0.082	0.732 ± 0.064
Females				
Liver				
4-Week Sacrifice				
Absolute (g)	6.46 ± 0.73	7.83 ± 0.97 (21%)**	7.61 ± 1.04 (18%)*	8.56 ± 1.02 (32%)**
Relative (%BW)	3.30 ± 0.25	3.70 ± 0.35 (12%)*	3.74 ± 0.32 (13%)*	4.15 ± 0.37 (26%)**
26-week Sacrifice				
Absolute (g)	8.12 ± 0.623	10.84 ± 0.816 (33%)**	10.87 ± 1.45 (34%)**	10.73 ± 1.30 (32%)**
Relative (% BW)	2.74 ± 0.14	3.55 ± 0.241 (29%)**	3.46 ± 0.278 (26%)**	3.53 ± 0.263 (29%)**
4-week Recovery				
Absolute (g)	9.02 ± 0.515	9.66 ± 0.758	9.57 ± 1.04	9.70 ± 1.33
Relative (% BW)	2.64 ± 0.127	2.97 ± 0.118 (12%)*	2.93 ± 0.255	3.11 ± 0.174 (18%)**
Brain				
4-Week Sacrifice				
Absolute (g)	1.93 ± 0.07	1.88 ± 0.07	1.83 ± 0.06 (5%)**	1.88 ± 0.08
Relative (%BW)	0.99 ± 0.07	0.89 ± 0.07 (10%)*	0.90 ± 0.08 (9%)*	0.91 ± 0.05 (8%)*
4-week Recovery				
Absolute (g)	2.05 ± 0.059	2.00 ± 0.08	2.04 ± 0.115	2.07 ± 0.070
Relative (% BW)	0.604 ± 0.045	0.617 ± 0.032	0.624 ± 0.009	0.667 ± 0.049 (10%)*
Kidneys				
4-Week Sacrifice				
Absolute (g)	1.66 ± 0.13	1.93 ± 0.11 (16%)**	1.80 ± 0.09 (8%)*	1.88 ± 0.12 (13%)**
Relative (%BW)	0.86 ± 0.03	0.91 ± 0.07	0.89 ± 0.06	0.91 ± 0.08
26-week Sacrifice				
Absolute (g)	2.22 ± 0.17	2.45 ± 0.18 (10%)*	2.46 ± 0.29 (11%)*	2.40 ± 0.215
Relative (% BW)	0.750 ± 0.059	0.804 ± 0.068	0.785 ± 0.084	0.793 ± 0.072
Adrenal Glands				
26-week Sacrifice				
Absolute (g)	0.067 ± 0.009	0.073 ± 0.008	0.081 ± 0.013 (21%)**	0.083 ± 0.012 (24%)**
Relative (% BW)	0.023 ± 0.003	0.024 ± 0.003	0.026 ± 0.003	0.027 ± 0.005 (24%) **
4-week Recovery				
Absolute (g)	0.070 ± 0.010	0.073 ± 0.015	0.064 ± 0.009	0.082 ± 0.010
Relative (% BW)	0.021 ± 0.004	0.022 ± 0.003	0.019 ± 0.002	0.026 ± 0.004*

*p<0.05; **p<0.01

Gross pathology: No treatment-related effects
Histopathology: In the males at 4 weeks (interim sacrifice, n=10/group), the treatment-related observations were centrilobular hypertrophy in the liver (1, 7, 8, and 8 rats at 0, 5, 20, and 50 mg/kg/day, Grade 1/minimal), kidney pelvic dilation (0, 1, 2, and 3 rats at 0, 5, 20 and 50 mg/kg/day, Grades 1, 2-4, and 1-2 at LD, MD, HD), kidney papillary mineralization (1, 6, 3, and 4 rats at 0, 5, 20, and 50 mg/kg/day, Grade 1), and kidney hyaline droplets (1, 4, 4, and 5 rats at 0, 5, 20, and 50 mg/kg/day, Grade 1/minimal). At 26 weeks (n=15/group), the treatment-related observations in the males were centrilobular hypertrophy in the liver (1, 1, 5, and 5 rats at 0, 5, 20, and 50 mg/kg/day, Grade 1/minimal), inflammation of the prostate (3, 0, 6, and 12 rats at 0, 5, 20, and 50 mg/kg/day, Grades 1-3/minimal to moderate), cortical mineralization in the kidneys (5 rats at 50 mg/kg/day, Grade 1/minimal), hyaline droplets in the kidneys (1 rat at 20 and 5 at 50 mg/kg/day, Grade 1/minimal), and dilatation of the tubules in the kidneys (2 rats at 0 and 5 rats at 50 mg/kg/day, Grade 1/minimal).

In the females at 4 weeks (n=10/group), the treatment-related observations were centrilobular hypertrophy in the liver (0, 2, 3, and 8 rats at 0, 5, 20, and 50 mg/kg/day, Grade 1/minimal). At 26 weeks (n=15/group), the treatment-related observations in the females were colloid decrease in the thyroid glands (0, 5, 5, and 7 rats at 0, 5, 20, and 50 mg/kg/day, Grades 1-2, minimal to slight), centrilobular hypertrophy in the liver (0, 3, 4, and 5 rats at 0, 5, 20, and 50 mg/kg/d, Grade 1/minimal), transitional cellular hyperplasia in the kidneys (1, 0, 0, and 4 rats at 0, 5, 20, and 50 mg/kg/day, Grades 1-3, minimal to moderate), and tubular dilatation in the kidneys (3 rats at 50 mg/kg/day, Grades 1-2, minimal to slight). There were no findings that differed from control observations in the recovery animals.

Toxicokinetics: The results of the toxicokinetic evaluation are presented in the following table:

Toxicokinetic Parameters in Rats Administered Dextromethorphan and Quinidine by Oral Gavage for 26 Weeks

TK Parameter	5:100 mg/kg/d DM:Q		20:100 mg/kg/d DM:Q		50:100 mg/kg/d DM:Q	
Dextromethorphan						
	Males	Females	Males	Females	Males	Females
Tmax (h) Day 0	2.0	0.2	0.5	1.0	0.5	1.0
Day 27	2.0	2.0	6.0	1.0	0.5	2.0
Day 91	2.0	0.2	0.5	1.0	0.5	2.0
Day 182	0.2	2.0	0.5	1.0	0.5	2.0
Cmax (ng/ml) Day 0	17	12	85	122	351	363
Day 27	26	29	53	391	482	495
Day 91	20	70	107	292	522	693
Day 182	20	34	132	295	546	598
AUC_{0-t} (ng.h/ml) Day 0	55	113	200	975	1852	2623
Day 27	78	147	429	2231	2231	4072
Day 91	121	364	393	2355	2631	5129
Day 182	122	153	584	2573	2724	4220
AUC_{0-24} (ng h/ml) Day 0	64	113	216	975	1852	2623
Day 27	87	177	484	2231	2231	4072
Day 91	132	364	461	2355	2631	5129
Day 182	136	213	616	2573	2724	4220
T1/2 (h) Day 0	NC	8.6	NC	NC	NC	9.5
Day 27	NC	NC	NC	NC	2.64	5.5
Day 91	2.3	NC	3.32	NC	4.09	6.1
Day 182	2.8	NC	NC	NC	5.05	3.9
Dextrorphan						
Tmax (h) Day 0	6.0	0.2	6.0	6.0	12.0	1.0
Day 27	6.0	6.0	6.0	0.2	12.0	6.0
Day 91	6.0	0.2	12.0	6.0	0.2	12.0
Day 182	6.0	12	12.0	6.0	0.5	12.0
Cmax (ng/ml) Day 0	335	214	935	702	2509	2318
Day 27	376	386	1289	1131	2390	2203
Day 91	511	400	1623	1006	2920	2527
Day 182	540	330	924	1188	3144	2445
AUC_{0-t} (ng h/ml) Day 0	4232	3080	13353	11482	41302	25806
Day 27	5031	5534	24854	13743	47414	42966
Day 91	6846	7985	30603	15583	49730	40892
Day 182	6624	6166	20553	14389	54773	41161
AUC_{0-24} (ng h/ml) Day 0		3080	13353	11482	41302	25806
Day 27	4232	5534	24854	13743	47414	42966
Day 91	5031	7985	30603	15583	49730	40892
Day 182	6846	6166	20553	14389	54773	41161
	6624					
T1/2 (h) Day 0	7.56	13.74	10.22	NC	NC	NC
Day 27	15.4	12.0	16.9	NC	NC	NC
Day 91	7.36	NC	NC	19.10	32.33	NC
Day 182	7.90	NC	NC	19.70	12.05	NC
Quinidine						
Tmax (h) Day 0	2.0	6.0	0.5	1.0	2.0	1.0
Day 27	2.0	1.0	2.0	1.0	2.0	2.0
Day 91	6.0	0.2	1.0	6.0	6.0	2.0
Day 182	6.0	2.0	6.0	1.0	6.0	2.0
Cmax (mcg/ml) Day 0	1.6	0.7	1.3	1.1	1.6	1.6
Day 27	2.6	1.9	2.6	3	2.5	2
Day 91	2.8	3.5	2.5	2.9	3.4	3.6
Day 182	3.1	3.1	2.8	3	3.3	3.2

AUC_{0-t} (mcg h/ml) Day 0	10.8	9.5	8.7	14.0	14.0	13.0
Day 27	19.1	14.5	20.8	32.5	28.2	25.8
Day 91	26.2	38.1	21.1	40.3	35.1	38.1
Day 182	28.9	26.7	30.9	29.6	38.8	36.6
AUC_{0-24} (mcg h/ml) Day 0	11.4	9.5	10.2	14.0	16.8	13.0
Day 27	23.5	18.7	26.6	32.5	28.2	25.8
Day 91	33.7	38.1	28.8	40.3	35.1	38.1
Day 182	35.4	30.7	30.9	44.1	38.8	36.6
T1/2 (h) Day 0	1.7	6.2	5	5.3	4	7
Day 27	4.8	7.9	6.4	2.9	3.1	4
Day 91	NC	7	16.3	3.8	3.1	6.4
Day 182	NC	3	4.2	NC	2.6	4.6

NC: Not Calculated

After a single and repeated dosing of dextromethorphan and quinidine combined, the increase in Cmax and AUC values for dextromethorphan were greater than dose-proportional in males and females. The dextromethorphan Tmax was 0.5-2 hours in the, with no effect of increasing dose on time to peak plasma level. The AUC values (systemic exposure) were higher in the female than in the male rats. There was no effect of dose on dextromethorphan half-life (approximately 9 hours in the females and 2-5 hours in the males). Exposure and peak plasma dextrorphan levels were similar in the males and females throughout the study. There was no effect of DM and Q doses, and repeated dosing compared to single dose on dextrorphan Tmax values. Increasing doses of DM had no effect, and there were no gender effects on the quinidine pharmacokinetic parameters. The increases in AUC values with repeated dosing indicated accumulation of dextromethorphan, dextrorphan and quinidine, to a similar extent in the males and females.

Accumulation of dextromethorphan, dextrorphan, and quinidine is presented in the following table (percent increase in AUC0-24 from the Day 0 value):

Plasma Accumulation of Dextromethorphan and Quinidine Administered to Rats by Oral Gavage for 26 Weeks

Dose Level (mg/kg/d DM/Q	Day 27 vs Day 0	Day 91 vs Day 0	Day 182 vs Day 0
Dextromethorphan			
5/100 Male	136	207	214
Female	157	322	188
20/100 Male	225	214	286
Female	229	241	264
50/100 Male	120	142	147
Female	155	196	161
Dextrorphan			
5/100 Male	119	162	157
Female	180	259	200
20/100 Male	186	229	154
Female	120	136	125
50/100 Male	115	120	133
Female	166	158	160
Quinidine			
5/100 Male	206	296	311
Female	196	400	322
20/100 Male	261	282	303
Female	232	287	315
50/100 Male	168	209	231
Female	199	294	283

Summary of individual study findings: Male and female Sprague Dawley rats were administered control vehicle, or dextromethorphan hydrobromide (DM) at 5, 20, and 50 mg/kg/d in combination with quinidine sulphate (Q) at 100 mg/kg/d by oral gavage, daily for 26 weeks. There were deaths in 3 male rats at 5 mg/kg/d DM + 100 mg/kg/d Q (5/100 mg/kg/d DM/Q), 3 males at 20/100 mg/kg/d DM/Q, and 1 female rat at 20/100 mg/kg/d DM/Q, but no deaths at the high dose combination of 50/100 mg/kg/d DM/Q. The deaths, observed sporadically throughout dosing on Days 2-134, were attributed to gavage error or unknown causes. The clinical signs of treatment were salivation, lasting up to 45 minutes after dosing. There were no treatment-related effects on body weights, although food consumption was increased in some weeks in the female rats. The hematology evaluation showed slight (4%-8%) increases in red blood cells, hemoglobin, and packed cell volume, and decreased (24%-33%) activated partial thromboplastin times, without relationship to dose, or consistent across gender and time points, and were therefore, not considered to be treatment-related. Treatment-related clinical chemistry changes included increased Ca (4%-11%) and decreased Na (1%-2%) in the males and females in all dose groups, and increased K (5%-6%) in the males in all dose groups, without a dose-relationship in severity. Alkaline phosphatase was increased in the males (28%-66%) and females (8%-103%) and aspartate aminotransferase was increased in the males (27%-33%), at all doses without dose relationship. Alanine aminotransferase was increased (20%-33%) without statistical significance in the males in Week 27, and significantly (70%-82%) in the females in Week 14, but not in Week 27. The lack of a dose relationship in the clinical chemistry changes suggests that these effects were induced by Q at the dose of 100 mg/kg/d. The urinalysis showed significantly increased

urine volume in both males (21%-32%) and females (46%-70%), and decreased specific gravity in the females (0.3%-1%) in all dose groups throughout the study, without relationship to DM dose. The observed clinical chemistry and urinalysis changes were reversible during the 4-Week recovery period.

Absolute (15%-34%) and relative (12%-29%) liver weights were increased in all treated male and female groups compared to controls, without relationship to DM dose. This effect, apparently quinidine-related, was not reversible after the 4-Week treatment-free period. Reversible increases in absolute (10%-16%, statistically significant) and relative (non-significant) kidney weights were observed in the females in all treated groups compared to controls, without relationship to dose. Absolute (11%-15% in males, 21%-24% in females) and relative (5%-17% in females) adrenal gland weights were increased with a slight dose-relationship in the females, and persisted in the high dose females after the recovery period (24% increase in relative adrenal weight). The high dose males showed decreased epididymides weights (11% absolute and relative), that was not reversible (16% and 22% absolute and relative, respectively) after the recovery period.

The microscopic observations in the males showed centrilobular hypertrophy in the liver at 4 weeks (1, 7, 8, and 8 rats at 0, 5, 20, and 50 mg/kg/d) and 26 weeks (1, 1, 5, and 5 rats at 0, 5, 20, and 50 mg/kg/d), kidney pelvic dilation at 4 weeks (0, 1, 2, and 3 rats at 0, 5, 20 and 50 mg/kg/d) and 26 weeks (2 rats at 0 and 5 rats at 50 mg/kg/d), kidney papillary mineralization at 4 weeks (1, 6, 3, and 4 rats at 0, 5, 20, and 50 mg/kg/d) and cortical mineralization in the kidneys (5 rats at 50 mg/kg/d) at 26 weeks, kidney hyaline droplets at 4 weeks (1, 4, 4, and 5 rats at 0, 5, 20, and 50 mg/kg/d) and 26 weeks (1 rat at 20 and 5 at 50 mg/kg/d), and inflammation of the prostate (3, 0, 6, and 12 rats at 0, 5, 20, and 50 mg/kg/d) at 26 weeks. There were no histopathology abnormalities in the 4-Week recovery males.

The treatment-related microscopic observations in the females were centrilobular hypertrophy in the liver at 4 weeks (0, 2, 3, and 8 rats at 0, 5, 20, and 50 mg/kg/d) and 26 weeks (0, 3, 4, and 5 rats at 0, 5, 20, and 50 mg/kg/d), transitional cellular hyperplasia in the kidneys at 26 weeks (1, 0, 0, and 4 rats at 0, 5, 20, and 50 mg/kg/d), tubular dilatation in the kidneys at 26 weeks (3 rats at 50 mg/kg/d), and colloid decrease in the thyroid glands at 26 weeks (0, 5, 5, and 7 rats at 0, 5, 20, and 50 mg/kg/d). There were no histopathology abnormalities in the 4-Week recovery females.

The toxicokinetic analysis showed greater than dose-proportional increases in Cmax and AUC values for DM after single and repeated dosing in the males and females. The DM Tmax was 0.5-2 hours, with no effect of increasing dose on time to peak plasma level. The AUC values (systemic exposure) were higher in the female than in the male rats. There was no effect of DM dose on half-life (approximately 9 hours in the females and 2-5 hours in the males). Exposure and peak plasma dextrorphan levels were similar in the males and females throughout the study. There was no effect of DM and Q doses, and repeated dosing compared to single dose on dextrorphan Tmax values. Increasing doses of DM had no effect, and there were no gender effects on the Q pharmacokinetic

parameters. The increases in AUC values with repeated dosing indicated accumulation of DM, dextrorphan and Q, to a similar extent in the males and females.

The target organs of toxicity were clearly the liver and kidneys. Although the hematology, clinical chemistry and urinalysis results failed to show a dose-response, suggesting that the observed toxicity may be due to quinidine effects, the results of the histopathology evaluation showing reversible hepatic and renal findings (e.g. hypertrophy, dilatation, and mineralization) clearly suggested an effect of dextromethorphan dose. A NOAEL was not determined in this study.

Study title: ***Dextromethorphan – determination of the maximum tolerated dose by the oral route (gavage) in the beagle dog***

Key study findings:

- No spontaneous deaths at up to 34.3 mg/kg/day DM, although the dogs were sacrificed *in extremis* at 24 and 34.3 mg/kg/day
- Treatment-related clinical signs were hot, red abdomen and inguinal area, facial edema, red ocular mucous membranes, inner pinna, oral and ocular membranes, stiff movement, stiff forelimbs, hind-limbs and tail, slow irregular movements, hesitant gait, tremor, rapid or blinking reflexes, abnormal head movements, ventral decubitus, slow breathing, difficulty standing, dilated pupils, groaning, immobility, loss of balance, and at the highest dose convulsions
- NOAEL not determined in this study

Study no.: DMQ-102 ((b) (4) study # 84/002)
Volume # Electronic submission folder m2\4 nonclinical study reports**, and page #** 1
Conducting laboratory and location: (b) (4)
Date of study initiation: December 7, 2001
GLP compliance: Yes
QA report: yes (x) no ( )
Drug Dextromethorphan hydrobromide USP**, lot # DM9912074, and % purity**: 99.7%

Methods

Doses:

- First animal (male no. 191):

Treatment days	0-1	2-3	4-5	6-7	8-9	10-11	12-13	14-15	16-17
Dose level (mg/kg/day)	0.3	0.6	1.2	2.4	4.8	7.2	8.4	9.6	10.8

Treatment days	18-19	20-21	22-29	30-31	32-34	35-36	37-38	39-41	42
Dose level (mg/kg/day)	12.0	13.2	0.0[(1)]	10.0	13.2	17.1	20.6	27.4	34.3[(2)]

[(1)] animal was placed on wash-out between days 22 and 29, no treatment was administered.
[(2)] dose level subsequently terminated due to major clinical signs.

- Second animal (female no. 192):

Treatment days	0-1	2-4	5-6	7-8	9-11	12
Dose level (mg/kg/day)	10	13.2	17.1	20.6	27.4	34.3[(2)]

The first 2 dogs were treated on a dose-escalation schedule as described above. The next 2 dogs (Dog 3 and Dog 4) were administered 24 mg/kg/day daily for 4 days, and sacrificed due to unexpected toxicity. The last 2 of the 6 dogs (Dog 5 and Dog 6) were administered 13.4 mg/kg/day DM gel capsules by gavage (Day 0) and oral suspension by gavage (Days 1-14) for 14 consecutive days.

Species/strain: Beagle dogs (Harlan France)
Number/sex/group or time point (main study): 3/sex/group
Route, formulation, volume, and infusion rate: The test article was dissolved in methylcellulose (400 centipoise [a unit of viscosity] at 2%) in water for injection, and administered to dogs 1-4 by oral gavage at 5 ml/kg/day, once daily. The test article was administered to dogs 5 and 6 in gel capsules (by gavage) on the first dosing day, and then in oral gavage suspension on the remaining dosing days.
Satellite groups used for toxicokinetics or recovery: None
Age: 5-7 months
Weight: 9-11 kg
Unique study design or methodology: The 1st dog was sacrificed on Day 43 (1 day after the last dose), the 2nd dog was sacrificed for necropsy on Day 13 (1 day after the 12th dosing day), the 3rd and 4th dogs were sacrificed on Day 4 (1 day after the 4th treatment day), and the 5th and 6th dogs were sacrificed on Day 15 (1 day after the end of the 14-day treatment period).

Observations

Mortality: Twice daily

Clinical signs: Daily, before and at least once during the 2-hour period after dosing

Body weights: Baseline, treatment Day 1, and at each dose change or twice weekly at constant doses

Food consumption: Baseline and daily

Gross pathology: External surface, all orifices, cranial cavity, external surface of brain, thoracic and abdominal cavities and organs, cervical tissues and organs, and carcass, of all animals

Organ weights: Adrenal glands, brain, heart, kidneys, and liver of all animals

Histopathology: Planned for organs/tissues showing gross pathology abnormalities, only: Adrenal glands, bone marrow smears, brain, heart, kidneys, liver, lungs, esophagus, ovaries, pancreas, prostate, stomach, testes, thymus, thyroid glands, trachea, and all gross lesions

Toxicokinetics: Blood samples (2 ml) from the jugular vein at baseline (before dosing), and at 15 and 30 minutes, and 1, 2, 4, 8 and 24 hours after dosing:
Dog 1: Day 30 (at 10 mg/kg PO DM)
Dog 2: Day 0 (first dosing day, at 10 mg/kg PO DM)
Dog 3: First (Day 0) and last (Day 3) dosing days (at 24 mg/kg PO DM)
Dog 4: First (Day 0) and last (Day 3) dosing days (at 24 mg/kg PO DM)
Dog 5: First (Day 0, capsule) and last (Day 14, oral suspension) dosing days (at 13.4 mg/kg PO DM)
Dog 6: First (Day 0, capsule) and last (Day 14, oral suspension) dosing days (at 13.4 mg/kg PO DM)

Results

Mortality:

- 1 male and 1 female sacrificed after 15 consecutive daily doses at 13.4 mg/kg/day
- 1 male and 1 female sacrificed after 4 consecutive daily doses at 24 mg/kg/day DM, *in extremis*
- 1 male sacrificed on day 43 *in extremis*, at 34.3 mg/kg/day
- 1 female sacrificed on day 14, 2 days after last dose of 34.3 mg/kg

Clinical signs:

- hot, reddened abdomen and inguinal area at 4.8 mg/kg/day on days 8 onward
- facial edema at 10-13.4 mg/kg
- reddened stomach/abdomen, ocular mucous membranes, inner pinna, oral and ocular membranes at 10-13.2 mg/kg
- stiff movement, stiff fore and hind-limbs and tail, slow irregular movements/hesitant gait, tremor, and rapid or blinking reflex at 27.4 mg/kg
- stiff hind-limbs, hesitant gait, collapsed hindquarters, abnormal head movement, marked reflex at 34.3 mg/kg

- convulsions at 34.3 mg/kg on Day 43
- continued dosing at 24 mg/kg/day led to ventral decubitus, slow breathing, difficulty standing, dilated pupils, convulsions, groaning, immobility, loss of balance

Body weights: Slight body weight loss (up to 3%) in female at 34.3 mg/kg/day, 4%-8% BW losses in male and female at 24 mg/kg/day

Food consumption: No treatment-related effects, except in one female at 24 mg/kg/day DM (-90% on Day 2)

Gross pathology: No treatment-related effects

Organ weights: No treatment-related effects

Histopathology: Not done

Toxicokinetics: Not submitted

Histopathology inventory

Study	DMQ-101	DMQ-118	Dmq-119	DMQ-105	DMQ-103	DMQ-102
Species	Rat Single dose	Mouse 28-Day	Mouse 26-Week CA	Rat 2-Week	Rat 26-Week	Dog Variable durations of 4-42-Days
Adrenals		X	X		X*	X*
Aorta		X	X		X	
Bone Marrow smear		X	X		X	X
Bone (femur)		X	X		X	
Brain	X only	X*	X*		X*	X*
Cecum		X	X		X	
Cervix					X	
Colon		X	X		X	
Duodenum		X	X		X	
Epididymis		X	X		X*	
Esophagus		X	X		X	X
Eye		X	X		X	
Fallopian tube						
Gall bladder		X	X			
Gross lesions		X	X			X
Harderian gland		X	X			
Heart		X*	X		X*	X*
Ileum		X	X		X	
Injection site						
Jejunum		X	X		X	
Kidneys		X*	X*	* only	X*	X*
Knee Joint					X	
Lachrymal gland						
Larynx					X	
Liver		X*	X*	* only	X*	X*
Lungs		X*	X		X	X
Lymph nodes, cervical						
Lymph nodes mandibular		X	X		X	
Lymph nodes, mediastinal			X			
Lymph nodes, mesenteric		X	X		X	
Mammary Gland		X	X		X	
Nasal cavity		X	X			
Optic nerves						
Ovaries		X*	X*		X*	X
Pancreas		X	X		X	X
Parathyroid		X	X		X	
Parotid gland					X	
Peripheral nerve						
Peyer's patches					X	
Pharynx						
Pituitary		X	X		X*	
Preputial glands					X	

Prostate		X	X		X*	X
Rectum		X	X		X	
Salivary gland		X	X			
Sciatic nerve		X	X		X	
Seminal vesicles		X	X		X	
Skeletal muscle		X	X		X	
Skin			X		X	
Spinal cord		X	X			
Spleen		X	X		X*	
Sternum		X			X	
Stomach		X	X		X	X
Testes		X*	X*		X*	X
Thymus		X*	X		X	X
Thyroid		X	X		X*	X
Tongue					X	
Trachea		X	X		X	X
Urinary bladder		X	X		X	
Uterus		X	X		X	
Vagina		X	X		X	
Zymbal gland						

X, histopathology performed
*, organ weight obtained
^histopathology planned but not conducted, organ weights conducted

GENETIC TOXICOLOGY

Study title: ***Dextromethorphan Hydrobromide Bacterial Reverse Mutation Test***

Key findings:

- No evidence of mutagenicity by dextromethorphan hydrobromide at concentrations up to 5000 mcg/plate with and without S9 in the Ames test under the conditions of this study

Study no.: DMQ-112; (b) (4) AWN/004
Volume # 1 (SN 040)**, and page #** 57
Conducting laboratory and location: (b) (4)
Date of study initiation: April 29, 2002
GLP compliance: yes (x) no ( )
QA reports: yes (x) no ( )
Drug Dextromethorphan hydrobromide**, lot #** DM 9912074**, and % purity** 99.7%

Methods

Strains/species/cell line: *Salmonella typhimurium* strains TA 1535, TA 100, TA 1537, TA 98, and *Escherichia coli* strain WP2*uvr*A/pKM101

Doses used in definitive study: 50-5000 mcg/plate with and without S9

Basis of dose selection: Range-finding study using solvent and 5-5000 mcg/plate dextromethorphan hydrobromide with and without S9 in TA 98, TA 100, TA 1535, TA 1537, and WP2*uvr*A/pKM101: no microbial contamination found, solvent controls within 99% confidence limits of current historical control range of the laboratory, mutagenicity by the positive control articles confirmed, no increases in revertant colony numbers by dextromethorphan hydrobromide at any concentration with and without S9 mix in range-finding test, 5000 mcg/plate selected as the high concentration for the 2nd mutagenicity test

Negative controls: No treatment, and solvent dimethyl sulphoxide (DMSO, dextromethorphan insoluble in water)

Positive controls: In the presence of S9:
Sodium azide (0.5 mcg/plate) for strains TA 1535 and TA 100
9-Aminoacridine (50 mcg/plate) for strain TA 1537
2-Nitrofluorene (1 mcg/plate) for strain TA 98
2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide (AF-2, 0.05 mcg/plate) for strain WP2*uvr*A/pKM101

In the absence of S9:
2-Aminoanthracene (10 mcg/plate) for strain WP2*uvr*A/pKM101
(2 mcg/plate) for strain TA 1535
Benzo[a]pyrene (5 mcg/plate) for strains TA 1537, TA 98, and TA 100

Incubation and sampling times: 30 minutes before addition of agar overlay, and then 72 hours

Results

Study validity:

- Validity requirement included mean of solvent/vehicle control revertant colony numbers for each strain within 99% confidence limits of current historical control range of the laboratory (historical control data provided) and doubling of mean revertant colony numbers over negative control by the positive control compounds
- Mutagenic activity defined as presence of ≥2X increase in revertant colony numbers compared to concurrent solvent/vehicle controls, with positive dose-relationship, in 2 separate experiments
- Revertant colonies counted using a Domino automated colony counter

Study outcome: No increases in revertant colony numbers in the dextromethorphan-treated plates compared to solvent controls at any concentration with and without S9; substantial (4X-20X) increase in numbers of revertant colonies by the positive control articles

Study title: ***Quinidine Sulphate Bacterial Reverse Mutation Test***

Key findings:

- No evidence of mutagenicity by Quinidine sulphate at up to 5000 mcg/plate in the Ames test under the conditions of this study

Study no.: DMQ-109; (b) (4) AWN/001

Volume # 1 (SN040) and 8 (SN043)**, and page #** 88 (SN040) and 218 (SN043)
Conducting laboratory and location: (b) (4)

Date of study initiation: April 25, 2002
GLP compliance: yes (x) no ( )
QA reports: yes (x) no ( )
Drug Quinidine sulphate**, lot #** 9900130**, and % purity** 100.1%

Methods

Strains/species/cell line: *Salmonella typhimurium* strains TA 1535, TA 100, TA 1537, TA 98, and *Escherichia coli* strain WP2*uvr*A/pKM101

Doses used in definitive study: 5 concentrations from 50-5000 mcg/plate quinidine sulphate in dimethyl sulphoxide (DMSO, quinidine insoluble in water), with and without S9

Basis of dose selection: Range-finding study: DMSO or quinidine sulphate at 5 concentrations from 5-5000 mcg/plate in all strains with 72 hour incubation; no microbial contamination found, solvent controls within 99% confidence limits of current historical control range of the laboratory, mutagenicity by the positive control articles confirmed, no increases in revertant colony numbers by quinidine sulphate at any concentration with and without S9 mix in range-finding test, 5000 mcg/plate selected as the high concentration for the 2nd mutagenicity test

Negative controls: No treatment and DMSO, with and without S9

Positive controls: In the presence of S9:
Sodium azide (0.5 mcg/plate) for strains TA 1535 and TA 100
9-Aminoacridine (50 mcg/plate) for strain TA 1537
2-Nitrofluorene (1 mcg/plate) for strain TA 98
2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide (AF-2, 0.05 mcg/plate) for strain WP2*uvr*A/pKM101

In the absence of S9:
2-Aminoanthracene (10 mcg/plate) for strain WP2*uvr*A/pKM101
(2 mcg/plate) for strain TA 1535

Benzo[a]pyrene (5 mcg/plate) for strains TA 1537, TA 98, and TA 100

Incubation and sampling times: 72 hours in addition to 30 minute pre-incubation before addition of agar overlay

Results

Study validity:

- Validity confirmed by solvent/vehicle control revertant colony numbers within 99% confidence limits of the current historical control range for the laboratory and 2X mean revertant colony numbers by the positive control compounds compared to negative control numbers
- Positive response defined as increase in revertant colony numbers of ≥2X the number of revertant colonies by the vehicle control, with a dose-relationship in 2 separate tests, with or without S9 and in any bacterial strain
- Revertant colonies counted using a Domino automated colony counter

Study outcome: no microbial contamination found in the quinidine sulphate and positive control compounds; mean revertant colony numbers for the solvent control-treated strains were within 99% confidence limits of the historical control range for the laboratory; 3X-20X increase in revertant numbers by the positive control articles compared to solvent controls; no increases in revertant colony numbers that were ≥2X the numbers of revertants by the solvent in any strain with and without S9; some thinning of background lawn of non-revertant cells in all strains without S9 and in some strains with S9

Study title: **Dextromethorphan Hydrobromide Mouse Micronucleus Test**

Key findings:

- No evidence of chromosome damage (increased micronucleated immature or micronucleated mature erythrocytes) and no bone marrow toxicity by dextromethorphan hydrobromide at up to 250 mg/kg PO in male mice at 24 and 48 hours after dosing, under the conditions of this study

Study no.: DMQ-114; (b) (4) AWN/006

Volume # 1 (SN040)**, and page #** 118 (SN040)
Conducting laboratory and location: (b) (4)

Date of study initiation: May 15, 2002
GLP compliance: yes (x) no ( )
QA reports: yes (x) no ( )
Drug Dextromethorphan hydrobromide**, lot #** DM 9912074**, and % purity** 99.7%

Methods

Strains/species/cell line: CD-1 mice (b) (4) weights 28-32 g males and 22-26 g females, n=2/sex/dose in the preliminary toxicity test, and n=14 males given vehicle, 7 males each given low-dose and mid-dose dextromethorphan, 14 males given high-dose dextromethorphan, and 5 males given positive control article in the definitive study with an additional 3 males given the high dose of 250 mg/kg for replacement due to potential deaths in the high dose group).

Doses used in definitive study: 62.5, 125, and 250 mg/kg PO (gavage)

Basis of dose selection: Preliminary toxicity test at 125, 250, 500, and 600 mg/kg PO (gavage) dextromethorphan hydrobromide with 48-hour observation for toxicity; results showed deaths in all mice at the highest 2 doses, and underactivity, flattened posture, abnormal gait, fast/irregular respiration and uncoordinated movements at 250 mg/kg and abnormal gait, overactivity, fast/irregular respiration and uncoordinated movements at 125 mg/kg, with no differences in toxicity between the male and female mice; the high dose selected for the definitive study in male mice was 250 mg/kg PO

Negative controls: 1% w/v methylcellulose PO (gavage)

Positive controls: Mitomycin C at 12 mg/kg PO (gavage)

Incubation and sampling times: Sacrifice and bone marrow smears obtained from femurs at 24 hours after dosing in 7 negative control, LD, MD, and HD mice and 5 positive control mice, and at 48 hours after dosing in 7 negative control and 6 HD mice; micronucleated cells per 2000 polychromatic erythrocytes per animal were counted using light microscopy of stained (10% Giemsa) smears; 3 additional animals were added to the high dose group due to severe clinical signs

Results

Study validity:

- Micronuclei identified as deeply stained and large enough to discern morphology under light microscopy, with round shape and clearly defined outline, in same focal plane as cell, without internal structure (pyknotic)
- Bone marrow cell toxicity defined by statistically significant dose-related decrease in proportion of immature erythrocytes ($p<0.01$)
- Positive response defined as statistically significant ($p<0.01$) dose-related increase in incidence of micronucleated immature (mie) or micronucleated mature (mme) erythrocytes compared to concurrent control group and exceeding laboratory historical control range

Study outcome: In the definitive study, there were clinical signs at 125 and 250 mg/kg, including overactivity, hunched posture, abnormal gait, fast/irregular respiration, uncoordinated movements, piloerection, prominent eyes, fasciculations and partially closed eyelids at the highest dose. There were 4 of the 17 males given the high dose

found dead (one at 30 minutes, one at 1 hour 10 minutes, and 2 at approximately 3 hours 45 minutes).

There were no statistically significant increases in micronucleated immature erythrocytes (mie) in the treated mice (mean incidences of 0.0, 0.1, and 0.4 mie at 62.5, 125, and 250 mg/kg PO at 24 hours) compared to the vehicle controls (mean incidence 0.4 at 24 hours), and no statistically significant increase in micronucleated mature erythrocytes (mme) in test article and positive control treated mice compared to vehicle controls. The positive control article significantly increased the frequency of micronucleated immature erythrocytes (mean incidence 14.2) when compared to vehicle controls, at 24 hours after dosing. No decrease in the proportion of immature erythrocytes by the test or positive control articles were observed.

