

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021879Orig1s000**

**OTHER REVIEW(S)**

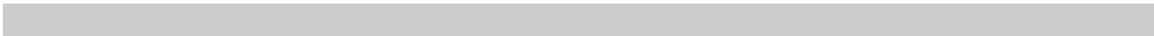
**505(b)(2) ASSESSMENT**

<b>Application Information</b>		
NDA # 021879	NDA Supplement #: S- N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Nuedexta Established/Proper Name: (dextromethorphan/quinidine) Dosage Form: Capsules Strengths: dextromethorphan 20mg with quinidine 10 mg		
Applicant: Avanir Pharmaceuticals, Inc.		
Date of Receipt: April 30, 2010		
PDUFA Goal Date: October 30, 2010		Action Goal Date (if different):
Proposed Indication(s): indicated for the treatment of pseudobulbar affect (PBA) secondary to either amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS)		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
quinidine sulfate	nonclinical safety
literature	nonclinical safety

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Ⓢ According to the Sponsor, the primary pharmacologic effect of quinidine in this product is to inhibit the metabolism of dextromethorphan (DM) by CYP2D6, increasing plasma concentrations of DM and enhancing potential for desired pharmacological effect of DM. PK studies have been performed to determine optimal dose of quinidine (Q) to inhibit DM metabolism by CYP2D6. PK studies 100 and 101 evaluate BA of either DM as DM/Q given separately (100) or as DM/Q in a combination (study 101). Study 101 was an extension of Study 100, such that it was a 1-way crossover in a limited number of subjects. These two studies included a limited number of subjects and a limited number of samples (in Study 100). Since this combination is for a new indication and there is data on DM alone as well as the combination DM/Q, a relative BA assessment could be made. BA assessments are based on DM as the Sponsor considers that the therapeutic activity resides with that moiety. Study 102 is a factorial design clinical efficacy study that looks at each component (DM and Q) given separately and given together as the combination product.

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

If “NO,” proceed to question #10.

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Quinidine Sulfate	Sponsor lists “various” under application holder (the Orange Book lists ANDAs 083288 and 085583 as RLD for quinidine sulfate)	Y

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer “N/A”.*

*If “NO”, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

Antiarrhythmics containing Quinidine gluconate, quinidine hydrochloride, quinidine sulfate, and procainamide hcl.

c) Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph: dextromethorphan hydrobromide (21 CFR 341.14)

d) Discontinued from marketing?

YES  NO

*If "YES", please list which drug(s) and answer question d) i. below.*

*If "NO", proceed to question #9.*

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This 505b2 application provides for a new indication to treat pseudobulbar affect in patients with underlying MS or ALS. In addition, the application provides for a new combination product.

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

*If "NO" to (a) proceed to question #11.  
If "YES" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES  NO

*If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO   
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES  NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

**PATENT CERTIFICATION/STATEMENTS**

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): there are no unexpired patents for Quinidine Sulfate

No patents listed  proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUSAN B DAUGHERTY  
10/29/2010

## Nuedexta™ (Dextromethorphan/Quinidine) PMR #1

PMR Description: Pharmacokinetic dose-ranging and safety study in pediatric patients

PMR Schedule Milestones:	Final protocol Submission Date:	<u>10/2011</u>
	Study Completion Date:	<u>04/2013</u>
	Final Report Submission Date:	<u>10/2013</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Nuedexta is a combination of two approved drugs, dextromethorphan and quinidine, and is ready for approval for a serious indication only in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

There has not yet been a development program for Nuedexta in pediatrics. Under the Pediatric Research Equity (PREA) an assessment of the safety and effectiveness of Nuedexta for the claimed indication is required in the pediatric population. This PMR will address this requirement, in part. The goal of this trial is to conduct a pharmacokinetic dose-ranging and safety study in patients 2 to 16 years of age with pseudobulbar affect (PBA).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - Assess a known serious risk related to the use of the drug?
  - Assess signals of serious risk related to the use of the drug?
  - Identify an unexpected serious risk when available data indicate the potential for a serious risk?
  
- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  
  - Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
  - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  
  - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a pharmacokinetic dose-ranging and safety study in patients 2 to 16 years of age with PBA.

Required

- Observational pharmacoepidemiologic study
  - Registry studies
- Continuation of Question 4*
- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

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Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

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Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Nuedexta™ (Dextromethorphan/Quinidine) PMR #2

PMR Description: Efficacy and safety study in pediatric patients

PMR Schedule Milestones:	Final protocol Submission Date:	<u>10/2013</u>
	Study Completion Date:	<u>04/2015</u>
	Final Report Submission Date:	<u>10/2015</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Nuedexta is a combination of two approved drugs, dextromethorphan and quinidine, and is ready for approval for a serious indication only in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

There has not yet been a development program for Nuedexta in pediatrics. Under the Pediatric Research Equity (PREA) an assessment of the safety and effectiveness of Nuedexta for the claimed indication is required in the pediatric population. This PMR will address this requirement, in part. The goal of this trial is to conduct a controlled efficacy and safety study in patients 2 to 16 years of age with pseudobulbar affect (PBA).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - Assess a known serious risk related to the use of the drug?
  - Assess signals of serious risk related to the use of the drug?
  - Identify an unexpected serious risk when available data indicate the potential for a serious risk?
  
- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  
  - Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
  - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  
  - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a Phase 3, 12-week, multiple center, double-blind, placebo-controlled efficacy and safety study in pediatric patients 2 to 16 years of age with PBA.

Required

- Observational pharmacoepidemiologic study
  - Registry studies
- Continuation of Question 4*
- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

PREA-required efficacy and safety study

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Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

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Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

### Nuedexta™ (Dextromethorphan/Quinidine) PMR #3

PMR Description: Phase 3 open-label extension safety study in pediatric patients

PMR Schedule Milestones:	Final protocol Submission Date:	<u>10/2013</u>
	Study Completion Date:	<u>04/2015</u>
	Final Report Submission Date:	<u>10/2015</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Nuedexta is a combination of two approved drugs, dextromethorphan and quinidine, and is ready for approval for a serious indication only in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

There has not yet been a development program for Nuedexta in pediatrics. Under the Pediatric Research Equity (PREA) an assessment of the safety and effectiveness of Nuedexta for the claimed indication is required in the pediatric population. This PMR will address this requirement, in part. The goal of this trial is to conduct a phase 3 open-label extension safety study in patients 2 to 16 years of age with pseudobulbar affect (PBA).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - Assess a known serious risk related to the use of the drug?
  - Assess signals of serious risk related to the use of the drug?
  - Identify an unexpected serious risk when available data indicate the potential for a serious risk?
  
- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  
  - Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
  - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  
  - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a phase 3 open-label extension safety study in pediatric patients 2 to 16 years of age with PBA.

Required

- Observational pharmacoepidemiologic study
  - Registry studies
- Continuation of Question 4*
- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

---

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

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Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Nuedexta™ (Dextromethorphan/Quinidine) PMR #4

PMR Description: Juvenile Neurotoxicology Study in Rats

PMR Schedule Milestones:	Final protocol Submission Date:	<u>02/2011</u>
	Study Completion Date:	<u>06/2012</u>
	Final Report Submission Date:	<u>09/2012</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Nuedexta is a combination of two approved drugs, dextromethorphan and quinidine, and is ready for approval for a serious indication.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonists, of which dextromethorphan is an example, have recently come under investigation for induction of widespread neuronal degeneration in neonatal rats when administered during the postnatal period demonstrated to be the most vulnerable to this lesion. The period of vulnerability in rat pups corresponds to a period of neurological development in the human beginning approximately two months before birth. The potential for Nuedexta 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 Nuedexta-induced apoptotic neuronal degeneration needs to be addressed by conducting a study in an appropriate animal species.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A juvenile neurotoxicity study in neonatal rats intended to assess the potential for Nuedexta to induce apoptotic neuronal degeneration in the human fetus. Dextromethorphan/quinidine should be administered during the postnatal period demonstrated to be the most vulnerable to this lesion.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## Nuedexta™ (Dextromethorphan/Quinidine) PMR #5

PMR Description: Pre- and Post-natal Development Study in Rats

PMR Schedule Milestones:	Final protocol Submission Date:	<u>01/2011</u>
	Study Completion Date:	<u>01/2012</u>
	Final Report Submission Date:	<u>04/2012</u>
	Other: <u>N/A</u>	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Nuedexta is a combination of two approved drugs, dextromethorphan and quinidine, and is ready for approval for a serious indication.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The pre- and post-natal development study in rats submitted in the original NDA was inadequate due to the absence of observable maternal toxicity at the highest dose tested. Adverse effects on offspring were observed; however, the available data indicate that higher doses could have been tolerated. Therefore, the potential for DM/Q to induce developmental, reproductive and neurobehavioral toxicity has not been fully assessed.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A pre- and post-natal development (including maternal function) study in rats, testing doses up to a high dose of 50 mg/kg/day dextromethorphan in combination with 100 mg/kg/day quinidine.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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**Nuedexta™ (Dextromethorphan/Quinidine) PMR #6**

PMR Description: Embryo-Fetal Development Study in Rabbits

PMR Schedule Milestones:	Final protocol Submission Date:	<u>01/2011</u>
	Study Completion Date:	<u>07/2011</u>
	Final Report Submission Date:	<u>10/2011</u>
	Other: <u>N/A</u>	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Nuedexta is a combination of two approved drugs, dextromethorphan and quinidine, and is ready for approval for a serious indication.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The embryo-fetal toxicity study in rabbits contained in the original NDA was inadequate due to the absence of maternal toxicity at the highest dose tested. Adverse effects on fetal development were observed; however, the available data indicate that higher doses could have been tolerated. Therefore, the potential for DM/Q to induce developmental toxicity has not been fully assessed.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An embryo-fetal development study in rabbits, testing doses up to a high dose of 50 mg/kg/day dextromethorphan in combination with 100 mg/kg/day quinidine.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## Nuedexta™ (Dextromethorphan/Quinidine) PMR #7

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PMR Description: Juvenile rat toxicology study to evaluate effects of DM/Q on growth, reproductive development, and neurological and neurobehavioral development.

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PMR Schedule Milestones:	Final protocol Submission Date:	<u>04/2011</u>
	Study Completion Date:	<u>07/2012</u>
	Final Report Submission Date:	<u>12/2012</u>
	Other: <u>N/A</u>	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Nuedexta is a combination of two approved drugs, dextromethorphan and quinidine. This product is ready for approval for use in adults and pediatric studies have not been conducted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A juvenile rat toxicology study under PREA to identify the unexpected serious risk of adverse effects of DM/Q on postnatal growth and development. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study must evaluate effects of DM/Q on growth, reproductive development, and neurological and neurobehavioral development.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A juvenile rat toxicology study is required to identify the unexpected, serious risk of adverse effects of DM/Q on postnatal growth and development. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study must evaluate effects of dextromethorphan/quinidine on growth, reproductive development, and neurological and neurobehavioral development.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## Nuedexta™ (Dextromethorphan/Quinidine) PMR #8

PMR Description: Studies to characterize the in vitro binding affinity and functional activity of quinidine at the 5HT<sub>2B</sub> receptor.

PMR Schedule Milestones:	Final protocol Submission Date:	02/2011
	Study Completion Date:	08/2011
	Final Report Submission Date:	11/2011
	Other: N/A	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Nuedexta is a combination of two approved drugs, dextromethorphan and quinidine, and is ready for approval for use in adults. A recent publication has identified quinidine as a 5HT<sub>2B</sub> agonist (Huang *et al. Mole Pharm*, 2009). 5HT<sub>2B</sub> agonism is a mechanism of action associated with cardiac valvulopathy in humans, a serious adverse event that has resulted in the withdrawal of certain drug products from the market.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent publication has identified quinidine as a 5HT<sub>2B</sub> agonist (Huang *et al. Mole Pharm*, 2009). This is the first report that quinidine has 5HT<sub>2B</sub> agonist activity. 5HT<sub>2B</sub> agonism is a mechanism of action associated with cardiac valvulopathy in humans, a serious adverse event that has resulted in the withdrawal of certain drug products from the market. Therefore, it is important that this activity be confirmed and, if it is, to assess the potential for quinidine to induce valvulopathy in vivo.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Studies to assess the in vitro binding affinity and functional activity of quinidine at the 5HT <sub>2B</sub> receptor.
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Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## Nuedexta™ (Dextromethorphan/Quinidine) PMR #9

PMR Description: An in vivo study to investigate the potential for quinidine to induce valvulopathy, if 5HT<sub>2B</sub> agonism is confirmed.

PMR Schedule Milestones:	Final protocol Submission Date:	04/2012
	Study Completion Date:	03/2013
	Final Report Submission Date:	06/2013
	Other: N/A	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Nuedexta is a combination of two approved drugs, dextromethorphan and quinidine, and is ready for approval for use in adults. A recent publication has identified quinidine as a 5HT<sub>2B</sub> agonist (Huang *et al. Mole Pharm*, 2009). 5HT<sub>2B</sub> agonism is a mechanism of action associated with cardiac valvulopathy in humans, a serious adverse event that has resulted in the withdrawal of certain drug products from the market.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent publication has identified quinidine as a 5HT<sub>2B</sub> agonist (Huang *et al. Mole Pharm*, 2009). This is the first report that quinidine has 5HT<sub>2B</sub> agonist activity. 5HT<sub>2B</sub> agonism is a mechanism of action associated with cardiac valvulopathy in humans, a serious adverse event that has resulted in the withdrawal of certain drug products from the market. Therefore, it is important that this activity be confirmed and, if it is, to assess the potential for quinidine to induce valvulopathy in vivo.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

If quinidine is confirmed to be a 5HT<sub>2B</sub> agonist, then an investigative study to assess the potential for quinidine to induce cardiac valvulopathy will be needed.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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SALLY U YASUDA  
10/29/2010  
PMR/PMC development template

# Internal Consult

## \*\*\*Pre-decisional Agency Information\*\*\*

To: Russell Katz, MD, Director, Division of Neurology Products (DNP)  
Ronald Farkas, MD, PhD, Lead Medical Officer, DNP  
Susan B Daugherty, Senior Regulatory Project Manager, DNP

From: Quynh-Van Tran, PharmD, BCPP  
Regulatory Reviewer, Division of Drug Marketing, Advertising, and  
Communications, (DDMAC)

Date: October 22, 2010

Re: Comments on draft labeling (Package Insert) for Nuedexta  
(dextromethorphan hydrobromide and quinidine sulfate) Capsules  
  
NDA 21-879

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Thank you for the opportunity to review the proposed PI for Nuedexta (FDA dated version 10/19/2010). Please see attached PI with our comments incorporated therein.

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QUYNH-VAN TRAN  
10/25/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: October 28, 2010

To: Russell Katz, MD, Director  
Division of Neurology Products

Through: Kristina A. Toliver, PharmD, Team Leader  
Denise P. Toyer, PharmD, Deputy Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Loretta Holmes, BSN, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name: Nuedexta  
(Dextromethorphan Hydrobromide and Quinidine Sulfate) Capsules  
20 mg/10 mg

Application Type/Number: NDA 021879

Applicant: Avanir Pharmaceuticals

OSE RCM #: 2010-987

## Contents

1	INTRODUCTION .....	3
2	METHODS AND MATERIALS.....	3
3	RECOMMENDATIONS.....	3
3.1	Comments to the Division.....	3
3.2	Comments to the Applicant.....	4
	APPENDICES .....	5

## 1 INTRODUCTION

This review responds to a request from the Division of Neurology Products for DMEPA's assessment of the container labels for Nuedexta (Dextromethorphan Hydrobromide and Quinidine Sulfate) Capsules 20 mg/10 mg, (NDA 021879).

## 2 METHODS AND MATERIALS

DMEPA uses Failure Mode and Effects Analysis (FMEA) to evaluate container labels, carton and insert labeling. This review summarizes our evaluation of the container labels, carton and insert labeling submitted by the Applicant on October 27, 2010 (see Appendices A through C).

DMEPA notes that in a labeling meeting held on October 7, 2010, (b) (4) Nuedexta (20 mg/10 mg (b) (4) approval.

- Trade, 60-count
  - Container Label
- Professional Sample, 13-count
  - Container Label
  - Carton Labeling
- Insert Labeling

## 3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1 *Comments to the Division* for discussion during the review team's label and labeling meetings. We note additional DMEPA comments have been voiced during labeling meetings and are included in the working copy of the insert labeling. Section 3.2 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Laurie Kelley, at 301-796-5068.

### 3.1 COMMENTS TO THE DIVISION

In the Full Prescribing Information, Section 16 *How Supplied/Storage and Handling* provides information on the 13-count professional sample. Since professional samples are only distributed directly to prescribers, we recommend information concerning the professional sample be deleted.

### 3.2 COMMENTS TO THE APPLICANT

#### A. General Comments for all Container Labels and Carton Labeling

1. As currently presented, the font type and weight used for the established name and dosage form makes it appear less than ½ the size of the proprietary name. Ensure the established name is printed in letters that are at least ½ as large as the letters comprising the proprietary name. Additionally the established name should have a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features [21 CFR 201.10(g)(2)]. Ensure the dosage form statement is the same size, type, font, etc. as the established name.
2. In the established name, the two active ingredients are separated by a forward slash (/). Replace the forward slash with the word “and” (i.e., dextromethorphan HBr and quinidine sulfate).
3. In the “Each capsule contains” statement, connect the two active ingredients with the word “and” (i.e., 20 mg of dextromethorphan hydrobromide and 10 mg of quinidine sulfate).
4. As currently presented the bolded, green net quantity statement is as prominent as the proprietary name. Decrease the prominence of the net quantity statement by revising the color (e.g., white font) and debolding.

#### B. Container Labels (Trade)

1. Relocate the strength to appear immediately below the proprietary and established names (as presented on the carton labeling). You may have to delete the blue/green graphic, which is as prominent as the strength, in order to accomplish this. The proprietary name, established name and strength should be the most prominent information on the principal display panel.
2. Relocate the ‘Each capsule...’ statement to the side panel, which is the usual customary location for this statement.

#### C. Container Labels (Professional Sample)

Relocate the strength to appear immediately below the proprietary and established names (as presented on the carton labeling). You may have to delete the blue/green graphic, which is as prominent as the strength, in order to accomplish this. The proprietary name, established name and strength should be the most prominent information on the principal display panel.

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/s/

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LORETTA HOLMES  
10/28/2010

DENISE P TOYER  
10/28/2010

**DIVISION OF PULMONARY AND ALLERGY PRODUCTS**  
**MEDICAL OFFICER CONSULTATION**

Date: October 7<sup>h</sup> , 2010

To: Susan Daugherty  
Division of Neurology products (DNP)

From: Lydia I. Gilbert-McClain M.D. FCCP, Deputy Director  
Division of Pulmonary and Allergy Products, HFD-570

Through: Badrul A. Chowdhury, M.D., Ph.D., Director  
Division of Pulmonary and Allergy Products, HFD-570

Subject: NDA 021-879/ Zenvia (dextromethorphan/quinidine)

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**General Information**

Date of Request: June 10<sup>th</sup> , 2010

Materials Reviewed: Consult request, NDA resubmission Module 5.3.5.3 “Respiratory Report”, literature references, Oct 2006 approvable letter; Primary Medical Officer review (Dr. D Jillapalli)

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**Recommendation**

The Division responses to the specific questions can be found in the body of the consult.

**Introduction**

The Division of Neurology products (DNP) is reviewing a complete response to NDA 21-879 for a fixed dose combination product containing dextromethorphan and quinidine under development by Avanir Pharmaceuticals (Avanir) for the proposed indication of treatment of pseudobulbar effect (PBA). The application was originally submitted on January 27, 2006 (received January 30, 2006), and was given an approvable action on October 30, 2006. Among the clinical deficiencies, there were a number of safety issues raised including safety concerns regarding the occurrence of 48 deaths many in ALS patients presumably due to respiratory failure. The Division raised concerns regarding the possibility of respiratory depression due to high levels of dextromethorphan in this vulnerable population and stated the following in the action letter:

*“We note the occurrence of 48 deaths in the open-label experience, many in ALS patients, presumably due to respiratory failure. However, you have not provided evidence that this number of deaths, from this cause, would be expected in this time period in this population. We are concerned that the very high levels of DM produced by Zenvia in this vulnerable population may have contributed to respiratory depression in these patients. We also note the occurrence of a relatively large number of respiratory depression and failure events, categorized as serious adverse events. You will need to address our concern that this product may be associated with*

*respiratory depression and failure in this vulnerable population (we include in this vulnerable population other populations in whom PBA may occur, including patients with stroke and Alzheimer's disease, groups in whom you have obtained very little clinical experience)."*

In the original NDA application, the proposed combination product contained dextromethorphan 30 mg and quinidine 30 mg. To address the Division's concerns, the applicant conducted additional studies including a phase 3 clinical study (07-AVR-123) assessing new formulations using a lower dose of quinidine (10 mg) and (b) (4) 2 formulations in the resubmission containing 20 and 30 mg of dextromethorphan with 10 mg of quinidine (Zenvia 30/10 and Zenvia 20/10). The consult notes that in the double-blind phase of study 07-AVR-123, there were 7 deaths, all of them in patients with ALS and 6 of these deaths occurred in patients on Zenvia (vs. one in the placebo group. The sponsor submitted an analysis based on consultation with a pulmonologist and concluded that the respiratory-related deaths were in line with the mortality expectations in the ALS population. The consult requests our input on the following:

### **Consult question**

***While no statistically significant differences were present in the treatment groups for diurnal O<sub>2</sub> values, the values were numerically worse in the Zenvia treatment groups compared to placebo in both the diurnal and nocturnal O<sub>2</sub> values. Please provide an expert assessment of these numerical differences between treatment groups, and whether the respiratory risk associated with Zenvia has been adequately assessed and appropriately characterized. Do you agree with the applicant's conclusions regarding the overall respiratory safety profile of Zenvia?***

### **DPARP Response**

*(See Background Information for specific details)*

The case narratives for the deaths that occurred in study 07-AVR-123 were reviewed. Of the 6 deaths that occurred in the Zenvia treatment group in the double-blind treatment period, there was sufficient information in the case narrative to propose a cause of death. For four of these cases, the case narrative is supportive of death due to respiratory failure related to the underlying disease of ALS. In two of the cases, there is not sufficient information in the case narrative to determine a specific cause of death, but from the limited information presented, it is reasonable to conclude that the patients died from causes related to the underlying disease of ALS. There were three deaths in the open labeled period and the case narratives are consistent with a cause of death due to respiratory failure (associated with pneumonia in two of the cases).

The oxygen saturation data as presented are not helpful. Depending on the time of day or night the O<sub>2</sub> values were taken, and whether a single measurement was taken versus overall monitoring of oxygen saturation over several hours will impact the utility of this information. A single measurement of O<sub>2</sub> saturation is not very informative of the overall status of the patient in terms of adequate tissue oxygenation. Nevertheless, the mean O<sub>2</sub> saturation values (and CI) are within the 90% range which is within normal limits. Although they are shifts in the O<sub>2</sub> values in both diurnal and nocturnal O<sub>2</sub> values, these do not appear to have fallen to levels low enough to be of clinical concern (based on summary data in the applicant's submission the summary tables

of O<sub>2</sub> saturation values are within the 90% range which is normal). As expected, patients with ALS had O<sub>2</sub> levels at baseline and at follow up that were numerically lower than patients with MS. This is consistent with the natural history of ALS, since progressive respiratory compromise causes nocturnal O<sub>2</sub> desaturations. It would be helpful to review the actual line listings of oxygen saturations to look for outliers. Values that are persistently below 90% saturation may be clinically significant. For those cases with O<sub>2</sub> saturation values below 90% it may be helpful to review the oximetry graphs to see the pattern of O<sub>2</sub> saturation throughout the entire nighttime (assuming that the sponsor monitored O<sub>2</sub> saturation throughout the night) instead of taking one measurement.

I reviewed the applicant's response in the respiratory report (provided by expert consultation) and the conclusions of the consultant regarding the cause of death for the cases are in essence consistent with my conclusions. The information in the case narratives does not support a treatment-related effect. The study population included more patients with ALS than MS, so that could explain why all the deaths that were seen were only in ALS patients. Nevertheless, it is understandable that the imbalance in the Zenvia-treated vs. placebo-treated patients would raise a concern. Pharmacologically, dextromethorphan can cause respiratory depression. However, only two of the patients were actually still on active treatment at the time of death, and the number of deaths in the two Zenvia treatment arms (Zenvia 30/10 and Zenvia 20/10) were the same, making the hypothesis of increased respiratory depression due to increased exposure to dextromethorphan unlikely.

The median survival time for ALS patients from symptom onset is reported to be 2 – 4 years, but there are reports of survival ranging from less than a year to considerably longer. Differences in age of disease onset, disease presentation (bulbar vs. non bulbar disease), use of NIPPV, and overall care all play a role in affecting survival in ALS. Therefore, Evaluation of the baseline differences in the active vs. the placebo treatment group in the ALS patients may be useful to help address the imbalances in the number of deaths seen in the development program.

The primary medical officer review (Dr. D Jillapalli, MD) note baseline differences between the active treatment groups and placebo that could help explain the imbalance seen in study 07-AVR-123. The [ALS] patients in the Zenvia treatment groups were older than the patients in the placebo group (mean age 56.1 years in any Zenvia treatment group vs. 54.5 years in the placebo group. Additionally, the time from diagnosis of ALS was considerably longer in the Zenvia treatment group compared to the placebo group (mean = 18.5 months in any Zenvia treatment group vs. 12.7 months in the placebo treatment group. The percentages of patients with the two types of ALS onset (bulbar vs. spinal) were similar across the Zenvia and the placebo groups [*Primary Medical officer review pg 45 – 46*].

It is plausible that these baseline differences can explain the imbalance in the death rate between the Zenvia treatment groups and placebo. From the ALS literature it appears that age at diagnosis is a strong predictor of prognosis with longer survival time for those who receive a diagnosis under age 45 compared to those who receive a diagnosis at age 65. Furthermore, the longer time of diagnosis in the Zenvia-treated patients suggest that these patients had the disease for a longer time compared to their placebo counterparts.

## **Background**

Avanir Pharmaceuticals (Avanir) is developing a fixed dose combination of dextromethorphan and quinidine for the treatment of pseudobulbar affect (PBA), a neurological condition characterized by spells of inappropriate crying and or laughing. Dextromethorphan is a widely-used antitussive and is available in many over the counter cough-cold preparations and also in prescription products in combination with promethazine and codeine for cough/cold indications. The literature notes that small studies have shown therapeutic benefits with dextromethorphan (DM) in patients with amyotrophic lateral sclerosis (ALS), stroke, and neurosurgery. Dextromethorphan is rapidly metabolized to dextrophan via CYP2D6 and systemic concentrations of DM can be increased via co-administration of quinidine which reversibly inhibits its first-pass metabolism via CYP 2D6. There is no pharmacological therapy that is FDA approved for PBA. Clinical use of dextromethorphan and the cytochrome P450 2D6 enzyme inhibitor quinidine reportedly improves PBA and concomitant use of DM and quinidine is reportedly used ‘of label’ in clinical practice to treat PBA.

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder affecting the voluntary motor system for which no effective treatment is available. The disorder is characterized by progressive muscular paralysis reflecting degeneration of motor neurons in the primary motor cortex, corticospinal tracts, brainstem, and spinal cord. The incidence of the disease is about 1.89/100,000. Patients with ALS can present with symptoms related to focal muscle weakness and wasting either distally or proximally in the upper and lower limbs. Patients with ALS can also present at onset with bulbar symptoms (dysarthria, dysphagia) and limb symptoms can develop almost simultaneously with bulbar symptoms, and in the vast majority of cases will occur within 1 – 2 years<sup>1</sup>. Paralysis in ALS is progressive and leads to death due to respiratory failure within 2 – 3 years for bulbar onset cases, and 3 -5 years for limb onset ALS cases. It is reported that pulmonary complications and respiratory failure are responsible for at least 84% of deaths in ALS patients<sup>2</sup>. Forced vital capacity (FVC) is considered the physiologic marker for tracking respiratory failure and patients are considered for Noninvasive Positive Pressure Ventilation (NIPPV) when the FVC falls < 50%. With the use of Non-invasive ventilation, survival may be prolonged somewhat, but ultimately all patients succumb to respiratory failure and death. The prevalence of PBA in ALS patients varies among different literature references but is reported as high as 49%<sup>3</sup>.

Following the complete response, the sponsor conducted an additional study 07-AVR-123 to address the Agency’s safety concerns. This was a double-blind controlled study comprised of a 12 week treatment period, followed by an open label period. The study was conducted at 52 sites (36 in the U.S. and 16 in Latin America [Argentina and Brazil]). A total of 326 patients were randomized to the double-blind treatment period. Of these, 109 were in the placebo group and 110 and 107 patients (total on active treatment =217) were randomized to the Zenvia 30/10 and Zenvia 20/10 treatment groups respectively. The study enrolled patients with ALS and

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<sup>1</sup> Review: ALS Lokesh C wijesekera and P Nigel Leigh; orphannet Journal of Rare Diseases 2009, 4:3

<sup>2</sup> Amyotrophic Lateral Sclerosis\* prolongation of life by noninvasive respiratory aids: John Robert Bach; CHEST 2002; 122:92-98

<sup>3</sup> Review of pseudobulbar affect including a novel and potential therapy (J Neuropsychiatry Clin Neusci 2005 Fall; 17 (4);447-54; Schiffer R, Pope LE.

multiple Sclerosis (MS). The percentage of patients with ALS in the active treatment groups was considerably higher (133[61%]) than the percentage of patients with MS (n = 84 (39%)), similarly, the percentage of patients with ALS in the placebo group was considerably higher (n = 64 [59%]) than the percentage of patients with MS (n = 45 [41%]). The double-blind treatment period was followed by a 12-week open label treatment period in which 253 patients were treated with Zenvia 30/10 twice daily. As in the double-blind phase, more patients (n = 146 [58%]) had ALS than MS (n = 107 [42%]).

In the double-blind treatment period, there were 7 deaths. All the deaths were in ALS patients 6 of whom were in the active treatment group (3 each in Zenvia 30/10 and Zenvia 20/10) and one in the placebo. In the open label treatment period there were 3 deaths in ALS patients. The deaths that occurred in the double-blind treatment period (active treatment arms) are described below from the case narratives.

**Patient 133/501** (b) (6) [ who was on study drug at the time of death] was a 55 year old Caucasian female with a history of ALS diagnosed in March 2007 and a history of hypertension. The patient's condition decline rapidly following the diagnosis of ALS and required a gastrostomy tube placement (PEG) for nutritional support on June 2, 2008 due to swallowing difficulties and weight loss. The patient first received study drug on June 12, 2008 and the last dose was taken on (b) (6), approximately (b) (6) hours prior to her death.

The case report indicates that the patient had significant problems with swallowing and control of salivation. Furthermore, prior to enrollment in the study the patient was noted to have choking episodes and "compromised respiratory parameters", but the case report did not elaborate further regarding what that meant.

The patient was taken to the ER on (b) (6) with complaints of her PEG tube not functioning properly for approximately 3 – 4 days which resulted in poor intake. The patient complained of feeling sick, weak, and nauseated. The patient apparently had persistent gastrointestinal complaints and had become unable to swallow saliva. She had been on scopolamine patches (for excessive salivation), Phenergan for nausea, and Miralax for constipation. From the case report, the patient's inability to swallow had been getting progressively worse, so much so, that the family had notified the investigator that the patient was too ill to complete the end of study visit scheduled for (b) (6). The assessment in the ER notes normal respiratory effort and breath sounds, and an unremarkable chest X ray. The patient was later found without pulse and respiration about 3.5 hours later. No specific cause of death was found on autopsy. Of note the patient's lab work in the ER revealed a sodium level of 117mmol/L.

It appears that the death is probably more likely due to a combination of factors including dehydration (patient had problems with PEG tube for days and complained of poor intake, and severe excessive salivation) compounded with severe hyponatremia. The patient already had compromised respiratory status prior to study enrollment, and it is known that factors such as dehydration, and electrolyte imbalances can further weaken compromised respiratory muscles. I find it reasonable to conclude that the patient died of a combination of factors related to the underlying disease and not from a treatment-related event.

**Patient 126/501** was a 67 year old Caucasian male diagnosed with ALS on January 18, 2008 who died on [REDACTED] (b) (6). The time of death in relation to the diagnosis of ALS appears to be very short (a mere [REDACTED] (b) (6)), however, review of the case report provide details that suggest that the patient probably had symptoms of the disease since June 2007, so this may be just a delay in confirming the diagnosis. From the case report, the patient did not have a PEG tube placement, but had been using BIPAP (non invasive ventilation), which indicates that the patient was in respiratory failure (secondary to the disease), and severely compromised from a respiratory standpoint. The increase secretions, and need for frequent suctioning described in the report are consistent with a patient in respiratory failure due to the underlying disease. Further review of the case reports note that the patient had resting O<sub>2</sub> saturation of 94% and 92%, however it is not stated whether this was with or without supplemental oxygen. Although lower than what would be expected for a person with normal pulmonary physiology, levels of O<sub>2</sub> saturation that are ≥ 90% are adequate for tissue perfusion and to prevent tissue hypoxia. From review of the laboratory results however, it is apparent that this patient had chronic hypoxia, since the hematocrit levels (48% and 44% on two separate occasions) are consistent with polycythemia, which is seen as a result of chronic hypoxia. Taken together, the clinical signs of respiratory failure, and chronic hypoxia all support the conclusion that the cause of death is consistent with the underlying respiratory morbidity due to ALS.

**Patient 301/504** ([REDACTED] (b) (6)) was diagnosed with ALS in March 2007. The patient had bulbar symptoms of dysphonia and dysphagia reported in April 2009. The case report describing the circumstances surrounding his death indicates a case of pneumonia complicated with sepsis. The patient's hospital course for pneumonia and sepsis extended over a 3-week period and included an episode of cardio-respiratory arrest four days after admission from which she was successfully resuscitated. The case report notes increasing white blood cell count over the hospital course to 37, 500/mm<sup>3</sup> consistent with sepsis, anemia, hypoxic respiratory failure, and severe hypoalbuminemia. Based on the case report, the likelihood that the cause of death is pneumonia and the associated complications is very reasonable.

**Patient 135-501** ([REDACTED] (b) (6)) was a 42 year old Caucasian male diagnosed with ALS in March 2008, but the patient had ALS symptoms beginning in October 2007. The patient had a PEG tube placement for nutritional support (date not stated in report) and per the case report was terminated early from the study because of end stage ALS. He received hospice care and died at home on [REDACTED] (b) (6). The case report mentions that the patient also had (in addition to other complaints) insomnia and fecal impaction. The patient was on medication for insomnia. The expert report from the sponsor's consultant notes that the patient appeared to have significant respiratory compromise 10 days before his death. However, I could not find information in the case report to support that. There is no other information regarding the circumstances surrounding the patient's death, but it appears that the patient's disease was progressing rapidly as he was receiving hospice care, medications for insomnia, had a PEG tube for nutritional support, and suffered from constipation. Given all these circumstances, it is very likely that the patient died from his underlying disease.

In two of the cases (**patient 135-508**, [REDACTED] (b) (6) (on study drug at time of death] and **patient 301/501** ([REDACTED] (b) (6))), the patients died at home and the case report has very little information pertaining to the

actual circumstances surrounding the death. In the case of patient 301/501 ( (b) (6) ) (diagnosed with ALS in January 2007) it appears that the patient had episodes of hypoxia and apnea (? sleep-related). The patient reportedly died at home in his sleep and the patient caregiver noted that the patient was restless just prior to death. It is possible that the patient could have died from hypoxic respiratory failure since one of the oxygen saturation values noted in the report was as low as 83% which is clinically significant.

In the case of patient 135/508/ (b) (6) (diagnosed with ALS approx (b) (6) prior to death) , the report states that he died in his sleep, and there is no follow up information regarding his death. The case report notes that the patient had dysphagia (from January 2008, and aphasia from October 2007. The patient's death occurred on (b) (6) and given the history of aphasia, and dysphagia, it is probable that the death is related to the underlying ALS but there is not sufficient information in the report to conclude a respiratory cause of death.

In the case of the death that occurred in the patient who was on placebo, the patient had been on NIPPV (non-invasive pressure ventilation) prior to enrollment in the study which would indicate that the patient already had significant respiratory compromise.

There were 3 deaths in the open label period of this study (all in ALS patients). In all three cases, the patients had significant respiratory compromise as evidenced by the use of NIPPV (1 patient), hypoxemia, and oxygen supplementation, and concomitant acute illnesses (i.e. pneumonia in two patients). All of these concomitant conditions support the clinical assessment that the deaths were due to the underlying disease of ALS and the underlying respiratory compromise.

Oxygen saturations

Diurnal oxygen saturations were measured at baseline, day 15 and day 84, and nocturnal oxygen saturations were measured at baseline and day 15. The changes in the oxygen saturations are small and not clinically significant from a physiologic standpoint. The table below summarizes the baseline and day 15 O<sub>2</sub> saturation data for the ALS and overall population for the diurnal O<sub>2</sub> saturation, and the ALS and MS population for the nocturnal O<sub>2</sub> saturation (*data source Table 36.1 and 36.2 of study report*). Only data for the higher dose Zenvia 30/10 are shown. Data for the lower dose Zenvia 20/10 are similar.

Measure/Visit/Patient population		Zenvia -30/10	Placebo
<b><i>Diurnal O<sub>2</sub> saturation Overall and ALS population</i></b>			
Baseline resting Diurnal O <sub>2</sub> saturation (%) <b>Overall patients</b>	Mean [CI]	96.7 [96.45, 97.02]	96.9 [96.59, 97.12]
	Min, Max	90, 100	93, 100
	Median	97	97
Baseline resting Diurnal O <sub>2</sub> saturation (%) <b>ALS patients</b>	Mean [CI]	96.3 [ 95.7, 97.7]	96.5 [ 96.2, 96.8]
	Min, Max	90, 100	93, 99
	Median	96	96.5
Day 15 Resting Diurnal O <sub>2</sub> saturation (%) <b>Overall Patients</b>	Mean [CI]	96.2 [ 95.9, 96.5]	96.7 [96.3, 97]
	Min, Max	92, 99	90, 99
	Median	96	97
Day 15 Resting Diurnal O <sub>2</sub> saturation (%) <b>ALS Patients</b>	Mean [CI]	95 [ 95.2, 95.9]	96 [95.5, 96.4]
	Min, Max	92, 99	90, 99
	Median	95	96
<b><i>Resting Nocturnal O<sub>2</sub> saturation ALS and MS patients</i></b>			
Baseline Nocturnal O <sub>2</sub> saturation <b>ALS patients</b>	Mean [CI]	93 [91.7, 95]	93.9 [93.4, 94.3]
	Min, Max	<b>43</b> , 98	86, 98
	Median	94	94
Baseline Nocturnal O <sub>2</sub> saturation <b>MS patients</b>	Mean [CI]	95.2 [94.5, 95.9]	95.5 [94.8, 96.2]
	Min, Max	91, 99	87, 98
	Median	95	96
Day 15 Nocturnal O <sub>2</sub> saturation <b>ALS patients</b>	Mean [CI]	93.8 [93.2; 94.3]	93.8 [93.3,94.3]
	Min, Max	88, 98	89, 97
	Median	94	94
Day 15 Nocturnal O <sub>2</sub> saturation <b>MS patients</b>	Mean [CI]	95.2 [94.6,95.8]	95.2 [94.5, 96]
	Min, Max	91, 98	87, 99
	Median	96	96

The summary data are not concerning. The oxygen saturation values for the most part are within the 90% range which is normal.

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/s/

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LYDIA I GILBERT MCCLAIN  
10/07/2010

BADRUL A CHOWDHURY  
10/07/2010  
I concur



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** 10/07/2010

**To:** Russell Katz, M.D., Director  
 Division of Psychiatry Products

**Through:** Michael Klein, Ph.D., Director  
 Controlled Substance Staff

**From:** James R. Hunter, R.Ph., MPH, Pharmacist  
 Lori A. Love, M.D., Ph.D., Lead Medical Officer  
 Controlled Substance Staff

**Subject:** Zenvia (dextromethorphan hydrobromide and quinidine sulfate) NDA 21-879  
 Indication: Treatment of Pseudobulbar Affect (PBA)  
 Dosages: dextromethorphan and quinidine 30 mg/10 mg and 20 mg/10 mg  
 Sponsor: Avanir Pharmaceuticals, Inc.

**Materials reviewed:** Materials submitted April 23, 2010, by the sponsor as a Complete Response to Approvable Letter dated 10/30/2006, for NDA 21-879, completed CSS consults for NDA 21-879 by Geoffrey Zeldes dated 12/14/2005, by Silvia Calderon dated 10/05/2006, and minutes dated 11/18/2009 from a meeting between FDA/Avanir.

**Table of Contents**

**I. SUMMARY .....1**

A. BACKGROUND.....1

B. CONCLUSIONS:.....2

C. RECOMMENDATIONS:.....2

**II. REVIEW .....2**

A. CHEMISTRY.....2

B. PHARMACOLOGY OF DRUG SUBSTANCE AND ACTIVE METABOLITES .....2

C. CLINICAL STUDIES .....3

D. REVIEW OF REMS .....5

E. REVIEW OF ABUSE AND DEPENDENCE SECTION OF PRODUCT LABEL .....5

**I. Summary**

A. Background

This memo responds to the Division of Neurology consult to review the NDA 21-879 resubmission and comment on abuse potential issues and the sponsor’s proposed REMS.

The sponsor Avanir originally submitted NDA 21-879 on January 27, 2006, for Zenvia (formerly called AVP-923 or Neurodex™). FDA sent the sponsor an Approvable Letter for NDA 21-879 on October 30, 2006. Responding to deficiencies outlined in the Approvable Letter, the sponsor resubmitted NDA 21-879 on April 23, 2010. This NDA resubmission included an additional clinical study (07-AVR-123) assessing the safety and efficacy of a new formulation containing lower combination doses of dextromethorphan (DXM) hydrobromide and quinidine sulfate.

**B. Conclusions:**

1. The abuse potential of Zenvia can not be determined, as the Sponsor did not submit adequate animal or human data for this assessment. Because this product will be available by prescription only, and it has a proposed narrow indication for use, we expect that its abuse will be less than currently marketed, widely available, over-the-counter products containing DXM.
2. There are insufficient data to support a claim of lower abuse potential of Zenvia compared to DXM alone in product labeling for Zenvia.

**C. Recommendations:**

1. The sponsor must delete the following text in the Abuse and Dependence section of the proposed Zenvia product label: (b) (4)

[Redacted text block]

## **II. Review**

**A. Chemistry**

Zenvia is a combination drug product comprised of two FDA approved drugs, DXM hydrobromide and quinidine sulfate. Zenvia is an immediate release solid oral dosage form (hard gelatin capsule) available in (b) (4)  
[Redacted text] DXM 20 mg/quinidine 10 mg (Zenvia 20/10).

**B. Pharmacology of drug substance and active metabolites**

DXM is considered the central nervous system-acting component of Zenvia capsules. DXM is a sigma-1 receptor agonist and a noncompetitive antagonist of the N-methyl-D-aspartate-sensitive ionotropic glutamate receptor (NMDA receptor). Quinidine sulfate is a specific inhibitor of CYP2D6-dependent oxidative metabolism used in Zenvia to increase systemic bioavailability of DXM. The primary pharmacological action of the quinidine component in Zenvia is to inhibit competitively the metabolism of DXM by CYP2D6. Inhibiting first pass metabolism of DXM by quinidine increases systemic bioavailability of orally administered DXM, thus enhancing the potential for the pharmacological action of DXM. DXM is normally extensively converted by CYP2D6 to dextrorphan; another consequence of competitive inhibition by quinidine is decreased dextrorphan formation.

The sponsor asserts that the dextrorphan metabolite is responsible for most of the positive psychoactive effects associated with the abuse of DXM.

### C. Clinical Studies

The sponsor did not submit a human abuse potential study for Zenvia. The sponsor states that their search of the literature produced no evidence describing the abuse of prescription drug products containing DXM. Abuse using high doses of DXM-containing products sold over the counter is well documented in news reports and the medical literature.<sup>1,2</sup> There are documented public health problems associated with DXM abuse, especially in teenagers, and several large retail stores in the United States have voluntarily instituted age restrictions on the purchase of DXM-containing products sold over-the-counter. DXM is not currently a scheduled substance because it is currently exempted under the Controlled Substances Act [21, U.S.C. 811 (g) (2)].

Previously noted in the Calderon review (10/05/2006), DXM at high doses can produce dissociative effects similar to those of phencyclidine (PCP) and ketamine, both known drugs of abuse. Reports of DXM abuse describe symptoms of euphoria, decreased attention and concentration, ataxia, nystagmus, restlessness, lethargy, tactile and visual hallucinations, confusion, depression, synesthesias, insomnia, dilated pupils, slurred speech, and aggressive behavior.<sup>3,4,5,6</sup>

The sponsor reduced the amount of quinidine in each tablet of Zenvia from 30 mg to 10 mg in the resubmitted NDA 21-879. This change in formulation reduces the risk of cardiotoxicity from the quinidine component in Zenvia in overdose or in an abusing population relative to the initial formulation. However, cardiotoxicity from an overdose of the quinidine component remains a risk; therefore, the product label should continue to reflect that there are safety concerns associated with high doses of Zenvia.

#### 1. Adverse event profile through all phases of development - particularly those related to abuse potential

Phase 2/3 studies – Based on a series of meetings and discussions with the applicant, the agency suggested that the sponsor perform an additional clinical study (07-AVR-123) assessing the safety and efficacy of new formulations containing lower combination doses of DXM and quinidine. It was agreed that combined with previously submitted data, results from the 07-AVR-123 study would provide an acceptable basis for approval. This study included two combination doses of Zenvia: Zenvia 30/10 and Zenvia 20/10. In addition to the results of this study, six new final clinical study reports are submitted to NDA 21-879.

According to the sponsor, adverse events related to abuse were reported throughout all phases of Zenvia's development. The sponsor reported that 2% or less of the pseudobulbar affect patients reported adverse events associated with positive drug

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<sup>1</sup> Romanelli F, Smith KM. Dextromethorphan abuse: clinical effects and management. *J Am Pharm Assoc.* 2009;49(2):e20-5;quiz e26-27.

<sup>2</sup> Banken JA, Foster H. Dextromethorphan. *Ann N Y Acad Sci.* 2008;1139:402-411.

