CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OTHER REVIEW(S)

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:	November 26, 2018
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Division Deputy Director:	Sukhminder K. Sandhu, PhD, MS, MPH Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Firdapse (amifampridine phosphate)
Application Type/Number:	NDA 208078
Applicant/sponsor:	Catalyst Pharmaceuticals, Inc.
OSE RCM #:	2018-706

1. BACKGROUND INFORMATION

1.1. Medical Product

Firdapse® (amifampridine) is a voltage-gated potassium channel blocker with a proposed indication for the (b) (4) treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) in adults. Its blockade of potassium channels prolongs the depolarization of presynaptic membrane and inhibits repolarization, which results in opening of voltage dependent calcium channels. The increased concentration of intracellular calcium induces the release of acetylcholine (ACh) into the synaptic cleft of the neuromuscular junction [1-3], and thus, provides relief to symptoms caused by the impaired neuromuscular transmission due to reduced ACh release as a direct consequence of pathogenetic antibody binding to P/Q-type Ca^{2+} channels [4] in patients with LEMS. Amifampridine is administrated orally with a recommended starting dose at (b) (4) a day in divided doses 3 to 4 times per day. This product was approved for the treatment of LEMS by the European Medicines Authority in 2009.

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.[5] During the development of amifapridine, no effect on embryo-fetal viability and development was found in rabbits; however, an increased number of stillbirths was observed in rats. In the clinical trials of amifampridine, no pregnancies were reported. There were two case reports in the literature where women were exposed to amifapridine throughout the pregnancies at a dose of 10 mg six times daily[6] or adjusted according to the patient's level of fatigue (20 mg/day, with occasional additional doses of 5 mg).[7] In both cases the pregnancies were successful with a full-term delivery of a healthy infant. An additional exposed pregnancy identified in FDA Adverse Event Reporting System (FAERS case # (b) (6) was electively terminated by the patient due to intolerance of the treatment discontinuation. Taken together, there are no adequate human data on the developmental risk associated with the use of amifapridine in pregnant women and the effect of amifapridine on pregnancy outcomes is not known at this time.

In the current proposed labeling, as of October 26, 2018, the Risk Summary in Section 8.1 Pregnancy, states: (b) (4)

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. †

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***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: *Click here to enter text.*

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 November 20, 2018 for 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 Firdapse (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. Vohra MM, Pradhan SN. Pharmacology of 3, 4-Diaminopyridine. Arch Int Pharmacodyn Ther. 1964;150:413-424.
4. Spillane J, Ermolyuk Y, Cano-Jaimez M, et al. Lambert-Eaton syndrome IgG inhibits transmitter release via P/Q Ca2+ channels. Neurology. 2015;84(6):575-579.
5. 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 October 25, 2018.
6. Lecky BR. Transient neonatal Lambert-Eaton syndrome. J Neurol Neurosurg Psychiatry. 2006;77(9):1094.
7. Pelufo-Pellicer A, Monte-Boquet E, Roma-Sanchez E, et al. Fetal exposure to 3,4-diaminopyridine in a pregnant woman with congenital myasthenia syndrome. Ann Pharmacother. 2006;40(4):762-766.

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/s/

KIRA N LEISHEAR on behalf of HONGLIU DING
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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)

Date of This Memorandum:	November 14, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 208078
Product Name and Strength:	Firdapse (amifampridine) tablet 10 mg
Applicant/Sponsor Name:	Catalyst Pharmaceuticals, Inc.
FDA Received Date:	November 8, 2018
OSE RCM #:	2018-716-3
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Neurology Products (DNP) requested that we review the revised container labels and carton labeling for Firdapse (Appendix A) to determine if they are acceptable from a medication error perspective. We previously reviewed the draft labels and labeling for Firdapse, submitted to the Agency on August 8, 2018, and found the drafts to be acceptable from a medication error perspective.[a]

2 CONCLUSION

The revised container labels and carton labeling for Firdapse are acceptable from a medication error perspective. We have no further recommendations at this time.

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

[a] Rider B. Label and Labeling Review for Firdapse (NDA 208078). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 13. RCM No.: 2018-716-2.

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/s/

BRIANA B RIDER
11/14/2018

LOLITA G WHITE
11/14/2018

M E M O R A N D U M

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

Date: November 8, 2018

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:** Amifampridine phosphate (3,4-diaminopyridine phosphate)
NDA: 211230
Trade Name, dosages, formulations, routes: Firdapse is formulated as 10 mg oral tablets. A single dose is not to exceed 20 mg. The recommended starting dose is (b) (4) with a maximum of 80 mg/day, in divided doses 3 to 4 times per day.
IND Number: 106263
Indication(s): (b) (4) treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adult patients
Sponsor: Catalyst Pharmaceuticals, Inc.
PDUFA Goal Date: November 28, 2018

Materials Reviewed:

- Module 1.14 Labeling
- Module 2.3 Quality overall 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 January 10, 2018 to the Controlled Substance Staff (CSS) to evaluate abuse related preclinical and clinical data submitted by Catalyst Pharmaceuticals, Inc. (Sponsor) in NDA 208078 (IND 106263) for Firdapse (amifampridine). The drug product is indicated for the (b) (4) treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adult patients. The tablets contain 10 mg amifampridine with a recommended dose range of (b) (4) to 80 mg in divided doses 3 to 4 times per day. Amifampridine is

also known as 3,4-diaminopyridine (3,4-DAP) and had Sponsor codes of BMN-125, (b) (4), DAPP, (b) (4) and 3,4-DAP.

Catalyst submitted an NDA for amifampridine phosphate for the treatment of LEMS on December 16, 2015. In response, the FDA issued a refuse to file letter on February 12, 2016, outlining several issues including the full assessment of amifampridine's abuse potential. CSS requested that nonclinical in vivo studies be conducted in a Type-A meeting with the Sponsor held on April 7, 2016. In a Type C meeting on January 30, 2018 FDA agreed with the overall proposed abuse potential package to be submitted by the Sponsor which excluded a human abuse potential study. This decision was based on the results of the animal studies and AEs from clinical trials.

Amifampridine ([R]-2-amino-3-phenylpropylcarbamate hydrochloride), 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 amifampridine 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 amifampridine 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 amifampridine. An Irwin study in rats indicated that amifampridine 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 amifampridine 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 amifampridine 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 amifampridine 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 amifampridine does not have abuse potential.

- The receptor binding and activity data indicate that amifampridine is a nonspecific voltage dependent potassium channel blocker.

- The nonclinical in vivo abuse potential studies were conducted in an appropriate manner and indicate that amifampridine does not have reinforcing effects or produce stimulus generalization to the stimulant cocaine.

- The Sponsor did not conduct a HAP study because of the results of the nonclinical studies and lack of abuse-related adverse events from Phase 1 and Phase 3 clinical studies (no Phase 2 studies were conducted).

- No abuse-related adverse events occurred to any significant degree in clinical trials. The highest number of CNS mediated adverse events were paresthesias (47% of patients), dizziness (17% of patients), and headache (12.6% of patients).

- 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 amifampridine 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. (b) (4)

(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 syntheses that abusers may use to abuse the drug. An evaluation of the chemical properties of amifampridine and its known active metabolites is given below.

1.1 Substance Information

Amifampridine is an NME that is similar in structure to the potassium channel blocker 4-aminopyridine (4AP). (b) (4) The chemical characteristics of amifampridine are listed in **Table 1**.

Table 1 contains the general chemical attributes of the active pharmaceutical ingredient (API) amifampridine.

Table 1: General Chemical Properties of amifampridine

Nomenclature	
International non-proprietary name (INN)	Amifampridine
Chemical Abstract Number (CAS)	446254-47-3
Chemical Name (IUPAC)	Pyridine-3,4-diamine phosphate
Sponsor codes during development	BMN-125, (b) (4) DAPP, (b) (4) 3,4-DAP
Structure	
Molecular Formula	$C_5H_{10}N_3O_4P$
Molecular Weight	207.19; free base = 109.1
Structure	
General Properties	
Appearance	White crystalline powder
pH (1% solution in water)	4.4

pKa	11.8
Solubility (25°C)	freely soluble in water with decreasing solubility in less polar solvents
Melting point	225-231 °C

The Sponsor is manufacturing an immediate release tablet containing amifampridine phosphate as the API . The tablet is white to off white, round, flat-faced with a beveled edge and scored with "CATALYST" on one side. The components and quantitative composition of each tablet are listed in **Table 2**.

Table 2: Amifampridine Tablet Drug Product Composition (NDA 208078; Module 2.3.P; pg 1)

Component	Quantity per tablet (mg)	Percentage per tablet (%)	Function
Amifampridine phosphate	18.98[a]	(b) (4)	Active
Colloidal Silicon Dioxide, NF, Ph. Eur	(b) (4)		
Microcrystalline Cellulose, NF, Ph. Eur.			
Calcium stearate, NF, Ph. Eur.			
Total per Tablet	(b) (4)	100	

Ph. Eur. = European Pharmacopoeia; NF = National Formulary
[a] 18.89 mg of amifampridine phosphate drug substance corresponds to 10.00 mg of amifampridine base form.

1.2 Potential Drug Isomers

Amifampridine 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 amifampridine.

2.1 Receptor Binding and Functional Assays

The Sponsor conducted eight in vitro studies to assess the binding and functional activity of amifampridine 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 amifampridine's mechanism of action. The data, summarized below, indicate

that amifampridine is a voltage gated potassium channel blocker that maintains the depolarized state of neurons thereby decreasing their activity (**Table 3**).

Studies BMN125-10-084, BMN125-10-085, (b) (4) 100014186, and (b) (4) 100034669 were receptor panel and enzyme screens to determine the binding affinity of amifampridine 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 neither substance bound to any receptor, ion channels, enzymes, or transporters that are known to be associated with abuse potential. The binding affinity of amifampridine to K_v channels does not appear to have been determined, however, its activity was assessed.

Studies BMN125-10-111 and BMN125-10-112 were electrophysiology assays that used Chinese Hamster Ovary (CHO) cells transfected with human K_v channels to measure the activity of amifampridine at these channels. The data are presented in **Table 3** and indicate that amifampridine is an antagonist at hK_v 1.1, 1.2, 1.3, 1.4 and 1.5 channels. At the K_v1.7 channel, amifampridine was tested at doses of 1, 10, 30, 100, 300, 1000, and 3000 µM and produced an IC_{50} of 338.4 µM and blocked 80% of the current passing through the channels at a concentration of 3000 µM (IC_{80}). In comparison, the positive control, 4-aminopyridine (Ampyra) was found to have an IC_{80} of approximately 1000 µM, indicating it is approximately 3-fold more potent than amifampridine. The IC_{50} for the major metabolite of amifampridine, 3-N-acetyl amifampridine, could not be calculated for any of the channels because the highest dose of 3000 µM did not maximally inhibit the K^+ current (**Table 3**).

Table 3: Functional Activity of amifampridine at K_v channels

Drug	Functional activity, IC_{50} (µM)	
	Amifampridine	3-N-acetyl BMN125
Kv1.1	767.5	> 3000
Kv1.2	1278.8	> 3000
Kv1.3	524.8	> 3000
Kv1.4	1860.3	> 3000
Kv1.5	490.8	> 3000
Kv1.7	338.4	> 3000

2.2 Safety Pharmacology/Metabolites

The studies in section 2.1 indicate that the major metabolite of amifampridine, 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 has conducted 16 studies to assess the in vivo toxicity of amifampridine in mice, rats and dogs. Six of the studies are single dose acute studies: two in mice (IV and oral), three in rat (IV and oral), and one in beagle dogs (oral). Ten of the studies were repeat dose studies with six in rats (oral) ranging from seven days to 26 weeks and four in beagle dogs (oral) ranging from 14 days to 9 months. **Table 4** summarizes the results of some of the adverse events of the single and repeat dose toxicity studies. In general doses at or above 50 mg/kg in mice and rats resulted in jumping, convulsions, and death. Below 50 mg/kg animals showed activating effects including hyperactivation, increased limb movement, hyperexcitability, and tremors. These data indicate that at high single use doses the drug may have stimulant properties.

Table 4: Summary of Toxicity Studies on Amifampridine

Study #	Single/ Repeat	Dose	Administration	Animal	Adverse events	Cmax (ng/mL)	Tmax (hr)	NOAEL
S12300	repeat	1-3.29 (mg/kg/day)	oral	Beagle (Dog) (4)	hypersalivation, ptosis, shaking, coughing, diarrhea	156 - 446	0.63 - 0.63	
(b) (4)-266-007	single	12.5, 25, 50 mg/kg	IV	mouse	50 mg/kg resulted in convulsions and death; 25 mg/kg - hypersalivation, agitated forlimb movement, convulsions, irregular breathing, increased movemement (head and limbs)			NOEL of 10 mg/kg
(b) (4)-266-005	single	25, 50, 100 mg/kg	oral	mouse	100 mg/kg resulted in convulsions and death; 50 mg/kg rapid breathing, convulsions			NOAEL of 25 mg/kg
(b) (4)-266-006	single	2.5, 10, 25, 50 mg/kg	IV	rat (Sprague Dawley)	50 mg/kg convulsions and death; 25 mg/kg all animals convulsed and half died, hyperexcitability, jumping; 10 mg/kg irregular breathing, forelimb agitation, subdued behavior, jumping			NOEL of 2.5 mg/kg

(b) (4)-266-004	single	2.5, 10, 25, 50 mg/kg	oral	rat (Sprague Dawley)	50 mg/kg convulsions and death; 25 mg/kg all animals convulsed and 1/4 died, hyperexcitability, jumping, hyperactivity, excessive grooming;			NOEL of 10 mg/kg
(b) (4)-266-012	single	2.5, 10, 25, 50 mg/kg	oral	rat (Sprague Dawley)	50 mg/kg convulsions, excessive grooming, jumping, tremors, death; 25 mg/kg convulsions, hyperexcitability, jumping, excessive grooming;			NOEL of 10 mg/kg

2.4 Animal Behavioral Studies

CNS effects

The Sponsor conducted an Irwin screen to test amifampridine phosphate for its CNS mediated behavioral effects (Study 20070139PGR). Male Wistar rats were segregated into six groups of eight (N = 48); four of the groups were administered amifampridine at a dose of 5, 10, 20, or 40 mg/kg; one group was given vehicle and the last group was given clonidine at 5 mg/kg, all drugs were given PO. A satellite group of animals (N = 36) given the same drug concentrations were used for a PK analysis with blood draws at 5, 10, 15, 30, 60, 120, 240, 360 minutes. This study did measure significant differences between vehicle and the higher doses of amifampridine (20 and 40 mg/kg) in locomotor activity and rearings. However, the effects were not consistent, either dose, or time dependent, therefore it is not clear if these effects were the result of amifampridine. There were also no effects on body temperature at any dose of the drug. As a result, it appears as though amifampridine did not produce any CNS mediated behaviors in this assay. The study determined a No Observed Adverse Effect Level (NOAEL) of 40 mg/kg in rats. The data from this study does not correlate with the data from multiple toxicity studies which used doses from 2.5 to 50 mg/kg PO and demonstrated a series of AEs that may be signals of stimulant activity (Section 2.3)

The cardiovascular and respiratory effects of amifampridine were tested in studies BMN125-10-059 and BMN125-10-059, respectively. In the cardiovascular study, male beagle dogs received 0, 0.05, 0.15, or 0.5 mg/kg orally of drug in a latin square design. In the respiratory study, male beagle dogs received 0, 1, 3, 5, or 10 mg/kg orally of drug in a latin square design. The only cardiovascular effects were a shortening of the PR interval and an increase in arterial pressure. Overall the results of both of the studies indicate that, at these doses, amifampridine does not appear to produce significant cardiovascular or respiratory effects.

Abuse liability studies

Data collected from the toxicity studies indicate that amifampridine may have stimulant-like effects similar to drugs controlled in the CSA. These data are supported by published data indicating that amifampridine 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.

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 VPT5336 was conducted to determine the reinforcing effects of IV amifampridine using a cocaine self-administration substitution procedure in male Sprague Dawley rats. Animals were implanted with a femoral vein catheter and were trained to self-administer cocaine (2.8 mg/mL, 0.93 mg/kg/infusion) up to a fixed ratio 10 (FR10) schedule of reinforcement. After stable responding was obtained, the animals underwent extinction for up to 8 sessions, then cocaine treatment for 3 sessions to reacquire responding. The substitution phase was conducted with the following doses:

1. Negative control: vehicle (100 µl/infusion)
2. 0.075 mg/mL amifampridine (0.025 mg/kg/infusion)
3. 0.225 mg/mL amifampridine (0.075 mg/kg/infusion)
4. 0.75 mg/mL amifampridine (0.25 mg/kg/infusion)
5. Positive control: cocaine 2.8 mg/mL (0.93 mg/kg/infusion)

Cocaine was reinstated after the substitution phase for up to 6 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 amifampridine, all of the animals extinguished their self-administration behavior. The animals that substituted with the cocaine positive control continued responding to and maintained their cocaine seeking behavior validating the study. The range of doses used in the study provided a measured drug intake of amifampridine between 0.0039 and 0.585 mg/rat. This lead to drug plasma

levels that ranged from 40.691 to 411.899 ng/mL which covers therapeutic and supratherapeutic drug levels. As a result, this study indicates that amifampridine does not possess reinforcing effects.