Study title: ***Quinidine Sulphate Mouse Micronucleus Test***

Key findings:

- No statistically significant increases in number of micronucleated immature polychromatic erythrocytes and micronucleated mature erythrocytes in male (175-700 mg/kg PO quinidine) and female (125-500 mg/kg PO quinidine) mice at 24 and 48 hours after dosing
- No statistically significant decreases in proportion of immature erythrocytes in male and female mice at 24 and 48 hours after dosing
- Positive control, Mitomycin C significantly increased frequency of micronucleated immature erythrocytes ($p<0.01$), but did not decrease proportion of immature erythrocytes
- Quinidine sulphate negative for clastogenicity *in vivo*, in the mouse micronucleus test under conditions of this study

Study no.: DMQ-111; (b) (4) AWN/003

Volume # 1 (SN040)**, and page #** 151
Conducting laboratory and location: (b) (4)
Date of study initiation: May 8, 2002
GLP compliance: yes (x) no ( )
QA reports: yes (x) no ( )
Drug Quinidine sulphate**, lot #** 9900130**, and % purity** 100.1%

Methods

Strains/species/cell line: CD-1 mice ((b) (4) weights 28-32 g males and 22-30 g females, n=2/sex/dose in the preliminary toxicity test and 10/sex vehicle control, 10 male mid-dose and 10/sex high dose, and 5/sex low dose, 5 mid-dose females, and 5/sex positive control)

Doses used in definitive study: 175, 350, and 700 mg/kg PO (gavage) in the males and 125, 250, and 500 mg/kg PO (gavage) in the females (additional 5 males at 350 mg/kg were evaluated at 48 hours due to high mortality at 700 mg/kg)

Basis of dose selection: Preliminary toxicity test at 500, 600, 700, and 800 mg/kg PO (gavage) with 48 hour observation period for mortality and clinical signs of toxicity;

- deaths in 1 female (1h after dosing) and 1 female killed *in extremis* at 700 mg/kg, 1 male (20 min after dosing) at 800 mg/kg
- treatment-related under-activity, irregular respiration in males and females at ≥500 mg/kg PO
- flattened posture, abnormal gait, fasciculations, partially closed eyelids at ≥600 mg/kg PO
- convulsions, reddened skin in females at ≥700 mg/kg PO and in males at ≥800 mg/kg PO
- doses chosen for the definitive study were 175-700 mg/kg in the males and 125-500 mg/kg in the females

Negative controls: 1% w/v methylcellulose

Positive controls: Mitomycin C at 12 mg/kg PO (gavage)

Incubation and sampling times: 5/sex/dose and 5/sex negative and positive control mice sacrificed at 24 hours, and 5/sex negative control and 5/sex HD mice sacrificed at 48 hours; bone marrow (femurs) smears prepared (Giemsa stain) and examined by light microscopy for incidence of micronucleated cells per 2000 polychromatic erythrocytes per mouse

Results

Study validity:

- Micronuclei identified as deeply stained and large enough to discern morphology under light microscopy, with round shape and clearly defined outline, in same focal plane as cell, without internal structure (pyknotic)
- Bone marrow cell toxicity defined by statistically significant dose-related decrease in proportion of immature erythrocytes ($p<0.01$)
- Positive response defined as statistically significant ($p<0.01$) dose-related increase in incidence of micronucleated immature (mie) or micronucleated mature (mme) erythrocytes compared to concurrent control group and exceeding laboratory historical control range
- Adequate bioavailability/exposure demonstrated by treatment-related deaths and clinical signs

Study outcome:

- Deaths in 1 male at 350 mg/kg (1 h after dosing), 5 males at 700 mg/kg (within 3 h after dosing)

- Clinical signs: under-activity, hunched posture at ≥175 mg/kg in males and 125 mg/kg in females, fast/irregular respiration, abnormal gait, partially closed eyes at ≥350 mg/kg in males and 500 mg/kg in females, and piloerection fasciculations, at ≥700 mg/kg in males and 500 mg/kg in females

The results of the statistical analysis are presented in the following table (reproduced from the original IND submission):

Results of the Micronucleus Test in Mice Administered Quinidine Sulfate by Oral Gavage

Sampling Time	Treatment	Dose (mg/kg)	%ie/(ie+me) (mean)	Incidence mie (mean)	Incidence mme (group mean)
Males					
24 Hours	Vehicle control	-	32	1.0	0.6
	Quinidine sulphate	175	32	0.8	0.0
	Quinidine sulphate	350	46	0.6	0.7
	Mitomycin C	12	42	33.4**	0.0
48 Hours	Vehicle control	-	34	0.0	0.0
	Quinidine sulphate	350	45	1.2	0.7
Females					
24 Hours	Vehicle control	-	40	0.6	0.0
	Quinidine sulphate	125	40	1.0	0.0
	Quinidine sulphate	250	43	0.6	0.0
	Quinidine sulphate	500	42	0.6	0.0
	Mitomycin C	12	40	39.8**	0.0
48 Hours	Vehicle control	-	37	0.8	0.6
	Quinidine sulphate	500	39	0.6	0.6

**p<0.01
mie: number of micronucleated cells observed per 2000 immature erythrocytes examined
mme: number of micronucleated cells calculated per 2000 mature erythrocytes
Vehicle control: 1% w/v methylcellulose
5ie/(ie+me): proportion of immature erythrocytes

Study title: ***Dextromethorphan Hydrobromide – In vitro Mammalian Chromosome Aberration Test in Human Lymphocytes***

Key findings:

- Dextromethorphan hydrobromide was negative for clastogenicity in vitro in the chromosome aberration test in human lymphocytes, under the conditions of this study

- Increased polyploidy metaphase figures by dextromethorphan at the highest concentration of 400 mcg/ml compared to DMSO solvent control, in the presence of S9 mix in the 3h treatment

Study no.: DMQ-113; (b) (4) AWN/005

Volume # 1**, and page #** 190
Conducting laboratory and location: (b) (4)
Date of study initiation: May 13, 2002
GLP compliance: yes
QA reports: yes (x) no ( )
Drug Dextromethorphan Hydrobromide**, lot #** DM 9912074**, and % purity** 99.7%

Methods

Strains/species/cell line: Human blood lymphocytes from healthy, non-smoking male volunteers

Doses used in definitive study:
First test: (-S9) 3h treatment, 17h recovery: 50, 200, 300 mcg/ml
(+S9) 3h treatment, 17h recovery: 100, 300, 400 mcg/ml
Second test: (-S9) 20h continuous treatment: 20, 60, 100 mcg/ml
(+S9) 3h treatment, 17h recovery: 200, 400, 500 mcg/ml

Basis of dose selection: Toxicity tests at 39.06-5000 mcg/ml DM with and without S9 for 3h treatment with 17 hour recovery, and at 50-700 mcg/ml DM with and without S9 for 3h treatment with 17 hour recovery; results showed 100% cytotoxicity in first test at 625 mcg/ml and above concentrations with and without S9, and mitotic index of 40% and 17% at 300 and 400 mcg/ml, respectively, without S9 (0% survival at 500 mcg/ml and above), and 40% and 21% at 400 and 500 mcg/ml, respectively, with S9 (0% survival at 600 mcg/ml and above).

Negative controls: Dimethyl sulphoxide (DMSO)

Positive controls: Mitomycin C in sterile purified water ((b) (4), 0.2 mcg/ml for 3-hour treatment, 0.1 mcg/ml for continuous treatment) in absence of S9, and Cyclophosphamide in sterile purified water ((b) (4)., 10 mcg/ml) in presence of S9 mix

Incubation and sampling times: Human lymphocytes stimulated to divide by phytohaemagglutinin, then exposed to test article, positive control, or negative control with and without S9 mix for 3 hours with a 17 hour recovery period, or for 20 continuous hours; cell division arrested using Colcemid at 2 hours before end of incubation period; cell harvested and mounted for examination of metaphase cells for chromosome damage. Mitotic index calculated with test article and solvent control, to evaluate toxicity of test article

Results

Study validity:

- Negative and positive control values within current historical control range
- Positive response defined as statistically significant increase in frequency of metaphases with aberrant chromosomes (excluding gaps) in one or more test concentrations, increases exceeding negative control range of the laboratory, increases reproducible between replicate cultures, and not associated with large changes in osmolality of medium or extreme toxicity, and dose relationship present to support conclusions
- Negative response defined as no statistically significant increases in number of aberrant cells above concurrent control frequencies

Study outcome: The following results were observed (reproduced from the original IND submission):

Results of the Chromosome Aberration Test on Dextromethorphan Hydrobromide in Human Lymphocytes

Exposure Period (hours)	S9 Mix	Concentration DM (mcg/ml)	Cells with aberrations (Excl. gaps)			Cells with aberrations (Incl. gaps)			Relative Mitotic Index (%)
			Individual values (%)		Mean (%)	Individual values (%)		Mean (%)	
Test 1									
3	-	0 (DMSO)	2	1	1.5	5	2	3.5	100
		50	1	1	1.0	4	2	3.0	87
		200	3	1	2.0	5	5	5.0	54
		300	1	3	2.0	3	4	3.5	40
		0.2 (Mitomycin C)	22	24	23.0***	24	28	26.0***	-
3	+	0 (DMSO)	2	2	2.0	4	3	3.5	100
		100	4	3	3.5	5	6	5.5	87
		300	2	3	2.5	6	6	6.0	63
		400	4	4	4.0	5	6	5.5	40
		10 (Cyclophosphamide)	24	22	23.0***	24	24	24.0***	-
Test 2									
20	-	0 (DMSO)	0	2	1.0	0	2	1.0	100
		20	1	0	0.5	2	0	1.0	77
		60	0	2	1.0	0	2	1.0	59
		100	2	0	1.0	2	0	1.0	55
		0.1 (Mitomycin C)	26	28	27.0***	26	28	27.0***	-
3	+	0 (DMSO)	1	0	0.5	1	0	0.5	100
		200	0	0	0.0	0	0	0.0	96
		400	2	0	1.0	2	0	1.0	65
		500	1	1	1.0	1	1	1.0	54
		10 (Cyclophosphamide)	26	26	26.0***	26	26	26.0***	-

*** $p<0.001$ (otherwise $p\geq0.01$)

Polyploid figures were increased to 0.7% (mean, not statistically significant, 3h treatment) at 300 mcg/ml (vs. 0.2% by DMSO) without S9, and to 1.7% (statistically

significant at p<0.001, 3h treatment) at 400 mcg/ml (vs. 0.2% by DMSO) with S9 in the first test, and to 0.4% at 100 mcg/ml (vs. 0.1% by DSO, not statistically significant) without S9 (20h continuous treatment) and to 0.9% at 500 mcg/ml (vs. 0.3% by DMSO, not statistically significant, 3h treatment) in the second test.

Positive and negative control results were within historical control range for the laboratory (provided).

Study title: ***Quinidine Sulphate – In vitro Mammalian Chromosome Aberration Test in Human Lymphocytes***

Key findings:

- Quinidine sulphate was equivocal for clastogenicity in the chromosome aberration test, in human lymphocytes in the presence of metabolic activation with S9; the results were without a clear dose-response effect
- The numbers of cells with aberrations including and excluding gaps were statistically significantly increased at 600 and 800 mcg/ml with metabolic activation using S9, but not at the dose of 700 mcg/ml with S9
- Quinidine sulphate significantly increased (p<0.001) the numbers of polyploidy metaphase figures at 500 mcg/ml without and at 400, 600, and 800 mcg/ml with S9 in the 3hour tests, and at 25, 50 and 75 mcg/ml (all doses tested) in the 20h continuous exposure test without S9

Study no.: DMQ-110; (b) (4) AWN/002

Volume # 1**, and page #** 222
Conducting laboratory and location: (b) (4)
Date of study initiation: April 29, 2002
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug Quinidine sulphate**, lot #** 9900130**, and % purity** 100.1%

Methods

Strains/species/cell line: Human blood lymphocytes from healthy, non-smoking male volunteers

Doses used in definitive study: Test 1: 125, 250, and 500 mcg/ml without S9 (3h test) and 600, 700, and 800 mcg/ml with S9 (3h test); Test 2: 25, 50, and 75 mcg/ml without S9 (20h continuous exposure) and 400, 600, and 700 mcg/ml with S9 (3h exposure)

Basis of dose selection: Toxicity test: quinidine sulphate at 31.25-4000 mcg/ml with and without S9, for 3h incubation followed by 17h recovery period (test article removed), followed by 2nd toxicity test at 100-1500 mcg/ml quinidine sulphate; the results showed

100% cytotoxicity with and without S9 at 1000 mcg/ml and above, relative mitotic index 60% at 250 mcg/ml and 31% at 500 mcg/ml without S9, and 98% relative mitotic index at 500 mcg/ml, 73% at 700 mcg/ml and 76% at 800 mcg/ml with S9

Negative controls: Dimethyl sulphoxide (DMSO)

Positive controls: Mitomycin C in sterile purified water (b) (4), 0.2 mcg/ml for 3-hour treatment, 0.1 mcg/ml for continuous treatment) in absence of S9, and Cyclophosphamide in sterile purified water (b) (4) 10 mcg/ml) in presence of S9 mix

Incubation and sampling times: Human lymphocytes stimulated to divide by phytohaemagglutinin, then exposed to test article, positive control, or negative control with and without S9 mix for 3 hours with a 17 hour recovery period, or for 20 continuous hours; cell division arrested using Colcemid at 2 hours before end of incubation period; cell harvested and mounted for examination of metaphase cells for chromosome damage. Mitotic index calculated with test article and solvent control, to evaluate toxicity of test article

Results

Study validity:

- Negative and positive control values within current historical control range
- Positive response defined as statistically significant increase in frequency of metaphases with aberrant chromosomes (excluding gaps) in one or more test concentrations, increases exceeding negative control range of the laboratory, increases reproducible between replicate cultures, and not associated with large changes in osmolality of medium or extreme toxicity, and dose relationship present to support conclusions
- Negative response defined as no statistically significant increases in number of aberrant cells above concurrent control frequencies

Study outcome: The following results were observed (reproduced from the original IND submission):

Results of the Chromosome Aberration Test on Quinidine Sulfate in Human Lymphocytes

Exposure Period (hours)	S9 Mix	Concentration Quinidine sulphate (mcg/ml)	Cells with aberrations (Excl. gaps)			Cells with aberrations (Incl. gaps)			Relative Mitotic Index (%)
			Individual values (%)		Mean (%)	Individual values (%)		Mean (%)	
Test 1									
3	-	0 (DMSO)	1	0	0.5	1	0	0.5	100
		125	0	0	0.0	1	0	0.5	106
		250	1	0	0.5	1	0	0.5	60
		500	2	1	1.5	2	1	1.5	31
		0.2 (Mitomycin C)	24	28	[a] 26.0***	26	32	[a]29.0***	-
3	+	0 (DMSO)	0	1	0.5	0	1	0.5	100
		600	2	3	2.5	2	3	2.5	106
		700	2	0	1.0	3	1	2.0	73
		800	2	8	5.0**	3	10	6.5***	76
		10 (Cyclophosphamide)	20	22	[a] 21.0***	20	22	[a]21.0***	-
Test 2									
20	-	0 (DMSO)	1	2	1.5	1	2	1.5	100
		25	2	2	2.0	2	2	2.0	55
		50	1	2	1.5	1	2	1.5	57
		75	0	3	1.5	0	3	1.5	44
		0.1 (Mitomycin C)	28	26	[a] 27.0***	28	26	[a]27.0***	-
3	+	0 (DMSO)	2	2	2.0	2	2	2.0	100
		400	0	1	0.5	0	1	0.5	95
		600	4	12	8.0**	4	14	9.0**	56
		700	6.6 [b]	1.9 [c]	4.7	6.6 [b]	1.9 [c]	4.7	31
		10 (Cyclophosphamide)	30	24	[a] 27.0***	30	24	[a]27.0***	-

**p<0.01
*** p<0.001 (otherwise p≥0.01)
[a]50 cells analyzed due to high levels of aberrations seen
[b]76 cells analyzed due to toxicity
[c]53 cells analyzed due to toxicity

The numbers of polyploid metaphase figures were increased to 2.5% (mean, statistically significant at p<0.001, 3h treatment) at 500 mcg/ml (vs. 0.2% by DMSO) without S9, and to 1.3% (statistically significant at p<0.001, 3h treatment) at 800 mcg/ml (vs. 0.1% by DMSO) with S9 in the first test. In the second test, polyploidy figures were increased to 4.5%, 4.7% and 2.5% at 25, 50, and 75 mcg/ml, respectively, (vs. 0.5% by DSO, all 3 concentrations statistically significant at p<0.001) without S9 (20h continuous treatment) and to 1.6% and 5.3% at 400 and 600 mcg/ml, respectively (vs. 0.4% by DMSO, statistically significant at p<0.001, 3h treatment).

Positive and negative control results were within historical control range for the laboratory (provided).

Study title: ***In vitro Mammalian Chromosome Aberration Test (Combination of Dextromethorphan hydrobromide-USP and Quinidine sulphate-USP 24)***

Key findings:

- Dextromethorphan hydrobromide and quinidine sulphate combined in a 1:1 concentration ratio were negative for clastogenicity in human peripheral blood lymphocytes *in vitro* (mammalian chromosome aberration test), under the conditions of this study (up to 350 mcg/ml each for 4 hours of treatment, and up to 31.3 mcg/ml each for 20 hours continuous treatment, concentrations limited by cytotoxicity (mitotic inhibition compared to solvent control) of >50% at higher concentrations)

Study no.: DMQ-115

Volume # 9**, and page #** 97
Conducting laboratory and location: (b) (4)

Date of study initiation: October 29, 2002
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug Dextromethorphan hydrobromide USP(DM) and Quinidine sulphate USP (Q)**, lot #s** DM9912074 (DM) and 9900130 (Quin)**, and % purity** 99.7% and 100.1%, respectively

Methods

Strains/species/cell line: Blood lymphocytes from a healthy, adult, non-smoking, male volunteer

Doses used in definitive study: 31.3, 62.5, 125, 250, 350, 500, 750, and 1000 mcg/ml (final concentrations evaluated were 125, 250, and 350 mcg/ml each drug due to excessive toxicity) DM and Q in a 1:1 ratio with and without S9 in the 4 hour treatment with 20 hour harvest, and 1.95, 3.9, 7.8, 15.65, 31.3, and 62.5 mcg/ml each drug (final concentrations evaluated 7.8, 15.65, and 31.3 mcg/ml each drug) DM and Q in a 1:1 ratio without S9 in the 20 hour treatment with 20 hour harvest

Basis of dose selection: Preliminary toxicity assay: Mitotic index ([cells in mitosis/500 cells scored] X 100) evaluated at 0.5-5000 mcg/ml each DM and Q in a 1:1 ratio in the presence and absence of metabolic activation with S9, using a 4h treatment, and in the absence of S9 using a 20h continuous treatment; the following results were observed (reproduced in part from the original IND submission):

Treatment (mcg/ml DM and Q in a 1:1 ratio)	4 Hour Treatment				20 Hour Treatment	
	+S9		-S9		-S9	
	Mitotic Index (%)*	Percent Change (%)**	Mitotic Index (%)*	Percent Change (%)**	Mitotic Index (%)*	Percent Change (%)**
0 (DMSO)	8.0	-	8.8	-	8.8	-
0.5	8.2	3	7.2	-18	8.4	-5
1.5	7.6	-5	6.8	-23	8.6	-2
5	7.8	-3	7.6	-14	7.8	-11
15	8.4	5	7.2	-18	7.6	-14
50	7.8	-3	8.0	-9	3.4	-61
150	8.0	0	7.6	-14	0.0	-100
500	2.6	-68	3.4	-61	0.0	-100
1500	0.0	-100	0.0	-100	0.0	-100
5000	0.0	-100	0.0	-100	0.0	-100

*Mitotic Index = (Cells in mitosis/500 cells scored)X100
** Percent Change = (Treatment mitotic index - control mitotic index)/control mitotic index; expressed as a percentage

In the definitive assays, the Mitotic Index Reduction values (relative to solvent control at the high dose evaluated for chromosome aberrations) were 53% at 350 mcg/ml (each for DM and Q in a 1:1 ratio) in the 4h treatments with and without S9, and 51% at 31.3 mcg/ml (each for DM and Q in a 1:1 ratio) in the 20h treatment without S9.

Negative controls: Dimethyl sulphoxide (DMSO, (b) (4))

Positive controls: Mitomycin C ((b) (4)) at 0.6 mcg/ml in the 4h treatment and 0.3 mcg/ml in the 20h treatment without S9, and Cyclophosphamide ((b) (4)) at 20 mcg/ml in the 4h treatment with S9

Incubation and sampling times: 4 hours and 20 hours treatment with the test articles combined in a 1:1 concentration ratio, followed by recovery time of 16 hours after the 4 hour treatments and 0 hours after the 20 hour treatment, with a harvest time at 20 hours for all assays

Results

Study validity:

- Assays conducted in duplicate
- Blind evaluation of slides for metaphase cells with 46 centromeres (minimum 200 metaphase spreads examined and scored, 100/replicate), for chromosome aberrations (chromatid-type and chromosome-type), including chromatid and isochromatid breaks and exchange figures (e.g., quadriradials [symmetrical and asymmetrical interchanges], triradials, and complex rearrangements), chromosome breaks and exchange figures (e.g., dicentrics, rings), chromatid or acentric fragments in absence of exchange figures scored as chromatid or chromosome breaks, fragments with exchange figures scored as incomplete exchanges, also noted were pulverized chromosomes, pulverized cells and

severely damaged cells (10 or more aberrations), chromatid and isochromatid gaps
- Validity included frequency of cells with structural chromosome aberrations in solvent controls within historical range of the laboratory, percent cells with chromosome aberrations in the positive control cultures statistically increased at $p \leq 0.05$ compared to solvent control,
- Positive effect defined as statistically significant increase in chromosome aberrations compared to solvent controls, with a dose-response effect, at one or more concentrations evaluated, with reproducible effect in the duplicate assays

Study outcome: No statistically significant increase in % aberrant cells (numerical or structural), total number of structural aberrations (gaps, chromatid breaks and exchanges, chromosome breaks, dicentric chromosomes and rings), severely damaged cells and average aberrations per cell by dextromethorphan and quinidine at up to 350 mcg/ml each in a 1:1 ratio in the 4 hour treatment with and without S9, and at up to 31.3 mcg/ml each in a 1:1 ratio in the 20 hour treatment without S9. The positive control articles Mitomycin C and Cyclophosphamide statistically significantly increased the % aberrant cells (structural, 25%-31% by (b) (4) and 28% by (b) (4)), chromatid breaks (b) (4)) and exchanges (b) (4)). The average aberrations per cell in the negative control cultures were 0.01-0.02 (within historical control range).

CARCINOGENICITY

Study title: **26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 and CByB6F1 Mice**

Key study findings:
- No treatment-related effects on mortality
- Increased thin appearance in Tg.rasH2 mice (4/25 M at 50/50 and 100/100 mg/kg/d DM/Q, and 13/25 F at 50/50 and 8/25 F at 100/100 mg/kg/d DM/Q, compared to 1/25 M and 2/25 F controls
- Dose-related decrease in body weights in male (-7% at 100/100 mg/kg/d DM/Q and -8% at 100 mg/kg/d DM) and female (-8% at 100/100, -5% at 100/0, and -4% at 0/100 mg/kg/d DM/Q) Tg.rasH2 mice at end of study (Days 1-183); decreased body weights at 100/100 mg/kg/d DM/Q in the male and female CByB6F1 mice
- Decreased body weight gains in male (-39% at 100/100, -35% at 100/0, and -20% at 0/100 mg/kg/d DM/Q) and female (-34% at 100/100, -21% at 100/0, and -11% at 0/100 mg/kg/d DM/Q) Tg.rasH2 mice at end of study (Days 1-183)
- Decreased food consumption in the HD Tg.rasH2 males (100 mg/kg/d DM with and without Q) and females (100 mg/kg/d DM alone)
- Increased absolute heart (100 mg/kg/d DM with and without Q M and 100 mg/kg/d DM alone F) and relative (M at 100 mg/kg/d DM alone) brain weights; decreased absolute (M at 100 mg/kg/d DM alone) and relative (M at 50/50

mg/kg/d DM/Q and 100 mg/kg/day DM alone) kidney weights , absolute and relative liver weights (50/50 mg/kg/d DM/Q M and F, 100/100 mg/kg/d DM/Q M and F, 100/0 mg/kg/d DM/Q M and 0/100 mg/kg/d DM/Q F) in Tg.rasH2 mice; In the CByB6F1 mice, decreased absolute brain and heart weights in M and F, absolute kidney and liver weights in F, relative liver weights in F, and increased absolute liver weights in M and absolute and relative liver weights in F; no corresponding microscopic findings

- No statistically significant increase in treatment-related non-neoplastic and neoplastic lesions in the treated CByB6F1 and Tg.rasH2 male and female mice

Adequacy of the carcinogenicity study and appropriateness of the test model:

The 6-month carcinogenicity study on dextromethorphan in combination with quinidine in Tg.rasH2 mice used an adequate number of animals and parameters evaluated. The doses were based on the results of a preliminary 28-day dose range-finding toxicity study in adult male and female CByB6F1 mice, in which the maximum tolerated doses (MTDs) were established at 100 mg/kg/d dextromethorphan based on mortality data in the mice, and 100 mg/kg/day quinidine, chosen to achieve a higher multiple of human exposure and represent the proposed 1:1 ratio proposed for clinical use. Agency concurrence for the study protocol, including the use of the Tg.rasH2 mouse model and the dosing, was provided (Executive CAC meeting of 11/18/2003, letter to the sponsor dated 11/25/2003, and e-mail correspondence with the sponsor of 12/09/2003 concurring with modification of the proposed dosing). MTD values were confirmed in the carcinogenicity study by dose-related increased incidence of thin appearance, and decreased body weights, body weight gains and food consumption in the male and female mice. Additionally, there were treatment-related organ weight changes. The validity of the study was also confirmed by positive toxicity and neoplastic findings in the positive control groups given urethane.

Evaluation of tumor findings:

There were no statistically significant treatment-related increases in neoplastic lesions in the male and female mice given oral gavage doses of up to 100 mg/kg/day dextromethorphan with and without 100 mg/kg/day quinidine sulfate, and in the mice given quinidine alone at 100 mg/kg/day. There were occasional findings of pulmonary, adrenal, and Harderian gland adenomas, hemangiosarcomas in the spleen, mandibular bone, nasal cavity, eye, ileum, liver, testes, skin, and pancreas, and carcinomas in the lungs, stomach and prostate, in the male and/or female mice given vehicle and/or test article (without relationship to dose). The positive control (urethane) treated mice showed high incidences of pulmonary tumors and hemangiosarcomas in the spleen. The results of the Agency statistical evaluation of the histopathology findings concur with those of the sponsor. In conclusion there was no evidence of carcinogenic potential by Neurodex™ in Tg.rasH2 mice, under the conditions of this study. The Executive CAC agreed that the study was adequate and that no statistically significant drug related neoplasms were observed in the study.

Study no.: AA74UX.UY.7G8R.BTL, Sponsor Study No. DMQ-119
Volume # Folder M2 in the Electronic Submission**, and page #** 1
Conducting laboratory and location: (b) (4)

Date of study initiation: December 17, 2003
GLP compliance: Yes
QA report: yes (x) no ( )
Drugs Dextromethorphan hydrobromide (DM) and quinidine sulfate (Q)**, lot #s** DM0302015 (DM) and 4963 (Q)**, and % purity** 99.6% (DM) and 100.8% (Q)

Disclaimer: ***Tabular and graphical information are reproduced from the original submission, unless cited otherwise.***

Methods

Doses: (from the original NDA submission):

Text Table 3: Experimental Design

Group	Dose	Number of Animals			
		(Tg.rasH2)		(CByB6F1)	
		Male	Female	Male	Female
1	Vehicle control	25	25	25	25
2	Positive control (Urethane, 1,000 mg/kg in three i.p.[1] injections)	25	25	-	-
3	Low Dose DM/Q Combination (25/50 mg/kg/day)	25	25	-	-
4	Mid dose DM/Q Combination (50/50 mg/kg/day)	25	25	-	-
5	High dose DM/Q Combination (100/100 mg/kg/day)	25	25	25	25
6	High dose DM (100 mg/kg/day)	25	25	-	-
7	High dose Q (100 mg/kg/day)	25	25	-	-
Total		175	175	50	50

[1] i.p. = intraperitoneal

Basis of dose selection: MTD

- Preliminary 28-day dose range-finding toxicity study at 75-175 mg/kg/day DM in combination with 50 mg/kg/day Q, 175 mg/kg/day CM alone and 50 mg/kg/day Q alone

- Doses recommended by the CAC: 25-100 mg/kg/day DM in combination with 100 mg/kg/day Q, 100 mg/kg/day DM alone and 100 mg/kg/day Q alone based on the results of the 28-day study (see Minutes of the Executive CAC meeting of November 18, 2003)

  Species/strain: Tg.rasH2 mice and CByB6F1 mice (b) (4))
  Number/sex/group (main study): See under Doses, above
  Route, formulation, volume: Both test articles dissolved in 1% methyl cellulose (MC, 400 centipoises at 2% in sterile water for injection), administered by oral gavage at 10 ml/kg body weight
  Frequency of dosing: Once daily, 7 days/week for 26 weeks
  Satellite groups used for toxicokinetics or special groups: None
  Age: 9-11 Weeks
  Animal housing: Mice housed individually during dosing, in polycarbonate cages with hardwood bedding, in animal room with temperature range 69-75 degrees F and 30%-70% relative humidity, 12 hour light/dark cycle
  Restriction paradigm for dietary restriction studies: None
  Drug stability/homogeneity: Analytical reports on dose solutions including homogeneity provided: doses and homogeneity confirmed on samples taken in January, March, May and July, 2004 (See pages 371-415 of the electronic submission)
  Dual controls employed: No, one negative control group received 10 ml/kg body weight vehicle; however, there was a single negative control group used for each type mouse (transgenic and wild-type)
  Positive Control: Urethane in saline, 3 injections (Days 1, 3, and 5) during Study Week 1, at 100 mg/kg IP (100 mg/ml, 10 ml/kg)
  Interim sacrifices: None
  Deviations from original study protocol (reproduced from the original NDA submission):
  The dosages administered on May 31, 2004 were based upon individual body weights collected two weeks prior to the most recently collected body weights. However, the animals were at a slow growth rate age by that date and therefore the effect of the deviation was minimal.

  The dosing formulations were stored at 2-8^{o}C and not at room temperature as stated in the protocol. Since 2- 8^{o}C was the correct and intended storage temperature, the protocol was amended for formulations after May 13, 2004.

  During quarantine and prior to randomization, the animals were group housed (two mice per cage) instead of individually. The specification for individual housing during quarantine was actually an error in protocol preparation.

  The females were 11 weeks old on Day 1 instead of ≤ 10 weeks old as specified by the protocol, because the 26-Week study was delayed following the Sponsor's request to perform a 14-Day study using the extra animals designated to the 26-

Week study. Since the animals were only one week older than intended, the incidence of spontaneous neoplasms in the controls and treated animals was not expected to be significant or to interfere with interpretation of the study results.

The two groups of male CByB6F1 mice were not dosed on January 11, 2004. This amounted to the loss of only 1 of 183 doses.

Due to a mechanical malfunction, the humidity in the animal room was above the upper limit of 70% (to an average of 82% and a maximum of 84%) for approximately 2 hours on July 4, 2004. The period of this deviation was short and all groups, including the controls, were similarly exposed.

It is reasonable to conclude that the protocol deviations had no effect on the outcome of the study.

Observations

Mortality: Twice daily
Clinical signs: Once weekly at 2 hours after dosing
Body weights: Once weekly beginning on Dosing Day 1, for 13 weeks, then every 2 weeks thereafter, up to date of death if found dead, accidental death, unscheduled sacrifice and scheduled sacrifice
Food consumption: Weekly
Gross pathology: All animals found dead, and sacrificed, both unscheduled and scheduled
Organ weights: Scheduled sacrificed animals only: brain, liver, kidneys, testes, and ovaries
Histopathology: Peer review: yes ( ), no (x)
Adrenal glands, aorta, bone (femur and sternum), bone marrow (femur and sternum), brain, epididymides, esophagus, eyes, forestomach, gall bladder, gross lesions, Harderian glands, heart, kidneys, large intestine (cecum, colon, rectum), liver, lungs and bronchi, lymph nodes (mesenteric, mediastinal, mandibular), mammary gland with adjacent skin, nasal cavity, ovaries, pancreas, parathyroid glands, pituitary gland, prostate gland, salivary gland, sciatic nerve, seminal vesicles, skeletal muscle (thigh), small intestine (duodenum, jejunum, ileum), spinal cord (cervical, thoracic, lumbar), spleen, stomach, testes, thymus, thyroid glands, trachea, urinary bladder, uterus, and vagina
Toxicokinetics: Not done

Results

Mortality: the following tables present the survival and unscheduled survival results for the Tg.rasH2 mice (reproduced from the original NDA submission):

TABLE 1 – SUMMARY OF SURVIVAL

MALES

Group:	1	2	3	4	5	6	7
Found Dead	1/25	8/25	2/25	1/25	-	-	2/25
Scheduled Sacrifice	-	13/25		-	-	-	-
Moribund Sacrifice	-	4/25		1/25	-	1/25	-
Terminal Sacrifice	24/25	-	23/25	23/25	25/25	24/25	23/25

FEMALES

Group:	1	2	3	4	5	6	7
Found Dead	1/25	2/25	2/25	-	1/25	-	3/25
Scheduled Sacrifice	-	20/25	-	-	-	-	-
Moribund Sacrifice	-	3/25	-	1/25	-	1/25	-
Terminal Sacrifice	24/25	-	23/25	24/25	24/25	24/25	22/25

Note: Represents the number of animals affected / the number of animals started on test.

Statistical analysis (Fisher's Exact test) did not reveal any significant differences when the test article-treated groups were compared to the concurrent vehicle control.

Group 1M/F	0 mg/kg/day (Vehicle Control)
Group 2 M/F	Positive Control (1,000 mg/kg Urethane in three intraperitoneal injections)
Group 3 M/F	25/50 mg/kg/day (Low dose DM/Q Combination)
Group 4 M/F	50/50 mg/kg/day (Mid-high dose DM/Q Combination)
Group 5 M/F	100/100 mg/kg/day (High dose DM/Q Combination)
Group 6 M/F	100 mg/kg/day DM (High dose DM)
Group 7 M/F	100 mg/kg/day Q (High dose Q)

Unscheduled Mortality (reproduced from the original NDA submission)**:**

Group	1	3	4	5	6	7
Dose DM/Q (mg/kg/day)	0/0	25/50	50/50	100/100	100/0	0/100
Males:						
Animal Found Dead (Day)[1]	2003 (17)	2051 (112), 2071 (165)	2085 (97)	-	-	2155 (154), 2175 (132)
Animal Moribund Sacrificed (Day)	-	-	2078 (140)	-	2147 (179)	-
Females:						
Animals Found Dead (Day)[1]	2185 (168)	2226 (185), 2230 (118)	-	2290 (20)	-	2336 (93), 2332 (183), 2333 (120)
Animal Moribund Sacrificed (Day)	-	-	2274 (149)	-	2315 (117)	-

[1] Animal number for animal affected followed by (Study Day) found dead or sacrificed.

The following table presents the unscheduled deaths for the non-transgenic (CByB6F1) mice (reproduced from the original NDA submission):

Group	1	5
Dose DM/Q (mg/kg/day)	0/0	100/100
Males: Animal Found Dead (Day)[1]	-	2388 (43), 2400 (82)
Females: Animals Found Dead (Day)[1]	-	2430 (146)

The remaining CByB6F1 mice survived to scheduled necropsy.

There were no statistically significant treatment-related differences in survival in the Tg.rasH2 mice, compared to controls. Unscheduled mortality, related to increased tumors in the lungs and spleen and distress due to rapid, shallow breathing, was increased in the positive control animals. Therefore, the surviving positive controls were sacrificed on Day 120 to preserve an adequate number of control tissues for comparison with the tissues from the treated mice.

Clinical signs: Treatment-related thin appearance was noted in the Tg.rasH2 mice. The incidence of thin appearance is presented in the following table (reproduced from the original NDA submission):

Group	1	2	3	4	5	6	7
Dose DM/Q (mg/kg/day)	0/0	Positive Control[1]	25/50	50/50	100/100	100/0	0/100
Males:							
Incidence[2]	1/25	3/25	3/25	4/25	4/25	3/25	1/25
Days from – to[3]	99-99	22-120	43-155	43-155	43-155	29-185	85-85
Females:							
Incidence[2]	2/25	5/25	2/25	13/25*	8/25*	2/25	4/25
Days from – to[3]	8-8	15-120	8-85	8-155	8-127	36-85	8-93

* $p \leq 0.05$; Fisher's Exact Test, when compared to the vehicle control (Group 1).

[1] Positive control was 1000 mg/kg Urethane administered 3 times by i.p. injection
[2] Number of animals observed as thin/ number of animals started on test.
[3] "Days from – to" indicates the first and last day the observation was recorded within the group.

The treated (100/100 mg/kg/day DM/Q) CByB6F1 mice showed no increased incidence of thin appearance compared to controls. In the positive control group, ataxia was observed in all animals (Day 1), and rapid, shallow breathing in 14 males (Days 99-120) and 14 females (Days 113-120).