<sup>3</sup> Boyer, E.W., Dextromethorphan abuse. *Pediatr. Emerg. Care,* 2004, 20(12), 858-863.

<sup>4</sup> Miller, S.C., Coricidin (R) HBP cough and cold addiction. *J. Amer. Acad. Child Adolesc. Psychiatry,* 2005, 44(6), 509-510.

<sup>5</sup> Bobo, W.V., Fulton, R.B., Commentary on: Severe manifestations of coricidin intoxication. *Am. J. Emerg. Med.,* 2004, 22(7), 624-625.

<sup>6</sup> Ziaee, V., Akbari Hamed, E., Hoshmand, A., Amini, H., Kebriaeizadeh, A., Saman, K., Side effects of dextromethorphan abuse, a case series. *Addict Behav,* 2005, 30(8), 1607-1613.

effects<sup>7</sup>. The NDA resubmission, which takes into account the results of additional clinical studies, restates this finding<sup>8</sup>. The sponsor reports a 1.2% incidence rate of adverse events potentially related to abuse (euphoria and hallucinations) occurring in healthy subjects and in patients taking Zenvia in all clinical trials<sup>9</sup>. The incidence of adverse events reported in Sponsor-supported studies as either “euphoric mood” or “hallucinations” and coded as at least possibly related to Zenvia are included in Table 1 below. As shown in Table 2, the incidence of euphoric mood and hallucinations were more prevalent in the healthy subjects at higher doses of DXM when compared to the treated patient population.

Table 1. Incidence of Adverse Events (AEs) Reported as Euphoric Mood and Hallucinations by Subject Population in Avanir-Supported Studies

Population	Reported AEs		
	Euphoric Mood (%)	Hallucinations (%)	Combined Total (%)
Healthy Subjects (n=424)	14 (3.3)	4 (0.9)	18 (4.2)
Patients (n=1767)	5 (0.3)	1 (0.06)	5 (0.2)
Healthy Subjects + Patients (n=2191)	19 (0.9)	6 (0.4)	24 (1.1)

Table 2. Incidence of Adverse Events (AEs) Reported as Euphoric Mood and Hallucinations by Treatment

Population	Treatment: DXM mg/Q mg	Number of Subjects
Healthy Subjects (n=424)	<b>AEs Reported as Euphoric Mood</b>	
	60/60 BID	3
	60/45 BID	2
	60/15 BID	3
	60/15 Daily	1
	45/30 BID	2
	30/30 + 20 mg Paroxetine Daily	2
	30/30 BID + 10 mg Memantine Daily	1
	<b>AEs Reported as Hallucinations</b>	
	60/15 BID	2
30/30 + 20 mg Paroxetine Daily	2	
Patients (n=1767)	<b>AEs Reported as Euphoric Mood</b>	
	30/30 BID	5
	<b>AEs Reported as Hallucinations</b>	
20/10 BID	1	

<sup>7</sup> NDA 21,879. *Integrated Summary of Safety*, Section 13.7.3.1

<sup>8</sup> NDA 21,879, resubmission, *Integrated Summary of Safety*, Section 4.10.4 Summary of Abuse Potential

<sup>9</sup> NDA 21,879, REMS Supporting Document, Zenvia® (dextromethorphan and quinidine) Version 4.0 1 April 2010, Risk Management Plans Section 1.16

#### D. Review of REMS

A RiskMAP for this NDA was submitted June 4, 2006. On the basis of FDA comments, the sponsor prepared a revised RiskMAP dated December 22, 2006. The revised RiskMAP was reviewed and found adequate by both the review division and by CSS. Due to changes in FDA regulatory requirements affecting RiskMAPs, the sponsor prepared and submitted a REMS for Zenvia which retains the basic concepts in the previously approved RiskMAP. The stated goals of the Zenvia REMS are to promote the appropriate identification of patients with pseudobulbar affect for Zenvia treatment, reduce the occurrence of serious drug-drug interactions with Zenvia, and to reduce the potential for diversion or abuse. Physician and patient education will be administered via a Medication Guide, DHCP letters, and other educational efforts. The REMS includes the proposed Medication Guide and proposed Dear Healthcare Provider (DHCP) letter. A key message in these materials for patients is that there is a risk that Zenvia may be abused or diverted and patients must take care to properly store the drug to minimize this risk. The REMS also includes plans for monitoring databases for signals relating to abuse and diversion, such as internet surveillance to target websites frequented by DXM abusers and a plan to systematically review the medical literature for reports or articles that suggest Zenvia abuse.

#### E. Review of Abuse and Dependence Section of Product Label

The Abuse and Dependence section of the proposed Zenvia product label is adequate with the exception of the first two sentences of paragraph two, which read: (b) (4)

 These statements may imply that Zenvia has lower abuse potential compared to a product containing the same amount of DXM taken alone. Therefore, these statements taken together imply a comparative abuse potential and abuse deterrent claim for Zenvia. The sponsor cited submitted published preclinical studies and a 6-subject pilot study in normal subjects<sup>10</sup> to support these labeling claims. While these published literature citations are suggestive that the metabolic conversion of DXM to dextrophan may be a determinant of the abuse potential in humans, these citations alone are not sufficient to support an implicit claim for reduced abuse liability for Zenvia. Additionally, the Agency's current thinking on the topic of labeling claims for relative abuse potential is stated in FDA draft Guidance: Assessment of Abuse Potential of Drugs. Such claims may be supported by human pharmacology studies using positive controls, along with robust assessments of efficacy, safety, and biopharmaceutics. In addition, long-term epidemiologic studies may also be necessary to support comparative abuse potential and abuse deterrent claims. A previous CSS consult review of this NDA by Calderon (10/05/2006) also cautioned against the use of language describing a lower potential for abuse of the product based upon quinidine inhibition of the conversion of DXM to dextrophan. For the above reasons, we conclude that the sponsor has not provided sufficient data to support the claims made in these two labeling statements.

<sup>10</sup> Zawertailo LA, Tyndale RF, Busto U, Sellers EM. Effect of metabolic blockade on the psychoactive effects of dextromethorphan. Hum Psychopharmacol, 2010,25(1):71-9

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/s/

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JAMES R HUNTER  
10/08/2010

LORI A LOVE  
10/08/2010

LORI A LOVE on behalf of MICHAEL KLEIN  
10/08/2010



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL  
PRODUCTS

Date: October 4, 2010

From: Suchitra Balakrishnan, M.D., Ph.D.

Through: Norman Stockbridge, M.D., Ph.D.  
Division Director  
Division of Cardiovascular and Renal Products /CDER

To: Susan Daugherty  
Regulatory Project Manager  
Division of Neurology Products

Subject: Cardiac Safety Consult for Zenvia (NDA 21879)

This memo responds to your consult to us dated June 14, 2010 regarding cardiac safety issues related to Zenvia [quinidine (Q) 10 mg/dextromethorphan (DM)], sponsored by Avanir. Specifically we have been asked to evaluate the sponsor's cardiac risk assessments for Zenvia and proposed labeling. The QT-IRT received and reviewed the following materials:

- Your consult
- Cardiac safety report submitted by the sponsor
- Integrated Summary of Safety (ISS) for NDA 21879 and
- CSR for Study 07-AVR-123
- QT-IRT reviews of TQT studies 08-AVR-126 (September 17, 2010) & 05-AVR-119 (September 14, 2006)

## 1 BACKGROUND

Quinidine (Q) sulfate and dextromethorphan HBr (DM) are currently marketed individually. Quinidine sulfate is indicated for the reduction of frequency of atrial fibrillation/flutter beginning at a dose of 200 mg every 6 hours, conversion of atrial fibrillation/flutter to sinus rhythm beginning at a dose of 400 mg every 6 hours, and treatment of *P. falciparum* malaria. Dextromethorphan is an over-the counter drug that is

used as an antitussive agent and it is given in doses of 30 mg every 6 to 8 hours for up to 120 mg/day.

In this NDA, the sponsor is seeking the approval of Zenvia – a combination product containing dextromethorphan 20 mg (b) (4) and quinidine 10 mg, administered twice a day for the treatment of pseudobulbar affect. Pseudobulbar Affect (PBA), is an involuntary emotional expression disorder, characterized by such behaviors as pathological laughing and crying/weeping, emotional lability, and emotional incontinence. PBA occurs in patients with neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and Alzheimer's disease (AD) or in patients with neuronal damage following stroke or traumatic brain injury.

The applicant asserts that dextromethorphan, considered the active therapeutic agent, acts by controlling glutamate excitatory activity as an antagonist of sigma-1 and NDMA receptor activities. The action of quinidine in this product is to increase the plasma concentration of dextromethorphan by competitive inhibition of the metabolism of dextromethorphan (catalyzed by CYP2D6).

The definitive clinical trials in the original NDA submission (January 30, 2006) were conducted using a higher dose of quinidine, i.e., dextromethorphan 30 mg and quinidine 30 mg administered twice a day. In a previous thorough QT study (05-AVR-119), a standard dose of Neurodex (30 mg dextromethorphan and 30 mg quinidine) dosed twice daily for 7 doses caused QTcF elevation, observable prior to the last dose and maximal at 3 hours post-dose. The maximal mean placebo- and baseline- subtracted QTcF ( $\Delta\Delta\text{QTcF}$ ) for the therapeutic dose of Neurodex was 10.1 ms (mean), and the upper bound of the one-sided 95% CI was 15.0 ms. With the supra-therapeutic dose of dextromethorphan 60 mg and quinidine 60 mg, the maximal  $\Delta\Delta\text{QTcF}$  was 18.8 ms (mean) and the upper bound of the one-sided 95% confidence interval was 24.5 ms. The sponsor reported no significant changes in QRS intervals, PR intervals and HR.

- In an Approvable Letter (October 30, 2006), the division expressed concerns regarding the drug's association with an increase in the QT interval at the proposed daily dose in the context of the known proarrhythmic risk of quinidine. Based on PK/PD modeling of quinidine's effect on the QT interval; it was determined that 5% of the population who receives Q 30mg/DM would be expected to experience a prolongation of the QTc interval of about 19 ms.
- DNP also expressed concerns about quinidine being particularly dangerous in patients who are moving in and out of atrial flutter/fibrillation, due to the risk of torsade de pointes (TdP), and of supraventricular tachycardia from quinidine's effects on atrio-ventricular conduction.
- The 30-mg dose of quinidine was chosen in the earlier studies based on a finding that this dose converted 8/8 extensive metabolizers of CYP-2D6 (EMs) into poor metabolizers (PMs), as assessed by urinary metabolic ratio. DNP recommended that the sponsor evaluate a formulation with a lower dose of quinidine, given that a 10-mg dose of quinidine converted 6/7 EMs to PMs.

In this re-submission, the sponsor has now conducted additional studies including a phase 3 clinical study (07-AVR-123) and another thorough QT study (08-AVR- 126) assessing a new formulation (Zenvia) using a lower quinidine dose (dextromethorphan 20 mg or 30 mg and quinidine 10 mg). The new TQT study has been reviewed by the QT-IRT. Even at this dose, QT prolongation is noted with a maximum mean  $\Delta\Delta QTcF$  of 10.2 ms and largest upper bound of the 90% CI of 12.6 ms. The sponsor has also submitted an integrated cardiac safety report for Zenvia. The division has requested DCRP to review the same and to provide comments regarding cardiac risk and risk mitigation strategies.

## 1.1 PRECLINICAL INFORMATION FROM SPONSOR

*Source Pharmacology written Summary, eCTD 2.6.2*

### **“Effects of AVP-923 on HERG Tail Current Recorded from Stably Transfected HEK293 Cells (Study No. SPH04-040; Avanir No. DMQ-130)**

When tested as separate drugs, quinidine inhibited hERG current with an  $IC_{50}$  of 0.469  $\mu M$ , and dextromethorphan inhibited hERG current with an  $IC_{50}$  of 17.8  $\mu M$ . The combination product, DM/Q, inhibited hERG current with an  $IC_{50}$  of 347.5 ng/mL. This is equivalent to 0.444  $\mu M$  quinidine and 0.469  $\mu M$  dextromethorphan for the combination, which is consistent with quinidine inhibition (dextromethorphan concentration too low in this experiment to contribute meaningfully to hERG current inhibition). The positive control E-4031, at a high concentration of 100 nM, inhibited hERG current by over 90%. Given the high concentration of E-4031 utilized (the  $IC_{50}$  is approximately 10-15 nM), assay sensitivity was not convincingly shown.

### **“In Vitro Effects of Quinidine Sulfate on QRS, QT, $T_{p-e}$ and Proarrhythmias in the Rabbit Left Ventricular Wedge Preparation (Study DMQ-146).**

Q had no significant effect on the QRS interval. A statistically significant dose dependent prolongation of the QT interval was observed at 0.3 (+13%), 1.0 (+27%) and 3 (+50%)  $\mu M$ . A statistically significant increase in  $T_{p-e}$  intervals was observed at 0.1 (+8%), 0.3 (+26%), 1.0 (+53%) and 3.0 (+103%)  $\mu M$ . No significant effects were observed at 0.03  $\mu M$ ; 0.03  $\mu M$  is equivalent to a concentration of approximately 10 ng/mL.” It is concluded that quinidine alters repolarization parameters in this model.

*Reviewer’s Comment: Based upon the observed low potency of DM on hERG current ( $IC_{50} = 17.8 \mu M / 6,592 \text{ ng/mL}$ ), the sponsor assumes that the increase in  $QTc$  observed in patients given the combination product was due exclusively to quinidine. However, it is our non-clinical reviewer’s opinion that it is theoretically possible that dextromethorphan contributed to the prolongation in  $QTc$  observed in patients given the combination product (see below). In addition, in the TQT studies for the various combinations of DM/Q the clinical pharmacology reviewers concluded that the studies were not designed to separate effects of quinidine and DM.*

## 1.2 NON-CLINICAL LITERATURE REVIEW BY DR. JOHN KOERNER

Quinidine has been studied extensively non-clinically, and has been shown to prolong action potential duration and reduce maximum upstroke velocity in isolated cardiac

tissues, effects consistent with inhibition of potassium and sodium currents, respectively.<sup>1</sup> Whole cell voltage clamp studies demonstrate inhibition of hERG and cloned human sodium channel currents, as well as calcium and other cardiac ionic currents, at relevant concentrations. Quinidine appears to be more potent on hERG and IKr than on sodium and calcium currents, which is consistent with QT prolongation in the absence of other electrophysiological effects.

**Table 1: Effect of Quinidine on Cardiac Currents**

Current	Channel	Test System	IC50 (µM)	Reference
I <sub>Kr</sub>	hERG	HEK 293	0.41±0.04	Paul, et al. <sup>2</sup>
I <sub>K(r)</sub>	-	Feline VM*	0.18	Woosley, et al. <sup>3</sup>
	-	Rabbit VM	4.5±0.03^^	Wu, et al. <sup>4</sup>
I <sub>Kur</sub>	-	Human AM^	5.0	Wang, et al. <sup>5</sup>
	-	Canine AM	5.0±0.3	Yue, et al. <sup>6</sup>
I <sub>to</sub>	-	Human AM	5.0 (40% inhibition)	Wang, et al. <sup>5</sup>
	-	Rat VM	15.0	Michel, et al. <sup>7</sup>
	-	Rat VM	3.9	Slawsky, Castle. <sup>8</sup>
I <sub>Na (peak)</sub>	hNav1.5	HEK 293	10.4 (8.3-12.9) Conventional 5.2 (4.8-5.7) IonWorks®	Harmer, et al. <sup>9</sup>
	-	Rabbit VM	11.0±0.07	Wu, et al. <sup>4</sup>
I <sub>Na (late)</sub>	-	Rabbit VM	12.0±0.7	Wu, et al. <sup>4</sup>
I <sub>Ca (L-type)</sub>	-	Guinea pig VM	14.9±1.5	Zhang, Hancox. <sup>10</sup>
	-	Rat VM	10.0	Michel, et al. <sup>7</sup>
Na-Ca Exchanger	-	GP VM	~100 (33 % inhibition)	Zhang, Hancox. <sup>10</sup>

\* VM, ventricular myocytes; ^ AM, atrial myocytes

^^ It is not clear why potency on rabbit I<sub>Kr</sub> is less than that for hERG and IKr in feline ventricular myocytes, but given the disparity in potencies, this IC50 is presumed to be artifactually high.

<sup>1</sup> Salata JJ, Wasserstrom JA. Effects of Quinidine on Action Potentials and Ionic Currents in Isolated Canine Ventricular Myocytes. *Circulation Research*. 1988; 62: 324-337

<sup>2</sup> Paul AA, Witchel HJ and Hancox JC. Inhibition of the Current of Heterologously Expressed HERG Potassium Channels by Flecaïnide and Comparison with Quinidine, Propafenone and Lignocaine. *British Journal of Pharmacology*. 2002; 136: 717-729.

<sup>3</sup> Woosley RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the Cardiotoxic Actions of Terfenadine. *JAMA*. 1993; 269: 1532-1536.

<sup>4</sup> Wu L, Guo D, Li H, Hackett J, Yan G, Jiao Z, Antzelevitch C, Shyrock JC, Belardinelli L. Role of Late Sodium Current in Modulating the Proarrhythmic and Antiarrhythmic Effects of Quinidine. *Heart Rhythm*. 2008; 5: 1726-1734.

<sup>5</sup> Wang Z, Fermini B, Nattel S. Effects of Flecaïnide, Quinidine, and 4-Aminopyridine on Transient Outward and Ultrarapid Delayed Rectifier Currents in Human Atrial Myocytes. *JPET*. 1995; 272: 184-196.

<sup>6</sup> Yue L, Feng JL, Wang Z, Nattel S. Effects of Ambasalide, Quinidine, Flecaïnide and Verapamil on Ultrarapid Delayed Rectifier Potassium Currents in Canine Atrial Myocytes. *Cardiovascular Research*. 2000; 46: 151-161.

<sup>7</sup> Michel D, Wegener JW, Nawrath. Effects of Quinine and Quinidine on the Transient Outward and on the L-Type Ca<sup>2+</sup> Current in Rat Ventricular Myocytes. *Pharmacology* 2002; 65: 187-192.

<sup>8</sup> Slawsky MT, Castle NA. K<sup>+</sup> Channel Blocking Actions of Flecaïnide Compared to Those of Propafenone and Quinidine in Adult Rat Ventricular Myocytes. *JPET*. 1994; 269: 66-74.

<sup>9</sup> Harmer AR, Abi-Gerges N, Easter A, Woods A, Lawrence CL, Small BG, Valentin J-P, Pollard CE. Optimisation and Validation of a Medium Throughput Electrophysiology-based hNav1.5 Assay Using IonWorks®. *Journal of Pharmacological and Toxicological Methods*. 2008; 57: 30-41.

<sup>10</sup> Zhang YH, Hancox JC. Mode-Dependent Inhibition of Na-Ca Exchanger Current From Guinea Pig Isolated Ventricular Myocytes. *Clinical and Experimental Pharmacology and Physiology*. 2002; 29: 777-781.

Dextromethorphan inhibited hERG expressed in Chinese hamster ovary cells with an IC50 of  $5.1 \pm 0.04 \mu\text{M}$ .<sup>11</sup> Given plasma dextromethorphan levels in patients given the combination product (dextromethorphan hydrobromide (30 mg)/quinidine sulfate (10 mg, b.i.d.), the dextromethorphan component of the combination product could theoretically contribute to the observed QT effect in human subjects. Note that drugs with ratios (IC50 hERG/plasma drug level) of less than 30-fold have been reported for several drugs that prolong QT interval in human subjects.<sup>12</sup> Data are unavailable on other electrophysiological effects of dextromethorphan.

**Table 2: Effect of dextromethorphan on hERG current**

Dextromethorphan				
hERG IC50 ( $\mu\text{M}$ )	Cmax (day 8)		Ratio (IC50)/Cmax	
	Total	Free <sup>^</sup>	Total	Free
5.1 $\pm$ 0.04	0.42 $\mu\text{M}$	0.28 $\mu\text{M}$	12X	18X
	113 ng/ml			

\* Mean + 2SD; <sup>^</sup> Percent unbound drug, 66%

Limited information could be located on the nonclinical effects of quinidine and dextromethorphan metabolites. Quinidine metabolites have been reported to be electrophysiologically active, with concentration related action potential duration lengthening and reduction of maximum upstroke velocity.<sup>13</sup> Relative in vitro potencies on action potential duration are quinidine > 3-hydroxyquinidine > quinidine-N-oxide.<sup>14</sup> 3-hydroxyquinidine reduced maximum upstroke velocity, but less potently than parent drug.<sup>15</sup> Both quinidine and 3-hydroxyquinidine produced early afterdepolarizations *in vitro* at high concentrations. Other metabolites were not evaluated for electrophysiologic effects.

Data on electrophysiological effects of dextromethorphan metabolites could not be located. Additionally, this reviewer could not locate literature data on the effects of metabolites of quinidine and dextromethorphan on cardiac ionic currents, including hERG current.

### 1.3 PREVIOUS CLINICAL EXPERIENCE

*Source: Summary of Clinical Safety (eCTD 2.7.4), ISS and Cardiac Safety Report*

<sup>11</sup> Deisemann H, et al. Effects of Common Antitussive Drugs on the hERG Potassium Channel Current. *J Cardiovascular Pharmacol.* 2008; 52: 494-499.

<sup>12</sup> Redfern W, et al. Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. *Cardiovascular Research.* 2003; 28: 32-45.

<sup>13</sup> Thompson KA, Blair IA, Woosley RL, Roden DM. Comparative *In Vitro* Electrophysiology of Quinidine, Its Major Metabolites and Dihydroquinidine. *JPET.* 1987; 241: 84-90.

<sup>14</sup> Uematsu T, Sato R, Vozeh S, et al. Relative Electrophysiologic Potencies of Quinidine, 3-OH Quinidine, and Quinidine-N-Oxide in Guinea Pig Heart. *Arch. Int. Pharmacodyn.* 1989; 297: 29-38.

<sup>15</sup> Fautrez VM, Adamantidis MM, Caron JF, et al. Comparative Electrophysiologic Effects of Metabolites of Quinidine and Hydroxyquinidine. *J. Cardiovasc. Pharmacol.* 1993; 19: 308-318.

Quinidine, when used for treatment of atrial fibrillation and atrial flutter, has been associated with other cardiac arrhythmias including torsade de pointes (TdP)<sup>16</sup>, atrioventricular (AV) block/intraventricular conduction delay, supraventricular and ventricular tachycardia. In addition to delayed repolarization, quinidine decreases cardiac conduction velocity, including depression of atrioventricular and ventricular conduction. Quinidine also has autonomic effects which may increase heart rate, decrease blood pressure and AV nodal conduction velocity. The conduction depressant effects are the result of sodium and calcium channel blockade, while the acceleratory effects are thought to be adrenergically, and, to some extent, vagally (“vagolytic effect”) mediated<sup>17</sup>. However, the daily dose of quinidine in Zenvia is 1 to 3% of the recommended anti-arrhythmic dose of quinidine (200-400 mg 3 to 4 times daily = 600-1600 mg/day) and, at this lower dose level, quinidine acts as a selective inhibitor of the cardiac potassium channel,  $I_{Kr}$ , producing inhibition at  $I_{Kr}$  that is dose related. The sponsor asserts that the risk for QT prolongation leading to ventricular tachycardia or TdP with Zenvia is low. The sponsor also reports that inhibition of  $I_{Na}$  and prolongation of QRS are only observed at the upper region of the quinidine anti-arrhythmic dose-response curve and has not been observed for the quinidine concentrations found in Zenvia.

*Reviewer’s Comment: The IC50 for IKr blockade with quinidine has been reported to be as low as 0.18  $\mu$ M. Mean quinidine Cmax observed in the clinical pharmacokinetics (PK) study 07-AVR-125 for the DM 30 mg/Q 10 mg dose was 66 ng/ml ( about ~ 0.2  $\mu$ M) at Day 8. This indicates that even with exposures from the 10 mg quinidine dose QT prolongation is likely.*

### 1.3.1 Exposure in clinical studies

The total number of subjects exposed to DM/Q in all Avanir-sponsored studies is 1635, comprising 946 patients with PBA, 292 patients with diabetic polyneuropathy (DPN), 373 healthy volunteers (HV), and 24 subjects with renal or hepatic impairment. In the integrated studies, exposure to the DM/Q combination at any dose level ranged from 1 to 1612 days. In total, 392 subjects (28.2%) have been exposed to varying combinations of DM and Q for at least 180 days and 303 subjects (21.7%) have been exposed for at least 360 days. The sponsor pooled subjects in various clinical studies into 5 safety datasets:

- Pool 1-Integrated studies in healthy volunteers (Study 99-AVR-100, Study 99-AVR-101, Study 00-AVR-103, and Study 07-AVR-125), patients with DPN pain (Study 01-AVR-105 and Study 04-AVR-109), and patients with PBA (Study 99-AVR-102, Study 02-AVR-106, Study 02-AVR-107, and Study 07-AVR-123).
- Pool 2-Patients with PBA in Phase 3 controlled and uncontrolled studies (Study 99-AVR-102, Study 02-AVR-106, Study 02-AVR-107, and Study 07-AVR-123).
- Pool 3- Patients with PBA in controlled Phase 3 studies (Study 99-AVR-102, Study 02-AVR-106, and Study 07-AVR-123)
- Pool 4-Patients with PBA who had long-term exposure (Study 02-AVR-107 and Study 07-AVR-123). Study 02-AVR-107 was an open-label, safety study of AVP-923 (capsules containing 30 mg DM and 30 mg Q) for 52 weeks. Subjects

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<sup>16</sup> Selzer A, Wray HW. Quinidine Syncope. Paroxysmal Ventricular Fibrillation Occurring During Treatment Of Chronic Atrial Arrhythmias. *Circulation*. Jul 1964;30:17-26.

<sup>17</sup> Mason JW, Hondeghem LM. Quinidine. *Ann N Y Acad Sci*. 1984;432:162-176.

who completed 52 weeks of treatment could continue to receive study medication in an optional extension phase. The open label extension phase of 07-AVR-123 evaluating the DM 30 mg /Q 10 mg lasted 12 weeks only

- Other patients in Phase 2 and Phase 3 studies including DPN pain patients (Study 01-AVR-105 and Study 04-AVR-109), referred to as “Other Safety Patients (OSP).”

*Reviewer’s Comment: Underlying disease in patients with PBA was mainly ALS or MS. In Study 02-AVR-107, 154 patients with other neurological conditions were followed-46 patients with stroke, 21 with traumatic brain injury, 16 with primary lateral sclerosis, 15 with Parkinson’s disease, and 14 with Alzheimer’s disease. The division has expressed concern regarding the safety implications in patients with diseases other than ALS or MS because of the limited sample sizes.*

### **1.3.2 ECG effects**

#### Collection of ECGs

- In 02-AVR-107 (Phase 3 study in subjects with PBA evaluating the DM 30 mg/Q 30 mg dose) single 12 lead ECGs were performed at screening, Day 29, and Week 52 (or the final visit), and for subjects who continued in the extension phase-annually and at the extension termination visit.
- In 07-AVR-123 (Phase 3 study in subjects with PBA evaluating the DM 20 or 30 mg/Q 10mg dose), twelve-lead ECGs (including a 2-minute rhythm strip) were obtained at all visits for both double-blind (DB) and open-label extension (OLE) phases of the study, which were both 12 weeks in duration. ECGs were collected at baseline, Days 1, 15, 29, 57 and 84 in the DB phase and Days 1, 15, 42 and 84 in the OLE phase.
- ECGs were centrally read.

#### *Reviewer’s Comments:*

- *Information about ECG timing relative to dose is unavailable. Based on PK parameters and concentration vs. time profiles reported on Study 07-AVR-125, large peak-trough variations with quinidine concentrations (at 10 mg dose level) are not expected.*
- *Infrequent ECG sampling, specifically in the older studies limits conclusions regarding relationship of QT-prolongation related AEs to study drug in the absence of an ECG prior to the event.*

For QTcF in controlled studies in PBA patients (Pool 3), 10 subjects (2.9%) treated with any dose of the DM/Q combination showed a shift from <450 ms at baseline to  $\geq$ 450 ms during treatment, which was similar to the placebo group (3.9%) (Table 3). None of the patients exposed to any dose of DM/Q showed a shift in QTcF from < 480 ms at baseline to  $\geq$  480 ms during treatment, or from < 500 ms at baseline to  $\geq$ 500 ms during treatment.

**Table 3: Shifts in QTcF- controlled studies in PBA patients (Pool 3)**

Table 44.2.2  
Shifts in QT, QTcB, and QTcF Values from Baseline to Most Abnormal Post-Baseline Result  
Pool 3: All PBA Patients in Controlled Studies

Parameter and Shift Criterion	Baseline Value	Most Abnormal On-Treatment Value	AVF-923				
			20 mg DM/ 10 mg Q (N=107) [1]	30 mg DM/ 10 mg Q (N=110) [1]	All doses with 10 mg Q (N=217) [1]	All doses with 30 mg Q (N=146) [1]	All AVF-923 (N=363) [1]
QTcF >= 450 ms	< 450 ms	N [2]	97	107	204	139	343
	>= 450 ms	>= 450 ms	4 (4.1%)	6 (5.6%)	10 (4.9%)	0	10 (2.9%)
	>= 450 ms	>= 450 ms	0	1 (0.9%)	1 (0.5%)	0	1 (0.3%)
	< 450 ms	< 450 ms	91 (93.8%)	100 (93.5%)	191 (93.6%)	139 (100%)	330 (96.2%)
QTcF >= 480 ms	< 480 ms	N [2]	97	107	204	139	343
	>= 480 ms	>= 480 ms	0	0	0	0	0
	>= 480 ms	>= 480 ms	0	0	0	0	0
	< 480 ms	< 480 ms	97 (100%)	107 (100%)	204 (100%)	139 (100%)	343 (100%)
QTcF >= 500 ms	< 500 ms	N [2]	97	107	204	139	343
	>= 500 ms	>= 500 ms	0	0	0	0	0
	>= 500 ms	>= 500 ms	0	0	0	0	0
	< 500 ms	< 500 ms	97 (100%)	107 (100%)	204 (100%)	139 (100%)	343 (100%)

Table 44.2.2  
Shifts in QT, QTcB, and QTcF Values from Baseline to Most Abnormal Post-Baseline Result  
Pool 3: All PBA Patients in Controlled Studies

Parameter and Shift Criterion	Baseline Value	Most Abnormal On-Treatment Value	Placebo	DM 30 mg	Q 30 mg
			(N=183) [1]	(N=33) [1]	(N=37) [1]
QTcF >= 450 ms	< 450 ms	N [2]	178	31	35
	>= 450 ms	>= 450 ms	7 (3.9%)	0	0
	>= 450 ms	>= 450 ms	2 (1.1%)	0	0
	< 450 ms	< 450 ms	169 (94.9%)	31 (100%)	35 (100%)
QTcF >= 480 ms	< 480 ms	N [2]	178	31	35
	>= 480 ms	>= 480 ms	1 (0.6%)	0	0
	>= 480 ms	>= 480 ms	0	0	0
	< 480 ms	< 480 ms	177 (99.4%)	31 (100%)	35 (100%)
QTcF >= 500 ms	< 500 ms	N [2]	178	31	35
	>= 500 ms	>= 500 ms	0	0	0
	>= 500 ms	>= 500 ms	0	0	0
	< 500 ms	< 500 ms	178 (100%)	31 (100%)	35 (100%)

Note: Treatment categories are not mutually exclusive. Thus, patients may contribute to more than one treatment category.  
 Note: Percentages are 100\*(the number who experienced the indicated shift)/(the number of patients who had at least one on-treatment value).  
 Note: Patients who are missing a baseline value are included and are assumed to be NCS at baseline.  
 Note: DM = Dextromethorphan Hydrobromide USP; Q = Quinidine Sulfate USP.  
 [1] Number of patients in the population.  
 [2] Number of patients who had at least one on-treatment value for the parameter (included in analysis).  
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Source: Table 44.2.2, ISS

In Pool 1, for QTcF, 49 (3.9%) of 1251 subjects treated with any dose of the DM/Q combination showed a shift from < 450 ms at baseline to ≥ 450 ms during treatment; 9 (0.7%) of 1251 showed a shift from < 480 ms at baseline to ≥ 480 ms during treatment, and 4 (0.4%) of 1251 subjects showed a shift from < 500 ms at baseline to ≥ 500 ms during treatment (Table 4).

**Table 4: Shifts in QTcF-Integrated studies (Pool 1)**

Table 44.2.1  
Shifts in QT, QTcB, and QTcF Values from Baseline to Most Abnormal Post-Baseline Result  
Pool 1: Integrated Studies

Parameter and Shift Criterion	Baseline Value	Most Abnormal On-Treatment Value	AVP-923				
			20 mg DM/ 30 mg Q (N=107) [1]	30 mg DM/ 30 mg Q (N=283) [1]	All doses with 30 mg Q (N=314) [1]	All doses with 30 mg Q (N=947) [1]	All AVP-923 (N=1396) [1]
QTcF>=450 ms	< 450 ms	N [2]	97	261	288	872	1251
	>=450 ms	>=450 ms	4 (4.1%)	14 (5.4%)	18 (6.3%)	27 (3.1%)	40 (3.9%)
	<450 ms	<450 ms	0	3 (1.1%)	3 (1.0%)	5 (0.6%)	0 (0.7%)
	>=450 ms	<450 ms	91 (93.8%)	243 (93.1%)	264 (91.7%)	835 (95.8%)	1185 (94.7%)
QTcF>=480 ms	< 480 ms	N [2]	97	261	288	872	1251
	>=480 ms	>=480 ms	0	1 (0.4%)	1 (0.3%)	7 (0.8%)	0 (0.7%)
	<480 ms	<480 ms	0	0	0	0	0
	>=480 ms	<480 ms	97 (100%)	260 (99.6%)	287 (99.7%)	865 (99.2%)	1242 (99.3%)
QTcF>=500 ms	< 500 ms	N [2]	97	261	288	872	1251
	>=500 ms	>=500 ms	0	0	0	3 (0.3%)	4 (0.3%)
	<500 ms	<500 ms	0	0	0	0	0
	>=500 ms	<500 ms	97 (100%)	261 (100%)	288 (100%)	869 (99.7%)	1247 (99.7%)

Parameter and Shift Criterion	Baseline Value	Most Abnormal On-Treatment Value	Placebo	DM 30 mg	Q 30 mg
			(N=316) [1]	(N=62) [1]	(N=37) [1]
QTcF>=450 ms	< 450 ms	N [2]	293	55	35
	>=450 ms	>=450 ms	10 (3.4%)	0	0
	<450 ms	<450 ms	4 (1.4%)	0	0
	>=450 ms	<450 ms	276 (94.2%)	54 (98.2%)	35 (100%)
QTcF>=480 ms	< 480 ms	N [2]	293	55	35
	>=480 ms	>=480 ms	2 (0.7%)	0	0
	<480 ms	<480 ms	1 (0.3%)	0	0
	>=480 ms	<480 ms	290 (99.0%)	54 (98.2%)	35 (100%)
QTcF>=500 ms	< 500 ms	N [2]	293	55	35
	>=500 ms	>=500 ms	0	0	0
	<500 ms	<500 ms	0	0	0
	>=500 ms	<500 ms	293 (100%)	54 (98.2%)	35 (100%)

Note: Treatment categories are not mutually exclusive. Thus, patients may contribute to more than one treatment category.  
Note: Percentages are 100\*(the number who experienced the indicated shift)/(the number of patients who had at least one on-treatment value).

Note: Patients who are missing a baseline value are included and are assumed to be NCS at baseline.

Note: DM = Dextromethorphan Hydrochloride USP; Q = Quinidine Sulfate USP.

[1] Number of patients in the population.

[2] Number of patients who had at least one on-treatment value for the parameter (included in analysis).

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Source: Table 44.2.1, ISS

- Subject AVR107-003-008 (DM 30 mg/Q 30 mg), a female with MS, had a shift from a baseline QTcF of 455 to 505 ms at the end of study visit. Approximately one year before the time of the QTcF shift, before study entry, the subject had a history of prolonged QT, recorded as ongoing.
- Subject AVR103-001-039 (DM 45 mg/Q 60 mg), a healthy male subject, had a shift from a baseline QTcB of 363 ms to 522 ms at Day 8 and a shift from a baseline QTcF of 367 to 534 ms at Day 8. The ECGs in this study were not read by a central ECG laboratory. When these ECGs were re-read by a central laboratory, QTcB on Day 8 was determined to be 357 ms and QTcF was 364 ms.
- Subject AVR107-003-017 (DM 30 mg/Q 30 mg), a male with MS, had a shift from a baseline QTcB of 422 to 506 ms at Week 156. Approximately 5 months later, the subject had a shift from a baseline QTcB of 422 ms to 526 ms and a shift from a baseline QTcF of 413 to 506 ms.

- Subject AVR109-150-002 (DM 30 mg/Q 30 mg), a male patient with DPN pain, had a shift from a baseline QTcB of 428 to 502 ms at Day 29
- Subject AVR123-208-502 (placebo) had a shift from a baseline QTcB of 492 to 501 ms at Day 15

*Reviewer's Comments:*

*The subject on placebo had a baseline QTcF of 492 ms. All subjects on DM/Q were not on any concomitant QT prolonging medications. Given the infrequent ECG sampling in the older studies evaluating the 30 mg quinidine dose, it is possible that several outliers were not captured. The large difference between site and central core lab ECG reads for Subject AVR103-001-039 raises concerns regarding the quality of safety monitoring in this study.*

### **1.3.3 Integrated Cardiac AEs**

Although there are no reports of TdP or significant ventricular arrhythmias in the clinical studies, limited size of the safety database (~ 1500 patients in total) and infrequent ECG sampling limits conclusions regarding pro-arrhythmic liability, especially with the older studies evaluating the DM 30 mg/Q 30 mg dose.

#### **1.3.3.1 Cardiovascular deaths**

The sponsor convened a group of cardiologists to screen all 92 deaths that occurred in the clinical development program (see Table 5) in order to identify those that might have been due to cardiovascular causes. More specifically, the committee was asked to identify events of sudden death, where, as such, arrhythmia might have been involved. Cause specific mortality was first attributed to a general pathophysiological category: cardiovascular, respiratory, or other. A determination was then made as to whether the cardiovascular deaths were sudden and/or unexpected. Potential relationship to DM/Q treatment was also assessed. Nine of the 92 deaths were preliminarily screened as potentially due to cardiovascular-related events by the Committee (Table 6). Four cases of sudden death were identified for which arrhythmia could not be initially excluded and required further assessment (**Table 7**).

**Table 5: Deaths Reported by study number (Total deaths =92)**

Study Number	Dose	Primary Disease	Number of Deaths	Duration of Exposure (days)	Adverse Event / Cause of Death (study day)	Relationship to Study Medication
07-AVR-123 <sup>a</sup>	DM 30 mg/ Q 10 mg	PBA (ALS)	6	57 to 169	4 Respiratory Failure (41-95) Dyspnea (96) Pneumonia (113)	Unrelated/ Unlikely
	DM 20 mg/ Q 10 mg	PBA (ALS)	3	84	Respiratory Failure (84)	Unrelated
				23	Disease Progression (41)	Unlikely
				84	Oxygen Saturation Decreased (85), Respiratory Depression (85, 89)	Possible <sup>b</sup>
Placebo	PBA (ALS)	1	8 <sup>a</sup>	Disease Progression (40)	Unlikely	
99-AVR-100	DM 30 mg/ Q 75 mg	Healthy volunteer <sup>c</sup>	1	4	Myocardial infarction (6 days after last dose of study drug)	Unrelated
99-AVR-102	DM 30 mg/ Q 30 mg	PBA (ALS)	1	28 <sup>c</sup>	Respiratory failure (30)	Unrelated
01-AVR-105	DM 30 mg/ Q 30 mg	OSP	1	29	Arrhythmia (33) Myocardial Infarction (33)	Unlikely
02-AVR-107	DM 30 mg/ Q 30 mg	PBA (ALS) 64 PBA (Other*) 15	79	11 to 1393	53 Respiratory Failure 26 other (Described in text below)	Unrelated/ Unlikely
<b>Total</b>			<b>92</b>			

Source: Listing 21.3.1. In the source listing, where the date for the last dose was missing, the last date was imputed.

<sup>a</sup> Deaths are shown for both phases of the study, DB and OLE.

<sup>b</sup> Death of ALS patient AVR123-301-501 was reviewed by the Mortality Endpoint Adjudication Committee, which concluded that it was probably due to progression of the underlying disease, i.e. unlikely to be treatment-related.

<sup>c</sup> Not included in the integrated dataset; this death was previously discussed with FDA in NDA 21-879

<sup>d</sup> For the subjects with missing last dose dates in the database, the last dose date from the safety narrative was used.

<sup>e</sup> Primary diseases are discussed in detail in the text below.

DM = dextromethorphan hydrobromide USP; Q = quinidine sulfate USP; PBA = pseudobulbar affect; ALS = amyotrophic lateral sclerosis; OSP = other safety patients (DPN pain).

For additional information, see 5.3.5.3 Analysis of Cardiac Safety for Zenvia

Source Table 15, ISS

*Reviewers Comments: Respiratory system complications and abnormalities are common in patients with ALS, and respiratory failure remains the most common cause of death. Of the total number of deaths in all studies, 79 occurred in Study 02-AVR-107. Among these subjects, 64 had ALS and 15 had other CNS pathology. Given that all the deaths adjudicated as respiratory failure in the clinical program were reported in ALS patients only, this is expected to be the more likely cause of death. However, sudden cardiac death cannot be completely excluded, especially in unobserved deaths in the absence of an ECG shortly before the death. It is to be noted that routine ECGs in 02-AVR-107 were only collected at Day 29, week 52 and then annually (see 1.3.2).*

**Table 6: Preliminary Screening of Cause-of Death**

System	Number (Percent)	Subcategory	Number N = 92
Cardiovascular	9 (9.8%)	Congestive heart failure	0
		MI/Ischemia	1
		Sudden death*	4
		Other	4
		Specify: intracerebral hemorrhage (2) pulmonary embolism (1) hemorrhagic stroke (1)	
Respiratory	77 (83.7%)	Respiratory Failure	65
		COPD	0
		Pneumonia	10
		Other	2
		Specify: aspiration (1) asthma (1)	
Other cause	6 (6.5%)	Specify: septicemia (1)	6
		suicide (2)	
		overdose (1)	
		subdural hematoma (1)	
		bowel obstruction (1)	

\*Unable to exclude arrhythmia.

Source: Table 13-Cardiac safety Report for Zenvia

**Table 7: Summary of Sudden Deaths for which Arrhythmias could not be Initially Excluded**

Patient Study/ Number	Age (years)/ Sex	Primary Disease	Treatment Group	Study Day of Onset	Duration of Exposure (Days)	SAE Description**/ Summary of Event	Relationship to Study Drug**
02AVR107 30-001	64/F	ALS	DM 30 mg Q 30 mg	270	270	Cardiac arrest/ hypertensive cardiovascular disease. Patient died in the hospital.	Unrelated
02AVR107 34-035	62/M	ALS	DM 30 mg Q 30 mg	371	371	Respiratory arrest secondary to ALS. Subject died while getting into car after visiting his son shortly after a clinic visit.	Unrelated
02AVR107 34-039	51/F	Previous stroke	DM 30 mg Q 30 mg	41	41	Possible Stroke. Occurred in the home.	Unrelated
01AVR105 04-006	64/M	DPN pain	DM 30 mg Q 30 mg	33	29	Exacerbation of COPD, myocardial infarction, arrhythmia. Subject with Type 1 diabetes. Occurred in the hospital 4 days after last dose.	Unlikely

\*\* Based on Investigator assessment; M = male; F = female; ALS = amyotrophic lateral sclerosis; DPN = diabetic peripheral neuropathic

Source: Table 14-Cardiac Safety Report for Zenvia

*Reviewer's Comment: The sponsor's pathophysiological classification for cause of death seems acceptable. Narratives in appendix 3 of the cardiac safety report for cardiovascular and sudden deaths were reviewed; significant confounding due to comorbidities in this population limits assessment in some of the cases. Overall, sponsor's conclusions seem reasonable.*

There were 7 patients whose deaths were considered sudden in the clinical studies with DM/Q (Pool 1) based on the MedDRA coded term in the ISS database. All of these occurred in the long-term open-label safety study, Study 02- AVR-107. "Cardiac arrest" was recorded for 4 patients and "cardiorespiratory arrest" was recorded in Patient AVR107- 034-029. One of the patients identified from the listing with "cardiac arrest" (AVR107-052-002, a 74-year-old male with dementia) had a prolonged QTc interval. On Day 29, QTcB and QTcF intervals in this patient were prolonged by 38 and 39 ms, respectively, compared with baseline values. No concomitant treatments ( including CYP 3A4 inhibitors are reported in the narrative. However, he did not die until Day 213. None of the other 6 patients identified above from the listing as sudden death had prolonged QTc interval reported

*Reviewer's Comment: Narratives in appendix 2 of the cardiac safety report were reviewed. Again, limited information including infrequent ECG sampling in Study 02- AVR-107, and significant confounding due to co-morbidities in this population limits assessment. Overall, sponsor's conclusions seem reasonable.*

### **1.3.3.2 Cardiac arrhythmias**

In the sponsor's analysis of the integrated datasets (N = 1396 subjects treated with DM/Q), the incidence of arrhythmias reported with all doses of DM/Q was 3.1% (Pool 1, Table 8). A similar incidence of arrhythmia was found with all PBA patients in controlled studies treated with DM/Q (2.2%, 8/363) (Pool 3, Table 9). The incidence of arrhythmia with all doses of DM combined with 30 mg Q in this subset was 3.4% while the incidence of arrhythmia with Zenvia (all doses of DM with 10 mg Q) was 1.4%. The incidence of arrhythmia in patients receiving placebo in controlled studies was 1.6%. No occurrences of significant ventricular arrhythmias, seizure or TdP were reported in any study.

