

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209321Orig1s000**

**OTHER REVIEW(S)**

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MEMORANDUM  
REVIEW OF REVISED LABEL AND LABELING  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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Date of This Memorandum: April 26, 2019  
Requesting Office or Division: Division of Neurology Products (DNP)  
Application Type and Number: NDA 209321  
Product Name and Strength: Ruzurgi (amifampridine) tablets, 10 mg  
Applicant/Sponsor Name: Jacobus Pharmaceutical Company, Inc.  
FDA Received Date: April 26, 2019  
OSE RCM #: 2017-2500-3  
DMEPA Safety Evaluator (Acting): Briana Rider, PharmD

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## 1 PURPOSE OF MEMORANDUM

The Division of Neurology Products (DNP) requested that we review the revised carton labeling for Ruzurgi (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>a</sup>

## 2 ASSESSMENT

We note the placeholder for the expiration date and control number have been removed from the bottom flap of the carton labeling. In their submission, the Sponsor states that the expiration date and control number will be printed as part of the Drug Supply Chain Security Act requirement in the blank (unvarnished) area above the "Manufactured By:" information. The expiration date format (i.e., MMMYYYY) was previously reviewed and found to be acceptable from a medication safety perspective.

We confirmed that the carton labeling has been revised in accordance with our previous recommendations and the revisions do not introduce new risks of medication errors.

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<sup>a</sup> Rider, B. Label and Labeling Review for Ruzurgi (NDA 209321). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 17. RCM No.: 2017-2500-2.

### 3 CONCLUSION

The revised carton labeling for Ruzurgi is acceptable from a medication error perspective. We have no further recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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**Department of Health and Human Services  
Food and Drug Administration**

**Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)  
Epidemiology: ARIA Sufficiency Templates  
Version: 2018-01-24**

Date: April 24, 2019

Reviewer: Hongliu Ding, MD, PhD, MPH  
Division of Epidemiology I

Team Leader: Kira Leishear, PhD, MS  
Division of Epidemiology I

Division Deputy Director: Sukhminder K. Sandhu, PhD, MS, MPH  
Division of Epidemiology I

Subject: ARIA Sufficiency Memo for Pregnancy Safety Concerns

Drug Name: Ruzurgi (amifampridine)

Application Type/Number: NDA 209321

Applicant/sponsor: Jacobus Pharmaceuticals Company, Inc.

OSE RCM #: 2019-814

## Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

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### 1. BACKGROUND INFORMATION

#### 1.1. Medical Product

Ruzurgi (amifampridine) has a proposed indication for the [REDACTED] (b) (4) Lambert-Eaton myasthenic syndrome (LEMS) in patients [REDACTED] (b) (4). It blocks potassium channels and thus prolongs the depolarization at the nerve ending in the neuromuscular junction, which leads to an increase in quantal release of acetylcholine.<sup>1-4</sup> The increased release of acetylcholine provides relief to symptoms caused by the impaired cholinergic neuromuscular transmission as a consequence of pathogenetic antibody binding to voltage-gated calcium channels.<sup>5</sup> Ruzurgi is administered orally in divided doses (2 to 3 times per day). The recommended initial dosage is 15- 30mg daily and the titration regimen is increased daily in 5-10mg increments with maximum daily dosage of 100mg for patients [REDACTED] (b) (4) weighing 45 kg or more, and 7.5- 15mg daily initially, with increases in 2.5- 5mg increments with maximum daily dosage of 50mg for those less than 45 kg. This product has been provided by the sponsor for the treatment of LEMS through its compassionate distribution program over the last 25 years. The major safety concerns of this product are seizures and hypersensitivity reactions.

#### 1.2. Describe the Safety Concern

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.<sup>6</sup> While there was a dose-related increase in dams with stillborn offspring in the 22.5 and 75 mg/kg/day dose groups found in rats (albeit no effect on viability at doses up to 57mg/kg/day in pregnant rabbits) for the phosphate salt form of the drug (amifampridine)<sup>7</sup> approved for the same indication (LEMS) in the European Union in 2009,<sup>8</sup> no reproductive or developmental toxicity studies have been conducted specifically for Ruzurgi. In addition, there is no controlled clinical study of Ruzurgi in pregnant women. Although there were 6 known completed pregnancies among 3 patients with LEMS treated with Ruzurgi throughout their pregnancies in the compassionate distribution program (i.e., 1 woman with 1 pregnancy, 1 woman with 2 pregnancies, and 1 woman with 3 pregnancies), all pregnancies delivered either term (5 babies delivered after approximately 37 weeks or later) or healthy babies (1 baby induced at 36 weeks with APGAR scores of 9 at both 1 and 5 minutes) and no adverse pregnancy outcomes were reported. However, for 1 of these pregnancies, amniotic fluid, umbilical blood, and maternal blood were analyzed and Ruzurgi and its inactive 3-Ac-DAP metabolite were found to cross the placenta and enter the fetal circulation and amniotic fluid. Taken together, there are

no adequate human data on the developmental risk associated with the use of Ruzurgi in pregnant women and its effect on pregnancy outcomes is not known at this time.

In the current proposed labeling, as of April 16, 2019, the Risk Summary in Section 8.1 Pregnancy, states: “There are no data on the developmental risk associated with the use of RUZURGI in pregnant women.” and “Animal (b) (4) studies have not been conducted with RUZURGI.”

**1.3. FDAAA Purpose (per Section 505(o)(3)(B))**

*- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS*

*Purpose (place an “X” in the appropriate boxes; more than one may be chosen)*

Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

**2. REVIEW QUESTIONS**

**2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.**

- Specific FDA-approved indication in pregnant women exists and exposure is expected
- No approved indication, but practitioners may use product off-label in pregnant women
- No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
- No approved indication, but use in women of child bearing age is a general concern

**2.2. Regulatory Goal**

- Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.<sup>†</sup>
- Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).<sup>†</sup>

<sup>†</sup> *If checked, please complete [General ARIA Sufficiency Template](#).*

**2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.**

- Pregnancy registry with internal comparison group
- Pregnancy registry with external comparison group
- Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- Electronic database study with chart review
- Electronic database study without chart review
- Other, please specify: 45T



**2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?**

- Study Population
- Exposures
- Outcomes
- Covariates
- Analytical Tools

For any checked boxes above, please describe briefly:

Analytical Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

Because broad-based signal detection is not currently available, other parameters were not assessed.

**2.5. Please include the proposed PMR language in the approval letter.**

The following language has been proposed by Division of Neurology Products (DNP) as of April 24, 2019 for a PMR related to pregnancy outcomes:

*“Establish a Pregnancy Surveillance Program to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to Ruzurgi (amifampridine) during pregnancy. Provide a complete protocol that includes details regarding how you plan to encourage patients and providers to report pregnancy exposures (e.g., telephone contact number and/or website in prescribing information), measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring, and plans for comprehensive data analysis and yearly reporting.”*

**3. References**

1. Maddison P, Newsom-Davis J, Mills KR. Distribution of electrophysiological abnormality in Lambert-Eaton myasthenic syndrome. *J Neurol Neurosurg Psychiatry*. 1998;65(2):213-217.
2. Maddison P, Newsom-Davis J, Mills KR. Effect of 3,4-diaminopyridine on the time course of decay of compound muscle action potential augmentation in the Lambert-Eaton myasthenic syndrome. *Muscle Nerve*. 1998;21(9):1196-1198.
3. Molgo J, Lundh H, Thesleff S. Potency of 3,4-diaminopyridine and 4-aminopyridine on



mammalian neuromuscular transmission and the effect of pH changes. *Eur J Pharmacol.* 1980;61(1):25-34.

4. Vohra MM, Pradhan SN. Pharmacology of 3, 4-Diaminopyridine. *Arch Int Pharmacodyn Ther.* 1964;150:413-424.

5. Spillane J, Ermolyuk Y, Cano-Jaimez M, et al. Lambert-Eaton syndrome IgG inhibits transmitter release via P/Q Ca<sup>2+</sup> channels. *Neurology.* 2015;84(6):575-579.

6. M. D. Division of Pediatric and Maternal Health, FDA. The pregnancy and lactation labeling rule (PLLR).

Available: <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM520454.pdf>. Accessed April 18, 2019.

7. Jacobus Pharmaceutical Company I. Nonclinical Overview, ORIG-1, NDA 209321. June 15, 2018.

8. EMA. Firdapse (previously Zenas)

Available: <https://www.ema.europa.eu/en/medicines/human/EPAR/firdapse-previously-zenas#authorisation-details-section>. Accessed April 18, 2019.

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MEMORANDUM  
REVIEW OF REVISED LABEL AND LABELING  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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Date of This Memorandum: April 17, 2019  
Requesting Office or Division: Division of Neurology Products (DNP)  
Application Type and Number: NDA 209321  
Product Name and Strength: Ruzurgi (amifampridine) tablets, 10 mg  
Applicant/Sponsor Name: Jacobus Pharmaceutical Company, Inc. (Jacobus)  
FDA Received Date: April 4, 2019  
OSE RCM #: 2017-2500-2  
DMEPA Team Leader (Acting): Briana Rider, PharmD

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## 1 PURPOSE OF MEMORANDUM

The Division of Neurology Products (DNP) requested that we review the revised container label and proposed carton labeling for Ruzurgi (Appendix B) to determine if they are acceptable from a medication error perspective.

### 1.1 REGULATORY HISTORY

We previously reviewed the proposed container label<sup>a</sup> and the container label was found to be acceptable from a medication safety perspective in OSE Review #2017-2500-1, dated November 26, 2018.<sup>b</sup>

On March 13, 2019, the Sponsor submitted proposed carton labeling. Upon review of the carton labeling, we noted that the proposed carton labeling appeared to utilize the standardized Drug Facts Label format and content requirements for nonprescription drug products. Subsequently, we sent an Information Request (IR) to inform the Sponsor that the proposed carton must comply with the format and content requirements for prescription drug product labels. In their April 4, 2019 response to our IR, the Sponsor responded that the carton

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<sup>a</sup> Rider B. Label and Labeling Review for Ruzurgi (NDA 209321). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 30. RCM No.: 2017-2500.

<sup>b</sup> Rider B. Label and Labeling Review for Ruzurgi (NDA 209321). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 26. RCM No.: 2017-2500-1.

labeling complies with the format and content requirements for prescription drug labels (Appendix A).

## 2 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note the storage conditions on the container label have been revised in response to recommendations provided by the Office of Pharmaceutical Quality (OPQ) (Appendix A). We reviewed the revised container label and find it to be acceptable from a medication safety perspective.

We note that the proposed carton labeling continues to utilize the standardized Drug Facts Label format and content requirements for nonprescription products. We note the Office of Prescription Drug Promotion's (OPDP) review<sup>c</sup> of the proposed carton labeling found that the:

*labeling is highly promotional in tone and contains numerous false or misleading claims... the "Drug Facts" Label format is reserved for non-prescription drugs and may be misleading when presented on a prescription drug product.*

We agree with OPDP's assessment that the "purposes", "uses", "warnings", "when using this product", and "directions" sections should be deleted from the carton labeling.

Additionally, our evaluation of the proposed carton labeling identified the following areas of vulnerability that may lead to medication errors:

- The statement [REDACTED] (b) (4) is unnecessary because "Rx only" replaces this cautionary statement and appears on the Principal Display Panel.
- The "usual dose" statement is missing from the proposed carton labeling. The "usual dose" statement is required per 21 CFR 201.55.

## 3 CONCLUSION & RECOMMENDATIONS

The revised container label is acceptable from a medication safety perspective. However, we identified areas of the proposed carton labeling that are vulnerable to medication error. Additionally, we agree with OPDP's assessment that the "purposes", "uses", "warnings", "when using this product", and "directions" sections should be deleted from the carton labeling. We ask that the Division convey our recommendations to Jacobus so that the recommendations are implemented prior to approval of this NDA.

## 4 RECOMMENDATIONS FOR JACOBUS PHARMACEUTICAL COMPANY, INC.

### Carton Labeling

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<sup>c</sup> Shah D. OPDP Labeling Comments for RUZURGI (amifampridine) tablets, for oral use (NDA 209321). 2019 APR 16. Available in DARRTS via: [https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804ecf34&\\_afRedirect=1549016476070495](https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804ecf34&_afRedirect=1549016476070495)

- A. The statement [REDACTED] (b) (4) appears on the side panel of the carton labeling. However, this statement is unnecessary because "Rx only" replaces this cautionary statement and appears on the Principal Display Panel. Therefore, we recommend removing the statement [REDACTED] (b) (4) from the carton labeling.
- B. The "usual dose" statement is missing from the proposed carton labeling. The "usual dose" statement is required per 21 CFR 201.55. Add the statement "Usual dosage: see prescribing information" or a similar statement to the carton labeling in accordance with 21 CFR 201.55.

APPENDIX A. JACOBUS' RESPONSE TO THE AGENCY'S MARCH 21, 2019 INFORMATION REQUEST FOR REVISED LABELS AND LABELING, RECEIVED ON APRIL 4, 2019

Accessible in EDR via: <\\cdsesub1\evsprod\nda209321\0024\m1\us\m1-1-cover-letter-seq-0024.pdf>

Excerpted from submission:

As recommended by the Agency in its 21 March 2019 DMEPA/CMC Information Request, Jacobus is providing replacement container and carton draft labels with the following changes:

1. The proposed carton labeling complies with the format and content requirements for prescription drug labels.
2. The storage conditions on the side panel of the container label for the amifampridine tablets have been revised to state:  
**“Prior to dispensing: Must be refrigerated, store at 2°C to 8°C (36°F to 46°F). After dispensing: store at 20°C to 25°C (68°F to 77°F) for up to 3 months; excursions permitted between 15°C to 30°C (59°F to 86°F)”.**
3. The Other Information paragraph on the side panel of the carton labeling has been replaced with the following storage statement:  
**“Prior to dispensing: Must be refrigerated, store at 2°C to 8°C (36°F to 46°F). Keep container tightly closed with desiccant canister inside after opening. Protect from moisture and light. After dispensing: store at 20°C to 25°C (68°F to 77°F) for up to 3 months; excursions permitted between 15°C to 30°C (59°F to 86°F).”.**
4. The following statement has been added to the principal display panel of the container and carton labels:  
**“Refrigerate prior to dispensing”.**
5. The carton label has been revised to list the inactive ingredients alphabetically and the name *dibasic calcium phosphate* has been replaced with *dibasic calcium phosphate dihydrate*.
6. The revised labels comply with the 2018 FDA draft guidance on product identifiers. The right panel above the bar code on the carton (the blank space) and the non-varnished area on the label are both set up to accept product identifiers. These identifiers are printed at the time of packaging.

**APPENDIX B. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 4, 2019**

**Container labels**



**Carton labeling**



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BRIANA B RIDER  
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**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: April 17, 2019

To: William Dunn, MD  
Director  
**Division of Neurology Products (DNP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Sharon W. Williams, MSN, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Dhara Shah, PharmD, RAC  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG) and  
Instructions for Use (IFU)

Drug Name (established name): FIRDAPSE (amifampridine)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 209321

Applicant: Jacobus Pharmaceutical Company, Inc.