Body weights: The mean body weights and body weight gains for the Tg.rasH2 mice are presented in the following tables (reproduced from the original NDA submission):

TABLE 3 – SUMMARY OF BODY WEIGHTS

Bodyweight (Grams) - Identity (No Transformation)

Group Sex		Day numbers relative to Start Date 1	8	15	22	29	36
1m	Mean	24.48	24.82	25.05	25.39	25.37	25.52
	S.D.	1.10	1.06	1.45	1.44	1.97	1.66
	N	25	25	25	24	24	24
2m	Mean	24.31	22.85*	24.30	24.69	25.48	26.20
	S.D.	1.16	1.09	0.94	2.02	1.33	1.44
	N	25	25	24	24	23	23
3m	Mean	24.34	24.79	25.24	25.11	25.53	25.58
	S.D.	1.03	1.13	1.37	1.41	1.29	1.38
	N	25	25	25	25	25	25
4m	Mean	24.50	24.98	25.43	25.56	25.70	25.88
	S.D.	1.34	1.26	1.58	1.52	1.57	1.48
	N	25	25	25	25	25	25
5m	Mean	24.25	24.57	25.00	25.14	24.63	24.96
	S.D.	1.20	1.33	1.62	1.72	1.67	1.56
	N	25	25	25	25	25	25
6m	Mean	23.69	24.32	24.64	24.90	24.45	24.76
	S.D.	1.67	1.72	1.48	1.52	1.65	1.52
	N	25	25	25	25	25	25
7m	Mean	24.14	24.77	25.01	25.02	25.38	25.26
	S.D.	1.33	1.36	1.47	1.44	1.52	1.65
	N	25	25	25	25	25	25

Statistics Test: Dunnett Test: * - 5% significance level
Arithmetic Mean Values Presented

Nominal Dose: Group 1 - 0:0 mg/kg/day Group 2 - 1000 mg/kg Urethane Group 3 - 25/50 mg/kg/day DM/Q
Group 4 - 50/50 mg/kg/day DM/Q Group 5 - 100/100 mg/kg/day DM/Q Group 6 - 100 mg/kg/day DM
Group 7 - 100 mg/kg/day Q

TABLE 3 – SUMMARY OF BODY WEIGHTS (CONTINUED)

Bodyweight (Grams) - Identity (No Transformation)

Group Sex		Day numbers relative to Start Date 43	50	57	64	71	78
1m	Mean	25.79	26.35	26.65	26.80	26.93	27.04
	S.D.	1.51	1.65	1.71	1.88	2.10	1.98
	N	24	24	24	24	24	24
2m	Mean	26.63	27.02	27.60	27.79	28.51*	28.77*
	S.D.	1.58	1.55	2.30	2.24	2.22	2.34
	N	23	23	23	23	22	21
3m	Mean	25.31	26.00	26.16	26.06	26.38	26.42
	S.D.	1.93	1.40	1.44	1.74	1.59	1.63
	N	25	25	25	25	25	25
4m	Mean	25.70	26.12	26.39	26.54	26.55	26.62
	S.D.	1.76	1.68	1.68	1.63	1.75	1.65
	N	25	25	25	25	25	25
5m	Mean	24.58	25.41	25.28*	25.14*	25.38*	25.50*
	S.D.	1.83	1.94	2.01	2.14	1.91	2.02
	N	25	25	25	25	25	25
6m	Mean	24.74	24.96*	25.02*	25.16*	25.22*	25.31*
	S.D.	1.58	1.64	1.59	1.70	1.75	2.03
	N	25	25	25	25	25	25
7m	Mean	25.37	25.64	25.74	25.67	25.81	26.07
	S.D.	1.48	1.57	1.64	1.72	1.62	1.71
	N	25	25	25	25	25	25

TABLE 3 – SUMMARY OF BODY WEIGHTS (CONTINUED)

Bodyweight (Grams) - Identity (No Transformation)

Group	Sex	Day numbers relative to Start Date: 85	99	113	120	127	141	155	169	183
1m	Mean	27.45	27.56	28.18	.	28.21	28.20	26.97	28.58	29.04
	S.D.	2.23	2.76	2.59	.	2.48	2.54	2.66	2.38	2.58
	N	24	24	24	0	24	24	24	24	24
2m	Mean	28.69	28.73	29.45	29.14n	.	.	.	.	.
	S.D.	2.20	2.43	2.74	3.07	.	.	.	.	.
	N	20	20	14	13	0	0	0	0	0
3m	Mean	26.72	26.46	27.23	.	27.60	27.69	27.63	28.32	28.28
	S.D.	1.82	2.24	1.78	.	1.81	1.79	1.95	1.77	1.91
	N	25	25	24	0	24	24	24	23	23
4m	Mean	26.67	26.64	27.08	.	27.42	27.50	26.21	28.05	28.09
	S.D.	1.88	1.88	1.80	.	2.32	1.95	2.46	1.90	1.83
	N	25	24	24	0	24	23	23	23	23
5m	Mean	25.35*	25.27*	25.88*	.	26.05*	25.95*	25.76	26.71*	27.05*
	S.D.	2.13	2.16	2.13	.	2.08	2.06	2.38	2.07	2.17
	N	25	25	25	0	25	25	25	25	25
6m	Mean	25.46*	25.67*	25.92*	.	26.14*	26.44*	26.34	26.74*	26.65*
	S.D.	2.00	2.05	2.07	.	2.28	2.24	2.45	2.57	3.06
	N	25	25	25	0	25	25	25	25	24
7m	Mean	26.29	26.52	27.00	.	27.10	27.27	27.04	27.83	27.80
	S.D.	2.02	2.02	1.95	.	2.01	2.05	1.95	2.11	2.01
	N	25	25	25	0	25	24	23	23	23

TABLE 3 – SUMMARY OF BODY WEIGHTS (CONTINUED)

Bodyweight (Grams) - Identity (No Transformation)

Group	Sex	Day numbers relative to Start Date: 1	8	15	22	29	36
1f	Mean	20.26	19.77	20.46	20.80	20.86	21.21
	S.D.	0.83	1.36	0.83	0.91	0.86	0.88
	N	25	25	25	25	25	25
2f	Mean	20.35	19.55	20.07	20.38	21.11	21.68
	S.D.	1.01	0.85	1.16	1.24	0.97	1.00
	N	25	25	25	25	25	25
3f	Mean	20.11	20.14	20.34	20.62	20.73	21.02
	S.D.	1.18	1.56	1.22	1.43	1.16	0.97
	N	25	25	25	25	25	25
4f	Mean	20.07	18.86	19.86	20.58	20.36	20.78
	S.D.	0.87	2.09	1.46	1.05	1.13	1.18
	N	25	25	25	25	25	25
5f	Mean	19.78	19.25	19.81	20.03	19.81*	20.16*
	S.D.	1.08	1.76	1.72	1.09	1.14	1.05
	N	25	25	25	24	24	24
6f	Mean	20.05	20.22	20.54	20.47	20.48	20.46
	S.D.	0.93	1.07	0.97	0.86	1.02	1.44
	N	25	25	25	25	25	25
7f	Mean	19.57	19.89	20.49	20.38	20.47	20.80
	S.D.	1.11	0.95	1.06	0.91	0.85	0.92
	N	25	25	25	25	25	25

TABLE 3 – SUMMARY OF BODY WEIGHTS (CONTINUED)

Bodyweight (Grams) - Identity (No Transformation)

Group Sex		Day numbers relative to Start Date 43	50	57	64	71	78
1f	Mean	21.10	21.53	21.40	21.28	21.72	21.53
	S.D.	0.84	0.88	0.78	0.93	1.22	0.85
	N	25	25	25	25	25	25
2f	Mean	21.64	21.78	22.10	22.08*	22.26	22.16
	S.D.	0.84	1.18	1.28	0.99	0.90	0.92
	N	25	25	25	25	25	25
3f	Mean	20.93	21.14	21.06	21.26	21.33	21.40
	S.D.	1.11	1.37	1.44	1.10	1.05	1.05
	N	25	25	25	25	25	25
4f	Mean	20.63	20.98	21.24	21.32	21.32	21.24
	S.D.	1.07	1.38	1.25	1.21	1.04	1.18
	N	25	25	25	25	25	25
5f	Mean	20.11*	20.43*	20.68	20.73	20.82*	20.52*
	S.D.	1.22	1.25	1.26	1.25	1.30	1.35
	N	24	24	24	24	24	24
6f	Mean	20.69	20.94	21.11	21.00	21.14	21.16
	S.D.	0.96	0.93	1.05	0.88	1.09	1.07
	N	25	25	25	25	25	25
7f	Mean	20.80	20.88	21.18	21.05	21.31	21.31
	S.D.	0.99	1.06	0.77	0.75	1.00	0.87
	N	25	25	25	25	25	25

TABLE 3 – SUMMARY OF BODY WEIGHTS (CONTINUED)

Bodyweight (Grams) - Identity (No Transformation)

Group Sex		Day numbers relative to Start Date 85	99	113	120	127	141	155	169	183
1f	Mean	21.72	22.18	22.77	.	22.86	22.88	22.77	22.99	23.38
	S.D.	0.94	1.01	1.00	.	1.22	1.25	1.06	1.00	1.38
	N	25	25	25	0	25	25	25	24	24
2f	Mean	22.68*	23.45*	23.29	23.05n	.	.	.	.	.
	S.D.	1.08	1.19	1.33	1.42	.	.	.	.	.
	N	25	25	21	20	0	0	0	0	0
3f	Mean	21.56	21.76	22.37	.	22.34	22.23	22.49	22.62	22.95
	S.D.	1.57	1.32	1.24	.	1.32	1.23	1.25	1.34	1.35
	N	25	25	25	0	24	24	24	24	24
4f	Mean	21.54	21.68	21.95	.	22.11	22.14	22.27	22.82	22.78
	S.D.	1.20	1.06	1.22	.	1.37	1.71	1.70	1.55	1.55
	N	25	25	25	0	25	25	24	24	24
5f	Mean	20.78*	20.96*	21.38*	.	20.95*	21.14*	21.50*	21.73*	21.78*
	S.D.	1.30	1.31	1.37	.	1.47	1.25	1.29	1.50	1.68
	N	24	24	24	0	24	24	24	24	24
6f	Mean	21.25	21.34*	21.78*	.	21.63*	21.80*	22.03	22.33	22.54
	S.D.	1.19	1.06	1.02	.	1.10	1.03	1.17	1.04	1.01
	N	25	25	25	0	24	24	24	24	24
7f	Mean	21.64	21.37	21.80*	.	22.07	21.87*	22.17	22.49	22.38
	S.D.	0.87	0.91	0.98	.	1.00	0.89	1.01	0.96	0.92
	N	25	24	24	0	23	23	23	23	22

TABLE 4 – SUMMARY OF BODY WEIGHT GAINS

Body Weight Gain (Grams) - Transformation: Identity (No Transformation)

Day numbers relative to Start Date

Group Sex	Base Weight Day 1	From: To:	1 8	8 15	15 22	22 29	29 36	36 43
1m	24.48	Mean	0.34	0.22	0.28	-0.02	0.15	0.27
	1.10	S.D.	0.47	0.72	0.60	0.89	1.24	0.97
	25	N	25	25	24	24	24	24
2m	24.31	Mean	-1.46*	1.39*	0.39	0.83*	0.72*	0.44
	1.16	S.D.	0.65	0.83	1.53	1.44	0.64	0.61
	25	N	25	24	24	23	23	23
3m	24.34	Mean	0.45	0.45	-0.13	0.42	0.04	-0.26
	1.03	S.D.	0.58	0.78	0.51	0.41	0.42	0.97
	25	N	25	25	25	25	25	25
4m	24.50	Mean	0.48	0.44	0.13	0.14	0.18	-0.18
	1.34	S.D.	0.47	0.50	0.58	0.58	0.41	1.06
	25	N	25	25	25	25	25	25
5m	24.25	Mean	0.32	0.43	0.14	-0.51	0.34	-0.38*
	1.20	S.D.	0.57	0.62	0.53	0.53	0.63	0.90
	25	N	25	25	25	25	25	25
6m	23.69	Mean	0.63	0.33	0.26	-0.45	0.30	-0.02
	1.67	S.D.	0.85	1.14	0.62	1.04	0.87	0.39
	25	N	25	25	25	25	25	25
7m	24.14	Mean	0.64	0.24	0.01	0.36	-0.13	0.12
	1.33	S.D.	0.45	0.52	0.50	0.40	0.57	0.53
	25	N	25	25	25	25	25	25

Statistics Test: Dunnett Test: * - 5% significance level
Arithmetic Mean Values Presented

Nominal Dose: Group 1 - 0:0 mg/kg/day Group 2 - 1000 mg/kg Urethane Group 3 - 25/50 mg/kg/day DM/Q
Group 4 - 50/50 mg/kg/day DM/Q Group 5 - 100/100 mg/kg/day DM/Q Group 6 - 100 mg/kg/day DM
Group 7 - 100 mg/kg/day Q

TABLE 4 – SUMMARY OF BODY WEIGHT GAINS (CONTINUED)

Body Weight Gain (Grams) - Transformation: Identity (No Transformation)

Day numbers relative to Start Date

Group Sex	Base Weight Day 1	From: To:	43 50	50 57	57 64	64 71	71 78	78 85	85 99
1m	24.48	Mean	0.56	0.30	0.14	0.14	0.10	0.41	0.12
	1.10	S.D.	0.47	0.59	0.42	0.41	0.37	0.50	1.18
	25	N	24	24	24	24	24	24	24
2m	24.31	Mean	0.39	0.58	0.19	0.56	0.33	-0.17*	0.04
	1.16	S.D.	0.71	1.15	0.82	0.94	0.76	0.85	1.33
	25	N	23	23	23	22	21	20	20
3m	24.34	Mean	0.68	0.16	-0.10	0.32	0.04	0.30	-0.25
	1.03	S.D.	1.06	0.30	0.69	0.76	0.39	0.53	0.81
	25	N	25	25	25	25	25	25	25
4m	24.50	Mean	0.42	0.28	0.14	0.02	0.07	0.05	0.03
	1.34	S.D.	0.48	1.09	0.45	0.43	0.38	0.64	0.63
	25	N	25	25	25	25	25	25	24
5m	24.25	Mean	0.83	-0.13	-0.14	0.24	0.12	-0.15*	-0.08
	1.20	S.D.	0.88	0.52	1.37	1.02	0.40	0.80	0.82
	25	N	25	25	25	25	25	25	25
6m	23.69	Mean	0.22	0.07	0.14	0.06	0.09	0.16	0.20
	1.67	S.D.	0.33	0.29	0.29	0.29	0.76	0.72	0.53
	25	N	25	25	25	25	25	25	25
7m	24.14	Mean	0.27	0.10	-0.07	0.14	0.26	0.22	0.23
	1.33	S.D.	0.34	0.41	0.56	0.73	0.66	0.91	0.91
	25	N	25	25	25	25	25	25	25

TABLE 4 – SUMMARY OF BODY WEIGHT GAINS (CONTINUED)

Body Weight Gain (Grams) - Transformation: Identity (No Transformation)

			Day numbers relative to Start Date						
Group Sex	Base Weight Day 1	From: To:	99 113	113 127	127 141	141 155	155 169	169 183	Abs Gain 1 183
1m	24.48	Mean	0.62	0.03	-0.00	-1.23	1.60	0.46	4.59
	1.10	S.D.	1.21	0.67	0.43	1.19	1.25	0.57	2.38
	25	N	24	24	24	24	24	24	24
2m	24.31	Mean	0.56	.	.	.	.	.	.
	1.16	S.D.	1.60	.	.	.	.	.	.
	25	N	14	.	.	.	.	.	.
3m	24.34	Mean	0.48	0.37	0.10	-0.06*	0.59*	-0.04*	3.93
	1.03	S.D.	0.47	0.53	0.81	1.25	0.73	0.72	1.54
	25	N	24	24	24	24	23	23	23
4m	24.50	Mean	0.44	0.34	-0.20	-1.29	1.84	0.04	3.55
	1.34	S.D.	0.48	0.96	0.55	1.01	1.03	0.61	0.97
	25	N	24	24	23	23	23	23	23
5m	24.25	Mean	0.60	0.17	-0.10	-0.19*	0.95	0.34	2.80
	1.20	S.D.	0.78	0.84	0.72	1.13	1.24	0.45	1.54
	25	N	25	25	25	25	25	25	25
6m	23.69	Mean	0.26	0.22	0.30	-0.10*	0.40*	-0.14*	2.99
	1.67	S.D.	0.45	0.93	0.86	0.59	0.87	1.02	2.59
	25	N	25	25	25	25	25	24	24
7m	24.14	Mean	0.48	0.10	0.14	-0.30*	0.78*	-0.03	3.66
	1.33	S.D.	0.42	0.38	0.47	0.60	0.57	0.47	1.45
	25	N	25	25	24	23	23	23	23

TABLE 4 – SUMMARY OF BODY WEIGHT GAINS (CONTINUED)

Body Weight Gain (Grams) - Transformation: Identity (No Transformation)

			Day numbers relative to Start Date					
Group Sex	Base Weight Day 1	From: To:	1 8	8 15	15 22	22 29	29 36	36 43
1f	20.26	Mean	-0.49	0.68	0.34	0.06	0.35	-0.12
	0.83	S.D.	1.30	1.34	0.55	0.57	0.68	0.45
	25	N	25	25	25	25	25	25
2f	20.35	Mean	-0.80	0.52	0.31	0.74*	0.57	-0.04
	1.01	S.D.	0.76	1.17	1.02	0.92	0.75	0.65
	25	N	25	25	25	25	25	25
3f	20.11	Mean	0.04	0.20	0.28	0.12	0.29	-0.10
	1.18	S.D.	1.00	0.76	0.78	0.76	0.45	0.57
	25	N	25	25	25	25	25	25
4f	20.07	Mean	-1.22	1.01	0.72	-0.22	0.42	-0.15
	0.87	S.D.	1.92	1.74	1.41	0.52	0.50	0.56
	25	N	25	25	25	25	25	25
5f	19.78	Mean	-0.53	0.56	0.23	-0.21	0.35	-0.05
	1.08	S.D.	1.67	1.86	1.25	0.43	0.69	0.66
	25	N	25	25	24	24	24	24
6f	20.05	Mean	0.17	0.32	-0.07	0.00	-0.02	0.24
	0.93	S.D.	0.48	0.96	0.77	0.46	1.12	1.08
	25	N	25	25	25	25	25	25
7f	19.57	Mean	0.32	0.60	-0.12	0.09	0.33	0.00
	1.11	S.D.	1.40	1.01	0.76	0.61	0.52	0.48
	25	N	25	25	25	25	25	25

TABLE 4 – SUMMARY OF BODY WEIGHT GAINS (CONTINUED)

Body Weight Gain (Grams) - Transformation: Identity (No Transformation)

Day numbers relative to Start Date

Group Sex	Base Weight Day 1	From: To:	43 50	50 57	57 64	64 71	71 78	78 85	85 99
1f	20.26	Mean	0.44	-0.14	-0.12	0.44	-0.18	0.19	0.46
	0.83	S.D.	0.65	0.59	0.78	1.26	0.72	0.77	0.97
	25	N	25	25	25	25	25	25	25
2f	20.35	Mean	0.14	0.32	-0.02	0.18	-0.10	0.52	0.77
	1.01	S.D.	0.98	1.45	1.11	0.58	0.36	0.56	0.95
	25	N	25	25	25	25	25	25	25
3f	20.11	Mean	0.22	-0.09	0.20	0.07	0.07	0.16	0.20
	1.18	S.D.	0.78	1.23	1.18	0.44	0.44	0.93	1.01
	25	N	25	25	25	25	25	25	25
4f	20.07	Mean	0.35	0.26	0.08	0.00	-0.08	0.30	0.14
	0.87	S.D.	0.85	0.69	0.50	0.55	0.56	0.67	0.59
	25	N	25	25	25	25	25	25	25
5f	19.78	Mean	0.31	0.25	0.06	0.09	-0.30	0.26	0.18
	1.08	S.D.	0.62	0.40	0.61	0.43	0.59	0.56	0.43
	25	N	24	24	24	24	24	24	24
6f	20.05	Mean	0.24	0.18	-0.12	0.15	0.02	0.09	0.09
	0.93	S.D.	0.40	0.32	0.40	0.58	0.60	0.83	0.75
	25	N	25	25	25	25	25	25	25
7f	19.57	Mean	0.08	0.30	-0.13	0.26	0.00	0.33	-0.24*
	1.11	S.D.	0.69	0.74	0.46	0.58	0.53	0.34	0.54
	25	N	25	25	25	25	25	25	24

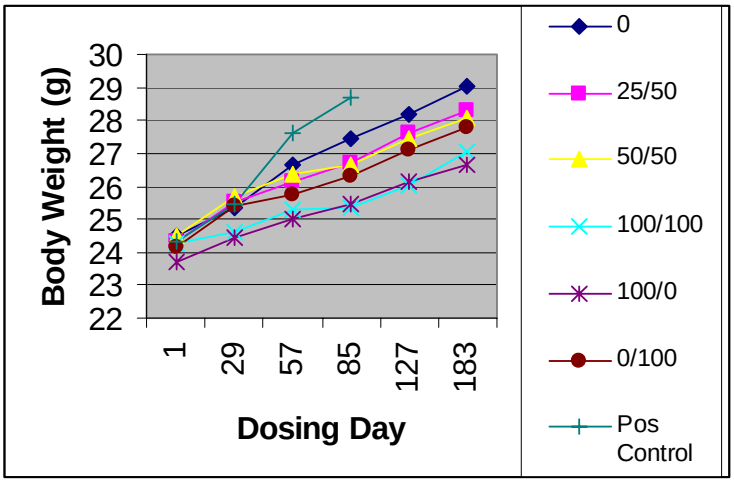
TABLE 4 – SUMMARY OF BODY WEIGHT GAINS (CONTINUED)

Body Weight Gain (Grams) - Transformation: Identity (No Transformation)

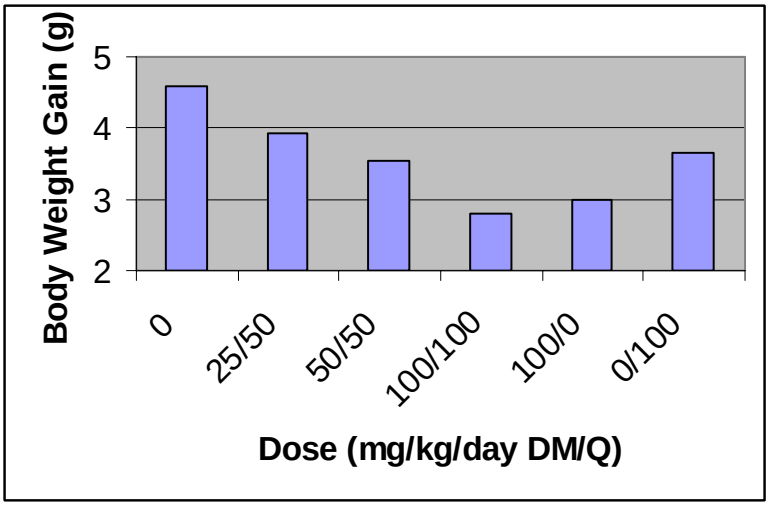
Day numbers relative to Start Date

Group Sex	Base Weight Day 1	From: To:	99 113	113 127	127 141	141 155	155 169	169 183	Abs Gain 1 183
1f	20.26	Mean	0.60	0.09	0.02	-0.10	0.30	0.39	3.06
	0.83	S.D.	0.64	0.86	0.67	0.73	0.58	0.61	1.23
	25	N	25	25	25	25	24	24	24
2f	20.35	Mean	-0.25*	.	.	.	.	.	.
	1.01	S.D.	1.32	.	.	.	.	.	.
	25	N	21	.	.	.	.	.	.
3f	20.11	Mean	0.61	-0.03	-0.10	0.26	0.13	0.34	2.84
	1.18	S.D.	0.71	0.70	0.74	0.66	0.90	0.86	0.81
	25	N	25	24	24	24	24	24	24
4f	20.07	Mean	0.27	0.16	0.03	-0.06	0.56	-0.04	2.72
	0.87	S.D.	0.58	0.92	1.02	1.25	1.32	0.53	1.38
	25	N	25	25	25	24	24	24	24
5f	19.78	Mean	0.42	-0.43	0.19	0.36	0.23	0.05	2.03
	1.08	S.D.	0.66	0.95	0.75	0.40	0.60	0.76	1.25
	25	N	24	24	24	24	24	24	24
6f	20.05	Mean	0.44	-0.21	0.17	0.23	0.30	0.21	2.42
	0.93	S.D.	0.70	1.00	0.92	0.53	0.60	0.70	0.93
	25	N	25	24	24	24	24	24	24
7f	19.57	Mean	0.44	0.20	-0.19	0.29	0.33	-0.17*	2.73
	1.11	S.D.	0.57	0.64	0.69	0.52	0.70	0.69	1.06
	25	N	24	23	23	23	23	22	23

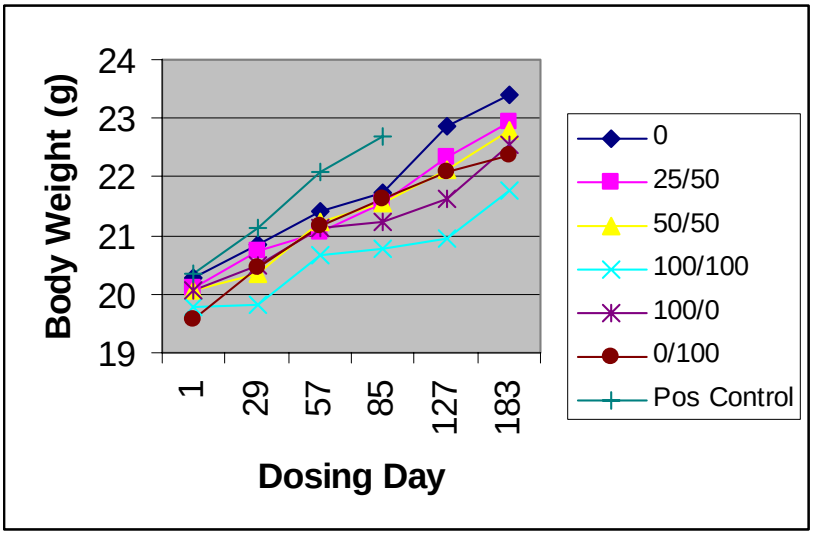
Mean Body Weights in Male Tg.rasH2 Mice Administered Vehicle Control, Dextromethorphan and Quinidine Alone in Combination (mg/kg/day DM/Q), and Urethane by Oral Gavage for 26 Weeks (graphical information constructed by the reviewer)



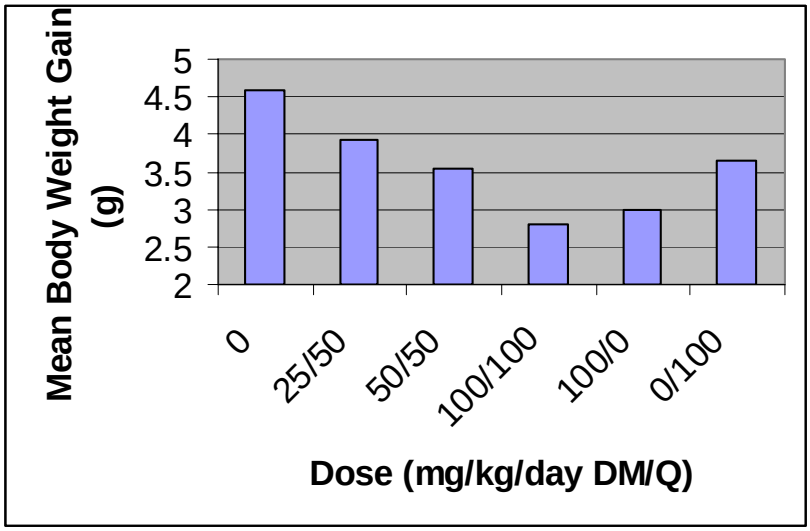
Mean Body Weight Gains in Male Tg.rasH2 Mice Administered Vehicle Control, Dextromethorphan and Quinidine Alone in Combination, and Urethane by Oral Gavage for 26 Weeks (graphical information constructed by the reviewer)



Mean Body Weights in Female Tg.rasH2 Mice Administered Vehicle Control, Dextromethorphan and Quinidine Alone in Combination (mg/kg/day DM/Q), and Urethane by Oral Gavage for 26 Weeks (graphical information constructed by the reviewer)



Mean Body Weight Gains in Female Tg.rasH2 Mice Administered Vehicle Control, Dextromethorphan and Quinidine Alone in Combination (mg/kg/day DM/Q), and Urethane by Oral Gavage for 26 Weeks (graphical information constructed by the reviewer)



In the CByB6F1 mice (100/100 mg/kg/day DM/Q), mean body weights were statistically significantly decreased compared to controls in the males on Days 113, 169, and 186, and in the females throughout the dosing period. Mean body weight gains were significantly decreased on 2 occasions in the males and 4 occasions in the females, but there were no overall differences from controls at the end of the dosing period (total gains during the period from Dosing Days 1-186) in the male and female CByB6F1 mice.

Food consumption: Statistically significant decrease in the Tg.rasH2 males at 100 mg/kg/day DM with and without Q during 16-18 of the last 24 dosing weeks, and occasionally (6 observations) at 100 mg/kg/day Q, compared to controls. Statistically significant decrease in the Tg.rasH2 females, occasionally (9 observations) at 100 mg/kg/day DM alone, compared to controls. In the CByB6F1 mice, mean food consumption was significantly decreased compared to controls in the males for 10 of 26 dosing weeks, and in the females for 8 of the 26 dosing weeks, but total consumption (Weeks 1-26) was not different from controls overall, at the end of the study.

Gross pathology: No treatment-related effects were observed in the negative control and treated (Tg.rasH2) groups. In the positive control mice, pulmonary lesions including red and tan nodules were observed in 23/25 males and 25/25 females. Also, lesions in the spleen (red/black/brown nodules, masses, clear or red focus, cysts, and ulcers) were observed in 22/25 males and 25/25 females given the positive control article, urethane.

The treated (100/100 mg/kg/day DM/Q) CByB6F1 mice showed no statistically significant increases in gross lesions in any organ or tissue, compared to controls.

Organ Weights: The following statistically significant changes compared to negative controls were observed in the Tg.rasH2 mice:

- Heart weights: Decrease in absolute weights at 100/100 mg/kg/day DM/Q in males (-7%) and females (-8%), and at 100 mg/kg/day DM alone in the males (-8%)
- Brain: Decreased absolute brain weights in females at 100/100 mg/kg/d DM/Q (-4%); Increase in relative (to body weight) brain weights in the males at 100 mg/kg/day DM alone (+8%)
- Kidneys: Decreased absolute (-13% at 100 mg/kg/day DM alone) and relative (to body weight, -4% at 50/50 mg/kg/d DM/Q and -6% at 100 mg/kg/day DM alone) weights in males, increased relative weights (+5% at 50/50 mg/kg/day DM/Q) in females
- Liver: Decreased absolute (-9% at 50/50 and -15% at 100/100 mg/kg/d DM/Q, -12% at 100 mg/kg/d DM alone, and -14% at 100 mg/kg/d Q alone in males, and -8% at 50/50 and -17% at 100/100 mg/kg/d DM/Q, and -9% at 100 mg/kg/d Q alone in females) and relative (to body weights, -7% in males and -6% in females) weights at 50/50 mg/kg/d DM/Q, and -9% in males and -12% in females at 100/100 mg/kg/d DM/Q), -4% at 100 mg/kg/d DM alone in males, and -11% in males and -6% in females at 100 mg/kg/day Q
- No corresponding microscopic findings in the histopathology examination in the organs with significant weight changes

In the CByB6F1 mice given 100/100 mg/kg/d DM/Q (when compared to negative controls), there was a statistically significant decrease in absolute brain (-2% in males and -3% in females) and heart (-5% in males and –5% in females) weights in the treated (100/100 mg/kg/day DM/Q) mice compared to controls, decreased absolute kidney weights in the females (-5%), and decreased absolute liver weights in the males (-7%) and females (17%). Relative (to body weights) brain weights were statistically significantly increased (+5%) and relative liver weights were significantly decreased (-11%) in the females.

Histopathology:

Non-neoplastic:

In the CByB6F1 mice (administered 100/100 mg/kg/day DM/Q), there were no statistically significant increases in non-neoplastic lesions, compared to controls. One of 25 treated males showed pigmented spleen and stomach mineralization, and one of 25 treated females showed uterine hyperplasia.

Neoplastic: Tg.rasH2 mice: The following pulmonary tumors were observed (reproduced from the original NDA submission):

Male Mice: 25 animals per dose group

Groups	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Adenoma Single	1	0	4	1	1	4	0
Adenoma Multiple	0	24	1	0	0	0	0
Total Adenomas	**1**	**24***	**5**	**1**	**1**	**4**	**0**
Carcinoma	**0**	**8***	**1**	**1**	**0**	**1**	**0**

* $p \leq 0.05$, Fisher's Exact Test

Female Mice: 25 animals per dose group

Groups	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Adenoma Single	2	0	4	1	3	0	2
Adenoma Multiple	0	24	0	0	0	0	0
Total Adenomas	**2**	**24***	**4**	**1**	**3**	**0**	**2**
Carcinoma	**0**	**17***	**0**	**1**	**0**	**0**	**0**

* p≤0.05, Fisher's Exact Test

Group 1 = Vehicle Control
Group 2 = Positive Control (1,000 mg/kg urethane in three intra-peritoneal injections)
Group 3 = 25/50 mg/kg/day DM/Q
Group 4 = 50/50 mg/kg/day DM/Q
Group 5 = 100/100 mg/kg/day DM/Q
Group 6 = 100 mg/kg/day DM only
Group 7 = 100 mg/kg/day Q only

The following table presents the incidence of hemangiosarcomas in the spleen (reproduced from the original NDA submission):

Groups

Sex	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Male	**0**	**22***	**0**	**0**	**1**	**1**	**3**
Female	**1**	**25***	**3**	**2**	**0**	**0**	**1**

* p≤0.05, Fisher's Exact Test

Group 1 = Vehicle Control
Group 2 = Positive Control (1,000 mg/kg urethane in three intra-peritoneal injections)
Group 3 = 25/50 mg/kg/day DM/Q
Group 4 = 50/50 mg/kg/day DM/Q
Group 5 = 100/100 mg/kg/day DM/Q
Group 6 = 100 mg/kg/day DM only
Group 7 = 100 mg/kg/day Q only

Additionally, the following neoplastic lesions were observed in the Tg.rasH2 mice (reproduced from the original NDA submission):

	Male						
Tumor/Site	1	2	3	4	5	6	7
Hemangiosarcoma							
Mandibular bone	0	1	0	0	0	0	0
Nasal Cavity	0	0	0	0	0	1	0
Eye	0	0	0	0	0	1	0
Ileum	0	0	1	0	0	0	0
Liver	0	0	1	0	0	0	0
Testes	1	0	0	0	0	1	0
Skin	0	1	0	0	0	0	0
Total of Above (Multiple Organ Hemangiosarcomas)[1]	**1**	**2**	**2**	**0**	**0**	**3**	**0**

Neoplastic Lesions Other than Multiple Organ Hemangiosarcoma:							
Hemangioma							
Pancreas	0	0	1	0	0	0	0
Adenoma							
Adrenal cortex	1	0	2	2	1	1	0
Harderian gland	0	0	0	2	0	0	0
Thymoma	0	0	0	0	0	2	0
Adenocarcinoma							
Salivary gland	0	1	0	0	0	0	0
Squamous Cell Carcinoma							
Non-glandular stomach	0	3	0	0	1	0	0
Transitional Cell Carcinoma							
Prostate	0	1	0	0	0	0	0

[1] Fisher's Exact Test did not reveal any significant differences when positive control or test article treatment groups were compared to Group 1.

Group 1 = Vehicle Control
Group 2 = Positive Control (1,000 mg/kg urethane in three intra-peritoneal injections)
Group 3 = 25/50 mg/kg/day DM/Q
Group 4 = 50/50 mg/kg/day DM/Q
Group 5 = 100/100 mg/kg/day DM/Q
Group 6 = 100 mg/kg/day DM only
Group 7 = 100 mg/kg/day Q only

	Female						
	1	2	3	4	5	6	7
Tumor/Site							
Hemangiosarcoma							
Skin	1	0	0	0	0	0	0
Ovary	0	1	0	0	0	0	0
Uterus[1]	2	0	1	5	1	3	1
Vagina	0	0	0	1	0	0	0
Kidneys	0	0	1	0	0	0	0
Total of Above (Multiple Organ Hemangiosarcomas)[1]	**3**	**1**	**2**	**6**	**1**	**3**	**1**
Neoplastic Lesions Other than Multiple Organ Hemangiosarcoma:							
Adenoma							
Adrenal cortex	0	0	2	0	0	0	1
Carcinoma							
Harderian gland	0	0	1	0	1	0	0
Thymoma	0	0	2	0	0	1	2
Lymphoma							
Thymus	0	0	0	0	0	1	0
Adenocarcinoma							
Salivary gland	0	1	0	0	0	0	0
Papilloma							
Non-glandular stomach	0	0	1	0	0	0	0

[1] Fisher's Exact Test did not reveal any significant differences when positive control or test article treatment groups were compared to Group 1.

Group 1 = Vehicle Control
Group 2 = Positive Control (1,000 mg/kg urethane in three intra-peritoneal injections)
Group 3 = 25/50 mg/kg/day DM/Q
Group 4 = 50/50 mg/kg/day DM/Q
Group 5 = 100/100 mg/kg/day DM/Q
Group 6 = 100 mg/kg/day DM only
Group 7 = 100 mg/kg/day Q only

In the CByB6F1 mice (administered 100/100 mg/kg/day DM/Q), there were no statistically significant increases in neoplastic lesions, compared to controls.

Study Summary (reproduced from the original NDA submission)**:**

Table 2.6.7-10A Carcinogenicity **Test Articles: Dextromethorphan and Quinidine**

Report Title: 26-week repeated dose oral carcinogenicity study in Tg.rasH2 and CByB6F1 mice		
Species/Strain: Mouse/ Tg.rasH2 and CByB6F1	**Duration of Dosing:** 26 weeks	**Study Number:** DMQ-119
Initial Age: 9-11 weeks at initiation of dosing	**Method of Administration:** Oral gavage	**Location in CTD:** Section 2.6.6.5
Date of First Dose: 6 January 2004 (males), and 12 January 2004 (females)	**Vehicle/Formulation:** 1% methylcellulose	**GLP Compliance:** Yes
Basis for High-Dose Selection: Toxicity-based endpoints from previous studies in transgenic mice.	**Treatment of Controls:** 1% methylcellulose (vehicle control group), and urethane (1,000 mg/kg in three i.p. injections; positive control group).	
Special Features: None		

Daily Dose (mg/kg)	**Vehicle Control**		**Positive Control**		**100 (DM)**		**100 (Q)**		**25/50 (DM/Q)**		**50/50 (DM/Q)**		**100/100 (DM/Q)**	
Gender	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Toxicokinetics: AUC (µg·h/mL)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Number of Animals:														
At Start	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Died/Sacrificed Moribund	1	1	12	5	1	1	2	3	2	2	2	1	0	1
Terminal Sacrifice	24	24	13	20	24	24	23	22	23	23	23	24	25	24
Survival (%)	96	96	52	80	96	96	92	88	92	92	92	96	100	96
Body Weight (%)†	29 g	23 g	29 g	23 g	-8*	-4	-4	-4	-3	-2	-3	-3	-7*	-7*
Food Consumption (%)†	4 g/d	4 g/d	-4	7	-11*	0	-2	5	-3	8	-3	1	-7	-5
Number of Animals Evaluated	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Number of Animals with Neoplastic Lesions:														
Lungs with bronchi	1	2	24	24	4	0	0	2	5	4	1	1	1	3
Spleen	0	1	22	25	1	0	3	1	0	3	0	2	1	0
Other neoplastic lesions	2	3	7	2	6	5	0	4	5	8	4	6	2	2
Noteworthy Findings:														
Gross Pathology	N	N	E	E	N	N	N	N	N	N	N	N	N	N
Histology – Non-Neoplastic Lesions	N	N	E	E	N	N	N	N	N	N	N	N	N	N

AUC = area under the concentration versus time curve; DM = dextromethorphan hydrobromide; Q = quinidine sulfate; ND = not done; N = no treatment related effects; E = expected findings in the positive controls

* $p < 0.05$ (vehicle control group vs. all treatment test article-treated groups)

† At end of treatment period. For controls, group means are shown and units for food consumption are g/animal/day. For treated groups, percent differences from vehicle controls are shown. Statistical significance is based on actual data (not on the percent differences).