**Table 8: Arrhythmias in Integrated Studies (Pool-1)**

Incidence of Sponsor-Defined Groups of Treatment-Emergent Adverse Events,  
by Treatment  
Pool 1: Integrated Studies

Sponsor-Defined AE Grouping/ Preferred Term	AVP-923					Placebo (N=316)	DM 30 mg (N=149)	Q 30 mg (N=37)
	20 mg DM/ 10 mg Q (N=107)	30 mg DM/ 10 mg Q (N=283)	All doses with 10 mg Q (N=314)	All doses with 30 mg Q (N=947)	All AVP-923 (N=1396)			
Arrhythmia	1 (0.9%)	6 (2.1%)	7 (2.2%)	33 (3.5%)	43 (3.1%)	7 (2.2%)	0	0
ARRHYTHMIA	0	0	0	2 (0.2%)	2 (0.1%)	1 (0.3%)	0	0
ARRHYTHMIA SUPRAVENTRICULAR	0	1 (0.4%)	1 (0.3%)	0	2 (0.1%)	0	0	0
ATRIAL FIBRILLATION	0	0	0	4 (0.4%)	4 (0.3%)	0	0	0
ATRIAL FLUTTER	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0
ATRIOVENTRICULAR BLOCK FIRST DEGREE	1 (0.9%)	1 (0.4%)	2 (0.6%)	1 (0.1%)	3 (0.2%)	2 (0.6%)	0	0
ATRIOVENTRICULAR BLOCK SECOND DEGREE	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0
BRADYCARDIA	0	0	0	4 (0.4%)	4 (0.3%)	1 (0.3%)	0	0
BUNDLE BRANCH BLOCK LEFT	0	0	0	2 (0.2%)	2 (0.1%)	1 (0.3%)	0	0
BUNDLE BRANCH BLOCK RIGHT	0	0	0	3 (0.3%)	4 (0.3%)	0	0	0
SINUS ARRHYTHMIA	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0
SINUS BRADYCARDIA	1 (0.9%)	1 (0.4%)	2 (0.6%)	5 (0.5%)	7 (0.5%)	0	0	0
SINUS TACHYCARDIA	0	0	0	5 (0.5%)	5 (0.4%)	1 (0.3%)	0	0
SUPRAVENTRICULAR EXTRASYSTOLES	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0
SUPRAVENTRICULAR TACHYCARDIA	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0
TACHYCARDIA	0	1 (0.4%)	1 (0.3%)	4 (0.4%)	5 (0.4%)	0	0	0
VENTRICULAR EXTRASYSTOLES	0	2 (0.7%)	2 (0.6%)	0	3 (0.2%)	1 (0.3%)	0	0

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

Note: Percentages are calculated as the number of patients in the indicated population and treatment category who experienced an event divided by the number of patients in the population and treatment category.

Note: In each AE group or preferred term, a patient is counted only once within each treatment category, ie, only first occurrences are tabulated within each treatment category.

Note: DM = Dextromethorphan Hydrobromide USP; Q = Quinidine Sulfate USP. NOS = not otherwise specified.

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Source: Table 10.1.1, ISS

**Table 9: Arrhythmias in PBA patients in controlled studies (Pool 3)**

Incidence of Sponsor-Defined Groups of Treatment-Emergent Adverse Events,  
by Treatment  
Pool 3: All PBA Patients in Controlled Studies

Sponsor-Defined AE Grouping/ Preferred Term	AVP-923					Placebo (N=182)	DM 30 mg (N=33)	Q 30 mg (N=37)
	20 mg DM/ 10 mg Q (N=107)	30 mg DM/ 10 mg Q (N=110)	All doses with 10 mg Q (N=217)	All doses with 30 mg Q (N=146)	All AVP-923 (N=363)			
Arrhythmia	1 (0.9%)	2 (1.8%)	3 (1.4%)	5 (3.4%)	8 (2.2%)	3 (1.6%)	0	0
ATRIAL FLUTTER	0	0	0	1 (0.7%)	1 (0.3%)	0	0	0
ATRIOVENTRICULAR BLOCK FIRST DEGREE	1 (0.9%)	1 (0.9%)	2 (0.9%)	0	2 (0.6%)	0	0	0
BRADYCARDIA	0	0	0	1 (0.7%)	1 (0.3%)	1 (0.5%)	0	0
BUNDLE BRANCH BLOCK LEFT	0	0	0	1 (0.7%)	1 (0.3%)	0	0	0
SINUS BRADYCARDIA	1 (0.9%)	0	1 (0.5%)	1 (0.7%)	2 (0.6%)	0	0	0
SINUS TACHYCARDIA	0	0	0	0	0	1 (0.5%)	0	0
SUPRAVENTRICULAR TACHYCARDIA	0	0	0	1 (0.7%)	1 (0.3%)	0	0	0
TACHYCARDIA	0	1 (0.9%)	1 (0.5%)	0	1 (0.3%)	0	0	0
VENTRICULAR EXTRASYSTOLES	0	0	0	0	0	1 (0.5%)	0	0

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

Note: Percentages are calculated as the number of patients in the indicated population and treatment category who experienced an event divided by the number of patients in the population and treatment category.

Note: In each AE group or preferred term, a patient is counted only once within each treatment category, ie, only first occurrences are tabulated within each treatment category.

Note: DM = Dextromethorphan Hydrobromide USP; Q = Quinidine Sulfate USP. NOS = not otherwise specified.

Source: W:\biostat\avanir\nda\_new\iss\_amended\programs\production\tables\T\_SDTEAE1.sas, Date/time of run: 24FEB2010:17:54

Source: Table 10.1.3, ISS

### 1.3.3.2.1 Bradycardia

In the Avanir-sponsored controlled studies in PBA patients (Pool 3), there were 4 reports of bradycardia in MS patients (combining bradycardia NOS and sinus bradycardia in: heart rate <60 beats/minute or decrease in baseline >10 beats/minute). Three of these cases were in DM/Q treatment groups and one case was in the placebo group. One discontinuation was attributed to bradycardia in an MS patient treated with DM 30 mg/Q 30 mg (Subject AVR106-011-000). The subject presented with a heart rate of 58 beats/minute on Day 1 before dosing. On Day 3, his self-reported heart rate was 48

beats/minute, and the heart rate recorded in the CRF was 72 beats/minute. Bradycardia was not reported for any of ALS patients in these studies.

#### **1.3.3.2.2 Conduction disorders**

In Avanir-sponsored controlled studies in PBA patients (Pool 3 Table 9), 2 instances of AV block (first degree AV block = PR interval prolongation) were reported, both in subjects treated with Zenvia (DM 20 mg/Q 10 mg or 30 mg/Q 10 mg) and one instance of bundle branch block with the DM 30 mg/Q 30 mg dose. For one of these subjects (AVR123-126-701), the first degree AV block was considered “possibly” due to treatment, and study drug was discontinued as a result of this AE. This patient also had abnormal ECG at screening (left anterior hemiblock, axis > -45 degrees), which were also noted during treatment with DM/Q. In this set of patients (Pool 3), the sponsor reports that no significant dose- or time-related trends were observed in PR interval or QRS complex duration with quinidine dose levels of 10 or 30 mg in DM/Q combinations.

In the assessment of all integrated studies (Pool 1, Table 8), there were 3 additional cases of AV block, but 2 of these cases were in the placebo group. One case of second degree AV block was reported in one patient in the DM 30 mg/Q 30 mg group in Pool 1 (Table 8). The incidence of AV block in all patients treated with DM/Q was 0.3% (including the patient with second degree AV block). There were 6 cases of RBBB/LBBB with DM/Q compared to one case with placebo with a rate of 0.3% in both groups. No cases of bundle branch block were reported in the 314 patients treated with Zenvia.

#### **1.3.3.2.3 Atrial flutter/fibrillation**

No subjects treated with Zenvia DM 20 mg/Q 10 mg or DM 30 mg/Q 10 mg reported atrial fibrillation (AF) or atrial flutter (Pool 1, Table 8). In the DM 30 mg/Q 30 mg treatment group, there were 4 reports of atrial fibrillation and one report of atrial flutter (Pool 1, Table 8) yielding an incidence of atrial fibrillation or flutter across all studies with DM/Q of 0.4% (5/1396). The sponsor reports that none of these patients had atrial fibrillation or atrial flutter recorded in their medical histories but did have risk factors such as age, hypertension and CAD.

The divisions raised concerns in their approvable letter that patients with paroxysmal AF may be at increased risk for TdP and SVT while taking quinidine. In response, the sponsor identified that in Pool 1, six subjects had atrial fibrillation and one subject had atrial flutter identified in their medical history; none of the patients receiving DM/Q reported any significant arrhythmias while on study. However, one of the patients receiving DM 30 mg/Q 30 mg b.i.d. (AVR107-052-002) suffered cardio-respiratory arrest (discussed under 1.3.3.1).

The sponsor also submitted a literature search and discussion by Jay Mason, MD.

- Dr. Mason concludes that patients with AF or atrial flutter are not at increased risk for TdP or other arrhythmias with Zenvia compared to other patients for the following reasons:
  - Increased risk of TdP in patients with paroxysmal atrial fibrillation or flutter compared to permanent AF/atrial flutter is not documented in the

literature. In his discussion, he states that that the most important reason for the association of quinidine-induced TdP with AF (paroxysmal or permanent) is that the condition was once the most common target for quinidine administration.

- He states that quinidine induced TdP in patients with paroxysmal or permanent atrial fibrillation or flutter is not a consequence of those arrhythmias, but simply a result of administration of an anti-arrhythmic dose of quinidine. He deliberates that while relative bradycardia with heart rate variations and rhythm sequences associated with termination of atrial fibrillation or flutter might enhance arrhythmogenicity, this phenomenon is unlikely with Zenvia since the extremely low quinidine dose (10 mg BID or 20 mg/day) would not promote termination of AF or flutter.
- Dr. Mason also concludes that the phenomenon of heart rate acceleration by quinidine in the presence of atrial fibrillation or flutter is very unlikely at the 10 mg BID quinidine dosage in Zenvia, as no effect on the PR interval or on heart rate was observed in TQT study 05-AVR-119, at quinidine doses up to 60 mg BID.

Reviewer's Comments:

- *Most of the sponsor's discussions regarding no additional risk for TdP with Zenvia, in patients with paroxysmal or permanent AF or atrial flutter when compared to other subjects seem reasonable. However, co-morbidities like congestive heart failure or an underlying conduction defect resulting in slow heart rates can translate to additional risk for TdP in patients with atrial fibrillation or flutter who receive Zenvia.*
- *Effects of quinidine unrelated to IKr blockade (sodium channel blockade, vagolytic effects etc.)*
  - *There are no studies in animals or humans that examine the dose-response relationship for rate acceleration during AF after quinidine administration.*
  - *To verify the sponsor's assertions that only IKr blockade is expected at low doses of quinidine, the QT-IRT statistical reviewer analyzed the PR, QRS and heart rate data from the previous TQT study (05-AVR- 119) evaluating DM 30 mg/Q 30 mg BID and DM 60 mg/Q 60 mg BID, since only QT data have been reviewed previously by the QT-IRT. We expect that the DM 60 mg/Q 60 mg dose should cover high-exposure scenarios with Zenvia (DM 20 mg or 30 mg/Q 10 mg). There were no clinically relevant effects on the PR and QRS intervals with no mean trends or over 25% change from baseline for outliers (refer to QT-IRT review of 08-AVR-126, September, 17, 2010), which is consistent with the non-clinical data regarding channel potencies. There was a trend for HR decrease over the dosing interval. The largest placebo adjusted mean changes of heart rate for DM/Q-30 mg and DM/Q-60 mg were -6.2 bpm and -6.3 bpm; both occurred at 14 hours after dosing.*

### 1.3.3.3 Arrhythmia related events

In addition to sudden death, other clinical events that may represent unrecognized cardiac arrhythmia are syncope, palpitations and seizures. No seizures were reported in any subjects in the clinical studies.

In the analyses of all patients with PBA in controlled studies (Pool 3), syncope was reported in 6 subjects. Three of these subjects were in the Zenvia (any dose DM/Q 10 mg) group, 1 was in the any dose DM/Q 30 mg group, and 2 were in placebo group. The incidence of palpitations was similar in patients treated with DM/Q (n=3) and placebo (n=2)

In the integrated pool of all DM/Q studies (Pool 1), 17 subjects (1.2%) were identified with syncope, and 24 subjects (1.7%) were identified with palpitations. Three of the patients with syncope (AVR107-017-003, AVR107-025-030, and AVR107-107-002) and one of the patients with palpitations (AVR107-003-013) had QTcB and/or QTcF interval increases > 30 ms (but < 60 ms) compared with baseline. In addition, QTcB and/or QTcF interval values of  $\geq 450$  ms (but < 500 ms) were noted in one subject with syncope (AVR109-107-002) and in 2 subjects with palpitations (AVR106-016-001 and AVR109-121-505).

Syncope was reported as an SAE in 3 subjects. Two subjects were discontinued from studies due to syncope or syncope vasovagal. Palpitations were reported as other SAE in one subject. Four subjects were discontinued from the studies due to palpitations. The sponsor reports that no subjects with syncope or palpitations with clinically significant ECG changes were discontinued from any study.

*Reviewer's Comments: ECGs were collected less frequently in the older studies in contrast to the new phase 3 clinical study 07-AVR-123. Thus QT prolongation playing a contributory role in these AEs cannot be excluded.*

### 1.3.4 Cardiac AEs in Study 07- AVR-123

In this phase 3 placebo-controlled study with the lower dose Zenvia formulations, (DM 20 mg/Q 10 mg and DM 30 mg/ Q 10 mg), there were 3 deaths in the DM 20 mg/Q 10 mg group, 3 deaths in the DM 30 mg/Q 10 mg group, and one death in the placebo group. Additionally, 3 ALS patients died in the OLE phase of Study 07-AVR-123, where all patients received DM 30 mg/Q 10 mg b.i.d. None of the deaths in the controlled trials were reported as cardiovascular, and all were considered to be due to progression of ALS. Only one death, in Study 07-AVR-123 (Subject 301-501), was judged as possibly related to the study drug by the investigator, with alternative causality related to ALS progression. This subject completed the study and died 5 days after receiving the last dose of study medication.

Table 10: Adverse Events Leading to Death, by System Organ Class and Preferred Term (Safety Population)-study 07-AVR-123

System Organ Class/ Preferred Term	n (%)				
	DB Phase			Overall (N = 326)	OLE Phase AVP-923-30 <sup>a</sup> N = 253
	AVP-923-30 (n = 110)	AVP-923-20 (n = 107)	Placebo (n = 109)		
Subjects with at least 1 adverse event leading to death	3 (2.7)	3 (2.8)	1 (0.9)	7 (2.1)	3 (1.2)
<b>Respiratory, thoracic, and mediastinal disorders</b>	<b>2 (1.8)</b>	<b>2 (1.9)</b>	<b>0</b>	<b>4 (1.2)</b>	<b>3 (1.2)</b>
Respiratory failure	2 (1.8)	1 (0.9)	0	3 (0.9)	2 (0.8)
Respiratory depression	0	1 (0.9)	0	1 (0.3)	0
Dyspnea	0	0	0	0	1 (0.4)
Increased bronchial secretion	1 (0.9)	0	0	1 (0.3)	0
<b>General disorders and administration site conditions</b>	<b>0</b>	<b>1 (0.9)</b>	<b>1 (0.9)</b>	<b>2 (0.6)</b>	<b>1 (0.4)</b>
Disease progression	0	1 (0.9)	1 (0.9)	2 (0.6)	1 (0.4)
<b>Investigations</b>	<b>0</b>	<b>1 (0.9)</b>	<b>0</b>	<b>1 (0.3)</b>	<b>0</b>
Oxygen saturation decreased <sup>b</sup>	0	1 (0.9)	0	1 (0.3)	0
Oxygen saturation decreased	0	1 (0.9)	0	1 (0.3)	0
<b>Infections and infestations</b>	<b>1 (0.9)</b>	<b>0</b>	<b>0</b>	<b>1 (0.3)</b>	<b>0</b>
Pneumonia	1 (0.9)	0	0	1 (0.3)	0

Source: DB phase, Section 14.1, Table 29; OLE phase, Section 14.2, Table 29.

DB = double blind; OLE = open-label extension.

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

<sup>a</sup>Includes only adverse events experienced since Visit 5 of the double-blind study or while on the OLE study.

<sup>b</sup>Decreased oxygen saturation was reported at Visit 5 and was not considered clinically significant by the investigator.

Source: Table 12-7, CSR for Study 07-AVR-123

The most common cardiac disorders reported in the pivotal controlled study (07-AVR-123) by preferred term were sinus bradycardia, palpitations, and first-degree atrioventricular block, which each occurred in 2 subjects overall, and in no more than 1 subject in each treatment group (Table 11). AEs related to cardiac disorders were reported in 2.8% of subjects overall in the DB phase: 3.6%, 2.8%, and 1.8% of subjects in the AVP-923-30, AVP-923-20, and placebo groups, respectively (Table 11). In the OLE phase, AEs related to cardiac disorders were reported in 2.8% of subjects (Table 12).

**Table 11-Cardiac AEs in double blind phase-study 07-AVR-123**

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

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

Note: A patient who reported 2 or more adverse events with the same preferred term was counted only once for that term.

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

Source: Table 25, CSR for AVR-123

**Table 12 Cardiac AEs in DB and OLE phases-Study 07-AVR-123**Adverse Events by System Organ Class and Preferred Term  
(Safety Population)

System Organ Class Preferred Term	Open-Label AVP-923-30 (N=253) n (%)	Double-Blind AVP-923-30 (N=94) n (%)	Double-Blind AVP-923-20 (N=76) n (%)	Double-Blind Placebo (N=83) n (%)
CARDIAC DISORDERS	7 ( 2.8%)	4 ( 4.3%)	2 ( 2.6%)	1 ( 1.2%)
SINUS BRADYCARDIA	2 ( 0.8%)	1 ( 1.1%)	1 ( 1.3%)	0 ( 0.0%)
VENTRICULAR EXTRASYSTOLES	2 ( 0.8%)	1 ( 1.1%)	0 ( 0.0%)	1 ( 1.2%)
ARRHYTHMIA SUPRAVENTRICULAR	1 ( 0.4%)	1 ( 1.1%)	0 ( 0.0%)	0 ( 0.0%)
ATRIAL FIBRILLATION	1 ( 0.4%)	0 ( 0.0%)	1 ( 1.3%)	0 ( 0.0%)
ATRIOVENTRICULAR BLOCK FIRST DEGREE	1 ( 0.4%)	1 ( 1.1%)	0 ( 0.0%)	0 ( 0.0%)
SINUS TACHYCARDIA	1 ( 0.4%)	1 ( 1.1%)	0 ( 0.0%)	0 ( 0.0%)

Note: A patient who reported 2 or more adverse events with the same preferred term was counted only once for that term.  
A patient who reported 2 or more adverse events with different preferred terms within the same system organ class was counted only once in the system organ class total.  
[1] Includes only adverse events experienced since Visit 5 of the double-blind study or while on the OLE study.

Source: Table 25-1, CSR for 07-AVR-123.

In the DB phase, syncope was reported in 5 subjects overall (2-DM 30 mg/Q 10 mg, 1-DM 20 mg/Q 10 mg, 2-placebo). Presyncope was reported in 2 subjects in the DM 30mg/Q 10 mg group. In the OLE phase pre-syncope was reported in only one subject in the DM 30 mg/Q 10 mg group.

In the DB phase, QT prolonged was reported as an AE in 2 subjects, 1 in the DM 20 mg/Q 10 mg group and 1 in the placebo group. In the OLE phase, no prolongations of QT interval were reported as AEs. ECGs were collected more frequently in this study compared to previous studies: baseline, Days 1, 15, 29, 57 and 84 in the DB phase and Days 1, 15, 42 and 84 in the OLE phase.

*Reviewer's Comments: Overall the number of cardiac AEs were low and there were no AEs related to QT prolongation but it is to be noted that this study was of short duration (6 months), subjects were carefully monitored and discontinued for any event suggestive/related to QT prolongation such as electrocardiogram QT prolonged, T wave inversion in ECG and minor events such as sinus bradycardia, first degree AV block, QRS axis abnormal (listed in Table 28 of the CSR for 07-AVR-123). That degree of monitoring is unlikely to occur during post-marketing use.*

### 1.3.5 Pro-arrhythmic liability of dextromethorphan

Since DM has been marketed for over 50 years as an over-the-counter cough suppressant, the sponsor refers to the safety database/published literature and concludes that there are no significant cardiac safety observations even in CYP-2D6-poor metabolizers.

The division expressed concern in their approvable letter about a contributory role for DM mainly in respiratory depression and not for cardiac AEs. In the TQT studies review the clinical pharmacology reviewers determined that while the QT effect is most likely due to quinidine, the study design was not adequate to rule out contributions from dextromethorphan and dextroprhan.

To verify the sponsor's conclusions about pro-arrhythmic liability with DM, this reviewer conducted an MGPS data mining analysis of the AERS database for arrhythmias related events with DM (see APPENDIX). There were no reports of TdP. The lower bound of the 90% confidence interval for the signal score (EB-05 value) was over 2 (indicating over twice the expected rate) only for tachycardia and supraventricular arrhythmias in combinations of DM with pseudophedrine, phenylpropanolamine and guaifenesin which

is expected. There were 29 cases of cardiac arrest and 17 cases of cardiorespiratory arrest with DM. On review of the cases, several were duplicate reports. Almost all of the cases were due to overdose of DM with multiple medications like amitriptylline, citalopram, escitalopram, bupropion and oxycodone.

## **2 RESPONSES TO QUESTIONS POSED BY REVIEW DIVISION**

**1. Please provide an expert assessment of whether the cardiovascular risk associated with Zenvia has been adequately assessed and appropriately characterized. Do you agree with the applicant's conclusions regarding the overall cardiac safety profile of Zenvia?**

*QT-IRT Response:*

1. Information from TQT studies:

- a. Based on our analysis of TQT Study 08-AVR-126 Zenvia (DM 30 mg/Q 10 mg) prolonged the QT interval with a mean effect of 10.2 ms. The largest upper bounds of the 2-sided 90% CI for the mean  $\Delta\Delta QTcF$  difference between Zenvia (DM 30 mg/Q 10 mg) and placebo was 12.6 ms at 3 hours after dose. Therefore some slight risk for QT prolongation related AEs exists even at this dose and we defer risk vs. efficacy considerations for the proposed condition/population to the review division.
- b. The sponsor indicates that only QT prolongation due to IKr blockade is expected at low doses of quinidine and other effects like direct depressant effects due to Na/Ca channel blockade or paradoxical increases in conduction/HR due to autonomic ("vagolytic") effects are absent. To address this issue regarding other pro-arrhythmic effects, PR, QRS and heart rate data from the previous TQT study (05-AVR- 119) were analyzed. In this study DM 30 mg/Q 30 mg BID and DM 60 mg/Q 60 mg BID were the therapeutic and supra-therapeutic doses respectively. We expect that the DM 60 mg/Q 60 mg dose should cover high-exposure scenarios with Zenvia (DM 20 mg or 30 mg/Q 10 mg). In this study, there were no clinically relevant effects on the PR and QRS intervals which is consistent with non-clinical data regarding channel potencies (refer to TQT study review-08-AVR-126, September, 17, 2010). There was a trend for HR decrease over the dosing interval. Hence we do not expect significant pro-arrhythmic effects with the 10-mg quinidine dose that are unrelated to IKr blockade.

2. Assessment of Patient Clinical Experience:

Although there are no reports of TdP or significant ventricular arrhythmias in the clinical studies, limited size of the safety database (~ 1500 patients in total), limited information in some cases and infrequent ECG sampling limits conclusions regarding pro-arrhythmic liability, especially with the older studies evaluating the DM 30 mg/Q 30 mg dose.

1. We reviewed the narratives for cardiovascular and sudden deaths in the clinical program and found the adjudications to be acceptable although significant

confounding due to comorbidities in this population limits assessment in some of the cases. With respect to the deaths due to respiratory failure, respiratory system complications and abnormalities are common in patients with ALS, and respiratory failure is the most common cause of death. Given that all the deaths due to respiratory failure were reported in ALS patients only, this adjudication is expected to be the more likely cause of death. However, sudden cardiac death cannot be completely excluded, especially in unobserved deaths in the absence of an ECG shortly before the death.

2. Overall, in Study 07-AVR-123 where the lower dose (10 mg quinidine combinations were studied) the number of cardiac AEs were low and there were no AEs related to QT prolongation. However, it is to be noted that the study was only of 6 months duration in total, subjects were carefully monitored and discontinued for any event suggestive/related to QT prolongation such as electrocardiogram QT prolonged, T wave inversion in ECG and minor events such as sinus bradycardia, first degree AV block, QRS axis abnormal (listed in Table 28 of the CSR for 07-AVR-123) which may not be reflective of post-marketing use. Hence the proposed risk mitigation strategies are certainly warranted.
3. Underlying disease in patients with PBA was mainly ALS or MS. We have a limited database in patients with diseases other than ALS or MS (only 154 patients in total). While we defer to the review division regarding the sponsor's justifications for studying mainly PBA patients with ALS or MS and making a global claim, it is to be noted that the pro-arrhythmic risk in these populations may vary due to their underlying disease or risk factors.
4. The division has expressed concerns regarding increased risk for SVT or TdP in patients with atrial fibrillation or flutter. The risk for SVT has been addressed in response 1.b. The sponsor's discussions (Dr. Mason's report) regarding no additional risk for TdP with Zenvia, in patients with paroxysmal or permanent AF or atrial flutter when compared to other patients seem reasonable. However, co-morbidities like congestive heart failure or underlying conduction defects resulting in slow heart rates can translate to additional risk for TdP and related events in patients with AF or flutter who receive Zenvia.

**2. The applicant proposes the following Contraindication:** (b) (4)

**, and following Warnings and Precautions:** (b) (4)

**. The applicant also proposes a Medication Guide. Please provide an expert opinion whether the cardiovascular risk with Zenvia can be adequately mitigated with these proposed mitigation strategies (label restrictions and REMS). If not, what are your recommendations?**

*QT-IRT Response*

Please see our comments for sponsor's proposed label below. Otherwise, the sponsor's proposed risk mitigation strategies seem adequate.

**3 SPONSOR'S PROPOSED LABEL**

(b) (4)





## APPENDIX

**Configuration:** (b) (4) (S) (v2) **Run :** Generic (S) **Run ID:** 3665  
**Dimension:** 2 **Selection Criteria:** Generic name(...) + PT(...) **Where:** EBGM > 1.0  
**45 rows** Sorted by Generic name, EBGM desc

Generic name	PT	HLT	N	EBGM	EB05	EB95
Acetaminophen And Dextromethorphan	Sudden death	Death and sudden death	1	1.32	0.305	4.13
Acetaminophen And Dextromethorphan	Cardiac arrest	Ventricular arrhythmias and cardiac arrest	1	1.14	0.266	3.55
Acetaminophen And Dextromethorphan	Cardio-respiratory arrest	Ventricular arrhythmias and cardiac arrest	1	1.08	0.251	3.35
Acetaminophen And Dextromethorphan And Doxylamine	Arrhythmia	Rate and rhythm disorders NEC	1	1.23	0.287	3.85
Acetaminophen And Dextromethorphan And Doxylamine	Bradycardia	Rate and rhythm disorders NEC	1	1.23	0.286	3.84
Acetaminophen And Dextromethorphan And Doxylamine	Tachycardia	Rate and rhythm disorders NEC	1	1.17	0.272	3.63
Acetaminophen And Dextromethorphan And Doxylamine And Ethanol And Pseudoephedrine	Ventricular tachycardia	Ventricular arrhythmias and cardiac arrest	1	1.34	0.308	4.20
Acetaminophen And Dextromethorphan And Doxylamine And Ethanol And Pseudoephedrine	Cardio-respiratory arrest	Ventricular arrhythmias and cardiac arrest	1	1.28	0.297	4.00
Acetaminophen And Dextromethorphan And Doxylamine And Ethylene Glycol And Pseudoephedrine	Bradycardia	Rate and rhythm disorders NEC	1	1.37	0.314	4.35
Acetaminophen And Dextromethorphan And Doxylamine And Ethylene Glycol And Pseudoephedrine	Cardiac arrest	Ventricular arrhythmias and cardiac arrest	1	1.36	0.312	4.31
Acetaminophen And Dextromethorphan And Doxylamine And Pseudoephedrine	Arrhythmia supraventricular	Supraventricular arrhythmias	181	49.5	43.7	55.9
Acetaminophen And Dextromethorphan And Doxylamine And Pseudoephedrine	Rhythm idioventricular	Ventricular arrhythmias and cardiac arrest	2	3.12	0.753	49.8
Acetaminophen And Dextromethorphan And Doxylamine And Pseudoephedrine	Sinus tachycardia	Supraventricular arrhythmias	3	1.47	0.574	3.25
Acetaminophen And Dextromethorphan And Doxylamine And Pseudoephedrine	Cardiac arrest	Ventricular arrhythmias and cardiac arrest	10	1.22	0.717	1.97
Acetaminophen And Dextromethorphan And Doxylamine And Pseudoephedrine	Cardiac flutter	Rate and rhythm disorders NEC	1	1.09	0.255	3.40
Acetaminophen And Dextromethorphan And Doxylamine And Pseudoephedrine	Conduction disorder	Cardiac conduction disorders	1	1.09	0.255	3.39
Acetaminophen And Dextromethorphan And Doxylamine And Pseudoephedrine	Tachyarrhythmia	Rate and rhythm disorders NEC	1	1.07	0.250	3.33
Acetaminophen And Dextromethorphan And Doxylamine And Pseudoephedrine	Ventricular arrhythmia	Ventricular arrhythmias and cardiac arrest	1	1.01	0.237	3.15

Generic name	PT	HLT	N	EBGM	EB05	EB95
Acetaminophen And Dextromethorphan And Guaifenesin And Phenylpropanolamine	Arrhythmia supraventricular	Supraventricular arrhythmias	88	116.3	97.3	138.2
Acetaminophen And Dextromethorphan And Guaifenesin And Pseudoephedrine	Tachycardia	Rate and rhythm disorders NEC	1	1.27	0.295	3.96
Carbinoxamine And Dextromethorphan And Pseudoephedrine	Tachycardia	Rate and rhythm disorders NEC	2	1.26	0.411	3.16
Chlorphenamine And Dextromethorphan And Pseudoephedrine	Arrhythmia supraventricular	Supraventricular arrhythmias	38	158.0	119.9	205.0
Chlorphenamine And Dextromethorphan And Pseudoephedrine	Tachycardia	Rate and rhythm disorders NEC	7	4.17	2.16	7.80
Chlorphenamine And Dextromethorphan And Pseudoephedrine	Cardio-respiratory arrest	Ventricular arrhythmias and cardiac arrest	2	2.21	0.688	5.96
Chlorphenamine And Dextromethorphan And Pseudoephedrine	Arrhythmia	Rate and rhythm disorders NEC	1	1.09	0.254	3.38
Dextromethorphan	Tachycardia	Rate and rhythm disorders NEC	45	2.78	2.16	3.52
Dextromethorphan	Cardio-respiratory arrest	Ventricular arrhythmias and cardiac arrest	17	2.58	1.71	3.75
Dextromethorphan	Conduction disorder	Cardiac conduction disorders	3	2.47	0.953	5.56
Dextromethorphan	Cardiac arrest	Ventricular arrhythmias and cardiac arrest	29	2.33	1.71	3.13
Dextromethorphan	Sinus tachycardia	Supraventricular arrhythmias	4	1.54	0.673	3.12
Dextromethorphan	Electrocardiogram QT prolonged	ECG investigations	4	1.13	0.494	2.29
Dextromethorphan	Electromechanical dissociation	Ventricular arrhythmias and cardiac arrest	1	1.03	0.240	3.20
Dextromethorphan And Guaifenesin	Arrhythmia supraventricular	Supraventricular arrhythmias	96	34.8	29.3	41.0
Dextromethorphan And Guaifenesin	Tachycardia	Rate and rhythm disorders NEC	10	1.46	0.861	2.37
Dextromethorphan And Guaifenesin	Sinus tachycardia	Supraventricular arrhythmias	2	1.25	0.408	3.13
Dextromethorphan And Guaifenesin	Ventricular extrasystoles	Ventricular arrhythmias and cardiac arrest	2	1.17	0.382	2.94
Dextromethorphan And Guaifenesin And Phenylpropanolamine	Arrhythmia supraventricular	Supraventricular arrhythmias	136	33.5	29.0	38.5
Dextromethorphan And Guaifenesin		Supraventricular				

Generic name	PT	HLT	N	EBGM	EB05	EB95
And Phenylpropanolamine	Sinus bradycardia	arrhythmias	3	1.92	0.746	4.24
Dextromethorphan And Guaifenesin And Phenylpropanolamine	Ventricular extrasystoles	Ventricular arrhythmias and cardiac arrest	4	1.55	0.678	3.14
Dextromethorphan And Guaifenesin And Phenylpropanolamine	Sinus tachycardia	Supraventricular arrhythmias	3	1.26	0.491	2.78
Dextromethorphan And Guaifenesin And Phenylpropanolamine	Atrial tachycardia	Supraventricular arrhythmias	1	1.11	0.260	3.46
Dextromethorphan And Guaifenesin And Phenylpropanolamine	Cardiac flutter	Rate and rhythm disorders NEC	1	1.02	0.239	3.18
Dextromethorphan And Guaifenesin And Pseudoephedrine	Tachycardia	Rate and rhythm disorders NEC	3	2.25	0.875	5.01
Dextromethorphan And Guaifenesin And Pseudoephedrine	Cardio-respiratory arrest	Ventricular arrhythmias and cardiac arrest	2	2.00	0.643	5.10
Dextromethorphan And Guaifenesin And Pseudoephedrine	Atrial fibrillation	Supraventricular arrhythmias	1	1.22	0.284	3.80
<b>ID:</b>	3665					
<b>Type:</b>	MGPS					
<b>Name:</b>	Generic (S)					
<b>Description:</b>	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information					
<b>Project:</b>	(b) (4) Standard Runs					
<b>Configuration:</b>	(b) (4) (S) (v2)					
<b>Configuration description:</b>	(b) (4) data; best representative cases; suspect drugs only; with duplicate removal					
<b>As of date:</b>	09/03/2010 00:00:00					
<b>Item variables:</b>	Generic name, PT					
<b>Stratification variables:</b>	Standard strata					
<b>Highest dimension:</b>	2					
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<b>Calculate PRR:</b>	Yes					
<b>Calculate ROR:</b>	Yes					
<b>Base counts on cases:</b>	Yes					
<b>Use "all drugs" comparator:</b>	No					
<b>Apply Yates correction:</b>	Yes					
<b>Stratify PRR and ROR:</b>	No					
<b>Fill in hierarchy values:</b>	Yes					
<b>Exclude single itemtypes:</b>	Yes					
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<b>Created by:</b>	(b) (4) Administrator					

<b>Created on:</b>	09/11/2010 11:12:30 EDT
<b>User:</b>	(b) (4)
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```
SELECT * FROM OutputData_3665 WHERE (DIM=2 AND EBGm>1.0 AND ((P1='D' AND ITEM1 IN ('Acetaminophen And Caffeine And Dextromethorphan','Acetaminophen And Chlorphenamine And Dextromethorphan','Acetaminophen And Dextromethorphan','Acetaminophen And Dextromethorphan And Doxylamine','Acetaminophen And Dextromethorphan And Doxylamine And Ethanol And Pseudoephedrine','Acetaminophen And Dextromethorphan And Doxylamine And Ethylene Glycol And Pseudoephedrine','Acetaminophen And Dextromethorphan And Doxylamine And Phenylephrine','Acetaminophen And Dextromethorphan And Doxylamine And Pseudoephedrine','Acetaminophen And Dextromethorphan And Guaifenesin And Phenylephrine','Acetaminophen And Dextromethorphan And Guaifenesin And Phenylpropanolamine','Acetaminophen And Dextromethorphan And Guaifenesin And Pseudoephedrine','Acetaminophen And Dextromethorphan And Ibuprofen And Pseudoephedrine','Acetaminophen And Dextromethorphan And Phenylephrine','Acetaminophen And Dextromethorphan And Phenylpropanolamine','Aspirin And Chlorphenamine And Dextromethorphan','Aspirin And Chlorphenamine And Dextromethorphan And Phenylephrine','Brompheniramine And Dextromethorphan And Pseudoephedrine','Carbinoxamine And Dextromethorphan And Pseudoephedrine','Chlorphenamine And Dextromethorphan And Phenylephrine','Chlorphenamine And Dextromethorphan And Pseudoephedrine','Codeine And Dextromethorphan And Guaifenesin','Dextromethorphan','Dextromethorphan And Doxylamine And Ephedrine','Dextromethorphan And Ethanol','Dextromethorphan And Guaifenesin','Dextromethorphan And Guaifenesin And Phenylephrine','Dextromethorphan And Guaifenesin And Phenylpropanolamine','Dextromethorphan And Guaifenesin And Pseudoephedrine','Dextromethorphan And Iodinated Glycerol','Dextromethorphan And Phenylephrine','Dextromethorphan And Promethazine','Dextromethorphan And Pseudoephedrine','Dextromethorphan And Zincum Gluconicum') AND P2='E' AND ITEM2 IN ('Accelerated idioventricular rhythm','Accessory cardiac pathway','Adams-Stokes syndrome','Agonal rhythm','Anomalous atrioventricular excitation','Arrhythmia','Arrhythmia neonatal','Arrhythmia supraventricular','Atrial conduction time prolongation','Atrial fibrillation','Atrial flutter','Atrial
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tachycardia', 'Atrioventricular block', 'Atrioventricular block complete', 'Atrioventricular block first degree', 'Atrioventricular block second degree', 'Atrioventricular conduction time shortened', 'Atrioventricular dissociation', 'Atrioventricular extrasystoles', 'Bifascicular block', 'Bradyarrhythmia', 'Bradycardia', 'Bradycardia foetal', 'Bradycardia neonatal', 'Brugada syndrome', 'Bundle branch block', 'Bundle branch block bilateral', 'Bundle branch block left', 'Bundle branch block right', 'Cardiac arrest', 'Cardiac arrest neonatal', 'Cardiac death', 'Cardiac fibrillation', 'Cardiac flutter', 'Cardio-respiratory arrest', 'Cardio-respiratory arrest neonatal', 'Chronotropic incompetence', 'Conduction disorder', 'Electromechanical dissociation', 'Extrasystoles', 'Foetal arrhythmia', 'Foetal heart rate deceleration', 'Foetal heart rate disorder', 'Heart alternation', 'Heart block congenital', 'Long QT syndrome', 'Long QT syndrome congenital', 'Lown-Ganong-Levine syndrome', 'Neonatal tachycardia', 'Nodal arrhythmia', 'Nodal rhythm', 'Pacemaker complication', 'Pacemaker generated arrhythmia', 'Parasyctole', 'Paroxysmal arrhythmia', 'Postural orthostatic tachycardia syndrome', 'Rebound tachycardia', 'Reperfusion arrhythmia', 'Rhythm idioventricular', 'Sick sinus syndrome', 'Sinoatrial block', 'Sinus arrest', 'Sinus arrhythmia', 'Sinus bradycardia', 'Sinus tachycardia', 'Sudden cardiac death', 'Sudden death', 'Supraventricular extrasystoles', 'Supraventricular tachyarrhythmia', 'Supraventricular tachycardia', 'Tachyarrhythmia', 'Tachycardia', 'Tachycardia foetal', 'Tachycardia paroxysmal', 'Torsade de pointes', 'Trifascicular block', 'Ventricular arrhythmia', 'Ventricular asystole', 'Ventricular extrasystoles', 'Ventricular fibrillation', 'Ventricular flutter', 'Ventricular pre-excitation', 'Ventricular tachyarrhythmia', 'Ventricular tachycardia', 'Wandering pacemaker', 'Withdrawal arrhythmia', 'Wolff-Parkinson-White syndrome', 'Wolff-Parkinson-White syndrome congenital', 'Electrocardiogram QT interval', 'Electrocardiogram QT interval abnormal', 'Electrocardiogram QT prolonged', ''')))) ORDER BY ITEM1,EBGM desc

These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

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

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/s/

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SUCHITRA M BALAKRISHNAN  
10/04/2010

JOHN E KOERNER  
10/04/2010

NORMAN L STOCKBRIDGE  
10/07/2010

**Interdisciplinary Review Team for QT Studies Consultation:  
Thorough QT Study Review**

<b>NDA</b>	21879
<b>Brand Name</b>	Zenvia
<b>Generic Name</b>	AVP-923 (Dextromethorphan/Quinidine)
<b>Sponsor</b>	Avanir Pharmaceuticals, Inc.
<b>Indication</b>	Treatment of Pseudobulbar Affect
<b>Dosage Form</b>	Oral
<b>Drug Class</b>	Class Ia Anti-arrhythmic/OTC Antitussive
<b>Therapeutic Dosing Regimen</b>	Quinidine Sulfate(30 mg)/Dextromethorphan HBr(30 mg)
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	Quinidine Sulfate(10 mg)/Dextromethorphan HBr (30 mg)
<b>Submission Number and Date</b>	SDN 038 April 30, 2010
<b>Clinical Division</b>	DNP / HFD 120

**1 SUMMARY**

**1.1 OVERALL SUMMARY OF FINDINGS**

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

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

Study 08-AVR-126 is a randomized, double-blind (except for moxifloxacin), placebo-controlled, positive-controlled, multiple-dose, 3-treatment crossover study of the ECG

effects of dextromethorphan / quinidine (30 mg / 10 mg) administered in fasted normal healthy men and women with CYP2D6 extensive metabolizer (EM) genotype. Overall summary of findings is presented in Table 1.

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

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

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

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

## 1.2 QT INTERDISCIPLINARY REVIEW TEAM’S COMMENTS

- The sponsor states that at the 10-mg dose, quinidine is a pure IKr blocker and other effects such as sodium/calcium channel blockade resulting in decrease in atrioventricular (AV) or ventricular conduction and heart rate (HR) or ‘vagolytic’ effects resulting in an increase in heart rate/conduction velocity are absent. To address this issue the statistical reviewer analyzed the PR, QRS and HR data from the previous TQT study (05-AVR- 119) where dextromethorphan / quinidine (30 mg / 30 mg) BID and dextromethorphan / quinidine (60 mg/ 60 mg) BID were included. As noted in the statistical reviewer’s analysis, in Study 05-AVR-119, there were no clinically relevant effects on the PR and QRS intervals, with no mean trends or over 25% change from baseline for outliers (6.1.2,6.1.3, & 6.1.4). There was a trend for HR decrease over the dosing interval. The largest placebo adjusted mean changes of heart rate for dextromethorphan / quinidine (30 mg / 30 mg and 60 / 60

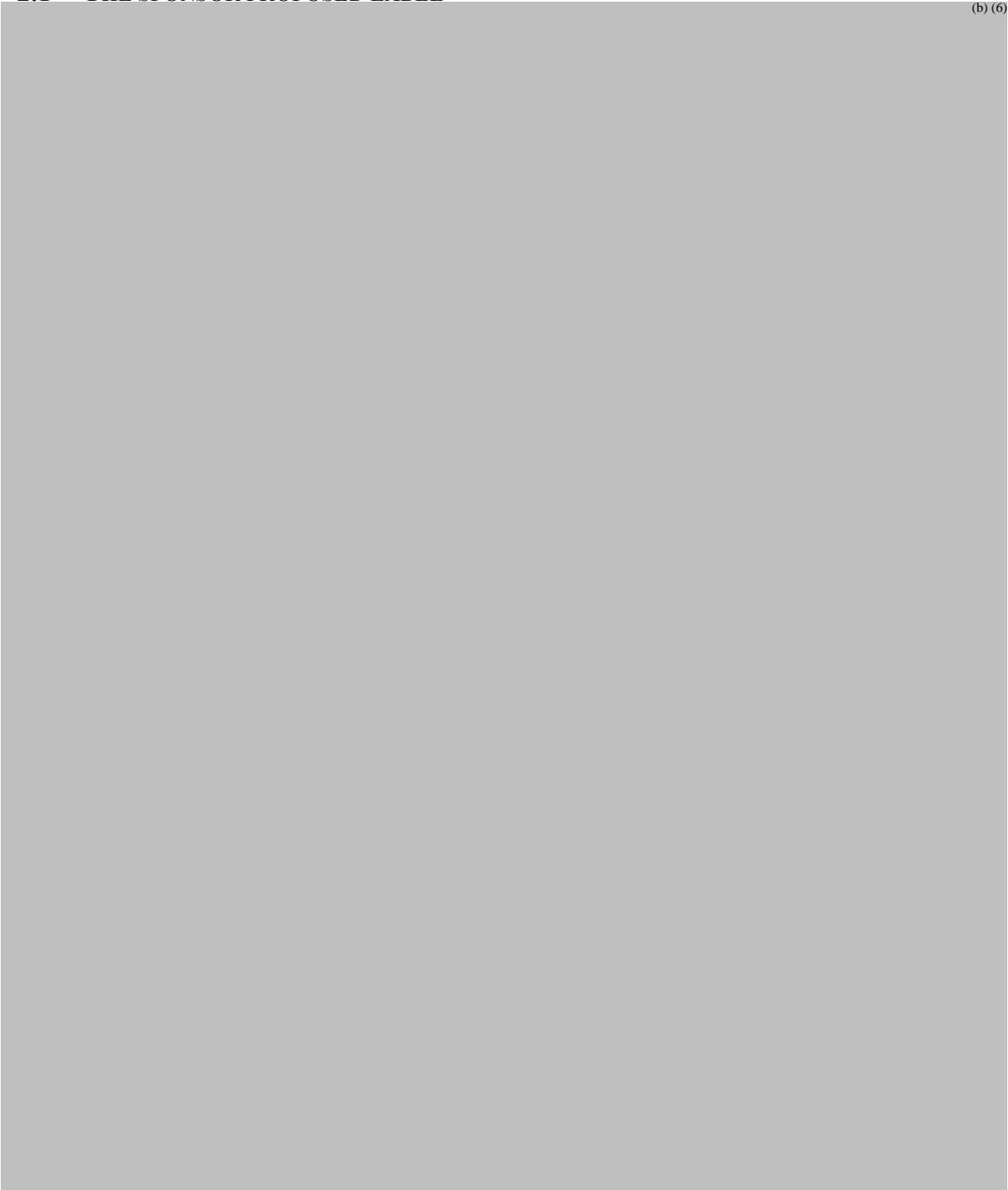
mg) both occurred at 14 hours after dosing. Hence pro-arrhythmic effects unrelated to QT prolongation at this dose of quinidine seem unlikely. This is discussed in further detail in the cardiac safety review.