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 ≥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 VPT5604 was conducted to test the discriminative stimulus effects of amifampridine to cocaine in a two-choice drug discrimination paradigm in male Sprague-Dawley rats. Rats were trained to distinguish cocaine (10 mg/kg) from saline in a two-lever food reinforced procedure to an FR10 schedule of reinforcement. Once all animals demonstrated discrimination to the desired criterion, the generalization phase was conducted. In the generalization phase, multiple dosses of cocaine or vehicle were given in a crossover design to determine the training drug dose response. Subsequently, generalization to amifampridine at doses of 0.25, 0.75, and 2.5 mg/kg IP and vehicle were given in a crossover design. Blood was collected at various time points to determine drug plasma levels in relation to therapeutic levels. The results of the study indicate that the positive control, cocaine, engendered 100% responding at 10 mg/kg and partial generalization at 3 mg/kg with 42.66% responding on the drug appropriate lever. For all doses of the test compound, amifampridine, animals responded almost exclusively to the vehicle lever with an average of ≤ 12% responding on the drug lever at all doses. The plasma exposure of amifampridine in these studies indicate that the animals had blood levels that were similar to or 2 to 3-fold higher than therapeutic levels with a mean C_{max} range of 22.2 to 291 ng/mL across the doses.

2.5 Tolerance and Physical Dependence Studies in Animals

Study VPT5401 was conducted to determine if amifampridine produces physical dependence. Male Sprague Dawley rats were given 7.5, 24, or 75 mg/kg/day PO amifampridine for 28 days followed by a 14-day treatment free period or chlordiazepoxide as a positive control. Physiological parameters to assess withdrawal were measured during dosing and in the treatment free period. Increases in piloerection and scratching as well as a decrease in defection were measured in the 75 mg/kg group, however, these were not consistent and do not appear to be related to a withdrawal syndrome. As a result, amifampridine does not appear to produce symptoms of withdrawal that are indicative of physical dependence.

3. Clinical Pharmacology

The clinical pharmacology of a substance is an assessment of how that substance, and its metabolites, associates 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 amifampridine 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 that were submitted as part of NDA 208078 in regard to the multitude of studies that were conducted to assess the pharmacokinetics, adsorption, distribution, metabolism, and elimination of amifampridine.

Pharmacokinetics and Absorption

Five studies were conducted to assess the PK and absorption of amifampridine in animals. These were single dose studies to determine the PK parameters of oral, IV, or IP administration of amifampridine in rats or beagle dogs.

Study BMN125-10-036 was conducted to determine the PK and bioavailability of amifampridine and its active metabolites, N-(4-aminopyridin-3-yl) acetamide and N-(3-aminopyridin-4-yl) acetamide in male and female Sprague Dawley rats as a single IV or three times a day (TID) oral dose. The IV dose for each sex was 0.8 mg/kg and the oral dose was 2, 8, or 25 mg/kg TID (~6 hours apart) for a total of 6, 24, or 75 mg/kg. The PK data are presented in tables 5-7, however, the data in **Table 5** are after a single oral dose of the indicated amount and not the TID amount. These data indicate that plasma C_{max} and AUC values increase at greater than dose proportional amounts suggesting possible saturation of first pass metabolism. Gender differences were generally less than 2-fold with female rats having the higher exposure levels. Oral dosing of amifampridine produced a T_{max} that ranged from 0.25 to 0.5 h and a half-life that ranged from 0.329 to 0.581 h indicating the fast onset and possible metabolism of the drug. Amifampridine is also highly orally bioavailable, especially at the higher doses with measurements ranging from 90.7 to 156% after a single dose of 25 mg/kg PO. The PK parameters of N-3-amifampridine are displayed in **Table 7** and indicate that the sex differences seen in the parent drug are mirrored by the metabolite. In other words, higher levels of the metabolite are seen in female rats who have greater exposure to the parent drug.

Table 5: PK Parameters Following IV Administration of Amifampridine in Rats (NDA 208078; Study BMN125-10-036; pg 509)

IV Dose (mg/kg)	Gender	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (ng•hr/mL)	Half-life (hr)	Cl (mL/hr/kg)	Vss (mL/kg)
0.8	M	187	0.083	49.6	0.436	16130	6654
	F	136	0.083	39.4	0.364	20313	8129

Table 6: PK Parameters Following Single Dose Oral Administration of Amifampridine in Rats (NDA 208078; Study BMN125-10-036; pg 510)

PO Single dose (mg/kg)	Gender	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (ng•hr/mL)	Half-life (hr)	F (%)
2	M	22.5	0.33	15.1	0.424	12.2
	F	52.1	0.25	27.2	0.329	28.1
8	M	179	0.5	144	0.404	29.1
	F	503	0.33	294	0.502	74.6
25	M	1393	0.5	1406	0.58	90.7
	F	1499	0.5	1921	0.581	156

Table 7: PK Parameters for 3-N-Acetyl Amifampridine Metabolite in Rat Following IV Administration (NDA 208078; Study BMN125-10-036; pg 512)

IV Dose (mg/kg)	Gender	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (ng•hr/mL)	half-life (hr)
0.8	M	218	0.083	338	1.2
	F	238	0.083	454	1.71

Study BMN125-10-004 was conducted in beagle dogs (3M/3F) to assess the PK and excretion of amifampridine ([^{14}C]3,4-diaminopyridine phosphate) following two different routes of administration. Animals received either a single IV dose of 0.05 mg salt/kg, 12.8 µCi/kg, or a single oral dose of 0.5 mg salt/kg, 30 µCi/kg. No obvious sex differences were noted in either route of administration throughout the plasma concentration curve indicating similar exposure levels of the drug for both sexes.

Four clinical studies were conducted to evaluate the PK of amifampridine in humans. There was considerable inter-subject variability in the PK parameters of amifampridine in both healthy subjects and subjects with LEMS (Study FIR-001 and Study LMS-002). Differences in exposure and C_{max} values were three to five-fold higher in slow acetylators vs. those that are considered rapid acetylators (Study FIR-001) and has resulted in a proposed dose escalation strategy for clinical use. The differences in acylation rates of the parent drug are the result of allelic variations of the N-acetyl transferase 2 (NAT2) metabolic enzyme. As a result, subjects in both studies were genotyped to correlate their PK parameters with their NAT2 allelic mutation. Furthermore, this study indicated that the fed state decreases the overall exposure and C_{max} and increases the half-life of amifampridine (20 mg oral) compared to the fasted state (**Table 8**).

The clinical studies indicate that, similar to the animal studies, amifampridine is rapidly absorbed, highly orally bioavailable, and has a half-life of approximately 2 hours. None of the clinical studies produced dimorphic PK parameters between sex or age.

Table 8: Human PK Parameters for Orally Administered Amifampridine (20mg) in Fed and Fasted Subjects (NDA 208078; Study FIR-001)

Parameters	Fed		Fasted	
	Mean	SD	Mean	SD
AUC_{0-t}	103	74.8	113	75
C_{max}	40.6	31.3	59.1	34.4
T_{max}	1.31	0.88	0.637	0.247
Half-life	2.28	0.704	2.5	0.73

Study QTC-002 was a phase 1 study in which healthy subjects were given therapeutic and supratherapetic doses of amifampridine to individuals who were determined to be slow acetylators (slow metabolizers) of the parent drug. In this study, subjects received 30, 60, 70, and 80 mg of amifampridine on day one and then had a three-day observation/washout period. The PK parameters from this study are presented in **Table 9** and support the previously mentioned conclusions. Of note is that there was a slightly larger than dose proportional increase in the systemic exposure and plasma concentration of amifampridine across the doses tested.

Table 9: Summary of PK for Orally Administered Amifampridine in Humans (NDA 208078; Study QTC-002; pg 97 – 98)

	Amifampridine			
PK parameters	30 mg (n=5)	60 mg (n=6)	70 mg (n=5)	80 mg (n=4)
AUC_{0-t} (h•ng/mL)	193 (52.9)	430 (22.7)	539 (138)	602 (101)
C_{max} (ng/mL)	65.1 (22.7)	134 (58.0)	152 (28.8)	184 (34.0)
T_{max} (h)	1.26 (0.494)	1.96 (2.05)	1.30 (0.274)	3.39 (0.928)
Half-life (h)	2.43 (0.274)	2.80 (0.940)	2.96 (0.504)	3.39 (0.928)

The data from the rat studies indicate that there may be sex differences in drug levels and exposure with females having higher levels than males, however, this conclusion is not supported by the dog or clinical studies which indicate no sex differences. All studies indicate that amifampridine is quickly orally absorbed with high bioavailability and a dose dependent half-life ranging from 30 to 270 minutes.

Distribution and Excretion

Study BMN125-10-041 was an in vitro study conducted to determine the plasma protein binding of[^{14}C]3,4-diaminopyridine phosphate to rat, dog, monkey, and human plasma proteins. The amount of plasma protein binding can give an indication as to the ease with which a drug can distribute throughout the body. At the concentrations of 0.3 to 30 µM the percent of unbound drug in all of the species ranged from 85.5% to 95.2% indicating that amifampridine is highly plasma protein unbound.

Similar to study BMN125-10-004 which was conducted in dogs, Study BMN125-10-005 used [^{14}C]3,4-diaminopyridine phosphate in rats to assess the absorption, distribution, and excretion of amifampridine.

In this study rats were administered a single oral dose of 25 mg salt/kg or an IV dose of 2.5 mg salt/kg. Drug administered IV was rapidly excreted with ~95% recovered in the urine and ~3% in the feces 169 hours after dosing in both male and female rats. In distribution studies, radioactivity was measured throughout the body 0.25 hours after oral administration and increased for up to 2 hours. Tissue levels in the plasma were generally similar to plasma levels except in the eye, fat, and CNS where levels were lower than plasma levels. Consistent with the PK measurements, female rats tended to have greater exposure than their male counterparts, however, both excreted ~88% of the drug in the urine and ~6.5% in the feces of the oral dose 168 hours after administration.

Study BMN125-10-004 was similar to the rat study but was conducted in beagle dogs (3M/3F). Animals received either a single IV dose of 0.05 mg salt/kg, 12.8 µCi/kg, or a single oral dose of 0.5 mg salt/kg, 30 µCi/kg. Similar to rats, the primary route of elimination was through the urine with 89% of the drug being recovered by 168 hours after dosing. Amifampridine was highly orally bioavailable and distributed throughout the body with two hours of administration. There were no sex differences in the distribution or amounts of the drug between the two groups.

The distribution of amifampridine was not directly assessed in clinical studies.

Excretion of amifampridine was found to be similar in humans with Study LMS-001 indicating that approximately 19% of the drug is eliminated unchanged in the urine. After 24 hours the 3-N-acetyl amifampridine metabolite was eliminated at 74% to 81.7% of the parent drug leaving approximately 0 to 6.8% of the drug to be excreted through nonrenal methods.

In conclusion, amifampridine is highly protein unbound and rapidly absorbed resulting in a high tissue distribution. Following a single oral dose, it is almost fully excreted within 168 hours, mostly in the urine with about 6.5% in the feces. The only sex differences noted were the levels of radioactivity that were higher in the tissue distribution of female rats compared to males, but there were no differences in the tissues that the drug distributed to. Data collected from Beagle dogs and from clinical trials did not show sex differences in any of the parameters measured.

Metabolism

Three in vitro studies were conducted to determine the hepatocyte metabolism of amifampridine; PR6958/CC2206, BMN125-10-038, BMN125-10-40, and BMN125-10-037. In these studies hepatocytes were isolated from rat, rabbit, dog, monkey, minipig, and humans and samples of [^{14}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 [^{14}C]3,4-diaminopyridine to an M1 metabolite called N-(4-aminopyridin-3-yl) acetamide. A low level of the M1 metabolite was detected in the rabbit hepatocytes and no M1 was detected in the minipig hepatocytes. 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 amifampridine 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, amifampridine 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-ren-002). However, it is only the rate at which amifampridine is metabolized that is affected, the drug is still metabolized and excreted in the same manner.

Studies BMN125-10-054 and BMN-10-053 indicate that amifampridine is unlikely to induce or inhibit CYP enzymes and therefore, would have little effect on drug induced interactions through these metabolic pathways.

Conclusion

The PK data indicate that amifampridine is rapidly absorbed orally and does not bind widely to plasma proteins resulting in a wide distribution throughout the body. Amifampridine 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 ten completed clinical studies in the amifampridine clinical program, 5 have been conducted in healthy subjects, and 5 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 amifampridine.

4.2 Adverse Event Profile Through all Phases of Development

Phase 1 Studies

The Sponsor conducted 5 Phase 1 studies in healthy subjects to determine the safety, PK, and tolerability of amifampridine. **Table 10** presents the combined neurologically mediated AEs collected from these five Phase 1 studies. The presented AEs do not present a specific concern for abuse at doses from 10 to 80 mg of orally administered amifampridine.

Table 10: Neurologically Mediated AEs in Healthy Volunteer Subjects N (%)

Preferred Term	Placebo (N = 2)	Total Treatment Dependent Adverse Events (N = 160)	≤ 30 mg (N = 128)	> 30 - 80 mg (N = 32)
Paresthesia	1 (33%)	161 (71%)	81 (65%)	80 (79%)
Dizziness	1 (33%)	41 (18%)	32 (26%)	9 (8.9%)
Headache	1 (33%)	12 (5.3%)	9 (7.2%)	3 (3%)
Hypoesthesia	0	12 (5.3%)	3 (2.4%)	9 (8.9%)

Phase 3 Studies

Because of the low numbers of individuals with LEMS, the Sponsor did not conduct Phase 2 studies and went directly to conducting Phase 3 studies to assess the efficacy of amifampridine in these subjects. The Sponsor conducted five Phase 3 studies; two of which were clinical efficacy studies, one was a safety study, and the last two were retrospective observational studies. The retrospective observational studies were able to be conducted because amifampridine is available as a marketed drug in Europe and is available in the U.S. under FDA expanded access programs.

Study LMS-002 was a Phase 3, multicenter, double-blind, placebo-controlled, randomized discontinuation study followed by an open-label extension period to evaluate the efficacy and safety of amifampridine in patients with LEMS. This study was conducted in 13 sites in eight countries with 38 subjects enrolled. Neurological adverse events for subjects who were treatment naïve with amifampridine (some had been receiving it before) were paresthesias (18 [42.9%]), headache (5 [11.9%]), and dizziness (3 [7.1 %]). These AEs were similar in frequency to those seen in the Phase 1 studies and do not suggest an abuse-potential for amifampridine.

Study LMS-003 was a Phase 3, double-blind, placebo-controlled, randomized parallel-group study to evaluate the efficacy and safety of amifampridine in patients with LEMS. There were 26 subjects in this study who received amifampridine 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.

Studies ATU, AGEPS, and Rennes CHU, were safety studies that were conducted to determine the diagnostic and therapeutic challenges associated with treating LEMS patients with amifampridine. Studies AGEPS and Rennes CHU were retrospective observational studies with patients that had received amifampridine over a long period of time at various doses for various indications.

1. In study ATU, 82 patients were treated with amifampridine and there were 6 reports of paresthesias.
2. In study AGEPS, 7 patients were treated with amifampridine and there were no reports of neurological AEs.
3. In study Rennes CHU, over a period of 5 years, 668 patients were given amifampridine for various reasons. In many cases the patients were treated with other drugs, therefore, the adverse event profile is confounded. . However, when segregated by body system class, a total of 71 (10.7%) nervous system disorders were identified that were segregated into the following AEs: paresthesias 51 (7% of the total), headache 5 (2.2%), convulsions 3 (0.5%), muscle rigidity 2 (0.3%), and drowsiness 2 (0.3%).

Conclusion

Adverse events from 10 clinical studies indicate that amifampridine does not produce pharmacodynamic effects that are typically associated with abuse. These data support the in vitro data indicating that amifampridine does not have abuse potential.

4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trials

There were no reports of amifampridine overdose. There was also no evidence of abuse or diversion of amifampridine 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 amifampridine.

4.5 Tolerance and Physical Dependence Studies in Humans

Amifampridine 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

Amifampridine 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.

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/s/

EDWARD G HAWKINS
11/08/2018

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11/08/2018

DOMINIC CHIAPPERINO
11/08/2018

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

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

Memorandum

Date: November 2, 2018

To: Teresa Buracchio, M.D.
Division of Neurology Products (DNP)

Heather Bullock, Regulatory Project Manager, (DNP)

Tracey Peters, PharmD, Associate Director for Labeling, (DNP)

From: Sapna Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Acting Team Leader, OPDP

Subject: OPDP Labeling Comments for FIRDAPSE® (amifampridine) tablets, for oral use

NDA: 208078

In response to the DNP consult request dated April 11, 2018, OPDP has reviewed the proposed product labeling (PI) for the original NDA submission for FIRDAPSE® (amifampridine) tablets, for oral use (Firdapse).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DNP (Heather Bullock) on October 17, 2018 and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under a separate cover on October 24, 2018

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 11, 2018, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Sapna Shah (240) 402-6068 or Sapna.Shah@fda.hhs.gov.

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/s/

SAPNA P SHAH
11/02/2018

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:	October 24, 2018
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)** Sapna Shah, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	FIRDAPSE (amifampridine)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 208078
Applicant:	Catalyst Pharmaceuticals

1 INTRODUCTION

On March 28, 2018, Catalyst Pharmaceuticals submitted for the Agency's review a resubmission of an Orignal New Drug Application (NDA) for FIRDAPSE (amifampridine) tablets, for oral use. The application was originally submitted on December 16, 2018 and the Agency issued a refusal to file (RTF) letter on February 12, 2016. The Applicant is seeking FDA approval for prescription marketing of the drug product for the (b) (4) treatment of the autoimmune disorder Lambert-Eaton myasthenic syndrome (LEMS).