Study title: ***Dextromethorphan/Quinidine: A 24-Month Oral (Gavage) Carcinogenicity Study in Rats – Month 12 Unaudited Status Report (DMQ-120)***

Key study findings:

- Interim (12-month) evaluation in rats showed adequate survival, with a slight treatment-related increase in mortality (3, 6, 11, 8 and 5 deaths in the males and 5, 5, 11, 9, and 8 deaths in the females at 5/100, 20/100, 50/100, 50/0, and 0/100 mg/kg/day DM/Q, respectively) compared to controls (2 deaths each in the males and females)
- Adequate tolerability: few, minor clinical signs (quinidine-related salivation, yellow anogenital staining and alopecia), and slight DM dose-related decrease in body weight gains in the males given DM and Q in combination compared to controls at 12 months (-5%, -6%, and -12% at 5/100, 20/100, and 50/100 mg/kg/day DM/Q, statistically significant at the MD and HD combinations).
- Highest doses of 50/100 mg/kg/d DM/Q represented 8X and 16X the MRHD (60/60 mg/d, 1/1 mg/kg/d, and 37/37 mg/m^2/d DM/Q) for dextromethorphan and quinidine, respectively

Adequacy of the carcinogenicity study and appropriateness of the test model: To be reported in the final study report

Evaluation of tumor findings: To be reported in the final study report

Study no.: DMQ-120
Volume # Electronic submission folder m2\26-nonclinical**, and page #** 1
Conducting laboratory and location: (b) (4)
Date of study initiation: July 10, 2003
GLP compliance: Yes
QA report: yes (x) no ( )
Drug Dextromethorphan hydrobromide (DM)**, lot # and % purity**: to be reported in the final study report
Drug Quinidine sulfate (Q)**, lot # and % purity**: to be reported in the final study report
CAC concurrence: Yes (see Executive CAC meeting minutes of June 12, 2003)

Methods

Doses: 0/0, 5/100, 20/100, 50/100, 50/0, and 0/100 mg/kg/day DM/Q

Basis of dose selection: MTD (see Executive CAC meeting minutes of June 12, 2003)

Species/strain: Albino VAF/Plus® Sprague-Dawley rats – derived (CD®) Crl: CD (SD) IGS BR ((b) (4))

Number/sex/group (main study): 60/sex/group

Route, formulation, volume: Oral by gavage at 5 ml/kg (0/0, 1/20, 2/20, 10/20, 10/0, and 0/20 mg DM/Q per ml); test articles suspended in aqueous 1% methylcellulose (400 centipoises at 2%)

Frequency of dosing: Once daily for 2 years

Satellite groups used for toxicokinetics or special groups: 9/sex/group for toxicokinetic analysis

Age: approximately 6-8 weeks at initiation of dosing

Weight: 125-225 g

Animal housing: Individually housed in suspended stainless steel wire mesh cages in temperature (18-26 degC) and humidity (30%-70%) controlled animal facility, with 12-hour light/dark cycle, cages rotated every 2 weeks to equalize local environment effects

Restriction paradigm for dietary restriction studies: None; the rats receive Certified Rodent Diet No. 5002 and water via automated watering system, both *ad libitum*

Drug formulation stability/homogeneity: Demonstrated for storage of 14 days, analysis performed by testing facility

Dual controls employed: No

Interim sacrifices: No

Deviations from original study protocol:

Observations:

Mortality: twice daily

Clinical signs: baseline and twice daily with physical examinations weekly

Body weights: baseline and weekly during dosing period

Food consumption: baseline and weekly during dosing period

Hematology: 0.25 ml blood collected from the orbital sinus to be collected for evaluation at study termination

Gross Pathology: All animals including those found dead or euthanized *in extremis,* after 24 months treatment; to be reported in the final study report

Histopathology: Adrenals, aorta, bone marrow smear (rib), bone (sternum and femur), bone marrow (sternum and femur), brain (medulla, pons, cerebrum, and cerebellum), epididymides, esophagus, eyes (with optic nerve), heart, kidneys, lacrimal glands/Harderian glands, large intestine (cecum,. Colon, rectum) liver, lungs (with mainstem bronchi), lymph node (mesenteric, mediastinal), mammary gland, muscle (*biceps femoris*), nerve (sciatic), ovaries, pancreas, pituitary, prostate, salivary glands (submandibular), seminal vesicles, skin, small intestine (duodenum, ileum, and jejunum), spinal cord (cervical, thoracic, lumbar), spleen, stomach, testes, thymus, thyroid (with parathyroid), trachea, urinary bladder, uterus (horns/body/cervix), vagina, Zymbal's gland, gross lesions, target organs); to be reported in the final study report

Toxicokinetics: 0.5 ml blood from the orbital sinus collected on Dosing Day 1, and at the end of 4, 13, and 26 weeks at baseline, and 1, 3, 6, 12, and 24 hours after dosing

Results

Mortality: The 12-month observations showed a slight increase in mortality in all drug-treated groups, with survival of 97% in the controls, and 82% at the high-dose DM/Q

combination in the males and females, but no statistically significant treatment-related differences in survival were found. The Week 57 interim evaluations showed the following cumulative mortality (reproduced from the original NDA submission):

	Daily Doses					Initial Number of Animals				Cumulative Mortality[a]			
	Dose (mg/kg/day)		Conc. (mg/mL)		Volume (mL/kg)	Carcinogenicity Phase		Toxicokinetic Phase		Carcinogenicity Phase		Toxicokineitc Phase	
Group	DM	Q	DM	Q		M	F	M	F	M	F	M	F
1	0	0	0	0	5	60	60	9	9	2	2	0	0
2	5	100	1	20	5	60	60	9	9	3	5	0	0
3	20	100	2	20	5	60	60	9	9	7	5	1	0
4	50	100	10	20	5	60	60	9	9	11	11	0	1
5	50	0	10	0	5	60	60	9	9	8 (1)	9	0	0
6	0	100	0	20	5	60	60	9	9	5	8 (1)	0	0

[a]Represents animals found dead, sacrificed in moribund condition or for humane reasons during the study period. Animals dying accidental deaths are presented in parentheses. Mortality excludes replacements made during the first 4 weeks of study for animals found dead, sacrificed in moribund condition or dying accidentally (per (b) (4) (b) (4) SOP).

DM = Dextromethorphan, Q = Quinidine, Conc. = Concentration, M = Male, F = Female

Key to Statistical Symbols:

* = $p<0.05$ (Group 1 vs. Groups 2, 3, 4, 5, 6)
** = $p<0.01$ (Group 1 vs. Groups 2, 3, 4, 5, 6)
\+ = $p<0.05$ (Group 4 vs. Group 5)
++ = $p<0.01$ (Group 4 vs. Group 5)
^ = $p<0.05$ (Group 4 vs. Group 6)
^^ = $p<0.01$ (Group 4 vs. Group 6)

The cumulative monthly mortality figures (accidental deaths, found dead, and sacrificed combined) are presented in the following tables (from the original NDA submission):

Males

Mortality Summary[a]

Initial Number	Potential Survivors	Month 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	Total Dead	Total Survivors	Percent Survivorship
Group 1 - 0/0 mg/kg/day (DM/Q)																												
60	60	0	0	0	1	0	1	0	0	0	0	0	0													2	58	97
		0	0	0	1	1	2	2	2	2	2	2	2															
Group 2 - 5/100 mg/kg/day (DM/Q)																												
60	60	0	0	0	0	0	0	0	0	1	1	0	1													3	57	95
		0	0	0	0	0	0	0	0	1	2	2	3															
Group 3 - 20/100 mg/kg/day (DM/Q)																												
60	60	0	0	0	1	1	0	1	1	0	1	1	1													7	53	88
		0	0	0	1	2	2	3	4	4	5	6	7															
Group 4 - 50/100 mg/kg/day (DM/Q)																												
60	60	0	0	1	2	0	1	0	1	3	2	1	0													11	49	82
		0	0	1	3	3	4	4	5	8	10	11	11															
Group 5 - 50/0 mg/kg/day (DM/Q)																												
		(1)																										
60	59	0	0	0	0	0	0	0	0	0	5	3	0													8	51	86
		0	0	0	0	0	0	0	0	0	5	8	8															
Group 6 - 0/100 mg/kg/day (DM/Q)																												
60	60	0	1	0	0	0	0	1	1	1	1	0	0													5	55	92
		0	1	1	1	1	1	2	3	4	5	5	5															

[a]The numbers above the line represent mortality occurring monthly and the numbers below the line represent cumulative mortality. Accidental deaths are presented in parentheses at the time of occurrence, but are excluded from cumulative and total values.

Females

Mortality Summary

Initial Number	Potential Survivors	Month 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	Total Dead	Total Survivors	Percent Survivorship
Group 1 - 0/0 mg/kg/day (DM/Q)																												
60	60	0	0	0	0	0	1	0	0	0	0	1	0													2	58	97
		0	0	0	0	0	1	1	1	1	1	2	2															
Group 2 - 5/100 mg/kg/day (DM/Q)																												
60	60	0	0	0	2	0	0	0	0	1	1	0	1													5	55	92
		0	0	0	2	2	2	2	2	3	4	4	5															
Group 3 - 20/100 mg/kg/day (DM/Q)																												
60	60	0	0	1	0	0	1	0	1	0	2	0	0													5	55	92
		0	0	1	1	1	2	2	3	3	5	5	5															
Group 4 - 50/100 mg/kg/day (DM/Q)																												
60	60	0	1	3	0	0	1	1	1	0	1	3	0													11	49	82
		0	1	4	4	4	5	6	7	7	8	11	11															
Group 5 - 50/0 mg/kg/day (DM/Q)																												
60	60	0	0	1	2	1	0	0	0	0	2	3	0													9	51	85
		0	0	1	3	4	4	4	4	4	6	9	9															
Group 6 - 0/100 mg/kg/day (DM/Q)																												
		(1)																										
60	59	0	0	0	0	4	1	0	2	0	0	1	0													8	51	86
		0	0	0	0	4	5	5	7	7	7	8	8															

[a]The numbers above the line represent mortality occurring monthly and the numbers below the line represent cumulative mortality. Accidental deaths are presented in parentheses at the time of occurrence, but are excluded from cumulative and total values.

Clinical signs: Salivation, lasting 15-30 minutes after dosing, was observed in the rats given Q at 100 mg/kg/day with and without DM from Dosing Day 1 through the 12-month observation period. The physical examinations showed slight increases in yellow anogenital staining and alopecia in the quinidine-treated rats.

Body weights: Slight DM dose-related decrease in body weight gains in the males given DM and Q in combination compared to controls at 12 months (-5%, -6%, and -12% at 5/100, 20/100, and 50/100 mg/kg/day DM/Q, statistically significant at the MD and HD combinations).

Food consumption: No treatment-related effects

Gross pathology: To be reported in the final 2-year carcinogenicity study report

Histopathology: To be reported in the final 2-year carcinogenicity study report

Toxicokinetics: To be reported in the final 2-year carcinogenicity study report

Summary (reproduced from the original NDA submission):

Table 2.6.7-10B Carcinogenicity **Test Articles: Dextromethorphan and Quinidine**

Report Title: Dextromethorphan/Quinidine: A 24-month oral (gavage) carcinogenicity study in rats - Month 12 unaudited status report

Species/Strain: Rat/Sprague-Dawley	**Duration of Dosing:** 24 months	**Study Number:** DMQ-120
Initial Age: 6 weeks at initiation of dosing	**Method of Administration:** Oral gavage	**Location in CTD:** Section 2.6.6.5
Date of First Dose: 10 July 2003 (Toxicity group) 7 August 2003 (Toxicokinetic group)	**Vehicle/Formulation:** 1% methylcellulose	**GLP Compliance:** Yes **Special Features:** 9 additional animals/sex/drug-treated group included for TK assessments at 4 time points during the first 26 weeks and then removed from the study.
Basis for High-Dose Selection: Toxicity-based endpoints from previous studies in rats.	**Treatment of Controls:** 1% methylcellulose	

Daily Dose (mg/kg)	Control		50 (DM)		100 (Q)		5/100 (DM/Q)		20/100 (DM/Q)		50/100 (DM/Q)	
Gender	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Toxicokinetic Phase:												
Number of Animals	0	0	9	9	9	9	9	9	9	9	9	9
AUC (µg·h/mL)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
C_{ss} (µg/mL)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Carcinogenicity Phase:												
Number of Animals:												
At Start	60	60	60	60	60	60	60	60	60	60	60	60
Died/Sacrificed Moribund	2	2	8	9	5	8	3	5	7	5	11	11
Terminal Sacrifice	0	0	0	0	0	0	0	0	0	0	0	0
Survival (%)	97	97	86	85	92	86	95	92	88	92	82	82
Body Weight (%)§	764 g	405 g	-4†	-5	-2‡	3	-5	5	-6*	7	-12**	-
Food Consumption (%)§	33	52	3†	2	15**‡	8	18**	4	21**	6	21**	6
Number Evaluated	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Number of Animals with Neoplastic Lesions	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Noteworthy Findings												
Gross Pathology	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Histology – non-neoplastic lesions	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

NA = not available within interim report
* $p < 0.05$ (control group vs. all treatment test article-treated groups)
** $p < 0.01$ (control group vs. all treatment test article-treated groups)
† $p < 0.01$ (DM50/Q100 group vs. DM50 only group)
‡ $p < 0.01$ (DM50/Q100 group vs. Q100 only group)
§ At end of Week 52 of the 104-week study. For controls, group means are shown and units for food consumption are g/kg/day. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

Study title: ***Dextromethorphan/Quinidine (DMQ): Preliminary (Dose Finding) Study in Rats***

Key study findings:

- Salivation in Q treated rats

- Reduced activity, lethargy, ataxia, and piloerection at 5 hours on Day 3 at 100/100 mg/kg/day
- Sponsor described 2 F at 100/100 mg/kg/day as "seemed to have some degree of hypothermia"
- Reduction in BWG at 100/100 was transitory
- Sponsor selected 50/100 mg/kg/day DM/Q for the reproductive toxicity studies in rats
- Accumulation of DX observed at 50/100 and 100/100 mg/kg/day DM/Q in the females
- The study summary does not correlate well with the individual line listing data
- The results of this study do not support the selection of 50/100 mg/kg/day DM/Q for the reproductive toxicity studies in rats, due to the absence of dose-limiting toxicity observed at the highest dose tested (100/100 mg/kg/day DM/Q).

Study no.: DMQ-122
Volume # m4-3-5-2 (electronic submission**), and page #** NA
Conducting laboratory and location: (b) (4)
Date of study initiation: April 8, 2003
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug Dextromethorphan hydrobromide USP (DM)**, lot #** DM9912074**, and % purity**: 99.7%
Drug Quinidine sulphate (Q), **lot #** 9900130, **% purity**: 100.1%

Methods

Doses: 0/0, 0/100, 50/100, and 100/100 mg/kg/day DM/Q
Species/strain: Albino Sprague-Dawley rats, strain Crl:CD®IGS BR ((b) (4) , ages 10 weeks, mean weights 369.6 g males and 240.7 g females)
Number/sex/group: 6/sex/group
Route, formulation, volume, and infusion rate: Test article in 1% methylcellulose, given by oral gavage once daily for 14 consecutive days
Satellite groups used for toxicokinetics: None
Study design: The rats were dosed once daily for 14 consecutive days (vehicle, and 100 mg/kg/day with and without dextromethorphan (50 mg/kg/day), or for 3 consecutive days (100/100 mg/kg/day DM/Q, dosing terminated after Day 3 due to clinical signs in this group)
Parameters and endpoints evaluated:
Mortality: Twice daily
Clinical Signs: Twice daily
Cage-side Observations: From 10 minutes before dosing through 1-2 hours after dosing
Physical Examinations: Twice weekly, from receipt through terminal sacrifice, before dosing on the dosing days
Body Weights: Baseline and daily during dosing period, then twice weekly until terminal sacrifice

Food Consumption: Baseline and daily during dosing period
Gross Necropsy: All animals
Toxicokinetics: Blood sampled from orbital sinus on Dosing Day 3 (Control, Q alone and DM/Q groups, at 1, 2, 4, and 24 hours after dosing), last Dosing Day for the DM/Q combination groups

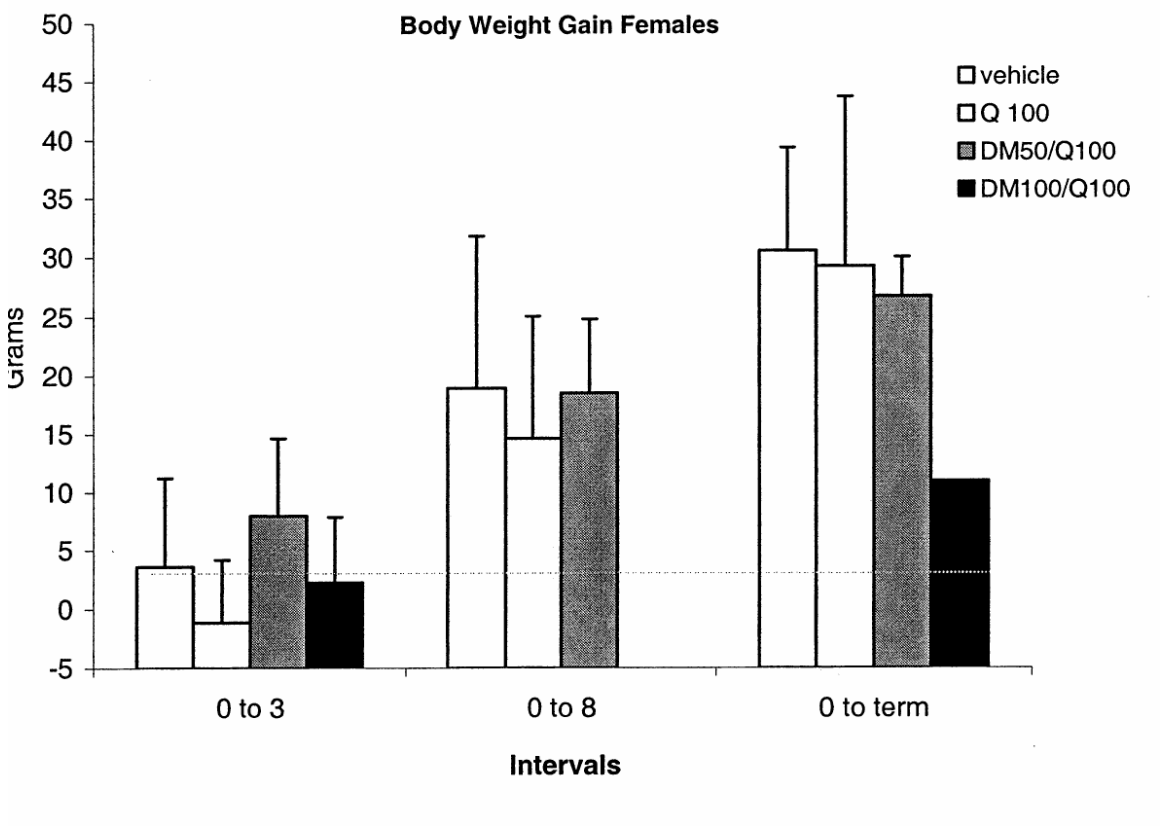
Results

Mortality: No treatment-related deaths

Clinical signs: Salivation related to Q treatment (100 mg/kg/day), lasting 30 minutes after dosing, was observed when Q was given alone and in combination with DM at 50 and 100 mg/kg/day. Reduced activity and lethargy, ataxia, and piloerection was reported but not clearly shown in the individual line listing data, at 5 hours after dosing on Day 3 at 100/100 mg/kg/day DM/Q, with greater severity in the females than in the males. The sponsor reported that hypothermia was observed in 2 females at 100/100 mg/kg/day DM/Q.

Body weight: No treatment-related effects in the rats dosed for 14 days, decreased body weights in the females dosed for 3 days at 100/100 mg/kg/day DM/Q

The decreased mean body weight gains in the female rats are presented in the following graph (reproduced from the original NDA submission):



Food consumption: No treatment-related effects

Gross Necropsy: No treatment-related effects

Toxicokinetics:

Systemic exposure to Q greater in females than in males (+ 30%-40%). Increased Q exposure (35%-70%) with DM (50 mg/kg/day) co-administration, although Q exposure decreased 24%-31% lower in males given DM at 100 mg/kg/compared to co-administration with DM at 50 mg/kg/day, and increased 57% in females given 100 mg/kg/day DM compared to co-administration with 50 mg/kg/day DM. No evidence of accumulation of Q with repeated dosing for 14 days.

Systemic exposure to DM (at 50 mg/kg/day, with Q at 100 mg/kg/day) 2X higher in females than in males. AUC_{0-24} dose proportional for the males from 50 to 100 mg/kg/day DM with 100 mg/kg/day Q, but in the females DM AUC0-24 was 10X higher at 100 mg/kg/day than at 50 mg/kg/day when given with 100 mg/kg/day Q. The DM Cmax was 5X higher at 100 than at 50 mg/kg/day when given with 100 mg/kg/day Q in the females, but not in the males. No evidence of accumulation of DM in males and females with repeated dosing for 14 days.

No differences in exposure to DX in males and females, on Dosing Days 3 and 14. Accumulation of the metabolite was suggested by an increase in Cmax of 50% in females

and 30% in males on Day 14 compared to Cmax on Day 3, and increased AUC_{0-24} of 38% in females and 12% in males on Day 14 compared to AUC_{0-24} on Day 3.

Study title: ***Dextromethorphan/Quinidine (DMQ): Preliminary (Dose Finding) Study in Rabbits***

Key study findings:

- The description of the study methodology was vague; the duration of dosing (variable from 4-10 days, with re-use of some rabbits in alternate groups) was not clearly described
- Treatment-related toxicity was minimal, consisting of sporadic increased respiration in some rabbits and reduced food consumption after 3 treatment days
- The study results failed to support the conclusion that the high dose group (100/100 mg/kg/day DM/Q) exceeded a MTD, and the study is considered to be inadequate for dose selection for the embryo-fetal toxicity study in rabbits

Study no.: DMQ-121
Volume # m4-2-3-5-2 (electronic submission)**, and page #** NA
Conducting laboratory and location: (b) (4)
Date of study initiation: April 8, 2003
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug Dextromethorphan hydrobromide USP (DM)**, lot #** DM9912074**, and % purity** 99.7%
Drug Quinidine sulphate (Q)**, lot #** 9900130**, and % purity** 100.1%

Methods

Doses (reproduced from the original NDA submission):

Group and Dosage		Abbreviation
Group 1:	Vehicle only (1% methylcellulose)	Control
Group 2:	50 mg Q /kg/day	Q50
Group 3:	100 mg Q /kg/day	Q100
Group 4:	50 mg DM, 100 mg Q /kg/day	DM50/Q100
Group 5: *(the Group 2 animals, re-used following a 19-day 'wash-out' period)*	100 mg DM, 100 mg Q /kg/day	DM100/Q100
Group 6:	50 mg DM /kg/day (naïve animals)	DM50

Q = Quinidine
DM = Dextromethorphan

Species/strain: Albino New Zealand White rabbits (Covance, ages 5 months, weights 3-4 kg))

Number/sex/group: 3 females/dose group

Route, formulation, volume, and infusion rate: Test article (12.5 mg/ml DM and 25 mg/ml Q for the DM50/100Q group) in 1% aqueous methylcellulose 400 centipoises USP, given by oral gavage at 2 ml/kg - 4 ml/kg

Satellite groups used for toxicokinetics: None

Study design: The test article administration schedule, as summarized in the Study Report, was vague and confusing. According to the protocol, all rabbits were initially dosed once daily for 4 days. Then, the vehicle control group continued dosing for a total of 10 days, except for the Dosing Days of 5-8 of Group 4. The remaining groups were dosed for up to a total 10 days. In the study summary, the dosing duration was described as 3 to 10 days. Additionally, the group that received 50 mg/kg/day Q for 4 days was re-used after 19-day washout period, and received 100/100 mg/kg/day DM/Q for an undescribed duration. The group that received 50/100 mg/kg/day DM/Q was apparently dosed for 10 days.

Parameters and endpoints evaluated:

Mortality: Twice daily

Clinical signs: Twice daily, and before and at 0.5 and 1-2 hours after dosing, physical examinations twice weekly

Body weight: Baseline and daily during dosing period, then twice weekly until terminal sacrifice

Food consumption: Daily

Toxicokinetics: Day 3 (all treated groups) and Day 10 (Groups 4 and 5) at 1, 2 , 4, and 24 hours after dosing; 0.75 mL whole blood collected from the marginal ear vein or auricular artery

Necropsy: All animals including unscheduled and scheduled deaths

Results

Mortality: No treatment-related effects.

Clinical signs: Increased respiration rate at 100/100 mg/kg/day DM/Q for 1 hour after dosing on Day 2 in all rabbits, and on Days 4 and 6 in 2 rabbits.

Body weight: No statistically significant treatment-related effects

Food consumption: Reduced 60% at 100/100 mg/kg/day DM/Q after 3 treatment days.

Toxicokinetics: Q exposure dose proportional, with and without DM co-treatment, Q AUC_{0-24} higher for 50/100 mg/kg/day DM/Q than for 100 mg/kg/day Q alone.

DM exposure and Cmax increased (greater than dose proportional) when given in combination with Q at 100 mg/kg/day. DM (at 50 mg/kg/day) AUC_{0-24} 5.4X higher with 100 mg/kg/day Q than when given alone on Day 3 and 9.3X higher with Q than when given alone on Day 10. DM AUC_{0-24}, in combination with Q, 2.6X higher on Day 3 than on Day 10. No evidence of DM accumulation, after 24-hour washout periods.

DX exposure decreased with co-treatment of DM and Q compared to DM alone on Days 3 and 10. No evidence of DX accumulation.

Q, DM, and DX Tmax values 1-4 hours.

Necropsy: No treatment-related effects.

Fertility and Early Embryonic Development

Study title: ***Dextromethorphan/Quinidine (DMQ): Study of Fertility and Early Embryonic Development to Implantation in Rats***

Key study findings:

- No effects by dextromethorphan hydrobromide (DM) and quinidine sulphate (Q) at up to 50/100 mg/kg/day DM/Q on fertility in rats
- NOAEL for fertility and early embryonic development = 50 mg/kg/day DM in combination with 100 mg/kg/day Q (8X for DM and 16X for Q, the daily clinical dose of 60/60 mg/kg/day DM/Q, on a mg/m^2 basis)
- This study is considered to be inadequate to fully characterize Neurodex™ effects on fertility and early embryonic development, based on lack of support for the dose selection in the dose range-finding study in rats (DMQ-122) and the absence of clearly dose limiting toxicity in support of a maternal MTD in this study; only salivation was observed at the highest dose level tested

Study no.: DMQ-126
Volume # m4-2-3-5-1 (electronic submission)**, and page #** NA
Conducting laboratory and location: (b) (4)
Date of study initiation: September 10, 2003
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug Dextromethorphan hydrobromide USP**, lot #** DM 0302015**, and % purity** 99.6%
Drug Quinidine sulphate**, lot #** 4963**, and % purity** 100.8%

Methods

Doses: See under Study design, below

Species/strain: Albino Sprague-Dawley Crl:CD®IGS BR rats ([redacted] (b) (4), ages 10-12 weeks, mean weights 347 g males and 263 g females)

Number/sex/group: See under Study design, below

Route, formulation, volume, and infusion rate: See under Study design, below. Test articles dissolved in 1% aqueous solution of methylcellulose (400 centipoises) USP, given by oral gavage once daily

Satellite groups used for toxicokinetics: None

Study design (reproduced from the original NDA submission):

2.3. EXPERIMENTAL OUTLINE

Group	Group Designation	Doses (once daily, by gavage)			Premating treatment (Overall treatment)		Number of animals	
		Dose	Concentration	Volume				
		mg/kg/day DM/Q	mg/mL DM/Q	mL/kg	Males	Females	Males	Females
1	Control	0/0	0/0	5	4 weeks (*ca* 9 weeks)	2 weeks (*ca* 4-5 weeks)	22	22
2	Low	5/100	1/20	5	4 weeks (*ca* 9 weeks)	2 weeks (*ca* 4-5 weeks)	22	22
3	Intermediate	15/100	3/20	5	4 weeks (*ca* 9 weeks)	2 weeks (*ca* 4-5 weeks)	22	22
4	High	50/100	10/20	5	4 weeks (*ca* 9 weeks)	2 weeks (*ca* 4-5 weeks)	22	22

Treatment for a suitable period prior to mating, to ensure adequate exposure of gamete maturation (4 weeks for males, 2 weeks for females), then throughout the mating period and for females until Gestation Day (GD) 7. Reproductive/pregnancy outcome was evaluated at GD 14. Treatment for males continued until the whole process of spermatogenesis had been exposed (about 9 weeks of treatment overall), prior to evaluation of that process by means of seminology and histology. Blood samples were taken for toxicokinetic analysis, 0.75 mL from all animals in each group at one of the following time-points: 0.5, 1, 4, 8 and 24 hours after dosing (providing for a nominal 4 samples per time-point per group), on the first day of treatment, again near the end of the pre-mating period and again at the end of the respective treatment periods for males and females.

Parameters and endpoints evaluated:

Mortality: Twice daily

Clinical Signs: Before, immediately after, and at 1 and 2 hours after dosing, with physical examinations weekly

Body Weights: Baseline, Dosing Day 1, and twice weekly, and for females on Gestation Days (GD) 0, 3, 7, 11, and 14, and at scheduled sacrifice

Food Consumption: Baseline and twice weekly, on GD 0-3, 3-7, 7-11, and 11-14 for the mated females

Toxicokinetics: Whole blood samples (0.75 mg from the retro-orbital sinus) at 1.5, 1, 4, 8, and 24 hours after dosing, on Dosing Days 1, before mating, and end of treatment period (GD 7 for females, Dosing week 9-10 for males)

Gross Necropsy: After 9 weeks treatment in the males, and on GD 14 in the females; all animals examined macroscopically, including lesions, kidneys, liver, and reproductive organs

Fertility parameters (Males): Right and left testes and epididymides weights, sperm evaluations (R. testes and epididymis) including sperm count (spermatids in testis), total number of sperm in caudal epididymis or spermatids in testis, and sperm morphology, sperm motility in the right vas deferens, and histopathology examination of the left testis and epididymis

Fertility parameters (Females): Estrous cycle monitoring before mating until mating or pregnancy, evidence of mating (copulatory plug *in situ* and/or sperm in vaginal smear), pregnancy, corpora lutea count from the intact ovaries, implantations in the intact uteri (total, live and dead implantations), resorptions, histopathology examination of the uteri and ovaries

Results

Mortality: Deaths in 2 males: one control male before mating, one LD (15/100 mg/kg/day DM/Q) male after mating, considered to be incidental.
Deaths in one female at 50/100 mg/kg/day MD/Q due to sacrifice after accident involving tail injury.

Clinical signs: DMQ related salivation.

Body weight: No treatment-related effects.

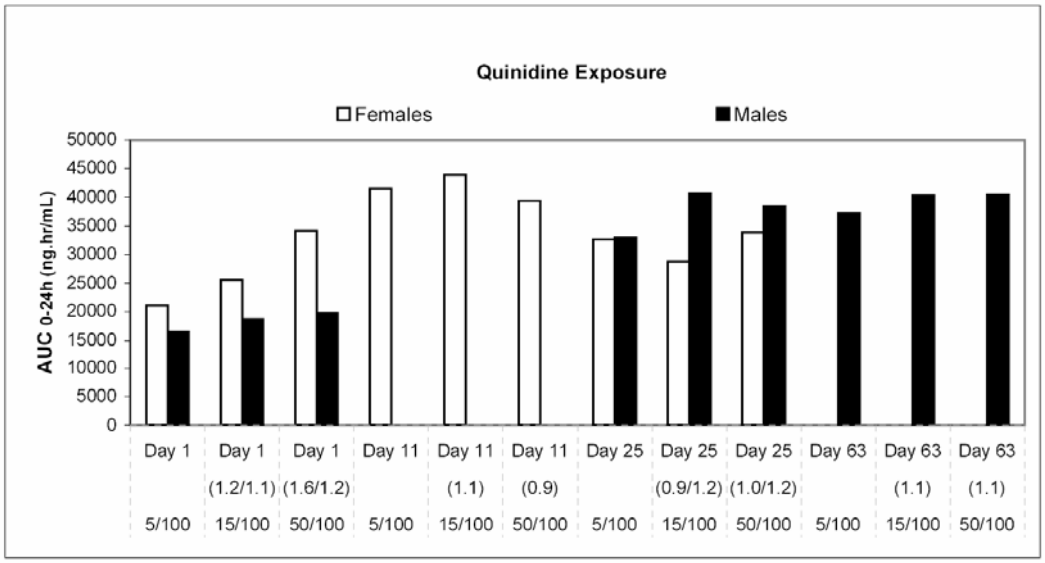
Food consumption: No treatment-related effects.

Toxicokinetics: Q exposure (AUC_{0-24}) 1.3X-1.7X higher in females than in males. Q exposure initially increased with increasing DM dose (1.2X-1.6X in females, 1.1X-1.2X in males).

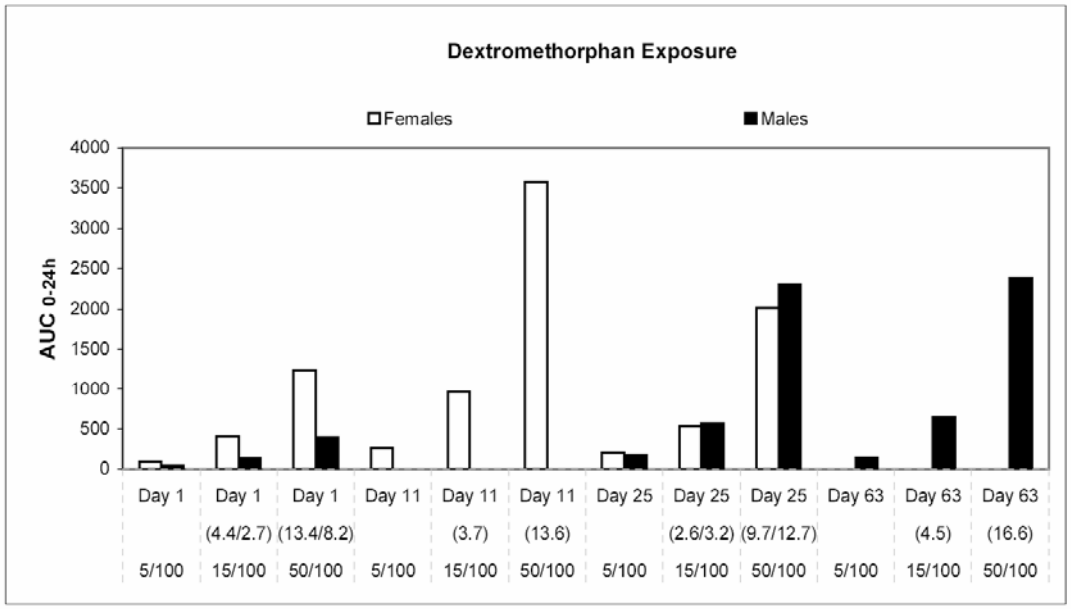
DM AUC_{0-24} increased in females by 2X-3X compared to DM exposure in the males, until Day 25 when exposure to DM was similar in males and females. DM exposure (AUC values) increased in > dose-proportional manner in females and < dose-proportional manner in males. Exposure increased 2X-3X in females (after 11 days) and 4X-6X in males (after 25 days) compared to Day 1 exposure.

DX exposure (AUC_{0-24}) higher in females than in males for up to 25 days, and dose-proportional in females up to Day 11, but less than dose-proportional in males for 25 days, with increasing DM dose.

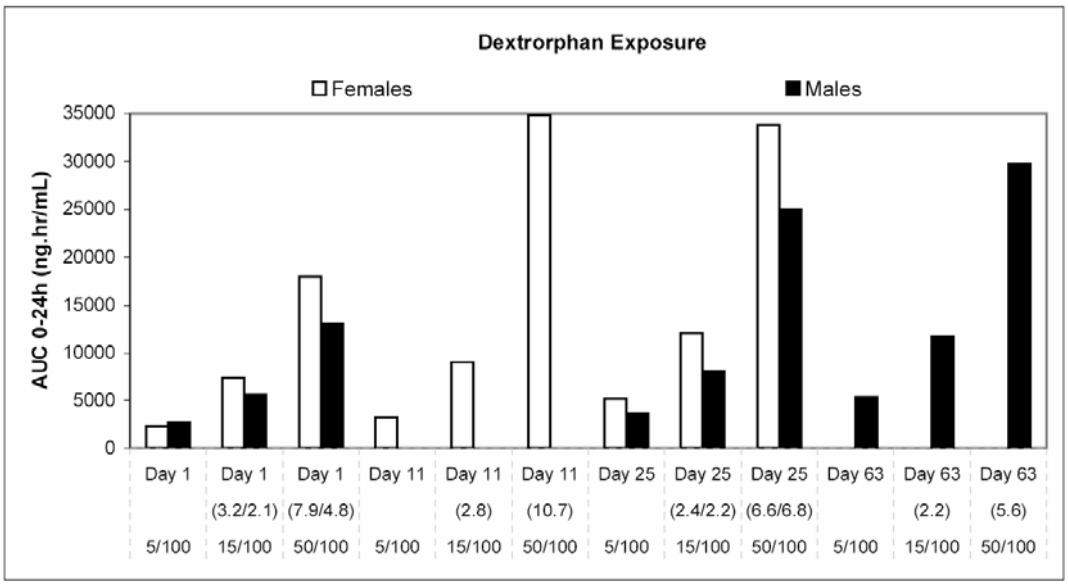
Mean quinidine, dextromethorphan and dextrorphan exposure is presented in the following graphs (reproduced from the original NDA submission):



Day 25 is nominal for females. (Actual range was 21-27 days, except for 3 females at 29-35 days). Second row of X-axis gives the fold-increase in female/male Q exposure with dose of DM, with respect to Q exposure at the lowest administered dose of DMQ. Third row shows administered dose of DM/Q.



Day 25 is nominal for females. (Actual range was 21-27 days, except for 3 females at 29-35 days). Second row of X-axis gives the fold-increase in female/male DM exposure with dose, with respect to DM exposure at the lowest administered dose of DMQ. Third row shows administered dose of DM/Q.



Day 25 is nominal for females. (Actual range was 21-27 days, except for 3 females at 29-35 days). Second row of X-axis gives the fold-increase in female/male DX exposure with dose, with respect to DX exposure at the lowest administered dose of DMQ. Third row shows administered dose of DM/Q.

Necropsy:

- No treatment-related effects on macroscopic findings
- No treatment-related effects on kidney, testes, and epididymides weights; relative (to body weight) liver weights increased 6%-10% in males and females (attributed to metabolic adaptation by the sponsor)

Fertility parameters:

- No treatment-related effects on spermatogenesis found in the histopathology examination of the testes and epididymides
- No treatment-related effects on sperm count, motility, or morphology
- No treatment-related effects on estrous cycling and mating performance (male and female mating index, fertility index, pregnancy index)
- No treatment-related effects on ovulation rate, pre-and post-implantation losses, litter size

Summary: Dextromethorphan hydrobromide (DM) and quinidine sulfate (Q), given in combination by oral gavage for 9 weeks beginning 4 weeks before mating in male rats, and for up to 5 weeks beginning 2 weeks before mating in female rats at doses of up to 50/100 mg/kg/day DM/Q (8X and 16X the clinical dose of 60/60 mg/day on a mg/m^2 basis) had no effect on mating, fertility, and pregnancy parameters in the males and females. However there was inadequate support in the dose range finding study (DMQ-122) to clearly establish an MTD for dose selection in this study, and insufficient maternal toxicity was observed at the highest dose level in this study to definitively demonstrate testing at up the maternal MTD. Therefore, this study is considered to be substandard and provides only limited information on Neurodex™ effects on fertility and early embryonic development in rats.

