CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209321Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application (NDA)
Application Number(s)	209321; Original 1 and Original 2
Priority or Standard	Priority
Submit Date(s)	June 15, 2018
Major Amendment	January 16, 2019
PDUFA Goal Date	May 15, 2019
Division/Office	Division of Neurology Products/Office of Drug Evaluation-I
Reviewer Name(s)	Rainer W. Paine, MD, PhD
Review Completion Date	January 31, 2019
Established/Proper Name	Amifampridine/3,4-diaminopyridine
(Proposed) Trade Name	Ruzurgi
Applicant	Jacobus Pharmaceutical Co. Inc.
Dosage Form(s)	Tablets: 10 mg, functionally scored
Applicant Proposed Dosing Regimen(s)	[redacted] (b) (4) The maximum recommended total daily dose [redacted] (b) (4)) mg per 24 hours taken in divided doses, with no single dose exceeding 30 mg.
Applicant Proposed Indication(s)/Population(s)	Lambert-Eaton Myasthenic Syndrome (LEMS)/patients [redacted] (b) (4)
Recommendation on Regulatory Action	Original 1: Approval Original 2: Tentative approval
Recommended Indication(s)/Population(s) (if applicable)	Original 1: Treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients 6 years to less than 17 years of age Original 2: [redacted] (b) (4)

Reference ID: 4428593

Table of Contents

Glossary 9

1. Executive Summary 11
   1.1. Product Introduction 11
   1.2. Conclusions on the Substantial Evidence of Effectiveness 11
   1.3. Benefit-Risk Assessment 12
   1.4. Patient Experience Data 18

2. Therapeutic Context 19
   2.1. Analysis of Condition 19
   2.2. Analysis of Current Treatment Options 20

3. Regulatory Background 21
   3.1. U.S. Regulatory Actions and Marketing History 21
   3.2. Summary of Presubmission/Submission Regulatory Activity 22
   3.3. Foreign Regulatory Actions and Marketing History 23

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety 24
   4.1. Office of Scientific Investigations (OSI) 24
   4.2. Product Quality 24
   4.3. Clinical Microbiology 25
   4.4. Nonclinical Pharmacology/Toxicology 25
   4.5. Clinical Pharmacology 25
      4.5.1. Mechanism of Action 25
      4.5.2. Metabolism and Elimination 25
      4.5.3. Pediatric Dosing 26
   4.6. Devices and Companion Diagnostic Issues 27
   4.7. Consumer Study Reviews 27

5. Sources of Clinical Data and Review Strategy 27
   5.1. Table of Clinical Studies 27
   5.2. Review Strategy 32

Reference ID: 4428593

6. Review of Relevant Individual Trials Used to Support Efficacy 33
6.1. Study JPC 3,4-DAPPER (DAPPER) 33
6.1.1. Study Design 33
6.1.2. Study Results 44
6.2. JPC 3,4-DAP DUKE RCT 59
6.2.1. Study Design 59
6.2.2. Study Results 61

7. Integrated Review of Effectiveness 66
7.1. Assessment of Efficacy Across Trials 66
7.1.1. Primary Endpoints 68
7.1.2. Secondary and Other Endpoints 68
7.1.3. Subpopulations 69
7.1.4. Dose and Dose-Response 69
7.1.5. Onset, Duration, and Durability of Efficacy Effects 70
7.2. Additional Efficacy Considerations 70
7.2.1. Considerations on Benefit in the Postmarket Setting 70
7.2.2. Evidence of Pediatric Efficacy 70
7.3. Integrated Assessment of Effectiveness 72

8. Review of Safety 73
8.1. Safety Review Approach 73
8.2. Review of the Safety Database 74
8.2.1. Overall Exposure 74
8.2.2. Relevant characteristics of the safety population: 77
8.2.3. Adequacy of the safety database: 79
8.3. Adequacy of Applicant's Clinical Safety Assessments 79
8.3.1. Issues Regarding Data Integrity and Submission Quality 79
8.3.2. Categorization of Adverse Events 79
8.3.3. Routine Clinical Tests 80
8.4. Safety Results 81
8.4.1. Deaths 81

Reference ID: 4428593

8.4.2. Serious Adverse Events ... 82
8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects ... 84
8.4.4. Significant Adverse Events ... 85
8.4.5. Treatment Emergent Adverse Events and Adverse Reactions ... 86
8.4.6. Laboratory Findings ... 92
8.4.7. Vital Signs ... 94
8.4.8. Electrocardiograms (ECGs) ... 94
8.4.9. QT ... 95
8.4.10. Immunogenicity ... 96
8.5. Analysis of Submission-Specific Safety Issues ... 96
8.5.1. Cardiac Disorders ... 96
8.5.2. Seizures ... 98
8.6. Safety Analyses by Demographic Subgroups ... 99
8.7. Specific Safety Studies/Clinical Trials ... 101
8.8. Additional Safety Explorations ... 101
8.8.1. Human Carcinogenicity or Tumor Development ... 101
8.8.2. Human Reproduction and Pregnancy ... 101
8.8.3. Pediatrics ... 101
8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound ... 102
8.9. Safety in the Postmarket Setting ... 104
8.9.1. Safety Concerns Identified Through Postmarket Experience ... 104
8.9.2. Expectations on Safety in the Postmarket Setting ... 104
8.9.3. Additional Safety Issues from Other Disciplines ... 104
8.10. Integrated Assessment of Safety ... 104

9. Advisory Committee Meeting and Other External Consultations ... 105

10. Labeling Recommendations ... 106
10.1. Prescription Drug Labeling ... 106
10.2. Nonprescription Drug Labeling ... 106

11. Risk Evaluation and Mitigation Strategies (REMS) ... 106

Reference ID: 4428593

12. Postmarketing Requirements and Commitments 106

13. Appendices 106

13.1. References 106

13.2. Financial Disclosure 108

13.3 Cardiac Disorder Narrative Tables 112

13.4 Changes in Translation of Verbatim Terms to Preferred Terms in RPV162 121

13.5 Pediatric Safety Data for 3,4-DAP in 22 Patients of the Expanded Access Program: 7 with LEMS, 15 with CMS 123

13.6 ECG Data Plots for DAPPER Study 127

13.7 DAPPER Study: Major Protocol Deviations by Subject – All Randomized Subjects. Source: CSR 129

13.8 Seizure Narrative Table 130

Reference ID: 4428593

Table of Tables

Table 1: Features of LEMS in patients with or without an underlying cancer..... 20
Table 2: Listing of Clinical Trials Relevant to this NDA/BLA 30
Table 3: Schedule of Procedures..... 36
Table 4: Subject Accrual by site 45
Table 5 Subject Disposition- All randomized subjects. Source: Applicant submission..... 46
Table 6: Baseline Demographic Characteristics in the DAPPER Study 47
Table 7: Baseline LEMS Characteristics, ITT Population 48
Table 8: LEMS Signs and Symptoms Characteristics, ITT Population 49
Table 9: 3,4,-DAP and other LEMS medication at baseline 50
Table 10: Primary Efficacy Endpoint: Summary of >30% Deterioration in the Final Timed Up & Go (3TUG) Test Upon Withdrawal of Study Drug (Stage II) – Efficacy, Intent-to-treat and Per-protocol Populations..... 53
Table 11: Summary of Categorized Degree of Change (7 Categories) in the Final Timed Up & Go (3TUG) Test Upon Withdrawal of Study Drug (Stage II) – Efficacy, Intent-to-treat and Per-protocol Populations. Source: Applicant submission 54
Table 12: Secondary Efficacy Endpoint: Summary of the Final W-SAS Assessment During Stage II – Efficacy and Per-protocol Populations..... 56
Table 13: Summary of the Last Available Post-Dose Compound Muscle Action Potential (CMAP) During Stage II – Efficacy Population. Source: DAPPER CSR 57
Table 14: Summary of Physician Assessment of Treatment Effect – Efficacy Population. Source: DAPPER CSR 58
Table 15: Comparison of placebo and treated groups at baseline. Source: Applicant submission. 62
Table 16: QMG Results from the Double-blind Portion of Duke RCT Study – Per-Protocol Population..... 63
Table 17: CMAP Results from the Double-blind Portion of the Duke RCT Study – Per-Protocol Population..... 64
Table 18: Symptomatic Response to Treatment: Patient Questionnaire..... 64
Table 19: Change in Swallowing Times After Therapy – Per-Protocol Population..... 65
Table 20: Change in Walking Times After Therapy – Per-Protocol Population 65
Table 21: Comparison of Efficacy Results Across Studies. Source: Reviewer summary of submitted results. 66
Table 22: Serial 3TUG measurements in a 9-year-old pediatric LEMS patient following 3,4-DAP initiation and dose titration. Source: Case narrative for subject (b) (6) 71
Table 23: 3,4-DAP Safety Population, Size, and Denominators..... 75
Table 24: Duration of Exposure in RPV162 Database..... 76
Table 25: Duration of Exposure in Special Populations Database..... 76
Table 26: Demographic and Baseline Characteristics in the Controlled DAPPER Study Population 77

Reference ID: 4428593

Table 27: Serious Treatment-emergent Adverse Events from Expanded Access RPV162 Dataset. Source: MAED analysis of submitted data. 82
Table 28: Applicant's Data - Adverse Events Leading to Discontinuation in the Expanded Access Population (RPV162, N=162) 84
Table 29: Severe Adverse Events Occurring in More Than One Subject in the Open-Label Expanded Access Database RPV162 85
Table 30: Treatment-emergent Adverse Events in the Controlled DAPPER Study. Source: MAED analysis of submitted data. 86
Table 31: Grouping of Treatment-emergent Adverse Events in the Controlled DAPPER Study Safety Database. 87
Table 32: Treatment-emergent Adverse Events from the RPV162 Dataset. Source: MAED analysis of submitted data. 88
Table 33: Grouping of Treatment-emergent Adverse Events from the RPV162 Dataset 89
Table 34: Adverse Events Grouped Under Arrhythmia in the RPV162 Dataset 90
Table 35: Adverse Events Summary Comparing the Expanded Access RPV162 and Special Populations Groups. Source: Applicant submission 91
Table 36: Treatment-emergent Adverse Events in ≥ 2 Subjects in the TQT study 92
Table 37: Adverse Events Related to 3,4-DAP Use with Frequency >5% by Sex in RPV162 Dataset 99
Table 38: Adverse Events Related to 3,4-DAP Use with Frequency >5% by Age in RPV162 Dataset: Age <= 60 100
Table 39: Cardiac-Related Deaths in 3,4-DAP Studies 112
Table 40: Cardiac-Related Non-Fatal Serious Adverse Events in 3,4-DAP Studies 115
Table 41: Seizure Adverse Events from the Expanded Access Program Classified as Probably or Definitely Related to 3,4-DAP Use. Source: Summary of Clinical Safety and Patient Narratives 130

Reference ID: 4428593

Table of Figures

Figure 1: Study design schematic 34
Figure 2: Lower extremity function scale (LEFS) 41
Figure 3: Mean (+/- SE) Percent Change from Baseline in 3TUG at 2 Hours After Dosing Versus Time by Treatment Groups – Efficacy Population. Source: Applicant submission 52
Figure 4: Mean QT versus Mean RR Intervals by Treatment and Time Point. Source: QT Study CSR 95
Figure 5: Adverse Events Related to 3,4-DAP Use with Frequency >5% by Age in RPV162 Dataset: Age >60 100
Figure 6: Bivariate Fit of Mean Trial PR By Mean Baseline PR Interval Duration (ms) 127
Figure 7: Bivariate Fit of QRS Duration Trial Mean By QRS Duration Baseline (ms) 128
Figure 8: Bivariate Fit of QTCB Trial Mean By QTCB Baseline (ms) 128

Reference ID: 4428593

Glossary

3,4-DAP	3,4-diaminopyridine/amifampridine
3TUG	Triple Timed-Up and Go
AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMAP	Compound muscle action potential
CMC	chemistry, manufacturing, and controls
CMS	congenital myasthenic syndrome
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
DNP	Division of Neurology Products
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety

Reference ID: 4428593

ITT	intent to treat
LEMS	Lambert-Eaton myasthenic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
QMG	Quantitative myasthenia gravis score
REMS	risk evaluation and mitigation strategy
RPV162	Expanded access 3,4-DAP dataset
RTF	Refuse to file
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TQT	thorough QT study
W-SAS	Subject Self-Assessment of LEMS-Related Weakness

Reference ID: 4428593

1. Executive Summary

1.1. Product Introduction

Drug and Indication: Amifampridine base (3,4-diaminopyridine, Ruzurgi™, hereafter referred to as 3,4-DAP) is a potassium channel blocker is proposed to lengthen the pre-synaptic depolarization at neuromuscular junctions, leading to increased acetylcholine release and muscle contraction. 3,4-DAP is proposed to treat [redacted] (b) (4) Lambert-Eaton myasthenic syndrome (LEMS).

Since 1993 the applicant has been supplying 3,4-DAP under the US Food and Drug Administration (FDA) expanded access Investigational New Drug (IND) provision. The IND holders are physicians–primarily neurologists–with expertise in the diagnosis and treatment of neuromuscular diseases. To date, the applicant has supported approximately 230 INDs for more than 600 patients.

Dosage Form: 3,4-DAP is proposed to be available as 10 mg, functionally scored tablets for oral use.

Note that reviewer commentary throughout the text is presented in *italics*.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The DAPPER study was an adequate and well-controlled efficacy study that provides adequate evidence to support the approval of 3,4-DAP for the treatment of LEMS. It was a well-designed study that has provided reliable and statistically strong ($p<0.0001$) evidence of an important clinical benefit, an effect on strength and ambulation as measured by the Triple Timed-Up and Go (3TUG) test. The study has also shown a clinically meaningful and statistically strong ($p<0.0001$) improvement in quality of life, as measured by the Subject Self-Assessment of LEMS-Related Weakness (W-SAS) score as a key secondary endpoint. Further, there was numerically greater worsening of symptoms in the taper-to-placebo group compared to the continuous 3,4-DAP group for other secondary endpoints, including compound muscle action potential (CMAP) change from baseline, LEMS-related activities of daily living, lower extremity function scale, and physician assessment of treatment effect.

The positive results of the DAPPER study are further supported by the positive results of the Duke RCT study, which showed a statistically significant difference in quantitative myasthenia gravis (QMG) score ($p=0.015$) and CMAP ($p = 0.002$) measurements between placebo and 3,4-

Reference ID: 4428593

DAP groups, indicating greater muscle strength in the 3,4-DAP group. The clinical significance of these results was supported by a patient-reported symptomatic response questionnaire, in which 75% of the 3,4-DAP group reported feeling better, compared to 29% of the placebo group.

The positive results of the DAPPER study and the supportive Duke RCT study are further supported by long-term expanded access data for 3,4-DAP in 162 patients for an average total duration of treatment of 4.9 years and with a range up to 27 years. Approximately 87% of these patients reported improvement in LEMS symptoms.

The sponsor has provided reports from seven pediatric LEMS patients, including a single patient's serial 3TUG data, as well as supportive data from published reports from five pediatric LEMS patients, that suggest that 3,4-DAP may also be effective in pediatric LEMS patients. The disease mechanism of LEMS, autoantibody-mediated removal of a subset of the P/Q-type Ca2+ channels at the neuromuscular junction, is the same in adults and children. A drug that is effective in adults by presynaptic potassium channel blockade would, therefore, also be expected to be effective in children. Based on the overall data, it appears reasonable to extrapolate the effectiveness of amifampridine for the treatment of LEMS from adults to pediatric patients.

1.3. Benefit-Risk Assessment

Reference ID: 4428593

Benefit-Risk Integrated Assessment

Amifampridine base (3,4-diaminopyridine, Ruzurgi™, hereafter referred to as 3,4-DAP) is a potassium channel blocker that lengthens the pre-synaptic depolarization at neuromuscular junctions, leading to increased acetylcholine release and muscle contraction. Clinical studies evaluated patients with Lambert-Eaton myasthenic syndrome (LEMS). Based on the positive results of a single adequate and well-controlled study, confirmatory evidence from a previously published supportive placebo-controlled study, and further confirmatory long-term data from expanded access use of 3,4-DAP in 247 patients, it is the conclusion of this reviewer that the effectiveness of 3,4-DAP has been established for the treatment of adults with LEMS. Limited data in pediatric patients and a common LEMS disease mechanism in adults and children lead this reviewer to conclude that 3,4-DAP is also effective in children with LEMS.

Lambert-Eaton myasthenic syndrome (LEMS) is a rare presynaptic disorder of neuromuscular transmission in which quantal release of acetylcholine (ACh) is impaired. It involves neuromuscular junction disruption from an autoantibody-mediated removal of a subset of the P/Q-type Ca2+ channels, which causes proximal muscle weakness, depressed tendon reflexes, post-tetanic potentiation, and autonomic dysfunction. Progressive proximal muscle weakness is the major clinical presentation with LEMS. Many patients are unable to climb stairs and some become bedridden, and even require mechanical ventilation and tube feeding. In 40%-60% of patients with LEMS, cancer is present when the weakness begins or is found later. Death usually occurs because of the underlying cancer. Patients without cancer generally have nearly normal longevity. The incidence of LEMS in the U.S. is 0.48-0.75 per million per year (~156 – 244 new cases/year in U.S.). The prevalence of LEMS is 2.3-5 per million (~400 cases in U.S.). Pediatric LEMS is very rare. A literature review found only 24 reported cases of pediatric LEMS.

The only FDA-approved treatments for LEMS are guanidine and Firdapse®. Guanidine is an inhibitor of voltage-gated potassium channels that enhances the release of acetylcholine. Guanidine was approved by the FDA in 1939, but has significant safety and tolerability issues, including fatal bone marrow suppression and renal failure. Firdapse® (amifampridine phosphate) was approved in 2018 and is similar to the free base form of 3,4-DAP, but with the addition of a phosphate group. Firdapse® is only approved in adults with LEMS and not in children. There remains an unmet clinical need for effective treatments for LEMS in children.

The DAPPER study was a week-long inpatient double-blind placebo-controlled withdrawal study of 3,4-DAP in adult subjects (18 taper-to-placebo; 14 continuous 3,4-DAP) with known Lambert-Eaton myasthenic syndrome (LEMS). The study evaluated strength and ambulation

Reference ID: 4428593

through a timed test of standing up and walking called the 3TUG. This test result worsened in the taper-to-placebo patients during the course of the trial, as would be expected if 3,4-DAP had been effective and was then stopped. In contrast, the average score in the patients continuously treated with 3,4-DAP remained stable. In the taper-to-placebo group, 13 of 18 subjects (72%) had a >30% deterioration in the final 3TUG test upon withdrawal of study drug compared to 0 of 14 (0%; p<0.0001) subjects in the continuous 3,4-DAP group. There was a similar pattern of positive results on a patient-reported subjective assessment of LEMS-related weakness.

Among 159 patients in the open-label expanded access program, the most common adverse events (>=10%) were infection, paresthesia/hypoesthesia, diarrhea, abdominal pain, fall, dyspepsia/nausea/vomiting, pneumonia, arrhythmia, arthralgia, and cancer (commonly associated with LEMS). Seizures were reported in 4% of patients in the 3,4-DAP expanded access program. Data from 22 pediatric patients treated with 3,4-DAP were evaluated and appear to be adequate to support the safety of 3,4-DAP in this population. Pediatric adverse events in more than one patient included two patients each with palpitations and seizures. The adverse events that caused the most patients to stop taking 3,4-DAP in the expanded access program were seizure, head titubation, tremor, cancer, bradycardia, pneumonia, suicide, and fall.

The conclusion of this review is that substantial evidence of clinical effectiveness and an acceptable safety profile have been established to support an approval of 3,4-DAP for the treatment of LEMS in (b) (4) children.