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 June 22, 2018 and April 11, 2018, for DMPP and OPDP respectively to review the Applicant's proposed MG for FIRDAPSE (amifampridine) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft FIRDAPSE (amifampridine) tablets, for oral use received on March 28, 2018, and received by DMPP and OPDP on October 17, 2018.
- Draft FIRDAPSE (amifampridine) tablets, for oral use Prescribing Information (PI) received on March 28, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 17, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additonally, 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 APHont to make medical information more accessible for patients with vision loss. We reformatted the MG documents using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is 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 is 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.

Please let us know if you have any questions.

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

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/s/

SHARON W WILLIAMS
10/24/2018

SAPNA P SHAH
10/24/2018

LASHAWN M GRIFFITHS
10/24/2018

Clinical Inspection Summary

Date	September 21, 2018
From	Cheryl Grandinetti, Pharm.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Heather Bullock, R.P.M. Veneeta Tandon, Ph.D., Clinical Reviewer Teresa Buracchio, M.D., Clinical Team Leader Billy Dunn, M.D., Division Director Division of Neurology Products
NDA #	208078
Applicant	Catalyst Pharmaceuticals, Inc
Drug	Firdapse (amifampridine)
NME	Yes
Review Priority	Priority
Proposed Indication	(b) (4) treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) in adults.
Consultation Request Date	April 11, 2018 (amended May 15, 2018)
Summary Goal Date	September 28, 2018
Action Goal Date	November 18, 2018
PDUFA Date	November 28, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Ubogu, Kostera-Pruszczyk, Shieh, and Kohrman, and the study sponsor, Catalyst Pharmaceuticals, Inc. were inspected in support of this NDA in order to verify data from study protocols LMS-002 and LMS-003. During the inspection of Catalyst Pharmaceuticals, review of monitoring reports revealed more than a year's gap in monitoring for Protocol LMS-002. In addition, the monitoring performed for this study was found to be insufficient and ineffective.

The data generated by these sites for both studies (LMS-002 and LMS-003) and submitted by the sponsor appear acceptable in support of the respective indication although monitoring practices were problematic for LMS-002. There monitoring issues included (but were not limited to) the following:

- Lack of study monitoring for at least a year
- Failure of study monitors to identify and document protocol deviations in a timely manner and implement corrective actions for sites with high numbers of PD

The violations do not appear to impact the overall efficacy or safety outcomes of LMS-002.

The final compliance classification of the inspections of Drs. Ubogi, Shieh, and Kohrman was No Action Indicated (NAI). The final classification of the inspections of Dr. Kostera-Pruszczyk was Voluntary Action Indicated (VAI), and the final classification of the inspection of the sponsor, Catalyst Pharmaceuticals, Inc, was VAI.

II. BACKGROUND

Catalyst Pharmaceuticals, Inc. submitted this NDA to support the use of Firdapse (amifampridine phosphate) for the (b) (4) treatment of patients with Lambert-Eaton Myasthenic Syndrome (LEMS). BioMarin was the original license holder and sponsor for Firdapse in the United States. In October 2012, Catalyst Pharmaceuticals, Inc. became the license holder in the United States and sponsor for the Firdapse clinical trials.

The key studies supporting this application were as follows:

- Protocol LMS-002, "A Phase 3, Multicenter, Double Blind, Placebo-Controlled Randomized Discontinuation Study Followed by an Open Label Extension Period to Evaluate the Efficacy and Safety of Amifampridine Phosphate (3,4-Diaminopyridine Phosphate) in Patients with Lambert-Eaton Myasthenic Syndrome (LEMS)"

- Protocol LMS-003, "A Phase 3, Double Blind, Placebo-Controlled, Randomized, Parallel Group Study to Evaluate the Efficacy and Safety of Amifampridine Phosphate (3,4 Diaminopyridine Phosphate) in Patients with Lambert Eaton Myasthenic Syndrome (LEMS)"

Protocol LMS-002

This was a double-blind, placebo-controlled, randomized discontinuation study designed to evaluate the efficacy and safety, including the long-term safety, of amifampridine phosphate as a symptomatic treatment for patients with LEMS. The primary objective of the study was to compare the efficacy of amifampridine phosphate versus placebo on muscle strength in patients with LEMS at the end of a 14-day discontinuation period. The secondary objective of the study is to compare the efficacy of amifampridine phosphate versus placebo on walking speed in LEMS patients at the end of a 14-day discontinuation period.

- *Subjects:* 77 patients were screened, 54 patients entered Part 1 of the study, 38 patients were randomized into Part 2, and 36 patients completed Part 3.
- *Sites:* 13 sites in 8 countries: France (1 site), Germany (1 site), Hungary (1 site), Poland (1 site), Russia (1 site), Serbia (1 site), Spain (1 site), and the United States (6 sites).
- *Study Initiation and Completion Dates*: September 12, 2011 to July 29, 2014 (Parts 1 through 3); Part 4 data will be reported separately

This study consisted of the following 4 parts:

- Part 1: Open-label run-in (Duration 7-91 days)

- Part 2: Double blind treatment discontinuation (Duration 7 days)
- Part 3: Double-blind treatment (Duration 7 days)
- Part 4: Open Label Extension (Duration patients received open-label IP until study was terminated 2 years after the last patient was enrolled into Part 4)

The *co-primary efficacy endpoints* were:

- The change in Quantitative Myasthenia Gravis (QMG) score from double-blind baseline (Day 1, Part 2) to Day 14 (end of Part 3)

- The change in Subject Global Impression (SGI) score from double-blind baseline (Day 1, Part 2) to Day 14 (end of Part 3).

The *secondary efficacy endpoint* of interest was the Day 14 (end of Part 3) Clinical Global Impression-Improvement (CGI-I) scale measurements.

Protocol LMS-003

This randomized (1:1), double-blind, placebo-controlled, two-period, two-treatment crossover study was designed to evaluate the efficacy and safety of amifampridine phosphate in patients diagnosed with LEMS.

- *Subjects:* 26 patients were enrolled
- *Sites:* 3 sites in the United States.
- *Study Initiation and Completion Dates*: January 13, 2017 to October 30, 2017

The duration of participation for each patient was 8 days, excluding the screening period, which could last up to7 days. Eligible patients receiving amifampridine phosphate treatment for LEMS and on a stable dose and frequency for at least 1 week before subjects were randomized (on Day 0) in a 1:1 ratio to one of the following two treatment sequences:

- Treatment Sequence I: Amifampridine Days 1 to 4 (Period 1) followed by Placebo Days 5 to 8 (Period 2)
- Treatment Sequence II: Placebo Days 1 to 4 (Period 1) followed by Amifampridine Days 5 to 8 (Period 2)

The *co-primary efficacy endpoints* were the changes in the QMG Score and SGI score from Day 0 to Day 4. The secondary efficacy endpoint was the CGI-I score on Day 4.

Rationale for Site Selection

The clinical sites were chosen for inspection because of their relatively large enrollments and their treatment effect.

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

Site #/ Name of CI/ Address	**Protocol #/ # of Subjects Enrolled**	**Inspection Dates**	**Classification**
Site #1227 **Eroboghene E. Ubogu, M.D.** (previous clinical investigators: Mohammad Alsharabati, M.D. and Shin Joong Oh, M.D.) 1720 7th Avenue South Sparks Center 272 Birmingham, AL 35233	LMS-002 Subjects: 6	4-7 June 2018	NAI
Site #1268 **Anna Kostera-Pruszczyk, M.D.** Samodzielny Publiczny Centralny Szpital Kliniczny w Warszawie, Katedra i Klinika Neurologii Banacha 1A 02-097 Warszawa, POLAND	LMS-002 Subjects: 6	11-13 July 2018	VAI
Site #2016 Site #01 **Perry Shieh, M.D.** 300 UCLA Medical Plaza Suite 2100 Los Angeles, CA 90095	LMS-002 Subjects: 2 LMS-003 Subjects: 12	23-27 July 2018	NAI
Site #03 **Bruce Kohrman, M.D.** 6141 Sunset Drive Suite 301 South Miami, FL 33143	LMS-003 Subjects: 11	9-13 July 2018	NAI
Sponsor: **Catalyst Pharmaceuticals, Inc.** 355 Alhambra Circle, Suite 1500 Coral Gables, FL 33134	LMS-002 LMS-003	23-27 July 2018	VAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable

1. Eroboghene E. Ubogu, M.D. (previous clinical investigators: Mohammad Alsharabati, M.D. and Shin Joong Oh, M.D.)

Dr. Shin Joong Oh was the principal investigator (and Dr. Alsharabati was the sub-investigator) for Protocol LMS-002 from November 2011 to June 2013. When Dr. Oh retired in June 2013, Dr. Alsharabati became the principal investigator and was responsible for study activities (from June 2013 to September 2015). Dr. Ubogu assumed responsibilities as the principal investigator in January 2016, and at the time of inspection, Dr. Ubogu was responsible for the study records that this inspection covered.

At this site for Protocol LMS-002, seven subjects were screened, six were enrolled, three discontinued, and three subjects completed the study. The first subject was enrolled at this site on November 14, 2011, and the last subject was enrolled on June 10, 2013. The FDA field investigator noted that there were no study monitoring visits conducted by the sponsor or contract research organization (CRO) from March 2012 to April 2013.

An audit of the study records for all six enrolled subjects was conducted. Records reviewed during the inspection included, but were not limited to, study and subject source records (including those for the primary and secondary efficacy endpoints), communications with the IRB and CRO, drug accountability, informed consents, subject study visits, randomization, and adverse events. The site maintained all study source documents in paper format. Site personnel entered data into an electronic data capture system. Paper source documents included worksheets used to collect all data needed to populate the eCRFs as well as paper source documents for informed consent, eligibility for enrollment and general protocol compliance, and reporting of serious adverse events.

Data line listings provided by the sponsor for the primary and secondary efficacy endpoints were verified against the paper source documents. No significant discrepancies were noted. There was no evidence of under-reporting of adverse events, and no protocol deviations were observed other than those listed in the data listings provided by the sponsor.

Of note, in some cases, site personnel incorrectly calculated the fifth Compound Muscle Action Potential (CMAP) Amplitude during repetitive stimulation. These incorrect values were carried forward into CRFs and subsequently reported to the FDA. Although this was not a primary or secondary endpoint, we are providing the table of all incorrect values calculated by site personnel.

Date/Visit	Subject Number	First Testing Amplitude	Fifth % Decrement	Correct Fifth Resting Amplitude (Calculated)	Fifth Resting Amplitude Reported to FDA
	(b) (6)	5.7	37%	3.6	3.5
		9.5	9%	8.6	9.5
		4.5	27%	3.3	3.8
		7.2	25%	5.4	5.6

(b) (6)	2.2	34%	1.5	1.6
	0.2 (recorded on CRF as 2.0)	2%	0.2	1.6

Reviewer's Comment: The CMAP was used to assess a tertiary efficacy endpoint. The calculation errors for the three subjects for the fifth resting amplitude, as shown in the table above, were for the most part minor. However, if the review division plans to analyze the data for this tertiary endpoint, we recommend that the above data for subjects (b) (6) *be corrected as shown in the table.*

2. Anna Kostera-Pruszczyk, M.D.

At this site for Protocol LMS-002, eight subjects were screened, six were enrolled, and six subjects completed the study. The first subject was enrolled on April 23, 2012, and the last subject enrolled was on April 17, 2014. The FDA field investigator noted a gap in site monitoring visits by the sponsor or CRO from May 2012 to April 2013. An audit of the study records for all enrolled subjects was conducted. Records reviewed during the inspection included, but were not limited to, study and subject source records (including those for the primary and secondary efficacy endpoints), communications with the IRB, drug accountability, informed consents, subject study visits, randomization, and adverse events.

This site also maintained all study source documents in paper format, including CRF templates and worksheets used to collect all data needed to populate the eCRFs. Site personnel entered data into an electronic data capture system. The data line listings provided by the sponsor were verified against the paper source documents for the primary and secondary efficacy endpoints available at the site. No discrepancies were noted.

There was evidence of under-reporting of adverse events, and an Form FDA 483 was issued for failure to conduct the investigation in accordance with the signed statement of the investigator and investigational plan. Specifically, for LMS-002, the investigator failed to report the following SAE to the sponsor.

Subject ID	SAE	SAE Onset/ Resolution Date	Date Site Notified/ Identified SAE	Date Site Notified Sponsor
(b) (6)	Lumbar pain requiring hospitalization	(b) (6)		Not reported

Reviewer's comment: Dr. Kostera-Pruszcsyk concurred with the inspectional observations in a written response, dated July 30, 2018, to the Form FDA 483 inspectional observations. With respect to Subject (b) (6)*, Dr. Kostera-Pruszcsyk stated that the condition of the patient was not an indication for hospitalization. The lumbar pain was a pre-existing*

condition, and the hospitalization was pre-planned to perform an inpatient MRI due to an unacceptably long waiting time (at almost 6 months) to schedule an outpatient MRI. Dr. Kostera-Pruszcsyk acknowledges that she should have obtained a protocol waiver for the pre-planned hospitalization and that she should have reported it as an SAE.

3. Perry Shieh, M.D.

At this site for Protocol LMS-002, three subjects were screened, two were enrolled, and two subjects completed the study. The first subject was enrolled on October 15, 2013, and the last subject enrolled was on February 18, 2014. At this site for Protocol LMS-003, 12 subjects were screened, all of whom were enrolled in and completed the study. The first subject was enrolled on January 19, 2017, and the last subject enrolled was on October 26, 2017.There was regular and routine site monitoring by the CRO for LMS-002 and by the sponsor for LMS-003; no gaps in monitoring were identified.

An audit of the study records for all enrolled subjects for both protocols, LMS-002 and LMS-003, was conducted. Records reviewed during the inspection included, but were not limited to, study and subject source records (including those for the primary and secondary efficacy endpoints), communications with the IRB, drug accountability, informed consents, subject study visits, randomization, and adverse events.

The primary and secondary efficacy endpoint data were verifiable. There was no evidence of under-reporting of adverse events. No protocol deviations were observed other than those listed in the data listings provided by the sponsor.

4. Bruce Kohrman, M.D.

At this site for Protocol LMS-003, 11 subjects were screened, all of whom were enrolled in and completed the study. The first subject was enrolled on January 13, 2017, and the last subject enrolled was on September 22, 2017. There was regular and routine site monitoring by the sponsor for this protocol; no gap in monitoring was identified.

An audit of the study records for all enrolled subjects was conducted. Records reviewed during the inspection included, but were not limited to, study and subject source records, (including those for the primary and secondary efficacy endpoints), communications with the IRB, drug accountability, informed consents, subject study visits, randomization, and adverse events.

This site also maintained all study source documents in paper format, including CRF templates and worksheets used to collect all data needed to populate the eCRFs. Site personnel entered data into an electronic data capture system. Data line listings provided by the sponsor for the primary and secondary efficacy endpoints were verified against the paper source documents available at the site. No discrepancies were noted. There was no evidence of under-reporting of adverse events, and no protocol deviations were observed other than those listed in the data listings provided by the sponsor.

5. Catalyst Pharmaceuticals, Inc.

The inspection of Catalyst Pharmaceuticals, Inc. focused on the control, oversight, and management of Protocols LMS-002 and LMS-003. The inspection covered roles and responsibilities, organization and its personnel, registration of studies on clinicaltrials.gov, selection and monitoring of clinical investigators, selection of monitors, monitoring procedures and activities, quality management, adverse event reporting, process for managing protocol deviations, data collection and handling, record retention, financial disclosure, electronic records compliance, and test article accountability. Records reviewed during the inspection included investigator agreements, vendor agreements, and contracts, written standard operating procedures, documentation of protocol deviations, validation of electronic data capture systems, adverse event reporting, drug accountability, relevant communication and correspondence, and monitoring activities.

For Protocol LMS-002, Catalyst Pharmaceuticals, Inc. contracted with (b) (6) to perform clinical trial monitoring. However, Catalyst retained primary responsibility for clinical trial monitoring for Protocol LMS-003. Monitoring records were reviewed for four clinical sites who participated in Protocol LMS-002. The review of monitoring reports showed that no study monitoring visits were conducted by the sponsor or CRO for at least a year for Protocol LMS-002. This occurred in part because (b) (4) the initial CRO contracted by BioMarin, ended its responsibility for monitoring on June 1, 2012, but (b) (4) did not assume this responsibility until December 1, 2012. (b) (4) then took several months to conduct their first monitoring visits.

An FDA Form 483, Inspectional Observations, was issued at the end of the inspection because the sponsor failed to ensure proper monitoring of the study and to ensure that the study was conducted in accordance with the protocol and/or investigational plan. Specifically, the table below shows the gap in monitoring for Protocol LMS-002 that was identified during both the sponsor and clinical investigator inspections.

Site Number	Last Monitoring Visit by (b) (4)	First Monitoring Visit by (b) (4)	Monitoring Gap Documented During Inspection of Sponsor or Clinical Investigator	Site Inspected by FDA
1216	16 April 2012	1 May 2013	Sponsor	No
1227	26 March 2012	24 April 2013	Sponsor	Yes
1232	28 March 2012	16 April 2013	Sponsor	No
1246	13 March 2012	7 May 2013	Sponsor	No
1268	16 May 2013	25 April 2013	Clinical Investigator	Yes

In addition to this gap, when monitoring was in fact performed, the monitoring was found to be insufficient or ineffective. Review of the deviations for Protocol LMS-002 at four sites (1216,

1232, 1227, and 1246) uncovered the following examples where the deviations were not identified by the monitor for many months or even years after the event.