## 1 INTRODUCTION

On August 11, 2017, Jacobus Pharmaceutical Company, Inc. submitted for the Agency's review Part 1 of 2 of a rolling submission for an Original New Drug Application (NDA) for RUZURGI (amifampridine), tablets for oral use. The purpose of the submission is to seek approval for marketing RUZURGI (amifampridine), tablets for oral use for the treatment of the autoimmune disorder Lambert-Eaton myasthenic syndrome (LEMS) in patients (b) (4). On December 7, 2017, the Applicant submitted for the Agency's review Part 2 of 2 of the rolling submission. The Agency issued a refusal to file (RTF) letter on January 31, 2018. The Applicant resubmitted the application for approval on June 12, 2018. On March 21, 2019, the Division of Medication Error Prevention and Analysis (DMEPA) and Chemical, Manufacturing, Controls (CMC) submitted an Information Request to the Applicant requesting a Medication Guide and Instructions for Use for RUZURGI (amifampridine). The Applicant submitted the MG and IFU on April 4, 2019.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on April 2, 2019, and August 13, 2018, for DMPP and OPDP respectively to review the Applicant's proposed MG and IFU for RUZURGI (amifampridine) tablets, for oral use.

## 2 MATERIAL REVIEWED

- Draft RUZURGI (amifampridine) tablets, for oral use MG and IFU received on April 3, 2019, and received by DMPP and OPDP on April 4, 2019.
- Draft RUZURGI (amifampridine) tablets, for oral use Prescribing Information (PI) received on April 3, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 4, 2019.
- Approved comparator labeling FIRDAPSE (amifampridine) tablets, for oral use dated November 28, 2018.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level.

Additionally, in 2008, the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the MG documents and using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG and IFU meet the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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LASHAWN M GRIFFITHS  
04/17/2019 02:53:01 PM

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

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

## Memorandum

**Date:** April 16, 2019

**To:** Teresa Buracchio  
Division of Neurology Products (DNP)  
  
Michelle Mathers, Regulatory Project Manager, DNP  
  
Tracy Peters, Associate Director for Labeling, DNP

**From:** Dhara Shah, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Aline Moukhtara, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for RUZURGI (amifampridine) tablets, for oral use

**NDA:** 209321

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In response to the DNP consult request dated August 13, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for RUZURGI (amifampridine) tablets, for oral use (Ruzurgi).

**PI:** OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DNP (Michelle Mathers) on April 3, 2019, and are provided below. Due to the administrative separation of the Original 1 [REDACTED] (b) (4) indications, the OPDP comments provided on the Original 2 labeling are intended to also be applied to Original 1 labeling.

**Medication Guide and IFU:** A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed patient labeling will be sent under separate cover.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on April 4, 2019, and comments are provided below on the labeling.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or [Dhara.Shah@fda.hhs.gov](mailto:Dhara.Shah@fda.hhs.gov).

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DHARA SHAH  
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## MEMORANDUM

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

**Date:** January 14, 2019

**To:** Billy Dunn, M.D., Director  
Division of Neurology Products

**Through:** Dominic Chiapperino, Ph.D., Director  
Silvia Calderon, Ph.D., Senior Pharmacologist  
Martin S. Rusinowitz, M.D., Senior Medical Officer  
Controlled Substance Staff

**From:** Edward Hawkins, Ph.D., Pharmacologist  
Controlled Substance Staff

**Subject:** **Product name:** 3,4-diaminopyridine (3,4-DAP), (amifampridine)  
**NDA:** 209321  
**Trade Name, dosages, formulations, routes:** Ruzurgi is formulated as 10 mg oral tablets. A single dose is not to exceed 30 mg. (b) (4)  
[REDACTED]  
[REDACTED]  
**IND Number:** 054313  
**Indication(s):** (b) (4) Lambert-Eaton myasthenic syndrome (LEMS) in patients (b) (4)  
**Sponsor:** Jacobus Pharmaceuticals Company  
**PDUFA Goal Date:** February 15, 2019

### Materials Reviewed:

- Module 1.14 Labeling
- Module 2.3 Quality summary
- Modules 2.4 and 2.6 Nonclinical summaries
- Modules 2.5 and 2.7 Clinical summaries
- Module 4 Nonclinical study reports
- Module 5 Clinical study reports

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## I. SUMMARY

### 1. Background

This memorandum responds to a consult request by the Division of Neurology Products (DNP) dated August 25, 2018, to the Controlled Substance Staff (CSS) to evaluate abuse-related preclinical and clinical data submitted by Jacobus Pharmaceutical Company (Sponsor) in NDA 209321 (IND 054313) for Ruzurgi (3,4 diaminopyridine [3,4-DAP]). The drug product is indicated for the (b) (4) treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients (b) (4). The tablets

contain 10 mg 3,4-DAP with a recommended dose range

(b) (4)

3,4-Diaminopyridine is a new molecular entity (NME), that is defined by its mechanism of action as a voltage gated potassium ( $K^+$ ) channel blocker. Several in vitro studies indicate that 3,4-DAP and its N-acetyl metabolite do not bind significantly to any receptors, ion channels, or transporters known to be associated with abuse potential. Blockage of the voltage dependent  $K^+$  channels cause prolonged depolarization of the presynaptic membrane. This results in opening of slow voltage-dependent calcium ( $Ca^{2+}$ ) channels producing an increased influx of  $Ca^{2+}$  and inducing exocytosis of neurotransmitters into the synaptic cleft. The Sponsor proposes that release of the neurotransmitter acetylcholine (ACh) provides symptomatic relief to patients with LEMS. However, published literature also indicates that 3,4-DAP causes the release of norepinephrine (NE) (Huang et al., 1989; Jackish et al., 1992), dopamine (DA) (Boireau et al., 1991), and serotonin (5-HT) (Schweizer et al., 2002). Many substances that produce a similar increase in monoamines in the synaptic cleft, albeit through a different mechanism of action, produce stimulatory behaviors and are controlled in Schedules II or IV of the Controlled Substances Act (CSA).

The Sponsor conducted several in vivo studies to determine the central nervous system (CNS) effects of 3,4-DAP. An Irwin study in rats indicated that 3,4-DAP did not produce any CNS-related behavioral effects up to a dose of 40 mg/kg PO. However, several single and multiple dose toxicology studies indicated that 3,4-DAP produced significant activating effects, including hyperlocomotion, hyperexcitability, tremors, and increased limb movements at doses ranging from 25 to 50 mg/kg. As a result, the Sponsor assessed the abuse potential of 3,4-DAP by conducting a drug discrimination assay and a self-administration assay. The results of both the drug discrimination and self-administration studies were negative. The Sponsor was not required to conduct a human abuse potential (HAP) study because of the outcome of the in vivo studies and the lack of evidence of abuse potential from the nonclinical abuse-related studies. Furthermore, there were no abuse-related adverse events (AEs) of concern reported in the ten clinical studies conducted by the Sponsor. As a result, it will not be necessary to control 3,4-DAP in any schedule of the CSA, and product labeling will not need to include section 9 Drug Abuse and Dependence in the prescribing information.

## 2. Conclusions

- Data from nonclinical animal studies and clinical studies indicate that 3,4-DAP does not have abuse potential.
- The receptor binding and activity data indicate that 3,4-DAP is a nonspecific voltage dependent potassium channel blocker.
- The nonclinical in vivo abuse potential studies were conducted in an appropriate manner and indicate that 3,4-DAP does not have reinforcing effects or produce stimulus generalization to the stimulant amphetamine.
- The Sponsor did not conduct a HAP study because of the results of the nonclinical studies and lack of abuse-related AEs from clinical studies.

- There were no events in clinical studies that appeared consistent with drug diversion, abuse, or misuse.
- There were no indications of withdrawal or signs of physical dependence in the clinical trials.

### 3. Recommendations

Based on the negative findings of the nonclinical abuse related animal studies, and the lack of abuse related AEs, we concur with the Sponsor that 3,4-DAP lacks abuse potential and should not be controlled in the CSA.

**Drug label:** CSS recommends the following changes to the Sponsor's label where additions are indicated in bold underlined text and deletions have been stricken through. Since 3,4-DAP does not have abuse potential, CSS recommends that Section 9 of the label not be included.

(b) (4)

## II. DISCUSSION

### 1. Chemistry

The chemical properties of a substance are important for an assessment of abuse potential because they can give an early indication as to the pharmacological effects, possible methods of administration, and methods of synthesis that abusers may use to abuse the drug. An evaluation of the chemical properties of 3,4-DAP and its known active metabolites is given below.

#### 1.1 Substance Information

3,4-DAP is an NME that is similar in structure to the potassium channel blocker 4-aminopyridine (4AP). The synthesis of 3,4-DAP is a six-step process that does not involve or produce any substances with a known potential for abuse. The chemical characteristics of 3,4-DAP are listed in **Table 1**.

Table 1 contains the general chemical attributes of the active pharmaceutical ingredient (API) 3,4-DAP.

**Table 1:** General Chemical Properties of 3,4-DAP

<b>Nomenclature</b>	
International non-proprietary name (INN)	Amifampridine
Chemical Abstract Number (CAS)	54-96-9
Chemical Name (IUPAC)	3,4-Pyridinediamine
Sponsor codes during development	3,4-DAP
<b>Structure</b>	
Molecular Formula	C <sub>5</sub> H <sub>7</sub> N <sub>3</sub>
Molecular Weight	free base = 109.1
Structure	
<b>General Properties</b>	
Appearance	White crystalline powder
pH (1% solution in water)	10.8
pKa	9.02 ± 0.01
Solubility (25°C)	freely soluble in water with decreasing solubility in less polar solvents
Melting point	217-222 °C

The formulated drug product has been produced by Jacobus from the intermediate 3,4-DAP acquired from (b) (4). The API, 3,4-DAP, is purified to extract impurities before mixing with the inactive ingredients and creation of the tablet. The tablet is white to off white, oval, (b) (4) scored with “JACOBUS” on one side. The components and quantitative composition of each tablet are listed in **Table 2**.

**Table 2:** 3,4-DAP Tablet Drug Product Composition (NDA 209321; Module 2.3.P.1; pg 1)

Component	Quantity per tablet (mg)	Percentage per tablet (%)	Function
3,4-DAP	10.0	(b) (4)	Active
Colloidal Silicon Dioxide, (b) (4)			(b) (4)
Microcrystalline Cellulose, (b) (4)			
Dibasic calcium phosphate dihydrate			

Sodium starch glycolate	(b) (4)
Magnesium Stearate	(b) (4)
Total per Tablet	(b) (4)

## 1.2 Potential Drug Isomers

3,4-DAP does not have chiral centers and therefore does not have any stereoisomers.

## 2. Nonclinical Pharmacology

Receptor binding and activity assays can give an indication as to whether or not a substance affects a receptor pathway that is known to be associated with abuse potential. For substances that are CNS active, the Sponsor is required to determine if their active pharmaceutical ingredient, or any major metabolites, will bind to and have activity at these receptors. The Sponsor provided eight binding or activity studies to determine the receptor binding and activity profile of 3,4-DAP.

### 2.1 Receptor Binding and Functional Assays

The Sponsor conducted six in vitro studies to assess the binding and functional activity of 3,4-DAP in order to determine its mechanism of action. The receptor binding screens include receptors, transporters, and ion channels associated with abuse as well as many individualized studies conducted to determine 3,4-DAP's mechanism of action. The data, summarized below, indicate that 3,4-DAP is a voltage gated potassium channel blocker that maintains the depolarized state of neurons thereby decreasing their activity (**Table 3**).

Studies 100017361, 100029813, and 100030464 were receptor panel and enzyme screens to determine the binding affinity of 3,4-DAP and its major metabolite, 3-N-acetyl amifampridine, to receptors, ion channels, enzymes, and transporters, including those associated with abuse potential. The results of the studies indicate that 3,4-DAP binds to the human norepinephrine transporter (NET) with a  $K_i = 470 \mu\text{M}$  which is higher than the typical cutoff of  $10 \mu\text{M}$ . Activity Study 100030865 indicated that 3,4-DAP acts as an antagonist at NET with an  $\text{IC}_{50} = 230 \mu\text{M}$ . Because of these high concentrations, 3,4-DAP is determined to have no appreciable activity at NET. The results of these studies indicate that 3,4-DAP and its metabolite do not bind to any receptor, ion channels, enzymes, or transporters that are known to be associated with abuse potential.

Study 160428.KBD was an electrophysiology assay that used Chinese Hamster Ovary (CHO) cells or Human Endothelial Kidney (HEK293) cells transfected with human  $K_v$  channels to measure the activity of 3,4-DAP at these channels. The family of  $K_v$  channels is large and are denoted numerically by the type of channel (e.g. slowly or rapidly inactivating, or outward rectifying) and by the number of channels in that class. Channels 1.X, 2.X, 3.X, and 4.X, that were tested in this assay, belong to the inactivating class of  $K_v$  channels which increase potassium conductance and decrease neuronal excitation. The data are presented in **Table 3** and indicate that 3,4-DAP is an antagonist at  $\text{hK}_v$  1.1, 1.2,

1.3, 1.4, 1.5, 2.1, 3.2, 3.4, and 4.3 channels. The potassium currents were measured three times in five-minute intervals after application of the test article. The K<sub>v</sub> channel IC<sub>50</sub> after 15 minutes of 3,4-DAP exposure ranged from 273.9 μM (Kv3.4) to 1744.8 μM (Kv2.1). The antagonist potency of 3,4-DAP tended to increase with time which is consistent with 3,4-DAP binding to the cytoplasmic side of the ion channel pore.

**Table 3:** Functional Activity of 3,4-DAP at K<sub>v</sub> Channels

Drug	Functional activity, IC <sub>50</sub> (μM) 3,4-DAP
Kv1.1	372.1
Kv1.2	278.3
Kv1.3	292.9
Kv1.4	720
Kv1.5	366.9
Kv2.1	1744.8
Kv3.2	243.7
Kv3.4	273.9
Kv4.3	1525.1

## 2.2 Safety Pharmacology/Metabolites

The studies in section 2.1 indicate that the major metabolite of 3,4-DAP, 3-*N*-acetyl amifampridine, did not significantly bind to or have significant activity at any of the tested receptors, ion channels, or enzymes. Therefore, all of the pharmacodynamic activity is assumed to be through the parent drug.

## 2.3 Findings from Safety Pharmacology and Toxicology Studies

The Sponsor conducted several studies to assess the in vivo toxicity of 3,4-DAP in rats and dogs. All of the studies were conducted as repeat-dose toxicity studies: three in mice (oral), five in rat (IV and oral), and two in beagle dogs (oral). The studies ranged in duration from 14 days to 6 months in rats and 10 days to 9 months in dogs. **Table 4** summarizes the results of some of the AEs of the repeat dose toxicity studies. These studies indicate that at high doses, 3,4-DAP produces increased weight loss, increased activity, tremors, convulsions, and staining around the eyes and urogenital region.