- By mechanism, QTc prolongation observed in the thorough QT studies is likely driven by quinidine. However, the study design is not adequate to rule out the contributions from dextromethorphan and dextrophan.

## **2 PROPOSED LABEL**

### **2.1 THE SPONSOR PROPOSED LABEL**

(b) (6)



### 3 BACKGROUND

This NDA is seeking the approval of Zenvia – a fixed-dose combination product containing dextromethorphan 20 mg <sup>(b) (6)</sup> and quinidine 10 mg, administered twice a day for the treatment of pseudobulbar affect.

The definitive clinical trials in original NDA submission (January 30, 2006) were conducted using a higher dose of quinidine, i.e., 30 mg or 60 mg administered twice a day. As outlined in the Approvable Letter (October 30, 2006), the division expressed concerns regarding the drug's association with an increase in the QT interval at the proposed daily dose in the context of the known proarrhythmic risk of quinidine. In thorough QT study 05-AVR- 119, two doses of dextromethorphan / quinidine (i.e., 30 mg / 30 mg and 60 mg / 60 mg) dosed twice daily for 7 doses caused QTcF elevation, observable prior to the last dose and maximal at 3 hours post dose. The QT-IRT reviewed the sponsor's analysis for QTc effects. As per current procedure, analysis of QTc and other ECG interval changes was not done at that time. The sponsor reported no significant changes in QRS intervals, PR intervals and a placebo-subtracted HR decrease of 7 bpm at hour 14 with the upper bound of the two-sided 95% CI of -3.4 at the therapeutic dose.

The sponsor has now conducted another thorough QT study (08-AVR- 126) assessing a new formulation (Zenvia) using lower quinidine dose (dextromethorphan 30 mg and quinidine 10 mg).

*Reviewer's Comment: Refer to Cardiac safety review for further details including non-clinical data and previous clinical experience.*

#### 3.1 MARKET APPROVAL STATUS

Quinidine sulfate and dextromethorphan HBr are currently marketed individually. Quinidine sulfate is indicated for the reduction of frequency of atrial fibrillation/flutter beginning at a dose of 200 mg every 6 hours, conversion of atrial fibrillation/flutter to sinus rhythm beginning at a dose of 400 mg every 6 hours, and treatment of *P. faciparum*

malaria. Dextromethorphan is an over-the counter drug that is used as an antitussive agent and it is given in doses of 30 mg every 6 to 8 hours up to 120 mg/day.

### **3.2 CLINICAL PHARMACOLOGY**

Appendix 7.1 summarizes the key features of dextromethorphan and quinidine's clinical pharmacology.

## **4 SPONSOR'S SUBMISSION**

### **4.1 OVERVIEW**

QT-IRT has reviewed the thorough QT study report at a higher dextromethorphan (DM) and quinidine (Q) doses (Please refer to QT-IRT report dated September 15, 2006). The sponsor submitted study report for the study drug, including electronic datasets, and waveforms to the ECG wavehouse.

### **4.2 TQT STUDY**

#### **4.2.1 Title**

A Double-Blind Randomized Crossover Trial to Define the ECG Effects of AVP-923 (Dextromethorphan/Quinidine) Using a Clinical Dose of 30-mg Dextromethorphan and 10-mg Quinidine Twice Daily Compared to Placebo and Moxifloxacin (A Positive Control) in Healthy Men and Women.

#### **4.2.2 Protocol Number**

08-AVR-126

#### **4.2.3 Study Dates**

14 November 2008 -- 24 December 2008

#### **4.2.4 Objectives**

##### **Primary Endpoint Variable**

Time-matched change from baseline in QTc based on an individual correction (QTcI) method that provides an optimization of QT correction for HR as compared to fixed exponent approaches such as Bazett (QTcB) or Fridericia (QTcF).

##### **Secondary Endpoint Electrocardiogram Variables**

- QTcB and QTcF (provided for historic reasons only)
- HR
- PR interval
- QRS interval
- Uncorrected QT interval
- Change in ECG morphological patterns
- Correlation between the QTcI change from baseline and plasma concentrations of the parent and metabolites

## 4.2.5 Study Description

### 4.2.5.1 Design

This study was a randomized, double-blind (except for moxifloxacin), placebo controlled, positive controlled, multiple dose, 3-treatment crossover study of the ECG effects of AVP-923-30/10 administered in fasted normal healthy men and women with CYP2D6 EM genotype.

### 4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

### 4.2.5.3 Blinding

Treatment arms are double blinded except for moxifloxacin.

## 4.2.6 Treatment Regimen

### 4.2.6.1 Treatment Arms

- **Therapeutic Dose (DT):** One AVP-923-30/10 capsule (30-mg DM/10-mg Q) administered orally (p.o.) with 240 ml room temperature water b.i.d. for 3 days with a single dose on the fourth day;
- **Placebo (P):** One capsule placebo to match AVP-923-30/10 administered p.o. with 240 ml room temperature water b.i.d. for 3 days with a single dose on the fourth day;
- **Positive Control (PC):** One capsule placebo to match AVP-923-30/10 administered p.o. b.i.d. for 3 days and a single dose of 1 tablet 400-mg moxifloxacin administered p.o. with 240 ml room temperature water on the fourth day.

A schematic of the study design is presented in Table 2.

**Table 2: Study Design**

Treatment 1		Treatment 2		Treatment 3
<b>DT:</b> 1 capsule AVP-923-30/10 b.i.d. on Days 1 through 3 and 1 capsule AVP-923-30/10 on Day 4. <b>OR</b> <b>P:</b> 1 capsule placebo to match AVP-923-30/10 b.i.d. on Days 1 through 3 and 1 capsule placebo to match AVP-923-30/10 on Day 4. <b>OR</b> <b>PC:</b> 1 capsule placebo to match AVP-923-30/10 b.i.d. on Days 1 through 3 and 1 tablet 400 mg moxifloxacin on Day 4.	<b>Washout</b>	<b>DT:</b> 1 capsule AVP-923-30/10 b.i.d. on Days 9 through 11 and 1 capsule AVP-923-30/10 on Day 12. <b>OR</b> <b>P:</b> 1 capsule placebo to match AVP-923-30/10 b.i.d. on Days 9 through 11 and 1 capsule placebo to match AVP-923-30/10 on Day 12. <b>OR</b> <b>PC:</b> 1 capsule placebo to match AVP-923-30/10 b.i.d. on Days 9 through 11 and 1 tablet 400 mg moxifloxacin on Day 12.	<b>Washout</b>	<b>DT:</b> 1 capsule AVP-923-30/10 b.i.d. on Days 17 through 19 and 1 capsule AVP-923-30/10 on Day 20. <b>OR</b> <b>P:</b> 1 capsule placebo to match AVP-923-30/10 b.i.d. on Days 17 through 19 and 1 capsule placebo to match AVP-923-30/10 on Day 20. <b>OR</b> <b>PC:</b> 1 capsule placebo to match AVP-923-30/10 b.i.d. on Days 17 through 19 and 1 tablet 400 mg moxifloxacin on Day 20.
DAY 1 → → → DAY 5 → → → DAY 9 → → → DAY 13 → → → DAY 17 → → → DAY 21				

**4.2.6.2 Sponsor’s Justification for Doses**

The dose of 30-mg DM/10-mg Q was selected because PK/PD modeling conducted by the sponsor suggested that the dose may be efficacious while the lower dose of Q was anticipated to minimize the risk of QTc prolongation and Torsade des Pointes associated with Q. Furthermore, lower exposure to DM was expected to minimize some of the neurological side effects associated with DM.

*Reviewer’s Comments:*

1. *Selection of 30-mg DM/10-mg Q was appropriate dose selection for exploring QT prolongation based on previously submitted TQT results and Modeling & Stimulation performed by the agency. A dosing recommendation of 30-mg DM/15-mg Q based on previous studies at 30-mg DM/30-mg Q and 60-mg DM/60-mg Q was provided to the sponsor based on predicted QT prolongation due to quinidine from concentration-QT analysis.*
2. *A treatment arm of 30-mg DM/30-mg Q should have been included in the present study to relate observations between the previous TQT study.*
3. *The thorough QT study was conducted in healthy subjects with CYP2D6 EM genotype. A three-day dosing is adequate to reach steady state in the tested population. In the general population, approximately 7-10% of Caucasians and 3-8% of African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PMs), whereas the rest are intermediate, extensive or ultrarapid metabolizers.*
4. *A 35% increase in DM AUC was observed in patient with moderate liver impairment compared to normal hepatic function. Exposures of DM in subjects with mild or moderate renal impairment was comparable to those with normal renal function while a 2-fold increase in steady-state dexrathphone(DX) AUC<sub>0-t</sub> was observed for patients with moderate renal*

*impairment. AUC was unchanged under fed or fasting conditions. Together, these results indicate that the previously studied supratherapeutic dose of 60-mg DM/60-mg Q was appropriate for describing exposures in these populations.*

#### **4.2.6.3 Instructions with Regard to Meals**

Morning doses were preceded by an overnight fast (i.e., at least 8 hours) from food (not including water) and evening doses were preceded by at least a 2-hour fast from food. All doses were followed by a fast from food (not including water) for at least 4 hours post-dose. Subjects could consume water on an ad libitum basis throughout the study.

*Reviewer's comments: Acceptable. The maximum concentration of DX, the major metabolite, reduces by 20% under fed conditions.*

#### **4.2.6.4 ECG and PK Assessments**

##### **ECG Assessment:**

Subjects rested for at least 10 minutes in the supine position prior to all ECGs. Three 12-lead ECGs (using ELI machines) were captured on Day 1 at -45, -30, and -15 minutes prior to Day 1 (first dose) of each treatment. Four 12-lead ECGs approximately 1 minute apart were extracted from H12+ ECG flash card 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 23 hours post-dose on Day 4 (recording began approximately 30 minutes prior to final dose of each treatment).

##### **PK Sampling:**

Blood samples for PK analysis of Q, DM, and the metabolite DX were collected at the following time points on the fourth day of each treatment: pre-dose (trough), and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 23 hours post-dose. Only predose and 3 hours post-dose (approximate  $T_{max}$  of Q) samples collected during placebo and moxifloxacin treatment were analyzed, all other samples were saved for possible future analysis.

*Reviewer's comments: Based on the clinical pharmacology of Zenvia, the QT measurement and concentration sampling schedule seems adequate to capture the effects of quinidine, dextromethorphan and dextrorphan at times of maximum concentrations and potential delayed effect up to 23 hours post-dose. However, the Sponsor did not collect PK samples to measure the concentration of the 3-hydroxyquinidine metabolite of quinidine—a metabolite known to have an effect on QT interval.*

#### **4.2.6.5 Baseline**

Pre-dose QTc within day was used as baseline.

#### **4.2.7 ECG Collection**

Electrocardiograms for statistical analysis were captured digitally using both standard ELI ECG machines and a Mortara Instrument (Milwaukee, WI) H-12+ ECG continuous

12-lead digital recorder. Subjects rested for at least 10 minutes in the supine position prior to all ECGs.

Three 12-lead ECGs (using ELI machines) were captured on Day 1 at -45, -30, and -15 minutes prior to Day 1 (first dose) of each treatment. Electrocardiograms were also obtained digitally using a Mortara Instrument H-12+ ECG continuous 12-lead digital recorder, which continuously recorded all 12 leads simultaneously for approximately 24 hours on Day 4 of each treatment. The ECG signal for the 24 hour session in each subject was recorded on flash memory cards provided to the site.

Without knowledge of subject treatment assignment, the core lab (eRT) generated four 10 second, 12-lead digital ECGs at each time point specified in the protocol. If targeted ECG timepoints were artifactual and of poor quality, eRT captured analyzable 10 second ECGs as close as possible to the targeted time points. These ECGs were not available for review until the card was received by the central ECG laboratory and analyzed.

Interval duration measurements were collected using computer assisted caliper placements on 3 consecutive beats. Trained analysts then reviewed all ECGs for correct lead and beat placement and adjudicated the pre-placed algorithm calipers as necessary using the proprietary validated electronic caliper system applied on a computer screen (manual adjudication methodology). A cardiologist then verified the interval durations and performed the morphology analysis, noting any T-U wave complex that suggested an abnormal form compatible with an effect on cardiac repolarization.

## **4.2.8 Sponsor's Results**

### **4.2.8.1 Study Subjects**

50 healthy subjects between 18 and 45 years of age, with a normal baseline ECG, body mass index (BMI) range 19 to 28 kg/m<sup>2</sup> were enrolled in the study. Forty-seven of the 50 enrolled subjects completed the study per protocol. Three subjects (Subject Nos. 019, 023, and 029) withdrew consent and withdrew from the study. Subject Nos. 019 withdrew on Days 20 and 21, respectively, and received all 3 study treatments (AVP-923-30/10, placebo, and moxifloxacin). Subject No. 023 withdrew on Day 11 after receiving AVP-923-30/10 and placebo treatments

### **4.2.8.2 Statistical Analyses**

#### ***4.2.8.2.1 Primary Analysis***

The time-matched analysis was conducted as the primary analysis as recommended by ICH E14 guidance. Mixed models were used to compute the 2-sided 90% or 1-sided 95% upper confidence boundary s for each treatment at each time point. The model includes terms for: treatment, time, gender, a time by treatment and a gender by treatment interactions and baseline QTc. It is showing the placebo and baseline corrected (delta-delta analysis) for moxifloxacin and the AVP-923-30/10 dose group at steady state on Day 4. The largest upper bound for AVP-923-30/10 was 14.3 ms at 3 hour after dose.

The largest lower bound of QTcI for moxifloxacin was 8.1 ms occurred also at 3 hours after dose.

#### **4.2.8.2.2 Categorical Analysis**

The outlier analysis was exploratory only since there was insufficient power to detect genetically sensitive individuals to potential QT prolonging drugs in the small sample of healthy volunteers. Nevertheless, the specific outlier criteria were a new abnormal U-wave, new >500 ms absolute QTc duration, and a >60 ms change from baseline. For QTcI there were no differences in these numeric criteria versus placebo for AVP-923-30/10. The nonspecific outlier criterion was a 30 ms to 60 ms change from baseline. No subjects receiving placebo, 3 subjects (6%) receiving AVP-923-30/10 and 8 subjects (16%) receiving moxifloxacin met this criterion.

#### **4.2.8.2.3 Additional Analyses**

The mean change from baseline placebo-corrected for heart rate showed a -2.8 bpm change. There was 1 bradycardic outlier with AVP-923-30/10 and 1 tachycardic outlier with placebo.

The mean change from baseline placebo-corrected for PR duration showed a -1.2 ms change with AVP-923-30/10. There were no outliers with AVP-923-30/10.

The mean change from baseline placebo-corrected for QRS duration showed a -0.2 ms change for AVP-923-30/10. There were no outliers with AVP-923-30/10.

The analysis based on QTcF was also performed and the results were consistent with QTcI.

#### **4.2.8.3 Safety Analysis**

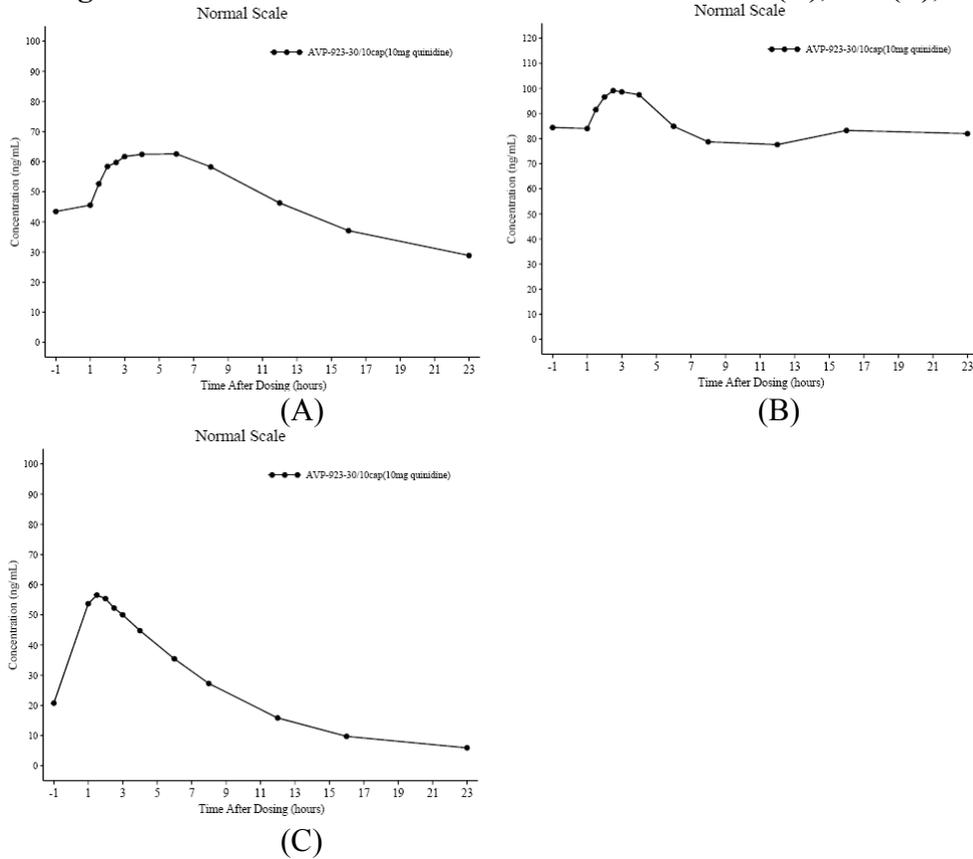
There were no deaths, SAEs or discontinuations due to AEs in this study.

#### **4.2.8.4 Clinical Pharmacology**

##### **4.2.8.4.1 Pharmacokinetic Analysis**

Pharmacokinetic parameters ( $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-12}$ ) for Q, DM, and DX were computed using noncompartmental method (Table 3). The mean PK profiles for DX, DM, and Q are shown in Figure 1.

**Figure 1: Mean Concentration-Time Profiles for DM (A), DX (B), and Q (C)**



(Source: Study report P-116 ~ P-118, Figure 14.2.1-1.1 ~ Figure 14.2.1-1.3)

**Table 3: Summary of Plasma Pharmacokinetic Parameters of AVP-923**

Analyte	C <sub>max</sub> (ng/mL)	T <sub>max</sub> <sup>a</sup> (hr)	AUC <sub>0-t</sub> (ng*hr/mL)	AUC <sub>0-12</sub> (ng*hr/mL)
Quinidine (Q)	59.4 (27.6)	1.50 (1.00, 3.00)	527 (215)	393 (138)
Dextromethorphan (DM)	67.4 (19.5)	4.00 (1.50, 8.00)	1076 (345)	659 (197)
Dextrophan (DX)	104 (26.4)	3.00 (2.00, 23.0)	1932 (468)	1022 (277)

(Source: Sponsor's report-body.pdf, Table 11-3, page 64)

*Reviewer Comments: This approach for calculating PK parameters for the study design is acceptable.*

#### 4.2.8.4.2 Exposure-Response Analysis

The PK-PD analysis explored the relationship between the placebo-corrected (placebo-adjusted) change from baseline in QTc intervals (QTcI, QTcF, and QTcB) and plasma concentrations of Q, DM, and DX. For this PK-PD analysis, a linear mixed effects modeling approach was used in which the relationship between the placebo-adjusted/corrected change from baseline in QTc intervals (QTcI, QTcF, and QTcB) and

plasma concentrations of Q, DM, and DX was a fixed effect with subject included as a random effect (see Equation 1 below). This model was used to estimate the population slope and the standard error of the slope of the relationship between the placebo-adjusted/corrected change from baseline in QTc intervals (QTcI, QTcF, and QTcB) and plasma concentrations of Q, DM, and DX.

$$\text{Equation 1: } \Delta\Delta\text{QTcI} = \alpha + \beta * (\text{plasma concentration}) + \gamma * (\text{subject effect})$$

A summary of model results for plasma concentrations of Q, DM, and DX are shown below in Table 4 -6. The concentration- $\Delta\Delta\text{QTcI}$  relationships for DM, DX, and Q are shown in Figure 2.

**Table 4: Placebo-Corrected Change from Baseline versus the Quinidine Plasma Concentration - Estimates from Linear Mixed Model QTc Individual, QTc Fridericia, and QTc Bazett Intervals (ms)**

QT Parameter	Slope of Plasma Concentration	Standard Error of Plasma Concentration	p-value	Predicted QTc at Average Cmax 58.250 ng/ml	One-sided Upper 95% Confidence Bound <sup>2</sup> of Predicted QTc	Overall Model Fit
QTcI	0.0514	0.0136	0.0002	10.0675	11.9638	<.0001
QTcF	0.0491	0.0123	0.0001	9.3111	11.0976	<.0001
QTcB	-0.0128	0.0144	0.3735	5.0630	7.3154	<.0001

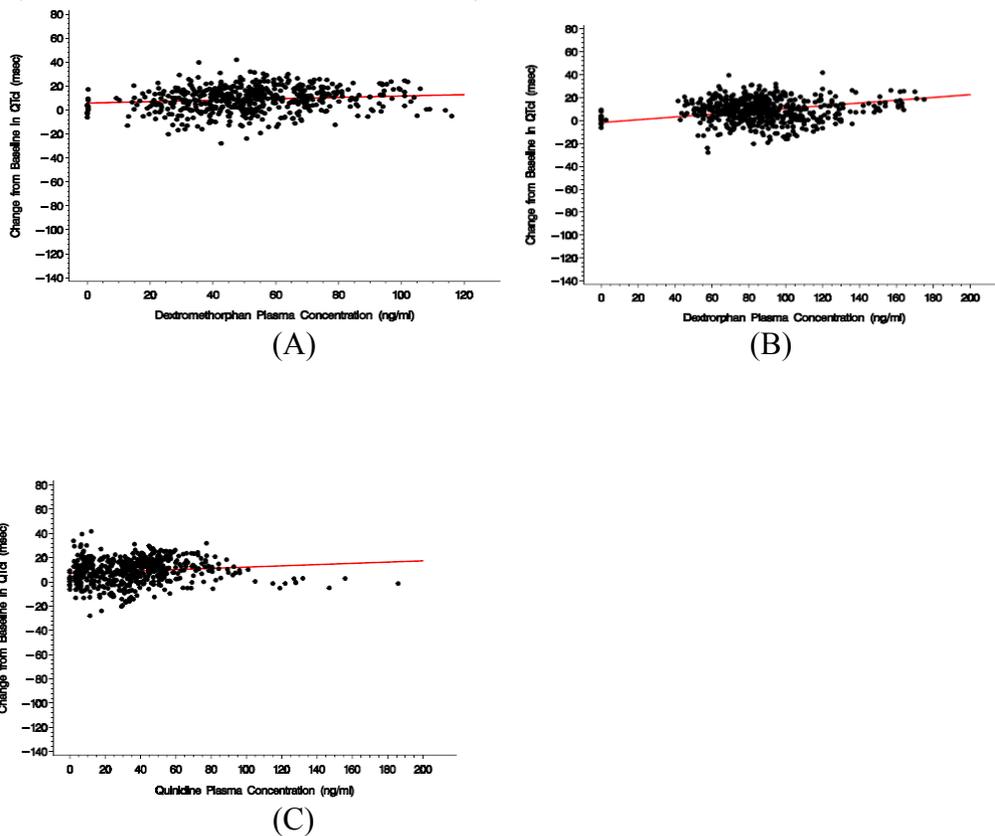
**Table: 5 Placebo-Corrected Change from Baseline versus the Dextromethorphan Plasma Concentration - Estimates from Linear Mixed Model QTc Individual, QTc Fridericia, and QTc Bazett Intervals (ms)**

QT Parameter	Slope of Plasma Concentration	Standard Error of Plasma Concentration	p-value	Predicted QTc at Average Cmax 66.086 ng/ml	One-sided Upper 95% Confidence Bound <sup>2</sup> of Predicted QTc	Overall Model Fit
QTcI	0.0586	0.0215	0.0067	9.6803	11.5378	<.0001
QTcF	0.0783	0.0194	0.0001	9.2657	11.0010	<.0001
QTcB	0.0975	0.0226	0.0000	6.6859	8.9309	<.0001

**Table 6: Placebo-Corrected Change from Baseline versus the Dextroprphan Plasma Concentration - Estimates from Linear Mixed Model QTc Individual, QTc Fridericia, and QTc Bazett Intervals (ms)**

QT Parameter	Slope of Plasma Concentration	Standard Error of Plasma Concentration	p-value	Predicted QTc at Average Cmax 102.255 ng/ml	One-sided Upper 95% Confidence Bound <sup>2</sup> of Predicted QTc	Overall Model Fit
QTcI	0.1218	0.0208	0.0000	10.6944	12.6933	<.0001
QTcF	0.1211	0.0188	0.0000	9.9863	11.8436	<.0001
QTcB	0.0327	0.0227	0.1503	5.7592	8.0105	<.0001

**Figure 2:  $\Delta\Delta$ QTc Individual Change from Baseline Versus DM (A), DX (B), and Q (C) Plasma Concentration**



(Source: Sponsor's report-body.pdf, Figure 11-2, 11-3, and 11-4, page 72-74)

The slopes for QTcI and QTcF for Q were 0.051 and 0.049 respectively. The slopes for QTcI and QTcF for DM were 0.06 and 0.08 respectively. The slopes for QTcI and QTcF for the metabolite DX were 0.12 and 0.12 respectively. These data support the premise that there is an effect of Q, DM, or DX on cardiac repolarization. While

presumably QTc effects are predominantly due to Q, it is not possible to discern an independent relationship of DM or DX to QTc change because their concentrations are proportional to that of Q.

*Reviewer’s Comments: A significant QT prolongation was observed in the sponsor’s study, however, the individual contribution of Q, DM, and DX to the QT prolongation can not be discerned from the data. A slope of 0.05 ms per ng/mL quinidine was identified from this study, which is approximately the estimated concentration-QT slope from the previous TQT study (0.04 ms per ng/mL quinidine). However, the intercept in the sponsor’s analysis was fixed to zero while a significant non-zero intercept of 5.7 ms was identified during the Reviewer’s analysis.*

## 5 REVIEWERS’ ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcI) submitted by the sponsor. Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the mixed model of the pooled post-dose data of QTcF and QTcI distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcI), and the interaction term of RR and correction type. The slopes of QTcF and QTcI versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 7, it appears that over all, QTcF had slightly smaller absolute slopes than QTcI.

**Table 7: Comparison of QTcF and QTcI Using the Mixed Model**

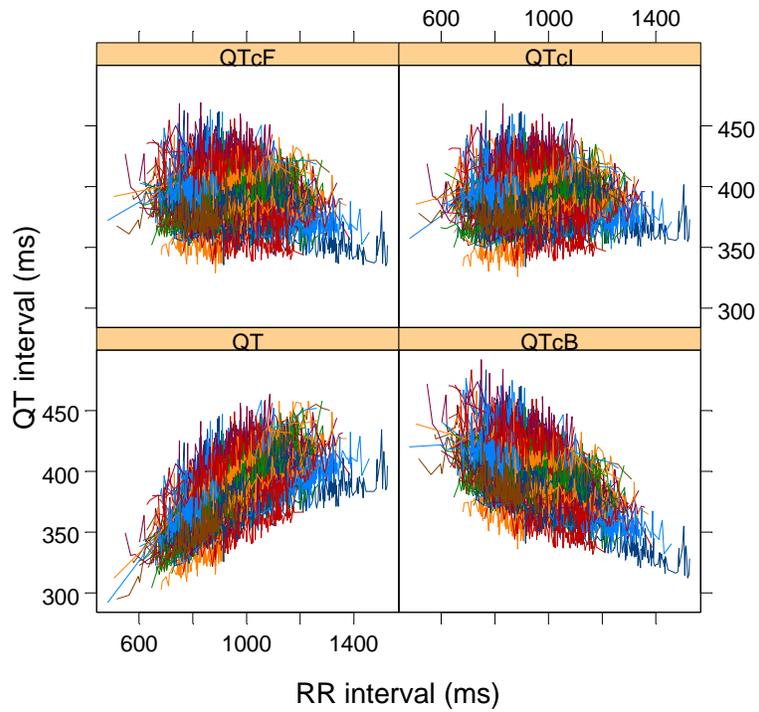
Treatment Groups	Slope of QTcF	Slope of QTcI	diff_p_value
All	0.01753	0.02392	0.00273
AVP-923	0.01716	0.02977	0.00381
Moxifloxacin	0.02001	0.02856	0.04849
Placebo	0.00977	0.01743	0.05331

We also used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 8, it appears that overall QTcF is also slightly better than QTcI. Thus, this statistical reviewer used QTcF for the primary statistical analysis. The sponsor used QTcI for their primary analysis in this study and they used QTcF as the primary endpoint in a TQT study conducted in 2006 (i.e., Study 05-AVR-119).

**Table 8: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

Method	Treatment							
	AVP-923		Moxifloxacin		Placebo		Z	
	N	MSSS	N	MSSS	N	MSSS	N	MSSS
QTcB	50	0.0034	49	0.0040	49	0.0055	50	0.0038
QTcF	50	0.0025	49	0.0017	49	0.0017	50	0.0015
QTcI	50	0.0045	49	0.0032	49	0.0017	50	0.0025

**Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)**



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for AVP-923-30/10

The statistical reviewer used linear mixed effects model to analyze the  $\Delta$ QTcF effect. The model includes gender, sequence and baseline QTc value in the model as covariates. The analysis results are listed in the Table 9. The largest upper bound of the 2-sided 90% CI for the mean difference between AVP-923-30/10 and placebo was 12.6 ms occurred at 3 hour after dose.

**Table 9: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Treatment Group AVP-923-30/10**

Time/(hr)	$\Delta$ QTcF (AVP-923-30/10)	$\Delta$ QTcF (Placebo)	$\Delta\Delta$ QTcF	
	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	7.1	-1.7	8.7	(6.2, 11.2)
1.5	7.5	-1.7	9.2	(6.4, 12.0)
2	7.3	-2.4	9.7	(7.0, 12.4)
2.5	10.5	1.6	8.9	(6.1, 11.7)
3	11.1	0.9	10.2	(7.8, 12.6)
4	10.3	1.4	9.0	(6.3, 11.6)
6	4.8	-2.7	7.5	(5.0, 9.9)
8	2.8	-4.6	7.3	(5.2, 9.5)
12	2.1	-3.0	5.1	(2.5, 7.7)
16	10.6	4.4	6.1	(2.9, 9.3)
23	2.9	-1.5	4.5	(1.6, 7.4)

#### 5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The model includes gender, sequence and baseline QTc value in the model as covariates. The analysis results are listed in the Table 10. The largest lower bounds of the 2-sided 90% CI for the mean difference between AVP-923-30/10 and placebo was 9.1 ms occurred at 4 hours after dose after Bonferroni adjustment of 3 time points.

**Table 10: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Moxifloxacin 400 mg**

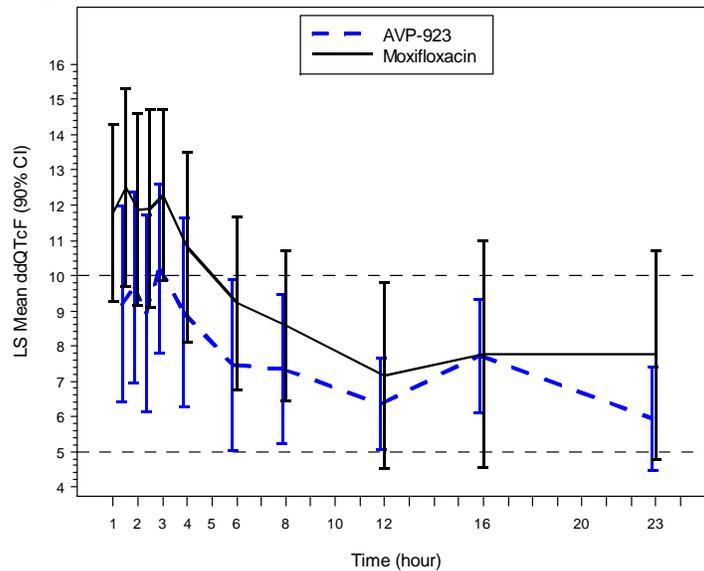
	$\Delta$ QTcF (Moxifloxacin 400 mg)	$\Delta$ QTcF (Placebo)	$\Delta\Delta$ QTcF	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)*
1	7.1	-1.7	8.7	(6.2, 11.2)
1.5	10.1	-1.7	11.8	(8.5, 15.1)
2	10.9	-2.4	12.5	(8.9, 16.2)
2.5	9.5	1.6	11.9	(8.3, 15.4)
3	13.5	0.9	11.9	(8.2, 15.5)
4	13.1	1.4	12.3	(9.1, 15.4)
6	12.2	-2.7	10.8	(7.3, 14.3)
8	6.5	-4.6	9.2	(6.0, 12.4)
12	4.0	-3.0	8.6	(5.8, 11.3)
16	4.2	4.4	7.2	(3.7, 10.6)
23	12.2	-1.5	7.8	(3.6, 12.0)

\* Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

### 5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

Figure 4 displays the time profile of  $\Delta\Delta$ QTcF for different treatment groups.

**Figure 4: Mean and 90% CI  $\Delta\Delta$ QTcF Time Course**



(Note: CIs are all unadjusted including moxifloxacin)

### 5.2.1.4 Categorical Analysis

Table 11 lists the number of subjects as well as the number of observations whose absolute QTcF values are  $\leq 450$  ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

**Table 11: Categorical Analysis for QTcF**

Treatment Group	Total N		Value $\leq$ 450 ms		450 ms<Value $\leq$ 480 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
AVP-923	50	550	49 (98.0%)	549 (99.8%)	1 (2.0%)	1 (0.2%)
Moxifloxacin	49	534	47 (95.9%)	528 (98.9%)	2 (4.1%)	6 (1.1%)
Placebo	49	523	48 (98.0%)	522 (99.8%)	1 (2.0%)	1 (0.2%)

Table 12 lists the categorical analysis results for  $\Delta$ QTcF. No subject's change from baseline was above 60 ms.

**Table 12: Categorical Analysis of  $\Delta$ QTcF**

Treatment Group	Total N		Value $\leq$ 30 ms		30 ms<Value $\leq$ 60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
AVP-923	50	550	47 (94.0%)	546 (99.3%)	3 (6.0%)	4 (0.7%)
Moxifloxacin	49	534	43 (87.8%)	525 (98.3%)	6 (12.2%)	9 (1.7%)
Placebo	49	523	48 (98.0%)	522 (99.8%)	1 (2.0%)	1 (0.2%)

### 5.2.2 PR Analysis

The statistical reviewer used linear mixed effects model to analyze the  $\Delta$ PR effect. The model includes gender, sequence and baseline PR value in the model as covariates. The analysis results are listed in Table 13. The largest upper bound of the 2-sided 90% CI for the mean difference between AVP-923-30/10 and placebo was 2.2 ms occurred at 4 hour after dose.

The outlier analysis results for PR are presented in Table 14.

**Table 13: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Group AVP-923-30/10**

Time/(hr)	$\Delta$ PR (AVP-923-30/10)	$\Delta$ PR (Placebo)	$\Delta\Delta$ PR	
	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	-2.5	-1.0	-1.5	(-3.7, 0.7)
1.5	-2.0	-1.2	-0.8	(-2.9, 1.3)
2	-1.7	-1.3	-0.4	(-2.5, 1.6)
2.5	-1.7	-2.0	0.3	(-2.5, 3.0)
3	-2.3	-2.0	-0.3	(-2.6, 2.0)
4	-3.4	-3.1	-0.3	(-2.8, 2.2)
6	-7.0	-4.7	-2.3	(-4.3, -0.2)
8	-9.6	-7.3	-2.3	(-4.2, -0.3)
12	-7.0	-5.0	-2.1	(-4.3, 0.2)
16	0.6	1.5	-0.9	(-3.2, 1.4)
23	-4.2	-2.2	-2.0	(-4.1, 0.1)

**Table 14: Categorical Analysis for PR**

Treatment Group	T		Value $\leq$ 200 ms		Value $>$ 200 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
AVP-923	50	550	48 (96.0%)	548 (99.6%)	2 (4.0%)	2 (0.4%)
Moxifloxacin	49	534	47 (95.9%)	532 (99.6%)	2 (4.1%)	2 (0.4%)
Placebo	49	523	47 (95.9%)	517 (98.9%)	2 (4.1%)	6 (1.1%)

### 5.2.3 QRS Analysis

The statistical reviewer used linear mixed effects model to analyze the  $\Delta\Delta$ QRS effect. The model includes gender, sequence and baseline QRS value in the model as covariates.

The analysis results are listed in Table 15. The largest upper bound of the 2-sided 90% CI for the mean difference between AVP-923-30/10 and placebo was 1.4 ms occurred at 2 hour after dose.

The outlier analysis results for QRS are presented in Table 16. No subjects had QRS greater than 110 ms.

**Table 15: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group AVP-923-30/10**

	$\Delta$ QRS (AVP-923-30/10)	$\Delta$ QRS (Placebo)	$\Delta\Delta$ QRS	
<b>Time/(hr)</b>	<b>Mean (ms)</b>	<b>Mean (ms)</b>	<b>Diff LS Mean (ms)</b>	<b>90% CI (ms)</b>
1	-0.1	-0.5	0.4	(-0.6, 1.3)
1.5	-0.2	-0.3	0.1	(-0.8, 1.0)
2	-0.2	-0.6	0.4	(-0.6, 1.4)
2.5	-0.5	-0.6	0.1	(-0.8, 1.1)
3	-0.3	-0.3	-0.0	(-1.0, 0.9)
4	-0.6	-0.4	-0.2	(-1.3, 0.8)
6	-0.4	0.1	-0.5	(-1.5, 0.5)
8	-1.2	-0.6	-0.5	(-1.5, 0.4)
12	-0.9	-0.6	-0.3	(-1.2, 0.6)
16	-0.5	0.6	-1.1	(-2.2, -0.1)
23	-0.4	0.4	-0.8	(-1.8, 0.1)

**Table 16: Categorical Analysis for QRS**

Treatment Group	Total		Value<=100 ms		100 ms<Value<=110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
AVP-923	50	550	43 (86.0%)	531 (96.5%)	7 (14.0%)	19 (3.5%)
Moxifloxacin	49	534	43 (87.8%)	512 (95.9%)	6 (12.2%)	22 (4.1%)
Placebo	49	523	43 (87.8%)	491 (93.9%)	6 (12.2%)	32 (6.1%)

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

#### 5.3.1 Exposure-Response Analysis Based on Quinidine Concentration

The relationship between  $\Delta\Delta\text{QTcF}$  and quinidine concentrations was investigated by linear mixed-effects modeling.

The following three linear models were considered:

Model 1 is a linear model with an intercept

Model 2 is a linear model with mean intercept fixed to 0 (with variability)

Model 3 is a linear model with no intercept

Table 17 summarizes the results of the quinidine-  $\Delta\Delta\text{QTcF}$  analyses. Model 1 was used for further analysis since the model with intercept was found to fit the data best. The estimated intercept indicates that a different model structure, such as an effect compartment, may be necessary to properly describe the data.

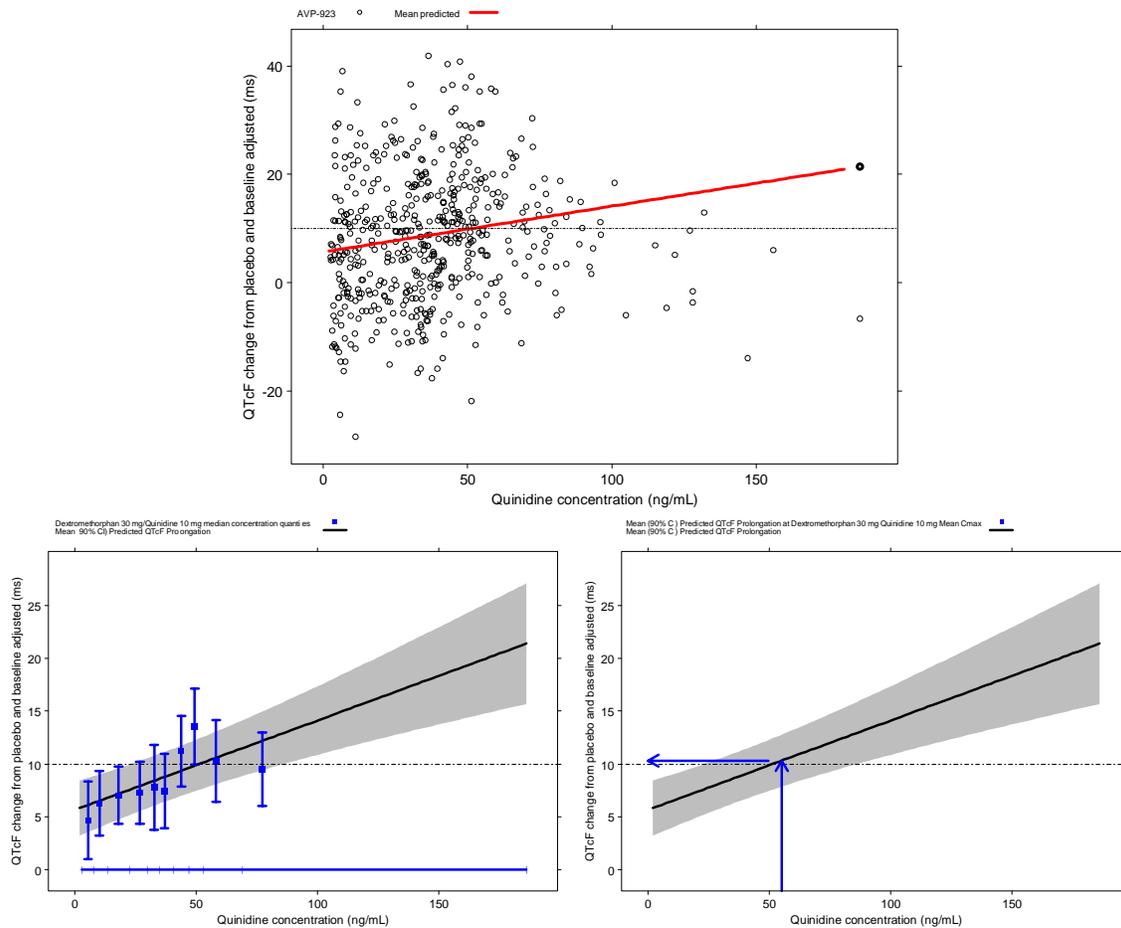
**Table 17: Exposure-Response Analysis of Quinidine Associated  $\Delta\Delta\text{QTcF}$  Prolongation**

Parameter	Estimate (90% CI)	P-value	IIV
Model 1: $\Delta\Delta\text{QTcF} = \text{Intercept} + \text{slope} * \text{Quinidine Concentration}$			
Intercept (ms)	5.66 (3.01; 8.3)	0.0008	9.95
Slope (ms per ng/mL)	0.0846 (0.05; 0.119)	0.0003	0.08
Residual Variability (ms)	6.67		
Model 2: $\Delta\Delta\text{QTcF} = \text{Intercept} + \text{slope} * \text{Quinidine Concentration}$ (Fixed Intercept)			
Intercept (ms)	0		11.47
Slope (ms per ng/mL)	0.12 (0.0877; 0.153)	<.0001	0.09
Residual Variability (ms)	6.65		
Model 3: $\Delta\Delta\text{QTcF} = \text{slope} * \text{Quinidine Concentration}$ (No Intercept)			

Slope (ms per ng/mL)	0.221 (0.159; 0.282)	<.0001	0.24
Residual Variability (ms)		8.52	

The relationship between quinidine concentrations and  $\Delta\Delta\text{QTcF}$  is visualized in the Figure 5. The predicted  $\Delta\Delta\text{QTcF}$  at the geometric mean peak quinidine concentrations can be found in Table 18

**Figure 5:  $\Delta\Delta\text{QTcF}$  vs. Quinidine Concentrations**



**Table 18: Predicted  $\Delta\Delta\text{QTcF}$  Interval at Geometric Mean Peak Quinidine Concentration**

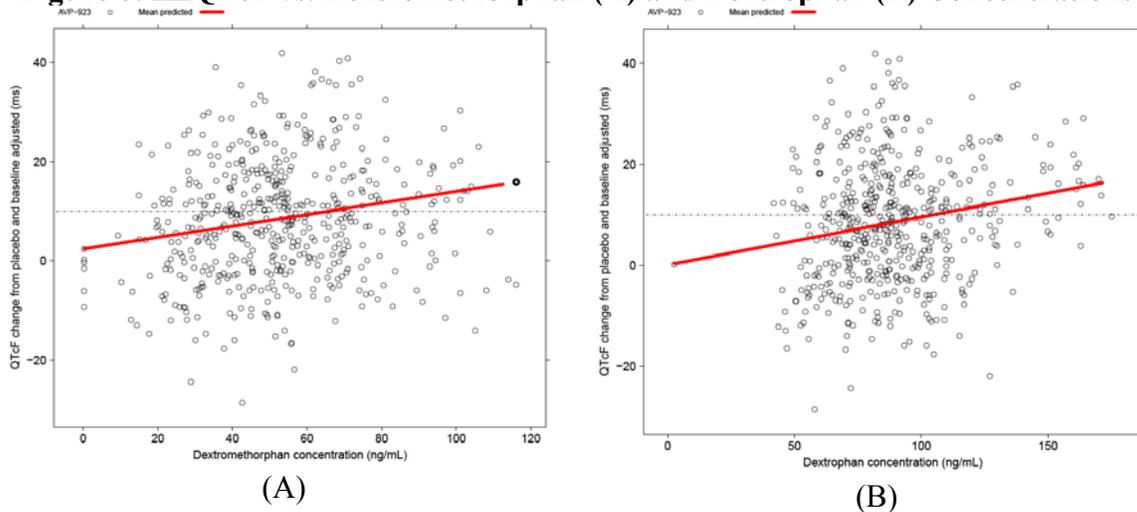
	Treatment	Conc	Pred	CI
1	Dextromethorphan 30 mg/Quinidine 10 mg	55 ng/mL	10.3	(7.85; 12.8)

### 5.3.2 Exposure-Response Analysis Based on Dextromethorphan or Dextrophan Concentration

In addition to the exposure-response relationship described above, similar exposure response relationships between  $\Delta\Delta\text{QTcF}$  and either dextromethorphan or dextrophan concentration were investigated. Similar linear mixed-effects modeling approaches as

described for quinidine were used in during this analysis. The relationship between dextromethorphan (Figure 6, A) and dextrophan (Figure 6, B) concentration and  $\Delta\Delta\text{QTcF}$  is visualized below. Significant trends with respect to  $\Delta\Delta\text{QTcF}$  and the concentration of either compound was observed, but this was not unexpected as the pharmacokinetic time course of both dextromethorphan and dextrophan are similar to quinidine (Figure 1) (i.e., the concentrations of quinidine, dextromethorphan, and dextrophan are highly correlated). It is also possible that one or both of these drugs also contributes to the total QT prolongation observed in this study, however, individual drug effects on QT prolongation cannot be identified given the design of the study.