Subject Number	Date Protocol Deviation Occurred	Protocol Deviation First Identified by Study Monitor	Protocol Deviation Description	Reported to FDA
(b) (6)			Missed collection of 4-hour post dose pharmacokinetic samples that were required per protocol on Day 1 and Day 2 of Part 2 (Double-Blind Treatment Discontinuation) of the study	Yes
			Missed ECG that was required yearly per protocol during Part 4 (Open label Extension) of the study	Yes
			Incorrect dose (40 mg/day instead of 80 mg/day) taken during Part 2 and Part 3 of the study	Yes
			Missed Day 19 visit (Part 4, Open label extension) and all assessments that were to be performed on that day	Yes

Of note, there was a very high number of protocol deviations for Protocol LMS-002 (i.e., 350 protocol deviations with 223 deviations classified as minor and 127 classified as major) for its 54 enrolled subjects. Furthermore, the sponsor inspection revealed over 506 protocol deviations reported from all sources, with 146 protocol deviations being downgraded to not a protocol deviation by either the Catalyst medical monitor or the (b) (4) medical monitor at the end of the trial. Catalyst could not provide sufficient documentation for these protocol deviations and the reasons why they were downgraded. The sponsor also could not provide documentation that the protocol deviations were handled according to the procedure for handling and processing protocol deviations as described in the protocol. Finally, the sponsor was unable to provide documentation that the Catalyst medical monitor was consulted on any protocol deviations during the conduct of Protocol LMS-002 after October 2012, when Catalyst Pharmaceuticals, Inc became the license holder and sponsor for Firdapse in the United States.

Actions taken by the sponsor to bring non-compliant clinical sites into compliance were also assessed. According to the sponsor and also noted in the Clinical Study Report, Section 10.2, the number of major protocol deviations at Site 2007 for Protocol LMS-002 caused the firm to reanalyze the data to exclude the data obtained from these subjects from the efficacy analysis. While no clinical investigators were terminated from either protocol (LMS-002 and LMS-003), the sponsor could not provide sufficient documentation on what type of corrective and preventative actions were taken at this site as well as other sites when the deviations were identified.

Contract agreements and sponsor responsibility transfer agreements were reviewed as appropriate. Reporting practices for AEs, SAEs, and protocol deviations were reviewed. There was no evidence of under-reporting of AEs/SAEs to the Agency.

Reviewer's Comment: For Protocol LMS-002, although monitoring practices were problematic, review of source data was conducted at the clinical investigator sites for a substantial percentage of randomized subjects (i.e., 14 out 38 [37%] subjects randomized), and the primary and secondary endpoint data were verifiable. For Protocol LMS-003, there was adequate monitoring and sponsor oversight, and support was provided to maintain clinical site GCP compliance and data integrity.

{See appended electronic signature page}

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/s/

CHERYL A GRANDINETTI
09/22/2018

PHILLIP D KRONSTEIN
09/22/2018

KASSA AYALEW
09/23/2018

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)

Date of This Memorandum:	August 13, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 208078
Product Name and Strength:	Firdapse (amifampridine) tablet 10 mg
Applicant/Sponsor Name:	Catalyst Pharmaceuticals, Inc.
FDA Received Date:	August 8, 2018
OSE RCM #:	2018-716-2
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Neurology Products (DNP) requested that we review the revised blister pack container label and carton labeling for Firdapse (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised blister pack container label and carton labeling for Firdapse are acceptable from a medication error perspective. We have no further recommendations at this time.

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

[a] Rider B. Label and Labeling Review Memo for Firdapse (NDA 208078). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUL 20. RCM No.: 2018-716-1.

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/s/

BRIANA B RIDER
08/13/2018

LOLITA G WHITE
08/13/2018

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)

Date of This Memorandum:	July 20, 2018
Requesting Office or Division:	Division of Neurology Products
Application Type and Number:	NDA 208078
Product Name and Strength:	Firdapse (amifampridine) tablet 10 mg
Applicant/Sponsor Name:	Catalyst Pharmaceuticals, Inc.
FDA Received Date:	June 29, 2018
OSE RCM #:	2018-716-1
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Neurology Products requested that we review the revised labels and labeling for Firdapse (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.[a]

2 CONCLUSION

The revised containers and carton labeling are unacceptable from a medication error perspective. The "Rx only" statement does not appear on the blister pack container label as required by Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act.

3 RECOMMENDATIONS FOR CATALYST PHARMACEUTICALS, INC.

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

[a] Rider B. Label and Labeling Review for Firdapse (NDA 208078). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 22. RCM No.: 2018-716.

A. The “Rx only” statement does not appear on the blister pack container label as required by Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act. Include the “Rx only” statement on the blister pack container label and ensure the “Rx only” statement appears less prominent than other important information (e.g., proprietary name, established name, strength).

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JUNE 29, 2018

- Container labels
  - 60-count bottle
  - 240-count bottle
  - Blister pack
- Carton labeling
  - Blister pack sleeve
  - Blister pack carton

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/s/

BRIANA B RIDER
07/20/2018

LOLITA G WHITE
07/20/2018

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*****

Date of This Review:	May 22, 2018
Requesting Office or Division:	Division of Neurology Products
Application Type and Number:	NDA 208078
Product Name and Strength:	Firdapse (amifampridine) tablet 10 mg
Product Type:	Singe-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Catalyst Pharmaceuticals, Inc.
FDA Received Date:	March 28, 2018
OSE RCM #:	2018-716
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

This review is in response to a request by the Division of Neurology Products (DNP) for DMEPA to evaluate the proposed labels and labeling for Firdapse (amifampridine) tablets submitted on March 28, 2018 as part of the Applicant's resubmission package under NDA 208078. DNP requested that DMEPA review the proposed labels and labeling for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Catalyst Pharmaceuticals, Inc. submitted this application as NDA 208078 on December 16, 2015. On February 12, 2016, the application received a Refuse to File because the published literature provided in support of the Lambert-Eaton myasthenic syndrome (LEMS) and congenital myasthenic syndromes (CMS) was inadequate and a full abuse potential assessment was not conducted. The Applicant resubmitted the application on March 28, 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

We reviewed the proposed Prescribing Information (PI), container labels and carton labeling for areas of vulnerability which could lead to medication error. We identified the following areas which may be improved to decrease risk of medication error.

Prescribing Information (PI):

- The readability of the dosing information in Section 2.2 of the full PI can be improved to increase the prominence of critical dosing information.

Container Labels and Carton Labeling:

- The strength is not presented with space between the numeral dose and unit of measure which poses risk of a 10- to 100-fold overdose.
- The established name lacks prominence commensurate with the proprietary name in accordance with 21CFR201.10(g)(2).
- It is not immediately clear that the designated strength is per one tablet on the blister pack, which may lead to wrong dose medication error.
- The blister pack container label includes the undefined abbreviation (b) (4) which could result in misinterpretation and confusion.
- The net quantity statement appears in close proximity to the product strength on the container labels of the 60- and 240-count bottles and may contribute to confusion of product strength.
- We note the expiration date of DEC2202 as presented on the container labels of the 60- and 240-count bottles is unclear, which may contribute to degraded drug medication error.

We provide recommendations regarding these areas below in Section 4.1 and 4.2 to help minimize the potential for medication errors to occur with the use of the product.

4 CONCLUSION & RECOMMENDATIONS

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

4.1 RECOMMENDATIONS FOR THE DIVISION

A. We recommend Section 2.2 of the full PI be revised as follows to improve readability and increase prominence of critical dosing information:

(b) (4)

- The recommended starting dose of Firdapse is (b) (4) a day taken orally in divided doses 3 or 4 times per day.
- The dose can be increased by 5 mg per day every 3 or 4 days.
- (b) (4)
- The maximum single dose is 20 mg.

4.2 RECOMMENDATIONS FOR CATALYST PHARMACEUTICALS, INC.

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

A. General Comments for all carton labeling and container labels
    1. The strength is not presented with space between the numeral dose and unit of measure (i.e., 10mg). Place adequate space between the numeral dose and unit

of measure (i.e., 10 mg instead of 10mg) because the "m" is sometimes mistaken as a zero or two zeros, risking a 10- to 100-fold overdose.[a]

2. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21CFR201.10(g)(2).

B. Blister Pack Container Label & Blister Pack Sleeve

1. It is not immediately clear that the designated strength (i.e., 10 mg) is per unit (one tablet). Revise the strength statement (b) (4) to state "10 mg per tablet" to make it clear that the designated strength is per unit.[b]

C. Blister Pack Container Label

1. (b) (4)

D. Container Labels (60- and 240-count bottles)

1. The net quantity statement appears in close proximity to the product strength on the container label and may contribute to confusion of product strength. Relocate the net quantity statement away from the product strength. From postmarketing 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.
2. We note the expiration date format as presented (DEC2202) on the container labels is unclear. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend using a format like either:

   DDMMMYYYY (e.g., 31JAN2013)

   MMMYYYY (e.g., JAN2013)

   YYYY-MMM-DD (e.g., 2013-JAN-31)

   YYYY-MM-DD (e.g., 2013-01-31)

   Please confirm the expiration date format and ensure the expiration date is correct on the container labels.

---

[a] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2018 APR 25]. Available from: https://www.ismp.org/recommendations/error-prone-abbreviations-list

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 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 Firdapse received on March 28, 2018 from Catalyst Pharmaceuticals, Inc.

Table 2. Relevant Product Information for Firdapse	
Initial Approval Date	N/A
Active Ingredient	Amifampridine
Indication	(b) (4) treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) in adults.
Route of Administration	Oral
Dosage Form	Tablet
Strength	10 mg
Dose and Frequency	The recommended starting dose is (b) (4) per day in 3 to 4 divided doses. The dose can be escalated to a maximum of 80 mg per day by increasing the dose 5 mg per day every 3 or 4 days. The maximum single dose is 20 mg.
How Supplied	• 60-count bottle • 240-count bottle • Blister pack containing 10 tablets. Blister packs are supplied in cartons containing twelve blister packs.
Storage	Store at controlled room temperature, 20°C to 25°C (68°F to 77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F).
Container Closure	• Round, white, 150 cc wide-mouth, heavy weight, HDPE bottle with a round, white, (b) (4) • (b) (4) which contain the drug product tablets.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 25, 2018, we searched DMEPA's previous reviews using the terms, amifampridine, NDA 208078. Our search 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,[c] along with postmarket medication error data, we reviewed the following Firdapse labels and labeling submitted by Catalyst Pharmaceuticals, Inc.

- Container label received on March 28, 2018
  - 60-count bottle
  - 240-count bottle
  - Blister pack
- Carton labeling received on March 28, 2018
  - Blister pack sleeve
  - Blister pack carton
- Prescribing Information (Image not shown) received on March 28, 2018

G.2 Label and Labeling Images

Container Label: 60-count bottle

(b) (4)

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

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

BRIANA B RIDER
05/22/2018

LOLITA G WHITE
05/22/2018

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

NDA	208078
Brand Name	FIRDAPSE
Generic Name	Amifampridine
Sponsor	BioMarin Pharmaceutical Inc.
Indication	For the (b) (4) treatment of Lambert Eaton Myasthenic Syndrome
Dosage Form	Tablets
Drug Class	Non-specific, voltage-dependent potassium ion channel blocker
Therapeutic Dosing Regimen	The recommended starting dose is (b) (4) and divided over three or four doses per day. The recommended single maximum dose is 20 mg. The maximum daily dose is 80 mg per day. (b) (4)
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Single 80 mg dose
Submission Number and Date	001, 1/5/2016
Review Division	Division of Neurology Products

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

At the doses (30 mg and 60 mg) and exposures achieved in this study, there was no significant QTc prolongation effect of amifampridine detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between amifampridine 30 mg and placebo, and between amifampridine 60 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, the moxifloxacin profile over time is adequately demonstrated in Figure 2, indicating that assay sensitivity was established.

Part 1 was a randomized, double-blind, single-dose, escalation study, 6 subjects received single oral doses of 30 mg, 60 mg, 70 mg, and 80 mg amifampridine for a total exposure of 240 mg amifampridine per subject. Part 2 was a double-blind (except for moxifloxacin), randomized, single-site, 4-arm crossover design, 51 subjects received 30-mg amifampridine, 60-mg amifampridine, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for for Amifampridine (dosed of 30 mg and 60 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis – Part 2)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
30-mg Amifampridine	3	3.6	(0.8, 6.4)
60-mg Amifampridine	4	5.6	(2.9, 8.4)
*400 mg Moxifloxacin	4	10.6	(7.9, 13.4)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 6.9 ms.

The supratherapeutic single dose (60 mg) produces mean amifampridine C_{max} approximately 2-fold the mean maximum therapeutic C_{max} (i.e., at steady state with the proposed highest clinical dosing regimen, 20 mg q.i.d., in slow acetylator phenotype). Renal impairment has been reported to increase amifampridine exposure. There was less than a 1.5-fold increase in C_{max} of amifampridine in subjects with renal impairment. Administration of amifampridine with food as conducted in this study significantly decrease amifampridine C_{max} (~ by 40%). (b) (4) Overall, the exposure with the supratherapeutic single dose (60 mg) covers the expected high clinical exposure scenario for amifampridine. However, the study was conducted in only slow acetylators in order to maximize amifampridine exposure. In this case, exposures of metabolite 3-N-acetyl-amifampridine may not be covered (clear information of 3-N-acetyl-amifampridine in fast acetylators (and especially in renal impairment patients) is not available. A statistically significant positive relationship

between ΔΔQTcF and amifampridine metabolite (3-N-acetyl-amifampridine) concentrations was observed (slope = 0.0193 with 95% CI (0.0125, 0.0261). Although the predicted placebo-corrected change in QTcF is less than 10 ms at the geometric mean C_{maxs} of the doses studied in this study, the drug effect on QTc interval in fast acetylators with renal impairment cannot be reliably predicted.

2 PROPOSED LABEL

The following is the sponsor's proposed labeling language related to QT.

12.2 Pharmacodynamics

(b) (4)

QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

(b) (4)

The effect of FIRDAPSE on QTc interval prolongation was studied in a double blind, randomized, placebo and positive controlled study in 52 healthy individuals who are slow acetylators. At the exposure 2-fold the expected maximum therapeutic exposure of amifampridine, FIRDAPSE did not prolong QTc to any clinically relevant extent.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Amifampridine (3, 4-diaminopyridine; 3,4-DAP) is a voltage-dependent potassium (K+) channel blocker. The blockade of K+ channels causes depolarization of the presynaptic membrane and slows down or inhibits repolarization. Prolonged depolarization results in opening of slow voltage-dependent calcium (Ca^{2+}) channels and allows a subsequent influx of Ca^{2+}. The increased concentration of intracellular Ca^{2+} induces exocytosis of more synaptic vesicles containing acetylcholine (ACh), thus releasing an increased level of ACh into the synaptic cleft. The influx of ACh into the presynaptic cleft enhances neuromuscular transmission, providing improved muscle function. It is developed for the (b) (4) treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) and Congenital Myasthenic Syndromes (CMS), (b) (4)

3.2 MARKET APPROVAL STATUS

Amifampridine is approved for marketing in EU the symptomatic treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) since 2010.

3.3 PRECLINICAL INFORMATION

See Appendix 6.1.

3.4 PREVIOUS CLINICAL EXPERIENCE

See Appendix 6.1.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of amifampridine's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 106263. The sponsor submitted the study report QTC-002 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Phase 1, Double-Blind, Randomized, Crossover Study to Define the ECG Effects of Amifampridine Phosphate Using a Therapeutic and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women Who are Slow Acetylators: A Thorough QT Study

4.2.2 Protocol Number

QTC-002

4.2.3 Study Dates

First Enrollment: 09 May 2013
Last Dose Given: 08 October 2013

4.2.4 Objectives

The primary objective of this study was to assess the steady-state effects of a single therapeutic and supratherapeutic dose of amifampridine (administered as phosphate salt) compared with placebo on electrocardiogram (ECG) parameters in healthy adult male and female subjects who were slow acetylators.

The secondary objectives of this study were as follows:

- To establish the maximum tolerated dose (MTD) of amifampridine (as phosphate salt) in healthy volunteers who were defined as slow acetylators based on N-acetyl transferase (NAT) genotype.

- To characterize and compare the pharmacokinetics (PK) of the therapeutic and supratherapeutic dose levels of amifampridine in slow acetylators.
- To assess the safety of amifampridine (as phosphate salt) in slow acetylators.

4.2.5 Study Description

4.2.5.1 Design

This was a Phase 1, 2-part, single-site study with differing structure and goals in the 2 parts of the study. Subjects in both parts of the study were slow acetylators as determined by NAT genotyping.

Part 1 was a randomized, double-blind, single-dose, within-subject dose escalation study to determine the MTD to be used as the supratherapeutic dose in Part 2 of the study.

Part 2 was a double-blind (except for moxifloxacin), randomized, single-site, 4-arm crossover design assessing the ECG effects of therapeutic and supratherapeutic doses of amifampridine in subjects who were slow acetylators.