**Table 4:** Summary of Toxicity Studies on 3,4-DAP

Study #	Single/Repeat	Dose	Administration	Animal	Adverse events	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	NOAEL
20050138	repeat	0-1500 mg/kg/day	Oral	Sprague Dawley rats (5F and 5M)	loss of body weight, increased activity			168 mg/kg/day in females

								and 212 in males
20149900	repeat	0, 15, 45, 135 mg/kg/day	Oral	Sprague Dawley rats	135 mg/kg resulted in weight loss, brown and wet fur in urogenital region			NOAEL in males of 100 mg/kg /day and females 42 mg/kg/day
20050137	repeat – 14 day	15, 45, 150, 450, 1500 mg/kg/day	Oral	Sprague Dawley rats	all animals at 450 and 1500 mg/kg/day were terminated due to low body weights			45 mg/kg/day
20049261	repeat – 28 day	15, 45, 135 mg/kg/day	Oral	Sprague Dawley rats	Yellow and brown fur staining in urogenital region, malaise, red fur staining around the eyes, weight loss at 135 mg/kg/day			50 mg/kg/day
20049262	repeat – 6 months	25, 45, 135 mg/kg/day	Oral	Sprague Dawley rats	Yellow and brown fur staining in urogenital region, malaise, red fur staining around the eyes, weight loss at 135 mg/kg/day			NOAEL 135 mg/kg/day
8345584	Repeat – 7 days	20, 60, 70 mg/kg	Oral	Rats	At 70 mg/kg – slow movements, tremors, vocalizations, stained fur around eyes and anus, salivation	At 30 mg/kg BID = 4110 males and 2810 females		MTD = 60 mg/kg
20062977	Repeat – 10 days	Up to 4.2 mg/kg/day	Oral	Beagle dogs	Tremors, convulsions, hyperactivity, incoordination, and severe salivation			

20055756	Repeat – 9 months	0.13, 0.52, 1.04, 2.1 mg/kg/day BID	Oral	Beagle dogs	Tremors, convulsions, hyperactivity, incoordination, and severe salivation			NOAEL 0.52 mg/kg/d ay
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## 2.4 Animal Behavioral Studies

### *Abuse liability studies*

Data collected from the toxicity studies indicate that 3,4-DAP may have stimulant-like effects similar to drugs controlled in the CSA. These data are supported by published data indicating that 3,4-DAP causes the direct release of neurotransmitters in the brain, such as norepinephrine (NE) (Huang et al., 1989; Jackish et al., 1992), dopamine (DA) (Boireau et al., 1991), acetylcholine (ACh) (Ries et al., 1996), and serotonin (5-HT) (Schweizer et al., 2002). When compared to Ampyra (dalfampridine; 4-aminopyridine), the literature indicates that 3,4-DAP is more potent at causing neurotransmitter release. Typically, drugs that cause high levels of NE and DA in the brain produce stimulant-like effects and should be evaluated for their abuse potential.

The next sections summarize the studies conducted by the Sponsor to assess the discriminative and reinforcing properties of 3,4-DAP.

### Self-administration studies

A self-administration assay is an experimental paradigm in which animals identify if a substance has positive reinforcing effects. Positive reinforcement occurs when the presentation of a desired stimulus results in an increase in behavior that is associated with the administration of the desired stimulus (Gauvin et al., 2017). For example, for abuse assessment purposes, animals are first trained to press a lever (behavior) resulting in the administration (typically IV) of a training drug (desired stimulus) known to be a drug of abuse (e.g. cocaine). Once properly trained, the animals undergo an extinction test to confirm that the training drug is the stimulus responsible for the reinforcing effects and not some other cue in the assay. Animals then receive test drug, and rates of lever pressing and rates of injections are measured. If the rates of administered drug are significantly different from placebo and the animals are not motor impaired by the drug, as measured by rates of lever pressing, the drug is said to be self-administered (Gauvin et al., 2017).

Study 8345586 was conducted to determine the reinforcing effects of IV 3,4-DAP using an amphetamine self-administration substitution procedure in male Lister Hooded rats. Animals were implanted with a femoral vein catheter and were trained to self-administer cocaine (0.32 mg/kg/infusion) up to a fixed ratio 10 (FR10) schedule of reinforcement. After stable responding was obtained, the animals underwent extinction defined as five or less rewards in each session over 3 consecutive sessions. Animals were then moved to the substitution phase. The substitution phase was conducted with the following doses:

1. Negative control: vehicle (100 µl/infusion)
2. 3,4-DAP (0.1 mg/kg/infusion)
3. 3,4-DAP (0.3 mg/kg/infusion)
4. 3,4-DAP (1.0 mg/kg/infusion)
5. Positive control: amphetamine (0.05 mg/kg/infusion)

Cocaine was reinstated after the substitution phase for up to four sessions to confirm that the animals were still trained to self-administer the reinforcer.

The results indicate that when substitution of the training dose of cocaine was conducted by vehicle, and all doses of 3,4-DAP, all of the animals extinguished their self-administration behavior. Animals given the amphetamine positive control (0.05 mg/kg/infusion) demonstrated statistically significant positive reinforcement with a group mean of 35 rewards. All three concentrations of the test drug, 3,4-DAP (0.1, 0.3, and 1.0 mg/kg/infusion) did not produce statistically significant positive reinforcing effects (means of 6.1, 5.4, and 6.2 rewards, respectively). These data indicate that 3,4-DAP does not produce statistically significant reinforcing effects at the tested doses.

### Drug Discrimination

Drug discrimination is an experimental method in which animals identify whether a test drug produces physical or behavioral effects (an interoceptive response) similar to those produced by another drug with known pharmacological properties. If the known drug is one with abuse potential, drug discrimination can be used to predict if a test drug will have abuse potential in humans (Balster and Bigelow, 2003). For abuse assessment purposes, an animal is first trained to press one bar when it receives a known drug of abuse (the training drug) and another bar when it receives placebo. A challenge session with the test drug determines which of the two bars the animal presses more often, as an indicator of whether the test drug is more like the known drug of abuse or more like placebo. A test drug is said to have "full generalization" to the training drug when the test drug produces bar pressing  $\geq 80\%$  on the bar associated with the training drug (Sannerud and Ator, 1995; Doat et al., 2003). Thus, a test drug that generalizes to a known drug of abuse will likely be abused by humans (Balster and Bigelow, 2003).

Study 8345588 was conducted to test the discriminative stimulus effects of 3,4-DAP to amphetamine in a two-choice drug discrimination paradigm in male Lister Hooded rats. Rats were trained to distinguish amphetamine (0.3 mg/kg subcutaneous) from saline in a two-lever food reinforced procedure to an FR20 schedule of reinforcement. Amphetamine was used as the training drug because 3,4-DAP potentiates neurotransmitter release and produces seizures at high doses as does 3,4-DAP. Once all animals demonstrated discrimination to the desired criterion, the generalization phase was conducted. In the generalization phase, multiple doses of amphetamine or vehicle were given in a crossover design to determine the training drug dose response. Subsequently, generalization to 3,4-DAP at doses of 10, 15.8, 21.6, and 27.4 mg/kg PO and vehicle were given in a crossover design. Blood was collected immediately following each test session to determine drug plasma levels so that they may be compared with plasma levels in humans administered the drug at therapeutic doses. The results of the study indicate that the positive control, amphetamine, engendered 86% responding at 0.3 mg/kg and 95.4 % responding at 1 mg/kg on the drug appropriate lever. For all doses of the test compound, 3,4-DAP, animals responded almost exclusively to the vehicle lever with an average of  $\leq 19.5\%$  responding on the

drug lever at all doses. The plasma exposure of 3,4-DAP in these studies indicate that the animals had blood levels that were similar to or 2 to 3-fold higher than plasma levels in humans from therapeutic doses, with a mean  $C_{max}$  range of 136.7 to 1584.6 ng/mL across the doses (a single 30 mg oral dose in healthy humans produces a  $C_{max}$  of 252.3 (111.6) ng/mL).

## 2.5 Tolerance and Physical Dependence Studies in Animals

Study 8345587 was conducted to determine if 3,4-DAP produces physical dependence. Male Han Wistar rats were given 20, 33, or 55 mg/kg/day PO 3,4-DAP for 28 days followed by a 14-day treatment free period or amphetamine (10 mg/kg/day) or codeine (200 mg/kg/day) as positive controls. Animals were dosed daily for 28 days after which they entered a 22 day no-treatment free period. Physiological parameters to assess withdrawal were measured during dosing and in the treatment free period. The highest dose of 55 mg/kg/day produced a significant decrease in body weight on day 30 of the study. The positive controls validated the study with amphetamine (10 mg/kg/day) producing a mild withdrawal syndrome and codeine (200 mg/kg/day) producing marked withdrawal with signs of irritability, increased pain response, diarrhea, writing, wet dog shakes, and increased body weight gain. As a result, 3,4-DAP does not appear to produce symptoms of withdrawal that are indicative of physical dependence.

### *Conclusion*

The in vitro binding and activity studies indicate that 3,4-DAP is a voltage gated potassium channel blocker. Although published data indicate that 3,4-DAP releases monoamines through this mechanism of action, similar monoamines as those released by Schedule II stimulants, stimulant like behavioral effects were not elicited in animal studies. Toxicity studies in rats indicate that at very high doses, 3,4-DAP can produce convulsions and uncoordinated movement, however there were no indications of significant locomotor activation. The direct assessment of the abuse potential of 3,4-DAP conducted in animal self-administration, drug discrimination, and physical dependence studies produced negative results indicating that 3,4-DAP does not have abuse potential or dependence.

## 3. Clinical Pharmacology

The clinical pharmacology of a substance is an assessment of how that substance, and its metabolites, associate with the body and typically includes measurements of PK, pharmacodynamics, toxicology, drug interactions and several other parameters. When conducting an abuse potential assessment of the substance, these clinical pharmacology data are used to determine mechanism of action, whether or not the drug enters and has activity in the CNS, and whether the drug produces psychoactive effects. The data that was submitted appears sufficient to conclude that 3,4-DAP has high oral bioavailability, is quickly absorbed, is metabolized to one major metabolite, and is excreted in the urine.

### 3.1 Absorption, Distribution, Metabolism, Elimination (ADME)

This section gives an overview of the nonclinical and clinical data characterizing pharmacokinetics (PK), absorption, distribution, metabolism, and elimination of 3,4-DAP that were submitted as part of NDA 209321.

### *Pharmacokinetics and Absorption*

Study CYP0638-R7 was conducted to determine the protein binding and stability of 3,4-DAP in human plasma, by incubating 3,4-DAP at 37°C in human plasma for 4 hours at a concentration of 5 µM. Propranolol and warfarin were used as positive controls. The positive controls demonstrated 79.9% and 93.1% mean plasma protein binding respectively indicating that they are highly plasma bound. 3,4-DAP was 25.3% plasma protein bound and its metabolite, 3-Ac-DAP, was 43.3% protein bound. These results indicate that 3,4-DAP, and its metabolite, are relatively available to cross the blood brain barrier and to block potassium channels in the CNS.

Study 8345584 was a dose range finding study that determined PK parameters of increasing doses of 3,4-DAP in HanWistar rats (**TABLE 5**). Male and Female rats were given doses of 10, 30 and, 35, mg/kg 3,4-DAP BID. The 35 mg/kg BID group was dropped down to 30 mg/kg BID because of intolerance of the drug at the higher dose. This study demonstrated a dose dependent increase in C<sub>max</sub> levels and exposure of the drug. The half-life of the drug also increased with dose to approximately 2.5 hours at study state and the T<sub>max</sub> remained relatively constant (~6 hours). It is unclear why the T<sub>max</sub> value in the male rats given 60 mg/kg/day of 3,4-DAP for 1 day have a value of 0.25 hours, as this does not match data from other studies, this is most likely a typographical error in the study report. This study further determined that C<sub>max</sub> and AUC parameters after a single dose of 3,4-DAP and at steady state are higher in female rats compared to male rats.

**Table 5:** PK of Oral 3,4-DAP in Male and Female Rats After Single Dose and at Steady State

PK Parameters	Dose Level 3,4-DAP (mg/kg/day)					
	20		60		70	
	Male	Female	Male	Female	Male	Female
Day 1						
C <sub>max</sub> (ng/mL)	64.3	1160	537	1150	963	2230
T <sub>max</sub> (h)	6.3	6.23	0.25	6.25	6.2	1
T1/2 (h)	0.94	0.78	3.74	2.88	2.42	1.38
AUC 0-last (ng•h/mL)	303	626	2150	2540	2950	5290
Day 7						
C <sub>max</sub> (ng/mL)	102	188	1550	1140	ND	ND
T <sub>max</sub> (h)	7	7	6.5	6.25	ND	ND
T1/2 (h)	0.76	NR	2.25	2.58	ND	ND
AUC 0-last (ng•h/mL)	393	535	3950	4400	ND	ND

ND = not determined; NR = no result calculable

Study 20055756 was a 9-month toxicity study conducted in beagle dogs given the following doses of 3,4-DAP as oral capsules; 0.13, 0.52, 1.04, and 2.1 mg/kg/day BID. PK parameters were measured as

part of the study on days 1, 136, and 273 (**TABLE 6**). The data in dogs are similar to that of rats indicating a dose dependent increase in plasma concentration and exposure. However, dogs have a half-life of approximately three to four hours (~2 hours in rats) and the exposure levels are not significantly different between male and female dogs. As expected, the levels at steady state (9 months) are higher than those after single administration of the drug.

**Table 6:** PK of Oral 3,4-DAP in Male and Female Dogs After Single Dose and at Steady State

PK Parameters	Dose Level 3,4-DAP (mg/kg/day BID)							
	0.13		0.52		1.04		2.1	
	Male	Female	Male	Female	Male	Female	Male	Female
Day 1								
C <sub>max</sub> (ng/mL)	29.8	32.9	112	100	170	185	409	500
T <sub>max</sub> (h)	5	1.5	1	1	2	4.5	1.5	7
T <sub>1/2</sub> (h)	1.59	2.93	2.71	3.28	2.5	2.58	2.93	2.57
AUC 0-last (ng•h/mL)	231	209	760	581	1140	1200	2370	2750
Day 273								
C <sub>max</sub> (ng/mL)	35.9	34.9	108	112	197	215	NC	NC
T <sub>max</sub> (h) <sup>a</sup>	7 (1,7)	1 (1,7)	4.5 (1,8)	7 (1,8)	4 (1,8)	4 (1,7)	NC	NC
T <sub>1/2</sub> (h)	3.65	2.2	2.88	2.73	2.72	2.69	NC	NC
AUC 0-last (ng•h/mL)	190	184	740	758	1440	1280	NC	NC

NC = not collected; <sup>a</sup> data reported as mean (min,max)

In humans the PK of 3,4-DAP was assessed in two clinical studies that determined the PK parameters after single doses in the fasted and fed state. **Table 7** indicates that, in healthy subjects, single oral doses of 20 or 30 mg 3,4-DAP produces lower C<sub>max</sub>, a longer T<sub>max</sub>, and slows clearance of the drug in the fed state compared to the fasted state. The fed state does not significantly affect overall exposure (AUC<sub>0-last</sub>) or plasma half-life of 3,4-DAP.