The TK analysis showed a mean quinidine AUC_{0-24} value on the last day of treatment in the males, of up to 40,500 ng.h/ml (17X the approximate clinical AUC_{0-24} value, estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d.) at the high dose. The mean AUC_{0-24} value for dextromethorphan on the last day of treatment in the males was 2390 ng.h/ml at high dose (0.8X the approximate clinical AUC_{0-24} value, estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d.). The mean dextrorphan AUC_{0-24} value at the same time point was 29,700 ng.h/ml (2.8X the approximate clinical AUC_{0-24} value, estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d.). In the females on the last treatment day, the TK analysis showed a mean AUC_{0-24} values of 33,900 ng.h/ml (14X the approximate clinical AUC_{0-24} value, estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d.) for quinidine, 2020 ng.h/ml for dextromethorphan (0.7X the approximate clinical AUC_{0-24} value, estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d.), and 33,800 ng.h/ml for dextrorphan (3X the approximate clinical AUC_{0-24} value, estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d.), at the HD.

The following tables summarize the results of the study on fertility and early embryonic development in rats (reproduced from the original NDA submission):

Table 2.6.7-12 Reproductive and Developmental Toxicity **Test Articles: Dextromethorphan and Quinidine**

Report Title: Dextromethorphan/Quinidine (DMQ): Study of fertility and early embryonic development to implantation in rats				
Design similar to ICH S5A 4.1.1? Yes	**Duration of Dosing:**		**Study Reference:** DMQ-126	
Species/Strain: Rat/Sprague-Dawley	M: 4 weeks prior to mating through 9 total weeks F: 2 weeks prior to mating through GD 7		**Location in CTD:** Section 2.6.6.6	
Initial Age: 10 weeks **Day of Mating:** Day 0	**Day of C-Section:** Gestational Day 14		**GLP Compliance:** Yes	
Date of First Dose: M - 18 Sept 2003 F - 02 Oct 2003	**Method of Administration:** Oral Gavage			
Special Features: None	**Vehicle/Formulation:** 1% aqueous methylcellulose			
No Observed Adverse Effect Level: **F_0 Males:** 50 mg DM/kg/d + 100 mg Q/kg/d **F_0 Females:** 50 mg DM/kg/d + 100 mg Q/kg/d **F_1 Litters:** 50 mg DM/kg/d + 100 mg Q/kg/d				
Daily Dose (mg/kg)	**Control**	**DM5/Q100**	**DM15/Q100**	**DM50/Q100**
Males				
Toxicokinetics: AUC_{0-24h} (ng·h/mL)				
Quinidine – first day of treatment	ND	16600	18700	19800
Quinidine – premating period	ND	33000	40800	38400
Quinidine – last day of treatment	ND	37200	40300	40500
Dextromethorphan - first day of treatment	ND	49	133	398
Dextromethorphan - premating period	ND	181	572	2300
Dextromethorphan - last day of treatment	ND	144	642	2390
Dextrorphan - first day of treatment	ND	2710	5580	13100
Dextrorphan - premating period	ND	3670	8010	25000
Dextrorphan - last day of treatment	ND	5320	11800	29700
Number Evaluated	22	22	22	22
Number Died or Sacrificed Moribund	1	0	1	0
Clinical Observations (number of animals / number of study days observed):				
Excessive postdose salivation	0	22/67	22/67	22/67
Transitory ventral staining (moderate)	0	0	0	1/8
Transitory anogenital staining (moderate)	0	0	0	1/3
Necropsy Observations:	–	–	–	–
Body Weight at 4 weeks (%)†	437 g	+2	+2	+3
Body Weight at 9 weeks (%)†	534 g	+3	+2	+3
Mean Number of Days Prior to Mating	3.2	2.2	3.3	2.6
Number of Males Placed with Females	21	22	22	21

Table 2.6.7 12 Reproductive and Developmental Toxicity Test Articles: Dextromethorphan and Quinidine (continued)

Daily Dose (mg/kg)	Control	DM5/Q100	DM15/Q100	DM50/Q100
Number of Males that Mated	21	22	21	21
Number of Fertile Males	20	20	21	20
Females				
Toxicokinetics: $AUC_{0\text{-}24h}$ (ng·h/mL)				
Quinidine – first day of treatment	–	21100	25500	34200
Quinidine – premating period	–	41600	43900	39400
Quinidine – last day of treatment	–	32700	28800	33900
Dextromethorphan - first day of treatment	–	92	408	1240
Dextromethorphan - premating period	–	262	962	3570
Dextromethorphan - last day of treatment	–	208	533	2020
Dextrorphan - first day of treatment	–	2280	7390	18000
Dextrorphan - premating period	–	3250	8940	34800
Dextrorphan - last day of treatment	–	5140	12100	33800
Number Evaluated	22	22	22	22
Number of Mated Females	22	22	22	21
Number Died or Sacrificed Moribund	0	0	0	1
Clinical Observations (number of animals / number of study days observed):				
Excessive postdose salivation	0	22/32	22/36	22/32
Transitory anogenital staining (severe)	0	1/1	0	0
Transitory anogenital staining and ventral staining (slight to extreme)	0	1/8	0	4/2
Necropsy Observations:				
Lungs – discolored foci	0	1	0	0
Liver – discolored foci	0	0	1	0
Kidneys – discolored foci	1	0	0	0
Uterus – placenta	0	1	0	1
Vagina – abnormal contents	0	0	0	2
Body Weight – End of Premating Period (%)†	276 g	-1	+1	0
Body Weight – End of Gestation Period(%)†	349 g	0	+1	0
Food Consumption - End of Premating (%)†	18 g/animal/day	-	-	6
Food Consumption – End of Gestation (%)†	16 g/animal/day	6	13*	13*
Mean Number Estrous Cycles/14 days	2.0	2.2	2.4	2.2
Mean Cycle Length (days)	4.4	4.2	4.2	4.3
Mean Number Days Prior to Mating	3.2	2.2	3.3	2.6
Number with Evidence of Mating	21	20	21	20

Table 2.6.7 12 Reproductive and Developmental Toxicity Test Articles: Dextromethorphan and Quinidine (continued)

Number of Pregnant Females	21	20	22	20
Daily Dose (mg/kg)	**Control**	**DM5/Q100**	**DM15/Q100**	**DM50/Q100**
Mean Number Corpora Lutea	17.0	15.7	17.2	16.3
Mean Number Implantations	15.1	14.6	15.2	15.4
Mean % Preimplantation Loss	10.0	8.2	10.6	6.2
Mean Number Live Conceptuses	14.4	14.1	14.2	14.6
Mean Number Resorptions	4.6	3.6	6.1	5.1
Number of Dead Conceptuses	0	0	0	0
Mean % Postimplantation Loss	4.6	3.6	6.1	5.1

DM = dextromethorphan hydrobromide; F = female; GD = gestational day; M = male; ND = not determined; Q = quinidine sulfate

* $p < 0.05$;

† For controls, group mean values are shown. For treated groups, percent differences from controls are shown.

Embryofetal Development

Study title: ***Dextromethorphan/Quinidine (DMQ): Embryo-Fetal Toxicity Study in Rats***

Key study findings:

- Dose-related reduced fetal weights and skeletal ossification (developmental delay), observed throughout skeleton at 50/100 mg/kg/day DM/Q (8X for DM and 16X for Q the clinical dose on a mg/m^2 basis) given from gestation days 6-17 in rats, attributed to the DM component
- NOAEL for embryo-fetal toxicity in rats not determined in this study (<5/100 mg/kg/day DM/Q, approximately 1X and 2X for DM and Q, respectively, the clinical dose on a mg/m^2 basis)

- This study is considered to be less than adequate, based on insufficient support in the dose range finding study (DMQ-122) to clearly establish an MTD for dose selection in this study, and lack of maternal toxicity at the highest dose level in this study to definitively demonstrate testing at up the maternal MTD. Therefore, this study provides only limited information on Neurodex™ effects on embryo-fetal development in rats.

Study no.: DMQ-124
Volume # m4-2-3-5-2 (electronic submission)**, and page #** NA
Conducting laboratory and location: (b) (4)
Date of study initiation: July 17, 2003
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug Dextromethorphan hydrobromide**, lot #** DM 0302015**, and % purity**: 99.6%
Drug Quinidine sulfate**, lot #** 4963**, and % purity**: 100.8%

Methods

Doses: The doses selected for the definitive study were based on results of a preliminary toxicity study (DMQ-122), showing piloerection, reduced activity, lethargy, and ataxia at 100/100 mg/kg/day DM/Q. The doses evaluated in the embryo-fetal toxicity study in rats are presented in the following table (reproduced from the original NDA submission):

Group Number	Designation	Dosage (mg/kg/day DM/Q)	Volume (mL/kg)	Number of Females
1	Control	0	5	24
2	Low	5/100	5	24
3	Intermediate	15/100	5	24
4	High	50/100	5	24

Q = Quinidine
DM = Dextromethorphan

Species/strain: Albino Sprague-Dawley Crl:CD®IGS BR rats ((b) (4) , ages 10-12 weeks, weights 243-312 g at start of treatment)

Number/sex/group: 24 females/dose group

Route, formulation, volume, and infusion rate: Oral by gavage at 5 ml/kg; test articles dissolved in methylcellulose (400 centipoises) USP, 1% aqueous solution

Satellite groups used for toxicokinetics: None

Study design: the mated females were dosed once daily, gestation days (GD) 6-17, and sacrificed on GD 20

Parameters and endpoints evaluated:
Mortality: Twice daily
Clinical signs: Twice daily

Physical examinations: Twice weekly
Body weights: Baseline (GD 0) and GD 4, 6, 9, 12, 15, 17 and 20
Food consumption: GD 4, 6, 9, 12, 15, 17, and 20
Toxicokinetics: Whole blood sampled (0.5 ml from the orbital sinus) at 0.5, 1, 2, 4, 8, and 24 hours on GD 6 and 17
Terminal examinations: Dams: Macroscopic examination, number of corpora lutea per ovary, number of live fetuses, dead fetuses, late embryo-fetal deaths, early embryonic deaths (evidence of implantation but no recognizable fetus), placental examination
Fetuses: External examination (including palate, all dead and live fetuses) and weight, soft-tissue and skeletal abnormalities (live fetuses only)

Results

Mortality (dams): No treatment-related effects.

Clinical signs (dams): Treatment-related salivation lasting 1 hour after dosing in all DMQ groups.

Body weight (dams): Slight reduction in body weight gain in all groups for first several dosing days, and at the high dose combination throughout dosing (5% compared to controls).

Food consumption (dams): Slight reduction in food consumption in the high dose combination group for first several dosing days.

Toxicokinetics: Q exposure (AUC_{0-24}) increased 2X on GD 17 compared to GD 6, and increased with DM dose. DM AUC_{0-24} increase >dose-proportional, and 3X the GD6 value on GD 17. DX AUC_{0-24} increase <dose-proportional (to DM dose), and increased 2X on GD 17 compared to AUC on GD 6, in the mid-dose group. Exposure to DX was greater in the mid-dose combination group than in the low dose and high dose combination groups. The sponsor proposed that the observation of higher DX values in the MD groups than in the HD groups may be due to competition for metabolism by Q that is more effective at higher DM doses than at lower DM doses.

The results of the toxicokinetic evaluation in the study on embryo-fetal toxicity in rats are presented in the following tables (reproduced from the original NDA submission):

	Toxicokinetic Parameters after Oral Dosing of 5/100, 15/100 and 50/100 mg/kg/day of Dextromethorphan/Quinidine in Female Rats on Gestation Days 6 and 17 (Groups 2-4)	**Table 1**

Analyte	**Group**	**Gestation Day**	**t_{max} hour**	**C_{max} ng/mL**	**AUC_{0-24h} ng.hour/mL**
Quinidine	2	6	0.5	1220	20300
		17	4.0	2940	44300
	3	6	4.0	1540	18300
		17	4.0	3540	46700
	4	6	2.0	1900	25400
		17	2.0	3410	48000
Dextromethorphan	2	6	0.5	15.2	166
		17	4.0	46.5	572
	3	6	4.0	58.8	891
		17	4.0	240	2300
	4	6	0.5	272	3360
		17	2.0	870	9410
Dextrorphan	2	6	0.5	177	2640
		17	8.0	221	3350
	3	6	0.5	293	4150
		17	24.0	458	9220
	4	6	1.0	139	1790
		17	2.0	139	1870

Dose Proportional Factors for Quinidine, Dextromethorphan and Dextrorphan following Oral Administration of 5/100, 15/100 and 50/100 mg/kg/day of Dextromethorphan/ Quinidine to Female Rats on Gestation Days 6 and 17 (Groups 2, 3 and 4)

Group	Dose Dextromethorphan/ Quinidine mg/kg/day	Analyte	Theoretical Increases in Exposure (fold)	Observed Increases in Exposure (fold)	
				C_{max}	AUC_{0-24h}
Gestation Day 6					
2	5/100	Quinidine*	1	1.00	1.00
3	15/100		1	1.26	0.903
4	50/100		1	1.56	1.25
2	5/100	Dextromethorphan	1	1.00	1.00
3	15/100		3	3.87	5.37
4	50/100		10	17.9	20.2
2	5/100	Dextrorphan	1	1.00	1.00
3	15/100		3	1.66	1.57
4	50/100		10	0.785	0.68
Gestation Day 17					
2	5/100	Quinidine*	1	1.00	1.00
3	15/100		1	1.20	1.05
4	50/100		1	1.16	1.08
2	5/100	Dextromethorphan	1	1.00	1.00
3	15/100		3	5.16	4.02
4	50/100		10	18.7	16.4
2	5/100	Dextrorphan	1	1.00	1.00
3	15/100		3	2.07	2.75
4	50/100		10	0.629	0.56

*Proportionality based on 100 mg/kg/day of Quinidine in Group 2

Changes During Repeated Administration of 5/100, 15/100 and 50/100 mg/kg/day of Dextromethorphan/Quinidine to Female Rats (Groups 2, 3 and 4)

Group	Analyte	$C_{max\ GD17}/C_{max\ GD6}$	$AUC_{0-24h\ GD17}/AUC_{0-24h\ GD6}$
2	Quinidine	2.41	2.18
3		2.30	2.54
4		1.79	1.89
2	Dextromethorphan	3.06	3.45
3		4.08	2.58
4		3.20	2.80
2	Dextrorphan	1.25	1.27
3		1.56	2.22
4		1.00	1.04

Terminal and necroscopic evaluations:

- Urogenital tract changes in 1 HD female (discolored kidneys, dilated renal pelves, distended ureters, bladder calculi)
- No treatment-related effects on pregnancy rats
- No treatment-related effects on ovulation (numbers of corpora lutea), numbers of implantations, pre-implantation loss
- Increased post-implantation loss at the high dose combination (50/100 mg/kg/day DM/Q), due to total litter loss in 3 dams (resorptions during embryogenesis)

Offspring (malformations, variations, etc.):

- Reduced mean fetal weight in male and female fetuses at the high dose on GD 20 (-11%, mean 3.4 g compared to mean of 3.8 g in the controls), compared to controls, and trend toward reduced fetal weights at the mid-dose (mean 3.6 g) and low dose (mean 3.6 g, -5%)
- No treatment-related external abnormalities
- No treatment-related soft-tissue and skeletal abnormalities, no major or minor malformations and variations
- Reduced ossification throughout skeleton at the high dose, and in some skeletal areas at the mid-dose (skull, sternum, vertebrae, extremities) and low-dose (skull, sternum, vertebrae), related to reduced fetal weights at the high dose

Skeletal Variations in Fetuses of Rats Administered Dextromethorphan (up to 50 mg/kg/d) and Quinidine (100 mg/kg/day) On Gestation Days 6-17

	Dose Dextromethorphan/Quinidine (mg/kg/day)			
# Fetuses (# litters)	**0**	**5/100**	**15/100**	**50/100**
# Examined (litters)	137 (21)	170 (24)	159 (23)	150 (21)
Incomplete ossification: Skull				
1-2 bones affected	12 (8)	23 (10)	31 (16)	44 (16)
3-5 affected	11 (7)	12 (7)	11 (7)	12 (7)
>5 affected	4 (3)	4 (3)	7 (3)	5 (5)
Sternebrae				
1 sternebra affected	38 (15)	56 (21)	47 (19)	24 (12)
2 sternebrae affected	20 (13)	64 (21)	61 (17)	77 (20)
3 or more sternebrae affected	3 (3)	9 (5)	8 (5)	39 (15)
Mean # caudal vertebrae ossified	3.9	3.6	3.7	3.4
Cervical centrum(a) ossified				
1 affected	44 (16)	46 (17)	16 (10)	26 (11)
2 or more affected	23 (8)	1 (1)	10 (3)	3 (3)
Incomplete ossification of vertebral centrum(a)				
1 affected	10 (8)	25 (11)	27 (13)	30 (13)
2 or more affected	1 (1)	4 (3)	10 (6)	13 (7)
Incomplete ossification of vertebral arch(es)				
1 pair affected	35 (14)	40 (14)	41 (18)	19 (12)
2 or more pairs affected	4 (2)	13 (6)	10 (4)	8 (6)
Incomplete ossified/unossified pelvic bones				
1-2 affected	4 (4)	2 (2)	7 (5)	23 (10)
3-4 affected	1 (1)	2 (2)	3 (2)	3 (2)
5-6 affected	0 (0)	0 (0)	0 (0)	0 (0)
5^{th} metacarpals ossified	114 (21)	98 (19)	80 (20)	30 (11)
Incompletely ossified/unossified ribs	1 (1)	1 (1)	2 (2)	6 (4)

Summary: Embryo-fetal toxicity was observed at 50/100 mg/kg/day DM/Q (8X and 16X for DM and Q, respectively, the clinical dose of 60/60 mg/day DM/Q, on a mg/m^2 basis), including reduced fetal weights, and reduced ossification throughout the skeleton, indicating developmental delay. A relationship to treatment cannot be ruled out for the observation of increased (3 dams) total pregnancy loss by early post-implantation resorptions at the high dose. The developmental delay is attributed to DM, because an increase in fetal toxicity was observed with increasing DM dose (from 5-50 mg/kg/day), but the Q dose was constant across treatment groups (100 mg/kg/day). Maternal toxicity is considered to be minor, with only slight reductions in body weight and food consumption, and not sufficient to account for the increased fetal toxicity. The observed fetal toxicity is probably not due to exposure to the metabolite DX, because fetal toxicity was lower at the mid-dose combination than at the high dose combination of DMQ, although exposure to DX was highest at the mid-dose combination.

This study is considered to be less than adequate, based on insufficient support in the dose range finding study (DMQ-122) to clearly establish an MTD for dose selection, and inadequate maternal toxicity at the highest dose level in this study to definitively demonstrate testing at up the maternal MTD. Therefore, this study is of limited value to describe Neurodex™ effects on embryo-fetal development in rats.

The mean AUC_{0-24} values on gestation day 17 were 44,300, 46,700, and 48,000 ng.h/ml for Q (approximately 18X, 19X, and 20X the approximate clinical AUC_{0-24} value, estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d. at the proposed clinical dose of 30/30 mg dextromethorphan/quinidine b.i.d., respectively), 572, 2300, and 9410 ng.h/ml for dextromethorphan (approximately 0.2X, 0.8X, and 3X, respectively, the approximate clinical AUC_{0-24} value, estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d.), and 3350, 9220, and 1870 ng.h/ml for dextrorphan (approximately 0.3X, 0.9X, and 0.2X, respectively, the approximate clinical AUC_{0-24} value, estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d.) at the LD, MD, and HD, respectively.

The NOAEL for embryo-fetal toxicity in rats by the combination of dextromethorphan and quinidine was not determined in this study. The results of the study on Neurodex effects on embryo-fetal development in rats are presented in the following table (reproduced from the original NDA submission):

Table 2.6.7-13A Reproductive and Developmental Toxicity **Test Articles: Dextromethorphan and Quinidine**

Report Title: Dextromethorphan/Quinidine (DMQ): Embryo-Fetal Toxicity Study in Rats				
Design similar to ICH S5A 4.1.3? Yes	**Duration of Dosing:** Gestation Days 6-17			**Study Reference:** DMQ-124
Species/Strain: Rat/Sprague-Dawley	**Day of C-Section:** Gestation Day 20			**Location in CTD:** Section 2.6.6.6
Initial Age: 10-12 weeks **Day of Mating:** Gestation Day 0	**Method of Administration:** Oral Gavage			**GLP Compliance:** Yes
Date of First Dose: 28 July 2003	**Vehicle/Formulation:** 1% aqueous methylcellulose			
No Observed Adverse Effect Level: **F_0 Females:** 15 mg DM/kg/d + 100 mg Q/kg/d **F_1 Litter Teratology:** ≥50mg DM/kg/d + 100 mg Q/kg/d **F1 Litter Embryotoxicity:** Not Determined	**Special Features:** None			
Daily Dose (mg/kg)	**Control**	**DM5/Q100**	**DM15/Q100**	**DM50/Q100**
Dams				
Toxicokinetics: AUC_{0-24h} (ng·h/mL)				
Quinidine – Gestation Day 6	–	20300	18300	25400
Quinidine – Gestation Day 17	–	44300	46700	48000
Dextromethorphan – Gestation Day 6	–	166	891	3360
Dextromethorphan – Gestation Day 17	–	572	2300	9410
Dextrorphan – Gestation Day 6	–	2640	4150	1790
Dextrorphan – Gestation Day 17	–	3350	9220	1870
Number Pregnant	21	24	23	24
Number Died or Sacrificed Moribund	0	0	0	0
Number Aborted or with Total Resorption of Litter	0	0	0	3
Clinical Observations:				
Salivation (postdose)	–	+	+	+
Necropsy Observations				
Uterus - Abnormal Contents	0	0	0	3
Uterus – Discolored Uterus	0	0	0	1
Uterus – Discolored Placenta	0	0	0	1
Vagina - Cyst	0	0	0	1
Vagina – Abnormal Contents	0	0	0	1
Body Weight at End of Dosing Period (%)†	349 g	-2	-2	-5
Food Consumption – Mean Daily Amount GD 6-17 (%)†	24 g	–	–	-8**
Mean Number Corpora Lutea	16.6	17.4	16.3	16.7
Mean Number Implantations	14.0	14.8	14.2	14.8
Mean % Preimplantation Loss	15.2	13.9	12.0	10.8

Table 2.6.7 13A Reproductive and Developmental Toxicity **Test Articles: Dextromethorphan and Quinidine** (continued)

Daily Dose (mg/kg)	Control	DM5/Q100	DM15/Q100	DM50/Q100
Litters				
Number Litters Evaluated	21	24	23	20
Number Live Fetuses	279	338	313	283
Mean Number Resorptions	0.8	0.7	0.6	2.5
Number Dead Fetuses	0	0	1	0
Mean % Postimplantation Loss	7	5	5	17
Mean Fetal Body Weight (g)	3.8	3.6	3.6*	3.4**
Fetal Sex Ratios (% males)	51	51	51	51
Fetal Anomalies				
Gross External				
Appears Small				
Number of Fetuses (%)	0	0	<1	0
Number of Litters (%)	0	0	4.3	0
Visceral Anomalies				
Hydrocephaly				
Number of Fetuses (%)	<1	0	0	0
Number of Litters (%)	5	0	0	0
Anopthalmia				
Number of Fetuses (%)	<1	<1	0	0
Number of Litters (%)	5	4	0	0
Dilated Lateral Ventricles				
Number of Fetuses (%)	<1	0	0	0
Number of Litters (%)	5	0	0	0
Retinas Folded				
Number of Fetuses (%)	0	0	<1	0
Number of Litters (%)	0	0	4	0
Additional Cartoid				
Number of Fetuses (%)	<1	0	0	0
Number of Litters (%)	5	0	0	0
Heart and/or Great Vessel Anomaly				
Number of Fetuses (%)	<1	0	0	0
Number of Litters (%)	5	0	0	0
Skeletal Anomalies				
Sternebra (e) Offset Alignment				
Number of Fetuses (%)	4	2	<1	0
Number of Litters (%)	19	13	4	0

Table 2.6.7 13A Reproductive and Developmental Toxicity **Test Articles: Dextromethorphan and Quinidine** (continued)

Daily Dose (mg/kg)	Control	DM5/Q100	DM15/Q100	DM50/Q100
Skeletal Anomalies, continued				
Sternebra (e) Bipartite				
Number of Fetuses (%)	0	<1	0	1
Number of Litters (%)	0	4	0	9
Rib (s) Kinked				
Number of Fetuses (%)	0	0	0	2
Number of Litters (%)	0	0	0	14
Offset Alignment of Pelvic Girdle				
Number of Fetuses (%)	<1	0	1	0
Number of Litters (%)	5	0	9	0
Total Affected Fetuses (Litters)	10 (7)	5 (5)	4 (4)	5 (4)

DM = dextromethorphan hydrobromide; GD = gestation day; Q = quinidine sulfate
– = not present; + = present
* = $p < 0.05$; ** = $p < 0.01$
† For controls, group mean weights are shown. For treated groups, percent differences from controls are shown.

Study title: ***Dextromethorphan/Quinidine (DMQ): Embryo-Fetal Toxicity Study in Rabbits***

Key study findings:

- This study is considered to be substandard based on inadequate support for dose selection and minimal treatment-related maternal toxicity that would demonstrate that dosing was conducted at up to the maternal MTD
- There were slight treatment-related reductions in body weights and food consumption in the maternal rabbits administered dextromethorphan and quinidine (at 5/100-50/100 reduced to 5/60-30/60 mg/kg/day DM/Q, on gestation days 6-19) (NOAEL not determined in this study)
- Treatment-related embryo-fetal toxicity was indicated by slight increases in total incidences of malformations at the mid-dose and high dose, with sporadic

observations of abnormalities including fused sternebrae, gastroschisis with phalangeal fusion, craniofacial abnormalities, diaphragmatic hernia, persistent truncus arteriosus, and vertebral fusions (NOAEL = 5/60 mg/kg/day DM/Q)

- There was a slight treatment-related effect on skeletal ossification (incomplete or non-ossification of sternebrae, hind limb long-bone epiphyses and hyoid) at the mid- and high doses

Study no.: DMQ-123
Volume # m4-2-3-5-2 (electronic submission)**, and page #** NA
Conducting laboratory and location: (b) (4)

Date of study initiation: October 27, 2003
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug Dextromethorphan hydrobromide USP**, lot #** DM 0302015**, and % purity** 99.6%
Drug Quinidine sulfate**, lot #** 4963**, and % purity** 100.8%

Methods

Doses: Dose range-finding study in rabbits (DMQ-121) at 0/0, 0/50, 0/100, 50/100, 100/100, and 50/0 mg/kg/day DM/Q. The dose range-finding study is considered to be inadequate due to the lack of sufficient treatment-related toxicity. In the embryo-fetal toxicity study, the rabbits were administered 0/0, 5/100, 15/100, and 50/100 mg/kg/day DM/Q, initially. During the Segment II study in rabbits, the high dose combination was reduced to 30/60 mg/kg/day DM/Q during GD 11-19 and the doses in the low dose (5/100) and mid-dose (15/100) groups were reduced to 5/60 and 15/60 mg/kg/day, respectively, during GD 18-19. Additional rabbits (10/group) were added to the total number of dams at the revised dose levels, due to loss of fetuses during processing. The additional 10 dams received the new dose levels of 0/0, 5/60, 15/60 and 30/60 mg/kg/day DM/Q during GD 6-19.

The doses in the main study on embryo-fetal toxicity in rabbits are presented in the following table (reproduced from the original NDA submission):

Group	Group Designation	Dosage (once daily, by gavage)			Number of females[c]
		Dose[b]		Volume	
		mg/kg/day DM/Q[a]	Gestation Days treated[b]	mL/kg	
1	Control	0	6 - 19	4	22 + 10
2	Low	5/100, 5/60	6 - 18 6 - 19	4	22 + 10
3	Intermediate	15/100, 15/60	6 - 18 6 - 19	4	22 + 10
4	High	50/100, 30/60	6 - 11 6 - 19	4	22 + 10

[a] Dextromethorphan is abbreviated to DM in this report, quinidine to Q, and the mixture to DMQ. The significant metabolite dextrorphan is abbreviated to DX.

[b] In response to unexpectedly severe maternal toxicity the dose levels were reduced as indicated above. Dosing was also withdrawn for 1-2 days for a few specific animals. The change in dose levels occurred on a particular calendar day and therefore had a varied effect on the number of days the animals in each group received either the initial or the final DMQ mixtures, because of the staggered nature of the study design. See General Preface (page 41) for details.

[c] The study was conducted in two sequential phases, the first containing 22 animals per group, the second containing a further 10 animals per group. The second phase was undertaken in response to accidental loss of some fetal specimens from the first phase during processing for skeletal evaluations. The revised, lower dose levels applied throughout the treatment period for this second phase.

Species/strain: Albino New Zealand White rabbits ((b) (4) , ages 5-6 months, weights 2.8-4.0 kg)

Number/sex/group: 22 + 10 dams/dose group

Route, formulation, volume, and infusion rate: The test articles were dissolved in 1% aqueous methylcellulose, and given by oral gavage at 4 ml/kg.

Satellite groups used for toxicokinetics: None

Study design: The mated female rabbits were dosed once daily from gestation day (GD) 6 through GD 19 (day of closure of hard palate), and sacrificed on GD 29. See under dosing above, for protocol changes, (addition of dams and dose reductions)

Parameters and endpoints evaluated: Maternal viability and mortality (twice daily), clinical signs of toxicity (twice daily), detailed physical examinations (twice weekly), body weights (baseline and GD 3, 6, 9, 12, 15, 19, 20, 23, 26, and 29) and food consumption (baseline and GD 3-6, 6-9, 9-12, 12-15, 15-19, 19-23, 23-26, 26-19, 6-19, and 19-29). The dams were sacrificed on GD 29, and examined for uterine and ovary weights, pregnancy, corpora lutea count, and numbers of live and dead implantations,

early and late embryo-fetal deaths (recognizable dead fetuses or evidence of implantation without recognizable fetuses). Stained uteruses were examined for very early resorptions. Placentas were examined. The fetuses were examined on GD 29 for external abnormalities (including palate), body weights, sex, soft tissue and skeletal abnormalities and state of ossification. Toxicokinetic parameters were evaluated; plasma samples (auricular central artery, 1 ml) taken on gestation days 6 and 19, at 1, 2, 4, 8, and 24 hours after dosing.

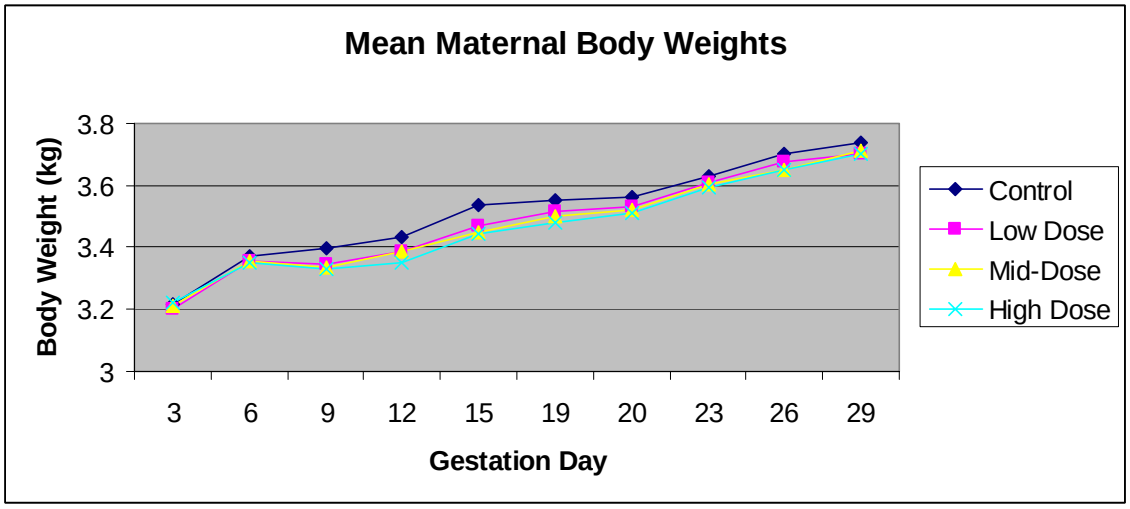
Results

Mortality (dams): Deaths in 1 low-dose dam (found dead, GD 19) with discolored lungs and trachea, and 1 mid-dose dam (found dead, GD 9); deaths not considered to be treatment-related. One high-dose dam sacrificed due to severe reduction in food consumption on GD 10.

Pregnancy rate: 84% or higher in all groups.

Clinical signs (dams): No treatment-related effects.

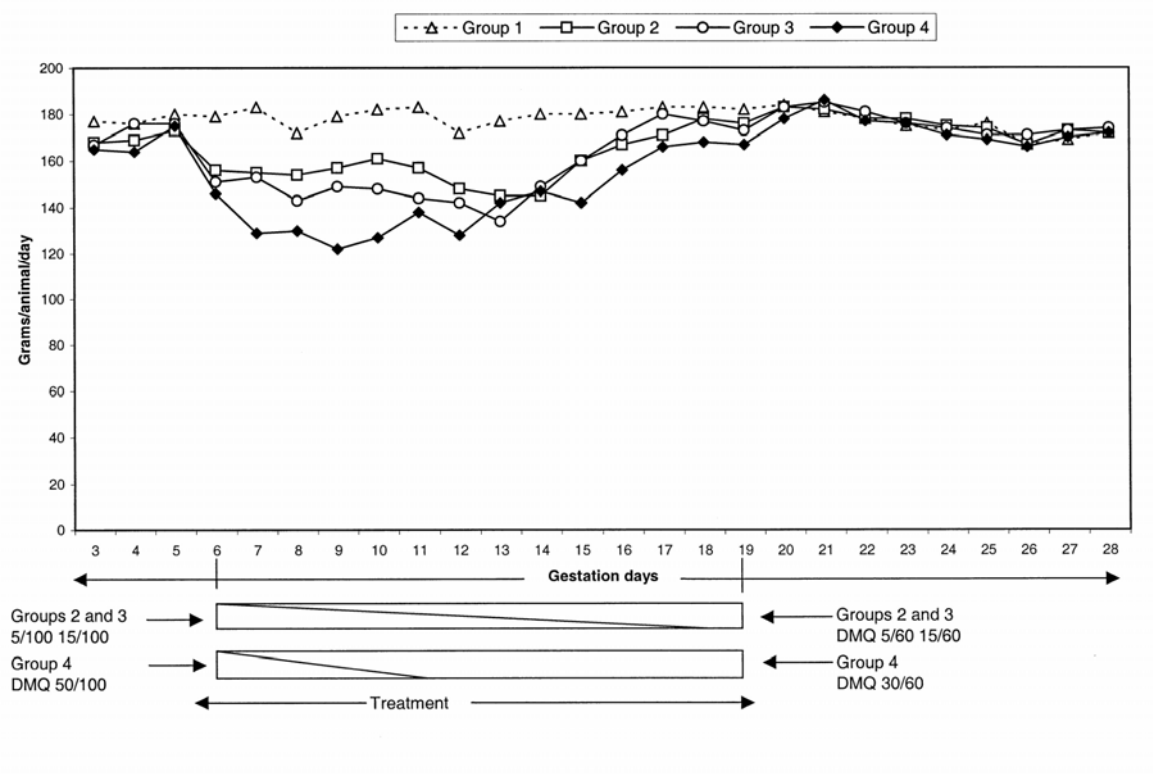
Body weight (dams): Reduced in several dams at the low (5/100 mg/kg/day DM/Q) and mid-doses (15/100 mg/kg/day DM/Q), and in 1/3 dams at the high dose (50/100 mg/kg/day DM/Q), before dosage adjustment. No treatment-related effects when dosages were reduced to 5/60, 15/60, and 30/60 mg/kg/day DM/Q.



Food consumption (dams): Reduced in several dams at the low (5/100 mg/kg/day DM/Q) and mid-doses (15/100 mg/kg/day DM/Q), and in 1/3 dams at the high dose

(50/100 mg/kg/day DM/Q), before dosage adjustment. No treatment-related effects when dosages were reduced to 5/60, 15/60, and 30/60 mg/kg/day DM/Q.

Food consumption in the maternal rabbits is presented in the following table (reproduced from the original NDA submission):



Toxicokinetics: AUC_{0-24} not determined, due to dosage changes. AUC_{0-4} values were calculated. Q exposure (AUC_{0-4}) increased 2X on GD 19 compared to GD 6 value, suggesting accumulation, but there was no increase in Q exposure with increased DM dose. DM exposure (AUC_{0-4} and Cmax) increases < dose proportional over the doses of 5-50 mg/kg/day and >dose proportional over the dose range of 5-30 mg/kg/day (revised dose schedule) on both GD 6 and 19. DM exposure greater on GD 19 (3X) than on GD 6, suggesting accumulation. DX exposure increase <dose-proportional during initial dosing schedule (from 15-50 mg/kg/day DM), but dose-proportional after dose adjustment of DM (5-30 mg/kg/day DM), and exposure was similar on GDs 6 and 19 (no accumulation).