**Figure 6:  $\Delta\Delta\text{QTcF}$  vs. Dextromethorphan (A) and Dextrophan (B) Concentrations**



## 5.4 CLINICAL ASSESSMENTS

### 5.4.1 Safety Assessments

None of the events identified to be of clinical importance per the ICh- E14 guidelines i.e. sudden cardiac death, syncope, seizure or significant ventricular arrhythmia occurred in this study.

### 5.4.2 ECG Acquisition and Interpretation

Waveforms submitted to the ECG warehouse for Study 08-AVR-126 were reviewed. Pre-dose ECGs were not available for review. According to ECG warehouse statistics, over 90% of the ECGs were annotated in the primary lead (ii) with V5 being the usual back-up lead. Less than 0.1% of the ECGs were reported to have significant QT bias, according to the automated algorithm. Overall, ECG acquisition and interpretation in these studies seems acceptable.

### 5.4.3 PR and QRS Interpretation

At this dose of Q/DM, there were no clinically relevant effects on the PR and QRS intervals.

## 6 TQT STUDY 05-AVR-119 –REVIEWER’S ASSESSMENTS

The sponsor states that at the 10-mg dose, quinidine is a pure IKr blocker and other effects such as sodium channel blockade and vagolytic effects resulting in an increase in heart rate are absent. To address this issue the statistical reviewer analyzed the PR, QRS and heart rate data from the previous TQT study (05-AVR- 119) where DM 30 mg/Q 30 mg BID and DM 60 mg/Q 60 mg BID, since only QTc data have been reviewed previously by the QT-IRT. The statistical reviewer also analyzed the QTc data since the previous review only involved an assessment of the sponsor’s analysis. We expect that the DM 60 mg/Q 60 mg dose should cover high-exposure scenarios with Zenvia (DM 20 mg or 30 mg/Q 10 mg).

### 6.1.1 The Primary Analysis for AVP-923-30 mg BID and AVP-923-60 mg BID

The statistical reviewer used linear mixed effects model to analyze the  $\Delta$ QTcF effect. The model includes gender and baseline QTc value in the model as covariates. The analysis results are listed in Table 19 and Table 20. The largest upper bound of the 2-sided 90% CI for the mean difference between AVP-923-30 mg BID, AVP-923-60 mg BID and placebo was 14.6 ms and 22.7 ms, occurred at 6 hours and 5 hours after dose, respectively.

**Table 19: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Treatment Group AVP-923-30 mg BID**

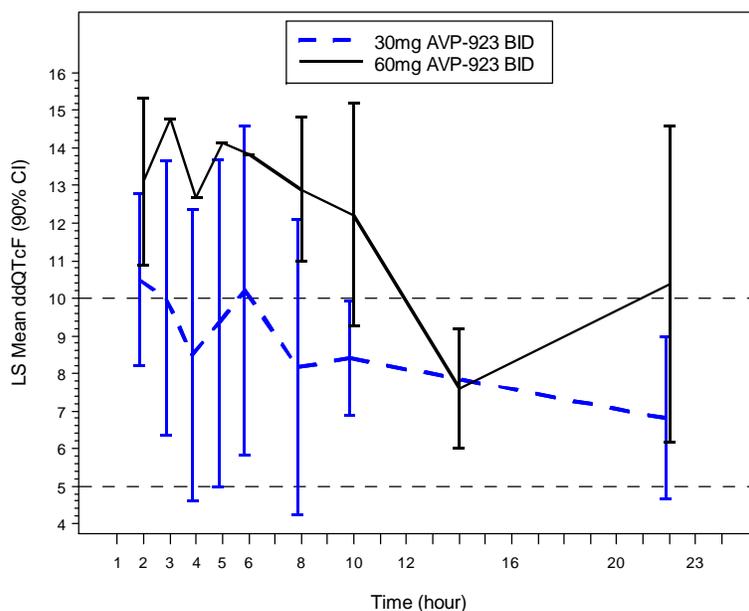
Time/(hr)	VP-923-30 mg BID $\Delta$ QTcF	Placebo $\Delta$ QTcF	$\Delta\Delta$ QTcF	
	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
2	9.5	1.3	8.2	(3.6, 12.8)
3	8.6	-1.4	10.0	(6.3, 13.6)
4	3.9	-4.6	8.5	(4.6, 12.4)
5	3.6	-5.7	9.3	(5.0, 13.7)
6	2.8	-7.4	10.2	(5.8, 14.6)
8	5.8	-2.4	8.2	(4.2, 12.1)
10	3.8	-3.1	6.9	(3.8, 9.9)
14	1.6	1.0	0.6	(-2.7, 3.9)
22	5.3	0.7	4.6	(0.3, 9.0)

**Table 20: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Treatment Group AVP-923-60 mg BID**

	VP-923-60 mg BID $\Delta$ QTcF	Placebo $\Delta$ QTcF	$\Delta\Delta$ QTcF	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
2	16.6	1.3	15.3	(10.9, 19.8)
3	16.9	-1.4	18.3	(14.8, 21.9)
4	11.8	-4.6	16.4	(12.7, 20.1)
5	12.7	-5.7	18.4	(14.1, 22.7)
6	10.6	-7.4	18.1	(13.8, 22.3)
8	12.5	-2.4	14.8	(11.0, 18.6)
10	9.1	-3.1	12.2	(9.3, 15.2)
14	7.0	1.0	6.0	(2.8, 9.2)
22	11.1	0.7	10.4	(6.2, 14.6)

Figure 7 displays the time profile of  $\Delta\Delta$ QTcF for different treatment groups.

**Figure 7: Mean and 90% CI  $\Delta\Delta$ QTcF Timecourse**



### 6.1.2 PR Analysis

The statistical reviewer used linear mixed effects model to analyze the  $\Delta\Delta\text{PR}$  effect. The model includes gender and baseline PR value in the model as covariates. The analysis results are listed in Table 21 and Table 22. The largest upper bound of the 2-sided 90% CI for the mean differences between AVP-923-30 mg BID AVP-923-60 mg BID and placebo were 4.1ms and 5.1 ms, both occurred at 14 hours after dose.

The categorical analysis results for PR are presented in Table 23 . The same one subject had PR > 200 ms under both drug treatment doses (Table 24).

**Table 21: Analysis Results of  $\Delta\text{PR}$  and  $\Delta\Delta\text{PR}$  for Treatment Group AVP-923-30 mg BID**

	AVP-923-30 mg BID $\Delta\text{PR}$	Placebo $\Delta\text{PR}$	$\Delta\Delta\text{PR}$	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
2	4.3	5.6	-1.3	(-5.3, 2.7)
3	2.2	3.7	-1.5	(-4.3, 1.2)
4	-0.4	4.0	-4.4	(-7.5, -1.4)
5	-1.0	2.3	-3.3	(-6.8, 0.2)
6	0.4	4.2	-3.8	(-7.1, -0.4)
8	-5.1	0.5	-5.6	(-9.4, -1.8)
10	-4.9	1.7	-6.7	(-10.3, -3.0)
14	0.8	0.6	0.2	(-3.8, 4.1)
22	-0.1	-0.4	0.3	(-3.2, 3.8)

**Table 22: Analysis Results of  $\Delta\text{PR}$  and  $\Delta\Delta\text{PR}$  for Treatment Group AVP-923-60 mg BID**

	AVP-923-60 mg BID $\Delta\text{PR}$	Placebo $\Delta\text{PR}$	$\Delta\Delta\text{PR}$	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
2	1.0	5.6	-4.6	(-8.6, -0.7)
3	1.4	3.7	-2.3	(-5.0, 0.4)
4	-1.1	4.0	-5.2	(-8.1, -2.2)

	AVP-923- 60 mg BID ΔPR	Placebo ΔPR	ΔΔPR	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
5	0.8	2.3	-1.5	(-4.9, 2.0)
6	3.2	4.2	-0.9	(-4.2, 2.3)
8	-2.0	0.5	-2.5	(-6.1, 1.1)
10	-3.3	1.7	-5.0	(-8.6, -1.4)
14	1.8	0.6	1.2	(-2.6, 5.1)
22	-2.3	-0.4	-1.9	(-5.3, 1.5)

**Table 23: Categorical Analysis for PR**

Treatment Group	Total		Value≤200 ms		Value>200 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
30 mg AVP-923 BID	34	299	33 (97.1%)	296 (99.0%)	1 (2.9%)	3 (1.0%)
60 mg AVP-923 BID	35	315	34 (97.1%)	310 (98.4%)	1 (2.9%)	5 (1.6%)
Baseline	36	104 9	35 (97.2%)	1046 (99.7%)	1 (2.8%)	3 (0.3%)
Placebo	35	314	34 (97.1%)	311 (99.0%)	1 (2.9%)	3 (1.0%)

**Table 24: Outlier Analysis for PR**

SUBJID	Treatment	$\bar{N}_{AM}$ $\bar{E}$	time 2	time 3	time 4	time 5	time 10	time 22
05-AVR-119-004	30 mg AVP- 923 BID	PR	207	204	201			
05-AVR-119-004	30 mg AVP- 923 BID	Baselin e	197	196	194			
05-AVR-119-004	60 mg AVP- 923 BID	PR	217	212		203	203	208
05-AVR-119-004	60 mg AVP- 923 BID	Baselin e	197	197		194	193	191

### 6.1.3 QRS Analysis

The statistical reviewer used linear mixed effects model to analyze the  $\Delta\Delta$ QRS effect. The model includes gender and baseline QRS value in the model as covariates. The analysis results are listed in Table 25 and Table 26. The largest upper bound of the 2-sided 90% CI for the mean difference between AVP-923-30 mg BID AVP-923-60 mg BID and placebo were 5.7 ms and 4.9 ms, both occurred at 22 hours after dose.

The categorical analysis results for QRS are presented in Table 27. The list of subjects with QRS greater than 110 ms is in Table 28.

**Table 25: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group AVP-923-30 mg BID**

	AVP-923-30 mg BID $\Delta$ QRS	Placebo $\Delta$ QRS	$\Delta\Delta$ QRS	
Time/(hr)	Mean (ms)	$\Delta$ QRS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
2	-0.7	-1.3	0.6	(-2.0, 3.2)
3	-1.7	-0.7	-1.0	(-3.8, 1.8)
4	-2.7	-3.0	0.3	(-2.7, 3.3)
5	-4.0	-3.4	-0.6	(-3.4, 2.2)
6	-3.6	-3.6	-0.0	(-2.5, 2.5)
8	-4.0	-2.7	-1.3	(-3.5, 1.0)
10	-4.0	-4.3	0.2	(-2.2, 2.7)
14	-2.8	-1.9	-0.9	(-3.8, 2.0)
22	-0.6	-3.8	3.2	(0.6, 5.7)

**Table 26: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group AVP-923-60 mg BID**

	AVP-923-60 mg BID $\Delta$ QRS	Placebo $\Delta$ QRS	$\Delta\Delta$ QRS	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
2	-2.9	-1.3	-1.6	(-4.2, 1.0)

	AVP-923-60 mg BID $\Delta$ QRS	Placebo $\Delta$ QRS	$\Delta\Delta$ QRS	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
3	-1.6	-0.7	-0.9	(-3.6, 1.8)
4	-1.5	-3.0	1.4	(-1.5, 4.3)
5	-2.1	-3.4	1.3	(-1.4, 4.0)
6	-3.0	-3.6	0.5	(-1.9, 3.0)
8	-2.2	-2.7	0.5	(-1.7, 2.7)
10	-3.8	-4.3	0.5	(-1.9, 2.9)
14	-2.2	-1.9	-0.3	(-3.1, 2.5)
22	-1.4	-3.8	2.4	(-0.0, 4.9)

**Table 27: Categorical Analysis for QRS**

Treatment Group	Total		Value $\leq$ 100 ms		100 ms<Value $\leq$ 110 ms		Value>110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
30 mg AVP-923 BID	34	299	14 (41.2%)	203 (67.9%)	13 (38.2%)	65 (21.7%)	7 (20.6%)	31 (10.4%)
60 mg AVP-923 BID	35	315	16 (45.7%)	213 (67.6%)	12 (34.3%)	69 (21.9%)	7 (20.0%)	33 (10.5%)
Baseline	36	1049	9 (25.0%)	742 (70.7%)	17 (47.2%)	196 (18.7%)	10 (27.8%)	111 (10.6%)
Placebo	35	314	14 (40.0%)	213 (67.8%)	15 (42.9%)	66 (21.0%)	6 (17.1%)	35 (11.1%)

**Table 28: Outlier Analysis for QRS**

SUBJID	Treatment	NAME	time 2	time 3	time 4	time 5	time 6	time 8	time 10	time 14	time 22
05-AVR-119-007	30 mg AVP-923 BID	QRS	117	117	113	113	114	118	111		
05-AVR-119-007	30 mg AVP-923 BID	Baseline	115	123	115	116	120	119	117		
05-AVR-119-008	30 mg AVP-923 BID	QRS				116				110	110

05-AVR-119-008	30 mg AVP-923 BID	Baseline				110				107	100
05-AVR-119-009	30 mg AVP-923 BID	QRS	110								
05-AVR-119-009	30 mg AVP-923 BID	Baseline	100								
05-AVR-119-013	30 mg AVP-923 BID	QRS				123					
05-AVR-119-013	30 mg AVP-923 BID	Baseline				97					
05-AVR-119-027	30mg AVP-923 BID	QRS	116	111							
05-AVR-119-027	30 mg AVP-923 BID	Baseline	109	119							
05-AVR-119-029	30 mg AVP-923 BID	QRS	118	129	126	120	124	126	131	124	123
05-AVR-119-029	30 mg AVP-923 BID	Baseline	113	114	117	112	118	117	118	113	116
05-AVR-119-030	30 mg AVP-923 BID	QRS	120	112	116	118	116	123	113	113	121
05-AVR-119-030	30 mg AVP-923 BID	Baseline		122	119	120	122	123	121	122	124
05-AVR-119-007	60mg AVP-923 BID	QRS	123	111	122		125	119	121	112	120
05-AVR-119-007	60 mg AVP-923 BID	Baseline	114	119	119		122	120	108	122	121
05-AVR-119-008	60 mg AVP-923 BID	QRS						112			
05-AVR-119-008	60 mg AVP-923 BID	Baseline						101			
05-AVR-119-010	60 mg AVP-923 BID	QRS						112			
05-AVR-119-010	60 mg AVP-923 BID	Baseline						99			
05-AVR-119-017	60mg AVP-923 BID	QRS	112								
05-AVR-119-017	60 mg AVP-923 BID	Baseline	104								
05-AVR-119-027	60 mg AVP-923 BID	QRS		114	113	115	115	115			
05-AVR-119-027	60mg AVP-923 BID	Baseline		105	107	122	119	119			
05-AVR-119-029	60 mg AVP-923 BID	QRS	116	125	116	118	118	122	123	116	120
05-AVR-119-029	60 mg AVP-923 BID	Baseline	114	117	124	118	119	119	119	119	116
05-AVR-119-030	60 mg AVP-923 BID	QRS		112	115	120	118	120	118	141	121
05-AVR-119-030	60 mg AVP-923 BID	Baseline		125	122	118	122	125	120	125	119

#### 6.1.4 Heart Rate Analysis

The statistical reviewer used linear mixed effects model to analyze the  $\Delta\Delta\text{HR}$  effect. The model includes gender and baseline HR value in the model as covariates. The analysis results are listed in Table 29 and Table 30. The largest placebo adjusted mean changes of heart rate for AVP-923-30 mg and AVP-923-60 mg were -6.2 bpm and -6.3 bpm, both occurred at 14 hours after dose.

**Table 29: Analysis Results of  $\Delta\text{HR}$  and  $\Delta\Delta\text{HR}$  for Treatment Group AVP-923-30 mg BID**

	AVP-923-30 mg BID	Placebo	$\Delta\Delta\text{HR}$	
	$\Delta\text{HR}$	$\Delta\text{HR}$	Diff LS Mean (bpm)	90% CI (bpm)
Time/(hr)	Mean (bpm)	Mean (bpm)		
2	-3.0	0.8	-3.8	(-5.5, -2.1)
3	0.4	2.3	-1.9	(-3.5, -0.3)
4	0.9	3.7	-2.8	(-4.6, -1.0)
5	1.0	4.2	-3.2	(-5.1, -1.3)
6	-0.8	2.4	-3.2	(-4.6, -1.7)
8	0.3	4.6	-4.3	(-5.9, -2.6)
10	-1.5	1.6	-3.1	(-4.8, -1.4)
14	-5.5	0.7	-6.2	(-8.1, -4.3)
22	0.7	2.8	-2.0	(-4.2, 0.1)

**Table 30: Analysis Results of  $\Delta\text{HR}$  and  $\Delta\Delta\text{HR}$  for Treatment Group AVP-923-60 mg BID**

	AVP-923-60 mg BID	Placebo	$\Delta\Delta\text{HR}$	
	$\Delta\text{HR}$	$\Delta\text{HR}$	Diff LS Mean (ms)	90% CI (ms)
Time/(hr)	Mean (ms)	Mean (ms)		
2	-2.4	0.8	-3.2	(-4.9, -1.5)
3	1.3	2.3	-1.0	(-2.6, 0.5)
4	1.1	3.7	-2.7	(-4.4, -0.9)

	<b>AVP-923- 60 mg BID ΔHR</b>	<b>Placebo ΔHR</b>	<b>ΔΔHR</b>	
<b>Time/(hr)</b>	<b>Mean (ms)</b>	<b>Mean (ms)</b>	<b>Diff LS Mean (ms)</b>	<b>90% CI (ms)</b>
5	-0.5	4.2	-4.7	(-6.6, -2.9)
6	-1.0	2.4	-3.4	(-4.9, -2.0)
8	-1.2	4.6	-5.8	(-7.4, -4.2)
10	-1.7	1.6	-3.3	(-5.0, -1.7)
14	-5.6	0.7	-6.3	(-8.2, -4.5)
22	1.4	2.8	-1.4	(-3.5, 0.7)

## 7 APPENDIX

### 7.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

(b) (6)



7 Pages of Appendix 7 that contains the “Highlights of Clinical Pharmacology” has been withheld as a duplicate copy of the original “Highlights” which can be found in the October 26, 2010 Clinical Pharmacology/Biopharmaceutics Review located in the “Clinical Pharmacology and Biopharmaceutics Review” section of this redacted Approval Package.

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/s/

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HAO ZHU  
09/17/2010

JEFFRY FLORIAN  
09/17/2010

QIANYU DANG  
09/17/2010

JOANNE ZHANG  
09/17/2010

SUCHITRA M BALAKRISHNAN  
09/17/2010

NORMAN L STOCKBRIDGE  
09/17/2010

**M E M O R A N D U M**

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

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**CLINICAL INSPECTION SUMMARY**

DATE: September 14, 2010

TO: Susan Daugherty, Regulatory Health Project Manager  
Devand Jillapalli, M.D., Medical Officer  
Division of Neurology Products

THROUGH: Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.  
Regulatory Pharmacologist  
Good Clinical Practice Branch II  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-879

APPLICANT: Avanir Pharmaceuticals.

DRUG: Zenvia (dextromethorphan and quinidine)

NME: No: New combination

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of patients with pseudobulbar affect (PBA)

CONSULTATION REQUEST DATE: June 16, 2010

DIVISION ACTION GOAL DATE: October 30, 2010

PDUFA DATE: Not listed/assume to be October 30, 2010

## **I. BACKGROUND:**

The Sponsor, Avanir Pharmaceuticals, submitted a New Drug Application for the marketing approval of Zenvia (dextromethorphan and quinidine) in the treatment of patients with Amyotrophic Lateral Sclerosis (ALS) and Multiple Sclerosis (MS). ALS is also known as Lou Gehrig's Disease. Amyotrophic Lateral Sclerosis is a neurologic disease characterized by gradual degeneration of the nerve cells in the central nervous system that control voluntary movement. The disorder causes muscle weakness and atrophy. Symptoms commonly appear in middle to late adulthood, with death in two to five years. The cause of this neurologic disorder is unknown, and to date there is no known cure.

Pseudobulbar affect (PBA) is characterized by pathological laughing and crying inconsistent with the underlying state of happiness or sadness. PBA can be a disabling condition because of the associated stigma of the loss of emotional control. PBA is associated with a number of neurological conditions including ALS.

In this NDA, the sponsor presented the results from the pivotal study 07-AVR-123 in support of the application:

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

In Study 07-AVR-123, male and female subjects, between 18 and 80 years of age, with clinically diagnosed Pseudobulbar Affect (PBA as a result of an underlying neurological disorder amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS) and having scored 13 or higher on the Center for Neurological Studies-Liability Scale (CNS-LS) will be randomized in a double-blind manner to receive treatment with either one or two doses of AVP-923 (AVP-923-30/10[DM]30mg/Q10mg or AVP-923-20mg/10[DM]20mg/Q/10[DM]20mg/Q10) or placebo.

Study Protocol 07-AVR-123's primary efficacy endpoint was the number of laughing and /or crying episodes as recorded in the patient diary. The primary efficacy analysis was based on the changes in laughing/crying episode rates recorded in the patient diary estimated using negative binomial regression on the daily episode counts. Episode counts were to be reported and analyzed as a rate expressed as episodes per day.

The review division requested inspection of two clinical investigators for the pivotal study (Protocol 07-AVR-123) as data from the protocol is considered essential to the approval process. Two domestic investigators were chosen to cover the protocol. These sites were targeted for inspection due to enrollment of a relatively large number of subjects and these sites demonstrating significant primary efficacy results pertinent to decision-making. This application is a new formulation. The sponsor, Avanir Pharmaceuticals is the sponsor of this application.

**II. RESULTS (by protocol/site):**

<b>Name of CI, site # and location</b>	<b>Protocol and # of subjects</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
Daniel Wynn, M.D. Constlants in Neurology, Ltd. 1535 Lake Cook Rd, Suite 601 Northbrook, IL 60062 Site# 101	Protocol 07-AVR- 123 Number of subjects listed 22	7/19-27/10	VAI
Erik Piore, M.D., Ph.D. Department of Neurology, S90 Cleveland Clinical 9500 Euclid Avenue Cleveland, OH 44195 Site#121	Protocol 07-AVR- 123 Number of subjects listed 22	7/20-30/10	VAI

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Protocol 07-AVR-123

1. **Daniel Wynn, M.D.**  
**Northbrook, IL 60062**

**a. What Was Inspected:** At this site, a total of 22 subjects were screened, 4 subjects were reported as screen failures and three subjects were discontinued and the reasons were documented. Eighteen (18) subjects were randomized and 15 subjects completed the double-blind phase of the study and 15 subjects enrolled in the open-label extension phase of the study. There were no deaths and no under-reporting of adverse events. Review of Informed consent documents for all records reviewed, verified that subjects signed prior to enrollment.

A review of the medical records/source documents was conducted. The medical records for 18 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory test results, IRB records and sponsor correspondence, and the use of concomitant medications; source documents were compared to case report forms and to data listings, including primary efficacy endpoints and adverse events.

**b. General observations/commentary:** At the conclusion of the inspection, No Form FDA 483 was issued to Dr. Wynn. However, our investigation found minor transcription errors in drug accountability counts and in the number of laughing/crying episodes in a few subjects. The clinical investigator acknowledged the errors and promised to exercise more care in the future.

#### Recordkeeping Violations

For three (3) subjects the number of inappropriate laughing/crying episodes was incorrectly recorded on the respective case report forms.

- Subject 101-706's Visit 5 diary indicated 3 episodes of inappropriate laughing from 3/14/08-3/20/08. The case report form and the data listings reflected 0 episodes during this time.
- Subject 101-715's Visit 4 diary indicated 3 episodes of inappropriate crying on 5/5/08. The case report form and the data listings reflected 2 episodes during this period.
- Subject 101719's Visit 5 diary indicated 2 episodes of inappropriate crying on 6/9/08. The case report form and the data listings reflected 0 episodes on this date.

#### Drug Accountability Discrepancies

- Subject 101-702: 157 capsules were reported as being taken in the case report form. The master accountability log and the patient diary reported 155 capsules.
- Subject 101706: 160 capsules were reported as being taken in the case report form. The master accountability log and patient diary report 159 capsules were taken during the study.
- Subject 101-717: 158 capsules were reported as being taken in the case report form; however, 154 capsules were reported as being taken per patient's diary.
- Subject 101-720: 160 capsules were reported as being taken in the case report form and 162 reported taken per patient diary. The master accountability log reports 159 capsules were taken during the course of the study

**c. Assessment of Data Integrity:** Although regulatory violations were noted, these are considered isolated in nature, and unlikely to affect data integrity; however, the review division may choose to consider the findings as outlined above with respect to transcription errors in the inappropriate laughing/crying episodes and drug accountability errors noted between the source documents and what was recorded in the case report forms in their assessment of efficacy. The remaining data generated from Dr. Wynn's site are considered reliable and appear acceptable in support of the application.

## **2. Erik P Pioro, M.D.** **Cleveland, OH 44195**

**a. What Was Inspected:** At this site, a total of 24 subjects were screened, and two (2) subjects reported as screen failures. Twenty two (22) subjects were randomized, 20 subjects completed the double-blind phase of the study and 18 subjects completed the open-label extension phase of the study. There were no deaths but several instances of under-reporting of adverse events were noted. Review of the Informed Consent

Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source data for all 24 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB records, prior and current medications, inclusion/exclusion criteria, and source documents were compared to data listings for primary efficacy endpoints and adverse events.

**b. General Observations/Commentary:** At the conclusion of the inspection, a two item Form FDA 483 was issued to Dr. Piro. Our investigation found protocol violations in terms of non-reporting of adverse events and inadequate record keeping.

**Protocol Violations:**

Five subjects, 121-508, 121-512, 121-514, 121-515 and 121-505, experienced adverse events according to the diaries which were not recorded in their respective case report forms (CRFs):

- Subject 121-508 coughed a lot while sleeping on 9/3/08; coughed a lot all night on 12/16/08 and 1/13/09 while on the study.
- Subject 121-512 started to use a nebulizer and get shaky on 3/5/09; feet and legs were swelling on 3/7/09 and felt dizzy on 3/8/09.
- Subject 121-514 experienced leg cramps on 1/26/09 and progressed during the study and experienced abdominal pain during the open-label extension according to the diary. These adverse events were not recorded on the case report form.
- Subject 121-515 experienced swollen feet on 1/31/09; nausea, bad stomach cramps and diarrhea three times on 4/21/09.
- Subject 121-505 a female of childbearing potential, did not receive a pregnancy tests during the double-blind phase of the study as required by the protocol as the subject claimed abstinence.

**Recordkeeping Violations:**

- Subject 12-515 the subject diary card listed the use of concomitant medications, cortisone shot on 2/25/09 and epidural shot on 3/31/09, which were not recorded in the case report form.
- Subject 121-519 took Tylenol on 4/5/09 which was not recorded in the case report form.
- Subject 121-506 Visit 4 (open-label) indicated the ECG result was “normal”. The source document (ECG tracing) indicated “Abnormal”, Intraventricular Conduction Defect” and determined to be “Not clinically significant”. The case report forms did not address the later ECG finding.

The medical records/source document reviewed disclosed no other adverse findings that would reflect negatively on the reliability of the data. With the exception of items noted above, the records reviewed were found to be in order and verifiable and the data

generated by this site appear acceptable in support of the respective indication. There were no known limitations to this inspection.

**c. Assessment of Data Integrity**

Although regulatory violations were noted, these are considered isolated in nature, and unlikely to significantly impact data integrity; however, the review division may choose to consider the findings as outlined above with respect to protocol violations and inadequate records in terms of non-reporting of concomitant medications. The remaining data from Dr. Pioro's site are considered reliable and appear acceptable in support of the pending application.

**III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

Two clinical investigators were inspected in support of this application. The inspections of Drs. Wynn and Pioro revealed minor problems, unlikely to adversely impact data acceptability. However, the review division may wish to consider the violations noted above in their final analyses of study outcome. Overall the data submitted from these sites are acceptable in support of the pending application.

*{See appended electronic signature page}*

Antoine El-Hage, Ph.D.  
Regulatory Pharmacologist  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

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ANTOINE N EL HAGE  
09/16/2010

TEJASHRI S PUROHIT-SHETH  
09/17/2010

Executive CAC

Date of Meeting: August 24, 2010

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair  
Paul Brown, Ph.D., OND IO, Member  
Karen Davis Bruno, Ph.D., DMEP, Alternate Member  
Lois Freed, Ph.D., DNP, Supervisor  
D. Charles Thompson, Ph.D., DNP, Presenting Reviewer

Author of Draft: D. Charles Thompson, Ph.D.

**The following information reflects a brief summary of the Committee discussion and its recommendations.**

**NDA:** 21-879  
**Drug Name:** Zenvia™ (dextromethorphan/quinidine)  
**Sponsor:** Avanir Pharmaceuticals, Inc.

**Background:** 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. (b) (4)

Dextromethorphan is considered to be the active component of Zenvia™ with respect to the proposed indication of PBA. Quinidine is included in the formulation to increase systemic exposure to dextromethorphan by inhibiting its metabolism by cytochrome P450-2D6. The pharmacology/toxicology of each drug given alone has been widely studied and well documented; however, neither drug is approved for chronic use. Therefore, nonclinical studies conducted for this application focused on assessment of the potential for adverse effects of the drug combination with chronic use.

Dextromethorphan and/or quinidine were negative in *in vitro* (Ames, chromosomal aberration in human lymphocytes) and *in vivo* (mouse micronucleus) genotoxicity assays. DM/Q was also 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.

**Rat Carcinogenicity Study:**

Study duration (weeks): 101

Study starting date: 10 July 2003

Study ending date: 9 June 2005

Rat strain: CrI:CD®(SD)IGS BR VAF/Plus®

Route: Oral gavage

Dosing comments: 1% Methylcellulose in water vehicle at 5 mL/kg dose volume

Basis for doses selected: MTD

Prior FDA dose concurrence: Yes (Executive CAC meeting, 12 June 2003)

Study design:

Dose Group	Animals/ Sex	Dextromethorphan Dose (mg/kg/day)	Quinidine Dose (mg/kg/day)
1 (vehicle)	60	0	0
2 (low combination)	60	5	100
3 (middle combination)	60	20	100
4 (high combination)	60	50	100
5 (high individual-1)	60	50	0
6 (high individual-2)	60	0	100

**Rat carcinogenicity:** Survival was decreased in all treated groups relative to controls. Dosing was stopped early in Group 4 males (during Wk 82) and Group 3 and 4 females (during Wks 94-95) and the entire study was terminated after 23 months due to excessive mortality. Based on the Agency's statistical analysis, there was an increase in the incidence of benign adenomas and of combined adenomas plus carcinomas of the pars distalis of the pituitary in Group 4 males and females versus control. In addition, the incidence of pituitary tumors was significantly increased in Group 6 versus control and Group 4 versus Group 5 in males. However, trend tests were negative and the control incidence was high ( $\approx 60\%$  in males, 75-80% in females).

**Executive CAC Recommendations and Conclusions:**

- The Committee agreed that the study was adequate.
- The Committee concluded that there were no biologically significant neoplastic findings for dextromethorphan and quinidine, alone or in combination, under the conditions tested.

Abigail Jacobs, Ph.D.  
Acting Chair, Executive CAC

cc:\n  
/Division File, DNP  
/LMFreed, DNP  
/DCThompson, DNP  
/SDaugherty, DNP  
/ASeifried, OND IO

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21879	ORIG-1	AVANIR PHARMACEUTICA LS INC	NEURODEX(DEXTROMETHOR PHAN PLUS QUINIDINE

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ADELE S SEIFRIED  
08/26/2010

ABIGAIL ABBY C C JACOBS  
08/26/2010

# DSI CONSULT: Request for Clinical Inspections

**Date:** June 16, 2010

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** Ronald Farkas, Ph.D., M.D., Medical Team Leader, Division of Neurology Products  
(DNP)

**From:** Susan Daugherty, Regulatory Health Project Manager/DNP

**Subject:** **Request for Clinical Site Inspections**

## **I. General Information**

Application#: NDA-021879 (may be accessed at  
<\\CDSESUB1\EVSPROD\NDA021879\021879.enx> )

Applicant/ Applicant contact information (to include phone/email):

Avanir Pharmaceuticals  
Randall Kaye, M.D., Vice President, Clinical and Medical Affairs or  
Arthur Rosenthal, Senior Director, Regulatory Affairs  
101 Enterprise, Suite 300  
Aliso Viejo, Ca 92656  
tel: 949-389-6748  
Cell: 949-371-7376  
fax: 949-643-6848  
[arosen@avanir.com](mailto:arosen@avanir.com)

Drug Proprietary Name: Zenvia (dextromethorphan and quinidine)

NME or Original BLA (Yes/No): no, new combination

Review Priority (Standard or Priority): response to approvable (6-month clock)

Study Population includes < 17 years of age (Yes/No): no

Is this for Pediatric Exclusivity (Yes/No): no

Proposed New Indication(s): for the treatment of pseudobulbar affect (PBA).

DSI Consult  
version: 5/08/2008

PDUFA: 10-30-10

Inspection Summary Goal Date:

**II. Protocol/Site Identification**

*Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.*

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
101 PI: Daniel Wynn, MD Consultants in Neurology, Ltd 1535 Lake Cook Road, Suite 601 Northbrook, IL 60062 <a href="mailto:d.wynn@mac.com">d.wynn@mac.com</a> 847-251-1800	07-AVR-123	22	PBA
106 PI: Gary Pattee, MD Neurology Associates 2631 South 70th Street Lincoln, NE 68506 <a href="mailto:gpattee@pol.net">gpattee@pol.net</a> 402 483-7226	07-AVR-123	22	PBA
121 PI: Erik Pioro, MD, PhD, Department of Neurology, S90 Cleveland Clinical 9500 Euclid Avenue Cleveland, OH 44195 <a href="mailto:PIOROE@ccf.org">PIOROE@ccf.org</a> 216 445-2998	07-AVR-123	22	PBA

**III. Site Selection/Rationale**

Study 07-AVR-123 is the only controlled study evaluating the safety and efficacy of (b) (4) dextromethorphan 30 or 20 mg and quinidine 10 mg combination formulations, underscoring the need to evaluate the integrity of the data prior to approval. The above three sites are tied for the largest number of subjects enrolled. DSI may choose to audit any two of these three sites.

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): see above

Should you require any additional information, please contact Susan Daugherty at 301-796-0878 or Devanand Jillapalli at 301-796-2164.

Concurrence:

Ronald, Farkas, Ph.D., M.D., Medical Team Leader  
Devanand Jillapalli, M.D. Medical Reviewer

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21879	ORIG-1	AVANIR PHARMACEUTICA LS INC	NEURODEX(DEXTROMETHOR PHAN PLUS QUINIDINE

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/s/  
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SUSAN B DAUGHERTY  
06/17/2010

**Meeting Question Zenvia NDA 21-879 (N 000 MR)**  
**QT IRT Response**  
**February 20, 2007**

**Clinical Efficacy**

- Question 5:** A reformulation of Zenvia containing a reduced amount of quinidine (10 mg) would be expected to reduce the proarrhythmic risk of quinidine. PK/PD modeling alone is valid for predicting changes in QTc interval. Does FDA agree?

**QT IRT Response:**

**Yes, we agree PK/PD modeling alone is valid for predicting changes in QTc interval.**

**A PKPD model for quinidine using the data from your TQT study was developed by the agency. Our assumption was QT prolongation observed for Zenvia is due only to quinidine and its metabolites. Both direct- and delayed-effect linear models were used to describe the relationship between quinidine concentrations and the change in the QTcI interval.**

**A model-based predicted mean and 90% confidence interval for various quinidine doses is summarized in the following table. The mean and 90% confidence interval for the prediction was computed by multiplying the mean Cmax by the mean and 90% confidence interval of the slope.**

**FDA Analysis: Mean Maximum and 90% Confidence Intervals for the Change in QTcI Interval by Zenvia Dose: Model Predictions vs. E14 Metric**

Quinidine Dose (Mean Cmax)	Mean (90% Confidence Interval)		
	FDA's Direct Effect Model <sup>1</sup>	FDA's Delayed Effect Model <sup>2</sup>	E14 Metric
30 mg (179 ng/ml)	8 (5, 10)	10 (7, 13)	10 (5, 15) <sup>3</sup>
60 mg (356 ng/ml)	15 (10, 20)	20 (14, 26)	18 (13, 25) <sup>4</sup>
10 mg (60 ng/ml) <sup>5</sup>	3 (2, 3)	3 (2, 3)	Not applicable
<b>1. Slope (90% CI): 42.8 (29.1, 56.4) ms per 1000 ng/l</b> <b>2. Slope (90% CI): 55.6 (38.8, 72.4) ms per 1000 ng/l</b> <b>3. Max mean change occurred at 6 h post dose</b> <b>4. Max mean change occurred at 5 h post dose</b> <b>5. Predicted Cmax value assuming linear pharmacokinetics</b>			

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/s/

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Karen Hicks  
2/20/2007 10:35:57 AM  
MEDICAL OFFICER

Christine Garnett  
2/20/2007 10:38:07 AM  
PHARMACOLOGIST

Norman Stockbridge  
2/20/2007 02:10:04 PM  
MEDICAL OFFICER

MEMORANDUM

Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research

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**Date:** October 5, 2006

**To:** Russell Katz, M.D.  
Director, Division of Neurology Products, HFD-120

**Through:** Deborah B. Leiderman, M.D.  
Director, Controlled Substance Staff, HFD-009

**From:** Silvia N. Calderon, Ph.D.  
Team Leader, Controlled Substance Staff, HFD-009

**Subject:** NDA 21-879. Neurodex (Dextromethorphan hydrobromide 30 mg / Quinidine Sulfate 30 mg, capsules). Abuse liability, product labeling and Risk Minimization Action Plan (RiskMAP)  
*Dosage Information:* One capsule every 12 hours for a total daily dose of 60 mg of dextromethorphan and 60 mg of quinidine.  
*Indication:* Involuntary Emotional Expression Disorder.  
*Sponsor:* Avanir Pharmaceuticals

The purpose of this memorandum is to convey to the Division of Neurology Products CSS's recommendations regarding the abuse liability of Neurodex: the proposed Drug Abuse and Dependence section of the product label; and the Risk Minimization Action Plan (RiskMAP).

**CONCERNS ASSOCIATED WITH THE ABUSE OF NEURODEX**

Dextromethorphan (DXM) is sought after for its psychoactive properties, hence the greatest risk associated with the abuse of Neurodex is the potential cardiotoxic effect mediated by quinidine in the context of an overdose, either accidental or deliberate.

DXM at high doses can produce dissociative effects similar to those of phencyclidine (PCP) and ketamine, both known drugs of abuse. Reports of DXM abuse describe symptoms of euphoria, decreased attention and concentration, ataxia, nystagmus, restlessness, lethargy, tactile and visual hallucinations, confusion, depression, synesthesias, insomnia, dilated pupils, slurred speech, and aggressive behavior.<sup>1, 2, 3, 4</sup>

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<sup>1</sup> Boyer, E.W., Dextromethorphan abuse. *Pediatr. Emerg. Care*, **2004**, 20(12), 858-863.

<sup>2</sup> Miller, S.C., Coricidin (R) HBP cough and cold addiction. *J. Amer. Acad. Child Adolesc. Psychiatry*, **2005**, 44(6), 509-510.

<sup>3</sup> Bobo, W.V., Fulton, R.B., Commentary on: Severe manifestations of coricidin intoxication. *Am. J. Emerg. Med.*, **2004**, 22(7), 624-625.

<sup>4</sup> Ziaee, V., Akbari Hamed, E., Hoshmand, A., Amini, H., Kebriaeizadeh, A., Saman, K., Side effects of dextromethorphan abuse, a case series. *Addict Behav*, **2005**, 30(8), 1607-1613.

The abuse of large quantities of cough and cold medications containing DXM and overdose cases are well described in medical literature. Children and adolescents are at particular risk.

The long history of abuse and the recent death of five teenagers prompted the FDA to issue a public warning addressing the potential harm associated with the abuse of DXM.<sup>5</sup>

In contrast to the abuse of over-the counter cough and cold preparations containing DXM, the prospect of abuse of the combination product of dextromethorphan with quinidine presents particular safety concerns. The ingestion of more than two tablets of Neurodex (60 mg dextromethorphan/ 60 mg quinidine) may achieve cardiotoxic levels.<sup>6</sup>

Although DXM abuse is a documented public health problem, DXM is not scheduled at the present because it is specifically exempted from scheduling controls under the Controlled Substances Act [21, U.C.S. 811 (g) (2)].

## RECOMMENDATIONS

### - Labeling

1. CSS recommends that the Sponsor modify the language in the “Drug Abuse and Dependence” section of the label that suggests that Neurodex has less abuse potential than DXM alone. DXM drug seeking is a public health problem and abuse of Neurodex raises safety concerns due to the potential cardiac effects of the formulation.

CSS cautions against the use of language describing a lower potential for abuse of the product based upon quinidine inhibition of the conversion of DXM to dextrorphan. The Sponsor asserts that dextrorphan mediates the positive psychoactive effects associated with the abuse of DXM. This message conveys a sense of safety that doesn't exist, since people looking for a “high” with this formulation might increase the dose to reach levels of quinidine that might affect the cardiac functionality. The Interdisciplinary Review Team for QT Studies, reviewed the QT studies conducted by the Sponsor and found that doubling the dose of Neurodex (60 mg DXM/60 mg) caused QTcF elevation<sup>2</sup> (See DFS, NDA 21879, Dr. Shari Targum's “*QT Team and QT review*” for further details)

Although the Sponsor submitted data to support the assertion that lower levels of dextrorphan might be associated with lower potential of abuse, the potential for seeking the product for misuse or abuse still exists.<sup>7,8,9</sup> In Neurodex clinical trials,

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<sup>5</sup> FDA Talk Paper, *FDA Warns Against Abuse of Dextromethorphan (DXM)*, May 20, 2005, <http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01360.html>

<sup>6</sup> DFS, NDA 21879, Dr. Shari Targum's “*QT Team and QT review*.”

<sup>7</sup> Dematteis, M., Lallement, G., Mallaret, M., Dextromethorphan and dextrorphan in rats: common antitussives-different behavioral profiles. *Fundam. Clin. Pharmacol.*, **1998**, 12(5), 526-537.

2% or less of the pseudobulbar affect patients reported adverse events associated with positive drug effects, including euphoric mood, disorientation, and hallucinations.<sup>10</sup>

The label should reflect that, although low, the potential of abuse of the formulation exists and that there are safety concerns associated with high doses of Neurodex.

2. CSS defers to the Division regarding specific comments to the “Overdosage” section of the label to address procedures on how to handle a suspected Neurodex overdose.

In this section of the label, the Sponsor instructs patients and health care providers to contact a regional poison control center if a Neurodex overdose is suspected. Sponsor recommends that in the case of a suspected overdose of Neurodex, to proceed as if managing an individual overdose of DXM or quinidine.

- *Risk Minimization Action Plan (RiskMAP)*

3. The Sponsor’s proposed Risk Minimization Action Plan (RiskMAP) focuses on educational efforts and surveillance of publicly available databases.

The sole goal of the proposed RiskMAP is to prevent Neurodex abuse by recreational drug users and misuse of the product by patients.

The Sponsor proposes to achieve the main RiskMAP goal through education of health care professionals, providing appropriate labeling and continuing medical education. The Sponsor proposes to monitor publicly available databases such as the Drug Abuse Warning Network (DAWN), the Treatment Episode Data Set (TEDS), Toxic Exposure Surveillance System (TESS) and the Internet for any indication of abuse of the product.

4. In addition to the proposed educational plan, the Sponsor should educate patients on the safe storage of Neurodex in the home, away from children, adolescents and from anyone for whom the product has not been prescribed.
5. The Sponsor needs to provide information on how it plans to collect, analyze and evaluate the information collected by monitoring various databases for abuse and misuse of the product; provide information on the frequency of reporting to the FDA on the outcomes of the proposed RiskMAP; and propose interventions if abuse or misuse of the product is determined.

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<sup>8</sup> Nicholson, K.L., Hayes, B.A., Balster, R.L., Evaluation of the reinforcing properties and phencyclidine-like discriminative stimulus effects of dextromethorphan and dextrorphan in rats and rhesus monkeys. *Psychopharmacology (Berl)*, **1999**,146(1), 49-59.

<sup>9</sup> Zawertailo, L.A., Kaplan, H.L., Busto, U.E., Tyndale, R.F., Sellers, E.M., Psychotropic effects of dextromethorphan are altered by the CYP2D6 polymorphism: a pilot study. *J Clin Psychopharmacol*, **1998**, 18(4), 332-337.

<sup>10</sup> NDA 21,879. *Integrated Summary of Safety*, Section 13.7.3.1

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/s/

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Silvia Calderon  
10/5/2006 04:07:08 PM  
CHEMIST

Deborah Leiderman  
10/5/2006 04:20:18 PM  
MEDICAL OFFICER

## **Interdisciplinary Review Team for QT Studies Response to a Request for Consultation: Study Review**

<b>NDA</b>	21879
<b>Brand Name</b>	Neurodex
<b>Generic Name</b>	AVP-923
<b>Sponsor</b>	Avanir Pharmaceuticals; QT Study by (b) (6)
<b>Indication</b>	Pseudobulbar Affect: Involuntary Emotional Expression
<b>Dosage Form</b>	Hard gelatin immediate release capsules
<b>Active Ingredients</b>	Quinidine sulfate(30 mg)/Dextromethorphan HBr(30 mg)
<b>Therapeutic Dose</b>	1 capsule orally twice daily
<b>Duration of Therapeutic Use</b>	Chronic
<b>Application Submission Date</b>	August 5, 2005, June 26, 2006
<b>Review Classification</b>	NDA Review
<b>Date Consult Received</b>	July 14, 2006
<b>Date Consult Due</b>	September 14, 2006
<b>Clinical Division</b>	Division of Neurology Products

Please note: Additional clinical pharmacology analyses of the concentration-QTc relationship are pending and will be submitted separately.