**Table 7:** Human PK Parameters After Single Oral Doses of 3,4-DAP in the Fed and Fasted State

PK Parameter	Dose of 3,4-DAP and Condition			
	Fasting Conditions		Fed Conditions	
	20 mg	30 mg	20 mg	30 mg
C <sub>max</sub> (ng/mL)	67.4 (28.7)	115.2 (45.1)	45.4 (24.6)	63.1 (39.2)
T <sub>max</sub> (h)	0.65 (0.34)	0.65 (0.24)	1.2 (0.48)	1.25 (0.79)
AUC <sub>0-last</sub> (ng•h/mL)	161.1 (84.6)	252.3 (111.6)	160.5 (95.1)	210.9 (121.8)
T <sub>1/2</sub> (h)	3.64 (0.92)	3.83 (0.94)	3.93 (1.54)	4.17 (1.22)
Cl/F (L/h)	172.2 (114.1)	148.8 (93.7)	214.2 (186.2)	204.3 (142.1)

### Metabolism

In vitro study XBL13655 was conducted to determine the hepatocyte metabolism of 3,4-DAP. In this study, hepatocytes were isolated from rat, dog, monkey, and humans and samples of [<sup>14</sup>C]3,4-

diaminopyridine were incubated and analyzed by HPLC and LC/MS as necessary. Using this method, the rat, monkey, and human hepatocytes rapidly metabolized [<sup>14</sup>C]3,4-diaminopyridine to an M1 metabolite called N-(4-aminopyridin-3-yl) acetamide. In study 038 the rates of generation of M1 were widely variable in the human samples and were determined to be the result of polymorphisms of the *N*-acetyl transferase enzyme. As a result, it appears as though 3,4-DAP is metabolized through *N*-acetylation by *N*-acetyl transferase enzymes to generate the M1 metabolite in humans. The extent of metabolism of the parent to this metabolite ranged from 33% to 40% in these studies. In order to determine the metabolic mechanism of action, 3,4-DAP was incubated in human hepatic microsomes and S9 fractions containing individual recombinant enzymes. The results indicated that the M1 metabolite is generated through the *N*-acetyl transferase 1 and 2 (NAT1 and NAT2) isoforms. Clinical studies indicated that allelic variations of NAT2 in the human population result in significant differences in plasma and exposure levels of the parent drug (Study # JPC 3,4-DAP.PK2). However, it is only the rate at which 3,4-DAP is metabolized that is affected, the drug is still metabolized and excreted in the same manner.

Studies JAC-2010-001, JAC-2010-002, and JAC-2010-003 indicated that 3,4-DAP is unlikely to induce or inhibit CYP enzymes and therefore, would have little effect on drug induced interactions through these metabolic pathways.

#### *Excretion*

The Sponsor did not conduct any studies to assess the excretion of 3,4-DAP or of its major metabolites.

#### Conclusion

The PK data indicate that 3,4-DAP is rapidly absorbed orally and does not bind widely to plasma proteins resulting in a wide distribution throughout the body. 3,4-DAP is metabolized to an *N*-acetyl metabolite through NAT1 and NAT2. In humans, allelic variation in the metabolic enzyme (NAT2) results in variation in the plasma concentration, exposure, and half-life of the parent and major metabolite. It is then excreted renally as the parent drug or as the metabolite.

## 4. Clinical Studies

Of the six completed clinical studies in the 3,4-DAP clinical program, two were conducted in healthy subjects, and four in subjects with LEMS.

### 4.1 Human Abuse Potential Studies

The Sponsor did not conduct a human abuse potential study as part of their assessment of the abuse liability of 3,4-DAP.

## 4.2 Adverse Event Profile Through all Phases of Development

### Phase 1 Studies

The Sponsor conducted two Phase 1 studies in healthy subjects to determine the safety, PK, and tolerability of 3,4-DAP. **Table 8** presents the CSS analysis of the combined neurologically mediated AEs collected from these two Phase 1 studies. The presented AEs do not present a specific concern for abuse at doses of 20 and 30 mg of orally administered 3,4-DAP.

**Table 8:** Neurologically Mediated AEs in Healthy Volunteer Subjects N (%)

Preferred Term	Placebo (N = 72)	20 mg (N = 20)	30 mg (N = 72)
Paresthesia	2 (2.8%)	4 (20%)	11 (15.3%)
Dizziness	0 (0%)	0 (0%)	4 (5.6%)
Headache	0 (0%)	0 (0%)	3 (4.2%)

### Phase 2 and Phase 3 Studies

The Sponsor conducted one Phase 2 study because of the low number of individuals in the U.S. who are diagnosed with LEMS. The Sponsor then conducted three Phase 3 studies; one of which was a clinical efficacy study and two of which were retrospective observational studies. The retrospective observational studies were able to be conducted because 3,4-DAP is available as a marketed drug in Europe and is available in the U.S. under an expanded access program.

Study JPC 3,4-DAPPER was a Phase 2, multicenter, double-blind, placebo-controlled, randomized discontinuation study conducted to evaluate the efficacy and safety of 3,4-DAP in patients with LEMS. This study was conducted in seven sites with 32 subjects enrolled. Neurological AEs for subjects who were treatment naïve with 3,4-DAP (some had been receiving it before) were paresthesias (1 [3.1%]), headache (2 [6.25%]), and dizziness (1 [3.1 %]). These AEs were similar in frequency to those seen in the Phase 1 studies and do not suggest an abuse-potential for 3,4-DAP.

Study JPC 3,4-DAP DUKE RCT was a Phase 3, double-blind, placebo-controlled, randomized parallel-group study to evaluate the efficacy and safety of 3,4-DAP in patients with LEMS. There were 32 subjects in this study who received 3,4-DAP orally at doses ranging from 30 to 80 mg/day. In this study there were no treatment dependent central nervous system AEs that were reported as a result of the test drug, there were two reports of a balance disorder in the placebo group.

Study JPC 3,4-DAP.RPV52, was a retrospective pharmacovigilance review and observational safety study that was conducted in 23 centers in the U.S., Canada, and Argentina. This safety study was conducted to determine the diagnostic and therapeutic challenges associated with treating LEMS patients with 3,4-DAP. Four patients experienced 8 new nervous system disorders: 2 events of cerebrovascular accident and aphasia, and 1 event each of hemiparesis, hypoesthesia, paresthesia, and tremor. This AEs are not associated with abuse potential.

### *Conclusion*

AEs from six clinical studies indicate that 3,4-DAP does not produce pharmacodynamic effects that are typically associated with abuse. These data support the in vitro data indicating that 3,4-DAP does not have abuse potential.

#### **4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trials**

There were no reports of 3,4-DAP overdose. There was also no evidence of abuse or diversion of 3,4-DAP in the Phase 3 trials. Misuse of the drug was more difficult to track, especially in the longer studies in which subjects received the drug over several years. However, there are no indications or reports of intentional misuse of 3,4-DAP.

#### **4.5 Tolerance and Physical Dependence Studies in Humans**

3,4-DAP was not evaluated in any clinical study as to whether it produces physical dependence.

### **5. Regulatory Issues and Assessment**

Based on the review of all abuse-related data submitted in the application, we do not consider it necessary to require any post-marketing studies or make use of other regulatory authorities for risk mitigation related to drug abuse and dependence.

### **6. Other Relevant Information**

3,4-DAP is a NME that is currently accepted for medical use in the European Union but not the U.S. Since 2009 there are no post marketing data available regarding its abuse potential and there is no information available regarding actual use or abuse in the community at large.

## **III. REFERENCES**

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### Clinical Inspection Summary

<b>Date</b>	December 4, 2018
<b>From</b>	Cheryl Grandinetti, Pharm.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
<b>To</b>	Michelle Mathers, R.P.M. Reiner Paine, MD, Clinical Reviewer Teresa Buracchio, M.D., Clinical Team Leader Billy Dunn, M.D., Division Director Division of Neurology Products
<b>NDA #</b>	209321
<b>Applicant</b>	Jacobus Pharmaceutical Company, Inc
<b>Drug</b>	Ruzurgi (3,4-dimanimopyridine)
<b>NME</b>	Yes
<b>Review Priority</b>	Priority
<b>Proposed Indication</b>	(b) (4) Lambert- Eaton myasthenia in patients (b) (4)
<b>Consultation Request Date</b>	August 29, 2018
<b>Summary Goal Date</b>	June 15, 2018
<b>Action Goal Date</b>	December 15, 2018
<b>PDUFA Date</b>	February 15, 2019

#### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Juel and Gordon-Smith, and the sponsor, Jacobus Pharmaceutical Company, Inc. were inspected in support of this NDA. During the sponsor inspection, significant data integrity concerns were identified with regard to the recording of the primary efficacy endpoint data (the triple-timed up and go [3TUG] test) by the independent central reviewer. OSI therefore recommended that DNP request the sponsor to re-read the 3TUG videos. Jacobus has committed to have all the 3TUG test videos re-read by a central reader (or multiple readers, if supported by adequate inter-rater reliability) and the data reanalyzed. The tables and listings using the re-read 3TUG test videos reportedly will be completed and submitted to FDA by December 17, 2018.

The final compliance classification of the inspections of Drs. Vern and Gordon-Smith was No Action Indicated (NAI). The final classification of the inspection of the sponsor, Jacobus Pharmaceutical Company, Inc, was VAI.

## II. BACKGROUND

Jacobus Pharmaceuticals Company, Inc. submitted this NDA to support the use of Ruzurgi (3,4-diaminopyridine) for [REDACTED] (b) (4) Lambert-Eaton Myasthenia in patients [REDACTED] (b) (4) Jacobus Pharmaceuticals Company, Inc received Orphan Drug designation for the use of 3,4-DAP in LEMS in 1990 and has been supplying Ruzurgi on a compassionate use basis for the past 25 years.

The key study supporting this application was Protocol JPC 3,4-DAPPER: “Inpatient Double-Blind, Placebo-Controlled Withdrawal Study of 3,4-Diaminopyridine Base (3,4-DAP) in Subjects with Known Lambert-Eaton Myasthenic Syndrome (LEMS)”

This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, withdrawal study in subjects with known clinically active LEMS who had been on a chronic stable dose of compassionate distribution Jacobus Ruzurgi (3,4-DAP) provided through FDA-approved individual investigator-held INDs.

*Subjects:* 52 subjects were screened, 32 subjects were randomized

*Sites:* 7 sites in the United States

*Study Initiation and Completion Dates:* First subject was screened on February 9, 2012; first subject was randomized on April 15, 2012; last subject was randomized on March 10, 2014; and last subject completed the study on March 14, 2014.

The objective of the study was to confirm the safety and to test the efficacy of Ruzurgi in subjects with known clinically active LEMS who had been on a chronic stable Ruzurgi dose (for at least 3 continuous months). The study design consisted of the following three consecutive stages:

- Stage I: Study subjects were admitted for 2.5 days of testing on their stable pre-study treatment regimen of Ruzurgi to establish each subject’s baseline and to determine eligibility to enter Stage II of the study
- Stage II: Study subjects were randomized (1:1 ratio) to one of two groups and received study drug in a blinded fashion:
  - Group A: Continuation of Ruzurgi
  - Group B: Tapered withdrawal of Ruzurgi
- Stage III: All subjects were discharged from the inpatient unit (after observation for 0.5 days or until the subject was deemed clinically stable) and received active tablets of Ruzurgi at the schedule and dose that the subjects used at home before entering the study.

The *primary efficacy endpoint* was the categorization of the degree of change in the 3TUG (last observation at the theoretical "peak drug effect", i.e., 2 hours post dose) upon withdrawal of active medication (Stage II) when compared with time matched average of the

3TUG assessments during Stage I, as assessed by an independent central reviewer who was blinded to the treatment and to the date, time, and sequence of the actual 3TUG test.

During each stage, the clinical investigator and site personnel conducted and videotaped the 3TUG testing 6 times daily, 15 minutes before and 2 hours after the morning, afternoon, and evening dose. The site's timed assessment was used as a primary efficacy variable when the videos malfunctioned or were of poor quality and for missing values.

The *secondary efficacy endpoint* was the self-assessment scale for LEMS-related weakness (W-SAS) obtained during Stage II (final assessment or time of rescue medication (pre-dose) whichever came first). During each study stage, W-SAS self-assessment was done three times daily, 2 hours after the morning, afternoon, and evening dose (or at bedtime, if appropriate).

**Rationale for Site Selection**

The clinical sites were chosen primarily based on numbers of enrolled subjects, treatment effect, and prior inspectional history.

**III. RESULTS (by site):**

Site / Name of CI/ Address	Protocol #/ # of Subjects Enrolled	Inspection Dates	Classification
Site: DUKE  <b>Vern Juel, M.D.</b> Duke University Medical Center Department of Medicine, Div. of Neurology 200 Trent Drive, Clinic 11, Rook 1255, Box 3403 Durham, NC 27710 Phone: 919-684-4044 Fax: 919-660-3853 Email: vern.juel@duke.edu	JPC 3,4-DAPPER  Subjects: 9	15-18 Oct 2018	NAI
Site: UUMC  <b>A. Gordon Smith, M.D., FAAN</b> University of Utah School of Medicine 30 North 1900 East, SOM 3R242 Salt Lake City, UT 84132 Phone: 801-585-1737 Fax: 801-585-2054 Email: gordon.smith@hsc.utah.edu	JPC 3,4-DAPPER  Subjects: 9	8-14 Nov 2018	NAI

Sponsor <b>Jacobus Pharmaceutical Company, Inc</b> 37 Cleveland Lane P.O. Box 5290 Princeton, NJ 08540 Contact: Laura R. Jacobus Phone: 609-921-7447, ex 207 Fax: 609-799-1176 Email: laura.jacobus@jacobus-pharmaceutical.com	JPC 3,4-DAPPER	15-23 Oct 2018	VAI
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Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable

**1. Vern Juel, M.D**

At this site for Protocol JPC 3,4-DAPPER, 13 subjects were screened and 9 were randomized, all of whom completed the study. Study and subject source records were reviewed during the inspection, including, but not limited to, IRB documentation and source records for the primary and secondary efficacy endpoints, drug accountability, informed consents, subject study visits, randomization, and adverse events.

There was no evidence of under-reporting of adverse events. All 3TUG test assessments performed by the clinical investigator at the site and all secondary efficacy data points were compared against the data listings provided by the sponsor. No discrepancies were noted.

**2. A. Gordon Smith, M.D.**

At this site for Protocol JPC 3,4-DAPPER, 7 subjects were screened, 5 were enrolled, and 4 subjects completed the study. One subject was rescued prior to completing the full 6 days. . Study and subject source records were reviewed during the inspection, including, but not limited to, financial disclosure, inclusion and exclusion eligibility criteria, screening procedures, informed consent forms, IRB documentation, randomization, adverse events, primary and secondary efficacy endpoints, drug accountability, subject study visits, and monitoring visits.

All 3TUG tests assessment performed by the clinical investigator at the site and all secondary efficacy data points were compared against the data listings provided by the sponsor. No discrepancies were noted.

However, the clinical investigator failed to report one adverse event to the sponsor. On 5/22/2012, Subject (b) (6) experienced a desaturation to 86%, which resulted in

the subject receiving oxygen.

*Reviewer's Comment: While no Form FDA 483 was issued for failing to report this adverse event, the FDA field investigator discussed this finding with Dr. Smith during the closeout meeting. Dr. Smith acknowledged that he should have reported the desaturation as an adverse event and committed to improvements in the future.*

### **3. Jacobus Pharmaceutical Company, Inc**

The inspection of Jacobus Pharmaceutical Company, Inc focused on the control, oversight, and management of Protocol JPC 3,4-DAPPER. The inspection focused on the adequacy of monitoring (monitoring plans and corrective actions taken by the sponsor), protocol deviations related to key safety and efficacy endpoints, contracts and transfer of obligations, quality management, data control and handling, adverse event evaluation and reporting, and training of monitors and clinical sites.