The results of the toxicokinetic evaluation in the embryo-fetal toxicity study in rabbits are presented in the following table (reproduced from the original NDA submission):

	Toxicokinetic Parameters for Quinidine, Dextromethorphan and Dextrorphan after Oral Dosing of 5/60, 5/100, 15/60, 15/100, 30/60 and 50/100 mg/kg/day of Dextromethorphan/Quinidine in Female Rabbits on Gestation Day 6 (Groups 2-4)	Table 1

Analyte	Group	Dose DM/Q mg/kg/day	t_{max} hour	C_{max} ng/mL	AUC_{0-4h} ng.h/mL	AUC_{0-24h} ng.h/mL
Quinidine	2	5/100	1	3590	11300	30000
	3	15/100	2	2990	9690	21600
	4	50/100	1	2460	7920	N.A.
Quinidine	2	5/60	2	2080	5910	N.A.
	3	15/60	2	2430	6860	N.A.
	4	30/60	2	2390	7030	10700
Dextromethorphan	2	5/100	1	11.1	18.0	45.9
	3	15/100	2	7.78	24.7	40.5
	4	50/100	1	79.1	183	N.A.
Dextromethorphan	2	5/60	2	3.25	6.63	N.A.
	3	15/60	2	11.2	30.2	N.A.
	4	30/60	1	33.9	92.4	130
Dextrorphan	2	5/100	1	1950	4300	9720
	3	15/100	2	2770	8370	19500
	4	50/100	2	5590	17500	N.A.
Dextrorphan	2	5/60	1	1290	4040	N.A.
	3	15/60	2	4680	13400	N.A.
	4	30/60	2	7580	23300	40300

DM/Q = Dextromethorphan/Quinidine
N.A. = Not applicable

	Toxicokinetic Parameters for Quinidine, Dextromethorphan and Dextrorphan after Oral Dosing of 5/60, 15/60 and 30/60 mg/kg/day of Dextromethorphan/Quinidine in Female Rabbits on Gestation Day 19 (Groups 2-4)	Table 2

Analyte	Group	Dose DM/Q mg/kg/day	t_{max} hour	C_{max} ng/mL	AUC_{0-4h} ng.h/mL	AUC_{0-24h} ng.h/mL
Quinidine	2	5/60	1	4050	12200	N.A.
	3	15/60	1	4500	14300	N.A.
	4	30/60	2	3820	11600	27700
Dextromethorphan	2	5/60	2	10.1	25.6	N.A.
	3	15/60	1	38.2	101	N.A.
	4	30/60	2	70.1	221	383
Dextrorphan	2	5/60	1	1570	4310	N.A.
	3	15/60	1	5180	12300	N.A.
	4	30/60	2	6830	20800	35400

DM/Q = Dextromethorphan/Quinidine

N.A. = Not applicable

Terminal and necroscopic evaluations:

The terminal and necroscopic evaluation results are presented in the following table (reproduced from the original NDA submission):

Pregnancy Results

	Dose Dextromethorphan/Quinidine (mg/kg/day)			
	0/0	5/60	15/60	30/60
# Females Mated	32	32	32	32
# Females Pregnant	31	31	31	28
#Died/Sacrificed	0	1	1	1
#Aborted Died/Sacrificed	0	0	0	0
# Females Nonpregnant	1	1	1	4
#Died/Sacrificed	0	0	0	0
Total # Females Died/Sacrificed (%)	0 (0)	1 (3.1)	1 (3.1)	1 (3.1)
# Examined at Scheduled C-Section	32	31	31	31
# Nonpregnant	1	1	1	4
# with Total Implant Loss (%)	0 (0)	0 (0)	0 (0)	0 (0)
# with Viable Fetuses (%)	31 (96.9)	30 (96.8)	30 (96.8)	27 (87.1)

Maternal necropsy results: No treatment-related effects on maternal necropsy observations including uterus and placenta. In the cesarean section examination, there was a statistically significant reduction in pre-implantation loss (# per animal and % per animal) at the mid-dose (15/60 mg/kg/day DM/Q) and high dose (30/60 mg/kg/day

DM/Q). The results of the cesarean section observations are presented in the following table (reproduced from the original NDA submission):

Cesarean Section Observations

	Dose Dextromethorphan/Quinidine (mg/kg/day)			
	0/0	**5/60**	**15/60**	**30/60**
Post-implantation Loss Total	25	13	7	9
Mean #/animal (± S.D.)	0.8 (±1.45)	0.4 (±0.73)	0.2 (±0.68)	0.3 (±0.73)
Mean % implants per animal (± S.D.)	7.7 (±13.17)	5.0 (±8.60)	2.2 (±6.05)	3.2 (±6.80)
Dead Fetuses Total	0	0	1	1
Mean #/animal (± S.D.)	0 (±0)	0 (±0)	0.0 (±0.18)	0.0 (±0.19)
Mean % of implants per animal (± S.D.)	0 (±0)	0 (±0)	0.3 (±1.52)	0.3 (±1.60)
Resorptions: Early Total	10	8	3	3
Mean # per animal (± S.D.)	0.3 (±0.70)	0.3 (±0.58)	0.1 (±0.40)	0.1 (±0.32)
Mean % of implants per animal	3.3 (±6.79)	3.1 (±6.92)	1.0 (±3.83)	1.2 (±3.60)
Resorptions: Late Total	15	5	3	5
Mean # per animal (± S.D.)	0.5 (±1.09)	0.2 (±0.46)	0.1 (±0.40)	0.2 (±0.48)
Mean % of implants per animal (± S.D.)	4.4 (±9.70)	1.9 (±5.45)	0.9 (±3.60)	1.7 (±4.31)
# Pregnant at scheduled sacrifice	31	30	30	27
#Dams with no viable fetuses	0	0	0	0
# Dams with viable fetuses	31	30	30	27
Corpora Lutea Total	297	269	271	253
Mean # per animal (± S.D.)	9.6 (±2.39)	9.0 (±1.71)	9.0 (±1.96)	9.4 (±1.88)
Implantation sites Total	270	247	264	244
Mean # per animal (± S.D.)	8.7 (±2.34)	8.2 (±2.05)	8.8 (±1.86)	9.0 (±2.10)
Pre-implantation loss Total	27	22	7	9
Mean # per animal	0.9 (±0.99)	0.7 (±1.08)	0.2 (±0.43)*	0.3 (±0.68)*
Mean % per animal (± S.D.)	9.0 (±9.68)	8.6 (±13.29)	2.3 (±4.39)*	4.1 (±10.10)*
Live fetuses Total	245	234	257	235
Mean # per animal (± S.D.)	7.9 (±1.94)	7.8 (±2.02)	8.6 (±1.72)	8.7 (±2.00)
Males Total	124	114	111	109
Mean % (± S.D.)	49.5 (±20.12)	47.9 (±17.19)	42.6 (±16.57)	45.1 (±18.62)
Females Total	121	120	146	126
Mean % (± S.D.)	50.5 (±20.12)	52.1 (±17.19)	57.4 (±16.57)	54.9 (±18.62)
Fetal body weight (g) Mean (± S.D.)	43.7 (±4.17)	45.0 (±4.80)	42.7 (±5.05)	41.3 (±3.63)
Male fetuses Mean # (± S.D.)	44.4 (±5.22)	45.2 (±5.23)	43.6 (±5.80)	41.7 (±3.51)
Female fetuses Mean # (± S.D.)	42.8 (±4.24)	44.6 (±4.77)	41.9 (±5.57)	41.0 (±4.61)

*p<0.05

Offspring: There was a slight dose-related increase in total number of fetuses with malformations (5, 7, 12, and 15 fetuses at 0, 5/60, 15/60 and 30/60 mg/kg/day DM/Q, respectively, in 5, 6, 10, and 11 litters at 0, 5/60, 15/60, and 30/60 mg/kg/day DM/Q, respectively). The increase in malformation incidences at the mid-dose and high dose reflect sporadic increases in minor and major malformations, including fused sternebrae, gastroschisis, phalangeal fusions, craniofacial abnormalities, diaphragmatic hernia, truncus arteriosis, and vertebral fusions, without evidence of syndrome or association with maternal toxicity. Historical data were not provided in this report. However, in the Historical Control Database provided by [redacted](b) (4)) of preclinical developmental teratology and reproductive toxicity parameters, the results of examined fetuses from 19 pregnant rabbits given 0.51%-2.0%

methylcellulose in water showed no incidence of persistent truncus arteriosus, diaphragmatic hernia, and fused sternebrae. There were no treatment-related effects on incidence of variations. There were slight increases in incomplete ossification of sternebrae, incomplete hyoid ossification, and unossified epiphysis (femur or tibia), suggesting developmental delay. The results of the fetal observations are presented in the following tables (from the original NDA submission):

SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS

DOSE GROUP DOSE LEVEL (MG/KG/DAY)	1 0/0	2 5/60	3 15/60	4 30/60
Litters Examined Externally and Viscerally	31	30	30	27
Fetuses Examined	245	234	258	236
Litters Examined Skeletally	22	21	26	21
Fetuses Examined	178	168	211	175
GASTROSCHISIS, OPEN EYELID(S), FUSED PHALANGES				
Fetal Incidence	0	0	0	1
Litter Incidence	0	0	0	1
MULTIPLE CRANIOFACIAL ABNORMALITIES				
Fetal Incidence	0	0	1	0
Litter Incidence	0	0	1	0
CARPAL FLEXURE (ONLY)				
Fetal Incidence	0	0	0	1
Litter Incidence	0	0	0	1
MICROPHTHALMIA, CARPAL FLEXURE				
Fetal Incidence	0	0	0	1
Litter Incidence	0	0	0	1
PERSISTENT TRUNCUS ATERIOSUS				
Fetal Incidence	0	0	0	1
Litter Incidence	0	0	0	1
DIAPHRAGMATIC HERNIA				
Fetal Incidence	0	0	1	0
Litter Incidence	0	0	1	0
AGENESIS OF LUNG LOBE(S)				
Fetal Incidence	1	0	0	0
Litter Incidence	1	0	0	0
JUGAL FUSED TO MAXILLA				
Fetal Incidence	0	1	1	0
Litter Incidence	0	1	1	0
CERVICAL AND THORACIC VERTEBRA (E) FUSED/ABSENT, RIB FUSIONS				
Fetal Incidence	0	0	1	0
Litter Incidence	0	0	1	0
TWO RIBS FUSED				
Fetal Incidence	1	0	0	0
Litter Incidence	1	0	0	0
THORACIC SCOLIOSIS WITH VERTEBRAL FUSIONS, STERNERAE FUSED				
Fetal Incidence	0	1	0	1
Litter Incidence	0	1	0	1
STERNEBRA(E)FUSED (ONLY)				
Fetal Incidence	0	0	3	2
Litter Incidence	0	0	3	1
OFFSET ALIGNMENT (PELVIS)				
Fetal Incidence	4	5	5	8
Litter Incidence	4	5	5	6
TOTAL NUMBER WITH MALFORMATIONS				
Fetal Incidence	5	7	12	15
Litter Incidence	5	6	10	11

SUMMARY OF FETAL OBSERVATIONS - VARIATIONS

DOSE GROUP DOSE LEVEL (MG/KG/DAY)	1 0/0	2 5/60	3 15/60	4 30/60
Litters Examined Externally	31	30	30	27
Fetuses Examined	245	234	258	236
Number with Findings	0	0	0	0
Litters Examined Viscerally	31	30	30	27
Fetuses Examined	245	234	258	236
HEMORRHAGIC RING AROUND IRIS				
Fetal Incidence	1	2	0	0
Litter Incidence	1	2	0	0
ADDITIONAL SUBCLAVIAN ARTERY				
Fetal Incidence	4	4	6	4
Litter Incidence	4	4	4	4
DISPLACED ORIGIN OF ARTERY FROM AORTIC ARCH				
Fetal Incidence	16	8	17	18
Litter Incidence	11	8	7	11
ADDITIONAL BRANCHING ARTERY				
Fetal Incidence	0	1	0	0
Litter Incidence	0	1	0	0
ADDITIONAL LIVER LOBE				
Fetal Incidence	0	0	0	1
Litter Incidence	0	0	0	1
GALL BLADDER ABSENT				
Fetal Incidence	0	0	0	1
Litter Incidence	0	0	0	1
Litters Examined Skeletally	22	21	26	21
Fetuses Examined	178	168	211	175
HYOID ARCH(ES) BENT				
Fetal Incidence	15	3	6	4
Litter Incidence	7	3	6	4
SMALL BRIDGE OF OSSIFICATION BETWEEN INTERPARIETAL AND SUPRAOCCIPITAL				
Fetal Incidence	0	0	0	1
Litter Incidence	0	0	0	1
SMALL SUTURAL BONE (LEFT NASAL)				
Fetal Incidence	0	0	1	0
Litter Incidence	0	0	1	0
CERVICAL RIB(S) PRESENT				
Fetal Incidence	0	0	2	0
Litter Incidence	0	0	1	0
THORACIC CENTRUM BIPARTITE				
Fetal Incidence	0	1	0	0
Litter Incidence	0	1	0	0
27 PRESACRAL VERTEBRA (E)				
Fetal Incidence	50	52	32	41
Litter Incidence	15	17	11	14
CAUDAL VERTEBRA MISSPHAPEN				
Fetal Incidence	0	1	0	0
Litter Incidence	0	1	0	0
ADDITIONAL STERNEBRA (E)				
Fetal Incidence	1	2	0	0
Litter Incidence	1	2	0	0
RIB(S) 13TH RUDIMENTARY				
Fetal Incidence	25	34	47	23
Litter Incidence	15	17	23	14
RIB(S) 13TH FULL				
Fetal Incidence	89	88	86	96
Litter Incidence	18	20	23	19
THICKENED RIBS				
Fetal Incidence	1	5	0	3
Litter Incidence	1	4	0	3

Ossification Parameters Summary in Fetuses of Rabbits Administered Dextromethorphan and Quinidine on Gestation Days 6-19

Observation	Group (Dose Level) 1 (0 mg/kg/day)	2 (DM5/Q60 mg/kg/day)	3 (DM15/Q60 mg/kg/day)	4 (DM30/Q60 mg/kg/day)
Number of Fetuses Examined (Litters)	178(22)	168(21)	211(26)	175(21)
Fetuses (Litters) Affected				
Incomplete ossification/unossified:				
Hyoid	17(8)	10(6)	9(8)	22(11)
Vertebral Centra Affected	1(1)	2(2)	1(1)	0(0)
Vertebral Arches Affected	53(14)	42(15)	80(21)	45(15)
Sternebrae				
1 sternebra affected	29(13)	28(14)	65(18)	43(16)
2 sternebrae affected	7(5)	5(4)	14(7)	14(8)
3 or more sternebrae affected	0(0)	0(0)	0(0)	1(1)
Mean number of caudal vertebrae ossified	17.6	17.7	17.7	17.6
Unossified epiphyses				
1 or more affecting humerus / radius	61(14)	36(9)	52(15)	56(12)
1 or more affecting femur / tibia	79(18)	81(17)	98(22)	110(17)
Ribs Affected	0(0)	1(1)	4(2)	0(0)
Olecranon ossified	15(7)	30(10)	25(16)	13(5)
Incomplete Pubis	0(0)	2(1)	0(0)	2(2)
Mean incidence per litter				
Incomplete Ossification of Hyoid	0.8	0.5	0.4	1.0
Vertebral Centra Affected	0.0	0.1	0.0	0.0
Vertebral Arches Affected	2.4	2.0	3.1	2.1
Sternebrae				
1 sternebra affected	1.3	1.3	2.5	2.1
2 sternebrae affected	0.3	0.2	0.5	0.7
3 or more sternebrae affected	0.0	0.0	0.0	0.1
Unossified epiphyses				
1 or more affecting humerus / radius	2.8	1.7	2.0	2.7
1 or more affecting femur / tibia	3.6	3.9	3.8	5.2
Ribs Affected	0.0	0.1	0.2	0.0
Olecranon ossified	0.7	1.4	1.0	0.6
Incomplete Ossification of Pubis	0.0	0.1	0.0	0.1

Summary: Maternal rabbits (22/dose) were administered dextromethorphan and quinidine in combination by oral gavage at 0/0, 5/100 (LD), 15/100 (MD), and 50/100 (HD) mg/kg/day dextromethorphan/quinidine from gestation days 6-11 to 6-18, and the doses were reduced to 0/0, 5/60, 15/60, and 30/60 mg/kg/day dextromethorphan/quinidine from gestation days 12-19 or 18-19 in the original groups of 22 rabbits due to severe maternal toxicity. Additional groups of 10 rabbits per dose level

were added and received the revised dose levels from gestation days 6-19. The total treatment period for all rabbits spanned gestation days 6-19 (inclusive). Treatment-related maternal toxicity included dose-related reduced body weights and food consumption. Embryo-fetal toxicity was observed at doses above the NOAEL of 5/60 mg/kg/day dextromethorphan/quinidine. There were slight increases in the total incidences of malformations at the MD and HD, with sporadic observations of abnormalities including fused sternebrae, gastroschisis with phalangeal fusion, craniofacial abnormalities, diaphragmatic hernia, persistent truncus arteriousus, and vertebral fusions. There was a slight treatment-related effect on skeletal ossification, with incomplete or non-ossification of the sternebrae, hind limb long-bone epiphyses and hyoid at the MD and HD. The mean AUC_{0-4} values (24-hour evaluations not completed due to dosage adjustments) on gestation day 19 in the maternal rabbits were 12200, 14300, and 11600 ng.h/ml for Q (approximately 5X-6X the approximate clinical AUC_{0-24} value, estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d.), 25.6, 101, and 221 ng.h/ml for dextromethorphan (0.01X, 0.03X, and 0.07X, respectively, the approximate clinical AUC_{0-24} value, estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d.), and 4310, 12300, and 20800 ng.h/ml for dextrorphan (0.4X, 1.2X, and 2X, respectively, the approximate clinical AUC_{0-24} value, estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d.) at the LD, MD, and HD, respectively.

The results of the study on Neurodex embryo-fetal toxicity in rabbits is presented in the following table (reproduced from the original NDA submission):

Table 2.6.7-13B Reproductive and Developmental Toxicity **Test Articles: Dextromethorphan and Quinidine**

Report Title: Dextromethorphan/Quinidine (DMQ): Embryo-fetal toxicity study in rabbits				
Design similar to ICH S5A 4.1.3? Yes	**Duration of Dosing:** Gestation Days 6-19		**Study Reference:** DMQ-123	
Species/Strain: Rabbit/New Zealand White	**Day of C-Section:** Gestation Day 29		**Location in CTD:** Section 2.6.6.6	
Initial Age: 5-6 months **Day of Mating:** Gestation Day 0	**Method of Administration:** Oral Gavage		**GLP Compliance:** Yes	
Date of First Dose: 15 Nov 2003	**Vehicle/Formulation:** 1% aqueous methylcellulose			
Special Features: None				
No Observed Adverse Effect Level: **F_0 Females:** Not Determined **F_1 Litters:** 5 mg DM/kg/d + 60 mg Q/kg/d				
Daily Dose (mg/kg)	**Control**	**DM5/Q100 (GD 6-7) DM5/Q60 (GD 8-19)**	**DM15/Q100 (GD 6-7) DM15/Q60 (GD 8-19)**	**DM50/Q100 (GD 6-7) DM30/Q60 (GD 8-19)**
Does				
Toxicokinetics: $AUC_{0\text{-}24h}$ (ng·h/mL)[†]				
Quinidine – Gestation Day 6	–	30000/NA	21600/NA	NA/10700
Quinidine – Gestation Day 19	–	– /NA	– /NA	– /27700
Dextromethorphan – Gestation Day 6	–	45.9/NA	40.5/NA	NA/130
Dextromethorphan – Gestation Day 19	–	– /NA	– /NA	– /383
Dextrorphan – Gestation Day 6	–	9720/NA	19500/NA	NA/40300
Dextrorphan – Gestation Day 19	–	– /NA	– /NA	– /35400
Number Pregnant	31	31	31	28
Number Died or Sacrificed Moribund	0	1	1	1
Number Aborted or with Total Resorption of Litter	0	0	0	0
Clinical Observations (frequency/animals):				
Decreased Food Consumption	0/0	1/1	3/2	7/4
Decreased Fecal Volume	0/0	3/3	5/3	6/4
Necropsy Observations				
Body Weight at End of Dosing Period (%)[‡]	3738 g	-1	-1	-1
Food Consumption – Mean Daily Amount GD 6-19[‡]	180 g	-12	-14	-23
Mean Number Corpora Lutea	9.6	9.0	9.0	9.4
Mean Number Implantations	8.7	8.2	8.8	9.0
Mean % Preimplantation Loss	9.0	8.6	2.3*	4.1*
Litters				
Number Litters Evaluated	31	30	30	27

Table 2.6.7-13B Reproductive and Developmental Toxicity **Test Articles: Dextromethorphan and Quinidine** (continued)

Mean Number Live Fetuses/Litter	7.9	7.8	8.6	8.7
Mean Number Early Resorptions/Litter	0.3	0.3	0.1	0.1
Daily Dose (mg/kg)	**Control**	**DM5/Q100 (GD 6-7) DM5/Q60 (GD 8-19)**	**DM15/Q100 (GD 6-7) DM15/Q60 (GD 8-19)**	**DM50/Q100 (GD 6-7) DM30/Q60 (GD 8-19)**
Mean Number Late Resorptions/Litter	0.5	0.2	0.1	0.2
Total Number Dead Fetuses	0	0	1	1
Mean % Postimplantation Loss	7.7	5.0	2.2	3.2
Mean Fetal Body Weight (g)	43.7	45.0	42.7	41.3
Fetal Sex Ratios (% males)	49.5	47.9	42.6	45.1
Fetal Anomalies				
Gross External	–	–	–	–
Visceral Anomalies				
Additiona Liver Lobe				
Number of Fetuses (%)	0	0	0	0.6
Number of Litters (%)	0	0	0	5
Gall Bladder Absent				
Number of Fetuses (%)	0	0	0	0.6
Number of Litters (%)	0	0	0	5
Skeletal Anomalies				
Gastroschisis, open eyelid(s), Fused Phalanges				
Number of Fetuses (%)	0	0	0	0.6
Number of Litters (%)	0	0	0	5
Multiple Craniofacial Abnormalities				
Number of Fetuses (%)	0	0	0.5	0
Number of Litters (%)	0	0	4	0
Carpal Flexure (only)				
Number of Fetuses (%)	0	0	0	0.6
Number of Litters (%)	0	0	0	5
Microphthalmia, Carpal Flexure				
Number of Fetuses (%)	0	0	0	0.6
Number of Litters (%)	0	0	0	5
Persistent Truncus Ateriosus				
Number of Fetuses (%)	0	0	0	0.6
Number of Litters (%)	0	0	0	5
Diaphragmatic Hernia				
Number of Fetuses (%)	0	0	0.5	0
Number of Litters (%)	0	0	4	0

Table 2.6.7-13B Reproductive and Developmental Toxicity Test Articles: Dextromethorphan and Quinidine (continued)

Sternebra (e) Fused (only)				
Number of Fetuses (%)	0	0	1	1
Number of Litters (%)	0	0	12	5
Daily Dose (mg/kg)	**Control**	**DM5/Q100 (GD 6-7) DM5/Q60 (GD 8-19)**	**DM15/Q100 (GD 6-7) DM15/Q60 (GD 8-19)**	**DM50/Q100 (GD 6-7) DM30/Q60 (GD 8-19)**
Sternerae Fused – Thoracic scoliosis with vertebral fusions				
Number of Fetuses (%)	0	0.6	0	0.6
Number of Litters (%)	0	5	0	5
Jugal Fused to Maxilla				
Number of Fetuses (%)	0	0.6	0.5	0
Number of Litters (%)	0	5	4	0
Rib Fusions, Cervical and Thoracic vertebra(e) Fused/Absent				
Number of Fetuses (%)	0	0	0.5	0
Number of Litters (%)	0	0	4	0
Offset Alignment of Pelvic Girdle				
Number of Fetuses (%)	2	3	2	5
Number of Litters (%)	18	24	19	29
Total Affected Fetuses (Litters)	6 (6)	7 (6)	12 (10)	15 (11)

DM = dextromethorphan hydrobromide; GD = gestation day; Q = quinidine sulfate
* = $p < 0.05$; ** = $p < 0.01$
† The first TK value represents measurements taken before the doses were reduced and the second value represents measurements taken after dose reduction.
‡ For controls, group mean values are shown. For treated groups, percent differences from controls are shown.

Prenatal and Postnatal Development

Study title: ***Dextromethorphan/Quinidine (DMQ): Pre- and Post-Natal Development Study in Rats, Including Maternal Function***

Key study findings:

- Slight treatment-related increase in gestation duration, pup mortality and decreased pup body weights at birth in rats administered DM/Q at 5/100-30/100 mg/kg/day from gestation day 6 through postnatal day 20, but not in the groups that received either 100 mg/kg/day Q alone or 50 mg/kg/day DM alone
- F1 developmental delay suggested by delayed acquisition of air-righting response and increased spontaneous activity at the mid-dose and high dose combination (15/100 and 30/100 mg/kg/day DM/Q), but not in pups exposed to Q alone at 100 mg/kg/day or DM alone at 50 mg/kg/day
- NOAEL for adverse effects on pregnancy and pre-natal and post-natal development not determined in this study
- This study is considered to be less than adequate based on insufficient support for dose selection and on the lack of adequate maternal toxicity to demonstrate dosing at up to the MTD; the substandard methodology and the results of this study should be clearly described in the product label, and the study should be repeated during Phase 4 with acceptable support for dose selection and dosing at up to the maternal MTD

Study no.: DMQ-125
Volume # m4-2-3-5-3 (electronic submission)**, and page #** NA
Conducting laboratory and location: (b) (4)

Date of study initiation: September 10, 2003
GLP compliance: Yes

QA reports: yes (x) no ( )
Drug Dextromethorphan hydrobromide**, lot #** DM0302015**, and % purity** 99.6%
Drug Quinidine sulfate**, lot #** 4963**, and % purity** 100.8%

Methods

Doses: The following table is from the original NDA submission:

Group	Group Designation	Doses (once daily, by gavage)			Days of Treatment	Number of animals	
		Dose	Concentration	Volume			
		mg/kg/day DM/Q	mg/ml DM/Q	ml/kg		F_0 females	F_1 weanlings*
1	Control	0/0	0/0	5	GD6-PND20	24	1/sex/litter
2	Low DMQ	5/100	1/20	5	GD6-PND20	24	1/sex/litter
3	Intermediate DMQ	15/100	3/20	5	GD6-PND20	24	1/sex/litter
4	High DMQ	30/100	6/20	5	GD6-PND20	24	1/sex/litter
5	Quinidine	100 (Q only)	20 (Q only)	5	GD6-GD17	20	-
6	DM	50 (DM only)	10 (DM only)	5	GD6-GD17	20	-

* Up to 20 of each sex per Group

Species/strain: Albino Sprague-Dawley Crl:CD®(SD) IGS BR rats (b) (4) , ages 70-84 days, weights 210-270 g on GD 0)

Number/sex/group: 24 (Groups 1-4) and 20 (Groups 5 and 6) females/dose

Route, formulation, volume, and infusion rate: Oral by gavage; test articles were dissolved in 1% methylcellulose aqueous solution

Satellite groups used for toxicokinetics: None

Study design and Parameters and endpoints evaluated:

F0: Groups 1-4 mated females (F0) treated by oral gavage once daily from gestation day 6 through postnatal day 20, and were sacrificed on postnatal day 21. Groups 5 and 6 mated females (F0) were dosed on gestation days 6-17 and were sacrificed on gestation day 20.

F1: Group 1-4 fetuses were culled to 1 male and 1 female from each litter (20/sex/dose group), and evaluated (physical and functional development, and reproductive function). Group 5 and 6 fetuses were examined for external abnormalities and fetal weights were measured.

Clinical signs: at least twice daily; before, immediately after and 1-2 hours after dosing
Physical examinations: twice weekly

Mortality: twice daily
Body weights: gestation days 0, 4, 6, 9, 12, 15, 17, 18, and 20, and postnatal day 0 (after parturition), 4, 7, 10, 14, 18, and 21
Food consumption: gestation days 4, 6, 9, 12, 15, and 18, and postnatal days 1, 4, 7, 10, 14, 18, and 21
Maternal (F0) terminal examinations: postnatal day 21, macroscopic observations, liver and kidney weights, uterine contents for implantation sites, corpora lutes, number and location of live and dead fetuses, late and early embryo or fetal deaths, placenta
Toxicokinetics: Blood samples (0.75 ml from the orbital sinus) from Groups 1-4 F0 females on gestation days 6 and 17 and postnatal day 16, at 0.5, 1, 2, 4, 8, and 24 hours after dosing. Blood samples from Groups 5 and 6 F0 females on gestation days 6 and 17 at 0.5, 1, 2, 8, and 24 hours after dosing
Parturition (postnatal day 0) and **lactation**: examination twice daily for 3 days for signs of parturition
Litter observations: number of live and dead pups, pup abnormalities, sex of pups, pup count twice daily until postnatal day 21
Culling: Postnatal day 4, to 10 pups per litter and equal sex distribution
F1 Pup evaluations: Pre-weaning:

-physical examinations on postnatal days 0, 4, 7, 14, and 21
-body weights
-pup sex
-functional observations
    -surface righting reflex from Day 1 of age until achieved
    -air righting reflex [drop from 12 inches] from Day 14 until achieved
    -auditory function [response to snap sound] on Day 20 of age
    -visual function [papillary response] on Day 20 of age
-necropsy on postnatal day 21 (remaining pups after cull)

Post-weaning (after postnatal day 21):
-cage-side observations twice daily
-body weights weekly
-physical examinations weekly
-male maturation (preputial separation from postnatal day 37 on)
-female maturation (vaginal patency) daily beginning postnatal day 28
-functional assessments
    -open field evaluations on postnatal days 22-23 for posture
    -gait
    -abnormal behavior or vocalization
-locomotor activity (spontaneous exploration for 60 minutes, postnatal day 28 or 29)
-learning and memory (from age 8 weeks using water-filled Biel maze or multiple T-maze)
-estrous cycle monitoring with vaginal smears from 10 days before mating through mating or 20-days of cohabitation
-mating (age 10 weeks, until positive evidence of mating or 20 nights of cohabitation)
-terminal examinations

-F1 females on gestation day 14 or if no signs of mating then 14 days after last exposure to a male, included macroscopic observations, liver and kidney weights and tissues, and uterine contents for corpora lutea counts, numbers of ovaries, total implantations, live and dead implantations

-F1 males after not required for mating or after F1 females sacrificed, included macroscopic examination, weights of testes, epididymides, prostate, seminal vesicles

-culls and weanlings: postnatal day 4, external examination, macroscopic examination of abnormalities

F1 gestation day 20 fetuses (from Groups 5 and 6 sacrificed dams): weights, macroscopic external examinations, sex, soft tissue abnormalities, skeletal abnormalities and ossification variations

Unscheduled deaths: all F0 females and F1 males and females found dead or sacrificed *in extremis*: macroscopic examination, in females count of uterine implantation scars, reproductive organs/tract examination, fetal malformations, internal examination of F1 pups including sex determination

Results

F_0 in-life:

Pregnancy: 24 pregnancies/group and 23-24 live litters/group in Groups 1-4, 20 pregnancies/group in Groups 5 and 6.

Mortality: Mid-dose (15/100 mg/kg/day DM/Q): One death on gestation day 17 due to undetermined cause, with normal implant sites in uterus (11), one sacrifice due to early litter loss during lactation period; High dose (30/100 mg/kg/day DM/Q): 2 sacrifices due to total loss of pregnancy in early gestation and total litter loss early in lactation period. One maternal rat given 100 mg/kg/day Q alone sacrificed due to accidental injury on gestation day 20.

Clinical signs: No treatment-related effects in groups 1-6, except salivation lasting 1-2 hours

Body weights: No treatment-related effects in groups 1-5. Slight reduction in body weights during gestation in Group 6 (50 mg/kg/day DM alone).

Food consumption: No treatment-related effects in groups 1-5. Slight reduction in food consumption during gestation in Group 6 (50 mg/kg/day DM alone).

Gestation duration: Slight dose-related increase in gestation length, from 21 to 22 days, within normal range, in Groups 2-4 compared to controls. The gestation lengths are presented in the following table (reproduced from the original NDA submission):

Gestation Length (days)	Incidence of Gestation Lengths			
	Control	DM5/Q100	DM15/Q100	DM30/Q100
21	14	8	4	5
22	10	16	19	18
23	0	0	0	0

F_0 necropsy: No treatment-related effects in the macroscopic examination and on maternal organ weights in groups 2-6.

F_1 physical development:
Mortality: Treatment-related increased mortality in pups on day of birth through postnatal day 4: 8, 15, 40, and 26 pups found dead at 0, 5/100, 15/100, and 30/100 mg/kg/day DM/Q, respectively, in 5, 11, 13, and 15 litters, respectively. The pup loss at the mid-dose was related to total loss of pups in one litter and loss of 5-6 pups each in 2 other litters, without evidence of maternal toxicity (body weight loss, clinical signs, etc). Remaining losses were 1-3 pups/litter in controls, low-dose and mid-dose litters, and 1-4 pups/litter at the high dose. No treatment-related effects on pup mortality during the remainder of the lactation period (to post-natal day 21).
Clinical signs: No treatment-related effects
Body weights: Slight reduction in body weights at the high dose (5% on postnatal day 4-7, 8% on postnatal day 21, compared to controls), mid-dose (5%-6% by postnatal day 21), and low dose (not statistically significant) DM/Q. The reduced pup body weights were observed in the pups born on gestation day 21 to a greater extent than in those born on gestation day 22. Body weights of pups born on gestation day 21 were 10-12% lower at the high dose, 10% lower at the mid-dose, and 7% lower at the low dose, than in the controls born on gestation day 21. The treatment-related effect on pup body weights persisted in all DM/Q treated groups (10% deficit compared to controls, across doses) until 6 weeks (females) to 8 weeks (males) after birth. No treatment-related effects on fetal body weights at 100 mg/kg/day Q alone and at 50 mg/kg/day DM alone.

F_1 behavioral evaluation: Before weaning, the mid-dose and high dose pups showed delayed acquisition of air-righting response (1/2 day delay) compared to control acquisition. No treatment-related effects on open-field behaviors, including posture, gait, and vocalization, and on learning and memory performance, including basic swimming performance. Increased spontaneous activity was observed in the mid-dose and high dose males and females, compared to control activity.

F_1 reproduction: No treatment-related effects on attainment of puberty (preputial separation, vaginal patency). No effects were observed, on estrous cycles or male and female mating and fertility parameters, clinical signs and body weights during gestation, pregnancy rate, ovulation (number of corpora lutea), implantations, and pre- and post-implantation losses.

F_1 necropsy: No treatment-related effects observed in the macroscopic examination and on organ weights. No external abnormalities in the Group 5 and 6 fetuses.

F_2 findings: Not done.

Toxicokinetics: DM Cmax and AUC_{0-24} increases greater than dose-proportional, DX (metabolite dextrorphan) Cmax and AUC_{0-24} increases less than dose-proportional, with

increased exposure to Q and DM (2X-3X) and DX (50%) on gestation day 17 than on gestation day 6, suggesting accumulation, while exposure to Q and DM was similar on postnatal day 16 and gestation day 6, although DX exposure was nearly 2X higher on postnatal day 16 compared to that on gestation day 6.

The results of the toxicokinetic evaluations in the prenatal and postnatal development study in rats are presented in the following tables (reproduced from the original NDA submission):

Dose Proportional Factors for Quinidine, Dextromethorphan and Dextrorphan following Oral Administration of 5/100, 15/100, 30/100, 0/100 and 50/0 mg/kg/day of Dextromethorphan/Quinidine to Female Rats on Gestation Days 6, 17 and Postnatal Day 16

Analyte	Group	Dose Dextromethorphan/ Quinidine (mg/kg/day)	Theoretical Increases in Exposure (fold)	Observed Increases in Exposure (fold) C_{max}	Observed Increases in Exposure (fold) AUC_{0-24h}
Gestation Day 6					
Quinidine*	2	5/100	1	1.00	1.00
	3	15/100	1	0.804	0.899
	4	30/100	1	0.952	1.14
	5	0/100	1	1.17	1.04
Dextromethorphan	2	5/100	1	1.00	1.00
	3	15/100	3	4.12	2.93
	4	30/100	6	8.70	9.38
	6	50/0	10	26.8	19.4
Dextrorphan**	2	5/100	1	1.00	1.00
	3	15/100	3	2.52	2.40
	4	30/100	6	6.03	4.61
	6	50/0	10	7.47	7.00
Gestation Day 17					
Quinidine*	2	5/100	1	1.00	1.00
	3	15/100	1	0.712	1.00
	4	30/100	1	0.873	0.985
	5	0/100	1	0.870	1.16
Dextromethorphan	2	5/100	1	1.00	1.00
	3	15/100	3	2.64	3.44
	4	30/100	6	6.83	9.61
	6	50/0	10	25.7	15.5
Dextrorphan**	2	5/100	1	1.00	1.00
	3	15/100	3	2.97	2.84
	4	30/100	6	5.09	5.45
	6	50/0	10	8.05	5.79
Postnatal Day 16					
Quinidine*	2	5/100	1	1.00	1.00
	3	15/100	1	0.925	1.11
	4	30/100	1	1.08	1.53
Dextromethorphan	2	5/100	1	1.00	1.00
	3	15/100	3	3.15	5.61
	4	30/100	6	8.40	10.0
Dextrorphan**	2	5/100	1	1.00	1.00
	3	15/100	3	1.68	1.57
	4	30/100	6	5.34	4.32

*Proportionality based on 100 mg/kg/day of Quinidine in Group 2 on each assessment occasion.
**Proportionality based on Dextromethorphan doses.

	Toxicokinetic Parameters for Quinidine, Dextromethorphan and Dextrorphan after Oral Dosing of 5/100, 15/100, 30/100, 0/100 and 50/0 mg/kg/day of Dextromethorphan/Quinidine in Female Rats on Gestation Days 6 and 17 (Groups 2-6)	**Table 1**

Day	Analyte	Group	t_{max} (hour)	C_{max} (ng/mL)	AUC_{0-24h} (ng.hour/mL)
Gestation Day 6	Quinidine	2	0.5	1890	22700
		3	0.5	1520	20400
		4	0.5	1800	25900
		5	1	2220	23600
	Dextromethorphan	2	0.5	21.5	130
		3	0.5	88.6	381
		4	0.5	187	1220
		6	0.5	576	2520
	Dextrorphan	2	4	150	2670
		3	0.5	378	6410
		4	0.5	905	12300
		6	8	1120	18700
Gestation Day 17	Quinidine	2	0.5	3470	39000
		3	8	2470	39100
		4	1	3030	38400
		5	8	3020	45100
	Dextromethorphan	2	0.5	59.9	308
		3	0.5	158	1060
		4	1	409	2960
		6	0.5	1540	4760
	Dextrorphan	2	8	185	3210
		3	8	550	9130
		4	4	942	17500
		6	1	1490	18600

	Toxicokinetic Parameters for Quinidine, Dextromethorphan and Dextrorphan after Oral Dosing of 5/100, 15/100 and 30/100 mg/kg/day of Dextromethorphan/Quinidine in Female Rats on Postnatal Day 16 (Groups 2-4)	**Table 2**

Day	Analyte	Group	t_{max} (hour)	C_{max} (ng/mL)	AUC_{0-24h} (ng.hour/mL)
Postnatal Day 16	Quinidine	2	0.5	2000	15600
		3	1	1850	17300
		4	1	2160	23800
	Dextromethorphan	2	0.5	18.8	148
		3	2	59.2	830
		4	1	158	1480
	Dextrorphan	2	0.5	266	4260
		3	0.5	447	6670
		4	4	1420	18400

	Dose Normalized C_{max} and AUC_{0-24h} Values for Quinidine, Dextromethorphan and Dextrorphan in Female Rats on Gestation Days 6 and 17 (Groups 2-6)	**Table 3**

Day	Analyte	Group	Normalized C_{max} ng/mL mg/kg/day	Normalized AUC_{0-24h} ng.hour/mL mg/kg/day
Gestation Day 6	Quinidine*	2	18.9	227
		3	15.2	204
		4	18.0	259
		5	22.2	236
	Dextromethorphan	2	4.30	26.0
		3	5.91	25.4
		4	6.23	40.7
		6	11.5	50.4
	Dextrorphan**	2	30.0	534
		3	25.2	427
		4	30.2	410
		6	22.4	374
Gestation Day 17	Quinidine*	2	34.7	390
		3	24.7	391
		4	30.3	384
		5	30.2	451
	Dextromethorphan	2	12.0	61.6
		3	10.5	70.7
		4	13.6	98.7
		6	30.8	95.2
	Dextrorphan**	2	37.0	642
		3	36.7	609
		4	31.4	583
		6	29.8	372

*C_{max} and AUC_{0-24h} were normalized based on 100 mg/kg/day of Quinidine.
**C_{max} and AUC_{0-24h} were normalized based on Dextromethorphan doses.