### **1.0 RECOMMENDATION**

The dose of quinidine and dextromethorphan in this product is associated with an increase in QTcF interval of 25 milliseconds in patients receiving double the prescribed dose of Neurodex (60 mg dextromethorphan and 60 mg quinidine), and an increase of 15 milliseconds in patients receiving the therapeutic dose of Neurodex (30 mg dextromethorphan and 30 mg quinidine) twice daily for 7 doses.

During the 24 hour period after receiving a dose of Neurodex, there were several observations of an increase of this magnitude that correlated with peaks in drug concentration.

The magnitude of the effect of Neurodex on QT interval, as well as the duration of the effect on QT interval, should be considered with regard to risk management of drug-drug interactions and other factors that may enhance QT prolongation.

### **2.0 SUMMARY OF FINDINGS**

In this study, repeated oral dosing of Neurodex at a supratherapeutic level (60 mg dextromethorphan and 60 mg quinidine bid for 7 doses) caused QTcF elevation, observable prior to the last dose and maximal at 6 hours postdose. The maximal mean placebo-subtracted, baseline-adjusted QTcF is 18.81 milliseconds and the upper bound of the one-sided 95% confidence interval for that value is 24.50 milliseconds.

A standard dose of Neurodex (30 mg dextromethorphan and 30 mg quinidine) dosed twice daily for 7 doses caused QTcF elevation, observable prior to the last dose and maximal at 3 hours post dose. The maximal mean placebo- and baseline- subtracted

QTcF for the standard dose of Neurodex was 10.12 msec, and the upper bound of the one-sided 95% CI was 15.05 msec.

QT prolongation can occur at any time during the 24 hour period after receiving a dose of Neurodex.

Assay sensitivity for the study was demonstrated by response to a 400 mg single dose of moxifloxacin, with an increase in QTcF of 14.35 msec one hour post-dose with the lower bound of the one-sided 95% confidence interval of 9.73 msec.

### **3.0 GOAL OF THE REVIEW**

The purpose of this review is to assess the impact of Neurodex on QT interval.

### **4.0 BACKGROUND**

**4.1. Indication:** Pseudobulbar Affect (PBA), is an Involuntary Emotional Expression Disorder, characterized by such behaviors as pathological laughing and crying/weeping, emotional lability, and emotional incontinence. The Sponsor states that PBA occurs in patients with neurodegenerative diseases such as ALS, MS, and Alzheimer's disease or in patients with neuronal damage following stroke or traumatic brain injury.

**4.2. Drug Class:** It is postulated that dextromethorphan, considered the active therapeutic agent, acts by controlling glutamate excitatory activity through modulation as an antagonist of sigma-1 and NDMA receptor activities. The action of quinidine in this product is to increase the plasma concentration of dextromethorphan by competitive inhibition of the metabolism of dextromethorphan (catalyzed by CYP2D6).

**4.3. Market approval status:** Quinidine sulfate and dextromethorphan HBr are currently marketed individually. Quinidine sulfate is indicated for the reduction of frequency of atrial fibrillation/flutter beginning at a dose of 200 mg every 6 hours, conversion of atrial fibrillation/flutter to sinus rhythm beginning at a dose of 400 mg every 6 hours, and treatment of P. faciparum malaria. Dextromethorphan is an over-the-counter drug that is used as an antitussive agent and it is given in doses of 30 mg every 6 to 8 hours up to 120 mg/day.

### **5.0 DRUG INFORMATION**

#### **5.1. Clinical Pharmacology**

Note that genetic polymorphisms in CYP2D6 are responsible for altered metabolism of dextromethorphan (DM) to dextrorphan (DX). Extensive metabolizers (EMs of CYP2D6) are phenotypically converted to PMs by the dose of quinidine (Q) in Neurodex. Dextromethorphan dosed alone to EMs gave urinary metabolic ratios of DM/DX of approximately 0.01-0.05. When given with 28.8 mg Q, the urinary metabolic ratio became 0.35 after a single dose and 1.42 after dosing every 12 hours for 13 doses. This metabolic ratio indicates conversion to the PM phenotype.

The following table summarizes the key features of Neurodex's clinical pharmacology.

**Table 1. Highlights of Clinical Pharmacology.**

<b>Therapeutic dose</b>	A single Quinidine sulfate(30 mg)/Dextromethorphan HBr(30 mg) capsule taken orally twice daily											
<b>Principal adverse events</b>	<p><u>Dextromethorphan</u>: drowsiness, dizziness, and fatigue, effects consistent with serotonin syndrome.</p> <p><u>Quinidine</u>: diarrhea, nausea, vomiting, lightheadedness, heartburn, esophagitis, dose-related prolongation of QTc.</p>											
<b>Absorption</b>	Tmax (hours) Study Day 8	<ul style="list-style-type: none"> <li>•Dextromethorphan</li> <li>•Quinidine</li> <li>•Dextrophan</li> </ul>	<table border="1"> <thead> <tr> <th>EMs</th> <th>PMs</th> </tr> </thead> <tbody> <tr> <td>8 (2-8)</td> <td>5 (4-6)</td> </tr> <tr> <td>2</td> <td>1.5</td> </tr> <tr> <td>48 (24-48)#</td> <td>3 (2-4)</td> </tr> </tbody> </table>	EMs	PMs	8 (2-8)	5 (4-6)	2	1.5	48 (24-48)#	3 (2-4)	
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48 (24-48)#	3 (2-4)											
<b>Elimination</b>	Route	<p><u>Quinidine</u>:</p> <ul style="list-style-type: none"> <li>•Primarily hepatic elimination</li> <li>•Primarily mediated by CYP3A4</li> <li>•When urine pH is &lt; 7, 20% of administered quinidine appears unchanged in the urine. When pH&gt;7, &lt;5% excreted unchanged.</li> <li>•Renal clearance by glomerular filtration and tubular secretion.</li> <li>•Several hydroxylated metabolites; most important: 3-hydroxyquinidine (3HQ).</li> <li>•3HQ at least half as pharmacologically active as quinidine with respect to cardiac effects (based on QTc studies in pre-clinical models)</li> <li>•Plasma concentrations of 3HQ can exceed those of quinidine.</li> <li>•Elimination half-life of 3-HQ: 12 hours.</li> </ul> <p><u>Dextromethorphan</u>:</p> <ul style="list-style-type: none"> <li>•Extensively metabolized.</li> <li>•DM and its metabolites are renally eliminated.</li> <li>•41% of a dose of DM was recovered in the urine in Extensive Metabolizers (EMs) and 64% in Poor Metabolizers (PMs).</li> <li>•In EMs this was accounted for by DX (27%), 3-hydroxymorphinan (16%, total including conjugated), and DM (0.2%).</li> <li>In PMs this was accounted for by DX (8%, total), 3-hydroxymorphinan (14%, total), DM (26%), and 3-methoxymorphinan (11%).</li> </ul>										
	t <sub>1/2</sub> (Study Day 8)	<ul style="list-style-type: none"> <li>•Dextromethorphan</li> <li>•Quinidine</li> <li>•Dextrophan</li> </ul>	<table border="1"> <thead> <tr> <th>EMs</th> <th>PMs</th> </tr> </thead> <tbody> <tr> <td>13 h (26)</td> <td>42 h (11)</td> </tr> <tr> <td>7.7 h (14)</td> <td>6.7 h (6)</td> </tr> <tr> <td>18 h (24)</td> <td>39 (13)</td> </tr> </tbody> </table>	EMs	PMs	13 h (26)	42 h (11)	7.7 h (14)	6.7 h (6)	18 h (24)	39 (13)	
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	(Day 8 vs 1)	<table> <tr> <td></td> <td><u>C<sub>max</sub></u></td> <td><u>AUC</u></td> </tr> <tr> <td>EM</td> <td>6</td> <td>8</td> </tr> <tr> <td colspan="3">Dextrmethorphan (DX)</td> </tr> <tr> <td></td> <td><u>C<sub>max</sub></u></td> <td><u>AUC</u></td> </tr> <tr> <td>EM</td> <td>1</td> <td>1</td> </tr> <tr> <td>PM</td> <td>2</td> <td>6</td> </tr> </table>		<u>C<sub>max</sub></u>	<u>AUC</u>	EM	6	8	Dextrmethorphan (DX)				<u>C<sub>max</sub></u>	<u>AUC</u>	EM	1	1	PM	2	6
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<b>Range of linear PK</b>	<p>DM: Proportional increase in DM exposure for 30 mg, 45mg and 60 mg doses of DM (administered with 30 mg quinidine).</p> <p>Q: Proportional increase in Q exposure for 2-fold and 3-fold increases in 50 and 75 mg doses.</p>																			
<b>Intrinsic Factors</b>	Renal Impairment	<p>The PK of DM, DX, and Q were evaluated in subjects with mild renal impairment (n=6), moderate impairment (n=6), or normal renal function (n=9)</p> <p style="text-align: center;"><b>Degree of Renal Impairment</b></p> <table> <thead> <tr> <th></th> <th><u>Mild</u></th> <th><u>Moderate</u></th> </tr> </thead> <tbody> <tr> <td>DM</td> <td>10% ↓ C<sub>max</sub> 10% ↓ AUC</td> <td>12% ↓ C<sub>max</sub> 12% ↓ AUC</td> </tr> <tr> <td>DX</td> <td>34% ↑ C<sub>max</sub> 23% ↑ AUC</td> <td>85 % ↑ C<sub>max</sub> 93 % ↑ AUC T<sub>max</sub> ↑ 9 hours</td> </tr> <tr> <td>Q</td> <td>30% ↓ C<sub>max</sub> 30% ↓ AUC</td> <td>3 % ↑ AUC</td> </tr> </tbody> </table> <p>The decrease in quinidine exposure in renal impairment is not likely to impact efficacy, since all subjects with mild renal impairment had a poor metabolizer phenotype on Day 7, based on urinary DM/DX ratio. These results are in contrast to the approved quinidine labeling that states that renal dysfunction causes the elimination of quinidine to be slowed and can lead to toxicity if dosage is not appropriately reduced. However, the approved labeling supports doses of more than 200 mg every 6 hours and that is significantly higher than the quinidine doses proposed for Neurodex (30 mg every 12 hours).</p>		<u>Mild</u>	<u>Moderate</u>	DM	10% ↓ C <sub>max</sub> 10% ↓ AUC	12% ↓ C <sub>max</sub> 12% ↓ AUC	DX	34% ↑ C <sub>max</sub> 23% ↑ AUC	85 % ↑ C <sub>max</sub> 93 % ↑ AUC T <sub>max</sub> ↑ 9 hours	Q	30% ↓ C <sub>max</sub> 30% ↓ AUC	3 % ↑ AUC						
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		<p>evaluated in patients with severe hepatic impairment. Note: total bound concentration is considered.</p> <p style="text-align: center;"><b>Degree of Hepatic Impairment</b></p> <table border="0" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th style="text-align: center;"><u>Mild</u></th> <th style="text-align: center;"><u>Moderate</u></th> </tr> </thead> <tbody> <tr> <td>DM##</td> <td style="text-align: center;">10% ↑ Cmax 10% ↑ AUC</td> <td style="text-align: center;">16% ↑ Cmax 16% ↑ AUC</td> </tr> <tr> <td>DX</td> <td style="text-align: center;">2% ↑ Cmax 2% ↑ AUC</td> <td style="text-align: center;">10% ↑ Cmax 10 % ↑ AUC</td> </tr> <tr> <td>Q</td> <td style="text-align: center;">3% ↓ Cmax 19% ↓ AUC</td> <td style="text-align: center;">23% ↓ Cmax 4% ↓ AUC 26 % ↑ AUCu####</td> </tr> </tbody> </table> <p>##There was a decrease in renal excretion of DM in subjects with moderate hepatic impairment.</p> <p>####This small increase in free concentration of quinidine could have resulted in additional inhibition of P-glycoprotein that would have interfered with elimination of DM (a P-gp substrate), resulting in a decrease in renal excretion of DM.</p>		<u>Mild</u>	<u>Moderate</u>	DM##	10% ↑ Cmax 10% ↑ AUC	16% ↑ Cmax 16% ↑ AUC	DX	2% ↑ Cmax 2% ↑ AUC	10% ↑ Cmax 10 % ↑ AUC	Q	3% ↓ Cmax 19% ↓ AUC	23% ↓ Cmax 4% ↓ AUC 26 % ↑ AUCu####
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	<p>Drug interactions</p>	<p><u>Quinidine</u> is a substrate as well as a potent inhibitor of P-gp. The IC<sub>50</sub> for inhibition of P-gp in Caco-2 cells is 2.2 μM. The IC<sub>50</sub> for P-gp inhibition is less than 10-fold higher than the relevant plasma concentrations of quinidine after administration of NEURODEX (approximately 0.6 μM). The effect of quinidine on P-gp after administration of 30 mg twice daily has not been evaluated.</p> <p><u>Dextromethorphan</u> appears to be a P-gp substrate based on a study showing increased bioavailability of DM with administration of grapefruit juice and Seville orange juice. (De Marco MP et al, Life Sciences; 71:2002: 1149-60).</p>												
		<p>•Congestive heart failure reduces quinidine’s apparent volume of distribution and requires a reduction in dosage to prevent toxicity, according to the quinidine labeling.</p>												

#Dextrophan Tmax was 4 hours (Range: 4-8) and 6 hours (Range: 4-8) in EMs and PMs, respectively, on Study Day 4. EMs = Extensive metabolizers, PMs = Poor metabolizers

The elimination half-life observed for quinidine when dosed in Neurodex is in agreement with the 6-8 hour elimination half-life described in the approved quinidine sulfate labeling.

## **6.0. SPONSOR'S SUBMISSION**

### **6.1. Overview**

The Sponsor conducted a Thorough QT Study to assess the impact of Neurodex on QT interval.

### **6.2. Study Design**

**6.2.1. Title:** Randomized, Double-Blind, Placebo Controlled, Crossover Study In Healthy Volunteers To Determine The Electrocardiogram Changes Associated With 2 Doses Of AVP-923 (Neurodex), With An Open-Label Active Control Arm Of Oral Moxifloxacin

**6.2.2. Protocol Number:** 05-AVR-119

**6.2.3. Synopsis** A three-arm, randomized, placebo-controlled, double-blind crossover design (2 dose levels of AVP-923 and placebo) and an additional open-label arm for a positive control (moxifloxacin).

#### **6.2.4. Primary Endpoints**

- The upper 95% confidence limit for the maximum mean change in QTcF from among the Neurodex arm observation times during suprathreshold (2 x standard dose) dose; determined by subtracting the mean baseline adjusted change in QTcF at the matching placebo observation time.
- The relationship between the concentration of dextromethorphan (DM), its major metabolite dextrorphan (DX), and quinidine (Q) and the change in QTcF for all observations during dosing.
- The maximum mean change compared to baseline of QTcF after moxifloxacin administration.

#### **6.2.5. Design**

##### **6.2.5.1. Description**

A three-arm, randomized, placebo-controlled, double-blind crossover design (2 dose levels of AVP-923 and placebo) and an additional open-label arm for a positive control (moxifloxacin).

Table 2. Sequence Descriptions.

Group	Arm 1 (Day 1-4)	Arm 2 (day 8-11)	Arm 3 (Day 15-18)	Arm 4 (Day 22)
A	Standard	Supratherapeutic	Placebo	Pos. Contr.
B	Standard	Placebo	Supratherapeutic	Pos. Contr.
C	Placebo	Standard	Supratherapeutic	Pos. Contr.
D	Placebo	Supratherapeutic	Standard	Pos. Contr.
E	Supratherapeutic	Standard	Placebo	Pos. Contr.
F	Supratherapeutic	Placebo	Standard	Pos. Contr.

### 6.2.5.2 Population

A total of 36 healthy male and female subjects were enrolled (9 females and 27 males). The average male was younger than the average female by approximately 10 years.

### 6.2.5.3. Dose/Treatment groups

Study Arm	Treatment Administered	Meal Instructions
Standard dose AVP-923	BID for 7 doses: •One 30 mg DM/30 mg Q capsule •One matching oral placebo capsule	Fast before morning dose
Supratherapeutic AVP-923	BID for 7 doses: •Two 30 mg DM/30 mg Q capsules	Fast before morning dose
Placebo	BID for 7 doses: •Two matching oral placebo capsules	Fast before morning dose
Positive Control	400 mg single dose	Fast before dose (morning)

Q: “Quinidine”, DM: “Dextromethorphan”, DX: “Dextrorphan”

### Table 3. Treatments Administered.

### 6.2.5.4. Instructions with regard to meals

Doses were administered in the fasting state.

### 6.2.5.5. Study Schedule and Timing of Samples

Randomized treatments were administered on days 1, 8, and 15 and the positive control on day 22. Baseline assessments were made on days 0, 7, 14 and pre-dose on day 22.

Treatment assessments were made on days 4, 11, 18, and 22.

Table 4. Sampling Schedule.

Study Day	0, 7, 14	4, 11, 18	22
Intervention	Day before start of Placebo or Neurodex	Last of 7 BID doses of Placebo or Neurodex	Single 400 mg moxifloxacin dose
12-Lead ECGs	Record ECGs* (Baseline)	Record ECGs*	Record ECGs** (Baseline and on-treatment)
PK Samples for drug	Collected***	Collected*	None collected
Meal Instructions	Fasted	Fasted	Fasted

\*-1,2,3,4,5,6,8,10,14,22 hours postdose

\*\* -1,1,2,3 hours

\*\*\* -1,-0.5 hours

#### **6.2.5.6. QT Measurement**

Three 10-second ECG segments were extracted within a 15- minute time window (between 7.5 minutes prior to and 7.5 minutes after each time point). The lead with the longest apparent QT interval was used for QT measurement. Fridericia and Bazett correction methods were used to correct QT data.

#### **6.2.5.7. Controls**

The Sponsor used both placebo and positive (moxifloxacin) controls. However, moxifloxacin was given as a single dose during a single, separate study period. Response to moxifloxacin was only assessed up to 3 hours post dose. The Sponsor did not collect PK samples during the moxifloxacin treatment period.

#### **6.2.5.8. Blinding**

The placebo and Neurodex treatments were blinded, but the moxifloxacin control was not blinded. ECG readers were blinded to all treatments.

#### **6.2.5.9. Baseline**

Baseline data observations were matched by time of day to treatment observations for the placebo and Neurodex treatment arms.

#### **6.2.5.10. ECG Methodology**

ECGs were digitally recorded onto flash cards using the Mortara H12+ 12-lead continuous ECG (Holter) Recorders. Twelve-lead ECGs, 10-second in duration, were extracted at predetermined times and analyzed by board-certified cardiologists blinded to treatment. For each of these time points, three 10-second ECG segments were to be extracted within a 15- minute time window (between 7.5 minutes prior to and 7.5 minutes after each time point).

Interval determination and diagnostic interpretations were based on established criteria and a fixed dictionary of terms in an on-screen digital analysis environment.

### **6.3. Results**

The following table highlights available data:

**Table 5. Subjects with Data by Treatment and Period.**

Treatment	Baseline Period	Treatment Period	Analyzable Data for Arm
Placebo	36	35	35
Standard	34	34	33
Supratherapeutic	35	35	35
Pos. Contr.	33	33	33

A total of 6661 ECGs were extracted from the Holter sessions. Of these, 45 were uninterpretable due to technical limitation. The results of the remaining extracted ECGs were combined by averaging those available for each time point into 2212 ECG values.

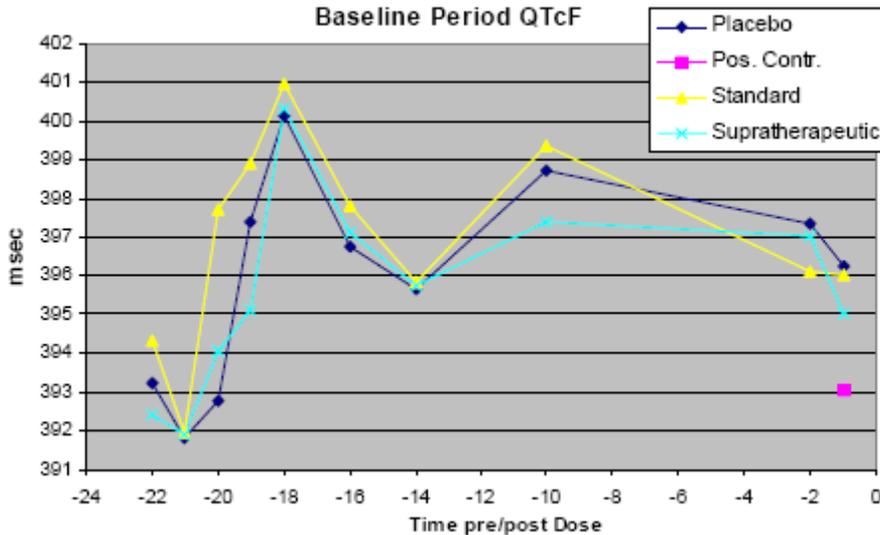
The average of the three (or maximum number available) measurements of each of the ECG intervals at each observation time are used as the ECG values for that nominal time point.

Change from baseline is defined as treatment value minus baseline value.

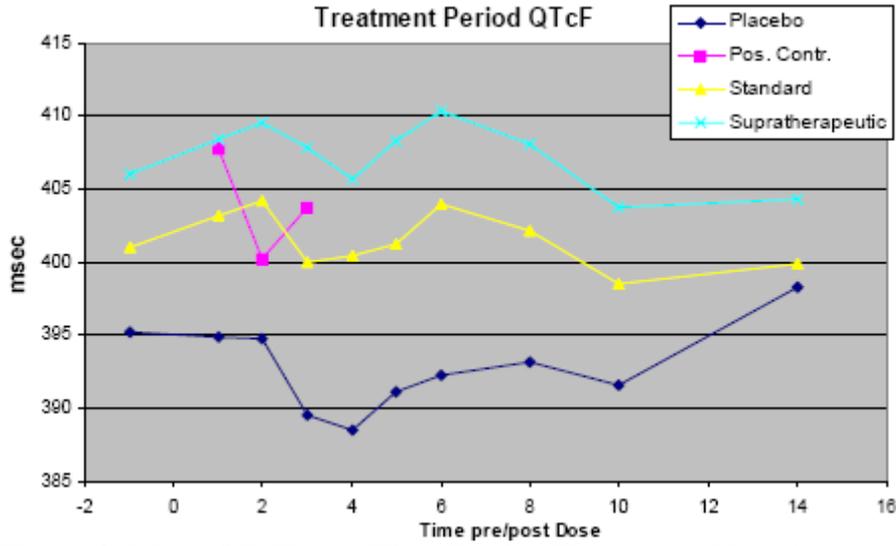
**6.3.1. QT Measurements:** 12-lead ECGs were submitted to the ECG warehouse under IND #62,567. A sampling of ECGs were reviewed; the QT measurement appears to be calculated appropriately at the end of the T-wave. For at least two subjects (#28, 31) different leads (e.g., lead II on one occasion, V5 on another occasion) were used for QT measurements on different 12-lead recordings; however, this method is consistent with the QT algorithm in the study (using the lead with the longest QT). The QT measurements, based on samples reviewed, appeared to be acceptable.

**6.3.2. Statistical Analysis**

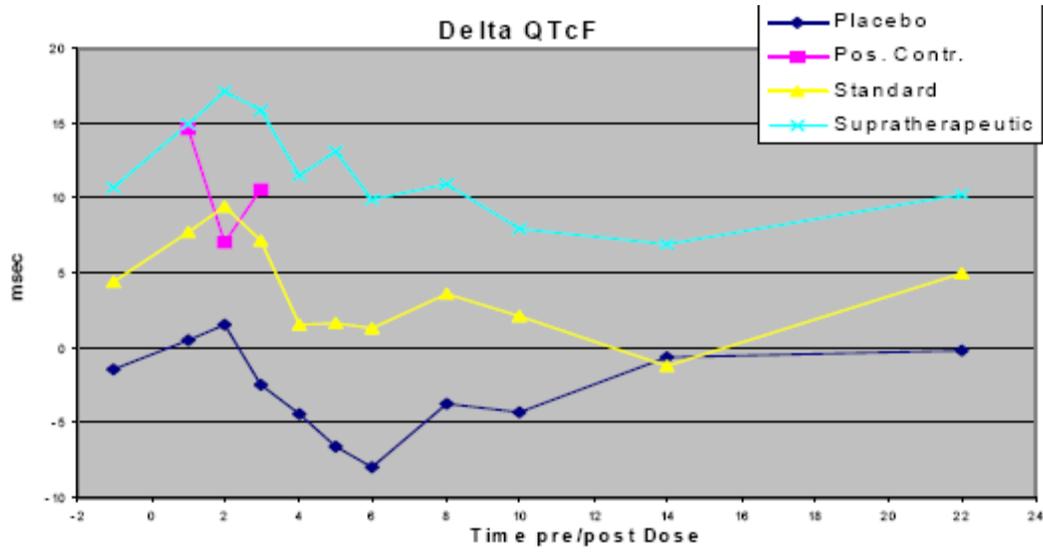
The Sponsor provided the following graphical analyses of the data. Note that the Sponsor did not provide information about variability in estimates in these graphics.



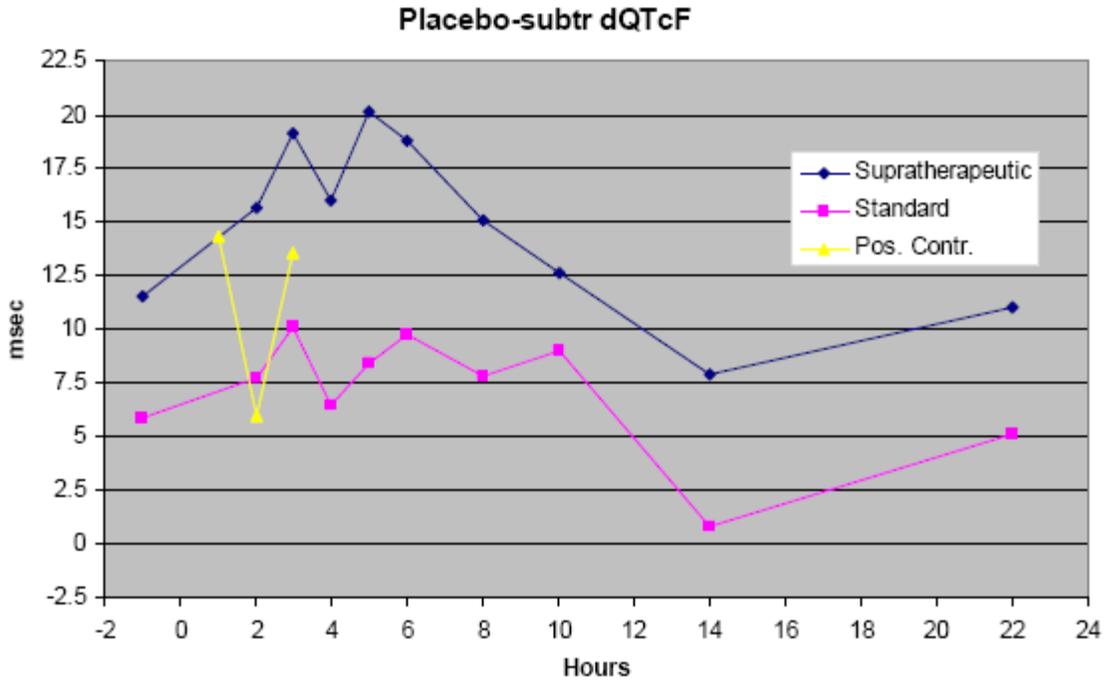
**Figure 1. Mean Baseline QTcF for All Treatment Arms.** Note that the Sponsor has only a single measure of baseline for the moxifloxacin treatment arm compared to the time-matched baseline for all other arms. The single measure of baseline QT/QTc for the moxifloxacin arm is closer in magnitude to the first measure taken for the placebo and Neurodex treatment arms. This may reflect a habituation of subjects over 24 hours of monitoring.



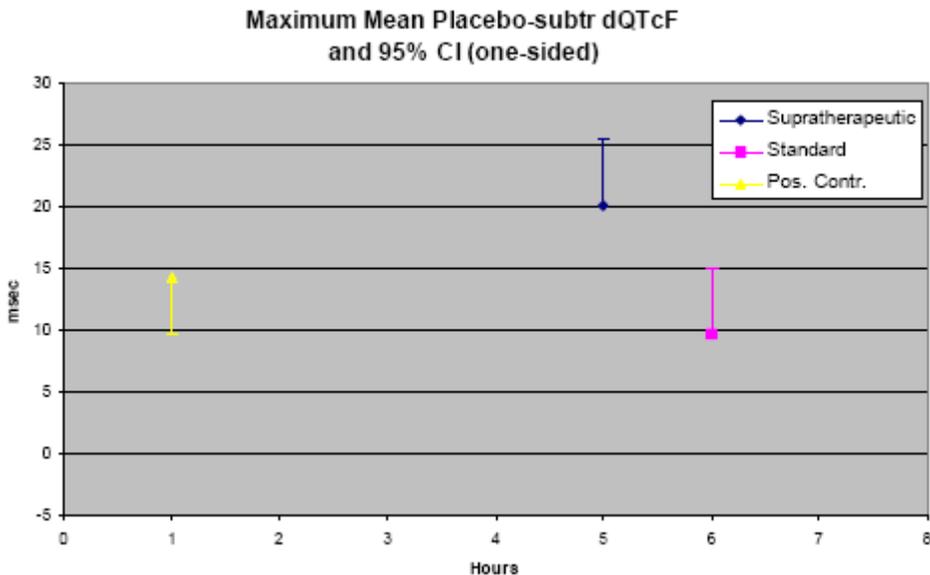
**Figure 2. Mean QTcF over Time During Treatment.** Note that response to moxifloxacin was assessed for only 3 hours post-dose.



**Figure 3. Mean Baseline-Adjusted QTcF ( $\Delta$ QTcF) by Treatment.**



**Figure 4. Mean Placebo- and Baseline- Subtracted QTcF (ΔΔQTcF).**



**Figure 5. Maximum Mean Placebo- and Baseline- Subtracted QTcF (ΔΔQTcF) Endpoints for Each Treatment.**

A suprathapeutic dose (2 x standard dose; 60 mg dextromethorphan and 60 mg quinidine) of Neurodex, dosed twice daily for 7 doses caused QTcF elevation, observable prior to the last dose and maximal at 6 hours post dose. The maximal mean placebo-and baseline- subtracted QTcF change for the suprathapeutic dose of Neurodex was 18.81 msec, and the upper bound of the one-sided 95% CI was 24.50 msec. (Note that the Sponsor’s report that the maximum effect for the suprathapeutic dose occurs 6 hours

post-dose does not agree with Figure 5 showing a maximum effect at 5 hours post-dose. The source of this discrepancy is unclear.)

A standard dose of Neurodex (30 mg dextromethorphan and 30 mg quinidine) dosed twice daily for 7 doses caused QTcF elevation, observable prior to the last dose and maximal at 3 hours post dose. The maximal mean placebo- and baseline- subtracted QTcF for the standard dose of Neurodex was 10.12 msec, and the upper bound of the one-sided 95% CI was 15.05 msec. (Note that the Sponsor’s report that the maximum effect for the therapeutic dose occurs at 3 hours post dose does not agree with Figure 5 showing a maximum effect at 6 hours post-dose. The source of this discrepancy is unclear.)

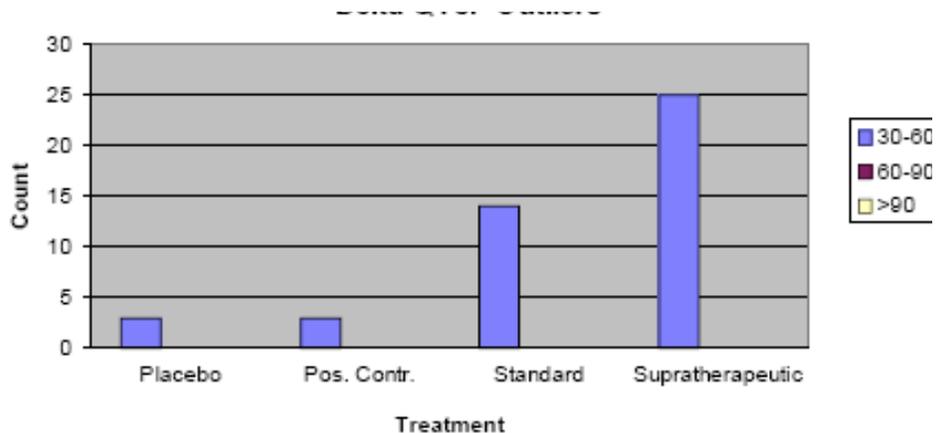
A single 400 mg oral dose of moxifloxacin caused QTcF elevation, observable prior to the last dose and maximal at 1 hour post dose. The maximal mean placebo- and baseline- subtracted QTcF for the moxifloxacin arm was 14.35 msec, and the lower bound of the one-sided 95% CI was 9.73 msec.

The following table summarizes these results.

**Table 6. Maximum Mean, Paired, Placebo- and Baseline- Subtracted QTcF ( $\Delta\Delta$ QTcF) Endpoints for Each Treatment.**

	Hour	Mean	SEM	N	p	Upper (lower) bound of 95% CI one-sided
Suprathereapeutic	6	18.81	3.36348	34	<.0001	24.50
Standard	3	10.12	2.90739	31	0.0015	15.05
Pos. Contr.	1	14.35	2.72976	33	<.0001	9.73

Figure 6 and Table 7 show the results of the Sponsor’s categorical analysis of the effect of drug on QTcF interval.



**Figure 6. Outliers for Baseline- Adjusted QTcF ( $\Delta$ QTcF) by Treatment.**

**Table 7. Number and Percent of Change from Baseline QTcF Outliers by Treatment.**

dQTcF	30-60	Treatment	Number	Percent
dQTcF	30-60	Placebo	3	0.86%
dQTcF	30-60	Pos. Contr.	3	3.03%
dQTcF	30-60	Standard	14	4.20%
dQTcF	30-60	Supratherapeutic	25	7.16%

The Sponsor reports no excessive QTc response for any subject in the study. The maximum QTcF observed was 454 msec. The number of outlier QTcF values (450-480 milliseconds) was 0, 0, 0 and 2 (0.57%), for placebo, standard, positive control or supratherapeutic respectively, and the number of outlier values for change in QTcF from baseline (30-60 msec): 3 (0.86%), 14 (4.20%), 3 (0.86%), and 25 (7.16%) for placebo, standard, positive control or supratherapeutic, respectively. No patient in any treatment group exceeded an absolute QTcF of >480 msec or absolute change of >60 msec.

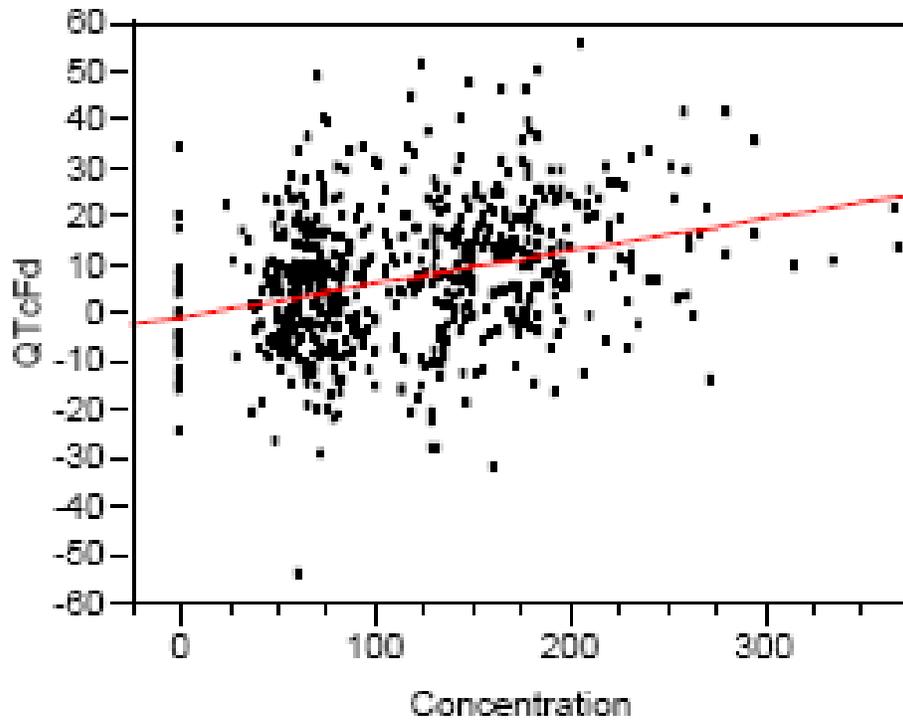
Other ECG Findings:

The Sponsor reports T wave abnormalities in 49 (0.0144%), 60 (0.0176%), 17 (0.50%) and 102 (0.0298%) for placebo, standard, positive control and supratherapeutic doses respectively. No appearances of abnormal U-waves were noted. No changes in QRS were noted. Since a higher percentage of T wave abnormalities were seen in the supratherapeutic dose group, the sponsor has noted a “moderate and dose-related trend for T-wave abnormalities.”

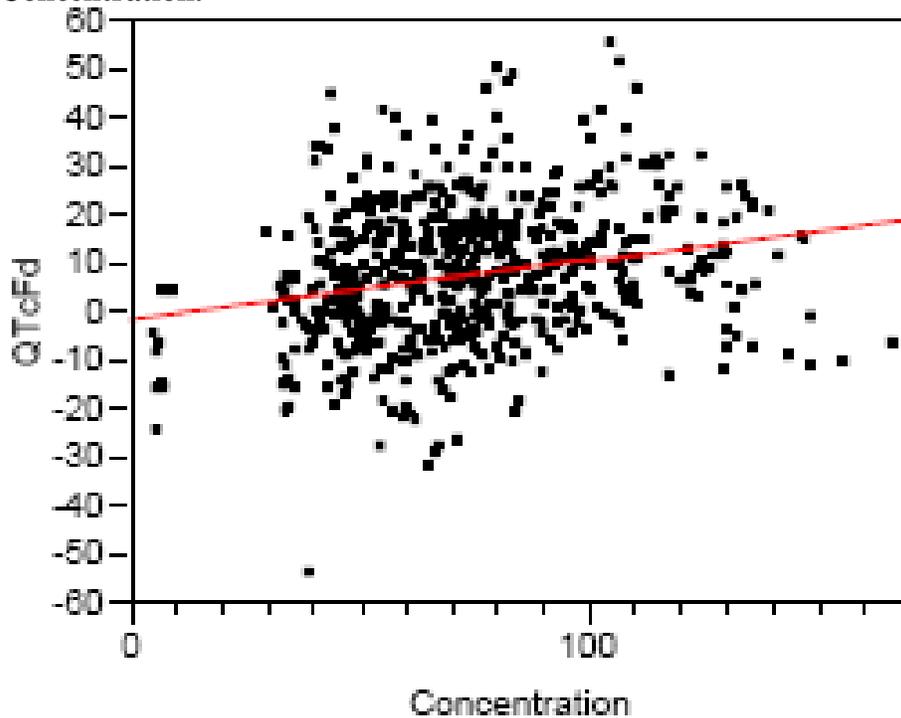
In addition, there was a mild decrease in heart rate and a slight decrease in PR interval with AVP-923.

**6.3.3. Exposure-Response Analysis**

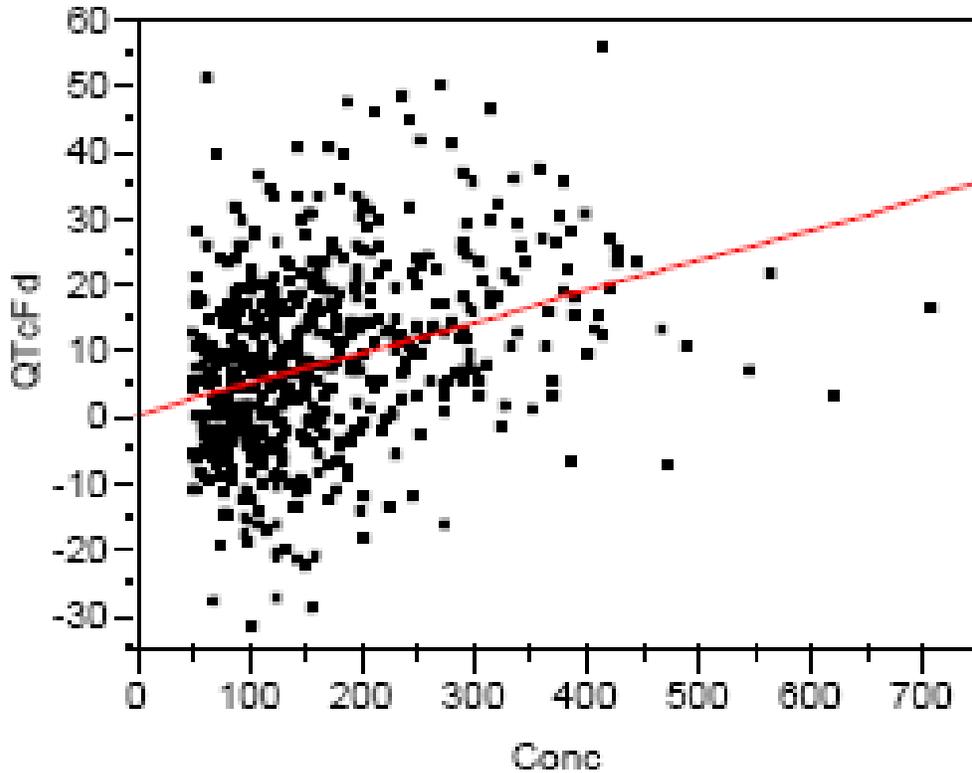
The Sponsor noted that a regression of change in QTcF as a function of concentration of DM, DX, and Q showed a strong relationship for each of the compounds, showing a slope that is highly statistically different from zero.



**Figure 7. Dextromethorphan: Change from Baseline QTcF as a Function of Concentration.**



**Figure 8. Dextroprorphan: Change from Baseline QTcF as a Function of Concentration.**



**Figure 9. Quinidine: Change from Baseline QTcF as a Function of Concentration.**

The following table summarizes the parameter estimates obtained in the above analyses.

**Table 8. The Relationship of the Concentration of DM, DX, and Q to the Change in QTcF for All Observations During Dosing.**

Compound	Slope	Intercept	Prob > F
DM	0.67	0.70	<.0001
DX	0.12	1.69	<.0001
Q	46.61	0.36	<.0001

Table 9 and Table 10 show the results of the Sponsor’s analyses of placebo- and baseline-adjusted QTcF ( $\Delta\Delta$ QTcF) as a function of the concentration of quinidine, dextromethorphan and dextroprphan. The Sponsor modeled the effect of the supratherapeutic and therapeutic doses separately.

**Population Slope, Standard Error of Slope, Mean Maximum Effect, Upper one-sided 95% Confidence Limit**

***Suggested best practices model:***

Mixed effects model of subject\*random + time + baseline QT for active treatment  
baseline QT for placebo + concentration of analyte vs. double delta QT

(each active treatment group separately, each QT method separately and each analyte separately)

Regimen	Correction method	Analyte	Slope	SE slope	Max Conc	Max Effect	Upper 95%CL
SupraT	Response ddQT	DM	0.02865	0.03177	201.23500	5.76	15.28
SupraT	Response ddQT	DX	-0.00735	0.04703	132.70600	-0.97	0.63
SupraT	Response ddQT	Q	29.70004	16.36185	0.35665	10.59	28.07
SupraT	Response ddQTcB	DM	0.07671	0.03301	201.23500	15.44	15.49
SupraT	Response ddQTcB	DX	-0.01107	-0.04740	132.70600	-1.47	-1.55
SupraT	Response ddQTcB	Q	18.70152	16.79904	0.35665	6.67	34.39
SupraT	Response ddQTcF	DM	0.04813	0.02656	201.23500	9.69	9.73
SupraT	Response ddQTcF	DX	0.00124	0.03865	132.70600	0.16	0.23
SupraT	Response ddQTcF	Q	19.19329	13.80099	0.35665	6.85	29.62
SupraT	Response ddQTcl	DM	0.05968	0.02873	201.23500	12.01	12.06
SupraT	Response ddQTcl	DX	-0.00428	0.04220	132.70600	-0.57	-0.50
SupraT	Response ddQTcl	Q	22.20047	14.53918	0.35665	7.92	31.91
Std	Response ddQT	DM	0.02539	0.07678	83.19680	2.11	5.60
Std	Response ddQT	DX	-0.00419	0.08843	85.63000	-0.36	0.23
Std	Response ddQT	Q	23.97253	35.88242	0.18029	4.32	11.45
Std	Response ddQTcB	DM	0.03778	0.07538	83.19680	3.14	8.33
Std	Response ddQTcB	DX	0.03646	0.08756	85.63000	3.12	8.27
Std	Response ddQTcB	Q	71.09245	34.86172	0.18029	12.82	33.97
Std	Response ddQTcF	DM	0.02966	0.06267	83.19680	2.47	6.54
Std	Response ddQTcF	DX	0.02219	0.07247	85.63000	1.90	5.04
Std	Response ddQTcF	Q	56.17023	28.94322	0.18029	10.13	26.84
Std	Response ddQTcl	DM	0.01919	0.06308	83.19680	1.60	4.23
Std	Response ddQTcl	DX	0.02234	0.07329	85.63000	1.91	5.07
Std	Response ddQTcl	Q	58.35910	29.21500	0.18029	10.52	27.88

**Table 9. Results of the Sponsor’s “Best Practices” Concentration- $\Delta\Delta$ QTc Analysis.**

**Population Slope, Standard Error of Slope, Mean Maximum Effect, Upper one-sided 95% Confidence Limit**

*Simple model:*

Mixed effects model of subject\*random + concentration of analyte vs. double delta QT

(each active treatment group separately, each QT method separately and each analyte separately)

Regimen	Correction method	Analyte	Slope	SE slope	Max Conc	Max Effect	Upper 95%CL
SupraT	Response ddQT	DM	0.06902	0.029427	201.23500	13.89	36.81
SupraT	Response ddQT	DX	-0.1459	0.051759	132.70600	-19.36	12.59
SupraT	Response ddQT	Q	16.72374	9.734459	0.35665	5.96	15.81
SupraT	Response ddQTcB	DM	0.103904	0.027155	201.23500	20.91	20.95
SupraT	Response ddQTcB	DX	-0.04384	0.04736	132.70600	-5.82	-5.74
SupraT	Response ddQTcB	Q	35.11774	9.327059	0.35665	12.52	27.91
SupraT	Response ddQTcF	DM	0.095804	0.023561	201.23500	19.28	19.32
SupraT	Response ddQTcF	DX	-0.07494	0.041863	132.70600	-9.95	-9.88
SupraT	Response ddQTcF	Q	29.56213	7.935784	0.35665	10.54	23.64
SupraT	Response ddQTcI	DM	0.0911	0.023462	201.23500	18.33	18.37
SupraT	Response ddQTcI	DX	-0.07886	0.04147	132.70600	-10.47	-10.40
SupraT	Response ddQTcI	Q	28.23791	7.82942	0.35665	10.07	22.99
Std	Response ddQT	DM	0.098036	0.063008	83.19680	8.16	21.61
Std	Response ddQT	DX	-0.06859	0.081172	85.63000	-5.87	3.82
Std	Response ddQT	Q	19.11965	16.47469	0.18029	3.45	9.13
Std	Response ddQTcB	DM	0.114084	0.064084	83.19680	9.49	25.15
Std	Response ddQTcB	DX	-0.0122	0.081477	85.63000	-1.05	-2.77
Std	Response ddQTcB	Q	48.04996	17.92216	0.18029	8.66	22.96
Std	Response ddQTcF	DM	0.108666	0.053893	83.19680	9.04	23.96
Std	Response ddQTcF	DX	-0.03961	0.069223	85.63000	-3.39	-8.99
Std	Response ddQTcF	Q	37.48562	14.52681	0.18029	6.76	17.91
Std	Response ddQTcI	DM	0.101694	0.054681	83.19680	8.46	22.42
Std	Response ddQTcI	DX	-0.01033	0.070375	85.63000	-0.88	-2.34
Std	Response ddQTcI	Q	36.9942	14.63392	0.18029	6.67	17.67

**Table 10. Results of the Sponsor’s “Simple” Concentration-ΔΔQTc Analysis.**

**7.0. REVIEWER’S ASSESSMENT**

**7.1. Comments on Study Design**

**7.1.1. Adequacy of Exposure Achieved**

Based on the 40 hour half life of dextromethorphan and dextroprphan, a 72 hour dosing regimen without a loading dose may not have been adequate to achieve steady state exposure in this study.