Clinical Monitoring was conducted by the CRO, (b) (4); however, there were no contracts that listed the responsibilities delegated to the CRO. It was noted during the inspection that Jacobus has no formal procedures for selecting clinical investigators and monitors and that they conduct no pre-qualification audits of vendors.

A Form FDA-483 was issued at the end of the inspection, which included an observation with regard to 70 data discrepancies. Specifically, the clinical investigation sites recorded all laps of the 3TUG Test on video and then entered their timed assessments (during the live session) and uploaded the actual videos in a part 11 compliant electronic data capture system (EDC system). The videos were then reviewed at a later date by an independent central reviewer who was blinded to the treatment as well as to the date and time and/or sequence of the actual 3TUG Test. It was the central reviewer's assessment that was primarily used for the primary efficacy endpoint.

Seventy data discrepancies were noted during the inspection when comparing the central reader's assessments as recorded on an Excel spreadsheet (which was the source) with the data listings submitted to the FDA. After the inspection, Jacobus identified 9 additional data entry errors (for a total of 79). The 79 data discrepancies occurred when the central reviewer incorrectly transcribed some of the assessment times from the Excel spreadsheet to the EDC system. The 79 data discrepancies were identified by the sponsor and are included as an attachment to this report.

*Reviewer's Comment: The 79 data entry errors represent a small percentage of the total 11,073 data entries in the EDC system for the primary efficacy endpoint. However, the Excel spreadsheet that was used to capture the central reviewer's initial assessment raises larger data integrity concerns. The spreadsheet was neither password-protected nor maintained as a fixed document as source data, over time, were being entered in the spreadsheet. In addition, there were no audit trails available to track any changes made to the spreadsheet after initial entries were made by the central reviewer, and the central reviewer did not transcribe data contemporaneously from the spreadsheet to the part 11 compliant EDC*

*system. Because of this, it is not possible to know whether the Excel spreadsheet accurately represents the central reader's initial entries. Therefore, OSI recommended, in an email dated October 23, 2018, that DNP request the sponsor to re-read the 3TUG videos.*

*The Division informed Jacobus of these concerns by email on October 25, 2018. On October 29, 2018, Jacobus committed to have all the 3TUG videos re-read by a central reader (or multiple readers, if supported by adequate inter-rater reliability) and the data reanalyzed. Per the email communication from Jacobus dated November 19, 2018, it is anticipated that the tables and listings using the re-read 3TUG videos will be completed and submitted by December 17, 2018.*

{ See appended electronic signature page }

Cheryl Grandinetti, Pharm.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Phillip Kronstein, M.D. Team Leader,  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Kassa Ayalew, M.D., M.P.H Branch Chief  
Good Clinical Practice Assessment Branch  
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cc:

Central Doc. Rm. NDA 208078  
DNP /Project Manager/Michelle Mathers  
DNP /Medical Officer/Reiner Paine  
DNP/ Clinical Team Leader/ Teresa Buracchio  
DNP/Division Director/Billy Dunn  
OSI /Office Director/David Burrow  
OSI/DCCE/Division Director/Ni Khin

OSI/DCCE/Branch Chief/Kassa Ayalew  
OSI/DCCE/Team Leader/Phillip Kronstein  
OSI/DCCE/GCP Reviewer/Cheryl Grandinetti  
OSI/ GCP Program Analysts/Yolanda Patague  
OSI/Database Project Manager/Dana Walters

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CHERYL A GRANDINETTI  
12/04/2018

PHILLIP D KRONSTEIN  
12/04/2018

KASSA AYALEW  
12/07/2018

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MEMORANDUM  
REVIEW OF REVISED LABEL AND LABELING  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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Date of This Memorandum: November 26, 2018  
Requesting Office or Division: Division of Neurology Products (DNP)  
Application Type and Number: NDA 209321  
Product Name and Strength: Ruzurgi (amifampridine) tablets, 10 mg  
Applicant/Sponsor Name: Jacobus Pharmaceutical Company, Inc.  
FDA Received Date: November 14, 2018  
OSE RCM #: 2017-2500-1  
DMEPA Safety Evaluator: Briana Rider, PharmD  
DMEPA Team Leader: Lolita White, PharmD

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## 1 PURPOSE OF MEMORANDUM

Division of Neurology Products (DNP) requested that we review the revised container label for Ruzurgi (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>a</sup>

## 2 CONCLUSION

The revised container label for Ruzurgi is acceptable from a medication error perspective. We have no further recommendations at this time.

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<sup>a</sup> Rider B. Label and Labeling Review for Ruzurgi (NDA 209321). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 30. RCM No.: 2018-2500.

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BRIANA B RIDER  
11/27/2018

LOLITA G WHITE  
11/28/2018

LABEL AND LABELING REVIEW  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

\*\*\* This document contains proprietary information that cannot be released to the public\*\*\*

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Date of This Review:	October 30, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 209321
Product Name and Strength:	Ruzurgi (amifampridine) tablets, 10 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Jacobus Pharmaceutical Company, Inc.
FDA Received Date:	June 15, 2018
OSE RCM #:	2017-2500
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

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## 1 REASON FOR REVIEW

This review is in response to a request from the Division of Neurology Products (DNP) to review the proposed labels and labeling for Ruzurgi (amifampridine) for areas of vulnerability that could lead to medication errors.

### 1.1 REGULATORY HISTORY

Jacobus Pharmaceutical Company, Inc. submitted NDA 209321 on December 5, 2017. The Division of Neurology Products (DNP) subsequently sent a Refuse to File (RTF) communication to Jacobus Pharmaceutical Company, Inc. on January 31, 2018.

Jacobus Pharmaceutical Company, Inc. resubmitted NDA 209321 on June 15, 2018.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed Prescribing Information (PI) labeling and container label identified areas which may be improved to decrease risk of medication error.

### Prescribing Information

- The Dosage & Administration Section of the highlights of PI (HPI) and full PI (FPI) can be improved to increase the prominence of critical dosing information, and minimize the risk of confusion and possible medication errors.
- The readability of the How Supplied/Storage and Handling information in Section 16 of the full PI can be improved to increase the prominence of critical information.

- Section 16 of the FPI contains the error prone symbol, <. The symbols, > and <, appear on ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations because these symbols are often mistaken as the opposite of intended. <sup>a</sup>
- [REDACTED] (b) (4)  
Because tablets may be split, we are concerned that the expression, X tablets, may lead to confusion and possible wrong dose medication errors.

### Container Label

- The net quantity statement appears in close proximity to the product strength and may contribute to confusion of product strength.
- The expiration date format is not consistent with FDA-recommended formats and may be prone to medication error.
- The principal display panel is visually cluttered and takes away from important product information.
- The proprietary name is currently denoted by the placeholder "TRADENAME®". The proposed proprietary name, Ruzurgi, was found conditionally acceptable on September 5, 2018.
- The established name is denoted as [REDACTED] (b) (4). However, the established name should be denoted as "amifampridine".
- The established name and the finished dosage form are not displayed in accordance with our current draft Guidance for Industry: "Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors"

## 4 CONCLUSION & RECOMMENDATIONS

We identified areas in the labels and labeling that are vulnerable to medication error and we recommend revision to increase prominence of critical information and to ensure safe use and handling of the proposed product. We provide recommendations in section 4.1 and 4.2 and recommend their implementation prior to approval of this NDA application.

### 4.1 RECOMMENDATIONS FOR THE DIVISION

#### A. General Recommendations for the Prescribing Information (PI)

1. Numeric doses are not consistently expressed with a corresponding unit of measure throughout the PI. We are concerned that the numeric dose values could be misinterpreted and should therefore be revised for clarity. We recommend that throughout the PI, each recommended dose have a corresponding unit of measure after the numeric value [REDACTED] (b) (4)

<sup>a</sup> ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2018 OCT 18]. Available from: <https://www.ismp.org/recommendations/error-prone-abbreviations-list>

2. The proprietary name is currently denoted by the placeholder "TRADENAME". The proposed proprietary name, Ruzurgi, was found conditionally acceptable on September 5, 2018. Remove the placeholder "TRADENAME" and replace with the conditionally acceptable name, Ruzurgi.
- B. Highlights of Prescribing Information (HPI)
1. Dosage and Administration (D&A) Section
    - a. The D&A Section of the HPI lacks the maximum single dose and maximum daily dose for pediatric patients. We are concerned that the lack of this information may lead to wrong dose medication errors. We recommend adding the maximum single dose and maximum daily dose for pediatric patients to the D&A Section of the HPI, or add a statement that refers the reader to the FPI for pediatric dosing information.
    - b. The readability of the dosing information can be improved to increase the prominence of critical dosing information. We recommend the third bullet point in the D&A Section of the HPI be revised to read:
      - Dose is not to exceed a maximum daily dose of (b) (4) 100 mg per day for pediatric patients
      - The maximum single dose is 30 mg (b) (4)
    - c. We note the dose titration instructions state (b) (4). However, the statement does not indicate how frequently the dose should be adjusted. We recommend revising the statement to indicate how frequently the dose may be adjusted (e.g., daily, weekly), for clarity.
- C. Full Prescribing Information (FPI)
1. Section 2: Dosage and Administration Section
    - a. See Recommendation B.1.c. above.
    - b. The frequency of administration within Section 2.1 (b) (4) the FPI lacks clarity because it informs the reader the total daily dose may be administered (b) (4). We recommend this section be revised for clarity to minimize the risk of wrong frequency of administration medication errors.
    - c. The readability of the dosing information in Section 2.1 (b) (4) of the FPI can be improved to increase the prominence of critical dosing information. For example, consider revising to a bulleted format to read:
      - The recommended starting dose of RUZURGI is (b) (4) taken orally 2 to 3 times per day.
      - The dose can be increased by 5 mg to 10 mg every [insert frequency].

(b) (4)

- The maximum single dose is 30 mg

(b) (4)

Section 2.1 (b) (4) the FPI should be revised for clarity to minimize the risk of confusion and wrong dose medication errors.

- f. The readability of the dosing information in Section 2.2 (b) (4) (*Pediatric Patients*) of the FPI can be improved to increase the prominence of critical dosing information. For example, consider revising to read:

(b) (4)

- g. Within (b) (4) Section 2.2 (*Administration Instructions*) of the FPI, the maximum single dose and maximum daily dose may be misleading (b) (4). To minimize the risk of wrong dose medication errors, (b) (4)

## 2. Section 16: How Supplied/Storage and Handling Section

- a. The readability of the How Supplied/Storage and Handling information in Section 16 of the FPI can be improved to increase the prominence of critical information. We recommend adding the following sub-headings to improve readability:
- 16.1 How Supplied
  - 16.2 Storage and Handling
- b. As currently presented, the package configuration (i.e., bottles of 100 tablets) and NDC number (i.e., NDC 49938-110-01) appear immediately after the storage and handling information. We recommend the package configuration and NDC number be relocated to the section 16.1 How Supplied to improve readability.
- c. We note Section 16 of the FPI includes the error-prone symbol, < (i.e., <25°C and <77°F). The symbols, > and <, appear on ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations<sup>b</sup> because these

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<sup>b</sup> ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2018 OCT 18]. Available from: <https://www.ismp.org/recommendations/error-prone-abbreviations-list>

symbols are often mistaken as the opposite of intended. Consider, replacing the symbol "<" with its intended meaning (i.e., less than 25°C and less than 77°F) to prevent misinterpretation and confusion.

3. Section 17: Patient Counseling Information

- a. We note the "TRADENAME Dosing" subsection of Section 17 (*Patient Counseling Information*) states:

(b) (4)

#### 4.2 RECOMMENDATIONS FOR JACOBUS PHARMACEUTICAL COMPANY, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. The net quantity statement appears in close proximity to the product strength and may contribute to confusion of product strength. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel.
2. The expiration date placeholder is denoted as: XX-XXXX. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
3. The statement (b) (4) clutters the principal display panel (PDP) and takes away from important product information. Consider moving this information to a side or back panel or removing the statement all together to maximize the prominence of other important information on the PDP. See *Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*
4. The statement (b) (4) clutters the principal display panel (PDP) and takes away from the other important

product information. Consider replacing the text [REDACTED] (b) (4) with "Rx only" on the PDP to maximize the prominence of other important information on the PDP.

5. The proprietary name is currently denoted by the placeholder "TRADENAME®". The proposed proprietary name, Ruzurgi, was found conditionally acceptable on September 5, 2018. Remove the placeholder "TRADENAME®" and replace with the conditionally acceptable name, Ruzurgi.
6. The established name is denoted as [REDACTED] (b) (4) on the container label. Revise the established name from [REDACTED] (b) (4) to "amifampridine".
7. The layout of the established name and the finished dosage form is not consistent with the presentation of the proprietary name, established name, strength, and dosage form for drug products.<sup>c</sup> The presentation should be reformatted to list the established name in parentheses followed by the dosage form and strength as follows:

Ruzurgi		Ruzurgi
(amifampridine)	OR	(amifampridine) Tablets
Tablets		10 mg
10 mg		

---

<sup>c</sup> Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 336-342). Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ruzurgi received on June 15, 2018 from Jacobus Pharmaceutical Company, Inc. .

Table 2. Relevant Product Information for Ruzurgi	
Initial Approval Date	N/A
Active Ingredient	amifampridine
Indication	(b) (4) Lambert-Eaton Myasthenia (LEM) in patients (b) (4)
Route of Administration	oral
Dosage Form	tablets
Strength	10 mg
Dose and Frequency	(b) (4)
How Supplied	Bottles of 100 tablets
Storage	Store in a refrigerator (b) (4) 46°F. Protect from moisture and light. (b) (4)
Container Closure	(b) (4)

## APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 18, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, NDA 209321 AND amifampridine AND 3,4-Diaminopyridine. Our search identified did not identify any previous reviews.

## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>d</sup> along with postmarket medication error data, we reviewed the following Ruzurgi labels and labeling submitted by Jacobus Pharmaceutical Company, Inc. .

- Container label received on June 15, 2018
- Prescribing Information (Image not shown) received on June 15, 2018

### G.2 Label and Labeling Images

#### Container Label

(b) (4)



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<sup>d</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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BRIANA B RIDER  
10/30/2018

LOLITA G WHITE  
10/30/2018

## Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA
Submission Number	209321
Submission Date	12/7/2017
Date Consult Received	8/8/2018
Clinical Division	DNP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT review dated 01/22/2014 in DARRTS;
- Proposed product [label](#) (Submission 0004); and
- [Highlights of clinical pharmacology and cardiac safety](#).

### 1 SUMMARY

No significant QTc prolongation effect of RUZURGI (3,4-diaminopyridine or 3,4-DAP) 120 mg was detected in this QT assessment.

The effect of RUZURGI was evaluated in Study JPC 3,4-DAP.TQT. The dose evaluated was 120 mg in 4 equal doses of 30 mg every 4 hours, which is the maximum tested dose (b) (4) The data from Study JPC 3,4-DAP.TQT was analyzed using central tendency as the primary analysis, which did not suggest that RUZURGI is associated with significant QTc prolonging effect (refer to section 4.3) - see Table 1 for overall results. The findings of this analysis are further supported by categorical analysis (section 4.4) and exposure-response analysis (section 4.5).