4.2.5.2 Controls

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

4.2.5.3 Blinding

Moxifloxacin group conducted in an open-label.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Part 2:

Subjects were randomized to receive a treatment sequence that included all 4 treatment regimens, with each dose administered for 1 day within 50 minutes of starting breakfast (a standard high-fat meal). The treatment regimens are defined as follows:

- Placebo;
- 400 mg moxifloxacin (positive control);
- 30 mg amifampridine (administered as phosphate salt; therapeutic dose); and
- 60 mg amifampridine (administered as phosphate salt at the MTD; supratherapeutic dose).

Subjects started their first treatment period on day 1. Each treatment period consisted of 4 days: 1 day of study drug treatment and assessments, and 3 days of washout. Treatment with study drug occurred on Days 1, 5, 9, and 13.

4.2.6.2 Sponsor's Justification for Doses

The amifampridine plasma steady state is achieved by the second or third dose of the day with 20 mg dosing 4 times daily (QID); (based on minimum observed plasma concentration values in slow and fast acetylators). Time-dependent changes in amifampridine exposure are unsubstantial over multiple days of dosing. When given at 20 mg QID, a single 30 mg dose produces a mean Cmax of 89.6 ng/mL and an area under the plasma concentration-time curve from time zero to infinity (AUC0-inf) of 234 ng-hr/mL in slow acetylators; this encompasses the steady state C_{max} and AUC ranges achieved with multiple dosing at 20 mg QID.

Therefore, a 30-mg single dose of amifampridine (administered as phosphate salt) represents steady-state exposure at 20 mg QID and was used in this study to test for potential changes in ECG parameters in healthy volunteers.

The MTD of amifampridine had not been determined with amifampridine (or base), nor has the influence of acetylator status on the MTD been investigated. To determine an appropriate supratherapeutic dose for the QT portion (Part 2) of this study, a within-subject, single daily dose, dose escalation study was conducted in slow acetylators to determine the MTD (Part 1 of this study) prior to the QT assessment portion of this study (Part 2). The maximum planned single dose was 100 mg.

Reviewer's Comment: The supratherapeutic single dose (60 mg) produces mean amifampridine Cmax approximately 2-fold the mean maximum therapeutic C_{max} (i.e., at steady state with the proposed highest clinical dosing regimen (20 mg q.i.d.) in slow acetylator phenotype). Renal impairment has been reported to increase amifampridine exposure. There was less than a 1.5-fold increase in C_{max} of amifampridine in subjects with renal impairment. Administration of amifampridine with food as conducted in this study significantly decrease amifampridine C_{max} (~ by 40%). [redacted] (b) (4) *Overall, the exposure with the supratherapeutic single dose (60 mg) covers the expected high clinical exposure scenario for amifampridine. However, the study was conducted only slow acetylators in order to maximize amifampridine exposure. In this case, exposures of metabolite 3-N-acetyl-amifampridine may not be covered and clear information of 3-N-acetyl-amifampridine in fast acetylators (and especially in renal impairment patients) is not available\.*

4.2.6.3 Instructions with Regard to Meals

Treatments for both parts of the study were administered with 240 mL of water in the morning on days of administration, within 50 minutes of starting breakfast (a standard high-fat meal). [redacted] (b) (4)

Reviewer's Comment: Acceptable. [redacted] (b) (4)

4.2.6.4 ECG and PK Assessments

ECG

Electrocardiograms for the treatment days were obtained as triplicate 12-lead ECGs at each timepoint, which were downloaded from the H-12+ flash card approximately one minute apart on Day 1 of each arm of the crossover trial. Baseline timepoints were obtained prior to each dose at -45 minutes, -30 minutes, and -15 minutes, and triplicate ECGs were obtained at the following times from dosing in each arm of the trial: 0.5 hours, 0.75 hours, 1.0 hours, 1.25 hours, 1.5 hours, 2 hours, 3 hours, 4 hours, 8 hours, 12 hours, 16 hours, and 24 hours post-dose. Therefore, triplicate ECGs were analyzed at each of the 3 baseline timepoints (a total of 9 ECGs) on Day 1 in each of each of the 4 arms, equaling a total of 36 baseline ECGs per subject. Triplicate ECGs were also analyzed at each of the 12 post-dose timepoints on Day 1 of each arm resulting in a total of 144 post-dose ECGs per subject.

PK

In Part 1, samples for plasma PK were collected at Pre-dose (trough level), and 0.5 hour, 0.75 hours (± 2 minutes); 1.0 hour, 1.5 hours, 2 hours, 4 hours, 6 hours, 8 hours(± 5 minutes); 10 hours, 12 hours, 16 hours, and 24 hours (± 10 minutes) post-dose.
During Part 2, individual PK sampling occurred after each individual QT ECG extraction. In Part 2, blood for PK sampling was obtained for all subjects on day of study drug administration (Days 1, 5, 9 and 13). Samples for plasma PK were collected at Pre-dose (trough level). Each post-dose PK draw was to occur after each QTc ECG: 0.5 hour (+2 minutes), 0.75 hour (+2 minutes), 1.0 hour (+5 minutes), 1.25 hours (+5 minutes), 1.5 hours (+5 minutes), 2 hours (+5 minutes), 3 hours (+5 minutes), 4 hours (+5 minutes), 8 hours (+5 minutes), 12 hours (+10 minutes), 16 hours (+10 minutes), and 24 hours (+10 minutes) post-dose.

Reviewer's Comment: The timing of ECGs and plasma samples for PK are acceptable.

4.2.6.5 Baseline

Sponsor used pre-dose QTc values at approximately 15, 30, and 45 min for the particular treatment period as baselines.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

All subjects in Part 1 and Part 2 were slow acetylators according to genotype, as per the inclusion criteria.

In Part 1, a total of 6 subjects (4 female and 2 male) received single oral doses of 30 mg, 60 mg, 70 mg, and 80 mg amifampridine (administered as phosphate salt) for a total exposure of 240 mg amifampridine per subject.

In Part 2, a total of 51 subjects (37 male and 14 female) received single oral doses of 30 mg and 60 mg amifampridine (administered as phosphate salt) for a total exposure of 90 mg amifampridine per subject. One subject (Subject (b) (6)) received a single oral dose of 30 mg amifampridine (as phosphate salt). Subject (b) (6) (Part 2) self-withdrew from the study on Day 4 due to a family bereavement.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was time-matched baseline-adjusted mean difference between amifampridine (30 mg and 60 mg) and placebo in ΔQTcF. The sponsor used a mixed effect model and the results are presented in Table 2. The model included period, treatment, time, and treatment by time interaction as fixed effects; subject as a random effect; and the baseline as covariate. The sponsor concluded that amifampridine has no QTcF prolongation effect, as the upper bounds of the 2-sided 90% CIs for the mean differences between amifampridine (dosed of 30 mg and 60 mg) and placebo were below 10 ms.

Table 2 : Sponsor's ΔΔQTcF Analyses for amifampridine 30 mg, amifampridine 60 mg, and Moxifloxacin 400 mg

Time (h)	30 mg Amifampridine (N=52)			60 mg Amifampridine (N=50)			400 mg Moxifloxacin (N=51)		
	Estimate [1][a]	Lower Bound [2][b]	Upper Bound [2][b]	Estimate [1][a]	Lower Bound [2][b]	Upper Bound [2][b]	Estimate [1][a]	Lower Bound [3][c]	Upper Bound [3][c]
0.5	1.1	-1.5	3.7	3.9	1.3	6.5	1.3	-2.3	4.8
0.75	2.0	-0.6	4.6	2.5	-0.1	5.2	2.5	-1.1	6.0
1.0	1.2	-1.4	3.8	3.7	1.1	6.3	3.4	-0.2	6.9
1.25	0.6	-2.0	3.2	2.9	0.3	5.6	3.2	-0.4	6.7
1.5	2.7	0.1	5.3	4.0	1.4	6.6	5.2	1.6	8.8
2	4.2	1.7	6.8	4.9	2.2	7.5	6.4	2.9	10.0
3	3.6	1.0	6.1	5.2	2.6	7.8	10.2	6.7	13.8
4	2.7	0.1	5.2	5.5	2.8	8.1	10.5	7.0	14.0
8	0.3	-2.3	2.9	4.1	1.5	6.7	9.5	6.0	13.1
12	-0.6	-3.2	2.1	-1.0	-3.6	1.6	7.3	3.8	10.8
16	0.0	-2.5	2.6	-0.0	-2.6	2.6	6.6	3.0	10.1
24	-1.5	-4.1	1.1	-2.3	-5.0	0.3	4.5	1.0	8.1

Source: Table 14.2.3.16

N, number of subjects studied; QTcF, QT interval corrected using Fridericia's formula.

[a] [1] The Mixed Effects General Linear Model is fit for change from baseline and includes terms for: treatment, time, baseline, sex, and the treatment by time interaction, as well as period and sequence (crossover design). Placebo correction was done using a diffs option within a LSMEANS statement in the SAS procedure PROC MIXED. Covariance structure is UN.

[b] [2] Lower/upper Bound = lower/upper two-sided 90% model-based confidence limit.

[c] [3] Lower/upper Bound = lower/upper two-sided 97.5% model-based confidence limit (moxifloxacin is Bonferroni-corrected for 4 timepoints).

Reviewer's Comments: We will provide our independent analysis results in Section 5.2. Our results are similar to the sponsor's results of QTcF.

4.2.8.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the ΔQTcF effect for moxifloxacin. The results are presented in Table 2. The lower bounds of the 2-sided 90% CI for the mean differences between moxifloxacin and placebo were greater than 5 ms met at 3 time points, therefore establishing assay sensitively.

Reviewer's Comments: We will provide our independent analysis results in Section 5.2. Our results are similar to the sponsor's results of QTcF.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc ≤450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms, and changes from baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. No subject QTcF > 480 ms and ΔQTcF > 60 ms.

Reviewer's Comments: We will provide our independent analysis results in Section 5.2. Our results are similar to the sponsor's result of categorical analyses.

4.2.8.3 Safety Analysis

Single oral doses of amifampridine (administered as phosphate salt) up to 70 mg in Part 1, and up to 60 mg in Part 2, were considered safe and well tolerated when administered to healthy male and female subjects. At the 80 mg dose level (Part 1), vomiting or significant nausea within 5 hours of drug administration was observed in 2 or more subjects, and therefore dose de-escalation criteria were met. There were no SAEs, and no discontinuations from the study due to an AE. One subject (Subject (b) (6)) withdrew from Part 2 of the study due to a family bereavement. The majority of AEs reported were mild in severity, and resolved without the need for concomitant medication. There were no severe AEs reported. The most frequently reported AEs were paraesthesias, which are well known side effects of treatment with amifampridine. Overall 309 (49.8%) of the 621 AEs reported in Part 1 and Part 2 were paraesthesias (including paraesthesia, hypoaesthesia, paraesthesia oral, and hypoaesthesia oral), all of which were considered related to the study drug.

The MTD of amifampridine (administered as phosphate salt) in Part 1 was considered to be 70 mg (as no de-escalation criteria had been met at this dose level). However, this dose was not considered to be suitable as the supratherapeutic dose level for Part 2, based on the fact that 70 mg was associated with distressing abdominal pain and vomiting in one subject (Subject (b) (6)) who demonstrated poor tolerability. Overall, abdominal pain (including abdominal pain upper) was observed in 3 (50.0%) subjects at the 70 mg dose level. It was therefore agreed that a dose level of 60 mg would be suitable as the supratherapeutic dose for Part 2 in order to avoid reductions in drug absorption caused by vomiting and heart rates effects secondary to abdominal pain and vomiting. In Part 2, single oral doses of amifampridine were well tolerated up to 60 mg by both male and female subjects.

There were no clinically significant findings in any clinical laboratory evaluations, vital signs, 12-lead ECG, or physical examination. Although paresthesias were reported during the study, no subjects demonstrated painful paresthesias, as assessed by the VAS scale, following treatment with amifampridine in Part 1.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The mean plasma amifampridine concentration-time profile following single dose administration of amifampridine (as phosphate salt) up to 80 mg in Part 1 and up to 60 mg in Part 2 are presented in Figure 1. The mean plasma 3-N-acetyl-amifampridine (amifampridine metabolite) concentration-time profile following single dose administration of amifampridine (as phosphate salt) up to 80 mg in Part 1 and up to 60 mg in Part 2 are presented in Figure 2.

Figure 1: Arithmetic Mean Plasma Concentration Profiles of Amifampridine in Part 1 (Top) and Arithmetic Mean Plasma Concentration Profiles of Amifampridine in Part 2 (Bottom)

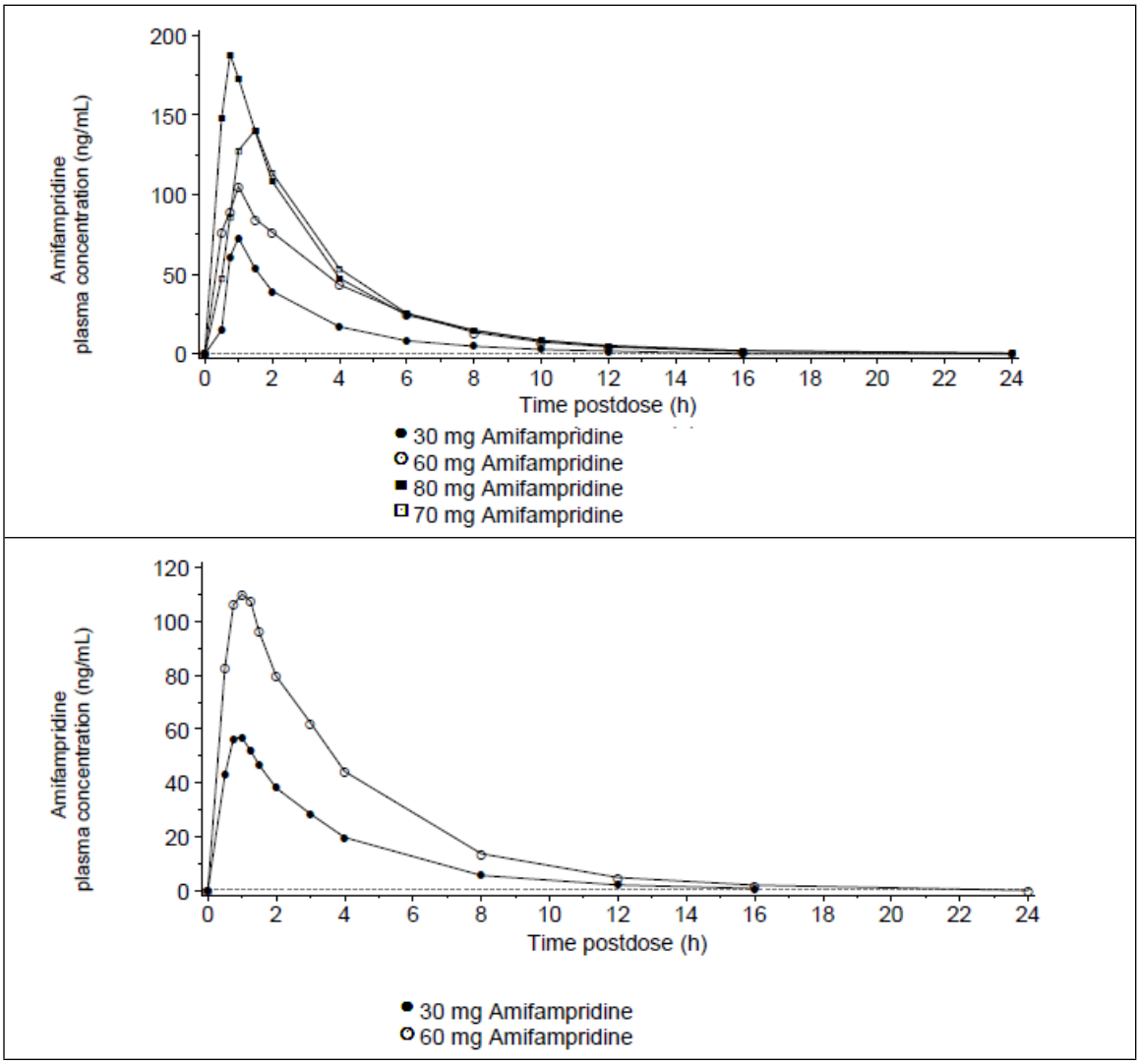
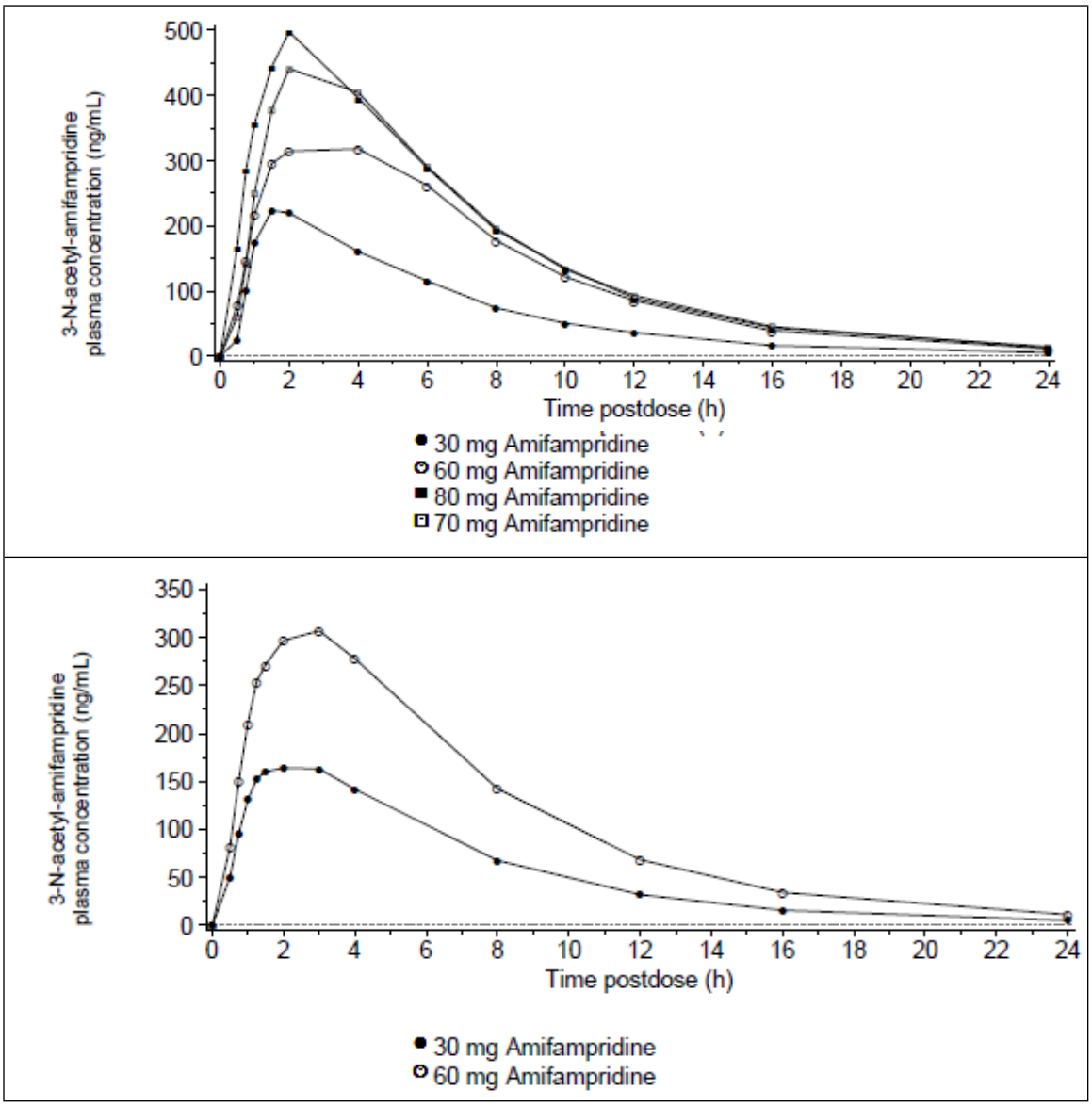