Benefit-Risk Dimensions

Reference ID: 4428593

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lambert-Eaton myasthenic syndrome (LEMS) is a rare disorder that involves neuromuscular junction disruption from an autoantibody-mediated removal of a subset of calcium channels, which causes proximal muscle weakness, depressed tendon reflexes, post-tetanic potentiation, and autonomic dysfunction. • Progressive proximal muscle weakness is the major clinical presentation with LEMS. Many patients are unable to climb stairs, and some become bedridden, and even require mechanical ventilation and tube feeding. • Cancer is present in 40%-60% of patients with LEMS. Death usually occurs because of the underlying cancer. Patients without cancer generally have nearly normal longevity. • The incidence of LEMS in the U.S. is from 156 to 244 new cases per year. • LEMS occurs very rarely in children, with 24 reported cases in the scientific literature.	LEMS is a serious disease that can lead to disability.
Current Treatment Options	• The only FDA-approved treatments for LEMS are guanidine and Firdapse®. • Guanidine was approved by the FDA in 1939, but has significant safety and tolerability issues, including fatal bone marrow suppression and renal failure. • Firdapse® (amifampridine phosphate) was approved in 2018 and is similar to the free base form of 3,4-DAP. Firdapse® is only approved in adults with LEMS and not in children.	There remains an unmet clinical need for effective treatments for LEMS in children.

Reference ID: 4428593

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• In a week-long inpatient, double-blind, placebo-controlled withdrawal study of 3,4-DAP in adult subjects (18 taper-to-placebo; 14 continuous 3,4-DAP) with LEMS, there was worsening of 3TUG scores, a timed test of standing up and walking, in patients when 3,4-DAP was gradually tapered and replaced with a placebo. In contrast, the average 3TUG score in the patients continuously treated with 3,4-DAP remained stable. • In the taper-to-placebo group, 13 of 18 subjects (72%) had a >30% deterioration in the final 3TUG test upon withdrawal of study drug compared to 0 of 14 (0%; p<0.0001) subjects in the continuous 3,4-DAP group. There was a similar pattern of positive results on a patient-reported subjective assessment of LEMS-related weakness. • Reports from seven pediatric LEMS patients, including a single patient's serial 3TUG data, as well as published reports from five pediatric LEMS patients, suggest that 3,4-DAP may also be effective in pediatric LEMS patients.	The results of the double-blind, placebo-controlled withdrawal study of 3,4-DAP in adults with LEMS provide reliable, clinically meaningful, and statistically strong evidence that 3,4-DAP is effective for the treatment of LEMS-related weakness in adult patients. The disease mechanism of LEMS is the same in adults and children. A drug that is effective in adults by presynaptic potassium channel blockade would therefore also be expected to be effective in children. It is reasonable to extrapolate the effectiveness of amifampridine for the treatment of LEMS from adults to pediatric patients.
Risk and Risk Management	• The safety database includes the double-blind, placebo-controlled withdrawal study in patients with LEMS, adverse events in the placebo-controlled QT study in healthy subjects, and the open-label expanded access program. Data from a published placebo-controlled study (Sanders et al., 2000) was reviewed and considered supportive. • Among 159 patients in the open-label expanded access program, the most common adverse events (>=10%) were infection, paresthesia/hypoesthesia, diarrhea, abdominal pain, fall, dyspepsia/nausea/vomiting, pneumonia, arrhythmia, arthralgia, and	The safety profile of 3,4-DAP is acceptable to support an approval in [redacted] (b) (4) children. WARNINGS and PRECAUTIONS should be included in labeling to describe the risk of seizure.

Reference ID: 4428593

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cancer (commonly associated with LEMS). • Seizures were reported in 4% of patients in the 3,4-DAP expanded access program. • Data from 22 pediatric patients treated with 3,4-DAP were evaluated. Pediatric adverse events in more than one patient included two patients each with palpitations and seizures. • The adverse events that caused the most patients to stop taking 3,4-DAP in the expanded access program were seizure, head titubation, tremor, cancer, bradycardia, pneumonia, suicide, and fall.	

Reference ID: 4428593

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	6.1.1, 6.1.2
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
X	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		X	Other: (Please specify)	6.2.1, 6.2.2: Symptomatic Response to Treatment questionnaire
□	Patient experience data was not submitted as part of this application.			

Reference ID: 4428593

2. Therapeutic Context

2.1. Analysis of Condition

Lambert-Eaton myasthenic syndrome (LEMS) is a rare presynaptic disorder of neuromuscular transmission in which quantal release of acetylcholine (ACh) is impaired. It involves neuromuscular junction disruption from an autoantibody-mediated removal of a subset of the P/Q-type Ca2+ channels, which causes proximal muscle weakness, depressed tendon reflexes, post-tetanic potentiation, and autonomic dysfunction.

Progressive proximal muscle weakness is the major clinical presentation with LEMS. The hip girdle is generally more affected than the shoulder girdle. Patients typically develop increasing difficulty rising from a chair, lifting their feet to walk, and have a characteristic waddling gait. Many patients are unable to climb stairs, and some become bedridden, and even require mechanical ventilation and tube feeding. Facial weakness, eye muscle complaints, bulbar muscular weakness, and distal pareses are relatively common. Autonomic dysfunction may also be a prominent feature of LEMS manifesting most commonly with dry mouth, dry eyes, impotence, difficulty swallowing, and constipation.

In 40%-60% of patients with LEMS, cancer is present when the weakness begins or is found later. Death usually occurs as a result of the underlying cancer. Patients without cancer generally have nearly normal longevity.

The incidence of LEMS in the U.S. is 0.48-0.75 per million per year (~156 – 244 new cases/year in U.S.). The prevalence of LEMS is 2.3-5 per million (~400 cases in U.S.) (Wirtz et al., 2003).

Pediatric LEMS is very rare. A literature review found 24 reported cases (Kostera et al. 2009; Wirtz et al., 2002; Hoffman et al., 2003; Agarwal et al., 2014; Della Marina et al., 2012; Hajjar et al., 2014; Portaro et al., 2014; Schuler et al., 2001; Verbeek et al., 2014). Cancer was present in 9 of them. There were two reported cases of transient neonatal LEMS caused by transplacental transfer of IgG antibodies. Not including the neonatal cases, LEMS onset has been reported in children as young as 3 years of age (Agarwal et al., 2014). The disease mechanism of LEMS, autoantibody-mediated removal of a subset of the P/Q-type Ca2+ channels at the neuromuscular junction, as well as the clinical signs, symptoms, and treatments are the same in adults and children. Children are more likely to have autoimmune LEMS without an underlying cancer.

Reference ID: 4428593

The following table summarizes the differences between LEMS associated with cancer and autoimmune LEMS without cancer.

Table 1: Features of LEMS in patients with or without an underlying cancer.

Cancer-associated LEMS	**Non-cancer LEMS**
~67% Small-cell lung cancer. Other cancers include lymphosarcoma, malignant thymoma, or carcinoma of the breast, stomach, colon, prostate, bladder, kidney, or gallbladder.	Seen in all ages.
median age of onset = 60 years	Two onset age peaks: 35 years and 60 years.
65% male (associated with smoking)	52% female
SOX protein serological marker in 67% of cases	More concurrent immunological disorders (27% vs. 6% in cancer)
More weight loss (28% vs. 8% in non-cancer)	Different autoantibody epitope reactivity than in cancer LEMS.
Prolonged artificial ventilation after anesthesia (9% vs. 1% in non-cancer)	Longer interval between onset and diagnosis (median 13.5 months vs. 5 months in cancer)
No association with any particular HLA haplotype	Autoimmune HLA-B8-DR3 haplotype in 65%

2.2. Analysis of Current Treatment Options

The only FDA-approved treatments for LEMS are guanidine and Firdapse®. Guanidine is an inhibitor of voltage-gated potassium channels that enhances the release of acetylcholine.

Reference ID: 4428593

Guanidine was approved by the FDA in 1939, but has significant safety and tolerability issues, including fatal bone marrow suppression and renal failure. Firdapse® (amifampridine phosphate) was approved in 2018 and is similar to the free base form of 3,4-DAP, but with the addition of a phosphate group. The mechanism of action of Firdapse® is the same as 3,4-DAP, potassium channel blockade that lengthens the pre-synaptic depolarization at neuromuscular junctions. The safety profile for Firdapse® is similar to that of 3,4-DAP. Firdapse® is only approved in adults with LEMS. Note that the current 3,4-DAP submission also includes some pediatric data.

There is no known cure for LEMS. Treatment is directed at optimizing function. Occasionally LEMS is cured in patients with an underlying cancer treated with antineoplastic therapies. Some patients benefit from pyridostigmine and immunomodulatory interventions (prednisone, azathioprine, intravenous immunoglobulin, plasmapheresis). In the United States, initial therapy for LEMS is usually pyridostigmine bromide (PB), an acetylcholinesterase inhibitor marketed under the trade name Mestinon®, which was approved for the related disorder myasthenia gravis. While PB may provide some relief of dry mouth and eyes, it does not usually provide sufficient benefit for the treatment of LEMS-associated weakness.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The free-base form of 3,4-DAP is not marketed in the US. However, the phosphate-salt form of 3,4-DAP, Firdapse®, was recently approved by the FDA for LEMS as discussed in Section 2.2.

Orphan drug status was granted for the treatment of LEMS patients with 3,4-DAP in December 1990. 3,4-DAP has been provided through 230 Investigator-held INDs for research and treatment protocols since 1993 to approximately 627 patients.

A pre-NDA meeting was held on September 7, 2010. The Division of Neurology Products (DNP) noted that the efficacy studies that had been conducted for 3,4-DAP were all of very limited duration. DNP concluded that a placebo-controlled study that demonstrated sustained efficacy for at least 3 months was needed.

An End-Of-Phase 2 (EOP2) meeting was held on June 17, 2014. DNP advised that short-duration efficacy studies of 3,4-DAP could be used in combination with positive findings on the new placebo-controlled study to support NDA filing.

Reference ID: 4428593

Fast Track was granted in 2014. At a Type B Pre-NDA meeting on February 17, 2016, there was discussion of the safety database and the single placebo-controlled study, with supportive data from a published study (Sanders et al., 2000).

This NDA was originally received on December 7, 2017. However, it was found to be not sufficiently complete to permit a substantive review. The Division refused to file (RTF) the application on January 31, 2018, under 21 CFR 314.101(d) because of inadequate chemistry, manufacturing, and controls (CMC) information. The RTF letter included the following concerns:

> "1) The NDA does not include supporting information needed for the Agency to assess the adequacy of your chemistry, manufacturing, and controls (CMC) strategy to assure the identity, strength, purity, and quality of the drug substance and drug product…
> 2) The CMC section is disorganized and we are unable to locate information for review without extensive searching through multiple subsections. Even then, the information is not always complete."

The applicant addressed these concerns and resubmitted the NDA on June 15, 2018.

3.2. Summary of Presubmission/Submission Regulatory Activity

Date	Summary of Regulatory Activities
Dec 18, 1990	Orphan status granted for the treatment of LEMS
Oct 20, 1997	Submission of initial IND
Sep 7, 2010	Pre-NDA meeting • Division noted that the efficacy studies that had been conducted were all of very limited duration. Division concluded that a placebo-controlled study that demonstrated sustained efficacy for at least 3 months was needed. Would also require at least 3 months of drug treatment in currently enrolled patients in the expanded access program.
June, 17, 2014	EOP 2 meeting • Short-duration efficacy studies of 3,4-DAP could be used in combination with positive findings on the new study to support NDA filing
Sep 19, 2014	Fast Track Granted

Reference ID: 4428593

Feb 17, 2016	Pre-NDA meeting • The Division would require complete protocols, statistical analysis plans, and source data in details from published studies to be used as supportive evidence of efficacy along with the DAPPER study for a future NDA submission. • A Thorough QT study and Abuse Potential study was recommended.
Mar 27, 2017	Type C meeting • Recommendations provided on the safety data from expanded access program. • Agreed on submission of a rolling application
December 7, 2017.	First NDA submission
January 31, 2018	Refuse to file (RTF) under 21 CFR 314.101(d) because of inadequate chemistry, manufacturing, and controls (CMC) information.
June 15, 2018	Second NDA submission.

Note that amifampridine phosphate (Firdapse), the salt form of amifampridine, was approved for the treatment of LEMS in adults on November 28, 2018, and is marketed by Catalyst.

(b) (4)

[redacted]

3.3. Foreign Regulatory Actions and Marketing History

3,4-DAP is not marketed in any foreign country, but it has been available through compounding pharmacies. Note that 3,4-DAP phosphate (Firdapse®) has been marketed in Europe since 2009.

Reference ID: 4428593

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The following issues were identified by the OSI inspections regarding insecure data storage and transcription errors.

The DAPPER study sites recorded all laps of the 3TUG Test (the test used to assess the primary endpoint) on video. The sites entered their timed assessments (during the live session) and uploaded the actual videos in an electronic data capture system (EDC system). The videos were then reviewed later by a central reviewer who was blinded to the treatment and to the date, time, and sequence of the actual 3TUG Test. It was the central reviewer's assessment that was primarily used for the primary endpoint. The sites' timed assessments were used when the videos malfunctioned or were of poor quality and for missing values.

During the sponsor inspection, the FDA field investigator found many data discrepancies when he compared the central reader's assessments with the data listings submitted to FDA. The FDA investigator found that after the central reviewer viewed the videos, he recorded his assessment time on an excel spreadsheet and then entered the source data from the excel spreadsheet in the EDC system. The data discrepancies occurred when the central reviewer incorrectly transcribed some of the assessment times from the spreadsheet to the EDC system. The vendor that performed the statistical analysis used the data that was in the EDC system without doing any edit checks on the source document (the excel spreadsheet).

Because of these findings, the placebo-controlled DAPPER study 3TUG test videos were re-read by two central readers to correct the data used to support the FDA efficacy analysis.

4.2. Product Quality

Analysis and discussion of the acceptability of product quality is deferred to the chemistry, manufacturing, and controls (CMC) reviewer.

Reference ID: 4428593

4.3. Clinical Microbiology

Not applicable. 3,4-DAP is not an antimicrobial or antiviral drug.

4.4. Nonclinical Pharmacology/Toxicology

The applicant reports the following results of nonclinical studies: decreases in body weight gain in a 6-month rat toxicity study at doses ≥45 mg/kg/day; decreases in body weight gain in males at 1.04 mg/kg/day in a 9-month dog study; and sustained convulsions in a 9-month dog study at a dose of 2.1 mg/kg/day. The reader is referred to the separate nonclinical review for further details and analysis.

The convulsions seen in dogs are consistent with the known risk of seizure in humans treated with 3,4-DAP, discussed in Section 8.5.2.

4.5. Clinical Pharmacology

The reader is referred to the review of the Office of Clinical Pharmacology (OCP) for further details.

4.5.1. Mechanism of Action

The proposed mechanism of action of 3,4-DAP is to facilitate release of ACh from the motor nerve terminal by presynaptic potassium channel blockade (Kirsch and Narahashi 1978, Molgo et al 1980). This blockade prolongs the duration of the action potential at nerve terminals and lengthens the open time of the voltage-gated calcium channels resulting in an increased influx of calcium. The increase in intracellular calcium facilitates exocytosis of synaptic vesicles and the release of acetylcholine.

4.5.2. Metabolism and Elimination

Genetic variants in the N-acetyltransferase gene 2 (NAT2) affect the rate and extent of RUZURGI metabolism. In normal healthy volunteers, the average plasma amifampridine concentration varies as a function of the subject's rate of metabolism, or "acetylation."

Reference ID: 4428593

In healthy subjects, 3,4-DAP is rapidly acetylated to the inactive 3-Ac-DAP metabolite. The average plasma Cmax for 3,4-DAP is 2.1- to 2.3-fold higher for slow acetylators than for intermediate acetylators in the fasted state and 2.0- to 4.5-fold higher in the fed state.

The mean elimination half-life (t1/2) of 3,4-DAP following administration of 20 or 30 mg doses is 3.6 to 4.2 hours and the t1/2 of 3-Ac-DAP is 4.1 to 4.8 hours. The mean recovery in urine among healthy subjects was greater than 65%.

In the general population, the NAT2 poor metabolizer (slow acetylator) phenotype prevalence is 40–60% in the White and African American populations, and in 10–30% in Asian ethnic populations (individuals of Japanese, Chinese, or Korean descent).

4.5.3. Pediatric Dosing

Pediatric patients in the expanded access program received doses ranging from 0.6 mg/kg/day to 1.1 mg/kg/day in the twelve patients for whom weight was reported. The total daily dose across all 22 pediatric subjects ranged from 5mg to 120mg. Only one pediatric subject received a total daily dose of 120mg. All other pediatric subjects received 95mg per day or less.

The clinical pharmacology review makes the following recommendations for pediatric dosing of 3,4-DAP.

The recommended oral dosage [redacted] (b) (4) dependent on body weight.

- Dosage should be increased based on clinical response and tolerability. Individual doses throughout the day do not need to be equal.
- If a dose is missed, patients should not take double or extra doses.
- RUZURGI can be administered without regard to food

Recommended dose [redacted] (b) (4) ***weighing 45 kg or more:***

- The recommended starting dosage is 15 mg to 30 mg daily, in divided doses (2 to 3 times per day)
- The dose can be increased to a maximum of 100 mg per day in 5 mg to 10 mg increments
- The maximum single dose is 30 mg

Recommended dose [redacted] (b) (4) ***weighing less than 45 kg:***

Reference ID: 4428593

- The recommended starting dosage is 7.5 to 15 mg daily in divided doses (2 to 3 times per day)
- The dose can be increased to a maximum of 50 mg per day in 2.5 mg to 5 mg increments
- The maximum single dose is 15 mg

4.6. Devices and Companion Diagnostic Issues

Not applicable to this application.

4.7. Consumer Study Reviews

Not applicable to this application.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The pivotal efficacy study, JPC 3,4-DAPPER (referred to as DAPPER), is a week-long, randomized, placebo-controlled withdrawal study. Supportive efficacy data were submitted from the 6-day, blinded, placebo-controlled study originally described in Sanders et al. (2000), JPC 3,4-DAP DUKE RCT (referred to as Duke RCT).

Although over 600 patients have received 3,4-DAP under expanded access INDs, the majority did not have adequate safety records for use in this review. The applicant was able to gather usable safety data from 247 patients (Figure 1). This included patients in the DAPPER and DUKE RCT studies and patients enrolled in expanded access programs. Additionally, safety data was provided for 82 healthy volunteers in Phase 1 studies.

A 72-patient subset of the expanded access population was defined as the “Special Populations” dataset and included the following patients.