**Table 1: The Point Estimates and the 90% CIs (FDA Analysis)**

ECG parameter	Treatment	Time	$\Delta\Delta$ (ms)	90% CI (ms)
<b>Combined Analysis</b>				
QTc	3,4-DAP 120 mg	15	5.0	(3.2, 6.9)

The Slow Metabolizer phenotype group provides high clinical exposure in subjects who are taking 30 mg RUZURGI at 4-hour intervals for no more than 4 doses per day. In clinical use, 3,4-DAP exposure may exceed that observed in this TQT study if RUZURGI is administered on a shorter dosing interval in the fasted state.

#### 1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

#### 1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

## 2 PROPOSED LABEL

Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

### 12.2 PHARMACODYNAMICS

#### Cardiac Electrophysiology

(b) (4)

In vitro, TRADENAME did not inhibit the human ether-à-go-go-related gene ion channel.

*We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.*

*We propose to specify the dose level and dosing interval in the TQT study. Because the product label does not specify dosing interval, drug exposure in clinical use may exceed what was observed in the TQT study (e.g. when the drug is administered on a shorter dosing interval in the fasted state). Drug effect on heart rate and QTc beyond the observed exposure range could not be determined.*

### 12.5 PHARMACOGENOMICS

(b) (4)

## 3 SPONSOR’S SUBMISSION

### 3.1 OVERVIEW

3,4-diaminopyridine is pyridine derivative and is being developed for the treatment of Lambert Eaton Syndrome. The drug has been used in Europe for more than 30 years. It was approved in the European Union before 2014. 3,4-DAP blocks voltage-dependent potassium channels but no effects on hERG potassium current were reported for 3,4-DAP or its metabolite.

The QT-IRT reviewed the protocol and QT assessment plan previously under IND 54313 (DARRTS 01/22/2014). Major comments were to administer the drug in the fasted state,

to collect additional ECG data at 30 min post-dose, to apply adjustment of multiple comparisons, to included categorical analysis of HR, PR, and QRS. Sponsor has addressed these comments based on information provided in the TQT study report.

Additional changes, including additional PK/ECG samples at 1.5 and 13.5 hours since first dose, were made after the previous protocol review. (b) (4)

The selection of study dose and PK/ECG sampling schedule remain acceptable. There is no major change to QT assessment strategy (i.e. primary analysis is IUT based on QTcF). We refer the reader to Appendix 5.1 for more information about current study protocol and QT assessment plan.

## **3.2 SPONSOR'S RESULTS**

### **3.2.1 Central tendency analysis**

The results of the reviewer's analysis are similar to the sponsor's results. Both FDA's analysis and sponsor's analysis confirm that the largest upper bound of 90% CI for  $\Delta\Delta\text{QTcF}$  is below 10 ms. Please see section 4.3 for additional details.

#### **3.2.1.1 Assay Sensitivity**

The results of the reviewer's analysis are similar to the sponsor's results. Both FDA's analysis and sponsor's analysis confirm that the assay sensitivity was established. FDA analysis is presented in section 4.3 for additional details.

##### **3.2.1.1.1 QT bias assessment**

Not applicable.

### **3.2.2 Categorical Analysis**

FDA analysis results are consistent with the sponsor's results. Please see section 4.4 for additional details.

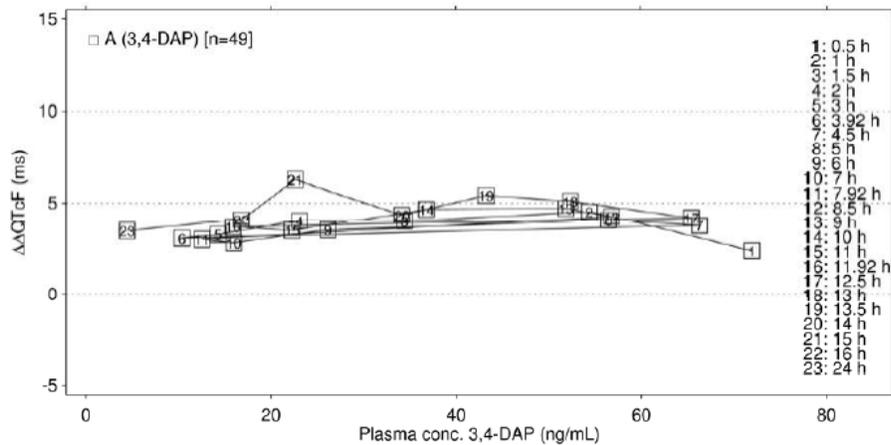
### **3.2.3 Safety Analysis**

No deaths, serious or severe events were reported and no subjects discontinued due to an AE during the study.

### **3.2.4 Exposure-Response Analysis**

Sponsor concluded a lack of significant delayed effect between DAP concentration and  $\Delta\Delta\text{QTcF}$  as all but one mean value (at 15 hours post first dose) were aligned and there were no signs of a larger loop in Figure 1.

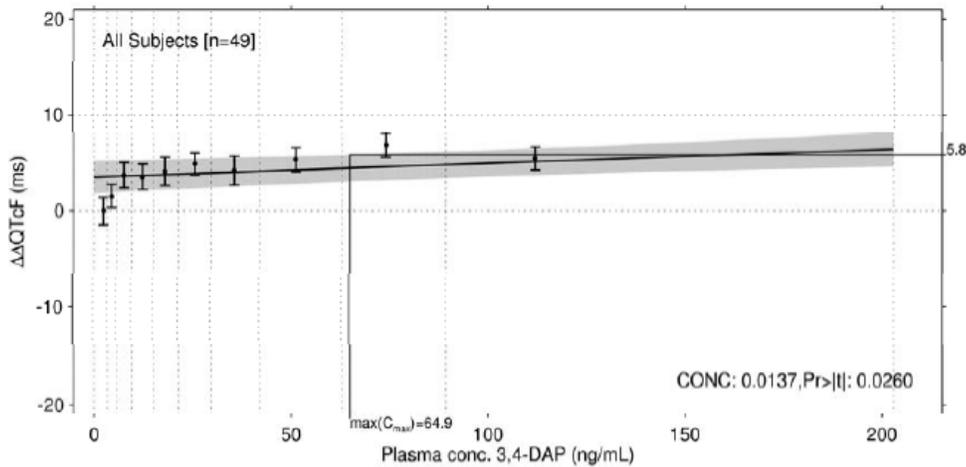
**Figure 1. Mean  $\Delta\Delta\text{QTcF}$  versus Mean Plasma Concentration of DAP**



Source: JPC 3,4-DAP.TQT study report, Figure 11-17

Sponsor's analysis suggested a small but statistically significant increase in slope of 0.014 ms/[ng/mL]. The upper 2 sided 90% CI of the estimated QTcF prolongation at the maximum mean plasma concentration was 5.8 ms. At low plasma concentration the relationship between the  $\Delta\Delta\text{QTcF}$  and plasma concentration showed a deviation from the linear model as the QTcF changes were smaller than predicted.

**Figure 2.  $\Delta\Delta\text{QTcF}$  versus Plasma Concentration of DAP: Linear Mixed Effects Model**



Source: JPC 3,4-DAP.TQT study report, Figure 11-19

Sponsor conducted similar analysis for 3,4-Ac-DAP and concluded a lack of significant exposure-response relationship between QTcF and metabolite concentrations.

The results of the reviewer's analysis with linear mixed effect modeling are similar to the sponsor's results. However, this analysis has major limitation of a delay between  $\Delta\Delta\text{QTcF}$  and DAP exposure. Please see section 4.5 for additional details.

## 4 REVIEWERS' ASSESSMENT

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

The sponsor used QTcF for the primary analysis, which is acceptable as no significant increases or decreases in heart rate (i.e. mean < 10 bpm) were observed (see Sections 4.3.1.3).

### 4.2 ECG ASSESSMENTS

#### 4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

#### 4.2.2 QT bias assessment

Not applicable.

### 4.3 CENTRAL TENDENCY ANALYSIS

#### 4.3.1 QTc

The statistical reviewer used mixed model to analyze the  $\Delta$ QTcF effect. The model includes treatment, time, sequence, period, treatment by time-point interaction, baseline QTcF as fixed effects and Subject(sequence) as a random effect. Compound symmetry covariance structure was used. The analysis results are listed in Table 2. The largest upper bounds of the 2-sided 90% CI for the mean difference between 3,4-DAP 120 mg and placebo was 6.9 ms. Figure 3: Mean and 90% CI  $\Delta\Delta$ QTcF Time course (unadjusted CIs). Figure 3 displays the time profile of  $\Delta\Delta$ QTcF for different treatment groups.

**Table 2: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for 3,4-DAP 120 mg**

Time (hrs)	Treatment Group			
	3,4-DAP 120 mg			
	$\Delta$ QTcF	Placebo	$\Delta\Delta$ QTcF	
LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	
0.5	-1.3	-2.2	0.9	(-0.9, 2.8)
1	1.5	-1.6	3.2	(1.3, 5.1)
1.5	1.3	-1.3	2.6	(0.8, 4.5)
2	0.1	-2.5	2.6	(0.7, 4.5)
3	-0.1	-1.8	1.7	(-0.2, 3.6)
3.92	0.2	-1.4	1.6	(-0.3, 3.5)
4.5	-0.0	-2.4	2.3	(0.5, 4.2)
5	2.3	-0.2	2.5	(0.6, 4.4)
6	-0.1	-2.4	2.3	(0.4, 4.2)
7	-4.2	-5.7	1.5	(-0.4, 3.4)
7.92	-5.3	-6.9	1.7	(-0.2, 3.5)
8.5	-6.1	-9.2	3.0	(1.1, 4.9)
9	-4.7	-7.9	3.3	(1.4, 5.1)
10	0.4	-3.2	3.5	(1.7, 5.4)
11	-3.9	-6.4	2.5	(0.6, 4.4)
11.92	-3.5	-5.8	2.3	(0.4, 4.2)
12.5	-4.6	-7.4	2.9	(1.0, 4.8)

	Treatment Group			
	3,4-DAP 120 mg			
	$\Delta$ QTcF	Placebo	$\Delta\Delta$ QTcF	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
13	-3.0	-6.9	3.8	(1.9, 5.7)
13.5	-1.4	-5.5	4.1	(2.2, 6.0)
14	-0.6	-3.6	3.0	(1.1, 4.8)
15	2.1	-3.0	5.0	(3.2, 6.9)
16	3.2	0.4	2.8	(0.9, 4.7)
24	-0.5	-2.5	2.1	(0.2, 3.9)

#### 4.3.1.1 Subgroup Analysis

The same mixed model to analyze the  $\Delta$ QTcF effect was performed by metabolizer subgroup (Intermediate/Rapid Metabolizer vs. Slow Metabolizer). Results are presented in Table 3 and Table 4. The largest upper bounds of the 2-sided 90% CI for the mean difference between 3,4-DAP 120 mg and placebo are below 10 ms in both subgroups.

**Table 3: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for 3,4-DAP 120 mg – Intermediate/Rapid Metabolizer Group**

	Treatment Group			
	3,4-DAP 120 mg			
	$\Delta$ QTcF	Placebo	$\Delta\Delta$ QTcF	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-1.8	-2.4	0.6	(-1.9, 3.1)
1	1.8	-2.2	3.9	(1.4, 6.5)
1.5	1.0	-1.7	2.7	(0.2, 5.2)
2	-0.8	-2.5	1.7	(-0.9, 4.2)
3	-1.4	-2.8	1.4	(-1.1, 4.0)
3.92	-1.4	-1.5	0.1	(-2.5, 2.6)
4.5	-1.2	-2.1	0.9	(-1.6, 3.5)
5	2.4	-0.6	2.9	(0.4, 5.5)
6	-0.4	-1.3	0.9	(-1.6, 3.5)
7	-3.1	-3.7	0.6	(-2.0, 3.1)
7.92	-4.0	-5.4	1.3	(-1.2, 3.9)
8.5	-6.2	-8.1	1.9	(-0.7, 4.4)
9	-4.6	-7.4	2.8	(0.3, 5.4)
10	-0.4	-3.0	2.6	(0.0, 5.1)
11	-5.1	-6.1	1.0	(-1.5, 3.6)
11.92	-4.2	-5.4	1.2	(-1.3, 3.8)
12.5	-4.8	-6.6	1.8	(-0.7, 4.4)
13	-3.9	-6.5	2.6	(0.0, 5.1)
13.5	-3.6	-4.8	1.2	(-1.4, 3.7)
14	-2.6	-3.1	0.5	(-2.1, 3.0)
15	0.3	-3.5	3.8	(1.3, 6.4)
16	1.0	-0.0	1.0	(-1.5, 3.6)
24	-1.5	-2.2	0.7	(-1.8, 3.3)

**Table 4: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for 3,4-DAP 120 mg - Slow Metabolizer Group**

	Treatment Group			
	3,4-DAP 120 mg			
	$\Delta$ QTcF	Placebo	$\Delta\Delta$ QTcF	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-1.1	-2.0	1.0	(-1.8, 3.8)
1	1.1	-1.5	2.6	(-0.2, 5.4)
1.5	1.2	-1.2	2.4	(-0.4, 5.2)
2	1.2	-3.0	4.2	(1.4, 7.0)
3	0.8	-0.8	1.6	(-1.2, 4.4)
3.92	2.1	-1.8	3.9	(1.1, 6.7)
4.5	1.3	-3.6	4.9	(2.1, 7.7)
5	3.0	-0.1	3.1	(0.4, 5.9)
6	0.4	-3.2	3.5	(0.8, 6.3)
7	-5.5	-7.3	1.8	(-1.0, 4.6)
7.92	-6.6	-8.3	1.8	(-1.0, 4.6)
8.5	-6.5	-10.2	3.7	(0.9, 6.5)
9	-4.6	-8.4	3.8	(1.0, 6.6)
10	0.7	-3.6	4.3	(1.5, 7.1)
11	-3.1	-7.0	3.9	(1.1, 6.7)
11.92	-3.3	-7.2	3.9	(1.1, 6.7)
12.5	-4.6	-8.7	4.2	(1.4, 7.0)
13	-2.4	-8.0	5.6	(2.8, 8.4)
13.5	0.1	-6.5	6.6	(3.8, 9.4)
14	0.7	-4.5	5.2	(2.4, 8.0)
15	3.4	-3.2	6.6	(3.8, 9.4)
16	4.7	-0.3	4.9	(2.1, 7.7)
24	0.1	-3.0	3.1	(0.3, 5.8)

#### 4.3.1.2 Assay sensitivity

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in **Error! Reference source not found.** The largest unadjusted 90% lower confidence interval is 11.0 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 10.3 ms, which indicates that at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