	Dose Normalized C_{max} and AUC_{0-24h} Values for Quinidine, Dextromethorphan and Dextrorphan in Female Rats on Postnatal Day 16 (Groups 2-4)	**Table 4**

Day	Analyte	Group	Normalized C_{max} ng/mL mg/kg/day	Normalized AUC_{0-24h} ng.hour/mL mg/kg/day
Postnatal Day 16	Quinidine*	2	20.0	156
		3	18.5	173
		4	21.6	238
	Dextromethorphan	2	3.76	29.6
		3	3.95	55.3
		4	5.27	49.3
	Dextrorphan**	2	53.2	852
		3	29.8	445
		4	47.3	613

*C_{max} and AUC_{0-24h} were normalized based on 100 mg/kg/day of Quinidine.
**C_{max} and AUC_{0-24h} were normalized based on Dextromethorphan doses.

Summary: Pre- and post-natal developmental toxicity was evaluated in female rats, administered dextromethorphan and quinidine at oral gavage doses of 0/0, 5/100, 15/100,

and 30/100 (n=24/group), and 0/100 and 50/0 mg/kg/day (n=20/group) dextromethorphan/quinidine, once daily by oral gavage from gestation day (GD) 6 through postnatal day (PND) 20 (the first 4 groups) or on GD 5-17 (quinidine and dextromethorphan alone groups). Salivation was observed in all groups after dosing, and slight reduction in maternal body weights and food consumption in the rats given 50 mg/kg/day dextromethorphan alone. However, the treatment-related toxicity in the maternal rats was insufficient to demonstrate a MTD.

There was a very slight (1 day) treatment-related increase in gestation length at 15/100 and 30/100 mg/kg/day dextromethorphan/quinidine (19 and 18 dams, respectively, compared to 10 and 16 dams in the controls and at 5/100 mg/kg/day, respectively). Treatment-related increased pup mortality was observed during the period from the day of birth through PND 4 (8, 15, 40, and 26 pups found dead at 0, 5/100, 15/100, and 30/100 mg/kg/day dextromethorphan/quinidine, respectively). The pup mortality was due to total loss of pups in one MD dextromethorphan/quinidine litter with loss of 5-6 pups in each of 2 other MD dextromethorphan/quinidine litters, 1-3 pups/litter in the controls, low-dose dextromethorphan/quinidine and remaining MD dextromethorphan/quinidine litters, and 1-4 pups per litter at the HD dextromethorphan/quinidine. There was a slight dose-related increase in postnatal pup body weight reduction, more frequently in the pups born on GD 21 than on GD 22, that persisted until 6-8 weeks after birth. The MD and HD dextromethorphan/quinidine-treated F1 pups showed treatment-related developmental delay, with delayed acquision of the air-righting response (1/2 day delay) and increased spontaneous activity compared to controls. The AUC_{0-24} values for dextromethorphan on GD17 were 308, 1060, 2960, and 4760 ng.h/ml at 5/100, 15/100, 30/100, and 50/0 mg/kg/day dextromethorphan/quinidine, respectively, representing 0.1X, 0.35X, 1X, and1.6X the the approximate clinical AUC_{0-24} value, estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d., respectively. The AUC_{0-24} values for quinidine on GD17 were 38400 (16X, the approximate clinical AUC_{0-24} value, estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d.) - 45100 (19X) ng.h/ml in all quinidine-treated groups. The AUC_{0-24} values for dextrorphan on GD17 were 3210 (0.3X), 9130 (0.9X), 17500 (1.6X), and 18600 (171.7X) ng.h/ml at 5/100, 15/100, 30/100, and 50/0 mg/kg/day dextromethorphan/quinidine, respectively (multiples represent the approximate clinical AUC_{0-24} value, estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d.).

On PND 16, the AUC_{0-24} values (multiples representing approximate clinical AUC_{0-24} value, estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d.) at 5/100, 15/100, and 30/100 mg/kg/day dextromethorphan/quinidine were 15600 (6.5X) - 23800 (10X) ng.h/ml for quinidine across dose levels, 148 (0.05X), 830 (0.3X), and 1480 (0.5X) ng.h/ml for dextromethorphan, respectively, and 4260 (0.4X), 6670 (0.6X), and 18400 (1.7X) ng.h/ml for dextrorphan, respectively. The NOAEL for adverse effects by dextromethorphan in combination with quinidine on pregnancy and pre-natal and post-

natal development were not determined in this study (<5/100 mg/kg/day dextromethorphan/quinidine).

The results of the study on Neurodex effects on prenatal and postnatal development in rats are presented in the following table (reproduced from the original NDA submission):

Table 2.6.7-14 Reproductive and Developmental Toxicity **Test Articles: Dextromethorphan and Quinidine**

Report Title: Dextromethorphan/Quinidine (DMQ): Pre- and post-natal development study in rats, including maternal function		
Design similar to ICH S5A 4.1.2? Yes	**Duration of Dosing:** GD 6 – Postnatal Day 20	**Study Reference:** DMQ-125
Species/Strain: Rat/Sprague-Dawley	**Day of Mating:** GD 0	**Location in CTD:** Section 2.6.6.6
Initial Age: 70-84 days	**Day of C-Section**	
Date of First Dose: 14 September 2003	**(F_0 supplemental groups):** GD 20	
Special Features: None	**(F_1 generation):** GD 14	
No Observed Adverse Effect Level:	**Method of Administration:** Oral Gavage	**GLP Compliance:** Yes
F_0 Females: 30 mg DM/kg/d + 100 mg Q/kg/d	**Vehicle/Formulation:** 1% methylcellulose	
F_1 Males: Not determined	**Litters Culled/Not Culled:** Culled to 1/sex/litter (up to 20 of each sex per group)	
F_1 Females: Not determined		

MAIN STUDY

Daily Dose (mg/kg)	**Control**	**DM5/Q100**	**DM15/Q100**	**DM30/Q100**
F_0 Females				
Toxicokinetics: $AUC_{0\text{-}24h}$ (ng·h/mL)				
Quinidine – Gestation Day 6	–	22700	20400	25900
Quinidine – Gestation Day 17	–	39000	39100	38400
Quinidine – Postnatal Day 16	–	15600	17300	23800
Dextromethorphan – Gestation Day 6	–	130	381	1220
Dextromethorphan – Gestation Day 17	–	308	1060	2960
Dextromethorphan – Postnatal Day 16	–	148	830	1480
Dextrorphan – Gestation Day 6	–	2670	6410	12300
Dextrorphan – Gestation Day 17	–	3210	9130	17500
Dextrorphan – Postnatal Day 16	–	4260	6670	18400
Number Pregnant	24	24	24	24
Number Died or Sacrificed Moribund	0	0	1	0
Clinical Observations (gestation):				
Salivation (postdose)	–	+	+	+
Clinical Observations (lactation):				
Salivation (postdose)	–	+	+	+
Necropsy Observations	–	–	–	–
Gestation Body Weight (%)[†]	392 g	-2	1	-2
Lactation Body Weight (%)[†]	327 g	4*	8**	6**
Gestation Food Consumption (%)[†]	25 g/animal/day	-4	-4	–
Lactation Food Consumption (%)[†]	57 g/animal/day	-4	–	-2
Mean Duration of Gestation (days)	21.4	21.7	21.8**	21.8*
Abnormal Parturition	0	0	0	0

Table 2.6.7-14 Reproductive and Developmental Toxicity Test Articles: Dextromethorphan and Quinidine (continued)

Daily Dose (mg/kg)	Control	DM5/Q100	DM15/Q100	DM30/Q100
F_1 Litters (preweening)				
Number Litters Evaluated	24	24	23	23
Mean Number Pups/Litter	13.6	13.0	13.7	13.3
Mean Number Liveborn Pups/Litter	13.4	12.6	12.8**	13.0
Mean Number stillborn Pups/Litter	0.17	0.38	0.83**	0.35
Postnatal survival to Day 4 (%)	98.8	98.0	92.9**	94.0**
Postnatal survival Day 5 - weening (%)	99.6	100	99.5	99.5
Mean Change in Pup Body Weights – Day 1 to Day 21 (g)	42.1	39.7	39.0*	38.7**
Pup Sex Ratios (% Males)	52.2	51.2	49.8	44.1
Pup Clinical Signs (No. of occurrences/No. of animals)				
Labored breathing	0/0	0/0	0/0	1/1
Poor condition	0/0	2/1	0/0	2/2
Emaciation	0/0	0/0	1/1	0/0
Pup Necropsy Observations	–	–	–	–
F_1 Males (Postweening)				
Number Evaluated Postweening	20	20	20	20
Number Died or Sacrificed Moribund	0	0	0	0
Clinical Observations	–	–	–	–
Necropsy Observations	–	–	–	–
Body Weight Change –Day 53-116 (%)	397 g	3	-1	–
Food Consumption (%)	ND	ND	ND	ND
Skeletal Anomalies	ND	ND	ND	ND
Preputial Separation (average days)	43.0	43.8	43.7	43.8
Sensory Function	–	–	–	–
Open Field Function	–	–	–	–
Motor Activity				
Spontaneous Motor Activity – slight increase	–	–	+	+
Air Righting Response – slightly delayed acquisition	–	–	+	+
Learning and Memory	–	–	–	–
Mean Number of Days Prior to Mating	3.7	2.5	2.5	4.2
Number of Males that Mated	20	20	20	20
Number of Fertile Males	20	20	18	19

Table 2.6.7-14 Reproductive and Developmental Toxicity Test Articles: Dextromethorphan and Quinidine (continued)

Daily Dose (mg/kg)	Control	DM5/Q100	DM15/Q100	DM30/Q100
F_1 Females (postweening)				
Number Evaluated Postweening	20	20	20	20
Number Died or Sacrificed Moribund	0	0	0	0
Clinical Observations	–	–	–	–
Necropsy Observations	–	–	–	–
Premating Body Weight Change (%)	NC	NC	NC	NC
Gestation Body Weight Change (%)	80 g	–	6	-1
Premating Food Consumption (%)	NC	NC	NC	NC
Gestation Food Consumption (%)	ND	ND	ND	ND
Mean Age of Vaginal Patency (days)	32.4	33.0	33.0	32.3
Sensory Function	–	–	–	–
Open Field Function	–	–	–	–
Motor Activity				
Spontaneous Motor Activity – slightly increased	–	–	+	+
Air Righting Response – slightly delayed acquisition	–	–	+	+
Learning and Memory	–	–	–	–
Mean Number of Days Prior to Mating	3.7	2.5	2.5	4.2
Number of Females Sperm Positive	19	20	20	20
Number of Pregnant Females	20	20	18	19
Mean Number Corpora Lutea	18.0	17.4	18.3	18.0
Mean Number Implantations	15.8	15.1	15.9	16.8
Mean % Preimplantation Loss	11.9	12.4	12.0	6.0
F_2 Litters				
Mean Number Live Conceptuses/Litter	15.1	14.4	15.4	15.8
Mean Number Resorptions	3.6	4.9	3.5	6.2
Number of Dead Conceptuses	0	0	0	0
Mean % Postimplantation Loss	0.6	0.7	0.6	1.0
Fetal Body Weights (g)	ND	ND	ND	ND
Fetal Sex Ratios (% males)	ND	ND	ND	ND
Fetal Anomalies	ND	ND	ND	ND

Table 2.6.7-14 Reproductive and Developmental Toxicity Test Articles: Dextromethorphan and Quinidine (continued)

SUPPLEMENTARY STUDY GROUPS		
Duration of Dosing: Gestation day 6 – 17	**Day of Mating:** Gestation Day 0	**Day of C-Section:** Gestation Day 20
Daily Dose (mg/kg)	**0DM/100Q**	**50DM/0Q**
F_0 Females		
Toxicokinetics: AUC (µg·h/mL)		
Quinidine – Gestation Day 6	23600	–
Quinidine – Gestation Day 17	45100	–
Dextromethorphan – Gestation Day 6	–	2520
Dextromethorphan – Gestation Day 17	–	4760
Dextrorphan – Gestation Day 6	–	18700
Dextrorphan – Gestation Day 17	–	18600
Number Mated	20	20
Number Pregnant	20	20
Number Died or Sacrificed Moribund	0	0
Number Aborted or with Total Implant Loss	1	0
Clinical Observations – (No. of Occurrences / No. of Animals)		
Salivation - Day 6 -17	170 / 20	210 / 20
Labored Breathing - Day 0 -20	1 / 1	0 / 0
Necropsy Observations		
Uterus - Abnormal Contents	1	0
Uterus – Placentae	1	0
Kidney – Dilated renal pelvis	1	0
Body Weight at End of Dosing Period (GD 17) (g)	341	337
Food Consumption – Mean Daily Amount GD 6-18 (g)	25	25
Mean Number Corpora Lutea	15.9	15.6
Mean Number Implantations	14.4	13.4
Mean % Preimplantation Loss	9.4	12.5
Litters		
Total Number Litters Evaluated	20	20
Mean Number Live Fetuses	12.9	12.9
Mean Number Resorptions	0.65	0.55
Number Dead Fetuses	15	0
Mean Postimplantation Loss (%)	9.8	4.1

Table 2.6.7-14 Reproductive and Developmental Toxicity Test Articles: Dextromethorphan and Quinidine (continued)

Mean Fetal Body Weight (g)	3.9	3.9
Daily Dose (mg/kg)	**0DM/100Q**	**50DM/0Q**
Fetal Sex Ratios (% males)	43.5	46.4
Fetal Anomalies		
Gross External Examination	–	–
Skeletal Examination	ND	ND
Visceral Examination	ND	ND

DM = dextromethorphan hydrobromide; GD = gestation day; NC = not calculated; ND = not done / not determined; No. = number; Q = quinidine sulfate
* $p < 0.05$; ** $p < 0.01$
– = not present or no difference from control; + = present

LOCAL TOLERANCE

No studies were performed to evaluate Neurodex™ local tolerance

SPECIAL TOXICOLOGY STUDIES

Study title: ***An acute oral neurotoxicity study in rats with dextromethorphan and quinidine (AVP-923)***

Key study findings:

- No treatment-related neuronal lesions, vacuolation, and degeneration suggestive of the "Olney Lesion" in the posterior cingulate and retrosplenial cortices of rats at DM doses from 2-50 mg/kg PO in combination Q at 50 mg/kg PO, at 6 and 24 hours, and 7 days after dosing

- Study validity supported by neurotoxicity characteristic of "Olney Lesion" in rats administered positive control, MK-801
- Toxicokinetic analysis demonstrated adequate exposure of the rats to dextromethorphan, the metabolite dextrorphan, and quinidine

Study no: (b) (4) Study No. 3584.1
Volume # 3**, and page #** 1
Conducting laboratory and location: (b) (4)
Date of study initiation: January 21, 2002
GLP compliance: yes (x) no ( )
QA report: yes (x) no ( )
Drug Dextromethorphan hydrobromide**, Manufacturer Lot No.** DM9912074, **Supplier Lot No.** 00-377**, radiolabel** Not applicable**, and % purity** 99.7% (Certificate of Analysis provided)
Drug Quinidine sulfate**, Manufacturer Lot No**. 9900130, **Supplier Lot No.** 00-376**, radiolabel** Not applicable**, and % purity** 100.1% (Certificate of Analysis provided)
Formulation/vehicle: Test article suspended in 1% Methyl Cellulose ((b) (4), Lot No. 56H0439) in Reverse Osmosis Deionized Water (RODI)

Methods (unique aspects)**:** The rats were housed individually in suspended stainless steel cages in a temperature (65-79°F) and humidity (30-70%) controlled animal facility, with 12-hour light/dark light cycle. The rats were fed PMI Certified Rodent Chow® #5002 (Purina Mills, Inc) *ad libitum*, and were provided drinking water (municipal tap) *ad libitum*. The test article doses were selected to equal or exceed intended clinical doses, and were based on the results of previous toxicology studies showing lethality at doses of 100/50 mg/kg DM/Q and above, with acceptable tolerability at the high dose combination of 50/50 mg/kg DM/Q. The animals were administered vehicle, DM/Q, or MK-801 on Day 0, and were sacrificed at 6 hours, 24 hours, and 7 days post-dose under sodium pentobarbital (50 mg/kg IP) anesthesia. At sacrifice, the animals were perfused (whole body perfusion) with sodium chloride/dextrose/sucrose/calcium chloride and sodium cacodylate (wash, 50 ml), followed by sucrose/paraformaldehyde/sodium cacodylate (fixative, 250 ml), and decapitated. The whole heads were placed in perfusion fixative solution. The brains were removed and hemispheres divided. The right hemispheres were embedded in paraffin, coronal sections were made (5 microns, 9 levels), and the sections were stained with H&E/Flurojade. The left hemispheres were embedded in gelatin matrix, coronal sections were made by freeze cut (40 microns, 9 levels) and the sections were stained with Amino Cupric Silver. The brain sections from the right and left hemispheres were examined, particularly at the levels of cortical layers III and IV of the cingulate and retrosplenial cortices, and photomicrographed.

Dosing:

Species/strain: Sprague Dawley Crl:CD®(SD)IGS BR rats (b) (4))

#/sex/group or time point (main study): 6/sex/dose/timepoint (4/sex/timepoint in the positive controls), see under study design, below
Satellite groups used for toxicokinetics or recovery: None
Age:11 weeks
Weight: 348-463 g males, 221-274 g females
Doses in administered units: See under study design below
Route, form, volume, and infusion rate: Oral by gavage: concentrations DM 0.4, 4, 10 mg/ml at 2, 20, and 50 mg/kg, respectively, and concentrations Q 10 mg/ml for all doses, concentrations MK-801 5 mg/ml, dose volume 5 ml/kg for DM and Q, 0.6 ml/kg for MK-801
Study Design:

Group	No. Males	No. Females	Treatment	DM (mg/kg PO)	Q (mg/kg PO)	MK-801 (mg/kg SC)
1	18	18	1%MC	0	0	0
2	18	18	DM/Q	2	50	0
3	18	18	DM/Q	20	50	0
4	18	18	DM/Q	50	50	0
5	12	12	MK-801	0	0	3
MC = methylcellulose; DM = dextromethorphan hydrobromide; Q = quinidine sulfate						

Observations and times:
Clinical signs: 0.25, 0.5, 1, and 2 hours after dosing, and 2X daily
Body weights: 3 days prior to dosing, only
Food consumption: Not done
Ophthalmoscopy: Not done
EKG: Not done
Hematology: Not done
Clinical chemistry: Not done
Urinalysis: Not done
Gross pathology: Not done
Organs weighed: Not done
Histopathology: As described under Methods, above
Toxicokinetics: Blood samples collected from orbital plexus (1 ml) at 0, 0.5, 1, 2, 6, 12, 24, 48, and 96 hours after dosing
Other: None

Results:
Mortality: No deaths
Clinical signs: DM/Q: transient decrease in activity and increased salivation, not dose-related; MK-801: decreased activity, salivation, tremors, rapid breathing, labored breathing, recumbency, prostration, inability to support itself
Histopathology: No treatment-related microscopic lesions, vacuolation, and degeneration in the posterior cingulate and retrosplenial cortex of control and DM/Q treated rats, indicative of the "Olney Lesion"; small focus of microglial cell infiltration within hypothalamus without cell degeneration at 24 hours after dosing in one rat administered 50/50 mg/kg DM/Q; singular observations in other regions (e.g., mild axon degeneration in the thalamus, etc.) in treated rats

were also observed in controls or were not observed at the high dose combination, and were therefore, not deemed to be treatment-related; neuronal vacuolation in posterior cingulate and retrosplenial cortex at 6 hours post dose, progressing to neuronal degeneration in the MK-801 treated animals

Toxicokinetics: The results of the toxicokinetic evaluation are presented in the following table:

Dose DM/Q (mg/kg)	Sex	Tmax (h)	Cmax (ng/ml)	AUC_{0-t} (ng.h/ml)	AUC_{0-inf} (ng.h/ml)	T1/2 (h)
Dextromethorphan						
2/50	Male	1.99	3.64	2.97	NC	NC
	Female	0.99	13.40	120.26	NC	NC
20/50	Male	0.48	111.30	482.78	NC	NC
	Female	0.98	112.84	630.57	637.01	3.44
50/50	Male	0.98	266.04	864.76	909.95	6.84
	Female	0.98	418.06	1370.26	1758.14	13.81
Dextrorphan						
2/50	Male	12.06	80.47	1145.30	NC	NC
	Female	12.06	96.47	1569.67	NC	NC
20/50	Male	12.01	557.10	10878.97	11183.13	9.00
	Female	11.96	759.41	18228.45	18507	6.43
50/50	Male	23.75	1302.13	39277.17	NC	NC
	Female	0.98	1085.96	33325.05	35991.22	10.67
Quinidine						
2/50	Male	0.99	630	3000	NC	NC
	Female	0.99	1100	5320	6.07	4.30
20/50	Male	0.99	1230	7850	8.63	3.81
	Female	5.97	990	8740	NC	NC
50/50	Male	0.98	870	8280	11.34	11.94
	Female	0.98	1000	9660	10.52	6.61

NC: not calculated; DM/Q: dextromethorphan hydrobromide/quinidine sulfate mixtures

The DM and Q Cmax and Tmax values were higher, and DX Cmax and Tmax were lower in the females than in males. At the dose combinations of 2/50-50/50 DM/Q, the DM Tmax values were 0.48-1.99 hours (not dose-related), Cmax values 3.64-418.06 ng/ml (dose-proportional), and AUC_{0-t} values 2.97-1370.26 ng.h/ml (approximately dose-proportional) in the males and females. DM exposure (Cmax and AUC values) were higher in the females than in the males. The Q Tmax values at the same dose combinations, were 0.98-5.97 hours (0.98-0.99 in all but the mid-dose females), Cmax values 0.63-1.23 mcg/ml, and AUC_{0-t} values 3-9.66 mcg.h/ml. The DM dose-related increase in AUC values for Q suggested accumulation. Q exposure was higher in the females than in the males at all dose combination levels. The DX Tmax values were 0.98-23.75 hours (no difference between the low and mid dose combinations, but extreme variability at the highest dose combination tested), Cmax 80.47-1302.13 ng/ml (less than dose proportional increase), and AUC_{0-t} values 1145.30-39277.17 ng.h/ml (approximately dose-proportional increase). Exposure was higher in the females than in the males at the low and mid-dose combinations, and higher in the males at the high dose combination.

Summary of individual study findings: No treatment-related neuronal lesions, vacuolation, and degeneration suggestive of the "Olney Lesion" were observed in the posterior cingulate and retrosplenial cortices of rats administered dextromethorphan hydrobromide (DM) at doses from 2-50 mg/kg PO in combination with the metabolic inhibitor quinidine (Q) at 50 mg/kg PO, when sampled at 6 and 24 hours, and 7 days after

dosing, under the conditions of this study. A small focus of microglial cell infiltration within hypothalamus without cell degeneration was observed at 24 hours after dosing in one rat administered 50/50 mg/kg DM/Q. Singular observations in other regions (e.g., mild axon degeneration in the thalamus, etc.) in treated rats were also observed in controls, or were not observed at the high dose combination, and were therefore, not deemed to be treatment-related. The validity of the study was supported by findings of neuronal cytoplasmic vacuolation within the retrosplenial cortices of 4/4 males and 2/4 females at 6 hours, shrunken necrotic neurons with eosinophilic cytoplasm within the retrosplenial cortex in 3/4 males and 4/4 females at 24 hours, and neuronal and axonal degeneration in all rats at 7 days after treatment with MK-801, similar to the findings reported in the published literature to be associated with the "Olney Lesion". Toxicokinetic analysis demonstrated adequate exposure of the rats to DM, the metabolite dextrorphan (DX), and Q. The NOAEL for the Olney Lesion by DM in combination with Q was 50/50 mg/kg DM/Q in this study.

SUMMARY AND EVALUATION

The pharmacology and toxicology of the individual marketed drugs, dextromethorphan hydrobromide (DM) and quinidine sulfate (Q) have been previously studied and are well documented. The nonclinical studies conducted for this submission, focused primarily on the potential interactive effects on toxicity when given in combination, on chronic toxicity to support the safety of chronic administration for the indication of treatment of pseudobulbar affect, and on genetic and reproductive toxicology and carcinogenicity of the proposed drug combination.

The results of the non-clinical toxicology studies on Neurodex™ indicated that the target organs toxicity were the central nervous system (CNS), kidneys, and liver. Adverse CNS effects attributed to the dextromethorphan component, were demonstrated in mice, rats, and dogs. These species showed high-dose dextromethorphan induced CNS depression, hypoactivity or hyperactivity, lethargy, tremors, and ataxia, and at the highest doses, convulsions in rats and dogs. The results of the study on HERG current in transfected HEK293 cells suggested a potential for delayed cardiac repolarization and cardiac arrhythmias at high plasma concentrations, attributable to the quinidine component. Renal toxicity was observed in rats and included increased urinary volume and relative kidney weights, with tubular dilation, papillary mineralization, and hyaline droplets. Hepatotoxicity was observed after 4 and 26 weeks of daily administration in rats, and included increased liver enzymes (ALP, AST), absolute and relative liver weights, and centrilobular hypertrophy. The changes in liver enzymes and weights were without relationship to dose level, suggesting a quinidine effect because the dose of quinidine was constant across dextromethorphan doses. On the other hand, there was a dextromethorphan-related increase in incidence of centrilobular hypertrophy in the males and females at 4 weeks and at 26 weeks, and therefore dextromethorphan is likely responsible for the hepatotoxicity observed in that study. Dextromethorphan increased bronchoconstriction by increasing lung resistance and decreasing dynamic lung compliance in guinea pigs, in a study reported in the published literature. The incidence and severity of toxicity by dextromethorphan was generally increased with dose and duration of treatment.

Primary and Secondary Pharmacodynamics: Dextromethorphan has agonist activity at the sigma$_1$-opioid receptor and uncompetitive antagonist activity at the N-methyl-D-aspartate (NMDA) receptor, which decreases glutamate excitatory activity in the central nervous system. Quinidine inhibits sodium and cardiac potassium currents, decreasing the Vmax for sodium influx and excitability, conduction velocity, and contractility, and increasing the duration of cardiac cell action potentials. Quinidine and its metabolites, dihydroquinidine, 3-hydroxyquinidine, O-desmethylquinidine and quinidine-N-oxide competitively inhibit the cytochrome P450 enzyme CYP2D6, responsible for metabolism of dextromethorphan to dextrorphan (DX). The Sponsor proposed that modulation of glutamate excitatory activity may reduce the incidence of involuntary emotional expressions, or pseudobulbar affect, in patients with amyotrophic lateral sclerosis, multiple sclerosis and other neurological disorders. Early clinical studies showed that dextromethorphan decreased pseudobulbar affect, inappropriate or pathological emotional outbursts of laughing and crying, in some patients with amyotrophic lateral sclerosis, stroke, Alzheimer's disease, and multiple sclerosis. Early clinical studies showed that dextromethorphan decreased pseudobulbar affect, inappropriate or pathological emotional outbursts of laughing and crying, in some patients with amyotrophic lateral sclerosis, stroke, Alzheimer's disease, and multiple sclerosis. Dextrorphan is pharmacologically active at 4 times the parent drug concentration. The rationale for co-administration of quinidine with dextromethorphan is to increase dextromethorphan plasma levels and duration of action by inhibiting its metabolism.

Dextromethorphan inhibited Ca2+ uptake via the NMDA Ca2+ channel in neuronal PC12 cells *in vitro* (IC50 = 13 mcg/ml), and showed inhibition of glutamate-induced neurotoxicity *in vivo*. Dextromethorphan also increased serotonin release by binding 5-HT$_{1B/D}$ receptors (30% at 10 mcM in rat solitary tract nucleus in brain stem slices).

Safety Pharmacology: No safety pharmacology studies on dextromethorphan and quinidine, given individually or in combination, were conducted for this submission. Central nervous system (CNS) toxicity was observed in the toxicology studies conducted for the NDA, and included CNS depression in mice, rats and dogs, with altered activity levels in mice, lethargy and convulsions in rats, and ataxia, hyper-excitability and tonic-clonic convulsions in dogs administered high doses of oral dextromethorphan. Oral quinidine in high doses induced hypoactivity and convulsions in mice. There was a dose-related increase in severity and incidence of CNS effects when dextromethorphan and quinidine were given in combination. The results of a study on HERG current in transfected HEK293 cells showed concentration-dependent inhibition by the dextromethorphan:quinidine combination that appeared to be quinidine-related, suggesting a potential for delayed cardiac repolarization and cardiac arrhythmias at high plasma Neurodex™ concentrations. Treatment-related changes in renal function were observed in the 26-week toxicity study in rats (increased urinary volume and increased relative kidney weights with slight tubular dilation). The results of a study reported in the published literature (Salonen, 1988) on lung mechanics in anesthetized guinea pigs, showed that dextromethorphan significantly increased bronchoconstriction (increased

lung resistance and decreased dynamic lung compliance) compared to controls, and induced bradycardia and hypotension at intravenous doses of 10 and 15 mg/kg.

Pharmacokinetics:

Absorption: Rapid oral absorption (Tmax 15 min – 1 hr) of quinidine and dextromethorphan was demonstrated in all species studied (mice, rats and dogs). When given together, quinidine increased systemic dextromethorphan exposure and decreased exposure to the dextromethorphan metabolite dextrorphan in both the males and females in all species evaluated. In mice, oral quinidine increased dextromethorphan (oral route) $AUC_{0\text{-}inf}$ and Cmax at all doses tested from 30-120 mg/kg, with a maximal effect on dextromethorphan exposure at the dose of 30 mg/kg quinidine, suggesting saturation of quinidine inhibitory effects on CYP2D activity. In Sprague-Dawley rats, oral quinidine at 2 to100 mg/kg increased dextromethorphan (oral, 20 mg/kg) $AUC_{0\text{-}t}$ by 1.3X to 4.1 X, and at 2 to 50 mg/kg increased the dextromethorphan (oral, 50 mg/kg) $AUC_{0\text{-}t}$ by 1.5X to 2.2X, compared to dextromethorphan alone, in Sprague Dawley rats. Systemic exposure to both dextromethorphan and quinidine was greater, and exposure to dextrorphan was lower under fasted than under fed conditions in rats.

Distribution: No information on Neurodex distribution was submitted. The volume of distribution of dextromethorphan in dogs was reported to be 5-6.4 L/kg ((b) (4)). Dextromethorphan is approximately 50%-60% bound to rat plasma proteins *in vitro* at concentrations of 0.5-500 mcM.

Metabolism: No metabolism studies were conducted in animals by the Sponsor and no data on nonclinical metabolism of dextromethorphan and/or quinidine were submitted for this NDA submission. Dextromethorphan is metabolized in humans by hepatic O-demethylation by CYP2D6 to dextrorphan, and by CYP3A4 and N-demethylation to 3-methoxymorphinan. Minor metabolites (<15% dose) include d-methoxymorphinane and d-hydroxymorphinane. Dextrorphan and 3-methoxymorphinan are demethylated to 3-hydroxymorphinan, which undergoes glucuronidation before excretion. Approximately 5%-10% of the human population are poor CPY2D6 metabolizers, with resulting plasma dextromethorphan levels of 10 ng/ml at 4 hours and 5 ng/ml at 24 hours after oral administration at 30 mg. In intermediate metabolizers (approximately 6.8% population), plasma dextromethorphan was 10-20 ng/ml at 4 hours and <5 ng/ml at 24 ours after oral administration of dextromethorphan at 30 mg. The plasma dextromethorphan level after an oral dose at 30 mg in extensive metabolizers is <5 ng/ml at 4 hours post-dose. Formation of CYP2D6 products is similar in mouse and human liver microsomes, and therefore it is assumed that dextromethorphan metabolism will be similar in mice and humans. Quinidine inhibition of dextromethorphan metabolism by interaction with cytochrome P450 CYP2D6 increased dextromethorphan plasma exposure in all species.

Quinidine is metabolized in rodents and humans by cytochrome P450 (CYP)3A4. Quinidine metabolites include 3-hydroxy-quinidine (10%), 2'-quinidinone (10%), quinidine-N-oxide (1%), quinidine 10,11-dihydroliol (3%), O-desmethyl-quinidine (1%-

2%), and 2'-Oxoquinidione. The 3-hydroxy-quinidine, quinidine-N-oxide, and 2'oxoquinidione metabolites are active.

Excretion: Excretion studies were not conducted for this NDA. In humans, dextromethorphan is excreted predominantly in the urine in the form of parent drug (0-11%) and demethylated, conjugated morphinan compounds, with the ratio depending on the metabolism phenotype. The plasma half life of dextromethorphan is 1.4-3.9 hours and the half-life of dextrorphan is 2.5 hours after single dose dextromethorphan at 2.5 mg in humans. Approximately 20% quinidine is excreted unchanged in urine, and clearance is 4.7 ± 1.8 mL/min/kg. Most oral quinidine is eliminated by CYP3A4 enzyme metabolism, and first pass metabolic effect. Quinidine clearance is increased with decreasing urinary pH. The elimination half-life is 3-16 hours (mean T1/2 = 6-8 hours in adults and 3-4 hours in children). The half-life of the major metabolite 3-hydroxy-quinidine is 6.1-10 hours.

Single Dose Toxicity: Mouse: Dose-related mortality was observed in a single dose oral toxicology study in mice (3/sex/dose, study DMQ-116), with deaths in 1 male at 200 mg/kg dextromethorphan + 50 mg/kg quinidine within 30 minutes of dosing, and in 3 males at 200 mg/kg dextromethorphan + 100 mg/kg quinidine within 120 minutes of dosing. In the female mice, dose-related mortality was observed with deaths in 1 female at 20 mg/kg dextromethorphan + 10 mg/kg quinidine, and in all other females at the higher dose combinations, within several hours after dosing.

Rat: In a single dose oral toxicology study in rats (3/sex/dose, study DMQ-101) given dextromethorphan and quinidine by oral gavage at doses of 0, 2, 20, 50, 100, and 200 mg/kg dextromethorphan alone, 0, 2, 20, 50, and 100 mg/kg quinidine alone, or both drugs combined at 2/2, 20/2, 20/20, 20/100, 50/2, 50/20, 50/50, and 100/50 mg/kg dextromethorphan/quinidine, 1 female died and the clinical signs were lethargy and convulsions at the high dose of 200 mg/kg dextromethorphan alone. The NOAEL for dextromethorphan alone was 100 mg/kg. There were no effects of quinidine alone. When dextromethorphan and quinidine were administered in combination, there were deaths in 1/3 males at 20/100 mg/kg, 1/3 females at 50/20 mg/kg, and 2/3 females and 1/3 males at 100/50 mg/kg. Treatment-related clinical signs were decreased locomotor activity, lethargy, and hindpaw swelling at 20/100, 50/20, and 100/50 mg/kg dextromethorphan/quinidine. The pharmacokinetic analysis showed increased exposure (Cmax and AUC) to dextromethorphan, but no change in exposure to dextrorphan) with quinidine co-administration. Exposure to dextromethorphan and dextrorphan were higher in females than in males with quinidine co-administration.

The treatment-related clinical signs in a single dose neurotoxicity and TK study in rats (DMQ-106) were salivation and decreased activity at doses of 2/50-50/50 mg/kg dextromethorphan/quinidine.

Dog: Acute oral dextromethorphan toxicity was evaluated in Beagle dogs given by oral gavage doses of up to 34.3 mg/kg (study DMQ-102). There were no spontaneous deaths, but several dogs were sacrificed *in extremis* (1 male and 1 female each at 13.4, 24, and 34.3 mg/kg), due to severe clinical signs of toxicity. Treatment-related weight loss and

reduced food consumption were observed, and the clinical signs were limb stiffness, and abnormal blinking. Higher doses produced weakness, spasmodic head movements, and tremors, and convulsions were observed at the highest dose of 34.3 mg/kg.

In a non-GLP single dose (10 mg/kg) oral toxicity study conducted in 12 Beagle dogs to identify poor and extensive dextromethorphan metabolizers (n=12, study DMQ-100), the clinical signs of toxicity were central nervous system depression, ataxia, and vomiting during the first hour after dosing, followed by hyper-excitability, muscular rigidity, vomiting and tonic-clonic convulsions after the first post-dose hour. Deaths were observed in 4 dogs at 3 hours after dosing, and all but 2 remaining dogs were euthanized at 4 hours after dosing. The dextromethorphan Cmax was 47.23-2478.65 ng/ml (0.4X-19X the clinical Cmax at the proposed dose of 30/30 mg dextromethorphan/quinidine b.i.d.), and the dextrorphan Cmax was 77.54-1104.9 ng/ml (0.7X-10X the clinical Cmax at the proposed dose of 30/30 mg dextromethorphan/quinidine b.i.d.).