- Pediatric patients
- Patients with a medical history of 1 or more of the following conditions of interest:
    - Seizure
    - Cardiac disorders or QT prolongation

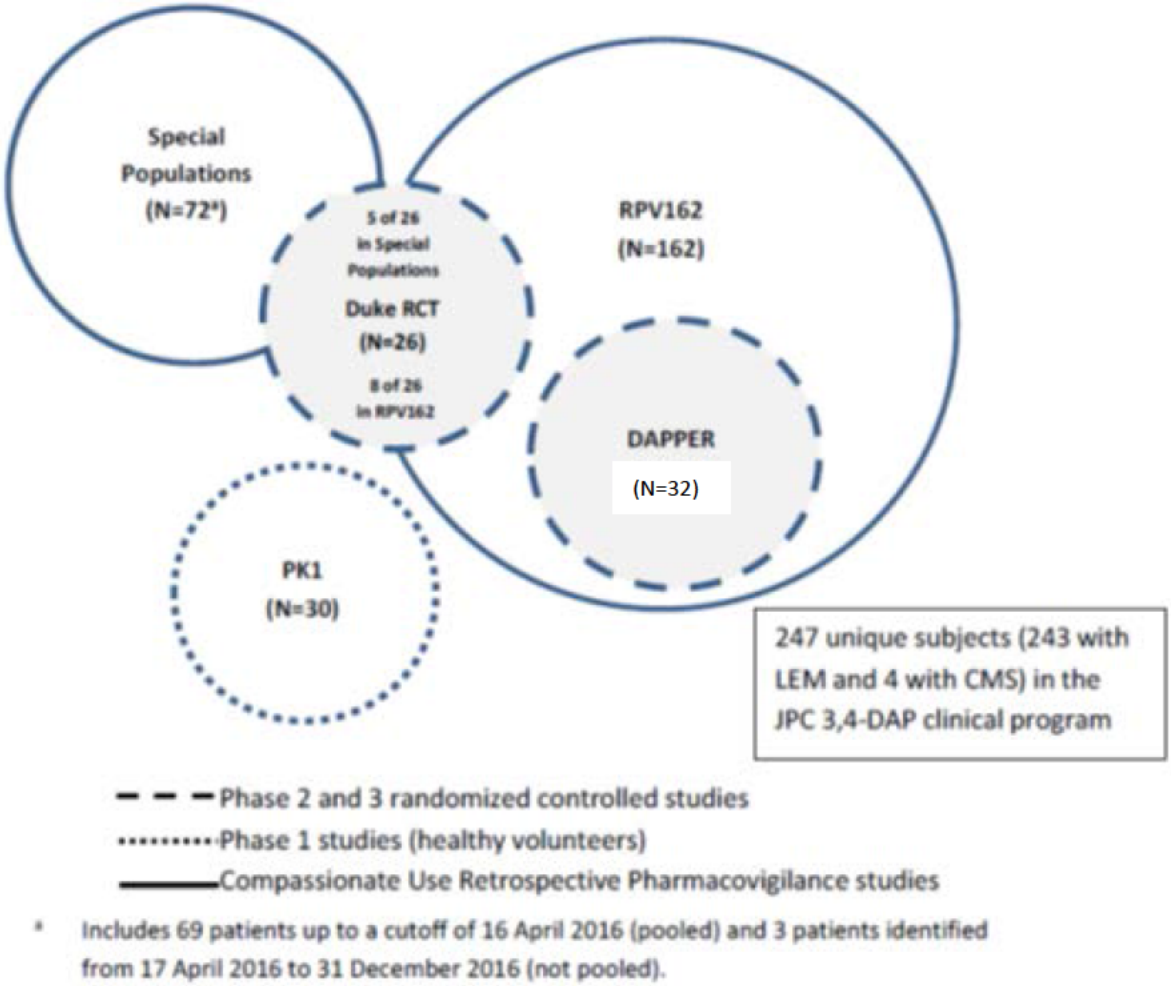
Reference ID: 4428593

    - Suicidal behavior (including suicidal ideation)
    - Renal impairment or other significant renal disorders
    - Hepatic impairment or other significant hepatic disorders
- Patients with 1 or more of the following treatment-emergent events of interest:
    - Pregnancy
    - Seizure
    - Cardiac disorders or QT prolongation
    - Suicidal behavior (including suicidal ideation)
    - Renal impairment or other significant renal disorders
    - Hepatic impairment or other significant hepatic disorders

An overview of the clinical studies performed by the applicant is shown in the figure below, copied from the applicant.

Reference ID: 4428593

Figure 1: 3,4-DAP-treated Patients Providing Safety Information. Source: Applicant submission



[a] Includes 69 patients up to a cutoff of 16 April 2016 (pooled) and 3 patients identified from 17 April 2016 to 31 December 2016 (not pooled).

Note: Not included in this figure are the 52 healthy subjects dosed with 3,4-DAP in the thorough QT study.
3,4-DAP = 3,4-diaminopyridine; CMS = congenital myasthenic syndrome; JPC = Jacobus Pharmaceutical Company, Inc.; LEM = Lambert-Eaton myasthenia; N = number of patients; PK1 = Phase 1 pharmacokinetic study; RCT = randomized controlled trial.

Reference ID: 4428593

Table 2: Listing of Clinical Trials Relevant to this NDA/BLA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
JPC 3,4-DAPPER	Phase 2, multicenter, randomized, placebo-controlled, double blind, withdrawal study of safety, efficacy, and PK: • Stage 1: active Tx (2.5 days including 0.5 days of acclimation) • Stage 2: continued active Tx or taper to placebo (up to 3.5 days with ≤16 hours without active drug) • Stage 3: Resume baseline Tx (observation: 0.5 days)	Continuous 3,4-DAP Taper to placebo	>30% deterioration in final 3TUG test performance upon withdrawal of 3,4-DAP Safety PK	~7 days treatment; 4 weeks follow-up	52 subjects screened; 32 subjects enrolled	Medically stable men and women ≥18 years with clinically active LEM; ambulatory with at least 30 mg/day of 3,4-DAP, maximum TDD 100 mg, and no single dose >30 mg, for at least 3 months before enrollment	7 centers/ US
JPC 3,4-DAP DUKE RCT	Prospective, placebo-controlled, randomized safety and efficacy study	10 to 20 mg 3,4-DAP Placebo Tx 3 to 4 times daily for 6 to 9 days/24-hr	CMAP QMG	6-9 days Tx 24 hours follow up 6 months	26 subjects	Men and women >18 years of age with LEMS and a QMG score ≥5	1 center/ Durham, NC

Reference ID: 4428593

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		washout/single dose followed by 24-hr observation Then open label for up to 6 months		open label			
Studies to Support Safety							
RPV52*	Retrospective Pharmacovigilance Review/ observational safety (first data cutoff 01 July 2014) (update cutoff 15 January 2016)	3,4-DAP Median total daily dose 80.0 mg (range: 35 to 120 mg), median of 4.7 doses per day (range: 3.0 to 7.0).	AEs Labs ECG	Mean (median) treatment duration of 8.8 (7.5) y (range: 0.7 to 26.16 y).	52 26M/26F 49.5 y 47W/5B	Medically stable men and women ≥18 y with clinically active LEMS who were screened for the DAPPER study	23 centers/ US, Canada, Argentina
RPV110*	Retrospective Pharmacovigilance Review/ observational safety (data cutoff 01 July 2014)	Median total daily dose 60.0 mg (range: 10 to 140 mg), median of 4 doses per day (range: 1.0 to 10.0).	AEs Labs ECG	3,4-DAP mean (median) treatment duration of 26.2 (8.3) months (range: 0.03 to 218.09 months).	110: 45M/61F (4 missing) 63.4 y 33W/2B/ 2Asian (73 missing)	Patients receiving at least 1 dose of 3,4-DAP within the expanded access program who had died, discontinued treatment, or been lost to follow-up as of the data cutoff date	NA
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							

Reference ID: 4428593

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
JPC 3,4-DAP.TQT	Randomized, thorough QT study	30 mg 3,4-DAP or placebo (q4h × 4 doses) 400 mg moxifloxacin or placebo	Cardiac intervals PK Acetylator phenotype Safety		52 subjects received at least 1 dose of 3,4-DAP; 49 subjects completed all 3 periods	Healthy volunteers	1 center/ US
JPC 3,4-DAP.PK1	Randomized, double-blind, placebo-controlled, parallel-group, PK study (fasting and fed)	Placebo 20 mg 3,4-DAP 30 mg 3,4-DAP	PK Safety		30	Healthy volunteers	

* RPV 52 and RPV 110 were combined into dataset RPV 162.

5.2. **Review Strategy**

An efficacy determination was made by evaluating the results from the placebo-controlled DAPPER study in adult LEMS patients. This reviewer assessed the primary endpoint, the degree of change in the 3TUG test upon withdrawal of active medication, by examining the source data provided by the applicant.

Statistical analysis of the data was performed and reported by a separate statistical reviewer.

The placebo-controlled study data from DUKE-RCT were evaluated for their potential to provide supportive evidence of efficacy.

Reference ID: 4428593

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study JPC 3,4-DAPPER (DAPPER)

6.1.1. Study Design

Overview and Objective

The DAPPER study was an inpatient double-blind placebo-controlled withdrawal study of 3,4-Diaminopyridine Base (3,4-DAP) in adult subjects with known Lambert-Eaton Myasthenic Syndrome (LEMS).

The objective of this study was to confirm the safety and test the efficacy of 3,4-DAP in the treatment of weakness associated with LEMS.

Trial Design

The DAPPER study was a multicenter, randomized, double-blind, placebo-controlled withdrawal study to assess the safety and efficacy of 3,4-DAP in ambulatory adult LEMS patients who had been on a stable regimen of 3,4-DAP, as well as any other LEMS-related treatments such as pyridostigmine or immunosuppressants, for a minimum of 3 months prior to study entry. Subjects who met all study entry criteria were randomized in a 1:1 ratio to continue their current treatment regimen (Group A, continuous 3,4-DAP) or to tapered withdrawal from 3,4-DAP (Group B, taper to placebo). This study included the following stages:

Screening Phase: 4 weeks

Stage I:	Eligible patients were hospitalized and observed for 2.5 days on their usual dose of 3,4-DAP. There was a half-day acclimation period before starting testing. Responsiveness to 3,4-DAP was assessed by the Triple Timed-Up and Go (3TUG) test before and after the first doses of morning, afternoon and evening.
Stage II:	This was the withdrawal period that spanned. Eligible patients were randomized to Group A (continuous dosing for 3.5 days) or Group B (taper to placebo over 3 days, followed by up to 16 hours with no active drug).
Stage III:	This was the reinstitution period. At the end of 3.5 days of withdrawal plus an additional 16 hours of no active drug (i.e., Day 6), all patients were reinstituted to their baseline regimen of 3,4 DAP. During Stage III, the subject was observed for 0.5 days or until deemed clinically stable and was then discharged from the inpatient unit.
Follow up:	4 weekly telephone follow-ups and diaries

Reference ID: 4428593

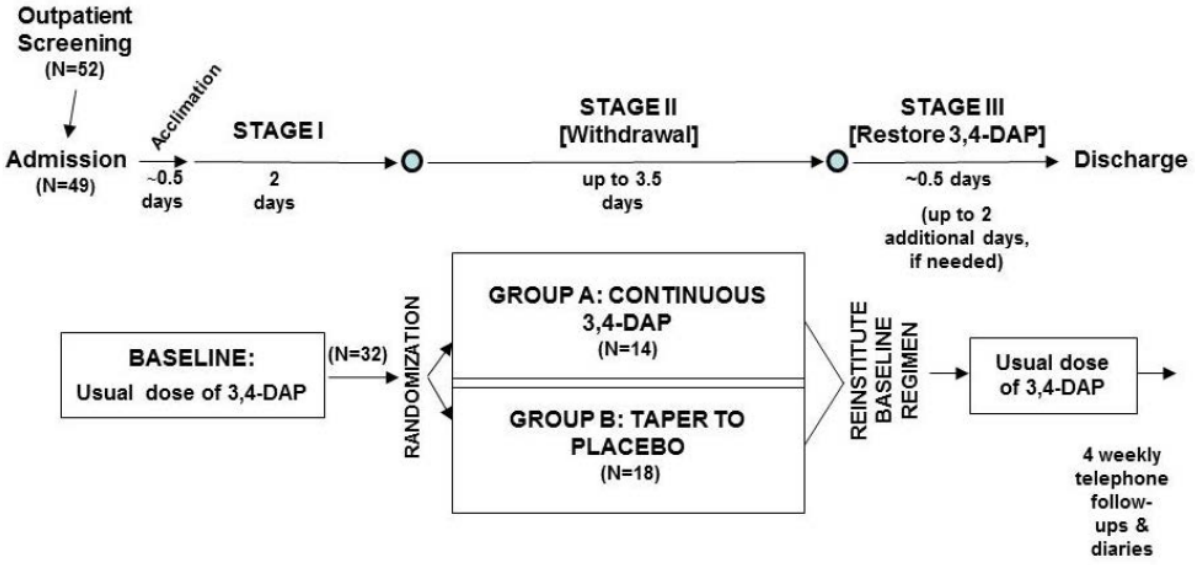
Eligible patients needed to have a sufficient 3TUG response defined as:

- a ≥27% improvement in 3TUG time compared to the 3TUG time before the first morning dose on 2 consecutive days or
- a ≥30% improvement after the first morning, afternoon, or evening dose on Day 1 plus a ≥12% improvement after the first dose of the morning on Day 2.

Subjects completed the entire 3.5-day period of Stage II without regard to 3TUG times. The only exceptions were if a subject met pre-defined criteria for rescue or early advancement, or withdrew or requested immediate resumption of baseline dosing. Rescued subjects, early advanced subjects, and other subjects who withdrew early from Stage II were categorized for analysis of the 3TUG according to their last observation at theoretical "peak drug effect" during Stage II carried forward.

A schematic of the study design is displayed in the following figure.

Figure 1: Study design schematic



Doses Administered:

The minimum required pre-study dose to meet entry criteria was 30 mg/day (10 mg, 3times daily, morning, afternoon and evening). The maximum allowable dose for study patients was

Reference ID: 4428593

100 mg/day.

The study tablets of different strengths were 0 mg [placebo tablet], 0.5 mg, 2 mg, 3 mg, 4 mg, 5 mg and 10 mg, all identical in appearance.

Choice of control group:

A double-blind, placebo-controlled withdrawal study with maintenance of standard-of-care therapy is an adequately rigorous and interpretable study design, given that it would be ethically unacceptable to have a completely untreated placebo group in this condition for which other treatments are available.

Blinding

The following methods were used for blinding. These methods appear adequate.

Identical tablets and centralized clinical supply packaging and randomization were used to ensure blinding of treatment identity to the subject, Investigator, site personnel, and Sponsor personnel. Emergency unblinding procedures were in place if necessary during the study. No subjects were unblinded during the study. The study was unblinded after database lock.

Administrative structure:

This multicenter study was performed at 7 centers in the USA.

There was no formal data safety monitoring committee for this study. The applicant's medical monitor actively supervised the conduct of the study and was involved in confirming eligibility of all randomized subjects and safety monitoring throughout the study. The Sponsor's designated monitoring CRO also performed periodic interim monitoring visits for source data verification.

Procedures and schedule:

The schedule of procedures and assessments from screening to discharge and follow-up is shown in the following table, based on the submission.

Reference ID: 4428593

Table 3: Schedule of Procedures

	Screening	Acclimation	Stage I	Stage II	Stage III	Discharge	1 Month Follow-Up
		INPATIENT					
Medical history or Med history update	X	X					
Medications Review	X	X					X
Physical examination	X	X				X	
Vital signs/pulse ox	X	4x/day	6x/day	6x/day	6x/day	X	
Continuous nighttime pulse ox monitoring		X	X	X	X		
CBC and Chemistry Panel	X				1st dose only		
VGCC antibodies	X						
NAT genotyping[15]	X						
Urinalysis with microscopic	X						
Urine drug screen	X						
Urine pregnancy test	X						
Plasma 3,4-DAP concentration			X	X	1st dose only		
Electrocardiogram (ECG)	X	QD	2x/day	2x/day	2x/day		
Echocardiogram			Pre/post 1st		Pre/post 1st dose		
3TUG	X	4x/day	6x/day	6x/day	6x/day		
W-SAS	X	2x/day	3x/day	3x/day	3x/day		X
LEMS signs & symptoms	X	2x/day	3x/day	3x/day	3x/day		X
CMAP optimization		Pre/post 1st dose					
CMAP sequence			2x/day	2x/day	X		
LEFS	X	X		End			X
ADLs affected by LEMS	X	QD	QD	QD			
PI assessment of treatment effect				End			
Verification of blinding						X	
Monitoring for Adverse Events			X	X	X		X

Key Inclusion Criteria:

The criteria listed below from the submitted protocol appear adequate to enroll adult patients with LEMS representative of the U.S. population.

To participate in this study, candidates were required to meet the following eligibility criteria at Screening:

1. Age 18 years or over;
2. Ambulatory while taking 3,4-DAP, i.e., the patient was able to perform the timed up and go [TUG], either with or without an assistive device;
3. Established diagnosis of LEMS, with documentation provided;
4. Continuous use of JPC 3,4-DAP for at least 3 months;
5. Minimum of 3 doses per day with no single dose less than 10 mg of 3,4-DAP;
6. The patient needed to wait about 15 to 30 minutes to experience an unequivocal improvement in a LEMS-induced dysfunction after they took their first dose of 3,4-DAP in the morning [a patient who remained in bed past this point by choice may still have been eligible];

Reference ID: 4428593

7. Stable regimen of all LEMS-related treatments for at least 3 months;
8. Stable daily regimen of other medications (prescription and over-the-counter) for a minimum of 1 month;
9. Willing to being tapered off 3,4-DAP over a 3-day period with up to an additional 16 hours with no 3,4-DAP;
11. If applicable, agreed to use birth control during heterosexual intercourse until at least 2 weeks after completion of the study;

Exclusion Criteria:

Subjects meeting any of the following criteria were not eligible for the study:

1. Last monoclonal antibody treatment (e.g., rituximab) was less than 6 months ago (i.e., recent treatment was an exclusion);
2. Clinically significant or poorly controlled condition that in the opinion of the study personnel might have posed an unacceptable risk to the patient if entered into the study;
3. Respiratory failure requiring intubation while on 3,4-DAP with no precipitating event or medication;
4. Use of any investigational drug other than 3,4-DAP within the last 30 days prior to study entry;
5. Pregnant or lactating;
6. Current use of other aminopyridines (e.g., 4-AP) or guanidine;
7. Did not display a sufficiently large response to 3,4-DAP during the baseline observation period in the clinical research unit (CRU) to detect a decline during withdrawal of 3,4-DAP ≥ (30% on 2 consecutive days, modified to ≥27% in an amendment).

Rescue or Early Advancement Criteria during the Withdrawal Stage: The following criteria were followed.

Rescue, i.e., urgent return to the baseline treatment regimen, was to occur if the subject experienced

- New dysphagia; or
- Drop in pulse oximetry of 5% from baseline or a decrease to < 90% with an accompanying description of shortness of breath.

Criteria for advancement to full treatment were

- Inability to rise from a chair, even with assistance, after 2 efforts about 1 hour apart;
- Inability to get out of bed, even with assistance, after 2 efforts about 1 hour apart.

Reference ID: 4428593

Subject Request for Termination: If a subject requested resumption of their usual medication because of intolerable weakness, side effects, signs, or symptoms, the following was to be conducted.

- A full description of signs and symptoms
- The next scheduled dose in the series was offered early;
- If the subject met criteria of requiring rescue, the baseline medication regimen could be restored without necessarily completing all assessments.
- If the subject did not meet criteria for rescue, the next scheduled set of evaluations should have been completed before the subject's baseline medication regimen was restored but no more than 2 hours after the subject's request.
- Subjects who requested withdrawal continued to be followed for safety until the end of the follow-up period.
- Such subjects were not replaced.

Prohibited Medications:
IVIg, plasmapheresis, use of other aminopyridines (e.g., 4-AP) or guanidine was prohibited.

Study Endpoints

Primary endpoint

Triple Timed Up and Go Test (3TUG): The primary efficacy endpoint was the categorization of the degree of change in the 3TUG test (last observation at the theoretical "peak drug effect", i.e., 2 hours post dose) upon withdrawal of active medication (Stage II) when compared with time matched average of the 3TUG assessments during Stage I. 3TUG was performed at pre-dose (15 mins prior) or post-dose (2 hours after) for the morning (12 am), afternoon (12 pm), and evening doses (5 pm), a total of 6 times a day.

The test requires the subject to stand up from a standard height (~46 cm or 18 inches) straight-backed armchair then walk at normal pace to a line 3 meters (~10 feet) from the front legs of the chair, turn around, return to the chair and sit back down (considered as one Lap). Subjects had to perform the TUG 3 times without rest.

3TUG scores were the average of the triplicate readings of total time to complete all laps performed divided by the number of laps performed. Specifically, if the subject completed 3 laps, the divisor was 3; if the subject completed 2 laps, the divisor was 2.

Seven Categories of 3TUG performance during Stage II were assigned as follows:

IMPROVEMENT	A- >30% faster
NO CHANGE	B- NO CHANGE, i.e. 30% slower to 30% faster

Reference ID: 4428593

DETERIORATION C- >30-50% slower
D- >50-100% slower
E- >100-200% slower
F- >200% slower
G- Cannot perform 3TUG

The 3TUG obtained 2 hours after the last dose of the withdrawal period (i.e., at time of theoretical "peak drug effect") were used for analysis of the primary outcome. Thus, the comparison was 3TUG at peak drug effect on fully active 3,4-DAP vs. 3TUG at peak drug effect on study drug (active 3,4-DAP for subjects in Group A or (taper to) placebo for subjects in Group B).