Figure 2: Arithmetic Mean Plasma Concentration Profiles of 3-N-acetyl-amifampridine in Part 1 (Top) and Arithmetic Mean Plasma Concentration Profiles of 3-N-acetyl-amifampridine in Part 2 (Bottom)



The PK results are presented in Table 3, Table 4 for amifampridine and Table 5, Table 6 for the metabolite (3-N-acetyl-amifampridine).

Table 3: Summary of Pharmacokinetic Parameters for Amifampridine – Part 1

		Amifampridine			
		30 mg (N=5)	60 mg (N=6)	70 mg (N=5)	80 mg (N=4)
$AUC_{0\text{-last}}$ (h.ng/mL)	Arithmetic mean (SD)	193 (52.9)	430 (22.7)	539 (138)	602 (101)
	Geometric mean (CV%)	188 (25.6)	429 (5.4)	525 (26.9)	596 (16.7)
	Median	186	431	550	588
	Min-Max	144-282	395-454	382-681	501-733
$AUC_{0\text{-inf}}$ (h.ng/mL)	Arithmetic mean (SD)	195 (53.0)	433 (22.1)	543 (136)	607 (101)
	Geometric mean (CV%)	190 (25.4)	433 (5.2)	529 (26.3)	601 (16.5)
	Median	189	434	554	594
	Min-Max	145-284	399-456	386-682	506-734
C_{max} (ng/mL)	Arithmetic mean (SD)	65.1 (22.7)	134 (58.0)	152 (28.8)	184 (34.0)
	Geometric mean (CV%)	61.7 (39.2)	123 (46.5)	150 (21.4)	181 (18.7)
	Median	62.1	117	157	182
	Min-Max	34.3-97.8	66.0-215	104-181	145-227
T_{max} (h)	Arithmetic mean (SD)	1.26 (0.494)	1.96 (2.05)	1.30 (0.274)	0.875 (0.144)
	Median	1.05	1.25	1.50	0.875
	Min-Max	0.750-2.00	0.500-6.00	1.00-1.50	0.750-1.00
$t_{½}$ (h)	Arithmetic mean (SD)	2.43 (0.274)	2.80 (0.940)	2.96 (0.504)	3.39 (0.928)
	Median	2.44	2.50	2.92	3.29
	Min-Max	2.00-2.69	2.09-4.58	2.40-3.76	2.41-4.57

Source: Table 11-6 on Page 98 in study-qtc-002.pdf

Table 4: Summary of Pharmacokinetic Parameters for Amifampridine – Part 2

		Amifampridine	
		30 mg (N=52)	60 mg (N=50)
$AUC_{0\text{-last}}$ (h.ng/mL)	Arithmetic mean (SD)	213 (56.0)	467 (95.4)
	Geometric mean (CV%)	206 (25.7)	458 (21.0)
	Median	203	465
	Min-Max	121-369	290-713
$AUC_{0\text{-inf}}$ (h.ng/mL)	Arithmetic mean (SD)	216 (56.3)	471 (95.7)
	Geometric mean (CV%)	209 (25.5)	461 (20.9)
	Median	205	468
	Min-Max	124-373	295-715
C_{max} (ng/mL)	Arithmetic mean (SD)	72.1 (33.3)	137 (49.2)
	Geometric mean (CV%)	65.7 (45.3)	128 (37.2)
	Median	62.2	125
	Min-Max	22.5-181	69.5-264
T_{max} (h)	Arithmetic mean (SD)	1.28 (0.888)	1.25 (0.823)
	Median	1.00	1.00
	Min-Max	0.500-4.00	0.500-4.00
$t_{½}$ (h)	Arithmetic mean (SD)	2.58 (0.416)	3.02 (0.641)
	Median	2.52	3.11
	Min-Max	1.88-4.12	2.02-4.92

Source: Table 11-7 on Page 99 in study-qtc-002.pdf

Table 5: Summary of Pharmacokinetic Parameters for 3-N-acetyl-amifampridine – Part 1

		Amifampridine			
		30 mg (N=5)	60 mg (N=6)	70 mg (N=5)	80 mg (N=4)
$AUC_{0\text{-last}}$ (h.ng/mL)	Arithmetic mean (SD) Geometric mean (CV%) Median Min-Max	1630 (254) 1614 (16.2) 1735 1320-1878	2988 (702) 2908 (27.2) 3008 1777-3764	3447 (502) 3419 (14.3) 3352 2929-4176	3836 (264) 3829 (6.8) 3789 3567-4199
$AUC_{0\text{-inf}}$ (h.ng/mL)	Arithmetic mean (SD) Geometric mean (CV%) Median Min-Max	1669 (273) 1651 (17.0) 1750 1348-1936	3062 (729) 2976 (28.0) 3142 1790-3803	3527 (525) 3496 (14.7) 3390 3012-4262	3946 (346) 3935 (8.5) 3839 3659-4447
C_{max} (ng/mL)	Arithmetic mean (SD) Geometric mean (CV%) Median Min-Max	245 (51.2) 241 (21.2) 234 188-301	411 (46.5) 409 (11.4) 409 363-469	410 (44.2) 408 (10.7) 409 362-471	489 (39.8) 488 (8.0) 479 453-544
T_{max} (h)	Arithmetic mean (SD) Median Min-Max	1.90 (1.19) 1.50 1.00-4.00	2.83 (1.81) 2.00 1.50-6.00	2.40 (0.894) 2.00 2.00-4.00	2.03 (0.0500) 2.00 2.00-2.10
$t_{½}$ (h)	Arithmetic mean (SD) Median Min-Max	4.08 (1.02) 3.55 3.40-5.80	3.98 (1.01) 3.46 3.37-5.91	4.06 (0.645) 4.00 3.42-4.95	4.31 (0.910) 4.07 3.55-5.53

Source: Table 11-8 on Page 103 in study-qtc-002.pdf

Table 6: Summary of Pharmacokinetic Parameters for 3-N-acetyl-amifampridine – Part 2

		Amifampridine	
		30 mg (N=52)	60 mg (N=50)
$AUC_{0\text{-last}}$ (h.ng/mL)	Arithmetic mean (SD) Geometric mean (CV%) Median Min-Max	1326 (235) 1305 (18.7) 1349 713-1900	2610 (488) 2565 (19.1) 2568 1492-3987
$AUC_{0\text{-inf}}$ (h.ng/mL)	Arithmetic mean (SD) Geometric mean (CV%) Median Min-Max	1355 (245) 1332 (19.1) 1374 724-1932	2677 (518) 2628 (19.6) 2626 1523-4146
C_{max} (ng/mL)	Arithmetic mean (SD) Geometric mean (CV%) Median Min-Max	191 (43.4) 187 (21.6) 184 121-312	340 (70.0) 333 (21.1) 334 197-506
T_{max} (h)	Arithmetic mean (SD) Median Min-Max	2.23 (1.01) 2.00 0.750-4.00	2.43 (0.918) 2.00 1.00-4.00
$t_{½}$ (h)	Arithmetic mean (SD) Median Min-Max	4.08 (0.548) 4.01 2.89-5.42	4.21 (0.557) 4.16 2.98-5.54

Source: Table 11-9 on Page 104 in study-qtc-002.pdf

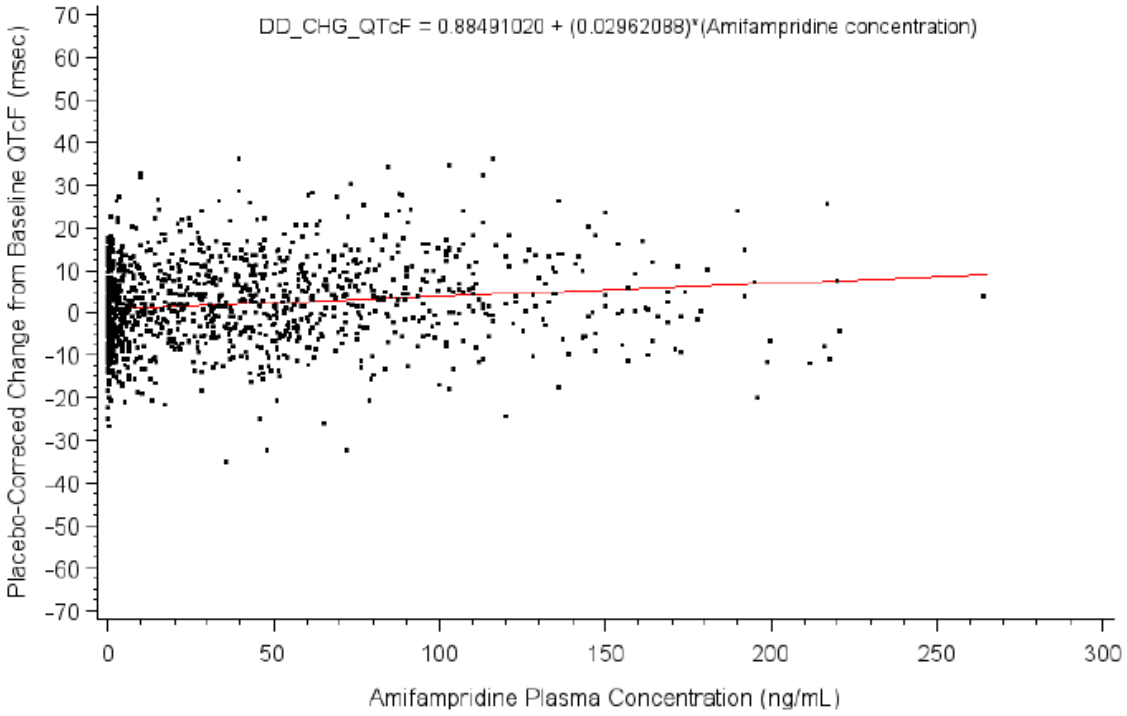
C_{max} and AUC values following administration of 60 mg amifampridine were about 2 fold those with 30 mg amifampridine. Similar increases were reported for 3-N-acetyl-amifampridine.

4.2.8.4.2 Exposure-Response Analysis

The pharmacokinetic-pharmacodynamic (PK-PD) analysis explored the relationship between the placebo-corrected change from baseline in QTc intervals (QTcF and QTcB) and plasma concentrations of amifampridine.

For this PK-PD analysis, a linear mixed effects modeling approach was used to examine the relationship between the placebo-corrected change from baseline in QTc intervals (QTcF and QTcB) and plasma concentration of amifampridine.

Figure 3: Relationship between the exposure (plasma concentration of amifampridine) and the effect (change in QTcF from baseline) for amifampridine



Source : Figure 11-6 on Page 92 in study-qtc-002.pdf

Table 7 details the PK-PD model results showing the slopes of the relationships for plasma concentration of amifampridine and the placebo-corrected change from baseline predicted change at Cmax for QTcF and QTcB.

Table 7: Placebo-Corrected Change from Baseline versus Amifampridine Plasma Concentration - Estimates from Linear Mixed Model

ECG Parameter	Slope of Plasma Concentration Effect on ΔΔQTc [1][a]	Standard Error of Slope of Plasma Concentration Effect on ΔΔQTc [1][a]	P-value for Slope of Plasma Concentration Effect on ΔΔQTc [1][a]	30 mg Amifampridine		60 mg Amifampridine	
				Predicted ΔΔQTc at Average C_{max}[c]	One-sided Upper 95% CI of Predicted ΔΔQTc [2]b	Predicted ΔΔQTc at Average C_{max}[d]	One-sided Upper 95% CI of Predicted ΔΔQTc [2][b]
QTcF	0.02962088	0.00922085	0.0025	3.03	4.74	4.91	7.30
QTcB	-0.01331572	0.01171195	0.2621	-0.96	1.15	-1.80	1.14

Source: Table 14.2.3.19

CI, confidence interval, ECG, electrocardiogram; N, number of subjects studied; QTcB, QT interval corrected using Bazett's formula; QTcF, QT interval corrected using Fridericia's formula.

[a] [1] Linear mixed effects model is fit for placebo-corrected change from baseline versus the amifampridine plasma concentration. Subject random effects on the intercept and slope (i.e., concentration) are included.

[b] [2] Upper CI = upper one-sided 95% linear mixed model based confidence limit.

[c] C_{max} = 72.4745098 ng/mL

[d] C_{max} = 135.7600000 ng/mL

Source : Table 11-4 on Page 91 in study-qtc-002.pdf

The PK-PD model showed that the slope for QTcF for amifampridine was relatively flat but statistically significant positive, and the predicted placebo-corrected change from baseline at C_{max} for the supratherapeutic dose of amifampridine was 4.91 ms.

Reviewer's Analysis: A plot of ΔΔQTc vs. drug concentrations is presented in Figure 6 based on the reviewer's independent analysis. Consistent with the sponsor's result, no clinically relevant QTc prolongation is expected at the studied amifampridine exposure range.

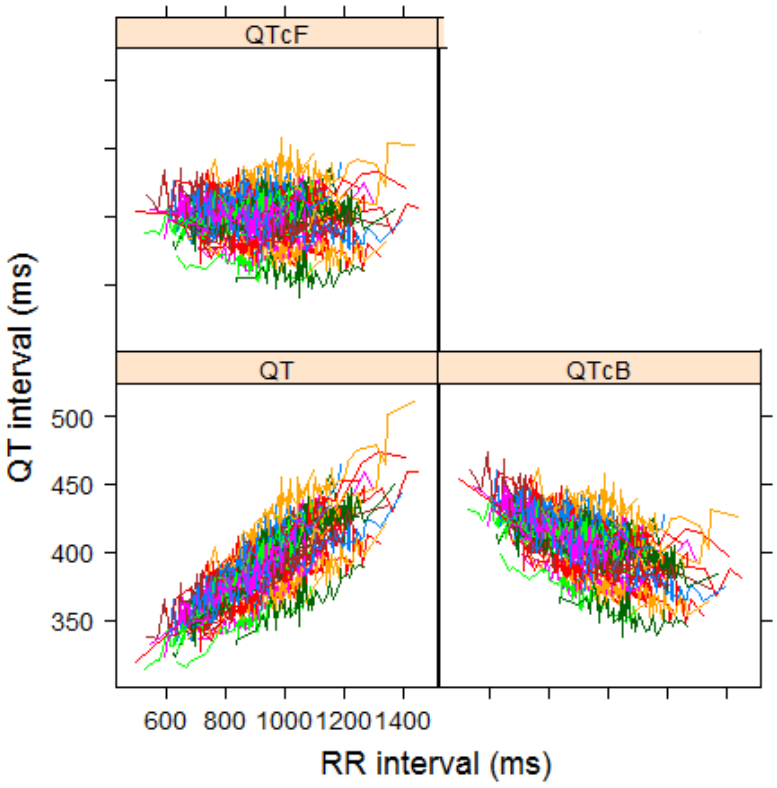
5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

This review did not evaluate of the QT/RR correction method because the sponsor provided only QTcB and QTcF correction intervals. QTcF was used for the primary statistical analysis.