**Table 5: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Moxifloxacin**

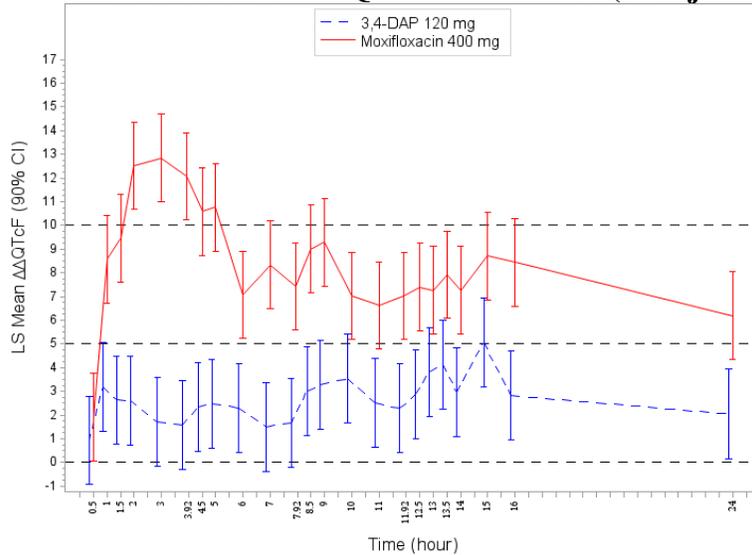
	Treatment Group				
	Moxifloxacin 400 mg				
	$\Delta$ QTcF	Placebo	$\Delta\Delta$ QTcF		
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	97.5% CI (ms)
0.5	-0.3	-2.2	1.9	(0.1, 3.7)	(-0.6, 4.4)
1	6.9	-1.6	8.6	(6.7, 10.4)	(6.1, 11.1)
1.5	8.2	-1.3	9.5	(7.6, 11.3)	(7.0, 12.0)
2	10.0	-2.5	12.5	(10.7, 14.4)	(10.0, 15.0)

Treatment Group					
Moxifloxacin 400 mg					
Time (hrs)	$\Delta$ QTcF	Placebo	$\Delta\Delta$ QTcF		
	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	97.5% CI (ms)
3	11.1	-1.8	12.8	(11.0, 14.7)	(10.3, 15.4)
3.92	10.6	-1.4	12.1	(10.2, 13.9)	(9.6, 14.6)
4.5	8.2	-2.4	10.6	(8.7, 12.4)	(8.1, 13.1)
5	10.6	-0.2	10.8	(8.9, 12.6)	(8.3, 13.3)
6	4.6	-2.4	7.1	(5.2, 8.9)	(4.6, 9.6)
7	2.6	-5.7	8.3	(6.5, 10.2)	(5.8, 10.9)
7.92	0.5	-6.9	7.4	(5.6, 9.3)	(4.9, 9.9)
8.5	-0.1	-9.2	9.0	(7.2, 10.9)	(6.5, 11.5)
9	1.4	-7.9	9.3	(7.4, 11.1)	(6.8, 11.8)
10	3.9	-3.2	7.0	(5.2, 8.9)	(4.5, 9.5)
11	0.2	-6.4	6.6	(4.8, 8.5)	(4.1, 9.1)
11.92	1.2	-5.8	7.0	(5.2, 8.9)	(4.5, 9.6)
12.5	-0.0	-7.4	7.4	(5.6, 9.3)	(4.9, 9.9)
13	0.4	-6.9	7.3	(5.4, 9.1)	(4.7, 9.8)
13.5	2.5	-5.5	7.9	(6.1, 9.8)	(5.4, 10.4)
14	3.7	-3.6	7.3	(5.4, 9.1)	(4.8, 9.8)
15	5.7	-3.0	8.7	(6.9, 10.6)	(6.2, 11.3)
16	8.8	0.4	8.4	(6.6, 10.3)	(5.9, 11.0)
24	3.7	-2.5	6.2	(4.3, 8.0)	(3.7, 8.7)

\* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

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

Figure 3: Mean and 90% CI  $\Delta\Delta$ QTcF Time course (unadjusted CIs).



### 4.3.2 HR

The same statistical analysis was performed on HR. The point estimates and the 90% confidence intervals are presented in Table 6. The largest upper bounds of the 2-sided 90% CI for the mean difference between 3,4-DAP 120 mg and placebo was 2.2 bpm.

**Table 6: Mean and 90% CI  $\Delta\Delta$ HR Time Course**

	Treatment Group			
	3,4-DAP 120 mg			
	$\Delta$ HR	Placebo	$\Delta\Delta$ HR	
Time (hrs)	LS Mean (bpm)	LS Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)
0.5	-2.1	-1.7	-0.4	(-2.0, 1.1)
1	-4.5	-2.2	-2.3	(-3.8, -0.7)
1.5	-4.2	-1.5	-2.7	(-4.2, -1.2)
2	-2.8	-2.5	-0.4	(-1.9, 1.2)
3	-1.2	-1.8	0.6	(-0.9, 2.2)
3.92	-0.8	-0.6	-0.3	(-1.8, 1.3)
4.5	-2.1	-1.2	-0.9	(-2.4, 0.6)
5	-3.6	-0.8	-2.8	(-4.3, -1.3)
6	6.8	8.9	-2.1	(-3.6, -0.5)
7	8.3	8.0	0.3	(-1.2, 1.9)
7.92	6.7	7.2	-0.5	(-2.0, 1.0)
8.5	3.2	4.5	-1.4	(-2.9, 0.1)
9	1.3	4.1	-2.9	(-4.4, -1.4)
10	5.1	7.2	-2.1	(-3.6, -0.6)
11	7.8	8.6	-0.8	(-2.3, 0.7)
11.92	7.9	9.0	-1.1	(-2.6, 0.4)
12.5	3.5	6.5	-3.1	(-4.6, -1.6)
13	2.7	5.9	-3.2	(-4.7, -1.7)
13.5	2.1	4.3	-2.1	(-3.6, -0.6)
14	2.3	4.2	-2.0	(-3.5, -0.4)
15	2.5	2.4	0.1	(-1.4, 1.7)
16	2.0	1.7	0.3	(-1.2, 1.8)
24	5.3	5.1	0.2	(-1.3, 1.7)

### 4.3.3 PR

The same statistical analysis was performed on PR intervals. The point estimates and the 90% confidence intervals are presented in Table 7. The largest upper bounds of the 2-sided 90% CI for the mean difference between 3,4-DAP 120 mg and placebo was 2.8 ms.

**Table 7: Mean and 90% CI  $\Delta\Delta$ PR Time Course**

	Treatment Group			
	3,4-DAP 120 mg			
	$\Delta$ PR	Placebo	$\Delta\Delta$ PR	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-0.5	0.3	-0.8	(-2.5, 0.9)
1	-3.8	-0.6	-3.2	(-4.9, -1.5)
1.5	-2.7	-1.0	-1.7	(-3.4, -0.0)
2	-0.8	-1.8	1.1	(-0.6, 2.8)
3	-2.3	-2.2	-0.1	(-1.8, 1.6)

	Treatment Group			
	3,4-DAP 120 mg			
	$\Delta$ PR	Placebo	$\Delta\Delta$ PR	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
3.92	-2.4	-2.5	0.0	(-1.6, 1.7)
4.5	-2.2	-2.0	-0.3	(-2.0, 1.4)
5	-4.2	-3.0	-1.2	(-2.9, 0.5)
6	-4.3	-4.3	-0.1	(-1.8, 1.6)
7	-5.2	-5.9	0.7	(-0.9, 2.4)
7.92	-5.6	-6.2	0.5	(-1.2, 2.2)
8.5	-6.0	-5.7	-0.3	(-2.0, 1.4)
9	-6.7	-6.3	-0.4	(-2.1, 1.3)
10	-7.8	-7.2	-0.5	(-2.2, 1.2)
11	-6.3	-7.2	1.0	(-0.7, 2.7)
11.92	-5.5	-5.5	0.1	(-1.6, 1.8)
12.5	-5.2	-4.4	-0.8	(-2.5, 0.9)
13	-6.2	-5.3	-0.9	(-2.6, 0.8)
13.5	-4.5	-3.6	-0.8	(-2.5, 0.9)
14	-2.8	-3.2	0.5	(-1.2, 2.1)
15	-2.0	-2.4	0.4	(-1.3, 2.1)
16	-0.3	-0.6	0.4	(-1.3, 2.1)
24	-3.1	-3.0	-0.1	(-1.8, 1.6)

#### 4.3.4 QRS

The same statistical analysis was performed based on QRS intervals. The point estimates and the 90% confidence intervals are presented in Table 8. The largest upper bounds of the 2-sided 90% CI for the mean difference between 3,4-DAP 120 mg and placebo was 1.2 ms.

**Table 8: Mean and 90% CI  $\Delta\Delta$ QRS Time Course**

	Treatment Group			
	3,4-DAP 120 mg			
	$\Delta$ QRS	Placebo	$\Delta\Delta$ QRS	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	0.6	0.5	0.1	(-0.3, 0.5)
1	0.9	0.1	0.8	(0.4, 1.2)
1.5	0.6	0.0	0.6	(0.2, 1.0)
2	0.5	-0.0	0.5	(0.1, 0.9)
3	0.3	0.1	0.2	(-0.2, 0.6)
3.92	0.2	-0.1	0.3	(-0.2, 0.7)
4.5	0.5	-0.1	0.6	(0.2, 1.0)
5	0.8	0.4	0.4	(0.0, 0.8)
6	1.3	0.7	0.7	(0.3, 1.1)
7	0.3	0.2	0.1	(-0.3, 0.5)
7.92	0.0	-0.3	0.4	(-0.0, 0.8)
8.5	0.1	-0.2	0.3	(-0.1, 0.7)
9	0.2	-0.5	0.6	(0.2, 1.0)
10	0.4	-0.2	0.6	(0.2, 1.0)
11	-0.2	-0.2	0.0	(-0.4, 0.5)

	Treatment Group			
	3,4-DAP 120 mg			
	$\Delta$ QRS	Placebo	$\Delta\Delta$ QRS	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
11.92	-0.6	-0.5	-0.1	(-0.5, 0.3)
12.5	0.3	-0.0	0.3	(-0.1, 0.7)
13	0.1	-0.5	0.6	(0.2, 1.0)
13.5	0.3	-0.2	0.5	(0.1, 0.9)
14	0.3	0.0	0.3	(-0.1, 0.7)
15	0.1	-0.2	0.2	(-0.2, 0.7)
16	0.1	-0.1	0.2	(-0.2, 0.6)
24	-0.5	-0.3	-0.2	(-0.6, 0.3)

#### 4.4 CATEGORICAL ANALYSIS

##### 4.4.1 QTc

Table 9 lists the number of subjects as well as the number of observations whose QTcF values are  $\leq 450$  ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

**Table 9: Categorical Analysis for QTcF**

Treatment Group	Total N		Value $\leq$ 450 ms		450 ms < Value $\leq$ 480 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
3,4-DAP 120 mg	52	1349	51 (98.1%)	1348 (99.9%)	1 (1.9%)	1 (0.1%)
Moxifloxacin 400 mg	54	1437	54 (100%)	1437 (100%)	0 (0.0%)	0 (0.0%)
Placebo	49	1303	49 (100%)	1303 (100%)	0 (0.0%)	0 (0.0%)

Table 10 lists the categorical analysis results for  $\Delta$ QTcF. No subject's change from baseline was above 60 ms.

**Table 10: 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.
3,4-DAP 120 mg	52	1173	52 (100%)	1173 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	54	1240	51 (94.4%)	1235 (99.6%)	3 (5.6%)	5 (0.4%)
Placebo	49	1127	49 (100%)	1127 (100%)	0 (0.0%)	0 (0.0%)

##### 4.4.2 PR

There were no subjects who experienced PR interval greater than 200 ms in 3,4-DAP 120 mg group.

### 4.4.3 QRS

The outlier analysis results for QRS are presented in Table 11. There was one subject who experienced QRS interval greater than 110 ms in 3,4-DAP 120 mg group.

**Table 11: Categorical Analysis for QRS**

Treatment Group	T		Value≤100 ms		100 ms<Value≤110 ms		Value>110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
3,4-DAP 120 mg	52	1349	40 (76.9%)	1127 (83.5%)	11 (21.2%)	209 (15.5%)	1 (1.9%)	13 (1.0%)
Moxifloxacin 400 mg	54	1437	43 (79.6%)	1206 (83.9%)	10 (18.5%)	202 (14.1%)	1 (1.9%)	29 (2.0%)
Placebo	49	1303	39 (79.6%)	1092 (83.8%)	9 (18.4%)	195 (15.0%)	1 (2.0%)	16 (1.2%)

### 4.4.4 HR

There were no subjects who experienced HR greater than 100 bpm in 3,4-DAP 120 mg group

## 4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between drug concentration (Parent drug: 3,4-DAP, or DAP; Metabolite: 3,4-Ac-DAP, or AC) and  $\Delta\Delta\text{QTcF}$ .

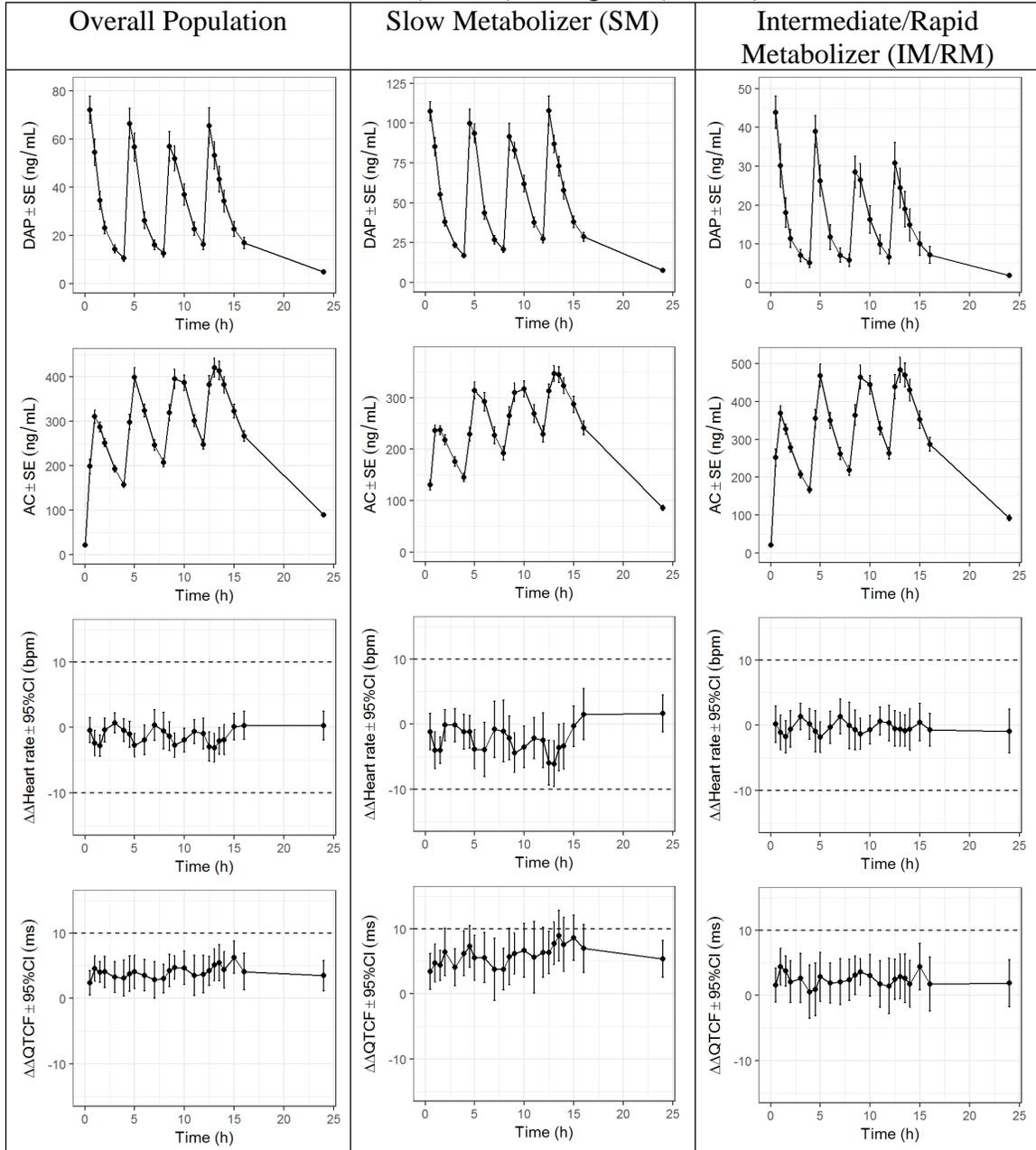
An evaluation of the time-course of drug concentration and changes in  $\Delta\Delta\text{HR}$  and  $\Delta\Delta\text{QTcF}$  is shown in Figure 4. The relationship between drug concentration and  $\Delta\Delta\text{QTcF}$  was evaluated in Figure 5 to determine if a linear model would be appropriate.