The calculation to obtain the subject's category for the primary efficacy endpoint was:

$$100 \times \left(1 - [3TUG_{Stage\ II} / 3TUG_{Baseline}]\right).$$

If a subject was unable to complete the full 3.5-day withdrawal period, the score from the last time the subject was tested 2 hours after a dose was used.

- If a subject who was able to complete 3 laps at baseline (Stage I) was unable to complete all 3 laps of the 3TUG at the end of Stage II (i.e., they can only complete 1 or 2 laps), the subject was scored as category F.
- If a subject was unable to get up from the chair or none of the 3 laps could be completed, the assigned category was "G".
- If a subject required an assistive device during Stage II not used at that specific time of day during Stage I for the safe performance of the 3TUG during Stage II, times to complete laps were still recorded, but the test was scored as category F.
- If a subject performed different numbers of laps at a specific time of day during Stage I (e.g., 3 laps at 3:00 PM on Day 1 and 2 laps at 3:00 PM on Day 2), the average of all available laps (regardless of the number) from the final 3TUG in Stage II was used to calculate and assign the performance category.
- Rescued subjects, subjects who were early advanced, and subjects who withdrew early from Stage II for other reasons were categorized for analysis of the 3TUG according to the last 3TUG tested 2 hours post dose during Stage II (last observation of 3TUG performed at "peak drug effect" carried forward).

Secondary Endpoint:

Subject Self-Assessment of LEMS-Related Weakness (W-SAS): The secondary efficacy endpoint was the self-assessment scale for LEMS-related weakness (W-SAS) obtained during Stage II (final assessment or time of rescue medication (pre-dose), whichever came first). W-SAS scores subjective global weakness across 7 levels (scores of -3 to 3 at 1-point increments), ranging from "much much weaker" for a score of -3 to "much much stronger" for a score of 3. W-SAS

Reference ID: 4428593

at the end of Stage II was compared to the baseline while on a stable regimen of fully active 3,4-DAP. The W-SAS was presented to the subject 3 times daily at the time of estimated peak drug effect. In addition, if a subject required rescue (or early advancement), an additional W-SAS beforehand was pursued. The last observation during Stage II served as the secondary endpoint.

Reviewer's Comment: The 3TUG test captures some of the key functional limitations experienced by untreated LEMS patients. Focusing on limb girdle weakness and compromised mobility is appropriate. Given the hypothesis that weakness would develop upon withdrawal, W-SAS is appropriate for a secondary endpoint.

Exploratory Endpoints without formal statistical hypothesis testing:

Compound Muscle Action Potential (CMAP): CMAP was recorded on Day 0 from the abductor digiti quinti (ADQ), abductor pollicis brevis (APB), and extensor digitorum brevis (EDB) muscles. The muscle with the greatest post-exercise facilitation was used for the endpoint. Each CMAP sequence included a measurement at trough (immediately pre-dose) and 2 hours ±10 minutes after the dose using the one nerve-muscle combination selected on Day 0. The change in CMAP during down-titration and after withdrawal of active medication was assessed.

LEMS-related activities of daily living (ADLs): LEMS-related ADLs were scored from 1 (worst) to 4 (best) and included toileting/bathing, dressing, eating/drinking, sit to stand, grooming, and bed mobility. The total score ranged from 6 (worst) to 24 (best). Scores were recorded with the last dose each day through the end of Stage II. The change in ADLs during Stage II was assessed.

Lower extremity function scale (LEFS): The LEFS (Binkley et al., 1999) consisted of a 20-item questionnaire, with an item score range from 0 (worst) to 4 (best), or a best possible score of 80 for the total LEFS. It was performed at baseline, at the end of Stage II, and during follow-ups.

Reference ID: 4428593

Figure 2: Lower extremity function scale (LEFS)

Activities	Extreme Difficulty or Unable to Perform Activity	Quite a Bit of Difficulty	Moderate Difficulty	A Little Bit of Difficulty	No Difficulty
a. Any of your usual work, housework, or school activities.	0	1	2	3	4
b. Your usual hobbies, recreational or sporting activities.	0	1	2	3	4
c. Getting into or out of the bath.	0	1	2	3	4
d. Walking between rooms.	0	1	2	3	4
e. Putting on your shoes or socks.	0	1	2	3	4
f. Squatting.	0	1	2	3	4
g. Lifting an object, like a bag of groceries from the floor.	0	1	2	3	4
h. Performing light activities around your home.	0	1	2	3	4
i. Performing heavy activities around your home.	0	1	2	3	4
j. Getting into or out of a car.	0	1	2	3	4
k. Walking 2 blocks.	0	1	2	3	4
l. Walking a mile.	0	1	2	3	4
m. Going up or down 10 stairs (about 1 flight of stairs).	0	1	2	3	4
n. Standing for 1 hour.	0	1	2	3	4
o. Sitting for 1 hour.	0	1	2	3	4
p. Running on even ground.	0	1	2	3	4
q. Running on uneven ground.	0	1	2	3	4
r. Making sharp turns while running fast.	0	1	2	3	4
s. Hopping.	0	1	2	3	4
t. Rolling over in bed.	0	1	2	3	4
Column Totals:					

Echocardiograms: Echocardiograms were conducted prior to and 2 hours after the first dose of Stage I and Stage III /rescue/early advancement dose. Cardiac ejection fraction was assessed.

Physician Assessment of Treatment Effect: Investigator assessment of treatment effect on a rating scale occurred once at the end of Stage II. The scale included the following categories: much worse than during baseline, somewhat worse than during baseline, no change from baseline, somewhat improved from baseline, and much improved from baseline.

Reviewer Comment: The exploratory efficacy endpoints are acceptable. Their results are reported descriptively in Section 6.1.2.

Statistical Analysis Plan

Reviewer Comment: Please refer to the statistical review for detailed evaluation of the applicant's planned statistical analysis.

The following definitions were used to classify the analysis populations.

Randomized: Subjects who were enrolled in the study and randomized to a treatment group

Reference ID: 4428593

Intent-to-Treat (ITT) Population: All subjects randomized, including subjects who were replaced due to withdrawal of consent after randomization but prior to admission
PP Population: All subjects who completed the clinical trial according to the protocol
Efficacy Population: All subjects who were randomized and took any of the study regimen, and had at least one post-baseline 3TUG test result (at the theoretical "peak drug effect", i.e., 2 hours post dose)

Primary Efficacy Analyses

The primary analysis compared the 2 treatment groups using Fisher's exact test after determining, for each treatment group, the response rate for outcomes C through G (3TUG deterioration) combined.

The individual 7 categories A though G, were summarized and compared by treatment groups using the Cochran-Mantel-Haenszel test with modified Ridit scores derived from category rankings.

A supportive analysis of 3TUG treated the variable as a continuous response.

Secondary Efficacy Endpoint Analyses
The last observation of subject self-assessment of LEMS-related weakness (W-SAS) during Stage II using a categorical scale was compared with the baseline. The possibility of improvements includes the categories Somewhat Stronger (+1), Much Stronger (+2), and Much Much Stronger (+3). Treatment groups were compared using a t-test. As a supportive analysis, the treatment group was compared using CMH test with modified Ridit scores derived from category rankings.

Other Efficacy Endpoints

Endpoints designed to support the results of the primary and secondary efficacy endpoints included

- CMAP after withdrawal of active medication (Stage II)
- Change in 3TUG and CMAP during down titration period. The intent of this analysis was to evaluate a possible dose response relationship in the withdrawal group.
- Onset and nature of LEMS-related signs and symptoms after withdrawal of active medication (Stage II)
- 50% or more deterioration in the 3TUG during Stage II
- Changes in drug levels at trough and peak during the study and relationship of blood levels to 3TUG, CMAP and LEMS-related signs and symptoms
- Comparison of morning 3TUG time with nadir 3TUG time later in the same day.
- Evaluation of 3TUG times at each of the time points during the day. The intent of this analysis was to assess consistency of the response during the testing period

Reference ID: 4428593

- Physician assessment of treatment effect
- Recovery on W-SAS, 3TUG, CMAP and LEMS-related signs and symptoms after reinstituting original treatment regimen (Stage III)
- Rescue, early advance and withdrawal from Stage II due to emergence of LEMS-related issues not captured by the criteria for rescue or early advance are all indicators of treatment failure (loss of efficacy)

Descriptive statistics were provided for the other efficacy endpoints above. No formal statistical hypothesis testing was performed for these efficacy endpoints.

Exploratory Variables

- Change in LEMS-related ADLs during Stage II
- Change in LEFS score during Stage II
- Recovery on each of the endpoints available after reinstituting original treatment regimen (Stage III)
- Cardiac ejection fraction

No formal statistical hypothesis testing was performed for these variables.

Protocol Amendments

The protocol was amended on May 1, 2012 (Version 1.2) to rectify an oversight so that patients under active treatment for sleep apnea were now admissible and maintained the exclusion of patients who experienced respiratory failure requiring intubation while on 3,4-DAP.

The protocol was further amended on May 16, 2013 (Version 1.3) to add that both 3,4-DAP and N-acetyl metabolite would be determined from blood sampling, and that an additional tube of blood would be drawn for NAT2 genotyping. It was also clarified that the evening post-dose 3TUG on Day 2 in a subject dosing 3 times per day was performed after the first tapering step and therefore by definition was in Stage II. The evening post-dose 3TUG from Day 0 was therefore used in establishing the baseline in combination with the evening post-dose 3TUG from Day 1. Lastly, the methodology for CMAP measurement was modified as requested by a neurology consultant to accommodate range of practice and improve its measurement.

Reviewer Comment: These protocol amendments are reasonable and do not adversely affect interpretation of the study results.

Reference ID: 4428593

Data Quality and Integrity: Sponsor's Assurance

Clinical research staff at the research sites entered the data required by protocol onto paper or electronic Case Report Forms (CRFs) in a secure, web-based electronic data capture (EDC) system. A Bradstreet Clinical Research study monitor performed 100% source document verification and reviewed the paper or electronic CRFs for completeness and accuracy, and interacted with site personnel on data queries and to make any required data corrections or additions which were made by the clinical research coordinator or data coordinator at the site.

Reviewer Comment: See Section 4.1 for a description of problems found during OSI inspections.

6.1.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in compliance with Good Clinical Practices, the Code of Federal Regulations (CFR), including the archiving of essential documents, and the ethical principles that have their origins in the Declaration of Helsinki.

Financial Disclosure

The applicant has adequately disclosed financial interests/ arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators.

Patient Disposition

A total of 52 subjects from 7 investigative sites were screened for this study. Twenty subjects were found to be ineligible due to insufficient response to 3TUG during Stage I (n=18) or a failed drug screen (n=2). Thirty-two subjects were confirmed to be eligible and were randomized and completed the study. Subject accrual by site is shown in the following table.

Reference ID: 4428593

Table 4: Subject Accrual by site

		Number (Percent) of Subjects			
		Taper to Placebo N=18		Continuous 3,4-DAP N=14	
Site / Investigator	Screened N=52	Randomized N=18	Rescued & Early Advance N=8[a]	Randomized N=14	Rescued & Early Advance N=2
BAYL / Harati	10 (19.2%)	6 (33.3%)	3 (16.7%)	2 (14.3%)	1 (7.1%)
DUKE / Juel	13 (25.0%)	3 (16.7%)	2 (11.1%)	6 (42.9%)	1 (7.1%)
INDI / Pascuzzi	5 (9.6%)	1 (5.6%)	0 (0.0%)	1 (7.1%)	0 (0.0%)
OHSU / Lou & Marburger	6 (11.5%)	3 (16.7%)	1 (5.6%)	0 (0.0%)	0 (0.0%)
UCDA / Richman	5 (9.6%)	1 (5.6%)	1 (5.6%)	1 (7.1%)	0 (0.0%)
UUMC / Smith	7 (13.5%)	3 (16.7%)	1 (5.6%)	2 (14.3%)	0 (0.0%)
VAND / Peltier	6 (11.5%)	1 (5.6%)	0 (0.0%)	2 (14.3%)	0 (0.0%)

[a]: Includes 1 subject who requested active medication.

Source; CSR JPC 3,4 DAPPER

Subject disposition of the randomized subjects is presented in Table 5. More subjects (n=8) in the taper-to-placebo group had early entry to Stage III compared to the continuous 3,4 DAP arm (n=2). The reasons for early entry are summarized in the following table.

Reference ID: 4428593

Table 5 Subject Disposition- All randomized subjects. Source: Applicant submission

	Number (Percent) of Subjects		
Disposition Status	**Taper to Placebo N=18**	**Continuous 3,4-DAP N=14**	**Total N=32**
All randomized population (Completed Stage I)	18 (100.0%)	14 (100.0%)	32 (100.0%)
Completed Stage II	18 (100.0%)	14 (100.0%)	32 (100.0%)
Early Entry to Stage III	8 (44.4%)	2 (14.3%)	10 (31.3%)
Rescued due to			
New dysphagia	5 (27.8%)	2 (14.3%)	7 (21.9%)
Drop in pulse/ox[a]	1 (5.6%)	0 (0.0%)	1 (3.1%)
Advanced due to			
Inability to rise from a chair[b]	1 (5.6%)	0 (0.0%)	1 (3.1%)
Inability to get out of bed[c]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subject Request for Active Medication	1 (5.6%)	0 (0.0%)	1 (3.1%)
Discontinued	0 (0.0%)	0 (0.0%)	0 (0.0%)

a: Drop in pulse/ox of 5% from baseline or a decrease to <90% with accompanying shortness of breath
b: Inability to rise from a chair, even with assistance, after 2 efforts - 1 hour apart
c: Inability to get out of bed, even with assistance, after 2 efforts - 1 hour apart

Source; CSR JPC 3,4 DAPPER

Protocol Violations/Deviations

A total of 249 protocol deviations were reported during the study, including 9 major deviations (4 in the continuous and 5 in the taper to placebo arm) and 240 minor deviations. As shown in the table in Appendix 13.7, the major deviations involved inclusion and exclusion criteria, primarily regarding the need to have stable medication regimens for at least 1 month prior to the study. One deviation occurred because a subject failed to use a cane to help with walking during one TUG test but used a cane for all other TUGs. *These deviations do not adversely affect interpretation of the study results.*

Table of Demographic Characteristics

The baseline demographic characteristics for the ITT population are summarized in the following table. See also Section 8.2.2 for relevant characteristics of the safety population.

Reference ID: 4428593

Table 6: Baseline Demographic Characteristics in the DAPPER Study

Parameter	Statistic	Taper to Placebo N=18	Continuous 3,4-DAP N=14	Total N=32
Age (years)	Mean (SD)	59.3 (14.99)	50.7 (15.97)	55.5 (15.77)
	Median	63.5	49.0	60.0
	Range	28, 78	23, 83	23, 83
Gender – n (%)	Male	7 (38.9%)	4 (28.6%)	11 (34.4%)
	Female	11 (61.1%)	10 (71.4%)	21 (65.6%)
Race – n (%)	American-Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Black or African-American	0 (0.0%)	3 (21.4%)	3 (9.4%)
	Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
	White or Caucasian	18 (100%)	11 (78.6%)	29 (90.6%)
	Other	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity – n (%)	Hispanic or Latino	1 (5.6%)	0 (0.0%)	1 (3.1%)
	Not Hispanic or Latino	17 (94.4%)	14 (100%)	31 (96.9%)
Height (cm)	Mean (SD)	169.6 (8.98)	167.2 (7.38)	168.6 (8.28)
	Median	167.6	167.6	167.6
	Range	160, 188	149.9, 177.8	149.9, 188
Weight (kg)	Mean (SD)	80.3 (18.95)	75.7 (20.28)	78.3 (19.36)
	Median	83.0	73.3	80.1
	Range	49.0, 117.0	45.8, 112.9	45.8, 117.0
BMI (kg/m^2)	Mean (SD)	27.7 (5.14)	26.8 (5.98)	27.3 (5.45)
	Median	28.6	25.3	26.6
	Range	18.9, 35.4	20.3, 39.0	18.9, 39.0

Source: Study Report

Reviewer's Comment: The median age is approximately 14 years older in the taper-to-placebo group, which might increase the number of AEs expected in that group.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The baseline LEMS characteristics and signs and symptoms are summarized in the following tables.

Reference ID: 4428593

Table 7: Baseline LEMS Characteristics, ITT Population

Parameter	Statistic	Taper to Placebo N=18	Continuous 3,4-DAP N=14	Total N=32
Age at Time of LEMS Diagnosis (years)	Mean (SD)	52.7 (14.76)	44.1 (13.79)	48.9 (14.76)
	Median	59.5	46.0	52.5
	Range	26, 72	20, 63	20, 72
Age of Onset of LEMS Symptoms (years)	Mean (SD)	50.4 (14.16)	43.1 (13.86)	47.3 (14.29)
	Median	56.0	45.0	50.5
	Range	23, 72	19, 63	19, 72
Time Between Onset of LEMS Symptoms and Diagnosis (years)	Mean (SD)	2.2 (3.00)	0.9 (0.62)	1.7 (2.35)
	Median	1.5	1.0	1.0
	Range	0, 13	0, 2	0, 13
Duration of LEMS Diagnosis Prior to Randomization (years)	Mean (SD)	6.7 (6.08)	6.7 (5.70)	6.7 (5.82)
	Median	5.9	4.7	5.5
	Range	0.3, 22.3	1.1, 19.8	0.3, 22.3
Paraneoplastic Syndrome – n (%)	Yes	1 (5.6%)	0 (0.0%)	1 (3.1%)
	No	17 (94.4%)	14 (100%)	31 (96.9%)
Positive P/Q Voltage Gated Antibodies at Screening – n (%)	Negative	1 (5.6%)	2 (14.3%)	3 (9.4%)
	Positive	17 (94.4%)	12 (85.7%)	29 (90.6%)
Positive CMAP c/w LEMS at Screening[a] – n (%)	Yes	10 (55.6%)	7 (50.0%)	17 (53.1%)
	No	8 (44.4%)	7 (50.0%)	15 (46.9%)
Indicators of Disease Severity or Complications due to LEMS:				
Ever Hospitalized? – n (%)	Yes	7 (38.9%)	6 (42.9%)	13 (40.6%)
	No	11 (61.1%)	8 (57.1%)	19 (59.4%)
Ever Intubated? – n (%)	Yes	0 (0.0%)	1 (7.1%)	1 (3.1%)
	No	18 (100%)	13 (92.9%)	31 (96.9%)
Difficulty Weaning off Ventilator? – n (%)	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	18 (100%)	14 (100%)	32 (100%)
History of Tracheotomy? – n (%)	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	18 (100%)	14 (100%)	32 (100%)
History of PEG Tube Placement? – n (%)	Yes	1 (5.6%)	0 (0.0%)	1 (3.1%)
	No	17 (94.4%)	14 (100%)	31 (96.9%)
Requiring assistive device to walk? – n (%)	Yes	2 (11.1%)	2 (14.3%)	4 (12.5%)
	No	16 (88.9%)	12 (85.7%)	28 (87.5%)

A positive CMAP definition, consistent with LEMS at Screening, was >100% facilitation on pre-dose CMAP after maximal exercise in at least 1 of 3 muscles tested (Source: CSR DAPPER).

Reviewer's Comment: The mean and median ages of LEMS onset are older in the taper-to-placebo group, which might increase the number of AEs expected in that group. There was only one subject with cancer-related LEMS. All other subjects had non-paraneoplastic autoimmune LEMS. Given that women have a higher prevalence of autoimmune illnesses than men, this

Reference ID: 4428593

difference may account for the unequal sex distribution in the study.