**7.1.2. Adequacy of Sampling: Moieties Sampled and Timing of Samples**

Based on the clinical pharmacology of Neurodex, the QT measurement and concentration sampling schedule seems adequate to capture the effects of quinidine, dextromethorphan and dextroprphan at time of maximum concentration. However, the Sponsor did not collect PK samples to measure the concentration of the 3-hydroxyquinidine metabolite of quinidine—a metabolite known to have an effect on QT interval.

### 7.1.3. Adequacy of Controls

The Sponsor used a placebo control and a positive control.

The placebo control was completely blinded with respect to all study interventions performed on the treatment arm.

The Sponsor used a positive control to demonstrate assay sensitivity. Response to moxifloxacin at 1, 2, and 3 hours post-dose was assessed to determine its effect at time of peak concentration. Note, however, the following limitations of the use of the positive control.

- The positive control was not included as an arm in the crossover design. It was administered at the end of the study in an unblinded fashion, making it a poor control for period effects.
- Unlike the placebo and Neurodex treatments, moxifloxacin was administered as a single dose on the first day of treatment. A proper control for the effect of study procedures on QT interval would have been achieved if a placebo for moxifloxacin had been dosed twice daily for 6 doses and the active moxifloxacin tablet dosed on the 7<sup>th</sup> dosing occasion.
- The effect of venipuncture on treatment would have been more adequately controlled for if PK samples had been drawn in subjects receiving moxifloxacin.
- Since PK samples were not collected in subjects receiving moxifloxacin, it is difficult to assess assay sensitivity for a concentration-response analysis.
- The baseline profile for the moxifloxacin treatment arm was not assessed to the same extent as for other treatment arms.
- Variation in QT interval over an entire day would have been more adequately controlled for if response to moxifloxacin had been measured for longer than 3 hours post dose.

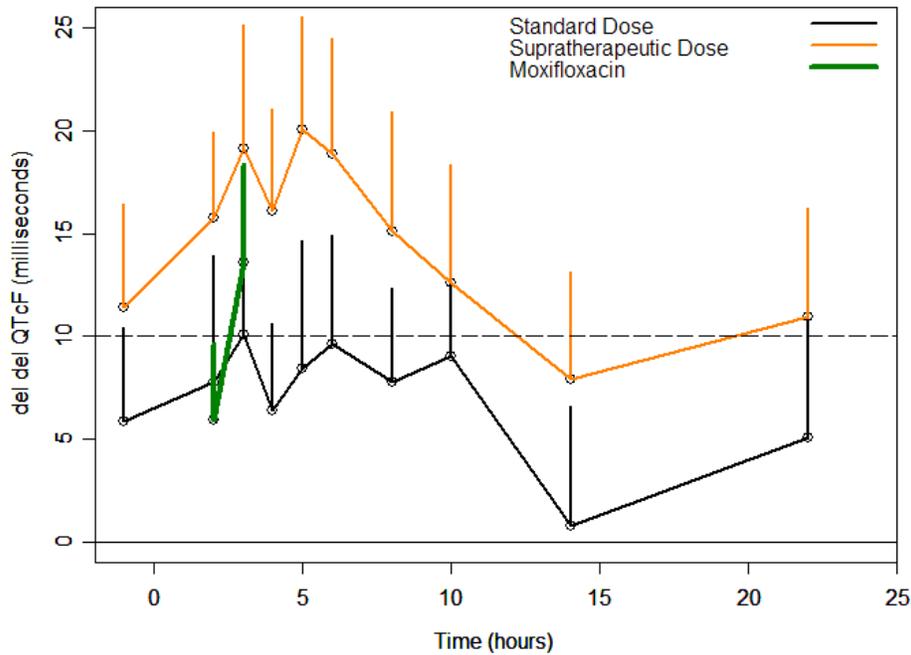
### 7.2. Reviewer's Analysis

The Sponsor did not provide information regarding the variability in estimates of QT response in their graphical displays of results (see Figure 1, Figure 2, Figure 3 and Figure 4).

The reviewer computed the placebo- and baseline- adjusted QTcF (del del QTcF or  $\Delta\Delta$ QTcF) as a function of time to show the variability in estimates. As Figure 10 shows, all but one of the upper, one-sided 95% confidence intervals for  $\Delta\Delta$ QTcF values for the standard/therapeutic dose exceed 10 milliseconds. All confidence intervals of  $\Delta\Delta$ QTcF for the supratherapeutic dose exceed 10 milliseconds.

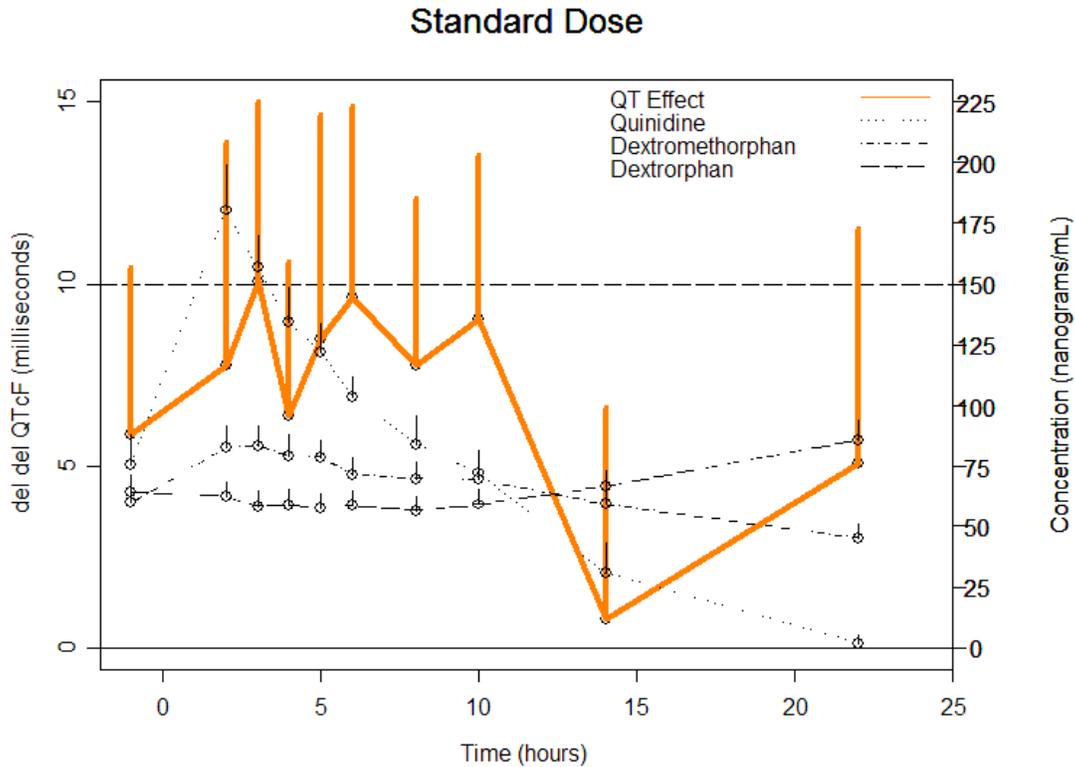
The upper 95% confidence interval for  $\Delta\Delta$ QTcF response to moxifloxacin ranges from 10 to 18 milliseconds.

**Reviewer's comment:** The response to the positive control is consistent with past experience with moxifloxacin.



**Figure 10. Placebo- and Baseline- Adjusted QTcF as a Function of Time for All Treatment Arms.** The mean value and one-sided, upper 95% confidence interval is shown at each time point.

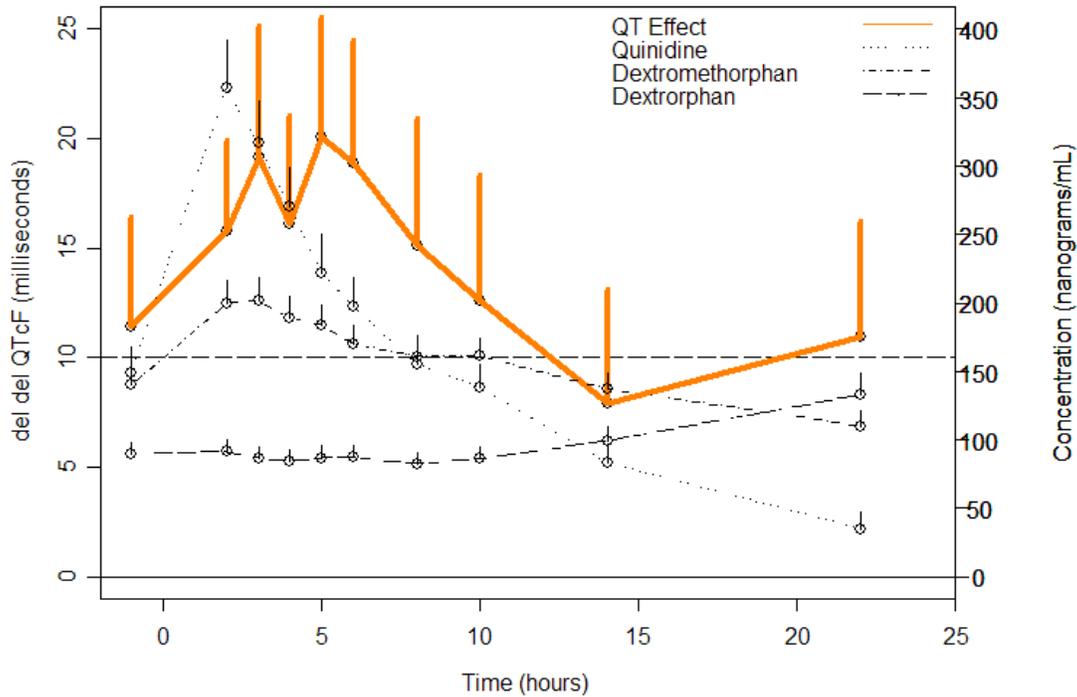
It was of interest to determine if there was any relationship between the time of maximum effect on  $\Delta\Delta\text{QTcF}$  and maximum concentration of drug and metabolites. Figure 11 and Figure 12 show this information for the standard and supratherapeutic doses of Neurodex, respectively.



**Figure 11. Mean Placebo- and Baseline- Adjusted QTcF vs. Time with Mean Concentration-Time Data for Quinidine, Dextromethorphan and Dextrophan Superimposed: Standard Dose.** Note that the one-sided upper 95% confidence interval is provided for the  $\Delta\Delta\text{QTcF}$  values and the upper 95% confidence interval is provided for the mean concentration data.

Figure 11 suggests that there is no clear single time of maximum effect on  $\Delta\Delta\text{QTcF}$  for the standard dose—response peaks at 3, 6 and 10 hours post-dose. No peak in  $\Delta\Delta\text{QTcF}$  directly correlates with peak quinidine concentration. The peak in  $\Delta\Delta\text{QTcF}$  observed 3 hours post-dose directly correlates with peak dextromethorphan concentration, and the delayed peak in  $\Delta\Delta\text{QTcF}$  at 22 hours post-dose correlates with the peak in dextrophan concentration.

## Supratherapeutic Dose



**Figure 12. Mean Placebo- and Baseline- Adjusted QTcF vs. Time with Mean Concentration-Time Data for Quinidine, Dextromethorphan and Dextrophan Superimposed: Supratherapeutic Dose.** Note that the one-sided upper 95% confidence interval is provided for the  $\Delta\Delta$ QTcF values and the upper 95% confidence interval is provided for the mean concentration data.

Figure 12 suggests that there is no clear single time of maximum effect on  $\Delta\Delta$ QTcF for the supratherapeutic dose—response peaks at 3 and 5 hours post-dose. No peak in  $\Delta\Delta$ QTcF directly correlates with peak quinidine concentration. The peak in  $\Delta\Delta$ QTcF observed 3 hours post-dose directly corresponds to the peak in dextromethorphan concentration, and the delayed peak in  $\Delta\Delta$ QTcF at 22 hours post-dose correlates with the peak in dextrophan concentration.

### Reviewer’s comment:

The results shown in Figure 11 and Figure 12 suggest that each component measured – quinidine, dextromethorphan and dextrophan – may have an effect on QT interval. The effect of quinidine is consistent with a delayed effect on QT interval, while the effect of dextromethorphan and dextrophan are consistent with a direct effect.

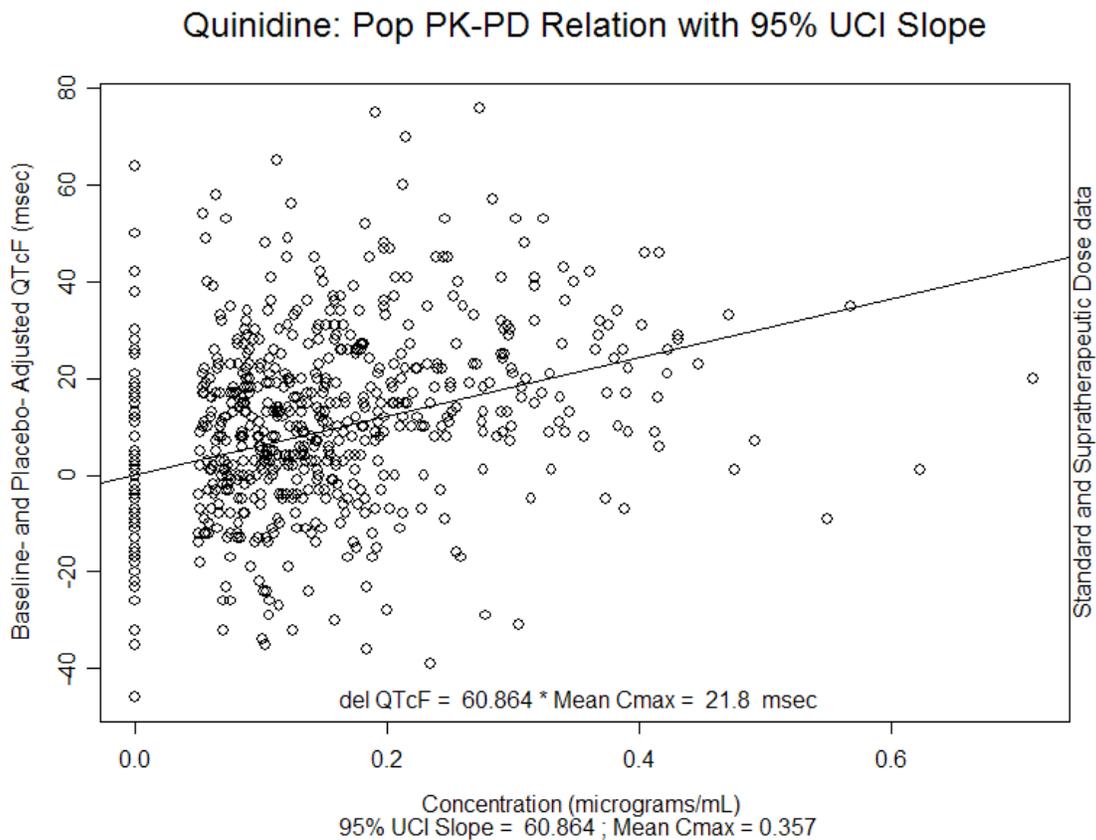
The clear correlation between maximum dextrophan concentration and a peak in effect on  $\Delta\Delta$ QTcF observed 22 hours post-dose may reflect that the concentration of dextrophan in plasma is in equilibrium with the concentration of dextrophan at the active site. In addition, it may reflect the loss of the confounding effect of quinidine concentration on  $\Delta\Delta$ QTcF.

It is known that the 3-hydroxy metabolite of quinidine has an effect on QT interval. However, the Sponsor did not measure the concentration of this metabolite. The effects observed on  $\Delta\Delta\text{QTcF}$  may reflect the effect of this metabolite, rather than the effect of dextromethorphan and/or dextrorphan.

The clinical consequence of the observed multiple peaks in response observed over the entire 24 hour period post-dose should be considered further. Since QT prolongation can occur at any time during the 24 hour period after receiving a dose of Neurodex, this should be taken into account when developing a plan for the risk management of drug-drug interactions and other factors that may enhance QT prolongation.

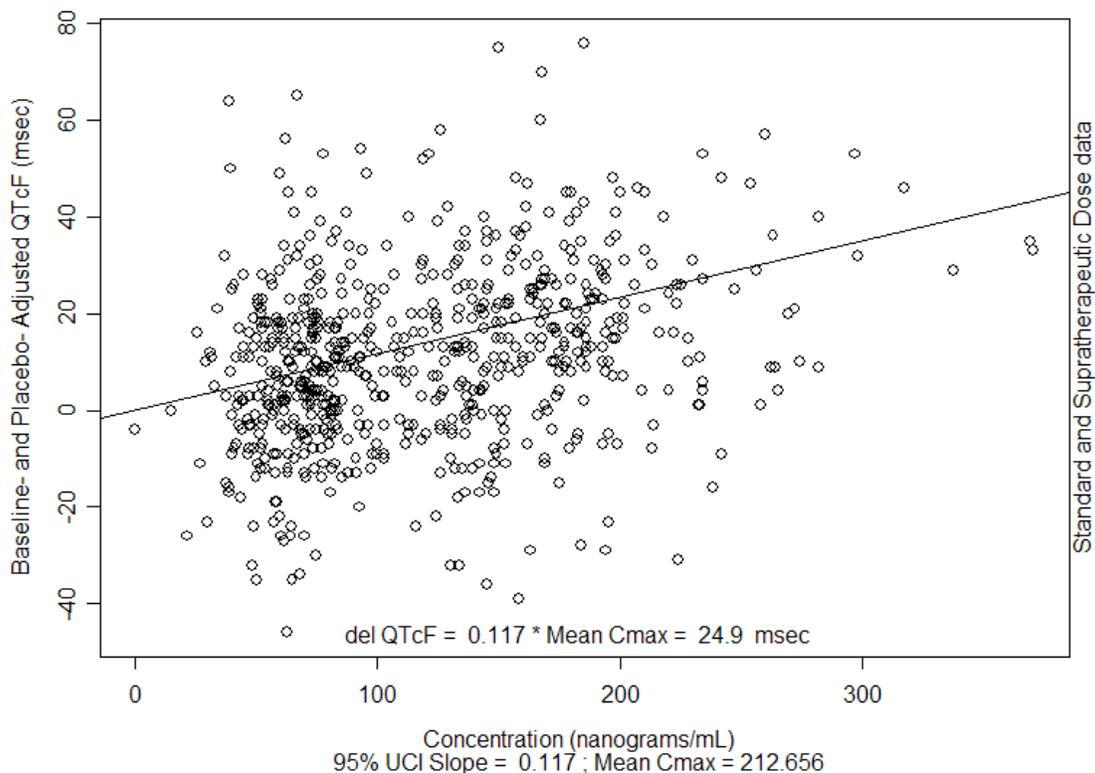
### Exposure-Response Modeling

It was of interest to model the relationship between  $\Delta\Delta\text{QTcF}$  and concentration of quinidine, dextromethorphan and dextromethorphan for a pooled dataset of standard and suprathreshold Neurodex doses. (Recall that the Sponsor did not provide this analysis.)



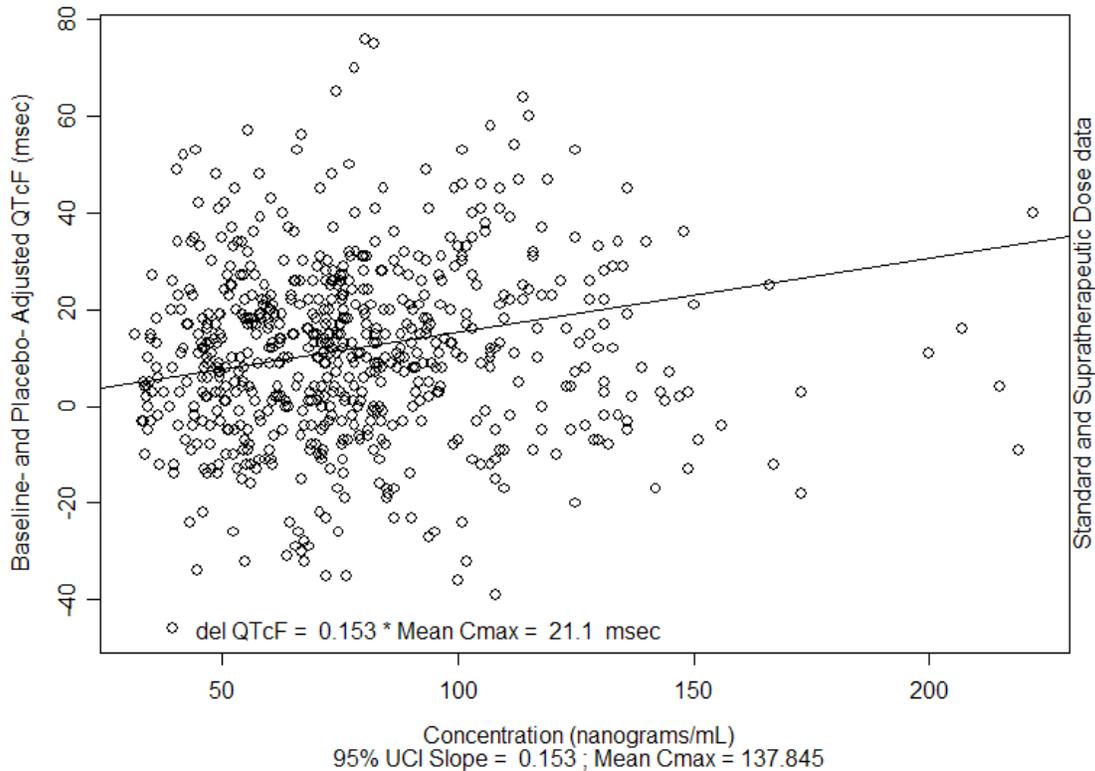
**Figure 13. Results of Fitting a Linear Mixed Effects Model to the  $\Delta\Delta\text{QTcF}$  and Quinidine Concentration Data.** Note that a dataset of pooled standard and suprathreshold doses was modeled. The upper 95% value of slope obtained is used in the predictions. The model predicts an increase of 22 milliseconds in  $\Delta\Delta\text{QTcF}$  at a  $\text{C}_{\text{max}}$  of 0.357 micrograms/mL quinidine.

### Dextromethorphan: Pop PK-PD Relation with 95% UCI Slope



**Figure 14. Results of Fitting a Linear Mixed Effects Model to the  $\Delta\Delta$ QTcF and Dextromethorphan Concentration Data.** Note that a dataset of pooled standard and supratherapeutic doses was modeled. The upper 95% value of slope obtained is used in the predictions. The model predicts an increase of 25 milliseconds in  $\Delta\Delta$ QTcF at a Cmax of 213 nanograms/mL DM.

## Dextrorphan: Pop PK-PD Relation with 95% UCI Slope



**Figure 15. Results of Fitting a Linear Mixed Effects Model to the  $\Delta\Delta$ QTcF and Dextrorphan Concentration Data.** Note that a dataset of pooled standard and supratherapeutic doses was modeled. The upper 95% value of slope obtained is used in the predictions. The model predicts an increase of 21 milliseconds in  $\Delta\Delta$ QTcF at a Cmax of 138 nanograms/mL DX.

The results of the linear mixed effects modeling analysis are consistent with the results of the E14 analysis. The analyses suggest that there may be up to a 25 millisecond increase in QTcF when adjusted for placebo- and baseline- effects in a supratherapeutic exposure scenario.

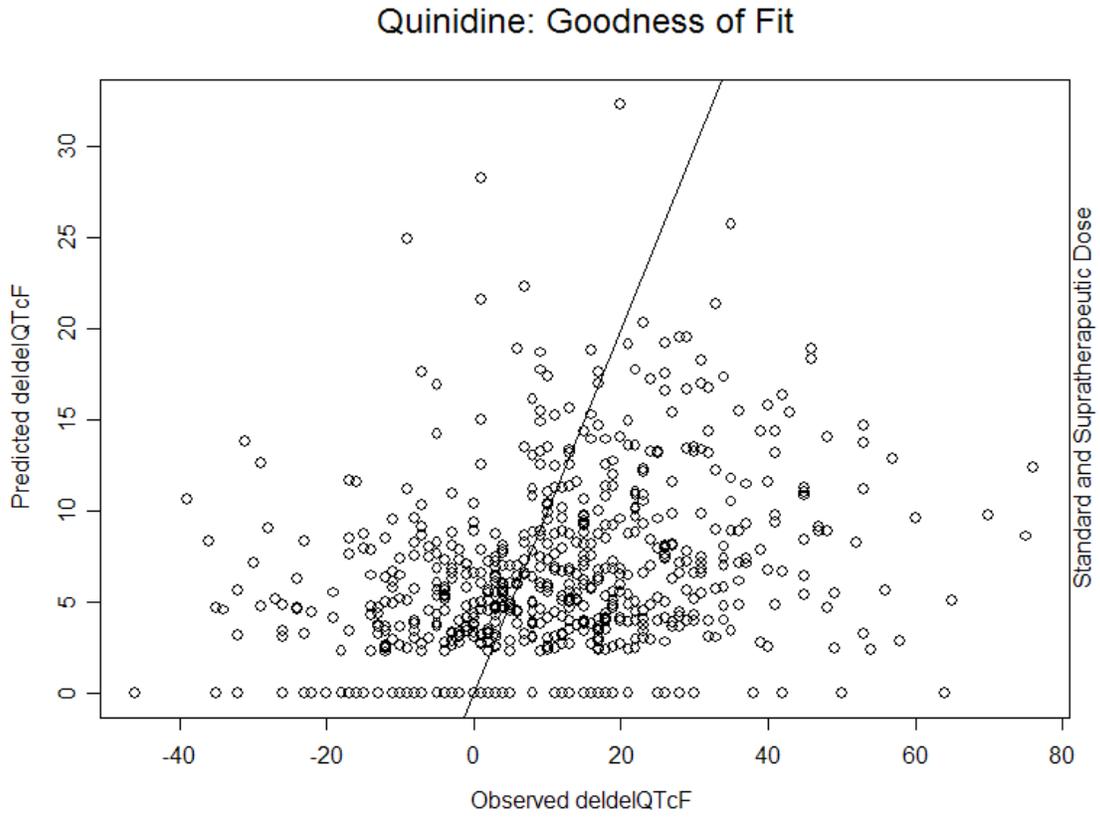
### Nonlinear mixed effects

The Sponsor fit a linear mixed effects model to the quinidine, dextromethorphan and dextrorphan concentration-QTc data for the supratherapeutic and therapeutic doses separately. These analyses yielded different slopes for the response for the therapeutic and supratherapeutic doses. This suggests that the data may be better described by a nonlinear mixed effects model.

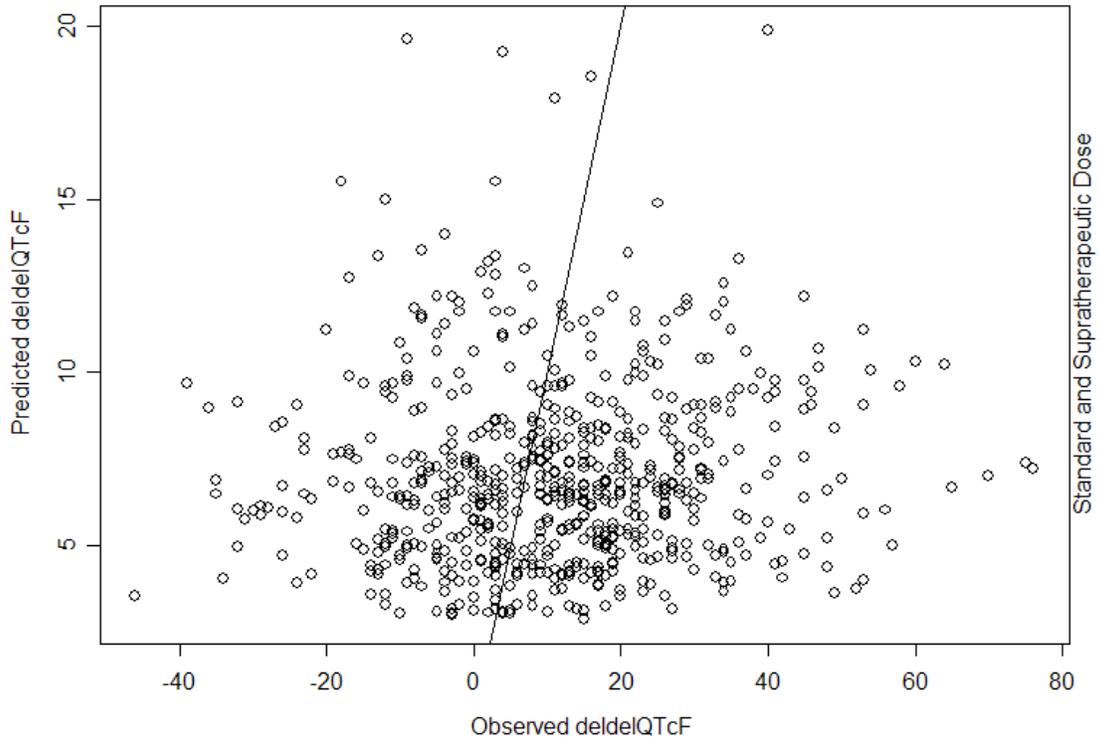
### Delay

Figure 11 and Figure 12 show that peak effect on QT interval did not correspond to peak quinidine concentration. This delay in QT response suggests that a direct effect model for the effect of quinidine on QT interval may not be appropriate.

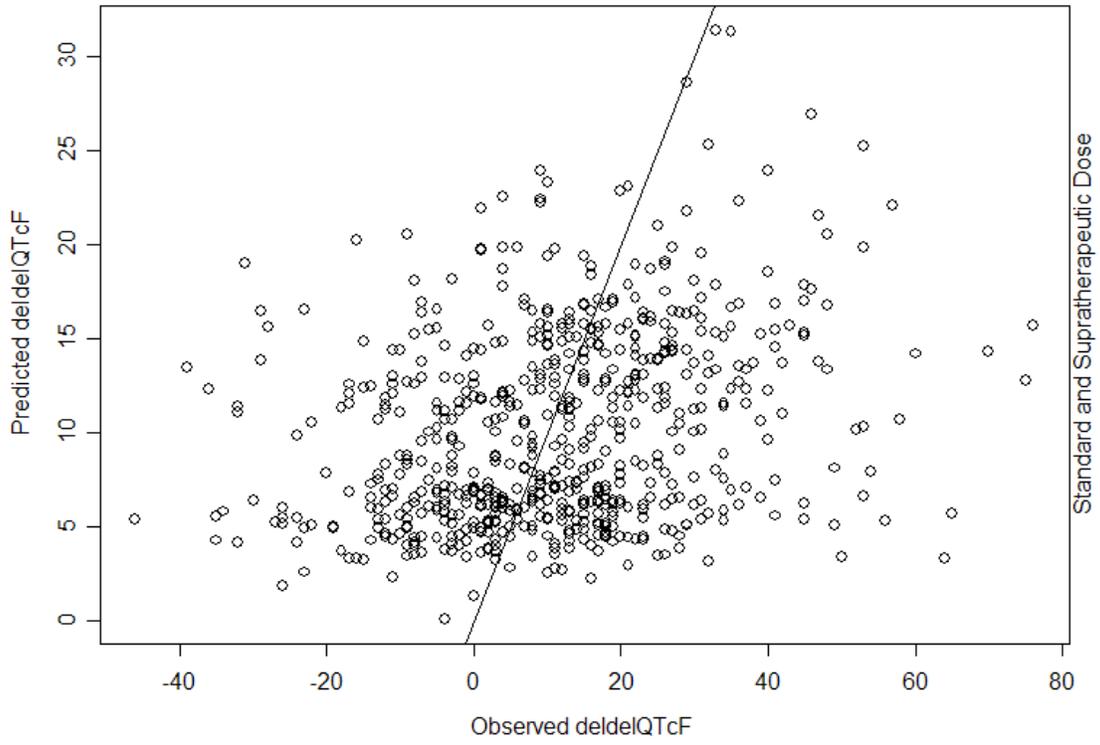
## 8.0. APPENDIX



### Dextrorphan: Goodness of Fit



### Dextromethorphan: Goodness of Fit



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Shari Targum  
9/15/2006 05:07:40 PM  
MEDICAL OFFICER

Norman Stockbridge  
9/15/2006 05:24:39 PM  
MEDICAL OFFICER

**M E M O R A N D U M**

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** June 22, 2006

**TO:** Melina Griffis, Regulatory Project Manager  
Ronald Farkas, M.D., Medical Officer  
Division of Neuropharmacological Drug Products, HFD-120

**THROUGH:** Constance Lewin, M.D., M.P.H.  
Chief, Good Clinical Practice Branch I (GCPB1, HFD-46)  
Division of Scientific Investigations (DSI)

**FROM:** Roy Blay, Ph.D.  
Reviewer, GCPB1, DSI, HFD-46

**SUBJECT:** Evaluation of a Clinical Inspection

**NDA:** 21-879

**APPLICANT:** Avanir Pharmaceuticals

**DRUG:** Dextromethorphan/Quinidine

**THERAPEUTIC CLASSIFICATION:** Priority Review

**INDICATION:** Treatment of pseudobulbar affect

**DIVISION ACTION GOAL DATE:** June 30, 2006

**PDUFA GOAL DATE:** July 30, 2006

**I. BACKGROUND**

Amyotrophic lateral sclerosis (ALS) is a neurological disease characterized by gradual degeneration of the nerve cells in the central nervous system that control voluntary muscle movement.

Pseudobulbar affect (PBA) is a disabling condition characterized by pathological laughing and crying inconsistent with the underlying state of happiness or sadness. PBA is associated with a number of neurological conditions including ALS.

Dextromethorphan (DM) is the dextrorotary isomer of levorphanol and is known to suppress the release of excitatory neurotransmitters. Because an excitotoxic process involving glutamate is implicated in the etiology of ALS, DM has been administered to subjects with ALS in attempts to modify disease progression. Since DM appears to be efficiently degraded by cytochrome P450 D26, even high doses of DM may be insufficient to affect the course of ALS. To overcome endogenous metabolic degradative effects, quinidine, an efficient inhibitor of DM metabolism has been co-administered. Neither DM nor quinidine is a new molecular entity.

In this NDA, the sponsor presents its results for studies 99-AVR-102 and 02-AVR-106. These studies which were selected for inspection, examine the safety and efficacy of the administration of DM, with and without quinidine, and quinidine alone, upon PBA in subjects with ALS.

#### Protocol 99-AVR-102

“A Double-Blind, Controlled, Multicenter Phase 2/3 Study to Assess the Safety and Efficacy of AVP-923 (Dextromethorphan/Quinidine) in the Treatment of Pseudobulbar Affect in Patients with Amyotrophic Lateral Sclerosis”

Subjects in this study had ALS, and, in addition, had clinically diagnosed PBA, having scored higher than 13 on the Center for Neurological Studies-Lability Scale (CNS-LS).

Subjects were treated with the study article (dextromethorphan/quinidine) or its individual components twice daily for 28 days. Each subject completed a diary noting the number of episodes of pseudobulbar affect experienced, medication schedule, and any adverse events.

The primary efficacy endpoint in this study was the CNS-LS score which was the difference in baseline (pretreatment) scores and the average of the scores at Days 15 and 29.

Dr. Benjamin Brooks’s site was selected for inspection as it was one of the higher enrolling sites.

#### Protocol 02-AVR-106

“A Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of AVP-923 (Dextromethorphan/Quinidine) in the Treatment of Pseudobulbar Affect in Patients with Multiple Sclerosis”

Subjects in this study had multiple sclerosis, and, in addition, had clinically diagnosed pseudobulbar affect (pathological laughing and crying), having scored higher than 13 on the CNS-LS.

Subjects were treated with the study article (dextromethorphan/quinidine) or with a matching placebo twice daily for twelve weeks. Each subject completed a diary noting the number of episodes of pseudobulbar affect experienced, medication schedule, and any adverse events.

The primary efficacy endpoint in this study was the CNS-LS score which was the difference in baseline (pretreatment) scores and the average of the scores at Days 15, 29, 57, and 85.

Dr. Gary Pattee's site was selected for inspection as it was one of the higher enrolling sites.

## II. RESULTS (by site):

Name	City, State, Country	Protocol	Insp. Date	EIR Received Date	Final Classification
Benjamin Brooks, M.D.	Madison, WI	99-AVR-102	3-10 May 06	19 Jun06	VAI
Gary Pattee, M.D.	Lincoln, NE	02-AVR-106	10-12 Apr 06	26 Apr 06	NAI

### Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

#### A. Protocol 99-AVR-102

##### 1. Benjamin Brooks, M.D. (Site 08, 17 subjects)

ALS Clinical Research Center  
University of Wisconsin  
H6/563 Clinical Science Center  
600 Highland Avenue  
Madison, WI 53792-5132

- a. 17 subjects were randomized to the study. There were no deaths or SAEs reported. An audit of all subjects' records was conducted, including, but not limited to, consent forms, inclusion/exclusion criteria, CRFs, source documents, clinical notes, ECGs, laboratory results, concomitant medications, and adverse event reporting, review of informed consent forms, efficacy endpoints, adverse event and concomitant medication reporting, and drug accountability.
- b. There were no limitations to the inspection.
- c. Inspection revealed that the investigator did not adhere to the investigational plan in that subject 0817 was randomized to the study despite taking quinine sulfate, a prohibited medication.

- d. The review division may wish to consider the impact, if any, of the above protocol violation on data acceptability. Otherwise, the data appear acceptable in support of the respective indication.

B. Protocol 02-AVR-106

2. Gary Pattee, M.D. (Site 34, 22 subjects)  
Neurology Associates, P.C.  
2631 South 70<sup>th</sup> Street  
Lincoln, NE 68506

- a. 23 subjects were screened and 22 subjects were randomized to the study. An audit of all of the subjects' records was conducted including, but not limited to, consent forms, the primary efficacy endpoint, adverse events and drug accountability.
- b. There were no limitations to the inspection.
- c. Inspection did not reveal any regulatory violations in the conduct of this study.
- d. The data appear acceptable in support of the relevant indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspection of Dr. Pattee did not identify any significant observations. The inspection of Dr. Brooks revealed that one subject (#0817) was enrolled despite taking a prohibited concomitant medication. The review division may wish to consider the impact, if any, of this protocol violation on data acceptability. Otherwise, the data for both sites appear acceptable in support of the respective indication.

*{See appended electronic signature page}*

Roy Blay, Ph.D.  
Reviewer, Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

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Roy Blay  
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CSO

Constance Lewin  
6/22/2006 03:48:19 PM  
MEDICAL OFFICER



Shari L. Targum, M.D.  
Division of Cardio-Renal Products, HFD-110

Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Tel (301) 796-1151

### Memorandum

**DATE:** June 4, 2006

**FROM:** Shari L. Targum, M.D., Team Leader, Division of Cardio-Renal Products, HFD-110

**THROUGH:** Norman Stockbridge, M.D., Ph.D., Director, Division of Cardio-Renal Products, HFD-110

**TO:** Melina Griffis, Project Manager, Division of Neurology Products, HFD-120  
Ron Farkas, M.D., Medical Officer, Division of Neurology Products, HFD-120

**SUBJECT:** NDA 21-879: Cardiovascular safety

**NAME OF DRUG:** AVP-923

**TRADE NAME:** Neurodex

**FORMULATION:** Oral

**RELATED APPLICATIONS:** N/A

**PROPOSED INDICATION:** Treatment of pseudobulbar affect

**APPROVED INDICATIONS:** N/A

**SPONSOR:** Avanir Pharm

**DOCUMENTS AVAILABLE FOR REVIEW:** 1. Consultation request; 2. NDA 21-879 (edr) .

**DATE CONSULT RECEIVED:** April 10, 2006

**DATE DUE:** June 5, 2006

**DATE CONSULT COMPLETED:** June 4, 2006

### BACKGROUND:

This Division has been asked to respond to seven questions posed by the primary medical reviewer (Dr. Farkas) of AVP-923 (neurodex).

AVP-923 is capsule containing a combination of dextromethorphan hydrobromide (30 mg) and quinidine sulfate (30 mg); the proposed dosing is one capsule b. i. d. Dextromethorphan is available as an over-the-counter cough suppressant. There is interest in developing high-dose dextromethorphan in neurological disorders; dextromethorphan apparently binds to high- and low-affinity sites at the N-methyl-D-aspartate (NMDA) receptor in the brain. Quinidine inhibits CYP 2D6, causing an increase in dextromethorphan (in rapid metabolizers).

The bioavailability of quinidine is about 70% but varies widely (45-100%). Quinidine is metabolized in the liver, mainly by CYP 3A4 to several pharmacologically active hydroxylated metabolites. According to current quinidine labeling, the most important of quinidine's metabolites is 3-hydroxyquinidine, which has at least half the antiarrhythmic activity of the parent compound. Renal clearance of quinidine involves both glomerular filtration and active tubular secretion, moderated by pH-dependent tubular reabsorption. When the urine pH is < 7, about 20% of quinidine appears unchanged in the urine; but this fraction drops to as little as 5% when the urine is more alkaline (Ref. 1).

The proposed dose of quinidine in AVP-923 is approximately 1/10 the individual dose and 1/10 to 1/80 the maximum daily dose recommended for immediate-release quinidine in the treatment of arrhythmias.

Quinidine, at doses of 200-400 mg every 6-8 hours, has been shown to be proarrhythmic (associated with ventricular arrhythmias such as torsades de pointes). In a publication of 20 patients with torsades de pointes (TdP) on quinidine, most patients developed the arrhythmia within days of starting quinidine, although four had tdP during long-term therapy, usually associated with hypokalemia. These patients were noted to have marked QT prolongation; however, plasma quinidine concentrations were low, being at or below the lower limit of the therapeutic range in half of patients (Ref. 2). In another series of 31 patients (all with heart disease) with documented tdP due to quinidine, tdP occurred within one week of initiation of therapy in 74% of patients; five patients had hypokalemia at the time of tdP. On quinidine therapy, QTc intervals in 23 patients ranged from 390 to 630 msec (mean 510 msec) and were prolonged in 21 patients (91%) (Ref. 3).

According to Dan Roden, quinidine concentrations in the 5-10  $\mu\text{mol L}^{-1}$  range block multiple potassium currents (IKr and IKs) as well as the inward sodium current. *In vitro* data suggest that quinidine's effect on IKr has been shown to be exquisitely sensitive to hypokalemia; in the presence of marked hypokalemia, low concentrations of quinidine were associated with marked IKr inhibition (Refs. 4,5).

The sponsor has submitted an NDA for the use of AVP-923 in the treatment of pseudobulbar affect (PBA), an affective disinhibition syndrome "characterized by the loss of emotional control, including episodes of involuntary crying and/or laughing."<sup>1</sup> PBA has been associated with neurologic disease or injury in a variety of conditions, including multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and Alzheimer's disease. The NDA submission included two controlled efficacy studies for PBA (99-AVR-102 (ALS) and 02-AVR-106 (MS)); of these two controlled studies, only 02-AVR-106 included a placebo control group. In 99-AVR-102, twelve-lead ECGs were obtained at screening and on Day 29 (or the final visit); in study 02-AVR-106, ECGs were obtained at screening, on Day 29, on Day 85, and at the discretion of the investigator or in accordance with local IRB requirements.

According to Dr. Farkas and Dr. Yasuda, the sponsor has also performed a "thorough QT study"; however, the results of this study are not yet available.