Exploratory analysis suggested a positive correlation between DAP concentration and  $\Delta\Delta\text{HR}$  (data not shown), nevertheless, significant changes in HR is absent at the study dose level in the overall population as well as in subgroups with high exposure to the parent drug (Slow Metabolizers, SM) or to the metabolite (Intermediate/Rapid Metabolizers, IM/RM) (Figure 4).

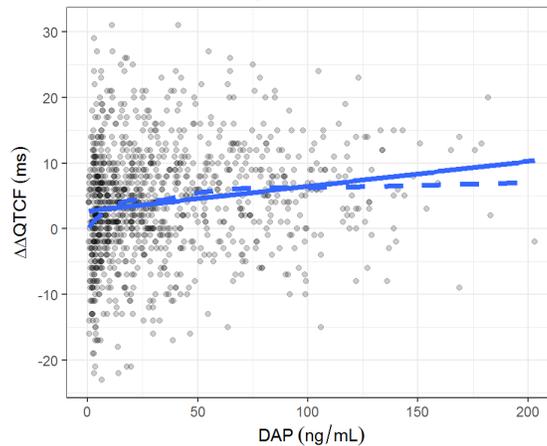
DAP exposure is substantially higher and AC exposure is lower in the SM subgroup than in the IM/RM subgroup.  $\Delta\Delta\text{QTcF}$  in SM group also appears higher than that in the IM/RM group, suggesting that DAP is the major driving force for  $\Delta\Delta\text{QTcF}$ .

There appears to be a small delay (0.5 hours) between DAP concentration and  $\Delta\Delta\text{QTcF}$  in the overall population and in the subgroups. Considering the short elimination half life in the fasted state (i.e. ~1.4 hr), there is apparent hysteresis in PK/ $\Delta\Delta\text{QTcF}$  data from the first 4 hours, leading to deviation from linearity in the high concentration range (Figure 5).

**Figure 4. Time course of drug concentration (Parent drug: DAP; Metabolite: AC), heart rate (middle) and QTcF (bottom)**



**Figure 5. Assessment of linearity of concentration-QTc relationship.**



A linear model was applied to the data using the equation:  $\Delta\Delta\text{QTcF} \sim 1 + \text{QTcF\_cBS} + \text{CONC} + (1|\text{USUBJID}) + (\text{CONC}|\text{USUBJID})$ . A positive relationship was identified between DAP exposure and  $\Delta\Delta\text{QTcF}$  with a slope of 0.0142 ms per ng/mL. Consistent with primary analysis, exposure-response analysis suggests an absence of significant QTc prolonging effect in the overall population or in slow metabolizers taking 120 mg daily in 4 equal doses every 4 hours. The model tends to under-predict the slope due to hysteresis; it cannot be used to predict QT effect beyond the studied exposure range.

#### **4.5.1 Assay sensitivity**

Not applicable.

#### **4.6 SAFETY ASSESSMENTS**

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

#### **4.7 OTHER ECG INTERVALS**

No clinically significant changes in PR or QRS were observed.

## 5 APPENDIX

### 5.1 EVALUATION OF QT ASSESSMENT PLAN

1. Product Information			
Generic Name	3,4-diaminopyridine	Brand Name	RUZURGI
Drug class	Voltage-dependent potassium channel blocker		
Combination product	No		
Indication	Treatment for Lamber-Eaton Syndrome		
Therapeutic Dose	(b) (4)		
Maximum Tolerated Dose	Unknown		
Dosage Form	Tablet	Route of Administration	Oral
2. Safety Pharmacology			
Amifampridine blocked a variety of Kv1, Kv2, and Kv3 ion channel subfamilies with potencies ranging from micromolar to millimolar concentrations. In a non-GLP in vitro study, amifampridine did not inhibit the human ether-à-go-go-related gene ion channel.			
3. Clinical cardiac safety			
<p>There have been 4 clinical trials involving 140 subjects, including 2 studies in 80 normal volunteers (JPC 3,4-DAP.TQT and JPC 3,4-DAP.PK1) dosed from 0 (placebo) to 120 mg and 2 studies in a total of 60 subjects with LEM (JPC 3,4-DAP JPC DUKE RCT and DAPPER) dosed with drug exposures ranging from 0 (placebo) to 100 mg. There were no episodes of syncope, seizure, ventricular arrhythmia, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden death in any of the 4 studies.</p> <ul style="list-style-type: none"> <li>JPC.3,4-DAP.TQT: 43 of 52 healthy volunteers were treated with the full 120 mg dose of amifampridine administered in 4 doses of 30 mg over 12 hours; 2 each received doses of 110, 90, or 80 mg, while 1 each received doses of 100, 50, or 30 mg.</li> <li>JPC 3,4-DAP.PK1: 30 healthy volunteers randomized to receive single doses of 20 mg (n=10), 30 mg (n=10), or placebo (n=10) in both fasting and fed states.</li> <li>DAPPER: 32 subjects on pre-established doses of amifampridine ranging from 30 to 100 mg per day were randomized to continue their usual doses or taper off of amifampridine.</li> </ul>			

- JPC DUKE RCT: 26 LEM subjects were randomized to amifampridine 10 to 20 mg, 3 or 4 times per day, or placebo, 3 or 4 times per day, for between 6 and 9 days.

In pooled safety data from 162 LEM patients with 766.4 patient years (PY) exposure to amifampridine in total daily doses ranging from 10 to 175 mg (RPV162), cardiac adverse events occurred at a rate of 5.3 events per 100 PY, convulsion at a rate of 0.7 events per 100 PY, and syncope at a rate of 0.1 events per 100 PY. Prolonged QT as an adverse event occurred at a rate of 0.3 per 100 PY. QTc  $\geq$ 500 ms was identified in only 1 patient with small cell lung cancer in the setting of recurrent metabolic acidosis with hypokalemia and transient atrial fibrillation 1 day after starting amifampridine. Twenty-five of the 162 LEM patients (15.4%) had pre-amifampridine histories of assorted cardiac disorders, 6 (3.7%) had prior seizures, 1 (0.6%) had previous syncope, and 1 (0.6%) had previous QT prolongation.

Pooled data for an additional 69 “Special Populations” patients with “pre-selected” conditions (identified in conjunction with FDA) was intended to present an enriched population. This group included all remaining patients in the compassionate use experience not captured in the RPV162 population with either medical history, medical events, or adverse events (AEs) of interest, including seizure, cardiac disorders or QT prolongation, suicidal behavior (including suicidal ideation), renal disorders, and hepatic disorders. Median exposure was 4.7 years (range 0.003 to 20.3) at a median dose of 75 mg (range 5 to 300). Pre-amifampridine medical history of interest included 19 patients (27.5%) with cardiac disorders, 3 (4.3%) with convulsion, 2 (2.9%) with syncope, and 1 (1.4%) with QT prolongation. Cardiac adverse events (44) occurred in 25 patients (37.3%), most commonly atrial fibrillation (6), congestive failure (4), and palpitations (4). Convulsion occurred in 20 (29.9%) patients, and most of these events occurred in patients with underlying malignancy and/or central nervous system (CNS) pathology (e.g., cerebrovascular accident (CVA) and brain or head injury) and/or overdose (either intentional or inadvertent). In 2 cases, convulsion was ascribed by the physician to other medications (theophylline, SAND101 and hydrocodone). In 1 case (SCHE104) with a seizure history, subsequent “spells” initially described as “seizure” was later described as “migraine”. Syncope occurred in 5 patients (7.5%), QT prolongation in 4 (6.0%), and loss of consciousness in 2 (3%). Eleven of the convulsions (15.9%) were considered related to amifampridine, 5 of the cardiac disorders (2 atrial fibrillation, 1 right bundle branch block, 1 palpitations, 1 sinus tachycardia, and 1 QT prolongation). The case of QT prolongation occurred in a non-LEM patient (41-year-old congenital myasthenic syndromes (CMS) patient who also had a possible seizure). There was 1 event of non-sustained ventricular tachycardia after more than 10 years of exposure to amifampridine in a patient with a pre-amifampridine history of cardiac disease and treated small cell lung cancer. Attribution of cardiac events and conduction issues is confounded as LEM patients age, develop additional medical conditions, and utilize concomitant medications.

## 4. QT Studies

### 4.1 Primary Studies

Protocol number / Population	ECG Quality		Arms		Sample size		ECG & PK assessments	
	Assessment	Ok?	Arms	High dose covers?	No subjects	Ok?	Timing	Ok?
Protocol number: JPC 3,4-DAP.TQT  Population: Healthy volunteers	Central read? Yes  Blinded? Yes  Method? Semi-manual  Replicates? Yes	Yes	Highest dose: 120 mg  Placebo: Yes  Positive control: Yes	High clinical	56 Subjects	Yes	Baseline: Pre-dose baseline  Timing: 0.5, 1, 1.5, 2, 3, 3.92, 5, 6, 7, 7.92, 8.5, 9, 10, 11, 11.92, 12.5, 13, 13.5, 14, 15, 24 hours.  PK samples for moxifloxacin at predose, 0.5, 1, 2, 3, 4, 7.92, and 24 hour post dose.	Yes

#### 4.2 Secondary Studies (Not Applicable)

#### 4.3 Data pooling

Data pooling?	No
Did sponsor propose an assessment for heterogeneity?	N/A
Is the data pooling appropriate?	N/A

### 5. Analysis plan

#### 5.1 Study Objective related to QT

What QTc effect size is the analysis trying to exclude?	10 ms (E14)
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#### 5.2 Dose Justification

The dose of 3,4-DAP in this study was 120 mg/day split over 4 equal doses every 4 hours. The usually recommended daily dose is 100 mg. The 120 mg/day dose was 20% above the usually recommended dose and had a reasonable safety and tolerability profile.

According to the ICH E14 Note for Guidance, the positive control used in the thorough-QT-trials should have an effect on the mean QT/QTc interval of about 5 msec. A single dose of 400 mg moxifloxacin was shown to significantly prolong the QT interval with the risk of inducing of Torsade de Pointes being minimal. Thus, moxifloxacin was used as a positive control in the current trial.

*Reviewer's comments: Dose/exposure would be adequate to cover high therapeutic exposure, provided that patients are instructed to take multiple doses at a minimum of 4-hour interval and to avoid prolonged fasting state.*

- *The recommended dosing regimen is oral administration with or without food. High fat meal decreases the C<sub>max</sub> of 3,4-DAP and 3,4-Ac-DAP by 40-50%. The effect of standardized meal on C<sub>max</sub> is not known. The first dose of the day was administered in the fasted state. A standardized lunch was given after the 2<sup>nd</sup> and 3<sup>rd</sup> doses. Meal schedule in this TQT study appears typical in daily life. Therefore, observed exposure in this TQT should be adequate to cover clinical exposure at the highest therapeutic dose, if the subject is not on a prolonged fasting status.*
- *No DDI studies or dedicated PK studies in patients with organ impairment have been conducted. In vitro studies suggest that 3,4-DAP and its major metabolite are not substrate of major metabolic enzymes or transporters. At this stage, the high clinical exposure scenario is expected to be observed in patients with slow metabolizer phenotype. 23 out of the 52 patients who contributed PK data in the current study are slow metabolizers. Therefore, observed exposure in the 23 slow metabolizers should represent the high clinical exposure with standardize meal.*
- *Drug label does not specify minimum dosing interval. If a patient takes 120 mg daily doses in less than 4-hour dosing intervals, maximum exposure to the parent drug and metabolite may be higher than observed in this TQT study.*

### 5.3 QT correction method

Is an HR increase or decrease greater than 10 bpm?	No
Primary method for QT correction	QTcF

### 5.4 Assay Sensitivity

Assay sensitivity methods proposed by sponsor	<input checked="" type="checkbox"/> Moxifloxacin <input type="checkbox"/> Exposure-margin <input type="checkbox"/> QT bias assessment	<input type="checkbox"/> Not applicable (objective is large mean effects) <input type="checkbox"/> Other
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### 5.5 Central Tendency Analysis

#### 5.5.1 Investigational drug

Primary analysis	Yes
Did the sponsor use IUT or descriptive statistics?	IUT
For IUT: Does the sponsor use MMRM to analyze longitudinal values that considers the correlation across time-points or use ANCOVA by time-point without considering correlation?	MMRM
For IUT: Is the MMRM model specified correctly with regards to covariance structure, covariates, etc.?	Yes
MODEL DQTcF = BASE PERIOD TRT HOUR PERIOD*HOUR TRT*HOUR / DDFM = KENWARDROGER S; RANDOM SUB; REPEATED HOUR / TYPE=UN;	

SUB = SUB*PERIOD;					
<b>5.5.2 Positive control</b>					
Primary analysis		Yes			
Did the sponsor adjust for multiplicity?		Unknown			
<i>The <math>\Delta QTcF</math> values are analyzed using ANCOVA model with treatment, period and sequence as fixed effects and subject nested within sequence as a random effect, for all subjects and separately for male and female subjects.</i>					
<b>5.6 Concentration-QTc analysis</b>					
<b>5.6.1 Investigational drug</b>					
Primary analysis		No			
What is the dependent variable in the sponsor's model?		Double delta			
White paper model?		No			
Which concentration covariate(s) are included in the model?		Multiple - Univariate			
Did the sponsor propose an assessment of delayed effects?		Yes			
Did the sponsor propose an assessment of linearity?		Yes			
Did the sponsor propose model selection criteria?		No			
What methods did the sponsor use for predicting the QT effect?		<input checked="" type="checkbox"/> Model-based confidence intervals <input type="checkbox"/> Bootstrap-derived confidence intervals			
PROC MIXED METHOD = ML; CLASS SUB; MODEL DDQTC=CONC / SOLUTION CL ALPHA=0.1 ALPHAP=0.1 / DDFM= KENWARDROGER OUTPM=OUT; RANDOM INT CONC / TYPE=UN; SUBJECT=SUB;					
<b>4.6.2 Positive control</b>					
Primary analysis		No			
Same model as investigational drug		Unknown			
<b>5.7 Categorical analysis</b>					
QTc?	Yes	PR?	Yes	HR?	Unknown
$\Delta QTc?$	Yes	QRS?	Yes	T-wave morphology?	Yes

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/s/  
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