Table 8: LEMS Signs and Symptoms Characteristics, ITT Population

Parameter	Number (Percent) of Subjects		
	Taper to Placebo N=18	Continuous 3,4-DAP N=14	Total N=32
Most Troubling LEMS Signs and Symptoms at Screening (occurring in at least 10% of all subjects)			
Early morning weakness before taking first 3,4-DAP of the day	13 (72.2%)	9 (64.3%)	22 (68.8%)
Heaviness in Legs	10 (55.6%)	10 (71.4%)	20 (62.5%)
Fatigue	9 (50.0%)	10 (71.4%)	19 (59.4%)
Difficulty Climbing Stairs	11 (61.1%)	7 (50.0%)	18 (56.3%)
Dry Mouth	8 (44.4%)	8 (57.1%)	16 (50.0%)
Difficulty Arising from a Seated Position	7 (38.9%)	8 (57.1%)	15 (46.9%)
Difficulty Swallowing	5 (27.8%)	5 (35.7%)	10 (31.3%)
Difficulty Lifting Feet	5 (27.8%)	4 (28.6%)	9 (28.1%)
Heaviness or Weakness in Upper Arms	4 (22.2%)	4 (28.6%)	8 (25.0%)
Difficulty Breathing	2 (11.1%)	5 (35.7%)	7 (21.9%)
Urinary Frequency	3 (16.7%)	4 (28.6%)	7 (21.9%)
Dry Eyes	4 (22.2%)	2 (14.3%)	6 (18.8%)
Increased Sweating	3 (16.7%)	3 (21.4%)	6 (18.8%)
Shortness of Breath with Exercise	3 (16.7%)	3 (21.4%)	6 (18.8%)
Muscle Cramps	4 (22.2%)	1 (7.1%)	5 (15.6%)
Muscle Pain	3 (16.7%)	2 (14.3%)	5 (15.6%)
Blurred Vision	1 (5.6%)	3 (21.4%)	4 (12.5%)
Coughing	3 (16.7%)	1 (7.1%)	4 (12.5%)
Depression	2 (11.1%)	2 (14.3%)	4 (12.5%)
Diarrhea	3 (16.7%)	1 (7.1%)	4 (12.5%)
Difficulty Emptying Bladder	1 (5.6%)	3 (21.4%)	4 (12.5%)
Sadness	1 (5.6%)	3 (21.4%)	4 (12.5%)
Slow Urination	1 (5.6%)	3 (21.4%)	4 (12.5%)
Abnormal Gait? - n (%)			
Yes	10 (55.6%)	8 (57.1%)	18 (56.3%)
No	8 (44.4%)	6 (42.9%)	14 (43.8%)
Requiring assistive device to walk - n (%)			
Yes	2 (11.1%)	2 (14.3%)	4 (12.5%)
No	16 (88.9%)	12 (85.7%)	28 (87.5%)

Reviewer's Comment: Fewer patients had baseline difficulty breathing in the taper-to-placebo group (11%) compared to the continuous 3,4-DAP group (36%), which might affect interpretation of any respiratory AEs in the groups.

Reference ID: 4428593

Table 9: 3,4,-DAP and other LEMS medication at baseline

Parameter	Statistic	Taper to Placebo N=18	Continuous 3,4-DAP N=14	Total N=32
Duration of 3,4-DAP Treatment Prior to Study Entry (years)	N	18	14	32
	Mean (SD)	5.5 (4.92)	6.2 (5.30)	5.8 (5.02)
	Median (Min, Max)	4.3 (0.3, 18.3)	4.6 (0.7, 18.9)	4.6 (0.3, 18.9)
Duration of Current 3,4-DAP Treatment Regimen (years)	N	18	14	32
	Mean (SD)	3.2 (3.55)	2.8 (2.81)	3.0 (3.21)
	Median (Min, Max)	1.3 (0.3, 12.0)	2.0 (0.3, 9.3)	1.8 (0.3, 12.0)
Total Daily Dose of 3,4-DAP at Randomization (mg)	N	18	14	32
	Mean (SD)	74.7 (22.26)	76.4 (19.46)	75.5 (20.77)
	Median (Min, Max)	80.0 (30, 100)	80.0 (35, 100)	80 (30, 100)
Number of 3,4-DAP Individual Daily Doses at Study Entry (n)	N	18	14	32
	Mean (SD)	4.6 (1.04)	4.7 (1.20)	4.7 (1.10)
	Median (Min, Max)	5.0 (3, 6)	4.5 (3, 7)	5.0 (3, 7)
Amount of 3,4-DAP Equal for Each Dose? - n (%)	Yes	11 (61.1%)	10 (71.4%)	21 (65.6%)
	No	7 (38.9%)	4 (28.6%)	11 (34.4%)
Current LEMS Treatment Regimen - Proportion of Patients – n (%)	3,4-DAP Alone	0 (0.0%)	1 (7.1%)	1 (3.1%)
	3,4-DAP + Pyridostigmine	11 (61.1%)	9 (64.3%)	20 (62.5%)
	3,4-DAP + pyridostigmine + Immunomodulators/ immunosuppressants	4 (22.2%)	2 (14.3%)	6 (18.8%)
	3,4-DAP + Immunomodulators/ immunosuppressants	3 (16.7%)	2 (14.3%)	5 (15.6%)
Currently On Pyridostigmine? – n (%)	Yes	15 (83.3%)	11 (78.6%)	26 (81.3%)
	No	3 (16.7%)	3 (21.4%)	6 (18.8%)
Total Daily Dose of Pyridostigmine (mg)	N	15	11	26
	Mean (SD)	236.0 (138.81)	219.5 (93.02)	229.0 (119.67)
	Median (Min, Max)	240 (60, 600)	180 (105, 360)	210 (60, 600)
Number of Pyridostigmine Doses Per Day	N	15	11	26
	Mean (SD)	3.9 (1.83)	3.9 (1.30)	3.9 (1.60)
	Median (Min, Max)	4.0 (1, 8)	4.0 (2, 7)	4.0 (1, 8)
Historical Exposure to Prednisone? – n (%)	Yes	9 (50.0%)	7 (50.0%)	16 (50.0%)
	No	9 (50.0%)	7 (50.0%)	16 (50.0%)
Currently On Prednisone? – n (%)	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	18 (100.0%)	14 (100.0%)	32 (100.0%)
Currently On IVIG? – n (%)	Yes	1 (5.6%)	3 (21.4%)	4 (12.5%)
	No	17 (94.4%)	11 (78.6%)	28 (87.5%)

Reference ID: 4428593

Reviewer's Comment: The groups are adequately balanced at baseline with respect to prior medication regimens. Note that IVIG use at baseline was permitted, but that admission to the study occurred at least one week after the last IVIG treatment and at least 2 weeks before the next scheduled treatment. No IVIG was given during the inpatient portion of the study.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

There were no major issues with treatment compliance. Study drug dose was administered, and dosing was recorded, by study personnel at the investigative sites. The number of subjects decreased from 14 to 12 on Days 5 and 6 in the continuous 3,4-DAP group because 2 subjects in this group experienced new dysphagia and were rescued early on Day 4. Neither subject reached the primary study endpoint prior to rescue.

Eight subjects in the taper to placebo group were rescued or had an early entry into Stage III. Five of the 8 subjects were rescued due to new dysphagia, 1 subject was rescued due to a drop in pulse oximetry, 1 subject requested active medication during Stage II, and 1 subject was advanced early to Stage III due to an inability to rise from a chair, even with assistance, after 2 efforts 1 hour apart. Two of the 8 subjects in the taper to placebo group who had early entry into Stage III did not meet the primary endpoint prior to rescue.

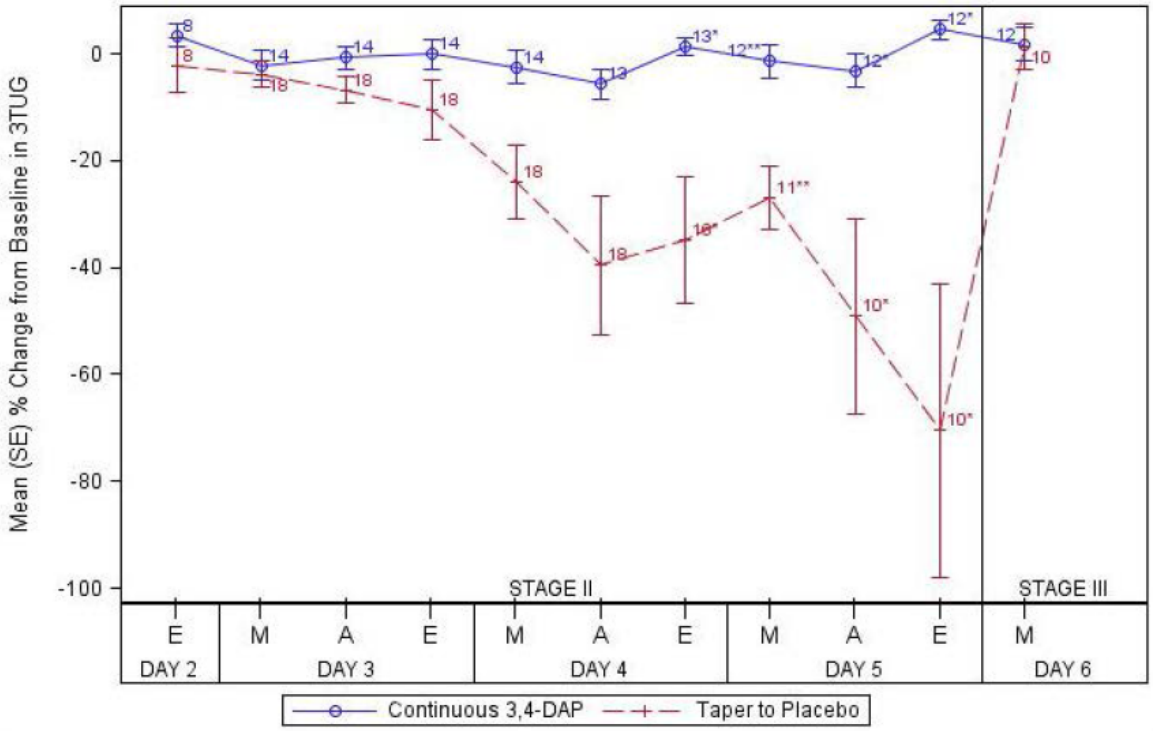
Efficacy Results – Primary Endpoint: Change in 3TUG test

The primary endpoint was the categorization of the degree of change in the 3TUG test (last observation at the theoretical "peak drug effect", i.e., 2 hours post dose) upon withdrawal of active medication (Stage II) when compared with the time-matched average of the 3TUG assessments during Stage I. In the taper to placebo group, 13 of 18 subjects (72.2%) had a >30% deterioration in the final 3TUG test upon withdrawal of study drug compared to 0 of 14 (0.0%; $p<0.0001$) subjects in the continuous 3,4-DAP group.

The following figure from the submission shows the mean change in 3TUG in the two groups over the course of the trial.

Reference ID: 4428593

Figure 3: Mean (+/- SE) Percent Change from Baseline in 3TUG at 2 Hours After Dosing Versus Time by Treatment Groups – Efficacy Population. Source: Applicant submission



M: Morning; A: Afternoon; E: Evening.
* P-value <0.05; ** P-value <0.01; *** P-value <0.001. P-value is based on the one-way ANCOVA model, with the baseline 3TUGs as the covariate.

Note that patients in the taper-to-placebo group returned to baseline 3TUG performance when therapy was reinitiated in Stage III in the above figure.

The following tables from the submission summarize the 3TUG change in the two groups over the course of the trial.

Reference ID: 4428593

Table 10: Primary Efficacy Endpoint: Summary of >30% Deterioration in the Final Timed Up & Go (3TUG) Test Upon Withdrawal of Study Drug (Stage II) – Efficacy, Intent-to-treat and Per-protocol Populations

	Number (Percent) of Subjects		
Category of Change in 3TUG	**Taper to Placebo**	**Continuous 3,4-DAP**	**P value[a]**
Efficacy Population	**N=18**	**N=14**	
A-B No Change or Faster	5 (27.8%)	14 (100.0%)	<0.0001
C-G >30% Slower	13 (72.2%)	0 (0.0%)	
Intent-to-treat Population	**N=18**	**N=14**	
A-B No Change or Faster	5 (27.8%)	14 (100.0%)	<0.0001
C-G >30% Slower	13 (72.2%)	0 (0.0%)	
Per-protocol Population	**N=18**	**N=13**	
A-B No Change or Faster	5 (27.8%)	13 (100.0%)	<0.0001
C-G >30% Slower	13 (72.2%)	0 (0.0%)	

a: P value based on Fisher's Exact Test

Reference ID: 4428593

Table 11: Summary of Categorized Degree of Change (7 Categories) in the Final Timed Up & Go (3TUG) Test Upon Withdrawal of Study Drug (Stage II) – Efficacy, Intent-to-treat and Per-protocol Populations. Source: Applicant submission

	Number (Percent) of Subjects		
Category of Change in 3TUG	**Taper to Placebo**	**Continuous 3,4-DAP**	**P value[a]**
Efficacy Population	**N=18**	**N=14**	
A- >30% Faster	0 (0.0%)	0 (0.0%)	0.0008
B- No Change	5 (27.8%)	14 (100%)	
C- >30-50% Slower	5 (27.8%)	0 (0.0%)	
D- >50-100% Slower	5 (27.8%)	0 (0.0%)	
E- >100-200% Slower	1 (5.6%)	0 (0.0%)	
F- >200% Slower	2 (11.1%)	0 (0.0%)	
G- Cannot Perform TUG	0 (0.0%)	0 (0.0%)	
Intent-to-treat Population	**N=18**	**N=14**	
A- >30% Faster	0 (0.0%)	0 (0.0%)	0.0008
B- No Change	5 (27.8%)	14 (100%)	
C- >30-50% Slower	5 (27.8%)	0 (0.0%)	
D- >50-100% Slower	5 (27.8%)	0 (0.0%)	
E- >100-200% Slower	1 (5.6%)	0 (0.0%)	
F- >200% Slower	2 (11.1%)	0 (0.0%)	
G- Cannot Perform TUG	0 (0.0%)	0 (0.0%)	
Per-protocol Population	**N=18**	**N=13**	
A- >30% Faster	0 (0.0%)	0 (0.0%)	0.0011
B- No Change	5 (27.8%)	13 (100%)	
C- >30-50% Slower	5 (27.8%)	0 (0.0%)	
D- >50-100% Slower	5 (27.8%)	0 (0.0%)	
E- >100-200% Slower	1 (5.6%)	0 (0.0%)	
F- >200% Slower	2 (11.1%)	0 (0.0%)	
G- Cannot Perform TUG	0 (0.0%)	0 (0.0%)	

a: P value based on Cochran-Mantel-Haenszel (CMH) Test

This result, verified by the FDA biometrics reviewer, shows that there is a statistically significant difference in the change in 3TUG scores between the continuous 3,4-DAP and taper-to-placebo groups, indicating a worsening in the ability of patients to stand up and walk when 3,4-DAP treatment is stopped.

Reference ID: 4428593

This reviewer also conducted an assessment comparing mean difference in 3TUG scores between the taper-to-placebo and continuous 3,4-DAP groups; specifically, the difference of mean 3TUGs between the final day of Stage 2 and the first day of Stage 1, using post-dose 3TUGs and averaging all of a day's numbers together per subject.

The continuous 3,4-DAP group had a mean increase in 3TUG of only 0.2 seconds, compared to a mean 6.4 second increase in the taper-to-placebo group. This result is consistent with the reported positive finding for the primary endpoint.

Data Quality and Integrity

As described in Section 4.1, data discrepancies occurred in 3TUG test results when the central reviewer incorrectly transcribed some of the assessment times from a spreadsheet to the EDC system. The vendor that performed the statistical analysis used the data that was in the EDC system without doing any edit checks on the source document (the excel spreadsheet).

Because of these findings, the placebo-controlled DAPPER study 3TUG test videos were re-read to correct the data used to support the FDA efficacy analysis. The result for the primary endpoint remains positive and supportive of efficacy using the re-read data.

Efficacy Results – Secondary and other relevant endpoints

The result for the secondary endpoint, the Subject Self-Assessment of LEMS-Related Weakness (W-SAS), is summarized in the following table from the submission. Approximately 56% of the taper-to-placebo patients felt "much much weaker", compared to only 7% of the continuous 3,4-DAP group. 64% of the continuous 3,4-DAP group felt "about the same", compared to approximately 6% of the taper-to-placebo group.

Reference ID: 4428593

Table 12: Secondary Efficacy Endpoint: Summary of the Final W-SAS Assessment During Stage II – Efficacy and Per-protocol Populations

		Taper to Placebo	Continuous 3,4-DAP	P value[b]
Efficacy Population				
Final W-SAS Category[a] - N (%)	Much Much Weaker (-3)	10 (55.6%)	1 (7.1%)	<0.0001
	Much Weaker (-2)	6 (33.3%)	1 (7.1%)	
	Somewhat Weaker (-1)	1 (5.6%)	1 (7.1%)	
	About the Same (0)	1 (5.6%)	9 (64.3%)	
	Somewhat Stronger (1)	0 (0.0%)	1 (7.1%)	
	Much Stronger (2)	0 (0.0%)	1 (7.1%)	
	Much Much Stronger (3)	0 (0.0%)	0 (0.0%)	
Final W-SAS Score	N	18	14	<0.0001
	Mean (SD)	-2.4 (0.85)	-0.2 (1.19)	
	Median (Min, Max)	-3.0 (-3.0, 0.0)	0.0 (-3.0, 2.0)	

This result shows that there is a statistically significant difference in the W-SAS scores between the continuous 3,4-DAP and taper-to-placebo groups, indicating that more patients felt weaker when 3,4-DAP was stopped than when it was continued.

Additional Results for Exploratory Endpoints without formal statistical hypothesis testing:

Compound Muscle Action Potential (CMAP): The change in CMAP during down-titration and after withdrawal of active medication was assessed. As seen in the following table from the submission, CMAP measurements decreased across all muscles in the taper-to-placebo group. For all muscle types, the percent change from baseline in the final post-dose CMAP was smaller for the continuous 3,4-DAP group (-4.6% for the site-read and -9.5% for the blinded-reviewer assessments) compared to the taper-to-placebo group (-48.5% for the site-read and -44.1% for the blinded-reviewer assessments).