The relationship between different correction methods and RR is presented in Figure 4.

Figure 4: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Amifampridine

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment as fixed effect and baselines as covariate. The analysis results are listed in Table 8. The largest upper bounds of the 2-sided 90% CI for the mean differences between amifampridine 30 mg and placebo, and between amifampridine 60 mg and placebo are 6.4 ms and 8.4 ms, respectively.

Table 8: Analysis Results of ΔQTcF and ΔΔQTcF for Amifampridine 30 mg and 60 mg (Part 2)

		Treatment Group							
	Placebo	30 mg Amifampridine				60 mg Amifampridine			
	ΔQTcF	ΔQTcF		ΔΔQTcF		ΔQTcF		ΔΔQTcF	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	-4.1	51	-2.8	1.3	(-1.0, 3.6)	51	0.1	4.2	(1.9, 6.5)
0.75	-4.7	52	-2.6	2.2	(-0.5, 4.8)	50	-2.0	2.7	(0.0, 5.4)
1	-4.4	52	-3.1	1.3	(-1.6, 4.1)	51	-0.7	3.7	(0.8, 6.6)
1.25	-4.5	52	-3.6	0.9	(-1.9, 3.7)	51	-1.3	3.2	(0.4, 6.0)
1.5	-4.9	52	-1.9	3.0	(0.3, 5.7)	50	-0.6	4.2	(1.5, 7.0)
2	-5.4	52	-1.0	4.4	(1.7, 7.1)	50	-0.4	5.0	(2.2, 7.7)
3	-3.9	52	-0.3	3.6	(0.8, 6.4)	51	1.3	5.2	(2.4, 8.0)
4	-1.5	51	1.2	2.7	(-0.0, 5.4)	50	4.1	5.6	(2.9, 8.4)
8	-0.9	52	-0.5	0.4	(-2.3, 3.2)	50	3.3	4.2	(1.5, 7.0)
12	-1.2	48	-2.1	-1.0	(-3.3, 1.4)	50	-2.1	-0.9	(-3.3, 1.4)
16	6.6	52	6.7	0.1	(-2.9, 3.1)	50	6.5	-0.1	(-3.2, 3.0)
24	1.7	51	0.1	-1.5	(-4.3, 1.3)	49	-0.8	-2.5	(-5.3, 0.4)

5.2.1.1 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9. The largest unadjusted 90% lower confidence interval is 7.9 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 6.9 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

Table 9: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin 400 mg

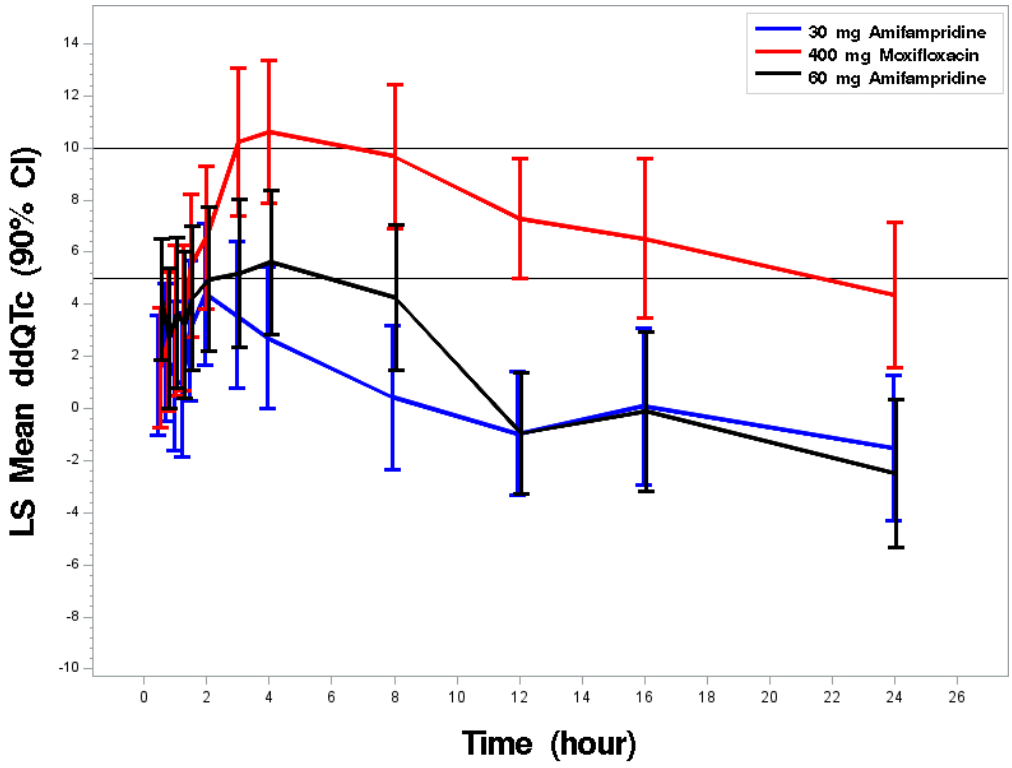
		Treatment Group				
	Placebo	400 mg Moxifloxacin				
	ΔQTcF	ΔQTcF		ΔΔQTcF		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	*Adj. 90% CI
30 min.	-4.1	51	-2.5	1.6	(-0.8, 3.9)	(-1.6, 4.7)
45 min	-4.7	50	-2.1	2.6	(-0.1, 5.3)	(-1.1, 6.2)
1	-4.4	50	-1.0	3.4	(0.5, 6.3)	(-0.6, 7.3)
1.25	-4.5	51	-1.0	3.5	(0.7, 6.3)	(-0.4, 7.3)
1.5	-4.9	51	0.6	5.5	(2.8, 8.2)	(1.8, 9.2)
2	-5.4	50	1.2	6.6	(3.8, 9.3)	(2.8, 10.3)
3	-3.9	50	6.3	10.2	(7.4, 13.1)	(6.3, 14.1)
4	-1.5	50	9.1	10.6	(7.9, 13.4)	(6.9, 14.4)
8	-0.9	50	8.7	9.7	(6.9, 12.4)	(5.9, 13.5)
12	-1.2	51	6.1	7.3	(5.0, 9.6)	(4.1, 10.5)
16	6.6	50	13.1	6.5	(3.5, 9.6)	(2.4, 10.7)
24	1.7	51	6.0	4.4	(1.6, 7.2)	(0.6, 8.2)

* Bonferroni method was applied for multiple endpoint adjustment of 4 time points (significant at the 0.025 level).

5.2.1.2 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

Figure 5: Mean and 90% CI ΔΔQTcF Time Course



5.2.1.3 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 450 ms and 480 ms, and >500 mg. No subject's QTcF is above 480 ms.

Table 10: Categorical Analysis for QTcF

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms	480 ms<Value<=500 ms	Value>500
30 mg Amifampridine	52	52 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
400 mg Moxifloxacin	51	49 (96.1%)	2 (3.9%)	0 (0.0%)	0 (0.0%)
60 mg Amifampridine	51	51 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Placebo	51	50 (98.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)

Table 11 lists the categorical analysis results for ΔQTcF. No subject's change from baseline is above 60 ms.

Table 11: Categorical Analysis of ΔQTcF

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms	60 ms<Value<=90 ms	Value>90 ms
30 mg Amifampridine	52	52 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
400 mg Moxifloxacin	51	49 (96.1%)	2 (3.9%)	0 (0.0%)	0 (0.0%)
60 mg Amifampridine	50	49 (98.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)
Placebo	51	51 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the ΔHR effect. The model includes treatment as fixed effect and baseline as covariate. The analysis results are listed in Table 12. The largest upper bounds of the 2-sided 90% CI for the mean differences between amifampridine 30 mg and placebo, and between amifampridine 60 mg and placebo are 1.9 bpm and 2.3 bpm, respectively. Table 13 presents the categorical analysis of HR. No subject who experienced HR interval greater than 100 bpm is in amifampridine group.

Table 12: Analysis Results of ΔHR and ΔΔHR for Amifampridine 30 mg, Amifampridine 60 mg, and Moxifloxacin 400 mg (Part 2)

		Treatment Group											
	Placebo	30 mg Amifampridine				400 mg Moxifloxacin				60 mg Amifampridine			
	ΔHR	ΔHR		ΔΔHR		ΔHR		ΔΔHR		ΔHR		ΔHR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	-4.0	51	-5.2	-1.2	(-3.1, 0.7)	51	-4.0	-0.1	(-2.0, 1.9)	51	-5.6	-1.6	(-3.6, 0.3)
0.75	-4.6	52	-7.4	-2.8	(-4.9, -0.7)	50	-4.7	-0.2	(-2.3, 1.9)	51	-9.0	-4.4	(-6.5, -2.3)
1	-5.3	52	-9.2	-3.9	(-5.9, -1.9)	50	-5.5	-0.1	(-2.2, 1.9)	51	-9.8	-4.4	(-6.5, -2.4)
1.25	-5.0	52	-10.4	-5.4	(-7.5, -3.3)	51	-6.0	-1.0	(-3.1, 1.1)	51	-9.7	-4.6	(-6.8, -2.5)
1.5	-5.4	52	-9.8	-4.4	(-6.2, -2.5)	51	-6.1	-0.6	(-2.5, 1.2)	50	-10.3	-4.9	(-6.8, -3.0)
2	-6.4	52	-9.4	-3.1	(-4.9, -1.2)	50	-6.7	-0.4	(-2.3, 1.5)	50	-11.4	-5.0	(-6.9, -3.1)
3	-8.3	52	-11.1	-2.8	(-4.6, -1.0)	50	-8.5	-0.1	(-1.9, 1.7)	51	-13.3	-5.0	(-6.8, -3.2)
4	-10.9	51	-11.2	-0.3	(-2.0, 1.4)	50	-9.8	1.1	(-0.6, 2.8)	50	-13.2	-2.2	(-3.9, -0.5)
8	-12.1	52	-13.2	-1.1	(-3.1, 0.8)	50	-10.4	1.6	(-0.4, 3.6)	50	-12.1	-0.1	(-2.0, 1.9)
12	-5.6	48	-7.5	-1.9	(-4.1, 0.3)	51	-6.1	-0.5	(-2.7, 1.6)	50	-7.4	-1.8	(-4.0, 0.4)
16	-15.6	52	-15.9	-0.3	(-2.4, 1.9)	50	-15.4	0.2	(-1.9, 2.4)	50	-15.5	0.1	(-2.1, 2.3)
24	-9.4	51	-11.1	-1.7	(-3.8, 0.3)	51	-10.1	-0.7	(-2.7, 1.3)	49	-10.2	-0.8	(-2.9, 1.3)

Table 13: Categorical Analysis for HR

Treatment Group	Total N	HR <= 100 bpm	HR >100 bpm
30 mg Amifampridine	52	52 (100%)	0 (0.0%)
400 mg Moxifloxacin	51	51 (100%)	0 (0.0%)
MTD Amifampridine	51	51 (100%)	0 (0.0%)
Placebo	51	51 (100%)	0 (0.0%)

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the ΔPR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 14. The largest upper bounds of the 2-sided 90% CI for the mean differences between amifampridine 30 mg and placebo, and between amifampridine 60 mg and placebo are 2.6 ms and 2.8 ms, respectively. Table 15 presents the categorical analysis of PR. Six subjects who experienced PR interval greater than 200 ms are in amifampridine 30-mg and 60-mg groups.

Table 14: Analysis Results of ΔPR and ΔΔPR for Amifampridine 30 mg, Amifampridine 60 mg, and Moxifloxacin 400 mg (Part 2)

		Treatment Group											
		30 mg Amifampridine				400 mg Moxifloxacin				60 mg Amifampridine			
	ΔPR	ΔPR		ΔΔPR		ΔPR		ΔΔPR		ΔPR		ΔΔPR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	0.9	51	-2.9	-3.8	(-6.2, -1.4)	51	-1.5	-2.4	(-4.8, 0.0)	51	-2.2	-3.1	(-5.5, -0.7)
0.75	1.0	52	-2.8	-3.8	(-6.0, -1.5)	50	-0.2	-1.2	(-3.4, 1.1)	51	-4.2	-5.1	(-7.4, -2.9)
1	0.8	52	-4.3	-5.1	(-7.6, -2.6)	50	-0.3	-1.1	(-3.7, 1.4)	51	-6.4	-7.2	(-9.8, -4.7)
1.25	1.0	52	-3.4	-4.3	(-7.0, -1.6)	51	-0.1	-1.1	(-3.8, 1.6)	51	-6.6	-7.5	(-10.3, -4.8)
1.5	-0.7	52	-3.3	-2.6	(-5.3, 0.1)	51	0.5	1.2	(-1.5, 3.9)	50	-7.4	-6.7	(-9.5, -4.0)
2	-1.1	52	-4.5	-3.4	(-6.2, -0.5)	50	-1.1	-0.0	(-2.9, 2.9)	50	-4.2	-3.1	(-6.0, -0.2)
3	-0.4	52	-2.8	-2.4	(-5.3, 0.5)	50	-0.9	-0.6	(-3.5, 2.3)	51	-3.7	-3.3	(-6.2, -0.4)
4	0.9	51	0.1	-0.8	(-3.4, 1.9)	50	-0.5	-1.4	(-4.1, 1.3)	50	-1.2	-2.1	(-4.8, 0.6)
8	3.1	52	1.8	-1.3	(-3.9, 1.2)	50	1.5	-1.6	(-4.1, 1.0)	50	1.0	-2.1	(-4.7, 0.5)
12	-0.0	48	0.1	0.1	(-2.5, 2.6)	51	-2.3	-2.3	(-4.8, 0.3)	50	0.2	0.3	(-2.3, 2.8)
16	6.7	52	4.1	-2.7	(-5.5, 0.1)	50	5.3	-1.4	(-4.3, 1.4)	50	4.4	-2.3	(-5.2, 0.5)
24	3.7	51	2.8	-0.9	(-3.6, 1.9)	51	4.5	0.8	(-2.0, 3.5)	49	2.0	-1.7	(-4.5, 1.1)

Table 15: Categorical Analysis for PR

Treatment Group	Total N	PR <= 200 ms	PR >200 ms
30 mg Amifampridine	52	46 (88.5%)	6 (11.5%)
400 mg Moxifloxacin	51	45 (88.2%)	6 (11.8%)
60 mg Amifampridine	51	46 (90.2%)	5 (9.8%)
Placebo	51	47 (92.2%)	4 (7.8%)

5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the ΔQRS effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 16. The largest upper bounds of the 2-sided 90% CI for the mean differences between amifampridine 30 mg and placebo, and between amifampridine 60 mg and placebo are 1.7 ms and 2.1 ms, respectively. **Error! Reference source not found.**Table 17 presents the categorical analysis of QRS. Three subjects who experienced QRS interval greater than 110 ms are in amifampridine 30-mg and 60-mg groups.

Table 16: Analysis Results of ΔQRS and ΔΔQRS for Amifampridine 30 mg, Amifampridine 60 mg, and Moxifloxacin 400 mg (Part 2)

		Treatment Group											
		30 mg Amifampridine				400 mg Moxifloxacin				60 mg Amifampridine			
	ΔQRS	ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS		ΔQRS		ΔQRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	0.9	51	0.8	-0.1	(-1.0, 0.7)	51	0.6	-0.3	(-1.1, 0.5)	51	0.9	-0.0	(-0.8, 0.8)
0.75	0.7	52	0.5	-0.1	(-1.1, 0.8)	50	0.4	-0.2	(-1.2, 0.7)	51	0.6	-0.1	(-1.0, 0.9)
1	0.7	52	0.7	-0.1	(-0.9, 0.8)	50	0.4	-0.3	(-1.2, 0.6)	51	0.3	-0.4	(-1.3, 0.5)
1.25	0.2	52	0.7	0.5	(-0.5, 1.4)	51	0.6	0.4	(-0.5, 1.3)	51	0.4	0.2	(-0.8, 1.1)
1.5	-0.1	52	0.4	0.5	(-0.5, 1.4)	51	0.5	0.6	(-0.3, 1.5)	50	0.4	0.5	(-0.5, 1.4)
2	0.8	52	0.2	-0.5	(-1.4, 0.3)	50	0.4	-0.4	(-1.3, 0.4)	50	0.3	-0.4	(-1.3, 0.4)
3	-0.4	52	0.3	0.8	(-0.2, 1.7)	50	0.4	0.9	(-0.1, 1.8)	51	0.1	0.6	(-0.4, 1.5)
4	-0.3	51	-0.0	0.2	(-0.6, 1.1)	50	0.5	0.7	(-0.1, 1.6)	50	0.7	1.0	(0.1, 1.9)
8	1.0	52	0.5	-0.5	(-1.4, 0.3)	50	0.4	-0.6	(-1.5, 0.3)	50	0.7	-0.3	(-1.2, 0.6)
12	0.0	48	0.3	0.3	(-0.6, 1.2)	51	0.6	0.5	(-0.4, 1.5)	50	0.6	0.6	(-0.3, 1.5)
16	0.7	52	1.2	0.5	(-0.6, 1.5)	50	1.4	0.6	(-0.4, 1.7)	50	1.7	1.0	(-0.1, 2.1)
24	0.8	51	1.2	0.4	(-0.7, 1.4)	51	0.1	-0.7	(-1.8, 0.3)	49	0.9	0.0	(-1.0, 1.1)

60 mg

Table 17: Categorical Analysis for QRS

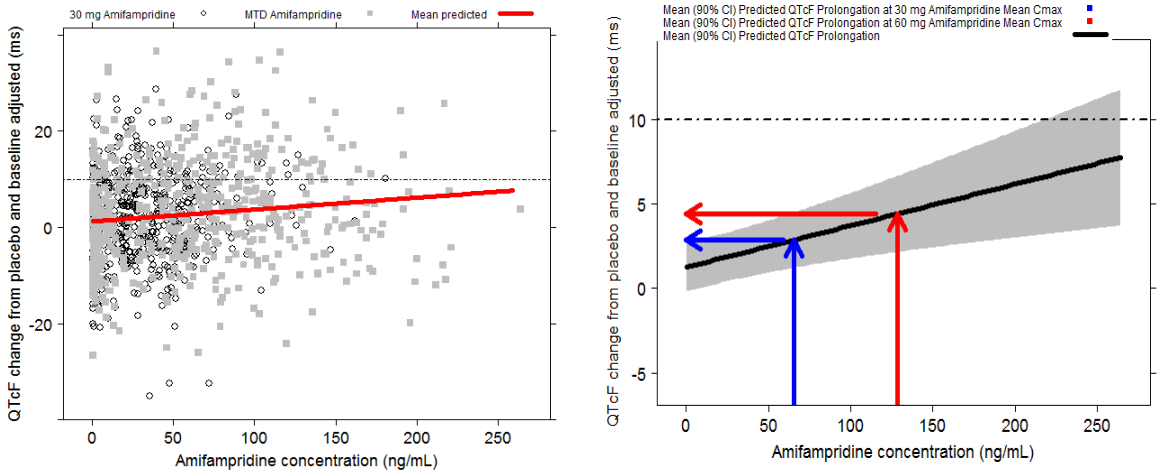
Treatment Group	Total N	QRS <= 110 ms	QRS > 110 ms
30 mg Amifampridine	52	49 (94.2%)	3 (5.8%)
400 mg Moxifloxacin	51	49 (96.1%)	2 (3.9%)
60 mg Amifampridine	51	49 (96.1%)	2 (3.9%)
Placebo	51	50 (98.0%)	1 (2.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean amifampridine concentration-time profile is illustrated previously in Figure 1.