**Table 1. Listing of clinical studies**

Study	Type	Population	N	D daily dose (mg)	Q daily dose (mg)	ECG collection
99-AVR-102	Efficacy/safety (pivotal)	PBA in ALS	70	60	60	Screening and Day 29
02-AVR-106	Efficacy/safety (pivotal)	PBA in MS	76	60	60	Screening, Day 29, Day 85 (or final)*
02-AVR-107	Open-label safety	PBA	463	60	60	Screening, Day 29, and week 52 (or final)
99-AVR-100	Open-label, clin pharm, PK, dose-ranging	Healthy	39	30,60	5-150	Baseline and 1-4 hours post-final dose
99-AVR-101	Open-label, single and multiple-dose, clin pharm, PK	Healthy	10	30	30	Baseline and 3 hours post-final dose

<sup>1</sup> The source of this definition was the Integrated Summary of Safety, NDA 21,879.

00-AVR-103	Clin pharm, PK, dose-ranging	Healthy	48	90, 120	60, 90, 120	Baseline and 1-4 hours post-dose
04-AVR-111	Single-dose, crossover, PK, food effect	Healthy	18	30	30	Pre-dose, and 2, 4, 6 and 8 hours post-dose
04-AVR-115	Open-label, multiple-dose, hepatic impairment PK/safety	Healthy, mild/mod hepatic impairment	21	30	30	Pre-dose and 2, 6, and 12 hours post-first dose on Day 1; and 2 and 6 hours post- 13 <sup>th</sup> dose on Day 7.
04-AVR-116	Open-label, multiple-dose, renal impairment PK/safety	Healthy, mild/mod renal impairment	21	30	30	Pre-dose and 2, 6, 12 hours post-first dose on Day 1, and 2 and 6 hours post-13 <sup>th</sup> dose on Day 7.
04-AVR-112	Drug interaction PK/safety	Healthy	16	30	30	Day 1: pre-dose and 3, 6, 12 hours post-dose; Day 7, 9-16: prior to and 6 hours post-dose; Day 8: prior to and 2, 6 hours post-dose
01-AVR-105	Open-label dose-escalation safety	Painful diabetic neuropathy	36	30-120	30-120	Screening, Days 1 (1 hour post-dose), 15, 29

\*or at the discretion of the investigator or in accordance with local IRB requirements.

Exposure in the development program: In the development program for AVP-923, 603 study subjects (normal volunteers and patients) were exposed to active drug; an additional 88 study subjects were exposed to different combinations of dextromethorphan (D) and quinidine(Q) (other than AVP-923). In the controlled studies in pseudobulbar affect (PBA) patients, 146 patients received AVP-923, 74 patients received placebo, 33 patients received dextromethorphan, and 37 patients received quinidine. Of the 603 exposed subjects in the integrated studies, about half were exposed to the intended AVP-923 dose for at least 180 days, and 196 (33%) were exposed to the intended dose of AVP-923 for at least one year. The sponsor has also cited 7 small studies using quinidine-dextromethorphan; these studies included healthy volunteers as well as patients with ALS and Parkinson’s disease. The largest of these trials enrolled 22 healthy subjects.

ECG analyses:

In studies 99-AVR-100, 99-AVR-101 and 00-AVR-103, ECGs were machine-read and reviewed by the Principal Investigator, who “was blinded to treatment where applicable.” ECG analyses in Study 99-AVR-102, 01-AVR-105, 02-AVR-106 and 02-AVR-107 were performed by (b) (4)

(b) (4) ECGs were machine-read and “over-read” by a cardiologist blinded to the treatment arm. According to the sponsor, because the Joint US FDA-Health Canada Concept Paper for QT/QTc evaluation recommended manual ECG reading, studies 99-AVR-100, 99-AVR-101, 99-AVR-102, 00-AVR-103, 02-AVR-106, and 01-AVR-105 underwent a second analysis by the (b) (4). In (b) (4) analysis, ECG intervals were read manually by a cardiologist and all abnormal ECGs were read by a second cardiologist. All readers were blinded to study groups and treatment arms and the same physicians performed all ECG readings. The QTc interval was evaluated by both QTcB and QTcF corrections.

The ECG results for pivotal study 02-AVR-106 is shown below:

**Table 2. Study 02-AVR-106: Change from Screening for QT, QTcF, QTcB**

Variable	ECG reading	Visit	AVP-923 (N=76)		Placebo (N=74)	
			Mean	Min/Max	Mean	Min/Max
QT (msec)	(b) (4)	Day 29	0.1	-64/60	2.1	-50/66
		Day 85	3.4	-70/66	0	-54/56
		Day 29	-5.6	-69/55	-1.0	-55/64
		Day 85	-0.6	-58/60	-3.0	-68/50
QTcF (msec)	(b) (4)	Day 29	4.8	-55/41	3.3	-35/36
		Day 85	6.1*	-49/37	0.4*	-39/44
		Day 29	-0.1	-32/40	-0.8	-39/18
		Day 85	2.1	-30/33	-1.9	-41/30
QTcB (msec)	(b) (4)	Day 29	7.3	-53/50	4.1	-29/51
		Day 85	7.5*	-37/38	0.5*	-46/55
		Day 29	2.8	-32/50	-0.4	-32/29
		Day 85	3.5	-30/38	-1.3	-38/29

\*Significant p-value for difference between treatment groups ( $p \leq 0.05$ , t test)

ECG results for study 99-AVR-102 (no placebo control: treatment groups included D alone, Q alone and AVP-923) showed mean changes in QTcB and QTcF in the -2.9 to 2.0 to range for AVP-923, in the -1.3 to 6.5 range for Q, and in the -4.9 to 3.0 range for D.

It should be noted that these ECGs were not time-matched and the relation to dosing is not clear. Variability in QT measurements (min/max), as well as inter-reader variability, can be seen. This reviewer was unable to access ECGs to verify QT measurements.

**Table 3. QTc outliers: 99-AVR-102 and 02-AVR-106 ( (b) (4) analysis)**

Method		99-AVR-102 (ALS)			02-AVR-106 (MS)	
		AVP-923 (N=67)	D (N=31)	Q (N=35)	AVP-923 (N=75)	Placebo (N=73)
QTc F	>450 msec	--	--	--	--	2 (3%)
	>480 msec	--	--	--	--	1 (1%)
	>500 msec	--	--	--	--	--
	Change $\geq$ 30 msec	3 (4%)	--	1 (3%)	8 (11%)	5 (7%)
QTcB	>450 msec	1 (1%)	1 (3%)	1 (3%)	7 (9%)	7 (10%)
	> 480 msec	--	--	--	--	--
	> 500 msec	--	--	--	--	--
	Change $\geq$ 30 msec	3 (4%)	--	4(11%)	15 (20%)	4 (5%)

In these two studies, there were no cases of  $\geq 60$  msec change from baseline in QTc.

ECG review: No ECGs from this NDA were submitted to the ECG warehouse.

## YOUR QUESTIONS:

1. Quinidine can cause a number of severe and potentially life-threatening adverse effects, including arrhythmia, autoimmune thrombocytopenia, systemic lupus-erythematosus-like condition, hepatitis, and cinchonism. Quinidine in Neurodex is dosed at 60 mg/day, lower than the normal therapeutic dose. However, the sponsor specifically notes that “deaths in patients on quinidine have been reported to occur early after initiation of treatment with quinidine (while blood concentrations are low), and are thought to be idiosyncratic rather than related to dose or concentration” (from NEW ISS Neurodex.pdf, section 12.4). Given the long history of quinidine use for cardiovascular indications, do you have an opinion on the safety of the quinidine dose from Neurodex?

**Response:** In the pivotal studies, the mean QTc change from baseline is relatively small (although no 95% CI are given). There are more outliers ( $\geq 30$  msec change from baseline) in subjects given AVP-923 compared with placebo, suggesting a signal. Furthermore, the safety margin for Neurodex is not clear. There are also cases of subjects that developed prolonged QT on therapy (see below, questions 6a and 6b). In addition, this reviewer does not understand the effect (on repolarization) of interactions that will increase quinidine exposure in Neurodex (for example, metabolic inhibitors or alkaline urine), or the effects of even mild hypokalemia on repolarization given a background of quinidine. This reviewer would have been interested in ECG analyses from those studies using higher doses than quinidine 30 mg b.i.d. At this stage, this reviewer has insufficient information to conclude that an adequate safety margin exists for the proarrhythmic effect seen at higher quinidine doses.

2. The current quinidine label specifies that a ‘test dose’ (200 mg) should always be given to detect hypersensitivity. Can you explain in more detail how this test is done in practice?

**Response:** It has been many years since this reviewer has prescribed quinidine; this reviewer cannot recall personal experience with test doses. The available labeling for quinidine sulfate does not mention a test dose. This reviewer is therefore unable to explain in more detail how this test is done in practice.

3. Quinidine is metabolized largely by CYP 3A4. Several inhibitors of CYP 3A4 were taken by patients in the Neurodex studies, and might be used with Neurodex if it is approved. This would increase quinidine levels, resulting in exposure closer to that expected from 120 mg oral quinidine daily (per (b) (6) estimation). Do you have an opinion on the safety of quinidine in non-cardiac patients at blood levels closer to those used for cardiovascular indications? Are there special concerns for concomitant use of quinidine and calcium channel blockers, which also block CYP 3A4?

**Response:** This reviewer would have concerns about proarrhythmia. In addition, since calcium channel blockers and quinidine (at anti-arrhythmic doses) are both negative inotropes, one wonders if there would be any additive effect on depression of myocardial contractility with this dose of quinidine.

4. Several important cardiovascular drugs (e.g., beta blockers) are metabolized by CYP 2D6, which is inhibited by quinidine. Do you have an opinion of the safety risk posed by concomitant use of quinidine with cardiovascular drugs metabolized by CYP 2D6? If the risk is significant, are other acceptable treatment options available? More generally, aside from metabolic interactions,

would the direct pharmacodynamic effect of 60 mg/day quinidine adversely affect other cardiovascular drugs or conditions?

**Response:** The NDA submission did not include interaction studies with beta blockers or other cardiovascular drugs. You can search the safety database for the use of concomitant beta-blockers. The safety risk posed by concomitant quinidine and cardiovascular drugs metabolized by CYP 2D6 is unknown. For most beta-blocker indications (e.g., hypertension, angina) there are available alternative therapies. However, for carvedilol or metoprolol use in reducing the risk of mortality in heart failure, there are no alternative therapies.

5. The sponsor examined the drug interaction between desipramine, a CYP 2D6 metabolized drug, and Neurodex, which inhibits CYP 2D6 (study 04-AVR-112). Multiple cardiovascular adverse effects were reported:

“Several abnormal electrocardiogram results occurred, and one was considered clinically significant. Subject No. 4’s ECG result revealed bigeminy with borderline QTc prior to dosing on Day 13. Of the postdose abnormal ECG results deemed not clinically significant, many were borderline prolonged QTc intervals, prolonged QTc, sinus tachycardia, sinus bradycardia, intraventricular conduction delay, solitary premature ventricular contraction, left axis deviation, sinus arrhythmia, and nonspecific precordial T wave change” (from study report [study 04-AVR-112.pdf]).

The primary investigator concluded “The results from this study indicate potential cardiac safety concerns when desipramine is administered with AVP-923 [Neurodex].”

Please comment on the relationship of Neurodex to the abnormal ECG findings, and the overall significance of the findings in terms of cardiovascular risk from Neurodex.

**Response:** Study 04-AVR-112 was a sequential treatment drug interaction study evaluating the effects of AVP-923 on steady-state plasma concentrations of desipramine in 16 healthy volunteers (9 males and 7 females). A single daily dose of oral 25 mg desipramine was administered for 16 days; on day 8, a single oral dose of AVP-923 was administered q 12 h for 9 days. ECGs were done at screening, on Day 1 prior to dosing and at 3, 6 and 12 hours postdose; On Days 7 and 9-16, ECGs were done each morning prior to dosing and at 6 hours post-dose; on Day 8, ECGs were done prior to dosing and at 2 and 6 hours post-dose. Two subjects were withdrawn from the study (due to abnormal urinalysis and asymptomatic ventricular bigeminy, respectively).

**Comment:** It is difficult to ascribe a relationship between asymptomatic ventricular bigeminy, which apparently also occurred on a subsequent Holter monitor (I assume off-drug for some time period) and AVP-923. However, it is of interest that mean QTc intervals increased from Days 1-19, with daily mean peaks at 6 hours post-dosing; according to the sponsor, the increases in mean QTc were not clinically significant (exact results not given). Mean QRS intervals also increased from Days 1-19, with marked increases starting from Day 15, and with daily peaks at 6 hours post-dosing. Mean pulse rates showed an increasing trend from Days 1-19, with daily peaks at 4 and 6 hours post-dosing. Mean pulse rates ranged from 68 bpm at baseline to ~105 on Day 16. According to labeling, desipramine is associated with tachycardia. Of the reported abnormal ECG results, this reviewer would highlight prolonged QTc and interventricular conduction delay (i.e., QRS widening) as potential quinidine effects; reports of left axis deviation or sinus arrhythmia are not expected quinidine effects. This reviewer would like to see the analysis of mean QT/QTc and QRS change from baseline, along

with 95% confidence limits and min/max changes. Despramine contains labeling for arrhythmia (including a report of sudden death in a child). The QT/QTc and QRS results suggest some possibility of interaction between desipramine and Neurodex; however, this reviewer is unable to make further inferences without additional analyses.

6. Several cases of QT prolongation occurred in the Neurodex development program. Please comment on the significance of the following cases:

- a. *Study 02-AVR-107, subject 107-18-008* had “clinically obvious and clinically important QT prolongation during treatment” with Neurodex (NEW ISS Neurodex.pdf, section 12/4/3). [note: in EDR under “Reports of Efficacy and Safety Studies/Study Reports of Uncontrolled Clinical Studies].

**Response:** According to the ISS, this patient was identified by (b) (4) as a female with  $\geq 60$  msec increase in QTc and a QTc value  $> 470$  msec during treatment. When reanalyzed by (b) (4), her baseline QTc was calculated as 400 msec; her week 52 QTcB was recalculated to be 468 msec (according to the sponsor the QTc  $> 470$  msec was not confirmed by this reanalysis). The sponsor concludes that QT prolongation, not present at baseline, was seen on the Week 52 ECG.

According to the CRF, this was a 58 year old Caucasian female with ALS, hypertension, diabetes, and CAD s/p stent placement. On her screening visit, she was normotensive and her ECG was reported as normal; there were no significant laboratory findings. On Day 29, her HR was 52 bpm, BP was 149/92 mm Hg, and her ECG was interpreted as “nonspecific ST and T abnormality” and felt to be “abnormal, not clinically significant.” She apparently withdrew consent at Week 52. Her final ECG showed sinus tachycardia (felt abnormal, clinically significant); there was no mention of QT/QTc in the CRF. She was on several concomitant medications, including Elavil 50 mg qd, Avandia and atenolol.

**Comment:** This reviewer agrees that this patient had QT prolongation on treatment that was not present at baseline. A drug effect cannot be excluded.

- b. *Study 02-AVR-107, subject 107-30-020* was a treatment-emergent QTc outlier, but changes were interpreted as not clinically obvious or clinically important.

**Response:** According to the CRF, this was a 23 year old Caucasian female s/p ventriculoperitoneal shunt placement (as infant) due to hydrocephalus. Screening ECG revealed a left anterior hemiblock (felt not clinically significant). She was on no concomitant medications and her labs had no clinically significant findings. On Day 29, her ECG was reported as normal. On her week 52/early termination assessment, she was normotensive (BP 108/82) and borderline tachycardic (HR 96); her final ECG showed sinus tachycardia, prolonged QT, nonspecific T-wave abnormality and QTc of 491 msec (per CRF). In the CRF, the ECG changes were reported as “abnormal, clinically significant.” She had received Zyprexa for headache 4 months before her final examination/ECG. In the ISS, the baseline QTcB was recalculated to be 396 msec; the week 52 QTcB was recalculated to be 480 msec. Both the  $\geq 60$  msec increase in QTc and  $> 470$  msec QTc were confirmed as treatment-emergent in this patient.

**Comment:** This reviewer would interpret a QTc of 491 msec (or even a QTcB of 480 msec) to be clinically important. Given that the QTc was not prolonged at baseline or on Day 29, a drug effect cannot be excluded.

- c. *Study 00-AVR-103, subject 103-46* had a  $> 60$  msec increase in QTc, while taking 45 mg DM and 60 mg Q [twice the final Neurodex formulation].

**Response:** According to the CRF, this was a 34 year old Caucasian male. On screening, HR 73 bpm, and ECG revealed QT 367 msec and QTc of 404 msec (normal). The patient was on no concomitant medications and routine chemistries were normal. A subsequent ECG on Study Day -1 showed HR 76 bpm; QT 333 msec; QTc 374 msec (also normal). On Study Day 1 (13 hours), HR was 55 bpm; QT 381 msec; QTc 364 msec. On Study Day 4 (72.5 hours), HR 72 bpm; QT 348 msec; QTc 381 msec. On Study Day 8 (169 hours), HR 51 bpm; QT 428 msec; QTc 394 msec. All ECGs were interpreted as normal. According to the ISS, this patient was noted to have prominent U waves at baseline and on Day 8, making QT measurements more difficult. When recalculated, baseline QTcB was 360 msec and Day 8 QTcB was 438 msec, for a confirmed QTc increase of 78 msec. However, the Day 8 QTcB did not qualify as an “QT prolongation.”

**Comment:** The original QT/QTc measurements were machine-generated, from a single 12-lead tracing, and “over-read.” On recalculation, the > 60 msec QTc increase was confirmed.

- d. *Study 02-AVR-107, subject 107-03-014* had syncope on day 5 with a prolonged QTc value. On Day 29, this patient had a QTcB value that was 61 msec greater than his baseline QTcB of 349 msec.

**Response:** According to the CRF, this was a 56 year old Caucasian male with hypertension, s/p carotid artery dissection, s/p stroke, with a normal screening ECG and laboratory tests only notable for hyperlipidemia. On Day 29 and Week 52 (final visit), his ECGs were interpreted as normal (per CRF—no actual QT/QTc values were entered). In the CRF, there is mention of a syncopal episode that was “mild”, nonserious, and felt unrelated to medication; the patient recovered without treatment and continued in the study. There was no mention of an ECG measurement near the syncope occurrence. According to the ISS, the patient had a (b)(4)-identified  $\geq 60$  msec increase in QTc at Day 29. When reanalyzed by (b)(4), U waves were present on the Day 29 ECG but not at baseline. Recalculated baseline QTcB was 338 msec, and recalculated Day 29 QTcB was 386, for a 48 msec increase during treatment.

**Comment:** The sponsor appears to be making an assumption that U waves are benign; this reviewer is not sure that this is the case. However, a QTcB of 386 would be within the normal range.

[Study 02-AVR-107 is in the EDR (along with Study 01-AVR-105) under Clinical Study Reports/Reports of Efficacy and safety studies—Pseudobulbar-Affect/Study Reports of Uncontrolled Clinical Studies].

7. Several deaths in the Neurodex development program may have been cardiovascular-related. Please comment on the following cases:

- a. *Study 02-AVT-107, subject 34-033:* A 48 year-old woman with primary lateral sclerosis died suddenly on day 5 of Neurodex treatment. She was concurrently taking erythromycin 250 mg (a CYP 3A4 inhibitor that prolongs QT) and venlafaxine 75 mg (metabolized by CYP 2D6 and labeled as (slightly?) prolonging QTc). Plausibly, venlafaxine and quinidine levels could have been elevated from 2D6 and 3A4 inhibition, respectively. Please comment on the possible relationship of this death to cardiovascular causes, including torsades de pointes.

**Response:** This was a 49 year old Caucasian female with primary lateral sclerosis and a normal screening ECG. There were no clinically significant hematology or chemistry findings and on (b)(6) she was enrolled into the study. On (b)(6), her husband

assisted her to the couch and set up her breakfast tray and morning medications. He left her alone to take a shower; upon returning, he found her supine on the couch with her head back, not breathing. He called 911 and tried unsuccessfully to resuscitate her. According to the site, her husband believed that she may have choked to death on her breakfast.

**Comment:** Five days after starting Neurodex, in the presence of erythromycin, the patient died. In the absence of data surrounding her demise, one cannot exclude an arrhythmic event. It should be noted that erythromycin has been associated with QT prolongation (Ref. 7); erythromycin is also extensively metabolized by CYP 3A isozymes

( Ref. 7). There is a case report of TdP in an elderly man receiving both quinidine (for atrial fibrillation) and erythromycin (for community-acquired pneumonia) (Ref. 6). However, the relationship between the dose of quinidine in Neurodex and an interaction with erythromycin is not clear.

- b. *Study 01-AVR-105, subject 04-006:* In a 29 day open-label trial of 36 patients with painful diabetic neuropathy, one patient experienced sinus tachycardia on day 15, followed by several additional adverse events, and death from apparent MI (b) (6) days after study termination. While the patient had multiple cardiovascular risk factors, the proximity of death to study drug may be concerning. Please comment on the possible relationship, if any, between Neurodex and this patient's death.

**Response:** According to the ISS narrative, this was a 64-year old Caucasian male diabetic, with a history of COPD, ASHD and vascular disease, enrolled in Study 01-AVR-105 for the treatment of painful diabetic neuropathy. He received AVP-923 in escalating doses: for 3 days, AVP-923 once daily; for 4 days, AVP-923 twice daily, and for the remaining 22 days, a total daily doses of 45 mg D and 60 mg Q. ECG results were read as normal on screening and Day 1, but read as sinus tachycardia on Day 15 (HR 100 bpm) and Day 29 (HR 109 bpm). On Day 27 he developed a moderate upper respiratory infection and mild drug mouth; on Day 28 he reported mild bilateral lower extremity edema. He completed the study on Day (b) (6); on study termination he was noted to have decreased air entry with bronchospasm, scattered rhonchi and bilateral edema. On the same day, he was hospitalized for severe exacerbation of COPD. (b) (6) days later, he developed renal failure, and the next day, he expired from a presumed arrhythmia/MI (no arrhythmia was apparently documented although I assume that he was still hospitalized). Autopsy results showed an acute left septolateral infarction with stenoses of the right coronary artery and left anterior descending artery.

**Comment:** This patient had several underlying diseases and multiple risk factors for coronary disease. He was hospitalized due to COPD exacerbation due to respiratory infection (this reviewer wonders if he had pneumonia or sepsis which led to renal failure). A relationship with AVP-923 appears unlikely in this case.

- c. *Study 02-AVR-107, subject 29-006:* In an open-label study of Neurodex, a 62 year-old man with MS had baseline ECG showing premature ventricular complexes and poor R-wave progression. On day (b) (6), he was found dead by his wife. Cause of death from autopsy was indicated as acute myocardial infarction. Given the proximity the patient's MI and death to initiating study drug, please comment on the possible relationship, if any, to Neurodex.

**Response:** According to the CRF, this was a 62 year old Caucasian male with MS, major depression, sleep apnea, and hypertension; screening ECG showed sinus rhythm with premature ventricular complexes and poor R wave progression (felt not clinically significant). According to the narrative, on Day 7, the patient's wife reported hallucinations with impaired awareness, continued bowel/bladder incontinence, poor appetite and lethargy. (The patient narrative includes a report of diarrhea). Study drug was apparently held on Day 7 (According to the patient narrative, study drug was held on Day 8). He withdrew consent on Day 10 and died on Day (b) (6); the cause was unknown but later deemed (by autopsy) to be myocardial infarction.

**Comment:** Given that study drug was withheld (b) (6) days prior to the fatal event, it is unlikely that the event was related to TdP.

- d. *Study 99-AVR-100, subject 23:* In a PK study, an 86 year-old otherwise healthy female received 3 doses of 30 mg dextromethorphan/75 mg quinidine [note the 2.5-fold higher quinidine concentration than in the final Neurodex formulation], experienced unremitting vomiting ~ 1.5 hours after the third dose, and died (b) (6) days later. Cause of death per the investigator was "bowel obstruction, aspiration, myocardial infarction." Nausea and vomiting are known adverse effects of high-dose dextromethorphan, but given the many unexpected characteristics of this death, DNP would appreciate your comments on possible cardiovascular relationships or role of quinidine.

**Response:** 86 year old Caucasian female with screening ECG interpreted as normal (QT375 msec, QTc 402 msec, HR 69 bpm, PR 202 msec [first degree AV block]), given dextromethorphan 30 mg/quinidine 75 mg terminated early from the study. According to the study report, she developed protracted vomiting after 4 doses of drug. (b) (6) days later, she went to an emergency room and was admitted with dehydration and vomiting. On the third day of hospitalization she was noted to have a firm, bloated abdomen; CT scan revealed an obstruction at the terminal ileum. Before a nasogastric tube could be inserted, the subject vomited, aspirated, and then 'coded' and was said to have suffered "myocardial damage" (this information was found in the study report but not in the CRF). No post-dosing ECGs were found in the CRF (according to the patient narrative, the early termination ECG was "inadvertently misplaced.")

**Comment:** This patient was found to have a small bowel obstruction which was probably unrelated to drug. Given the clinical story, it is likely that her terminal events were related to aspiration. Her vomiting does raise a concern about associated hypokalemia, and the effect of hypokalemia on quinidine and QT. However, there was no submitted record of potassium levels and post-dosing ECGs.

[Study 99-AVR-100 is in the EDR under: Reports of Efficacy and Safety.../Reports of Human Pharmacokinetic.../Study ID: Study 99-AVR-100].

## REFERENCES:

1. Current labeling for Quinidex.
2. Roden DM, Woosley RL, Primm RK. Incidence and clinical features of the quinidine-associated long QT syndrome: implications for patient care. *Am Heart J.* 1986; 111 (6): 1088-93.
3. Bauman JL, Bauernfeind RA, et. al. Torsade de pointes due to quinidine: observations in 31 patients. *Am Heart J.* 1984 Mar; 107 (3): 425-30.
4. Roden D. Long QT syndrome: reduced repolarization reserve and the genetic link. *Journal of Internal Medicine* 2006; 259: 59-69.
5. Personal communication with Dr. Roden on 5/31/2006.

6. Lin JC, Quasny HC. QT prolongation and development of torsades de pointes with the concomitant administration of oral erythromycin base and quinidine. *Pharmacotherapy*. 1997 May-Jun; 17 (3): 626-30.
7. Ray, WA et. al. Oral Erythromycin and the Risk of Sudden Death from Cardiac Causes. *NEJM* 2004; 351: 1089-96.

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MEDICAL OFFICER

## **Executive CAC**

**Date of Meeting:** April 25, 2006

**Committee:** David Jacobson-Kram, Ph.D., OND IO, Chair  
Joseph Contrera, Ph.D., OPS, Member  
Abby Jacobs, Ph.D., OND IO, Member  
Chuck Resnick, Ph.D., DCRP, Alternate Member  
Lois Freed, Ph.D., DNP Supervisor  
Kathleen Young, Ph.D., DNP, Presenting Reviewer

**Author of Draft:** Kathleen Young, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

### **NDA #21-879**

**Drug Name:** Neurodex™ (Dextromethorphan hydrobromide and quinidine sulfate)

**Sponsor:** Avanir Pharmaceuticals, 11388 Sorrento Valley Road, Suite 200, San Diego, CA 92121

**Background:** Neurodex™, a combination oral drug product composed of dextromethorphan hydrobromide (DM) and quinidine sulfate (Q), is under development for the treatment of several neuropathic pain and neurological disorders, including emotional lability (pseudobulbar affect) in patients with amyotrophic lateral sclerosis (ALS). DM, the d-isomer of the codeine analog levorphanol, is a sigma receptor agonist and noncompetitive N-methyl-D-aspartate-sensitive ionotropic glutamate (NMDA) receptor antagonist. Quinidine (Q), the d-isomer of quinine isolated from the cinchona tree, is an inhibitor of the hepatic cytochrome P450 metabolic enzyme, CYP2D6. Oral DM bioavailability is low, due to extensive first-pass metabolism by hepatic CYP2D6-dependent dextromethorphan O-demethylase, except in approximately 5-10% population with low levels of 2D6 (slow-metabolizers). When administered together, Q decreases the extent of DM metabolism and prolongs plasma levels for potentially sustained therapeutic efficacy.

**TgRasH2 Mouse Carcinogenicity Study:** DM and Q were administered by oral gavage to Tg.rasH2 mice at doses of 100 mg/kg/d for each drug alone, and combined at 25/50, 50/50, and 100/100 mg/kg/d DM/Q, once daily for 26 weeks. The doses were selected based on the results of a 28-day dose range-finding study in Tg.rasH2 mice, and received prior FDA dose concurrence. The high dose of 100 mg/kg/d for each drug represented 8 times the recommended human daily dose of 60 mg PO of each drug, on a mg/m<sup>2</sup> basis. Appropriate negative (1% methyl cellulose vehicle, 10 ml/kg PO daily for 26 weeks) and positive (Urethane, 1000 mg/kg IP, 3 injections over 5 days) control groups were evaluated. A statistically significant increase in thin appearance at 50/50 and 100/100 mg/kg/day DM/Q, and decreases in body weights and body weight gains confirmed that the dosing was adequate and up to the MTD in the male and female mice. There were no

treatment-related effects on survival. No statistically significant treatment-related increases in non-neoplastic or neoplastic lesions were observed. Positive findings of increased pulmonary adenomas and carcinomas, hemangiosarcomas in the spleen, and other neoplastic lesions in the urethane-treated mice supported the validity of the study. It is concluded that there was no evidence of carcinogenic potential by DM and Q at doses of up to 100 mg/kg/d administered alone and in combination, in Tg.rasH2 mice under the conditions of this study.

**Executive CAC Recommendations and Conclusions:** The Committee concurred that the study was adequate and that no drug related neoplasms were observed in the study.

David Jacobson-Kram, Ph.D.  
Chair, Executive CAC

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/Division File, DNP  
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/KAYoung, DNP  
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**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 21-879

Supplement #

Efficacy Supplement Type SE-

Trade Name: Neurodex

Established Name: Dextromethorphan Hydrobromide plus Quinidine Sulfate

Strengths: 30mg / 30mg

Applicant: Avanir

Agent for Applicant:

Date of Application: 11/27/06

Date of Receipt: 11/30/06

Date clock started after UN: N/A

Date of Filing Meeting: 2/28/06

Filing Date: 3/30/06

Action Goal Date (optional):

User Fee Goal Date:

Indication(s) requested: Therapy to reduce or eliminate pseudobulbar affect

Type of Original NDA:

(b)(1)

(b)(2)

OR

Type of Supplement:

(b)(1)

(b)(2)

**NOTE:**

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application

OR

NDA is a (b)(2) application

Therapeutic Classification: S

P

Resubmission after withdrawal?

Resubmission after refuse to file?

Chemical Classification: (1,2,3 etc.) 4

Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted:

YES  NO

User Fee Status:

Paid

Exempt (orphan, government)

Waived (e.g., small business, public health)

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES  NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES  NO
- Does the submission contain an accurate comprehensive index? YES  NO
- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A  YES  NO   
**If an electronic NDA, all forms and certifications must be in paper and require a signature.**  
Which parts of the application were submitted in electronic format?

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A  YES  NO
- Is it an electronic CTD (eCTD)? N/A  YES  NO   
**If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES  NO
- Exclusivity requested? YES, \_\_\_\_\_ Years NO   
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

**NOTE:** Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)**  
**NOTE:** Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y  NO
- PDUFA and Action Goal dates correct in COMIS? YES  NO   
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: \_\_\_\_\_
- End-of-Phase 2 Meeting(s)? Date(s) \_\_\_\_\_ NO   
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 5/17/2004 NO   
 If yes, distribute minutes before filing meeting.

**Project Management**

- Was electronic "Content of Labeling" submitted? YES  NO   
 If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES  NO
- Risk Management Plan consulted to ODS/IO? N/A  YES  NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y  NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A  YES  NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A  YES  NO
- Has DOTCDP been notified of the OTC switch application? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?  
YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? *N/A* YES  NO

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: 2/28/06

**BACKGROUND:**

(Provide a brief background of the drug; e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

**ATTENDEES:**

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline</u>	<u>Reviewer</u>
Medical:	
Secondary Medical:	
Statistical:	
Pharmacology:	
Statistical Pharmacology:	
Chemistry:	
Environmental Assessment (if needed):	
Biopharmaceutical:	
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Management:	
Other Consults:	

Per reviewers, are all parts in English or English translation? YES  NO   
If no, explain:

CLINICAL FILE  REFUSE TO FILE

• Clinical site inspection needed? YES  NO

• Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS N/A  FILE  REFUSE TO FILE

BIOPHARMACEUTICS FILE  REFUSE TO FILE

• Biopharm. inspection needed? YES  NO

PHARMACOLOGY

N/A

FILE

REFUSE TO FILE

- GLP inspection needed?

YES  NO

CHEMISTRY

FILE

REFUSE TO FILE

- Establishment(s) ready for inspection?
- Microbiology

YES  NO   
YES  NO

ELECTRONIC SUBMISSION:

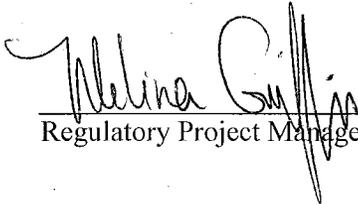
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:  
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

- If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
- If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
- Convey document filing issues/no filing issues to applicant by Day 74.

  
Regulatory Project Manager, HFD-120

## Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)?

YES



NO



*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

*Quinine Sulfate*

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

(a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES



NO



*(Pharmaceutical equivalents* are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "No," skip to question 4. Otherwise, answer part (b).*

(b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES



NO



(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

*If "Yes," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES



NO



*If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved?

YES



NO



*(Pharmaceutical alternatives* are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "No," skip to question 5. Otherwise, answer part (b).*

(b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)?

YES



NO



(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

**NOTE:** *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, YES  NO   
ORP?

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES  NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES  NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). *This application provides for a new indication in addition to a new combination of 2 approved drug products.*
7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES  NO
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES  NO
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES  NO
10. Are there certifications for each of the patents listed for the listed drug(s)? YES  NO
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s):

**NOTE:** IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)  
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?  
YES  NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?  
YES  NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?  
N/A  YES  NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).)?  
N/A  YES  NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a). YES  NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval. YES  NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# \_\_\_\_\_ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES  NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES  NO

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

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Melina Griffis  
4/17/2006 04:48:36 PM  
CSO

**MEMORANDUM**  
**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
**CONTROLLED SUBSTANCE STAFF**

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**Date:** December 14, 2005

**To:** Russell Katz, M.D., Director  
Division of Neurology Products  
(HFD-120)

**Through:** Deborah Leiderman, M.D., Director  
Silvia Calderon, Ph.D., Team Leader  
Controlled Substance Staff (HFD-009)

**From:** Geoffrey Zeldes, M.D., Pharm.D., Medical Officer  
Controlled Substance Staff (HFD-009)

**Subject:** CSS comments on sponsor response to previous comments submitted to sponsor regarding NDA 21-879 for AVP-923 (Neurodex) dextromethorphan 30mg / quinidine 30mg capsules , dose BID  
Indication: treatment of pseudobulbar affect  
Sponsor: Avanir Pharmaceuticals

**Background**

This memorandum responds to a consult from the Division of Neuropharmacological Drug Products, HFD-120, with respect to Avanir's response to the August 25, 2005 letter, sent by the FDA. This letter detailed deficiencies noted at the filing stage of NDA 21-879 for Neurodex capsules (dextromethorphan 30 mg + quinidine 30 mg). The sponsor has responded with additional information. CSS is asked to review this new material related to abuse potential and safety. This submission consists of several sections including "Controlled Substance", new literature review, and an Abuse Liability Report authored by Sellers and Schoedel. The Abuse Liability section of this submission was reviewed to prepare this response.

Neurodex is indicated for the treatment of pseudobulbar affect (PBA), also known as pathological laughing and crying/weeping, emotional lability, and emotional incontinence. PBA is an affective disinhibition syndrome characterized by disinhibition of emotional control, typically episodes of involuntary or exaggerated laughing and/or crying or weeping. PBA is associated with neurological disease or injury, particularly multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS). It more rarely occurs in Parkinson's disease, dementias, including Alzheimer's disease, stroke and traumatic brain

injury. The sponsor is requesting a priority review by the FDA because there are no other products currently approved for PBA. Neurodex is not approved in any country.

### **Pertinent Dextromethorphan Facts**

- DM is present in several OTC & prescription products, both as a single ingredient and in combination with other drugs. The recommended dose of DM in currently marketed products is 10 to 20 mg every 4 hours or 30 mg every 6 to 8 hours up to a maximum of 120 mg/day. A 4-oz bottle of OTC cough syrup contains approximately 354 mg of DM.
- DM is not a controlled substance under the CSA, and is explicitly exempted from scheduling (21 USC §811 (g) 2).
- Dextromethorphan hydrobromide (DM), the CNS pharmacologically active ingredient of Neurodex, is a sigma-1 receptor agonist and a noncompetitive antagonist of the *N*-methyl-D-aspartate-sensitive ionotropic glutamate receptor (NMDA receptor). Quinidine sulfate is a specific inhibitor of CYP2D6-dependent oxidative metabolism used in Neurodex to increase systemic bioavailability of DM.

### **Summary of Sponsor Submission**

- The sponsor states that dextrorphan (DX), the major metabolite of dextromethorphan, mediates the “positive subjective” effects associated with DM.
- The Sponsor states that quinidine totally prevents DX formation. The expert report provided by the company indicates that dextrorphan plasma levels can still be found after dosing with Neurodex. Plasma DX levels are lower when Neurodex is administered compared to dextromethorphan given alone (4-8 fold lower dextrorphan  $C_{max}$  and 2-4 fold lower dextrorphan AUC). If any dextrorphan is formed while taking this product, there is a possibility of abuse.
- The Sponsor states “that dextromethorphan itself appears to be associated with ‘aversive’ types of effects.” Quinidine interference with DM metabolism results in very high plasma levels which may represent a drug safety issue. The very high levels of unmetabolized dextromethorphan resulting from Neurodex may be responsible for adverse effects and abuse liability that have not been recognized yet. The safety of these extremely high plasma levels of dextromethorphan needs to be determined.
- The Sponsor points out that current dextromethorphan abuse patterns involve OTC forms of this drug and not a prescription form like the proposed product and as such, proposes no further post-marketing surveillance methodology beyond the spontaneous reporting of adverse effects. The possibility of abuse remains, however and post-marketing signals of abuse must be watched for through

monitoring. CSS disagrees with the statement “Other than standard AE reporting, post-marketing surveillance is not warranted”.

- A proposed revised abuse liability section of the labeling found on page 9 of “Expert Report: Abuse Liability Assessment of Neurodex” has been provided and reviewed. The following statement is excerpted from the proposed labeling. “With Neurodex, quinidine blocks the conversion of the dextromethorphan to dextrorphan and therefore it is expected to have less abuse potential than dextromethorphan alone.” No evidence was submitted to support the Sponsor’s assertion that since quinidine blocks the conversion of DM to DX, Neurodex is expected to have less abuse potential than DM alone.
- CSS understands that higher plasma levels of DM and lower plasma levels of DX are achieved with this formulation, but how this differential DM/DX ratio affects the overall abuse potential of the formulation needs further evaluation.

### **Conclusions / Recommendations**

- The proposed abuse liability section still lacks information related to overdose / safety issues. These topics need to be addressed at the time of filing of the NDA. CSS disagrees with the Sponsor’s assertion regarding the lower abuse potential of Neurodex when compared to other DM products.
- A plan to monitor for post-marketing abuse patterns must be submitted.
- The Division should notify the Sponsor that the CSS may have further comments and recommendations after reviewing the abuse liability section to be submitted in support of the NDA.
- The sponsor acknowledges 15 AEs associated with the use of DM in pediatrics from 1969-1981. CSS recommends the Division consult the Office of Drug Safety to evaluate the safety profile of DM and to review spontaneous reports associated with abuse, misuse and addiction of currently available DM products. CSS understands that this consultation will provide qualitative data since it is not possible to capture drug utilization values for DM OTC products.

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

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Geoffrey Zeldes  
12/21/2005 02:39:03 PM  
MEDICAL OFFICER

Silvia Calderon  
12/21/2005 02:56:16 PM  
CHEMIST

Deborah Leiderman  
2/1/2006 04:27:44 PM  
MEDICAL OFFICER

**MEMORANDUM**  
**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
**CONTROLLED SUBSTANCE STAFF**

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**Date:** August 9, 2005

**To:** Russell Katz, M.D., Director  
Division of Neuropharmacological Drug Products  
(HFD-120)

**Through:** Deborah Leiderman, M.D., Director  
Silvia Calderon, Ph.D., Team Leader

**From:** Geoffrey Zeldes, M.D., Pharm.D., Medical Officer  
Controlled Substance Staff (HFD-009)

**Subject:** Consultation on fileability of NDA 21-879 for AVP-923 (Neurodex)  
dextromethorphan 30mg / quinidine 30mg capsules , dose BID  
Indication: treatment of pseudobulbar affect  
Sponsor: Avanar

**Background**

The sponsor has submitted an NDA for Neurodex (dextromethorphan 30 mg + quinidine 30 mg capsules) and HFD-120 requests that HFD-009 review the format and content of the abuse potential pertaining sections of the NDA for filing purposes.

Neurodex is indicated for the treatment of pseudobulbar affect (PBA), also known as pathological laughing and crying/weeping, emotional lability, and emotional incontinence. PBA is an affective disinhibition syndrome characterized by disinhibition of emotional control, typically episodes of involuntary or exaggerated laughing and/or crying or weeping. PBA is associated with neurological disease or injury, particularly multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS). It more rarely occurs in Parkinson's disease, dementias, including Alzheimer's disease, stroke and traumatic brain injury. The sponsor is requesting a priority review by the FDA because there are no other products currently approved for PBA. Neurodex is not approved in any country.

**Pharmacology**

Dextromethorphan hydrobromide (DM), the CNS pharmacologically active ingredient of Neurodex, is a sigma-1 receptor agonist and a noncompetitive antagonist of the *N*-methyl-D-aspartate-sensitive ionotropic glutamate receptor (NMDA receptor). Quinidine sulfate is a specific inhibitor of CYP2D6-dependent oxidative metabolism used in Neurodex to increase systemic bioavailability of DM.

DM is currently exempted from scheduling (21 USC §811 (g) 2).

DM is present in several OTC & prescription products, both as a single ingredient and in combination with other drugs. DM is not a controlled substance under the CSA. The recommended dose of DM in currently marketed products is 10 to 20 mg every 4 hours or 30 mg every 6 to 8 hours up to a maximum of 120 mg/day. A 4-oz bottle of OTC cough syrup contains approximately 354 mg of DM.

### **Submission Review**

The EDR and DFS were utilized to review the NDA submission & IND submissions related to DM / quinidine.

The sponsor has completed three Phase 1 trials. In a 10-subject PK study in normal volunteers, DM levels increased 6-fold and 8-fold, respectively between days 1 and 8. In another study of 65 normal volunteers who were extensive metabolizers, 30 mg of quinidine compared to no quinidine, the day 8 plasma DM AUC was 46-fold higher and Cmax was 33-fold higher after 45mg of DM (similar increase seen with 60mg DM).

Two double-blind controlled trials were conducted to evaluate the safety and efficacy of DM and quinidine combination in patients with PBA, one in patients with ALS and the other in patients with MS. An open label study of patients with pseudobulbar affect is ongoing. Data from these studies indicate adverse effects (AE) reported for approximately 84% with approximately 24% dropout rate of patients taking Neurodex due to AE, including nausea, headache, and dizziness.

An additional clinical trial was conducted in 36 patients with painful diabetic neuropathy, with a combination of DM and quinidine in the dose range from 30 mg DM and 30 mg quinidine to 120 mg DM and 120 mg quinidine. The sponsor concluded that treatment with these doses was safe and well tolerated, although AEs that were statistically significant included nausea, dizziness, and headache.

The submission includes draft labeling, however, no Abuse Liability Section was identified.

### **Dextromethorphan Abuse Signal**

There was a previous concern by the reviewing medical officer, that when the quinidine component of this product inhibits DM metabolism, the result is dramatically increased plasma levels of DM. Due to recent published reports of DM-containing product abuse, including a recently released FDA Talk Paper, an abuse liability evaluation of AVP-923 is needed. No studies to assess abuse liability of this product were recommended by CSS at a meeting with the Sponsor on 5/17/04.

### **Conclusions**

- Administration of 30 mg DM and 30 mg quinidine combination results in plasma levels of DM 24-34 times higher than the plasma levels achieved with 30mg of DM alone.
- The clinical studies conducted to date reveal a rate of adverse effects of 80%, with a 24% drop out rate. Most of the adverse effects reported appear to be GI or CNS. It is unknown if there is a correlation between the adverse effects observed in clinical trials and those seen with abusing high doses of DM.

- There are reports of DM abuse, especially in teenagers, who abuse DM containing OTC products intended to treat cough. FDA issued a Talk Paper on May 20, 2005 warning of the problem. Doses used for this purpose range from 100 mg to 1800 mg with a dose-response pattern to symptoms described. It would appear that a dose of Neurodex would approximate the DM plasma levels seen with the higher abuse doses. It is unclear whether this pattern of abuse and pharmacokinetic profile of AVP-923 would contribute to abuse and diversion of this product as the sponsor claims that dextrorphan (DX), a metabolite of DM correlates with abuse potential and the quinidine component blocks this metabolite from forming.
- The sponsor has provided limited information in the supporting documents of the filing, where few references to more recent information on reports of abuse and dependence of DM have been included. The labeling for the substance abuse section is referenced to and taken directly from the package insert for the product Phenergan DM.
- This submission does not contain data specifically addressing the abuse potential of the product as required by 21 USC §314.50 (5) (vii) and is not fileable from the CSS standpoint.

### **Recommendations**

- An abuse liability section needs to be submitted. Please request from the sponsor an update of information related to the abuse potential of dextromethorphan (recent literature search with appropriate references, adverse event profile, post marketing experience), justification for scheduling (the case for maintaining exemption status), and information related to overdose / safety issues.
- The sponsor has not updated or revised the Abuse and Dependence section of the product label, although this was previously recommended. This section, as proposed, contains only a general comment, attributed to the WHO Expert Committee on Drug Dependence (but without a specific reference). This section must be revised to include the above requested information.

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/s/

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Geoffrey Zeldes  
8/11/05 10:20:17 AM  
MEDICAL OFFICER

Silvia Calderon  
8/11/05 02:46:43 PM  
CHEMIST