Reference ID: 4428593

Table 13: Summary of the Last Available Post-Dose Compound Muscle Action Potential (CMAP) During Stage II – Efficacy Population. Source: DAPPER CSR

Muscle Statistics	Taper to Placebo N=18 Measurement (mV)	Taper to Placebo N=18 % Change from Baseline[a]	Continuous 3,4-DAP N=14 Measurement (mV)	Continuous 3,4-DAP N=14 % Change from Baseline[a]
Final Post-Dose CMAP - All Records				
ADQ				
N	4	4	6	6
Mean (SD)	2.2 (1.96)	-43.2 (31.58)	6.0 (4.08)	3.9 (31.91)
Median (Min, Max)	1.8 (0.2, 4.8)	-47.0 (-70.8, -7.9)	7.1 (0.9, 11.2)	-8.3 (-18.2, 66.9)
APB				
N	12	12	5	5
Mean (SD)	2.7 (1.81)	-50.2 (17.68)	6.9 (4.27)	0.4 (17.97)
Median (Min, Max)	2.6 (0.3, 5.2)	-49.9 (-80.9, -28.0)	8.4 (2.1, 10.8)	-3.0 (-19.8, 27.3)
EDB				
N	2	2	3	3
Mean (SD)	1.3 (1.34)	-48.9 (8.59)	1.8 (1.38)	-30.1 (31.66)
Median (Min, Max)	1.3 (0.3, 2.2)	-48.9 (-55.0, -42.9)	1.1 (0.9, 3.4)	-14.8 (-66.5, -9.0)
All Muscle Types				
N	18	18	14	14
Mean (SD)	2.4 (1.77)	-48.5 (19.78)	5.4 (4.05)	-4.6 (28.95)
Median (Min, Max)	2.3 (0.2, 5.2)	-49.9 (-80.9, -7.9)	5.0 (0.9, 11.2)	-9.3 (-66.5, 66.9)
Final Post-Dose CMAP - Blinded Reviewer Approved Records				
ADQ				
N	3	3	4	4
Mean (SD)	2.8 (1.80)	-35.2 (30.96)	6.7 (4.11)	-6.3 (8.51)
Median (Min, Max)	2.3 (1.3, 4.8)	-28.9 (-68.9, -7.9)	7.1 (1.3, 11.2)	-8.3 (-14.3, 5.6)
APB				
N	9	9	4	4
Mean (SD)	3.1 (1.86)	-46.0 (17.81)	6.0 (4.24)	1.3 (20.63)
Median (Min, Max)	3.2 (0.4, 5.2)	-41.3 (-80.9, -28.0)	5.6 (2.1, 10.7)	-1.2 (-19.8, 27.3)
EDB				
N	2	2	3	3
Mean (SD)	1.3 (1.34)	-48.9 (8.59)	1.8 (1.38)	-28.2 (28.34)
Median (Min, Max)	1.3 (0.3, 2.2)	-48.9 (-55.0, -42.9)	1.1 (0.9, 3.4)	-14.8 (-60.7, -9.0)
All Muscle Types				
N	14	14	11	11
Mean (SD)	2.8 (1.79)	-44.1 (19.30)	5.1 (3.93)	-9.5 (21.57)
Median (Min, Max)	2.3 (0.3, 5.2)	-42.1 (-80.9, -7.9)	3.4 (0.9, 11.2)	-9.5 (-60.7, 27.3)

ADQ = abductor digiti quinti muscle
APB = abductor pollicis brevis muscle
EDB = extensor digitorum brevis muscle

Reference ID: 4428593

LEMS-related activities of daily living (ADLs): The change in ADLs during Stage II was assessed. There was a decrease in mobility in the taper-to-placebo group from 94% able to sit up and place feet on the ground at baseline, to 56% on day 5. In contrast, the change in the continuous 3,4-DAP group was from 100% at baseline to 86% on day 5.

Lower extremity function scale (LEFS): The LEFS was performed at baseline, at the end of Stage II, and during follow-ups. At baseline, the taper-to-placebo and continuous 3,4-DAP groups had similar mean scores of 41 and 42, respectively. At the end of Stage II, the taper-to-placebo group LEFS score had declined by 24 points to a mean of 17. The continuous 3,4-DAP group's LEFS score declined by 2 points to a mean of 40.

Echocardiograms: Echocardiograms were conducted prior to and 2 hours after the first dose of Stage I and Stage III /rescue/early advancement dose. Cardiac ejection fraction was assessed. No adverse changes in echocardiogram findings were noted during this study. The mean ejection fraction increased from baseline by 2% in the taper-to-placebo group, and by 4% in the continuous 3,4-DAP group. There does not appear to be a clinically significant difference in cardiac ejection fraction changes between the two groups.

Physician Assessment of Treatment Effect: Investigator assessment of treatment effect on a rating scale occurred once at the end of Stage II. As seen in the following table from the submission, 78% of subjects in the taper-to-placebo group were assessed as much worse than during baseline compared to 7% in the continuous 3,4-DAP group.

Table 14: Summary of Physician Assessment of Treatment Effect – Efficacy Population. Source: DAPPER CSR

Physician Assessment of Treatment Effect	Taper to Placebo (N=18)	Continuous 3,4-DAP (N=14)
Much worse than during baseline	14 (77.8%)	1 (7.1%)
Somewhat worse than during baseline	3 (16.7%)	1 (7.1%)
No change from baseline	1 (5.6%)	12 (85.7%)
Somewhat improved from baseline	0 (0.0%)	0 (0.0%)
Much improved from baseline	0 (0.0%)	0 (0.0%)

Reviewer Comment: The results of the secondary and exploratory endpoints are consistent with or do not contradict the positive findings for the primary endpoint.

Reference ID: 4428593

Dose/Dose Response

Subjects in the DAPPER study continued their usual dosing regimen of 3,4-DAP 30 mg to 100 mg/day during acclimation (0.5 day) and Stage I (2 days). Eligible subjects were then randomized to double-blind study medication in Stage II (~3.5 days) [Group A (continuous 3,4-DAP) or Group B (taper to placebo)]. Taper to placebo subjects had their 3,4-DAP dose gradually reduced until tapered to zero (or the subject was rescued or early advanced). Each subject's usual pre-study 3,4-DAP dosing regimen was reinstituted in Stage III (~0.5 day, with up to 2 additional days if needed to ensure clinical stability).

Reviewer Comment: Because of its design and small size, the DAPPER study does not allow for a meaningful comparison of efficacy at different doses.

See also section 7.1.4.

Durability of Response

See Section 7.1.5.

Persistence of Effect

As seen in the DAPPER study's dose-tapering design, the effect of 3,4-DAP wanes quickly over the course of hours as the dose is reduced and ultimately stopped.

See also Section 7.1.5.

6.2. JPC 3,4-DAP DUKE RCT

6.2.1. Study Design

Overview and Objective

The Duke RCT study was first described in the publication of Sanders et al. (2000). It was a prospective, placebo-controlled, randomized study of 3,4-diaminopyridine (DAP) in adult patients with Lambert-Eaton myasthenic syndrome. The applicant has obtained data from the original study for re-analysis. These data have been reviewed and are considered supportive of this NDA. The Duke RCT study is not the primary basis for efficacy because of its short duration and limitations with its primary endpoint, the Quantitative Myasthenia Gravis scale (QMG), as discussed in Section 7.1.1. DNP had previously advised the applicant that short-duration

Reference ID: 4428593

efficacy studies of 3,4-DAP could be used in combination with positive findings on the new placebo-controlled (DAPPER) study to support NDA filing.

The objective of this study was to evaluate the effectiveness of 3,4-DAP in treating LEMS and to determine its acute and long-term side effects.

Trial Design

Twenty-six patients with LEMS completed a two-arm parallel treatment protocol in which 3,4-DAP or placebo was given blindly for 6 days. Twelve patients received 3,4-DAP and 14 patients received placebo. Patients took one capsule of either placebo or 20mg 3,4-DAP three times a day (for a total daily dose of 60mg) for 6 days. QMG and nerve stimulation studies were repeated on the fifth and sixth days of study drug administration. After the sixth day of study drug administration, all patients received no study medication for 24 hours, then were given 10 or 20 mg DAP three times daily and observed in hospital for 24 hours. The DAP dose subsequently was adjusted to produce the maximum symptomatic benefit.

After the blinded study, patients were given open-label DAP and monitored for side effects as long as there was symptomatic improvement.

Study Endpoints

The primary efficacy endpoint was the change from baseline in the quantitative myasthenia gravis [QMG] score. The average of the baseline QMG scores obtained on 2 consecutive days before beginning study drug was compared with the average of post-baseline QMG scores obtained on the fifth and sixth days of study drug administration. The QMG is a clinical assessment of muscle weakness for muscle groups typically involved in myasthenia gravis and LEMS, with a score range of 0 to 39. Higher scores indicate greater weakness.

Other efficacy measurements were the change in the summated CMAP amplitude in 3 muscles (2 in the hand and 1 foot muscle), a Symptomatic Response to Treatment questionnaire, change in swallowing times, and change in walking times.

Statistical Analysis Plan

QMG scores from 2 assessments made prior to beginning treatment (baseline) were averaged and compared to the average of the values obtained on the 4th and 5th days on treatment. Determination of improvement in QMG was to be based on changes in the QMG score after taking 3,4-DAP versus that seen after taking placebo using a one-sided, two-sample t-test.

Reference ID: 4428593

As the data proved to be skewed, the analysis used descriptive statistics for continuous variables as medians and interquartile ranges, using the Wilcoxon's rank sum test to evaluate group differences. Fisher's exact test was used to evaluate group differences in categorical variables.

Compound muscle action potentials (CMAP) were measured from each tested muscle with a rest of at least 1 minute between stimuli. The mean of the 3 values was recorded as the CMAP amplitude for that muscle. The change in summated CMAP amplitude between baseline and post-baseline values was calculated for each patient. Descriptive statistics for continuous variables were presented as medians and interquartile ranges, using the Wilcoxon's rank sum test to evaluate differences between the treatment groups.

The intention-to-treat (ITT) population is defined as all randomized subjects who received at least 1 dose of 3,4-DAP or placebo during the double-blind phase.

The per-protocol (PP) population consists of all randomized subjects who received at least 1 dose of 3,4-DAP or placebo during the double-blind phase and had post-baseline efficacy assessments on the last 2 days of the study drug treatment using the primary outcome measure (QMG score).

Protocol Amendments

None.

6.2.2. Study Results

Compliance with Good Clinical Practices

Sanders et al. (2000) states that the study protocol was approved by the Duke University Medical Center Investigational Review Board, and informed consent was obtained from all patients.

Financial Disclosure

This study was supported by grant no. FD-R-001068 from the USPHS and grant no. M01 RR-30

Reference ID: 4428593

from the General Clinical Research Centers Program, National Center for Research Resources, NIH. Jacobus Pharmaceutical Co., Inc. provided 3,4-diaminopyridine for this study.

Patient Disposition

Thirty-seven patients with a confirmed diagnosis of LEMS were screened for this study. Eleven patients did not meet entry criteria and were not randomly assigned to a treatment. Twenty-six patients who met the inclusion criteria were randomly assigned with intention to treat. All these patients completed the study.

Protocol Violations/Deviations

None.

Table of Demographic Characteristics

The baseline demographic characteristics for the study population are summarized in the following table.

Table 15: Comparison of placebo and treated groups at baseline. Source: Applicant submission.

Characteristic	Placebo (N=14)	3,4-DAP (N=12)	p-Value
Gender, n (%)			1.000[a]
Male	6 (42.9)	5 (41.7)	
Female	8 (57.1)	7 (58.3)	
Age at onset (years), median (interquartile range)	56.5 (48.0 to 64.0)	56.5 (41.0 to 68.5)	0.719[b]
Subjects with SCLC, n (%)	5 (35.7)	4 (33.3)	1.000[a]
Baseline QMG, median (interquartile range)	12.3 (9.0 to 13.5)	8.5 (7.3 to 17.0)	0.625[b]
Baseline CMAP, median (interquartile range)	1.5 (0.8 to 2.2)	1.5 (0.6 to 2.6)	0.817[a]

3,4-DAP = 3,4-diaminopyridine; CMAP = compound muscle action potential; ITT = intention-to-treat; QMG = quantitative myasthenia gravis score; SCLC = small cell lung cancer.
[a] p value is derived from a Fisher exact test
[b] p value is derived from a 2-side 2-sample Wilcoxon's rank sum test, Normal Approximation.

Reviewer's Comment: The proportion of patients with small cell lung cancer (SCLC) is greater in the in the placebo group, which might increase the number of AEs expected in that group. Although the baseline QMGs appear to differ, the baseline CMAPs are similar in both groups.

Reference ID: 4428593

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Concomitant medications are only reported for 3 patients. They include Zantac, solumedrol, IVIG, prednisone, Synthroid, Accupril, Zantac, Metamucil and aspirin, Propulsid, metronidazole, Prilosec, Trimox Temazepam, Lorazepam, and Mestinon.

There were no reported issues with treatment compliance and no reported rescue medication use.

Reviewer's Comment: There are insufficient data to determine if the groups were adequately balanced at baseline with respect to prior medication regimens.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the change from baseline in the quantitative myasthenia gravis [QMG] score. The result is summarized in the following table, copied from the submission. The observed difference in QMG scores between the placebo and 3,4-DAP groups, with a larger decline in the score (indicating less weakness) in the 3,4-DAP group, is supportive of the positive results of the DAPPER study discussed above. *The clinical significance of this 1.5-point difference on the 39-point QMG score is unclear.*

Table 16: QMG Results from the Double-blind Portion of Duke RCT Study – Per-Protocol Population.

	Placebo (N=13)	3,4-DAP (N=12)	p-Value
QMG			
Baseline	11.5 (9.0 to 13.5)	8.5 (7.3 to 17.0)	0.806
Post-baseline	12.5 (9.0 to 13.5)	6.5 (5.0 to 14.3)	0.220
Change from baseline	-0.5 (-1.0 to 1.0)	-2.0 (-3.0 to 0.0)	0.015

Data Quality and Integrity

No problems with data quality and integrity were found. Given the age of the data, site inspections were not possible.

Reference ID: 4428593

Efficacy Results – Secondary and other relevant endpoints

The change in the summated CMAP amplitude from baseline in the placebo and 3,4-DAP groups is summarized in the following table, copied from the submission. The difference between the two groups, with a positive change in the 3,4-DAP group indicating a stronger muscle response, is supportive of the positive results of the DAPPER study discussed above.

Table 17: CMAP Results from the Double-blind Portion of the Duke RCT Study – Per-Protocol Population.

	Placebo (N=13)	3,4-DAP (N=12)	p-Value
Baseline	1.4 (0.8 to 2.2)	1.5 (0.6 to 2.6)	0.849
Post-baseline	1.2 (1.1 to 2.2)	3.1 (1.1 to 5.1)	0.087
Change from baseline	-0.1 (-0.1 to 0.1)	0.8 (0.1 to 2.5)	0.001
Percent change from baseline	-3.3 (-13.1 to 2.6)	41.7 (14.2 to 297.2)	0.002

Patients completed a symptomatic response questionnaire. The difference in responses between the patients in the placebo and 3,4-DAP groups is summarized in the following table, based on the submitted data from Sanders et al. (2000). This result is supportive of the positive results of the DAPPER study discussed above.

Table 18: Symptomatic Response to Treatment: Patient Questionnaire

Response to blinded drug	None	Better	Worse	p Value
Placebo (n=14)	9 (64%)	4 (29%)	1 (7%)	<0.05
3,4-DAP (n=12)	3 (25%)	9 (75%)	0 (0%)	

The change in the swallowing time from baseline in the placebo and 3,4-DAP groups is summarized in the following table, copied from the submission. There is no significant difference between the two groups.

Reference ID: 4428593

Table 19: Change in Swallowing Times After Therapy – Per-Protocol Population

	Placebo (N=13)	3,4-DAP (N=11)	p-Value
Swallowing Time (sec)			
Baseline	10.0 (6.5 to 21.0)	11.0 (5.0 to 17.5)	0.908
Post-baseline	7.0 (5.0 to 16.0)	9.0 (4.5 to 11.0)	0.885
Change from baseline	-0.5 (-4.5 to 1.0)	-1.2 (-5.5 to -0.5)	0.417
Percent change from baseline	-23.1 (-38.9 to 20.0)	-11.1 (-48.6 to -10.0)	0.750

The change in the time needed to walk 150 feet with 1 turn was assessed. The change in walking time from baseline in the placebo and 3,4-DAP groups is summarized in the following table, copied from the submission. There is no significant difference between the two groups.

Table 20: Change in Walking Times After Therapy – Per-Protocol Population

	Placebo (N=11)	3,4-DAP (N=9)	p-Value
Walking Time (sec)			
Baseline	70.5 (42.3 to 121.0)	42.5 (38.0 to 55.5)	0.080
Post-baseline	55.7 (44.0 to 101.0)	35.0 (29.5 to 43.0)	0.015
Change from baseline	-9.5 (-36.0 to -3.5)	-12.0 (-16.5 to -6.3)	0.939
Percent change from baseline	-15.2 (-33.5 to -6.6)	-21.6 (-36.3 to -15.3)	0.287

Dose/Dose Response

Because of its design and small size, the Duke RCT study does not allow for a meaningful comparison of efficacy at different doses.

See also section 7.1.4.

Durability of Response

See Section 7.1.5.

Persistence of Effect

Because of its design and small size, the Duke RCT study does not allow for a meaningful assessment of persistence of effect.

Reference ID: 4428593

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The following table compares key efficacy endpoint results between the pivotal DAPPER study and the supportive Duke RCT study. *As can be seen in the table and in the individual study results in Section 6, the two studies assessed different endpoints with generally positive results that were supportive of efficacy (with the exceptions of swallowing and walking times in Duke RCT). Both studies assessed change in CMAP and showed a consistently positive result.*

Table 21: Comparison of Efficacy Results Across Studies. Source: Reviewer summary of submitted results.

Endpoint	Clinical Study	
	DAPPER	**Duke RCT**
>30% 3TUG deterioration	Continuous Drug: 0%; Taper to Placebo: 72% p<0.0001	Not assessed
W-SAS: Felt much much weaker	Continuous Drug: 7% Taper to Placebo: 56% p<0.0001	Not assessed
CMAP change from baseline	Continuous Drug: -9.5% Taper to Placebo: -44.1%	Drug: 42% Placebo: -3% p = 0.002
LEMS-related ADLs: change from baseline mobility	Continuous Drug: -14% Taper to Placebo: -38%	Not assessed
LEFS: change from baseline	Continuous Drug: -5% Taper to Placebo: -59%	Not assessed

Reference ID: 4428593

Endpoint	Clinical Study	
	DAPPER	**Duke RCT**
Change in cardiac ejection fraction from baseline	Continuous Drug: 4% Taper to Placebo: 2%	Not assessed
Physician Assessment of Treatment Effect: Much worse than baseline	Continuous Drug: 7% Taper to Placebo: 78%	Not assessed
QMG score change from baseline	Not assessed	Drug: -2 Placebo: -0.5 p = 0.015
Symptomatic Response Questionnaire: Feeling better	Not assessed	Drug: 75% Placebo: 29% p < 0.05
Change in Swallowing Times After Therapy	Not assessed	Drug: -11% Placebo: -23% p = 0.75
Change in Walking Times After Therapy	Not assessed	Drug: -22% Placebo: -15% p = 0.29

Reference ID: 4428593

7.1.1. Primary Endpoints

The degree of change in the 3TUG test upon withdrawal of active medication was the primary endpoint used for the DAPPER study. As discussed in Section 6.1.1, the 3TUG is an acceptable endpoint. The results should be considered in the context of the positive results of the secondary and other endpoints. As seen in the comparison table above, there was >30% 3TUG deterioration in 72% of the taper-to-placebo group, whereas the continuous 3,4-DAP group remained stable with 0% who had >30% 3TUG deterioration.

The supportive Duke RCT also had a statistically significant positive result for its primary endpoint, the change in QMG score. However, the Quantitative Myasthenia Gravis scale (QMG) is problematic as a primary endpoint because a small, yet statistically significant change in the QMG might not reflect benefit that the patient could perceive. In part, this could occur because some items on the QMG measure physical signs elicited under exam conditions not usually occurring in everyday life, not symptoms that affect how the patient feels or functions. The clinical significance of the 1.5-point difference between placebo and drug groups on the 39-point QMG score is unclear but provides some additional support for the benefit observed in the DAPPER study.

Overall, the DAPPER primary endpoint result shows a clinically meaningful benefit, with increased difficulty getting up and walking as 3,4-DAP is tapered to placebo, that indicates that the drug has been having a beneficial effect for the patients.

7.1.2. Secondary and Other Endpoints

The table above shows the comparison of efficacy results across studies, including secondary and other endpoints.

The key secondary endpoint for the DAPPER study is the Subject Self-Assessment of LEMS-Related Weakness (W-SAS). It is a clinically meaningful endpoint that is appropriate for use in this study. As discussed in Section 6.1.2 and seen in the table in Section 7.1, 56% of the taper-to-placebo patients felt “much much weaker”, compared to only 7% of the continuous 3,4-DAP group. This result is consistent with the positive finding for the primary endpoint.

All other efficacy endpoints for the pivotal DAPPER study also had positive results that support the positive result for the primary endpoint.

For the Duke RCT study, the change in CMAP and the symptomatic response questionnaire also had positive results supportive of efficacy. The only endpoints without positive results were the

Reference ID: 4428593

changes in swallowing and walking times in the Duke RCT study.

Overall, the results of the secondary and other endpoints across both studies lend support to the positive efficacy results of the primary endpoint (3TUG) for the DAPPER study.