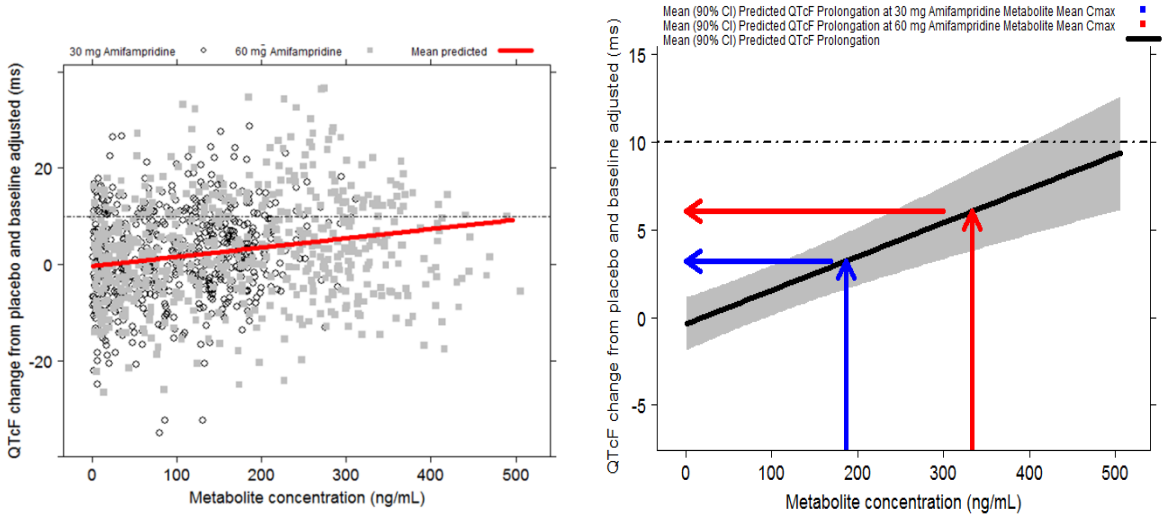
The relationship between ΔΔQTcF and amifampridine concentrations is visualized in Figure 6. Although a statistically significant positive slope was observed (slope = 0.0246 with 95% CI (0.0097, 0.0395), the predicted placebo-corrected change in QTcF is less than 10 ms at the geometric mean C_{maxs} of the studied doses.

Figure 6: ΔΔ QTcF vs. Amifampridine Concentration



The relationship between ΔΔQTcF and amifampridine metabolite (3-N-acetyl-amifampridine) concentrations is visualized in Figure 7. Although a statistically significant positive slope was observed (slope = 0.0193 with 95% CI (0.0125, 0.0261), the predicted placebo-corrected change in QTcF is less than 10 ms at the geometric mean C_{maxs} of the studied doses.

Figure 7: ΔΔ QTcF vs. Amifampridine Metabolite Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 ECG Parameters

No clinically relevant effect seen on heart rate as well as the PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure	The recommended starting dose is [redacted] (b) (4) and divided over three or four doses per day. The recommended single maximum dose is 20 mg. The maximum daily dose is 80 mg per day (Section 1.14.1.2 of NDA; ISE). At the single maximum proposed clinical dose (20 mg free base equivalents) C_{max} is 16.2 ± 4.56 ng/mL and $AUC_{0-\infty}$ is 26.2 ± 2.62 ng·h/mL in healthy subjects with a fast acetylator phenotype and C_{max} is 56.7 ± 16.1 ng/mL and $AUC_{0-\infty}$ is 146 ± 31.4 ng·h/mL in healthy subjects with a slow acetylator phenotype (Study FIR-001). At steady state with the proposed clinical dosing regimen (20 mg free base equivalents q.i.d., Day 4) mean C_{max} (%CV) is 13.6 (48.4) ng/mL and mean $AUC_{0-\infty}$ (%CV) is 31.9 (31.7) ng·h/mL in healthy subjects with a fast acetylator phenotype and mean C_{max} (%CV) is 72.5 (60.6) ng/mL and mean $AUC_{0-\infty}$ (%CV) is 190 (17.6) ng·h/mL in healthy subjects with a slow acetylator phenotype (Study FIR-001).	
Maximum tolerated dose	Single oral doses of amifampridine up to 70 mg were considered safe and well tolerated when administered to healthy subjects with a slow acetylator phenotype. Single oral doses up to 80 mg were tested (Study QTC-002).	
Principal adverse events	Nausea and vomiting were reported at a 80 mg single oral dose in healthy subjects with a slow acetylator phenotype (Study QTC-002). The following adverse events were reported at a rate of at least 5% of treatment naive LEMS patients treated with amifampridine: oral paresthesia, paresthesia, headache, nausea, diarrhea, dizziness, constipation, oral hypoesthesia, nasopharyngitis, upper respiratory infection, pain in extremity, and fall (Section 2.7.4.14.5.1). The following adverse events were reported at a rate of at least 5% in CMS patients treated with amifampridine: paresthesia or hypoesthesia, paresthesia oral, and palpitations (Section 2.7.4.14.6.5).	
Maximum dose tested	Single Dose	80 mg free base equivalents (Study QTC-002)
	Multiple Dose	20 mg free base equivalents q.i.d. for 3 days followed by a single morning dose on Day 4 (Study FIR-001)
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean C_{max} (%CV) is 181 (18.7) ng/mL and $AUC_{0-\infty}$ (%CV) is 601 (16.5) ng·h/mL in healthy subjects with slow acetylator phenotype (Study QTC-002).
	Multiple Dose	Following single morning dose on Day 4: mean C_{max} (%CV) is 13.6 (48.4) ng/mL and mean $AUC_{0-\infty}$ (%CV) is 31.9 (31.7) ng·h/mL in healthy subjects with a fast acetylator phenotype and mean C_{max} (%CV) is 72.5 (60.6) ng/mL and mean $AUC_{0-\infty}$ (%CV) is 190 (17.6) ng·h/mL in healthy subjects with a slow acetylator phenotype (Study FIR-001).

Range of linear PK	Amifampridine exhibits linear plasma PK with respect to C_{max} and $AUC_{0-\infty}$ over the tested single-dose range of 5 to 30 mg in healthy subjects (Study FIR-001).	
Accumulation at steady state	There was no accumulation of amifampridine following multiple doses (20-mg q.i.d. oral dosing regimen over 4 days in healthy subjects; Study FIR-001).	
Metabolites	Amifampridine is metabolized to a single major metabolite, 3-N-acetyl amifampridine (Study Nos. BMN125-10-037 and BMN125-10-038), which is considered inactive (Study No. (b) (4) 100014186).	
Absorption	Absolute/Relative Bioavailability	Peak concentration of amifampridine after a single 20 mg dose in healthy subjects was 56.7 ± 16.1 ng/mL for slow acetylators and 16.2 ± 4.56 ng/mL for fast acetylators (Study FIR-001).
	Tmax	• In healthy subjects, after a single 20 mg dose, mean T_{max} (SD) was 1.07 (0.543) hours for slow acetylators and 1.04 (0.368) hours for fast acetylators (Study FIR-001). • The primary metabolite of amifampridine, 3-N-acetyl amifampridine, is considered inactive. In healthy subjects, after a single 10 mg dose of amifampridine, T_{max} (%CV) of 3-N-acetyl amifampridine was 0.72 (27.4) hours in slow acetylators and 1.10 (27.4) hours in rapid acetylators (Study REN-002).
Distribution	Vd/F or Vd	Volume of distribution has not been determined in humans. Following a single i.v. administration in rats at an amifampridine free base dose level of 0.4 mg/kg, the volume of distribution at steady state (Vss) was estimated to be 6,654 mL/kg in males, and 8,129 mL/kg in females (Study No. BMN125-10-036).
	% bound	[^{14}C]amifampridine was observed to be stable in human plasma under in vitro experimental conditions. [^{14}C]amifampridine was not highly bound to plasma proteins in human plasma, with percent unbound ranging from 88.0% to 91.2% (Study BMN125-10-041).
Elimination	Route	Amifampridine and its metabolites are eliminated by renal excretion (urine). After single-dose administration of amifampridine, 93.2% to 100% of the administered dose is eliminated in the urine as parent drug and metabolite over 24 hours (Study LMS-001).
	Terminal t½	• After a single 20 mg dose of amifampridine in healthy subjects, $T_{1/2}$ (SD) was 2.93 (0.59) hours in slow acetylators and 1.23 (0.31) hours in fast acetylators (Study FIR-001).

		• The primary metabolite of amifampridine, 3-N-acetyl amifampridine, is considered inactive. After a single 10 mg dose of amifampridine in healthy subjects, $T_{1/2}$ (%CV) of 3-N-acetyl amifampridine was 4.03 (17.2) hours in slow acetylators and 4.28 (16.1) hours in rapid acetylators (Study REN-002).
	CL/F or CL	After a single 10 mg dose of amifampridine in healthy subjects, mean CL/F (%CV) in healthy subjects was 171.4 (19.9) in slow acetylators and 1052.1 (27.0) in rapid acetylators (Study REN-002).
Intrinsic Factors	Age	There is no clear relationship between amifampridine pharmacokinetic parameters and age. Pharmacokinetic parameters of amifampridine have not been evaluated in pediatric patients, and data from studies including subjects under 18 years of age are limited.
	Sex	No differences were observed between healthy males and females for both fast and slow acetylators with regard to pharmacokinetic parameters.
	Race	Because of the small nature of the subject population, evaluation of study results by race was not feasible.
	Hepatic & Renal Impairment	The effects of amifampridine have not been studied in patients with hepatic impairment. These studies will be completed as a post-marketing commitment. The exposure of amifampridine was approximately 3-fold higher in subjects with renal impairment compared with subjects with normal renal function. There was less than a 1.5-fold increase in C_{max} of amifampridine in subjects with renal impairment compared with subjects with normal renal function (Study REN-002).
Extrinsic Factors	Drug interactions	No specific drug interaction studies have been conducted with amifampridine. However, based on the pharmacodynamic properties of amifampridine and case reports, the following should be considered: drugs liable to lower the epileptic threshold and NAT2 inhibitors. In vitro studies showed no significant inhibition of human CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 (Study No. BMN125-10-054). There was no significant induction of human CYP1A2, CYP2B6, and CYP3A4 (Study

		No. BMN125-10-053). Transporter studies showed that [^{14}C]amifampridine at concentrations ranging from 1 to 100 µM was not a substrate or inhibitor of P-glycoprotein (Study No. BMN125-10-042). Amifampridine phosphate (30 µM) also did not significantly inhibit OCT1, OCT2, OAT1, OAT3, OATP1B1, BSEP, and BCRP mediated transport of probe substrates (Study No. BMN125-12-008). Compared to vehicle control, 30 µM amifampridine phosphate inhibited OATP1B3 mediated probe substrate transport by 16.8%. In addition, the 3-N-acetyl metabolite of amifampridine phosphate (40 µM) did not significantly inhibit any of the transporters studied (OCT1, OCT2, OAT1, OAT3, OATP1B1, OATP1B3, BSEP, BCRP, and P-gp).
	Food Effects	Administration of amifampridine with food had a statistically significant effect on reducing the maximal concentration and overall exposure. There was a statistically significant decrease of 40% in C_{max} and 20% in AUC when amifampridine was administered in the fed state (standard high fat breakfast) compared to fasting state (Study LMS-001).
Expected High Clinical Exposure Scenario	There is one published report of an overdose with amifampridine (Boerma, 1995). Seven days prior to hospital admission, the patient was given more than 3-times the maximum recommended total daily dose of amifampridine (360 mg); the patient's usual dose of 10 mg 6 times a day was mistakenly altered to 60 mg 6 times a day. Given the linear kinetic response to amifampridine, the expected fold-change in C_{max} and AUC would be 6-fold over her normal therapeutic dose. The patient was admitted to the hospital due to general weakness, paresthesia, nausea, vomiting, and palpitations. The patient experienced generalized convulsions and supraventricular tachycardia that resolved after intervention. Four days after admission, the patient experienced a sudden, unexplained cardiac arrest and was successfully resuscitated. The patient made a full recovery after withdrawal of amifampridine for 5 days and was later discharged.	
Preclinical Cardiac Safety	In vitro hERG assay (Study No. 1711/AGE/03): Amifampridine phosphate had no effect on K^+ currents in hERG CHO-K1 cells at concentrations of up to 30 µM (i.e., no IC_{50} value could be determined). In vitro action potential duration study in rabbit Purkinje fibers (Study No. 1710/AGE/03): After stimulation at 1 Hz and 0.2 Hz, amifampridine phosphate at concentrations of 30 and 100 µM lengthened the duration of the action potential by 18% and 40%, respectively, during bradycardia. The concentrations tested in Study 1710/AGE/03 and Study 1711/AGE/03 of 30 and 100 µM amifampridine phosphate were	

	approximately >50-fold higher than the mean maximum plasma concentration (Cmax) obtained in humans at a single dose of 20 mg (FIR-001; slow acetylators). In vivo CV safety pharmacology study in telemetered dogs (Study No. BMN125-10-059): Eight male telemetry-instrumented dogs were given vehicle control article (RO water) or amifampridine phosphate at 0.05, 0.15, or 0.50 mg/kg via oral gavage in a double Latin square study design to assess the potential effects on cardiovascular function. Treatment with amifampridine phosphate shortened the PR interval up to -8% and increased arterial pulse pressure up to +7%. Amifampridine phosphate had no apparent effect on QRS, QT, or QTc intervals, and no qualitative ECG abnormalities were attributable to treatment. It is important to note that dogs are non-acetylators. Additional in vivo cardiac safety information: Results from GLP dog repeat-dose toxicity studies showed no treatment-related adverse effects on ECGs following daily oral dosing of amifampridine phosphate for 4 weeks (Study Nos. (b) (4) 266/014 and (b) (4) AA40847) and 39 weeks (Study No. S12032).
Clinical Cardiac Safety	Included in the application are 4 clinical pharmacology studies and 1 controlled clinical study in LEMS subjects. A total of 219 subjects were exposed to amifampridine in sponsored studies. Additionally, there are 4 legacy studies which exposed subjects to amifampridine. These include 27 healthy subjects, 75 subjects with LEMS, 50 subjects with CMS, and 715 subjects with other neurological conditions (including multiple sclerosis). A total of 400 subjects were exposed to amifampridine in published literature reports. Amifampridine is a voltage-dependent potassium channel blocker, and as such, has the potential to be arrhythmogenic; however, there are relatively few reports of clinically significant cardiovascular reactions. In sponsored studies with available CRFs and data sets, 5 cases of palpitations were recorded. Each of these events was reported to resolve and no subjects discontinued amifampridine treatment due to palpitations. In legacy studies with no available CRFs, 8 cases of palpitations were reported; 3 were determined to be possibly related to amifampridine treatment. No relevant or significant change in corrected QT interval duration was observed in healthy subjects receiving amifampridine. Other cardiac events reported in subjects receiving amifampridine include atrial fibrillation, tachycardia, cardiac arrest, myocardial infarction, congestive cardiac failure, sinus bradycardia, and sick sinus syndrome. One event of tachycardia has been reported; this was determined to be possibly related to amifampridine treatment. The study drug was not changed. Three episodes of cardiac arrest and two episodes of myocardial infarction were reported across all tiers. None of these cases were considered related to amifampridine treatment. One episode of congestive cardiac failure was reported.

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