A summary of single dose studies conducted to evaluate acute Neurodex™ toxicity is presented in the following table:

Summary of Single Dose Toxicology Studies on Neurodex™

Species/Strain	Test Article Dose and Route (mg/kg)*	Lethality *	Treatment-Related Clinical signs*	Reference
Mouse	DM (20 – 200 mg/kg) + Q (10-200 mg/kg) PO (gavage)	100% lethal at 200/100 mg/kg DM/Q and in F at 200/0 mg/kg DM/Q, Lethal in 1/3 mice at 200/50 mg/kg DM/Q	Not reported	DMQ-116
Mouse (range-finding for Micronucleus assay)	DM (125-600 mg/kg PO) alone	100% lethal at 500-600 mg/kg	250 mg/kg: Underactivity, flattened posture, abnormal gait, fast/irregular respiration, uncoordinated movements; 125 mg/kg: abnormal gait, overactivity, fast/irregular respiration, uncoordinated movements	DMQ-111
Mouse (range-finding for Micronucleus assay)	Q (500-800 mg/kg PO) alone	Lethal in 1M at 800 and 1F at 700 mg/kg	≥700 mg/kg: convulsions, reddened skin ≥600 mg/kg: flattened posture, abnormal gait, fasciculations, partially closed eyelids ≥500 mg/kg: underactivity, irregular respiration	DMQ-114
Mouse	DM (PO)	LD50 165 mg/kg	Pronation, motor impairment, increased muscle tone, tremors, respiratory distress, convulsions, coma	Review of published studies in Eddy et al, 1969
Rat	DM (PO)	350 mg/kg		
Dog	DM (IV) DM (IV) DM (SC)	MLD 39 mg/kg LD50 10 mg/kg LD50>20 mg/kg		
Mouse	Q (IP) Q (PO)	562 mcmol/kg 535 mg/kg	- -	Published literature reports
Rat	Q (IV) Q (PO)	23 mg/kg 263 mg/kg	- -	Published literature reports

Rat (n=3/sex/dose)	DM (0-200 mg/kg) + Q (0-100 mg/kg) PO (gavage)	Deaths in all M & F at 200 mg/kg DM alone, 1/3M&2/3F at 100/50 mg/kg DM/Q, 1/3F at 50/20 mg/kg DM/Q, 1/6 at 50 mg/kg Q alone	Convulsions, lethargy, coma at 200 mg/kg DM +/- Q; ↓ mobility, lethargy, tremors, hind leg swelling at 100/50 mg/kg DM/Q; Lethargy, ↓ motor activity at 50/20, 50/50, 100/50, and 200/0 mg/kg DM/Q NOAEL 100 mg/kg DM alone, 100 mg/kg Q alone, 20/50 mg/kg DM/Q	DMQ-101
Dog (n=12)	DM alone: 10 mg/kg (metabolism study)	4 dogs at 3 hours found dead, all remaining dogs except 2 sacrificed at 4 hours	CNS depression, ataxia, vomiting, hyper-excitability, muscular rigidity, tonic-clonic convulsions	DMQ-100

*DM = dextromethorphan, Q = quinidine, M = male, F = female, MLD = minimum lethal dose, LD50 = lethal dose 50, PO = oral, IV = intravenous, SC = subcutaneous, NOAEL = no adverse effect dose

Repeated Dose Toxicity:

Mouse: Repeated dose toxicity by Neurodex in mice was predominantly due to the dextromethorphan component, and was enhanced by quinidine and by increasing duration of treatment. CB6F1-nonTg.ras H2 mice (5/sex/dose) given dextromethorphan at 0, and 200 mg/kg/day alone, and at 0 and 50-200 mg/kg/day in combination with 50 mg/kg/day quinidine by oral gavage for 5 consecutive days showed mortality at the highest dextromethorphan dose (4 deaths at 200 mg/kg/day dextromethorphan alone and 5 deaths at 200/50 mg/kg/day dextromethorphan/quinidine). The treatment-related clinical signs, noted at the highest dextromethorphan dose (200 mg/kg) with and without quinidine, were ataxia and tremors. There were no adverse effects in male and female Tg.rasH2 mice administered quinidine at 100 mg/kg/day alone and in combination with 100 mg/kg dextromethorphan by oral gavage for 14 days in a dose range-finding toxicology study (DMQ-127) to determine the MTD for a 26-Week carcinogenicity evaluation. However, the results of the 28-day dose range-finding study (DMQ-118) in CB6F1-nonTg ras H2 mice (10/sex/dose, 0, 75, 125, 150, and 175 mg/kg/day dextromethorphan in combination with quinidine at 0 and 50 mg/kg/day by oral gavage) showed deaths in 2 males and 1 female in the mid dose combination groups, 2 males in the high dose combination group, and 1 male given 175 mg/kg/day dextromethorphan alone. Body weights were reduced 9%-10% in the females at 150-175 mg/kg/day dextromethorphan in combination with 50 mg/kg/day quinidine, and body weight gains were reduced in the males (146%) and females (116%) at 175 mg/kg/day dextromethorphan alone, and in the females at 50 mg/kg/day quinidine alone (105%), 150 mg/kg/day dextromethorphan (129%) and 175 mg/kg/day dextromethorphan (140%) with 50 mg/kg/day quinidine. Food consumption was also reduced in these groups. The males showed decreased absolute and relative thymus weights and decreased absolute heart weights, without corresponding microscopic findings, at the higher dose combinations.

Rat: Unlike the results observed in mice, the treatment-related toxicity in the rat toxicology studies appeared to be related to the quinidine component, due to absence of a dose response in severity of the toxicity across dextromethorphan doses in combination with the fixed quinidine doses in each study. Also, treatment-related clinical signs were observed in all quinidine-treated rats in the 2-week study, with and without

dextromethorphan co-administration. The treatment-related toxicity observed in the rat studies clearly increased with quinidine dose across studies, and also increased as a function of duration of dosing. However, the dextromethorphan component appeared to potentiate quinidine toxic effects; there was an increase in duration of clinical signs with increased dextromethorphan dose in the rats given quinidine at a constant dose, and The main target organs of toxicity by the dextromethorphan/quinidine combination were the liver and kidneys in both the male and female rats.

In a 14-day repeated dose oral toxicity study in Sprague-Dawley rats (6/sexdose at 0, 5, 10, 20, and 50 mg/kg/day dextromethorphan in combination with quinidine at 0 and 50 mg/kg/day), post-dose salivation was observed at all combination drug doses from 5/50 to 50/50 mg/kg/day dextromethorphan /quinidine, with a dose-related increase in number of days the sign was observed. Mean relative kidney weights (% body weight) were decreased 11% in the low (10/50 mg/kg/day dextromethorphan /quinidine) and high dose (50/50 mg/kg/day dextromethorphan /quinidine) females.

Higher oral gavage doses (0, 50, and 100 mg/kg/day dextromethorphan in combination with 0 and 100 mg/kg/day quinidine) administered to Sprague Dawley rats (6/sex/group) in a 2-week oral toxicity study resulted in treatment-related clinical signs of toxicity, that included salivation in the rats that received quinidine with and without dextromethorphan, and reduced activity, lethargy, ataxia, piloerection, and hypothermia in the high dose combination groups (100/100 mg/kg/day dextromethorphan /quinidine), with greater severity in the females than in the males. Body weight gains were reduced in the high dose combination females.

Neurodex™ administration for 4 and 26 weeks in male and female Sprague-Dawley rats (10/sex/dose in the 4-week evaluation, 15/sex/dose in the 26-week evaluation, 6/sex/dose TK evaluation, and 5/sex/dose in the 4-week recovery evaluation), at doses of 0, 5, 20, and 50 mg/kg/day dextromethorphan in combination with quinidine at 0 and 100 mg/kg/day by oral gavage) resulted in increased treatment-related toxicity compared to the adverse effects observed in the studies of shorter duration. Treatment-related salivation, lasting 45 minutes after dosing, and sporadic increases in food consumption in the treated females from Weeks 3-26 of dosing, were observed. In the clinical chemistry analyses, there were slight treatment-related increases in Ca2+, K+, alkaline phosphatase, and aspartate aminotransferase, and slightly decreased Na+ at all dose combinations compared to controls, without dose-relationships in incidence or severity. Urine volume was increased in the treated males and females, and specific gravity was decreased in the females in all dose groups compared to controls, without a relationship to dose. Treatment-related organ weight changes in the 26-week study included increased absolute (15%-34%) and relative (12%-29%) liver weights at all doses (without dose-relationship), increased absolute (10%-16%) kidney weights (at all doses without dose-relationship in the treated females), increased absolute (11%-24%) and relative (5%-17%) adrenal gland weights (dose related in the females), and decreased absolute and relative epididymides weights (11%) in the high dose males. The histopathology results showed minimal to slight hypertrophy in the liver, kidney pelvic dilation kidney papillary mineralization and cortical mineralization, kidney hyaline droplets, and inflammation of

the prostate in the treated males at week 4, but not after 26 weeks of treatment. In the females, minimal to slight dose-related centrilobular hypertrophy in the liver, transitional cellular hyperplasia in the kidneys, tubular dilatation in the kidneys and colloid decrease in the thyroid glands were observed during Week 4. At the end of the 26-week treatment period, inflammation of the prostate was found in the males given 20 and 50 mg/kg/day dextromethorphan. The treated females showed increased minimal to slight colloid decrease in the thyroids. There were no treatment-related histopathologic abnormalities after the 4-week recovery period.

Rabbit: Dextromethorphan and quinidine in combination was less toxic in a study in rabbits than the observations showed in the rat studies. A 10-day oral gavage toxicity study was conducted in rabbits (3 females/dose, 0, 50, and 100 mg/kg/day dextromethorphan with 0, 50, and 100 mg/kg/day quinidine). The treatment-related effects were observed at the 100/100 mg/kg/day dextromethorphan/quinidine level only, and included increased respiration rate for 1 hour and reduced food consumption (60% compared to controls).

Dog: Dextromethorphan toxicity was observed in a repeated dose oral toxicity study in beagle dogs given 17 sequentially increasing doses from 0.3-34.3 mg/kg/day for up to 42 days (dose increases every 2 days with a washout period on Days 22-29, 2 dogs), 10-24 mg/kg/day for 4 days (2 dogs), or 13.4 mg/kg/day for 14 consecutive days (2 dogs). The dogs were sacrificed *in extremis* after 15 days at 13.4 mg/kg/day, after 4 days at 24 mg/kg/day, and after 12 and 43 days at the 34.3 mg/kg/day dose. The lower dextromethorphan doses produced hot/reddened abdomen and inguinal area, reddish oral/ocular membranes and inner pinna, and nasal discharges. Weight loss and reduced food consumption were observed at 24 mg/kg/day. The clinical signs of toxicity, at oral doses of 27.4 mg/kg and above, were limb stiffness, abnormal blinking, and at higher doses weakness, spasmodic head movements, and tremors. Convulsions were observed at the highest dose of 34.3 mg/kg PO.

Quinidine is known to be associated with development of thrombocytopenia in clinical use, and is attributed to platelet surface binding of quinidine resulting in autoantibody production and platelet lysis (Mitchell JA, *et al*., 1990, Drug Safety 5:168-78). There were no effects on platelet levels by Neurodex™ in the clinical pathology evaluations in the repeated dose toxicology studies in mice at quinidine doses of up to 14 times the proposed clinical dose for 26 weeks and in rats at up to 16 times the clinical dose for 2-26 weeks (clinical pathology examinations not conducted in the 1-year interim study in rats and in the 42-day study in dogs).

The repeated dose toxicity study results are summarized in the following table:

Summary of Repeated Dose Toxicology Studies on Neurodex™*

Species	Neurodex Dose (mg/kg/d PO DM/Q)	Duration	Mortality	Clinical Signs	Clinical Pathology	Organ Wts., Pathology: Gross & Microscopic	NOAEL (mg/kg/d) (multiple of MRHD)	Reference (Study #)
Mouse (CByB6F1) (n=5/sex/dose)	0/0, 200/0, 200/50, 100/50, 50/50, 150/50, 0/50 (gavage)	5-d range finding	200/0:2M,2F 200/50:1N,3F	Ataxia, & tremors (200/0, 200/50)	Not done	Not done	150/50 DM/Q (DM:12X and Q: 4X, mg/m^2 basis)	DMQ-118
Mouse (CByB6F1) (n=10/sex/dose)	0/0, 75/50, 125/50, 150/50, 175/50, 175/0, & 0/50 (gavage)	28-d (dose selection for CA)	125/50: 2M 150/50: 1F 175/50: 2M 175/0: 1M	↓BW, BWG, food cons	No treatment-related effects	↓thymus wts, heart wts, in M w/o microscopic correlates	0/50, 75/50 (DM:6X and Q: 4X, mg/m^2 basis)	DMQ-118
Mouse (CByB6F1) (n=25/sex/dose)	25/50, 50/50, 100/100, 100/0, 0/100 (gavage)	26-wk (CA)	0/0:1M,1F 25/50:2M,2F 50/50:2M,1F 100/100:1F 100/0:1M,1F 0/100:2M,3F	Thin appearance, ↓BW in M,F at 100/100, ↓food cons at 100/0, 100/100	Not done	↓heart, brain liver weights at 100/100, 100/0, ↓liver weights at 0/100, ↓ kidney weights at 50/50 and 100/0	50/100 (DM:4X, Q:8X, mg/m^2 basis)	DMQ-119
Rat (SD) (n=6)	DM (0, 50, 100 mg/kg/d) with and without Q (100 mg/kg/d)	2-wk (dose selection for reprotox)	No mortality	Salivation (100 mg/kg/d Q w/wo 50&100 mg/kg/d DM); reduced activity, lethargy, ataxia, piloerection, hypothermia, ↓ BWG (F) (100/100);	Not done	Not done	DM: 50 mg/kg/d (8X, mg/m^2 basis)	DMQ-122
Rat (SD) (n=6/sex/dose)	DM: 0, 5, 10, 20, 50 mg/kg/d with Q: 0, 100 mg/kg/d	14-d (dose selection for neurotox study)	No mortality	Salivation (all DM doses with 50 mg/kg/d Q);	Not done	↓rel kidney wts (10%, 10/50, 50/50)	Not determined	DMQ-105
Rat (SD) (n=10/sex/dose)	0/0, 5/100, 20/100, 50/100 (gavage)	4-wk (interim evaluation for 26-wk study)	(4-wk interim evaluation for the 26-wk study): 5/100: 1M, 20/50:2M	Dose-related salivation; convulsions (20/100:1F)	↑urine volume (M&F all doses); ↓specific gravity (F at all doses)	All DM doses: ↑abs&rel liver wts (no dose-relationship, Q effect), centrilobular hypertrophy (M&F, dose related), kidney pelvic dilation (M,dose related), papillary mineralization, hyaline droplets (M, dose related)	Not determined	DMQ-103
Rat (SD) (n=15/sex/dose main, 6/sex/dose TK, 5/sex/dose recovery)	0/0, 5/100, 20/100, 50/100 (gavage)	26-wk	Final: 5/100: 3M 20/50:3M,1F No HD deaths	Salivation (all doses); convulsions (5/100:1F; 20/100:1F, 50/100:1F)	↑RBC, Ca2+, ALP, AST, & ↓Na+, (all treated); ↓APTT(treated M); ↑urine volume (M&F all doses); ↓specific gravity (F at all doses)	↑abs&rel liver wts (no dose-relationship, Q effect, not reversible), ↑abs kidney (F, reversible), ↑abs&rel adrenal (F, not reversible at HD) wts, ↓ abs &relepididymides (HDM, reversible); centrilobular hypertrophy in liver (M&F, dose related), prostate inflammation(MD,HD), kidney	NOAEL Not determined LOAEL 5/100 for histopathology effects in liver, kidneys DM: approx 1X the 30/30 clinical dose, (mg/m2 basis)	DMQ-103

						cortical mineralization HDM)&hyaline droplets (MDM&HDM) &tubule dilatation(HDM &F), transitional cell hyperplasia (HDF); colloid↓ in thyroid (dose-related, F),		
Rat (SD) (n=60/sex/group)	0/0, 5/100, 20/100, 50/100, 50/0, 0/100 (gavage)	1-yr (interim report for 2-y CA study)	(week 57 cumulative) 0/0:2M,2F 5/100:3M,5F 20/100:7M,5F 50/100:11M, 11F 50/0:8M,9F 0/100:5M,8F	Salivation at 100 mg/kg/d Q with and without DM, ↓BWG, DM dose-related in M	Not done	To be reported in the final study report	To be determined at 2-yr	DMQ-120
Rabbit (New Zealand) (n=3F/dose)	0/0, 50/0, 50/100, 100/100, 0/50, 0/100 (gavage)	14-d (dose finding for reprotox)	No mortality	↑respiration rate (100/100) No BW effects, ↓food consumption (100/100)	Not done	No treatment-related effects	50/100 mg/kg/d DM/Q (DM:16X, Q: 32X, mg/m^2 basis)	DMQ-121
Dog (n=3/sex/dose)	DM alone at 0.30.6, 1.2, 2.4, 4.8, 7.2, 8.4, 9.6, 10, 10.8, 12, 13.2, 17.1, 20.6, 27.4, and 34.3 mg/kg, escalating dose paradigm, increased every 3 days	42-d	1M and 1F each sacrificed in extremis at 13.4, 24,and 34.3 mg/kg	↓BW and food cons at ≥24 mg/kg, limb stiffness, abnormal blinking at ≥27.4 mg/kg, weakness, spasmodic head movements, tremors and convulsions at 24.3 mg/kg	Not done	No treatment-related effects on organ weights, gross pathology (histopathology not done)	12 mg/kg (DM: 6.5X)	DMQ-102

*DM = dextromethorphan, Q = quinidine, SD = Sprague Dawley, d = day, wk = week, m = month, M = male, F = female, HD = high dose, BW = body weight, BWG = body weight gain, cons = consumption, PO = oral, sl = slight, rel = relative, wt = weight, NOAEL = no adverse effect dose, MRHD = maximum recommended human dose of 30/30 mg/day b.i.d. DM/Q, CA = carcinogenicity, reprotox = reprotoxicity

Genetic Toxicology: There was no evidence of mutagenicity by dextromethorphan hydrobromide in the Ames test at up to 5000 mcg/plate with and without metabolic activation with S9, and no evidence of clastogenicity *in vivo* in the mouse micronucleus test at up to 250 mg/kg PO, and *in vitro* in the mammalian chromosome aberration test in human lymphocytes at up to 400 mcg/ml with and without S9 mix. However, dextromethorphan increased polyploidy metaphase figures at the highest concentration (400 mcg/ml) in human lymphocytes in the presence of S9 mix in the 3-hour treatment, when compared to DMSO solvent control.

Quinidine sulphate was negative for mutagenicity in the Ames test at up to 5000 mcg/plate with and without metabolic activation, and for clastogenicity *in vivo*, in the mouse micronucleus test at up to 700 mg/kg PO in the male mice and 500 mg/kg PO in the female mice at 24 and 48 hours after dosing. However, quinidine was equivocal for clastogenicity in the chromosome aberration test in human lymphocytes in the presence of metabolic activation with S9, with positive results at 600 and 800 mcg/ml but not at 700 mcg/ml, and thus demonstrating no clear dose-response effect. Quinidine increased the numbers of cells with aberrations including and excluding gaps, and increased the

numbers of polyploidy metaphase figures with (at 400-800 mcg/ml, highest concentration tested at 3 hours, and at 25-75 mcg/ml, all doses tested, at 20 hours continuous exposure) and without (at 500 mcg/ml at 3 hours exposure) S9 metabolic activation.

Dextromethorphan hydrobromide and quinidine sulphate combined in a 1:1 concentration ratio was negative for clastogenicity *in vitro*, in the mammalian chromosome aberration test in human peripheral blood lymphocytes at concentrations of up to those limited by cytotoxicity (350 mcg/ml with and without S9 for 4 hours of exposure, and 31.3 mcg/ml each without S9 for 20 hours continuous treatment).

The results of the genetic toxicology evaluation are presented in the following table:

Results of Genotoxicity Studies on Neurodex™, Dextromethorphan, and Quinidine*

Test	Test Article	Concentrations/Doses	Results	Reference
Ames Test	DM +S9 DM – S9	50-5000 mcg/plate 50-5000 mcg/plate	Negative Negative	DMQ-112
Ames Test	Q + S9 Q – S9	50-5000 mcg/plate 50-5000 mcg/plate	Negative Negative	DMQ-109
Mouse Micronucleus Test (*in vivo*, in CD-1 mice)	DM: 24 and 28 h	62.5, 125, and 250 mg/kg PO (gavage)	Negative	DMQ-114
Mouse Micronucleus Test (*in vivo*, in CD-1 mice)	Q: 24 and 28 h	175, 350, and 700 mg/kg PO (gavage)	Negative	DMQ-111
Chromosome Aberration Test in Human Lymphocytes	DM + S9: 3h (test 1) DM + S9: 3h (test 2) DM – S9: 3h (test 1) DM – S9: 20h (test 2)	100, 300, 400 mcg/ml 200, 400, 500 mcg/ml 50, 200, 300 mcg/ml 20, 60, 100 mcg/ml	Negative (however, ↑polyploid metaphase figures at 400) Negative Negative Negative	DMQ-113
Chromosome Aberration Test in Human Lymphocytes	Q +S9: 3h (test 1) Q + S9: 3h (test 2) Q – S9: 3h (test 1) Q – S9: 20h (test 2)	600, 700, 800 mcg/ml 400, 600, 700 mcg/ml 125, 250, 500 mcg/ml 25, 50, 75 mcg/ml	Positive at 800 (equivocal, ↑polyploid metaphase figures at 800) Positive at 600 only (equivocal, ↑polyploid metaphase figures at 400&600 only) Negative (↑polyploid metaphase figures at 500) Negative (↑polyploid metaphase figures at all concentrations)	DMQ-110
Chromosome Aberration Test in Human Lymphocytes	DM:Q +S9:4h (test1) DM:Q-S9:4h(test1) DM:Q-S9:20h(test2)	DM:Q 1:1 dose ratio 125, 250, 350 mcg/ml 125, 250, 350 mcg/ml 7.8, 15.65 , 31.3mcg/ml	Negative Negative Negative	DMQ-115

*DM = Dextromethorphan, Q = quinidine,

Carcinogenicity: There were no statistically significant treatment-related increases in neoplastic lesions in the male and female Tg.rasH2 mice given oral gavage doses of up to 100 mg/kg/day dextromethorphan with and without 100 mg/kg/day quinidine sulfate, and in the mice given quinidine alone at 100 mg/kg/day. The positive control (urethane) treated mice showed high incidences of pulmonary tumors and hemangiosarcomas in the spleen. The results of the Agency statistical evaluation of the histopathology findings concurred with those of the Sponsor.

Reproductive Toxicology:

Fertility and Early Embryonic Development: In a study on fertility and early embryonic development, pregnant female rats (22/dose) were administered dextromethorphan/quinidine by oral gavage at the dose combination levels of 0/0, 5/100, 15/100, and 50/100 mg/kg/day, from 2 weeks before mating through gestation day 7 (approximately 4-5 weeks). The male rats (22/dose) were dosed by gavage at the same levels for 9 weeks, beginning 4 weeks before mating. The results showed no treatment-related effects on male and female mating and fertility parameters, and no adverse treatment-related effects on early embryonic development at up to the MTD in rats. The NOAEL for Neurodex™-induced adverse effects on fertility and early embryonic development in male and female rats was 50/100 mg/kg/day dextromethorphan/quinidine, under the conditions of this study. However, this study is considered to be less than adequate, based on insufficient support in the dose range finding study (DMQ-122) to establish an MTD for dose selection, and absence of sufficient maternal toxicity at the highest dose level in this study to definitively demonstrate testing at up the maternal MTD. Therefore, this study provides limited information on Neurodex™ effects on fertility and early embryonic development in rats.

Embryofetal Development: Embryo-fetal toxicity was evaluated in pregnant rats (24/dose) given 0, 5/100 (LD), 15/100 (MD), and 50/100 (HD) mg/kg/day dextromethorphan/quinidine by oral gavage, once daily from gestation days 6-17. Slight treatment-related maternal toxicity was observed, and included salivation at all doses and slight reductions in body weights (-5% compared to controls) and food consumption for the first several dosing days in the high dose group. However, the maternal toxicity observations were insufficient to establish that Neurodex was tested at up to the maternal MTD. The results showed dose-related reduced fetal weights (-11% compared to controls at the HD and -5% at the MD and LD) and reduced ossification throughout the skeleton at the HD, in the skull, sternum, vertebrae and extremities at the MD, and in the skull, sternum, and vertebrae at the LD. Reduced skeletal ossification suggests developmental delay, and is considered to be attributed to the dextromethorphan component based on the relationship of the dextromethorphan dose to the findings. It is doubtful that the embryo-fetal toxicity observed was induced by dextrorphan exposure because the dextrorphan levels were higher, but the severity of the delayed ossification was lower at the MD than at the HD. Neurodex™ was not teratogenic at up to the MTD (50/100 mg/kg/day dextromethorphan/quinidine), but the NOAEL for embryo-fetal toxicity was not determined (<5/100 mg/kg/day dextromethorphan/quinidine) in rats under the conditions of this study. Overall, this study is considered to be less than adequate, based on a lack of support for dose selection in the dose range-finding study (DMQ-122), and insufficient dosing at up to the maternal MTD in the definitive study. Therefore, this study is of limited value to describe Neurodex™ effects on embryo-fetal development in rats.

Maternal rabbits (22/dose) were administered oral gavage doses of 0/0 (vehicle control) and 5-50 mg/kg/d dextromethorphan in combination with 100 mg/kg/d quinidine from gestation days 6-11 to 6-18 (reduced to 0/0 and 5-30 mg/kg/d dextromethorphan in combination with 60 mg/kg/d quinidine from gestation days 12-19 or 18-19 in the

original groups of 22 rabbits due to severe maternal toxicity). Additional groups of 10 rabbits per dose level were added and received the revised dose levels from gestation days 6-19. The total treatment period for all maternal rabbits spanned gestation days 6-19 (inclusive). Minimal maternal toxicity was suggested by slight, treatment-related reduced body weights and food consumption in several dams. Teratogenicity was observed at doses above the NOAEL of 5/60 mg/kg/day dextromethorphan/quinidine. There were slight increases in the total incidences of malformations at the MD (15/100 reduced to 15/60 mg/kg DM/Q) and HD, with sporadic observations of abnormalities including fused sternebrae, gastroschisis with phalangeal fusion, craniofacial abnormalities, diaphragmatic hernia, persistent truncus arteriousus, and vertebral fusions. There was a slight treatment-related effect on skeletal ossification, with incomplete or non-ossification of the sternebrae, hind limb long-bone epiphyses and hyoid at the MD and HD.

The study on embryo-fetal toxicity in rabbits is considered to be inadequate based on insufficient support for dose selection in the dose range-finding study (DMQ-121) and on inadequate maternal toxicity to demonstrate that the study was conducted at up to the maternal MTD.

Prenatal and Postnatal Development: Pre-natal and post-natal toxicity was evaluated in female rats, administered dextromethorphan alone (50 mg/kg/day), quinidine alone (100 mg/kg/day), and both drugs combined (0/0, 5/100, 15/100, and 30/100 mg/kg/day dextromethorphan/quinidine, 24/dose), once daily by oral gavage from gestation day (GD) 6 through postnatal day (PND) 20 (first 4 groups) or on GD 5-17 (quinidine and dextromethorphan alone groups). Slight maternal toxicity (salivation, reduced body weights and food consumption at 50 mg/kg/day DM alone) were observed, but failed to demonstrate an MTD. There was a slight (1 day) treatment-related increase in gestation length at 15/100 and 30/100 mg/kg/day dextromethorphan/quinidine (19 and 18 dams, respectively, compared to 10 and 16 dams in the controls and at 5/100 mg/kg/day, respectively). Treatment-related increased pup mortality was observed during the period from the day of birth through PND 4 (8, 15, 40, and 26 pups found dead at 0, 5/100, 15/100, and 30/100 mg/kg/day dextromethorphan/quinidine, respectively). The pup mortality was due to total loss of pups in one MD dextromethorphan/quinidine litter with loss of 5-6 pups in each of 2 other MD dextromethorphan/quinidine litters, 1-3 pups/litter in the controls, low-dose dextromethorphan/quinidine and remaining MD dextromethorphan/quinidine litters, and 1-4 pups per litter at the HD dextromethorphan/quinidine. There was a slight dose-related increase in postnatal pup body weight reduction, more frequently in the pups born on GD 21 than on GD 22, persisting 6-8 weeks after birth. The pups in the MD and HD dextromethorphan/quinidine-treated groups showed treatment-related developmental delay, with delayed acquision of the air-righting response (1/2 day delay) and increased spontaneous activity compared to controls. The NOAEL was not determined in this study (<5/100 mg/kg/day dextromethorphan/quinidine).

The results of the studies on reproductive toxicity are presented in the following table:

Results of Reproductive Toxicity Studies on Neurodex™ *

Test	DM/Q Doses (mg/kg/day)	Treatment Period	Results	Reference
Dose Finding in Rat	0/0, 0/100, 50/100, 100/100 (gavage)	14-days	CNS toxicity at 100/100:salivation, ↓activity, lethargy, ataxia, piloerection, hypothermia in F, DX accumulation in F	DMQ-122
Dose Finding in Rabbit	0/0, 0/50, 0/100, 50/100, 100/100, 50/0 (gavage)	10-14 days	↑ respiration, ↓ food consumption (60%) at 100/100	DMQ-121
Fertility in Rat (SD) (n=22/sex/dose)	0/0, 5/100, 15/100, 50/100 (gavage)	M: 9wks beginning 4wks PM F: 4-5wks beginning 2wks PM	**Negative** Toxicity: treatment-related salivation Males: No treatment-related effects on spermatogenesis, sperm count, motility, morphology Females: No treatment-related effects on estrous cycling, mating performance, ovulation rate, pre- & post-implantation losses, litter size	DMQ-126
Embryofetal Development in Rat (SD) (n=24 females/dose/group)	0/0, 5/100, 15/100, 50/100 (gavage)	GD 6-17 inclusive, sacrifice GD20	Salivation in all treated groups, sl ↓BWG (all doses), ↓food cons (all doses) for first days, and at HD (-5%) throughout dosing ↑post-implantation loss (50/100, due to total litter loss in 3 dams, resorptions during embryogenesis) ↓fetal wt (HD) **Developmental delay**: ↓ossification throughout skeleton at HD and some skeletal areas at LD, MD, incl skull, sternum, vertebrae, extremities, related to ↓fetal wts Dose-relationship suggests relationship to DM, not Q NOAEL not determined	DMQ-124
Embryofetal Development in Rabbit (New Zealand) (n=32/ dams/dose/group)	0/0, 5/100, 15/100, 50/100 (GD6-10), reduced to 0/0, 5/60, 15/60, and 30/60 on GD 11-19 (gavage)	GD 6-19, inclusive, sacrifice GD 29	↓dam BW and food cons (all doses before dose adjustment) **Embryotoxicity**: ↑fetuses with **malformations** (all doses, dose-related) including fused sternebrae, gastroschisis, phalangeal fusions, craniofacial abnormalities, diaphragmatic hernia, truncus arteriosis, & vertebral fusions, ↓ossification of sternebrae, incomplete hyoid ossification, unossified epiphysis	DMQ-123
Pre-and Post-natal Development in Rat (SD) (n=24 dams/dose DM/Q, 20/dose Q and DM alone)	0/0, 5/100, 15/100, 30/100, 50/0, 0/100	GD 6-PND20 inclusive, sacrifice dams PND21, DM & Q alone groups dosed GD6-17, sacrificed GD20	Maternal deaths/sacrifices: 1 MD, 1 HD combination, 1 Q alone Dose-related ↑**gestation duration,** ↑**pup mortality** birth-PND4, ↓**pup wt**, dose-related (DM/Q groups, not DM or Q alone, PND4-21), persisted 6-8wks **Developmental delay**: delayed (1/2d) pup acquisition of righting response & ↑spontaneous activity (MD,HD) NOAEL not determined	DMQ-125

*DM = Dextromethorphan, Q = quinidine, DX = dextrorphan metabolite, SD = Sprague Dawley, PM = pre-mating, GD = gestation day, PND = post-natal day, sl = slight, cons = consumption, M = males, F = females, wk = week, LD = low dose, MD = mid dose, HD = high dose, incl = including

Special Toxicology:

Neurotoxicity: No treatment-related neuronal lesions (vacuolation, necrosis, and degeneration) characteristic of the "Olney Lesion", were observed in the posterior

cingulate and retrosplenial cortices of adult rats (6/sex/dose/timepoint) administered dextromethorphan at oral gavage doses from 2-50 mg/kg in combination with quinidine at 50 mg/kg, when sampled at 6 and 24 hours, and 7 days after dosing. The positive control, MK-801 induced cytoplasmic vacuolation within the retrosplenial cortices of 4/4 males and 2/4 females at 6 hours, shrunken necrotic neurons with eosinophilic cytoplasm within the retrosplenial cortex in 3/4 males and 4/4 females at 24 hours, and neuronal and axonal degeneration in all rats at 7 days after treatment with MK-801, similar to the findings reported in the published literature to be associated with the "Olney Lesion". Toxicokinetic analysis demonstrated adequate exposure of the rats to dextromethorphan, dextrorphan, and quinidine. The NOAEL for the Olney Lesion by dextromethorphan in combination with quinidine was 50/50 mg/kg dextromethorphan/quinidine in this study.

Impurities: The known impurities from the manufacture of the quinidine sulfate component are (b) (4). The known impurities from the manufacture of (b) (4) The acceptance criteria for the impurity, (b) (4) is at the limit for qualification, of (b) (4). This level is considered to be acceptable based on its presence in the (b) (4) lot used in the 28-day mouse, 26-week mouse carcinogenicity, and fertility (rat), embryo-fetal toxicity (rat and rabbit), and pre- and post-natal development studies (b) (4) in Lot #DM0302015). (b) (4)

Unresolved toxicology issues:

The Neurodex™ doses administered in the reproductive toxicity studies on fertility (DMQ-126), embryo-fetal development (DMQ-124) and pre- and post-natal development (DMQ-125) in rats are considered to be less than adequate, based on insufficient support in the dose range-finding study (DMQ-122) for the dose selection, and the absence of maternal toxicity in the definitive studies that clearly demonstrated maximum tolerated doses (MTD). In the dose range-finding study, treatment-related maternal toxicity was limited to salivation (in all groups), CNS depression observed 5 hours after dosing on Day 3 only, hypothermia in 2 F (described as "seemed to have some degree of…"), decreased BW for 3 days, and transient reduction in BWG. The description of maternal toxicity in the study report did not correlate well with the individual line listing data. In the definitive studies, treatment-related maternal toxicity was limited to salivation, and slight reductions in body weights and food consumption on some treatment days.

The Neurodex™ doses administered in the embryo-fetal toxicity study in rabbits (Study DMQ-123) are considered to be less than adequate, due to insufficient support by the results of the dose range-finding study (DMQ-121), and on insufficient treatment-related toxicity to unquestionably demonstrate a maternal MTD. There were very slight reductions in maternal body weights and food consumption, without inducing treatment-related clinical or other signs of toxicity. The NOAEL for Neurodex™-induced embryotoxicity in rabbits, based on observations of reduced ossification throughout the skeleton, fused sternebrae, gastroschisis, phalangeal fusions, craniofacial abnormalities,

diaphragmatic hernia, truncus arteriosis, and vertebral fusions, decreased ossification of the sternebrae, incomplete hyoid ossification and unossified epiphysis, was the lowest dose level tested (5/60 mg/kg/day DM/Q), representing only 0.01X the approximate clinical AUC_{0-24} value (estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d. on an AUC basis) and 2X on a mg/m^2 basis. The quinidine dose (60 mg/kg/day) represented approximately 5X-6X the proposed clinical quinidine dose (based on an approximate clinical AUC_{0-24} value, estimated from the clinical AUC_{0-12} value in poor metabolizers at the proposed dose of 30 mg DM/30 mg Q b.i.d.).

A carcinogenicity study in rats, initiated in mid-2003, should have completed the dosing phase in approximately mid-2005. It is reasonable to expect completion of study data analysis and submission of the final study report for review within 6-8 months following the end of the terminal sacrifice dates and tissue evaluations.

Non-competitive NMDA receptor antagonists, such as MK-801 have been shown to induce neurotoxicity in both adult and neonatal rats. In adult rats, NMDA antagonists induce "Olney lesions", characterized by intracytoplasmic vacuolation and necrosis in layers III and IV of the retrosplenial and posterior cingulate neocortices. Because [redacted] (b) (4) is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, the Sponsor was asked to conduct a special toxicology study in rats to evaluate the potential for inducing the neuronal lesions. Oral [redacted] (b) (4) doses from 2-50 mg/kg (up to approximately 6 times the highest recommended clinical dose of 120 mg/day dextromethorphan, and 12 times the proposed high dose of 60 mg/day, on a mg/m^2 basis) in combination with the metabolic inhibitor quinidine, also given orally at 50 mg/kg was negative for induction of vacuolation and necrosis in the retrosplenial and posterior cingulate cortices that characterize the neurotoxic lesion in rats, under the conditions of the study. NMDA receptor antagonists have recently come under investigation for induction of widespread neuronal degeneration in neonatal rats when administered beginning on postnatal day 7. The period of vulnerability in rat pups corresponds to a period of neurological development in the human beginning approximately 2 months before birth through age 3. The potential for Neurodex™ to induce apoptotic neuronal degeneration in the human fetus is unknown. Because the proposed patient population will include women of childbearing potential, the potential for Neurodex™-induced apoptotic neuronal degeneration should be addressed in the product label or by conducting a study in an appropriate animal species.

RECOMMENDATIONS

1. This NDA is considered to be approvable from a non-clinical perspective taking into consideration the severity of the indication in the proposed patient population, although there are inadequacies in the reproductive toxicity studies that will need to be addressed.

2. The results of the non-clinical studies on genetic toxicology and carcinogenicity in Tg.rasH2 mice should be presented in the product label, as recommended under separate review.

3. The final study report for the carcinogenicity study in rats, initiated in mid-2003, should be submitted for Agency review and inclusion in the product label as soon as possible.

4. The studies on reproductive toxicity by Neurodex™ in rats and rabbits are limited by inadequate support for dose selection using poorly conducted dose range-finding studies, and by insufficient maternal toxicity in the definitive studies that would clearly demonstrate dosing at up to the maternal MTD. The study methodology limitations and thorough discussion of the positive study findings should be discussed in the product label. Also, the reproductive toxicity studies on fertility, embryo-fetal development, and pre- and post-natal development should be repeated as soon as possible during Phase 4. Appropriate criteria for Neurodex™ dose selection should be used, with support from well-designed dose range-finding studies. Dosing at up to the maternal MTD levels should be demonstrated in the definitive studies, as described in the published ICH Guidelines for Industry in the definitive reproductive toxicity studies.

5. The potential for Neurodex™-induced apoptotic neuronal degeneration in the human fetus and human infant should be addressed in the product label and by conducting a juvenile neurotoxicity study in an appropriate animal species during Phase 4.

Appendix/attachments: None

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

/s/

Kathleen Young
10/30/2006 03:53:09 PM
PHARMACOLOGIST

Lois Freed
10/30/2006 05:41:13 PM
PHARMACOLOGIST
Please see separate memo for comments.