7.1.3. Subpopulations

Although the overall study populations in DAPPER and DUKE-RCT were small, there did not appear to be an appreciable difference in efficacy by sex or age > 65 years. As the large majority (>90%) of patients enrolled in both studies were White, analysis of race differences is not possible.

In the population pharmacokinetic analysis for the DAPPER study, neither age nor gender was an important factor in explaining the variability in 3,4-DAP PK parameters. In the population pharmacodynamic analysis, age was not a significant covariate for the 3TUG analysis. For CMAP, age was identified as a significant covariate, as would be expected given the known changes in nerve conduction with aging (Kurokawa et al. 1999, Taylor 1984).

7.1.4. Dose and Dose-Response

The applicant has proposed a maximum 3,4-DAP dose of (b) (4) mg/day. However, the available efficacy data come from doses of 100mg/day or less. In the DAPPER study, patients were on a range of doses from 30mg to 100mg per day that had been previously titrated to maximum effect before study entry.

The expanded access protocol limited the dose to 100mg/day because of seizure risk. The supportive Duke RCT publication states the following: “Based on this [seizure] experience, we limit the dose of DAP to 80 mg/day” (Sanders et al., 2000).

The design of the DAPPER and DUKE-RCT studies does not allow for an assessment of dose-response.

Reference ID: 4428593

7.1.5. Onset, Duration, and Durability of Efficacy Effects

In the DAPPER study, 3TUG measurements demonstrated onset of effect two hours after dosing in the taper-to-placebo group when 3,4-DAP was re-started in Stage 3. The Day 6 morning pre-dose 3TUG at the end of Stage 2 was similar between treatment groups (% change from baseline: taper-to-placebo = -9.6%; continuous 3,4-DAP = -2.4%; p=0.7). The Day 6 morning post-dose 3TUG two hours after dosing, for which both groups received 3,4-DAP, showed similar improvements in 3TUG in both groups (% change from baseline: taper-to-placebo = 1.3%; continuous 3,4-DAP = 1.8%; p=0.7).

Among the 162 patients from the JPC expanded access RPV162 dataset, the average total duration of treatment was 4.9 years, with a range from 1 day to 27 years. Approximately 87% of these patients reported improvement in LEMS symptoms from treatment. There were no reports of loss of efficacy over time.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

There are no additional postmarketing considerations with respect to the established benefit for the treatment of patients with LEMS.

7.2.2. Evidence of Pediatric Efficacy

No formal clinical study was performed to assess the efficacy of 3,4-DAP in pediatric LEMS patients. The following reports and data were submitted.

Seven pediatric LEMS patients, aged 9 to 16 years, received 3,4-DAP in the expanded access program. Only one pediatric patient (b) (6) had serial 3TUG assessments during treatment with 3,4-DAP to document drug response. These data are listed in the following table, copied from the patient narrative. They show a decrease in 3TUG times following the initiation of 3,4-DAP treatment. Note that the dose was titrated to effect from a starting dose of 2.5 mg, 3 times per day using a weight-based titration, advanced to 10 mg, 3 times per day on 12 April 2015 due to inadequate response, and then to 10 mg, 4 times per day on 13 April 2015.

Reference ID: 4428593

Table 22: Serial 3TUG measurements in a 9-year-old pediatric LEMS patient following 3,4-DAP initiation and dose titration. Source: Case narrative for subject (b) (6)

Date	Dose per day	Pre-dose 3TUG, sec	Post-dose 3TUG, sec	Comments
4/7/2015	7.5mg	13.84	20.74	interval between dose and post-dose 3TUG not recorded; query re post-dose not closed; suspect that the average of the 3 laps was not calculated and result might be 6.91
4/23/2015	40mg		5.9	Improvement over pre-dose 3TUG on 4/7/2015
6/17/2015	40mg		8.3	2.5 hr post dose; longer distance
7/15/2015	40mg		7.3	2 hr post-dose
8/13/2015	40mg		11.31	prednisone had been tapered from 30 daily to 10 mg every other day; frequency of plasmapheresis and IVIG increased
9/11/2015	40mg		9.15	prednisone increased to 20 mg/d
11/6/2015	40mg		9.32	
1/15/2016	40mg		7.06	rituximab x 2 doses in preceding month
2/12/2016	40mg		6.96	
3/11/2016	40mg		4.85	
4/8/2016	40mg		7.01	prednisone wean had already started; dose #3 rituximab administered
4/26/2016	40mg		7.3	
6/17/2016	40mg		5.9	
7/19/2016	40mg		6	
	40mg		8.3	prednisone 30mg alternating with 20 mg
8/23/2016	40mg			started Imuran 50 mg
8/26/2016	40mg		5.99	prednisone 30 mg alternating with 25 mg

Published reports of 3,4-DAP use in five pediatric LEMS patients, aged 11 to 16 years, describe clinical improvement in all cases, but they include no objective measures of efficacy (Della Marina et al., 2012; Hajjar et al., 2014; Portaro et al., 2014; Schüler et al., 2001; Verbeek et al., 2014). These reports were included in the submission and were reviewed, but were not considered adequate to provide evidence for the safety or effectiveness of amifampridine and will not be discussed further in the review.

Reviewer Comment: Efficacy can be extrapolated from adults to pediatric patients when it is reasonable to assume that children, compared with adults, have a similar progression of disease, similar response of disease to treatment, and similar exposure-response relationship.

Reference ID: 4428593

The disease mechanism of LEMS, autoantibody-mediated removal of a subset of the P/Q-type Ca2+ channels at the neuromuscular junction, is the same in adults and children. It is reported that pediatric LEMS patients have a similar response to treatment as adults. Although efficacy data for amifampridine in pediatric patients with LEMS is largely anecdotal, the applicant has provided data for one 9-year-old LEMS patient treated in the expanded access program that shows improvement on 3TUG performance after initiation of amifampridine. A drug that is efficacious in adults by presynaptic potassium channel blockade would, therefore, also be expected to be efficacious in children. The applicant has also provided dosing information in the reports for the pediatric patients and has performed simulation and modeling to show that proposed doses for pediatric patients are expected to provide similar exposures to those found to be therapeutic in adult patients. Based on the overall data, it appears reasonable to extrapolate the effectiveness of amifampridine for the treatment of LEMS from adults to pediatric patients.

7.3. Integrated Assessment of Effectiveness

The DAPPER study was an adequate and well-controlled efficacy study that can support approval of 3,4-DAP for the treatment of LEMS. It was a well-designed study that has provided reliable and statistically strong ($p<0.0001$) evidence of an important clinical benefit, an effect on strength and ambulation as measured by the 3TUG. The study has also shown a clinically meaningful and statistically strong ($p<0.0001$) improvement in quality of life, as measured by the W-SAS score as a key secondary endpoint. Further, there was numerically greater worsening of symptoms in the taper-to-placebo group compared to the continuous 3,4-DAP group for other secondary endpoints, including CMAP change from baseline, LEMS-related activities of daily living, lower extremity function scale, and physician assessment of treatment effect.

The positive results of the DAPPER study are further supported by the positive results of the Duke RCT study, which showed a statistically significant difference in QMG ($p=0.015$) and CMAP ($p = 0.002$) measurements between placebo and 3,4-DAP groups, indicating greater muscle strength in the 3,4-DAP group. The clinical significance of these results was supported by a patient-reported symptomatic response questionnaire, in which 75% of the 3,4-DAP group reported feeling better, compared to 29% of the placebo group.

The positive results of the DAPPER study and the supportive Duke RCT study are further supported by the long-term expanded access data for 3,4-DAP. Among the 162 patients from the JPC expanded access RPV162 dataset, the average total duration of treatment was 4.9 years, with a range from 1 day to 27 years. Approximately 87% of these patients reported improvement in LEMS symptoms as a result of treatment with 3,4-DAP.

Reference ID: 4428593

Reports from seven pediatric LEMS patients, including a single patient's serial 3TUG data, suggest that 3,4-DAP may also be effective in pediatric LEMS patients. The disease mechanism of LEMS, autoantibody-mediated removal of a subset of the P/Q-type Ca2+ channels at the neuromuscular junction, is the same in adults and children. A drug that is effective in adults by presynaptic potassium channel blockade would therefore also be expected to be effective in children. Based on the overall data, it appears reasonable to extrapolate the effectiveness of amifampridine for the treatment of LEMS from adults to pediatric patients.

8. Review of Safety

8.1. Safety Review Approach

Safety was assessed by evaluating the data submitted from the randomized, double-blind, placebo-controlled JPC 3,4- DAPPER study in patients with LEMS, adverse events in the placebo-controlled QT study in healthy subjects, and the open-label expanded access INDs (RPV162 and Special Populations datasets). Data from the placebo-controlled JPC 3,4-DAP DUKE RCT was reviewed and considered supportive. The safety review also includes updated information from the 120-day safety update. The available narratives for deaths, serious adverse events, laboratory studies, and vital signs were reviewed. The medical scientific literature was searched where appropriate for additional information. Details of the individual studies are described in the review of efficacy.

Analyses of Adverse Event Data:
Translation of verbatim terms to preferred terms: The ADAE.xpt datafiles for the submitted studies were examined for accuracy of translation from verbatim to preferred term through manual review of all unique pairs of verbatim and preferred terms. There were 44 unique adverse events in the DAPPER study. Verbatim and preferred terms were sorted and manually reviewed for completeness and accuracy. No recoding was needed.

The DUKE-RCT study data listed only monitored clinical events and did not include an adverse event database.

Reference ID: 4428593

The RPV162 database included 998 unique verbatim adverse event terms. Verbatim and preferred terms were sorted and manually reviewed for completeness and accuracy. Forty-one terms were recoded, as shown in Appendix 13.4, to reduce the splitting of related terms that would erroneously decrease reported AE frequency. The primary change was to recode "paresthesia oral", "dysesthesia" and "oral dysesthesia" as "paresthesia", resulting in a change from separate rates of "paresthesia oral" (18%) and "paresthesia" (25%) to more accurately reflect the rate of paresthesia in this study population, which is 36%. "Convulsion" was also recoded as "seizure," and cases of oral numbness were recoded as "hypoaesthesia" instead of "hypoaesthesia oral." The resulting adverse events tables are shown in Section 8.4.5. Additionally, a customized grouping from the Center for Drug Evaluation and Research, designed to combine important medically-related preferred terms to enhance safety signal detection, was used in the adverse event analysis.

Analyses of Laboratory Data:
In addition to assessing mean values over time, critical laboratory parameters were visually inspected in scatter plots.

This review was based on analyses of the data submitted by the applicant.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Safety data from the placebo-controlled DAPPER study included 32 LEMS patients (14 in the continuous 3,4-DAP group, and 18 in the taper-to-placebo group).

Approximately 627 patients have received 3,4-DAP since 1990 through open-label expanded access Investigational New Drug (IND) applications. From these INDs, safety data was pooled by retrospective review from 247 patients to support the current NDA. These 247 patients include those who participated in the DAPPER study. In the RPV162 dataset, patient age at the time 3,4-DAP was initiated ranged from 21 to 84 years (mean 58.7 years) and in the Special Populations dataset 3,4-DAP was initiated from 9 to 85 years (mean 50 years), as shown in Tables 14 and 15. Among patients with available exposure data, the median duration of treatment was 1.7 years (range 1 day to 27.6 years) for the RPV162 dataset and 4.7 years (range 1 day to 27.6 years) for the Special Populations dataset. The overall exposure to amifampridine in the expanded access database was estimated to be 1189 patient years (766.4 patient-years for the RPV162 population and 422.6 patient years for the 69 patients in the

Reference ID: 4428593

Special Populations pool) (See Table 24 and Table 25).

The 120-day safety update also included data from 8 pediatric patients, 4 of whom had not been previously reported. During the review, the applicant also submitted safety information for 12 additional pediatric patients with congenital myasthenic syndrome (CMS) treated with amifampridine, with treatment initiated as early as 1 year of age.

Investigators could titrate the dose to effect and decrease the dose for intolerance. Patients could be treated with 3,4-DAP at doses up to 100mg/day. Eleven patients received doses greater than the maximum recommended dose of 100mg/day, reaching up to 300mg/day with a median of 120mg/day.

Table 23: 3,4-DAP Safety Population, Size, and Denominators

Safety Database for 3,4-DAP Individuals exposed to any treatment in this development program N= 316 (N is the sum of all available numbers from the columns below)		
Clinical Trial Groups	**3,4-DAP (n= 298)**	**Taper-To-Placebo (n= 18)**
Healthy volunteers (Phase 1 pharmacokinetics study)	30	
Healthy volunteers (TQT Study)	52	
Controlled trials conducted for LEMS (DAPPER)	14	18
Open-label Expanded Access Data	202	

DAPPER study subjects were part of the expanded access RPV162 population but are listed separately in the above table. Duration of exposure is summarized in the following table for the expanded access database. In total, 234 subjects were treated for up to 27 years in the RPV162 and Special populations databases.

Reference ID: 4428593

Table 24: Duration of Exposure in RPV162 Database

	Statistic	Total (N=162)
Total duration of treatment: (Years)	n	158
	Mean (SD)	4.9 (6.2)
	Median	1.7
	Min, Max	0, 27.6
Patient years of exposure	Total	766.4
Maximum total daily dose: (mg)	n	142
	Mean (SD)	68.3 (30.8)
	Median	75
	Min, Max	10, 175

Table 25: Duration of Exposure in Special Populations Database

	Statistic	Total (N=72)
Total duration of treatment: (Years)	n	66
	Mean (SD)	6.4 (5.8)
	Median	4.7
	Min, Max	0, 20.3
Patient years of exposure	Total	422.6
Maximum total daily dose: (mg)	n	66
	Mean (SD)	73.7 (37.4)
	Median	75.0
	Min, Max	5, 300

Given the prevalence of LEMS, the cumulative 3,4-DAP exposure is deemed adequate to support a reasonable assessment of safety.

Reference ID: 4428593

8.2.2. Relevant characteristics of the safety population:

There were 32 subjects in the DAPPER study's controlled safety population, enrolled from 7 sites in United States. Demographic and important baseline characteristics are summarized in the following table.

Table 26: Demographic and Baseline Characteristics in the Controlled DAPPER Study Population

Characteristic	Statistic	Continuous 3,4-DAP (N=14)	Taper-To-Placebo (N=18)
Age	Mean (SD)	50.7 (16)	59.3 (15)
	Median	49	64
	Min, Max	23, 83	28, 78
Sex, n (%)	Male	4 (29)	7 (39)
	Female	10 (71)	11 (61)
Race, n (%)	Black or African American	3 (21)	0 (0)
	White	11 (79)	100 (0)
Study Site, n (%)	BAYL	2 (14)	6 (33)
	DUKE	6 (43)	3 (17)
	INDI	1 (7)	1 (6)
	OHSU	0 (0)	3 (17)
	UCDA	1 (7)	1 (6)
	UUMC	2 (14)	3 (17)
	VAND	2 (14)	1 (6)

There were 159 subjects in the open-label RPV162 expanded access safety population, enrolled from 93 sites in United States. Demographic and important baseline characteristics are summarized in the following table.

Reference ID: 4428593

Table 14: Demographic and Baseline Characteristics in the RPV162 safety population

Characteristic	Statistic	3,4-DAP (N=159)
Age	Mean (SD)	58 (14)
	Median	60
	Min, Max	21, 84
Sex, n (%)	Male	71 (45)
	Female	84 (53)
	Missing	4 (2)
Race, n (%)	Black or African American	7 (4)
	American Indian or Alaska Native	2 (1)
	White	80 (50)
	Missing/Not Reported	70 (44)

There were 69 subjects in the open-label Special Populations expanded access safety population, enrolled from 44 sites in United States. Demographic and important baseline characteristics are summarized in the following table.

Table 15: Demographic and Baseline Characteristics in the Open-label Special Populations safety population

Characteristic	Statistic	3,4-DAP (N=66)	Missing Data (N=3)
Age	Mean (SD)	53 (18)	Not reported
	Median	56	
	Min, Max	9, 85	
Sex, n (%)	Male	34 (51.5)	0 (0)
	Female	32 (48.5)	1 (33)
	Missing/Not Reported	0 (0)	2 (67)
Race, n (%)	Black or African American	3 (4.5)	Not reported
	White	31 (47)	Not reported
	Missing/Not Reported	32 (48.5)	3 (100)

Reference ID: 4428593

8.2.3. Adequacy of the safety database:

Based on the characteristics in the above demographics table, the development program is deemed to provide generally adequate representation across the disease population. The course of the disease is not known to differ importantly in minority populations, and there are no known factors that would predispose these populations to drug-induced toxicity. The patient exposure appears generalizable to the US patient population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No anomalies with safety data fitness were detected.

Routine clinical safety evaluations were scheduled (and generally occurred) for the DAPPER study: screening up to 30 days before admission to the clinical research unit, inpatient entry on the afternoon prior to the start of the two-day baseline period (including medical history, medication review, physical exam, vital signs with pulse oximetry, LEMS signs and symptoms review, global assessment of LEMS-related weakness (W-SAS), 12-lead ECG, and LEMS-related ADLs). During each study stage at specified times and frequencies, subjects received TUG testing, vital signs with pulse oximetry, W-SAS, LEMS signs and symptoms evaluation, 12-lead ECG, echocardiogram, and blood draws for safety labs and drug concentration. Subjects also received an end-of-study physical examination prior to discharge.

For the expanded access data, uniform time points for laboratory test results are not available and the amount of data varies greatly among the subjects of the multiple INDs which provided data for the pooled population, complicating safety assessments. Adverse events, serious adverse events, deaths, medical histories, dosing, and narratives of SAEs, deaths, seizures, cardiac AEs, and suicides have been adequately reported.

8.3.2. Categorization of Adverse Events

The applicant used standard procedures to collect and analyze adverse event data. Adverse events were recorded at all subject visits, and subjects were to be monitored for adverse events

Reference ID: 4428593

through 4 weeks after inpatient participation in the placebo-controlled DAPPER study.

Investigators were asked to assess causality and intensity (mild, moderate, severe, life-threatening, or fatal) of AEs.

Treatment-emergent adverse events were defined as any event that started on or after the time of the first study drug administration.

Multiple occurrences of adverse events were counted once, per the Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

MedDRA was used for coding of adverse events for all clinical studies.

The applicant designated the following as adverse events of special interest (AESI):

- Seizures
- Renal impairment or other disorders
- Suicidal behavior (including suicidal ideation)
- Cardiac disorders or QTc prolongation.

As noted above in Section 8.1, the ADAE.xpt datafile was reviewed for accuracy of translation from verbatim to preferred term through manual review. Changes in translation of verbatim terms made to reduce the splitting of related terms that would erroneously decrease reported AE frequency.

In summary, the applicant's translation (coding) of verbatim terms to preferred terms does not have any important inaccuracies, other than slightly underestimating paresthesia as described in Section 8.1. Grouping of related adverse event terms was not inconsistent and did not lead to significant underestimating of the magnitude of safety signals.

8.3.3. Routine Clinical Tests

Assessments of vital signs and laboratory monitoring were only routinely performed in the DAPPER study. Laboratory monitoring included assessments of hematological parameters (hemoglobin, hematocrit, total leukocytes, lymphocytes, neutrophils, eosinophils, or platelet count), blood chemistry (sodium, chloride, potassium, bicarbonate, calcium, total protein, glucose, and albumin), renal parameters (BUN and creatinine), liver transaminases, bilirubin, and alkaline phosphatase.

Reference ID: 4428593

8.4. Safety Results

8.4.1. Deaths

There were no deaths during the controlled DAPPER trial. One patient, (b) (6), died of cardiac arrest and respiratory acidosis at age 80, more than 1 year after completing participation in DAPPER and 8.3 years after starting 3,4-DAP. At the time of her death, the patient was taking 90 mg of 3,4-DAP per day. Her medical history was notable for COPD, hypercholesterolemia, and sleep apnea, with concomitant medications including tiotropium bromide, azelastine, albuterol sulfate, esomeprazole, and digoxin.

One hundred twenty-three deaths have been reported in the 3,4-DAP expanded access programs (RPV162 and Special Populations), including the 120-day safety update. Sixty-one of the death reports did not include a report of cause. Thirty-eight of the deaths were the result of cancer and cancer-related comorbidities, including pneumonia and respiratory failure. Twenty-five deaths were reported as fatal AEs: including stroke, small cell lung cancer, pancreatic cancer, respiratory failure, suicide, congestive heart failure, pneumonia, and traumatic head injury. None of the deaths were attributed to 3,4-DAP. Cardiac-related deaths included congestive heart failure, cardiac arrest in the setting of lung cancer and pneumonia, hypertensive cardiovascular disease, cardiac ablation with transient QT prolongation and atrial fibrillation (subject (b) (6)), and coronary artery occlusion with atrioventricular block. See Section 8.5.1 for a discussion of cardiac adverse events. There were no deaths reported from seizure.

Deaths within one month of starting 3,4-DAP were further reviewed. Of 13 deaths, 5 deaths were caused by lung cancer, 3 deaths were caused by respiratory failure, 1 death was from suicide in the setting of lung cancer and depression, 1 death was from congestive heart failure in a patient with a prior history of cardiomyopathy, and 3 deaths were from unreported causes.

The overall exposure to 3,4-DAP in the expanded access program is estimated to be 1189 patient years (766.4 patient-years for the RPV162 population and 422.6 patient years for the 69 patients in the Special Populations pool). The estimated death rate is therefore 0.08 per year, which is approximately ten times higher than the death rate in the general U.S. population.

Patients in the expanded access program were quite ill, often with respiratory compromise caused by lung cancer and worsened by muscular weakness related to LEMS. Given the patient population and the absence of a control group, it is difficult to attribute causality to 3,4-DAP; however, the contribution of 3,4-DAP to the events cannot be ruled out.

Reference ID: 4428593

8.4.2. Serious Adverse Events

Controlled Trials:

The only serious adverse event in the controlled DAPPER study was one subject with pneumonia in the taper to placebo group (1 subject of 18, or ~6%). There were no serious adverse events in the continuous 3,4-DAP group.

Uncontrolled Trials:

The following table shows the serious adverse events in the RPV162 dataset that occurred in more than one subject. SAEs that occurred in at least 2% of the population are highlighted in bold.

Table 27: Serious Treatment-emergent Adverse Events from Expanded Access RPV162 Dataset. Source: MAED analysis of submitted data.

3,4-Diaminopyridine (N = 159)			
Serious Adverse Event	**Number of Events**	**Number of subjects**	**Proportion (%)**
Pneumonia	15	14	**8.8**
Small cell lung cancer	11	11	**6.9**
Cerebrovascular accident	6	6	**3.8**
Metastases to central nervous system	6	6	**3.8**
Small cell lung cancer metastatic	6	6	**3.8**
Atrial fibrillation	5	5	**3.1**
Respiratory failure	6	5	**3.1**
Cardiac arrest	4	4	**2.5**
Fall	4	4	**2.5**
Hip fracture	4	4	**2.5**
Lung neoplasm malignant	4	4	**2.5**
Pulmonary embolism	4	4	**2.5**
Asthenia	3	3	1.9

Reference ID: 4428593

3,4-Diaminopyridine (N = 159)			
Serious Adverse Event	**Number of Events**	**Number of subjects**	**Proportion (%)**
Cardiac pacemaker insertion	3	3	1.9
Deep vein thrombosis	4	3	1.9
Hip surgery	3	3	1.9
Hypotension	3	3	1.9
Sepsis	3	3	1.9
Small cell lung cancer recurrent	3	3	1.9
Acute respiratory failure	2	2	1.3
Cardiac failure congestive	2	2	1.3
Dehydration	2	2	1.3
Dysphagia	2	2	1.3
Dyspnoea	2	2	1.3
Head injury	2	2	1.3
Headache	2	2	1.3
Hospitalization	2	2	1.3
Hypokalaemia	2	2	1.3
Lung cancer metastatic	2	2	1.3
Pneumonia bacterial	2	2	1.3
Renal failure acute	2	2	1.3

Reviewer Comment: Note that cancer is commonly associated with LEMS, as described in Section 2.1, so cancer-related SAEs are probably not caused by 3,4-DAP. It is difficult to make any conclusion about a relation between 3,4-DAP use and susceptibility to infection because of the small number of subjects in the controlled trial, the lack of a control group in the expanded access group, and the fact that many patients with LEMS are treated with immunosuppressants and immunomodulators which may make them more susceptible to infection. There is a theoretical risk of QT prolongation and cardiac arrhythmia with 3,4-DAP use because of its effect on voltage-gated potassium channels; however, a formal thorough QT study did not show a signal for QT prolongation. There is also a potential risk of seizures (convulsions) with 3,4-DAP

Reference ID: 4428593

use. The narratives of all patients with cardiac and seizure-related AEs and SAEs were reviewed and are discussed in section 8.5.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no subjects in the controlled DAPPER study who were discontinued from the study due to adverse events. Twelve subjects in the expanded access program (7.4%) reported adverse events leading to discontinuation of 3,4-DAP. The AEs leading to discontinuation are listed in the following table, generated from the submitted data. It is noted that one discontinuation was due to convulsion, an identified risk for 3,4-DAP (refer to Section 8.5.2 for further discussion of the seizures/convulsions). The events of head titubation and tremor occurred in the same patient. 3,4-DAP treatment was temporarily interrupted in 18 (11.1%) patients most commonly (>2 patients) because of SCLC (3 patients), oral paresthesia (2 patients), and cardiac arrest (2 patients). Additionally, treatment was temporarily interrupted for paresthesia (patient (b) (6)), burning sensation (patient (b) (6)), and palpitations (patient (b) (6)) in 1 patient each. This pattern follows the trends in adverse and serious adverse events, shown in Sections 8.4.2 and 8.4.5.

Table 28: Applicant's Data - Adverse Events Leading to Discontinuation in the Expanded Access Population (RPV162, N=162)

AE Preferred Term	Number of Subjects (%) Discontinued
Convulsion	1 (0.6%)
Head titubation	1 (0.6%)
Tremor	1 (0.6%)
Unresponsive to stimuli	1 (0.6%)
Small cell lung cancer	1 (0.6%)
Metastases to central nervous system	1 (0.6%)
Lung cancer metastatic	1 (0.6%)
Pulmonary mass	1 (0.6%)
Bradycardia	1 (0.6%)
Pneumonia	1 (0.6%)
Completed suicide	1 (0.6%)
Fall	1 (0.6%)
Gunshot wound	1 (0.6%)

Reference ID: 4428593

8.4.4. Significant Adverse Events

There were no severe treatment-emergent adverse events for the 3,4-DAP group in the controlled DAPPER trial. There was one (6%) severe AE in the taper to placebo group each for anxiety and pneumonia.

For the expanded access RPV162 data, there were severe AEs in 52 subjects (32% of the population). The most common severe AEs occurring in more than one subject are shown in the following table. This pattern follows the trends in adverse and serious adverse events, shown in Sections 8.4.2 and 8.4.5. As discussed there, lung cancer (with its associated comorbidities) is known to be associated with LEMS. Seizures/convulsions are a known potential risk of treatment with 3,4-DAP.

Table 29: Severe Adverse Events Occurring in More Than One Subject in the Open-Label Expanded Access Database RPV162

Severe AE Preferred Term	Number of Subjects (%) with Severe AE
Metastases to central nervous system	7 (4.3)
Small cell lung cancer	4 (2.5)
Lung cancer metastatic	4 (2.5)
Pneumonia	3 (1.9)
Convulsion	2 (1.2)
Sleep apnoea syndrome	2 (1.2)
Pulmonary embolism	2 (1.2)
Acute respiratory failure	2 (1.2)
Asthenia	2 (1.2)
Small cell lung cancer metastatic	2 (1.2)
Small cell lung cancer recurrent	2 (1.2)
Dehydration	2 (1.2)
Pancytopenia	2 (1.2)

Reference ID: 4428593

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The DAPPER study protocol defined an adverse event as "any unfavorable and unintended sign, symptom, syndrome, or illness that develops or worsens during the period of observation in the clinical study and up to 30 days after cessation of the study." A treatment-emergent adverse event (TEAE) was defined as any event that started on or after the time of first study drug administration in the DAPPER study. Adverse events present at baseline from prior 3,4-DAP use were not included. A total of 14 of 18 (78%) of subjects in the taper-to-placebo group and 6 of 14 (43%) subjects in the continuous 3,4-DAP group reported at least 1 TEAE. The following table shows TEAEs from the controlled trial. Adverse events that occurred at a frequency > 0% in drug-treated subjects with a difference between drug-treated and placebo group of ≥ 2% are included. The preferred term "neurological symptom" was coded by the applicant from the verbatim description "Patient reported feeling dizzy, tired, sluggish, and lightheaded, during diary week 4."

Table 30: Treatment-emergent Adverse Events in the Controlled DAPPER Study. Source: MAED analysis of submitted data.

	Continuous 3,4-DAP (N = 14)			*Taper to Placebo (N = 18)*			*3,4-DAP - Placebo (%)*
PT	*Events*	*Number of subjects*	***Proportion (%)***	*Events*	*Number of subjects*	*Proportion (%)*	
Headache	2	2	**14.3**	1.0	1.0	**5.6**	**8.7**
Gastritis	1	1	**7.1**	0.0	0.0	**0.0**	**7.1**
Injection site bruising	1	1	**7.1**	0.0	0.0	**0.0**	**7.1**
Instillation site irritation	1	1	**7.1**	0.0	0.0	**0.0**	**7.1**
Migraine	1	1	**7.1**	0.0	0.0	**0.0**	**7.1**
Musculoskeletal stiffness	1	1	**7.1**	0.0	0.0	**0.0**	**7.1**
Neuralgia	1	1	**7.1**	0.0	0.0	**0.0**	**7.1**
Neurological symptom	1	1	**7.1**	0.0	0.0	**0.0**	**7.1**
Oral herpes	1	1	**7.1**	0.0	0.0	**0.0**	**7.1**

The following table shows a customized grouping, designed to combine important medically-related preferred terms, from the controlled trial. Adverse events that occurred at a frequency > 0% in drug-treated subjects with a difference between drug-treated and placebo group of ≥ 2% are included.

Reference ID: 4428593

Table 31: Grouping of Treatment-emergent Adverse Events in the Controlled DAPPER Study Safety Database.

Analysis Columns	Continuous 3,4-DAP (N=14): Subjects	Continuous 3,4-DAP (N=14): %	Taper to Placebo (N=18): Subjects	Taper to Placebo (N=18): %	3,4-DAP - Placebo (%)
injection site reaction (all)	1	**7.1**	0	**0.0**	**7.1**
infection, viral	1	**7.1**	0	**0.0**	**7.1**
herpes virus	1	**7.1**	0	**0.0**	**7.1**
neuralgia, neuritis, neuropathy	1	**7.1**	0	**0.0**	**7.1**
migraine	1	**7.1**	0	**0.0**	**7.1**
headache	2	**14.3**	2	**11.1**	**3.2**

Reviewer Comment: Injection site reaction reflects other treatments in these patients with multiple co-morbidities and is not related to administration of 3,4-DAP, which is taken orally as a tablet. No clear conclusion about group differences for these medically-related terms can be made because of the small sample size, short duration, and small number of adverse events in the DAPPER study.

Uncontrolled Adverse Event Data:

488 treatment-emergent adverse events were recorded for the RPV162 dataset. Treatment-emergent adverse events that occurred in at least 5% of the patients are shown in the following table. The top 10% are shown in bold print. Note that falls may be related to the proximal muscle weakness commonly present in LEMS patients. Paresthesia (34%) has also been previously reported in other studies of amifampridine and amifampridine phosphate.

Reference ID: 4428593

Table 32: Treatment-emergent Adverse Events from the RPV162 Dataset. Source: MAED analysis of submitted data.

	10 mg 3,4-Diaminopyridine (N = 159)				
PT	*Events*	*Number of subjects*	*Proportion (%)*	*Proportion C.I. (lower bound) (%)*	*Proportion C.I. (upper bound) (%)*
Paraesthesia	99	58	**36.5**	29.4	44.2
Fall	22	21	**13.2**	8.8	19.4
Diarrhoea	21	20	**12.6**	8.3	18.6
Pneumonia	19	16	**10.1**	6.3	15.7
Small cell lung cancer	14	14	8.8	5.3	14.2
Dyspnoea	16	12	7.6	4.4	12.7
Muscle spasms	15	11	6.9	3.9	12.0
Nausea	12	11	6.9	3.9	12.0
Arthralgia	13	10	6.3	3.5	11.2
Asthenia	10	10	6.3	3.5	11.2
Depression	11	10	6.3	3.5	11.2
Dysphagia	10	10	6.3	3.5	11.2
Headache	9	9	5.7	3.0	10.4
Insomnia	10	9	5.7	3.0	10.4
Metastases to central nervous system	9	9	5.7	3.0	10.4
Vision blurred	9	9	5.7	3.0	10.4
Abdominal pain	8	8	5.0	2.6	9.6
Anaemia	9	8	5.0	2.6	9.6
Anxiety	8	8	5.0	2.6	9.6
Constipation	8	8	5.0	2.6	9.6
Feeling cold	8	8	5.0	2.6	9.6
Gastrooesophageal reflux disease	8	8	5.0	2.6	9.6
Pain	8	8	5.0	2.6	9.6

The following table shows a customized grouping, designed to combine important medically-related preferred terms, for the expanded access dataset. Treatment-emergent adverse events that occurred in at least 5% of the patients in the expanded access data are shown in the following table. Adverse events that occurred in at least 10% of the population are highlighted in bold.

Reference ID: 4428593

Table 33: Grouping of Treatment-emergent Adverse Events from the RPV162 Dataset

Adverse Event Grouping	3,4-Diaminopyridine (N=159) Number of Subjects	3,4-Diaminopyridine (N=159): Proportion (%)
infection, all	54	**34.0**
paresthesia, hypoaesthesia	54	**34.0**
solid neoplasia, ALL (benign, malignant, unknown)	39	**24.5**
cancer (non-squamous cell)	35	**22.0**
diarrhea, colitis, gastroenteritis	27	**17.0**
abdominal pain, distension	27	**17.0**
fall, dizziness, balance disorder	27	**17.0**
Fall	21	**13.2**
dyspepsia, nausea, vomiting, epigastric pain	20	**12.6**
Pneumonia	19	**11.9**
Arrhythmia	19	**11.9**
arthralgia, arthritis	17	**10.7**
asthenia, fatigue, malaise	15	9.4
respiratory distress	15	9.4
visual disturbance	15	9.4
respiratory failure	14	8.8
upper resp tract infection, flu-like illness	13	8.2
Nausea, vomiting	13	8.2
Fracture	12	7.5
diabetes, hyperglycemia	11	6.9
Depression	11	6.9
insomnia, sleep disturbance	11	6.9
muscle spasm	11	6.9
infection, viral	10	6.3
Headache	10	6.3
Dysphagia	10	6.3
supraventricular tachycardia	9	5.7
Tachycardia	9	5.7
neuralgia, neuropathy	9	5.7
Insomnia	9	5.7
Anemia	9	5.7

Reference ID: 4428593

Adverse Event Grouping	3,4-Diaminopyridine (N=159) Number of Subjects	3,4-Diaminopyridine (N=159): Proportion (%)
rash, eruption, dermatitis	8	5.0
Hypertension	8	5.0
chest pain (non-cardiac or unknown)	8	5.0
Stroke (embolic)	8	5.0
Anxiety	8	5.0
Bleeding	8	5.0
Cough	8	5.0
Constipation	8	5.0
reflux, GERD	8	5.0

Adverse events included under arrhythmia in the RPV162 dataset are shown in the following table.

Table 34: Adverse Events Grouped Under Arrhythmia in the RPV162 Dataset

AE Grouped under Arrhythmia	Number (%) of Patients with the AE
Atrial fibrillation	5 (3)
Atrial tachycardia	1 (0.01)
Bradycardia	3 (0.02)
Heart rate decreased	1 (0.01)
Heart rate increased	1 (0.01)
Heart rate irregular	4 (0.03)
Sinus tachycardia	2 (0.01)
Supraventricular tachycardia	5 (3)
Tachycardia	4 (0.03)

Reviewer Comment: The finding of paresthesia is consistent with prior adverse events reports for this drug. Note that cancer is commonly associated with LEMS, as described in Section 2.1, so cancer-related AEs are probably not caused by 3,4-DAP. It is difficult to make any conclusion about a relation between 3,4-DAP use and susceptibility to infection because of the small number of subjects in the controlled trial, the lack of a control group in the expanded access group, and the fact that many patients with LEMS are treated with immunosuppressants and immunomodulators which may make them more susceptible to infection. The custom adverse event grouping showed an increased incidence of arrhythmia terms, but it is unclear from the above table alone if the AEs under cardiac arrhythmia are related to 3,4-DAP use or to underlying medical comorbidities. See the discussion of cardiac adverse events in Section 8.5.1. There were no other new safety signals detected from the custom adverse event groups.

Reference ID: 4428593

Note that the rates of adverse events were generally greater in the Special Populations dataset (97% for any AEs in Special Populations vs. 78% in RPV162), as shown in the following table from the submission. The Special Populations cases were intentionally enriched by the applicant to include all remaining patients who were not captured in the RPV162 population with either medical history, medical events, or AEs of particular concern, including seizure, cardiac disorders or QT prolongation, suicidal behavior (including suicidal ideation), renal disorders, and hepatic disorders. *These higher AE rates likely occurred because the Special Populations dataset was enriched with higher-risk patients and is not representative of the general LEMS patient population.*

Table 35: Adverse Events Summary Comparing the Expanded Access RPV162 and Special Populations Groups. Source: Applicant submission

	RPV162 N=162 (766.4 PY Exposure)		Special Populations N=69 (422.6 PY Exposure)	
AE Category	**Patients, n (%)**	**Events (Rate[a])**	**Patients, n (%)**	**Events (Rate[a])**
Any AEs	127 (78.4)	1307 (170.5)	67 (97.1)	172.7
Related AEs	68 (42.0)	200 (26.1)	42 (60.9)	23.7
Severe AEs	52 (32.1)	105 (13.7)	38 (55.1)	23.7
Life-threatening AEs	26 (16.0)	34 (4.4)	12 (17.4)	5.0
Fatal AEs	19 (11.7)	21 (2.7)	6 (8.7)	1.4
Any paresthesia[b] AEs	60 (37.0)	113 (14.7)	27 (39.1)	9.5
Any GI[c] AEs	23 (14.2)	28 (3.7)	8 (11.6)	2.6
Deaths (all deaths, both AEs and non-AEs)	94 (58.0)	58 (7.6)	27 (39.1)	2.6
SAEs	87 (53.7)	222 (29.0)	51 (73.9)	52.1
Related SAEs	3 (1.9)	3 (0.4)	14 (20.3)	4.5
AEs leading to 3,4-DAP discontinuation	12 (7.4)	13 (1.7)	11 (15.9)	3.5
AEs leading to 3,4-DAP interruption	18 (11.1)	24 (3.1)	18 (26.1)	9.0
AEs leading to 3,4-DAP dose modification	24 (14.8)	41 (5.3)	19 (27.5)	7.6

3,4-DAP = 3,4-diaminopyridine; AE = adverse event; GI = gastrointestinal; PY = patient-years; SAE = serious adverse event.

[a] AE rate per 100 PY of exposure = (total number of AEs/total number of PY of drug exposure) × 100.

[b] Paresthesia AEs include paresthesia, paresthesia oral, feeling cold, hypoesthesia, hypoesthesia oral, and chills.

[c] GI AEs include abdominal discomfort, abdominal pain, abdominal pain upper, and dyspepsia.

Given the limitations of the clinical trial and expanded access data, safety data from the thorough QT study was also assessed, as this provided some controlled data to assess

Reference ID: 4428593

relatedness of adverse events to amifampridine with short-term administration. The TQT was a double-blind, double-dummy, placebo- and positive-controlled, 3-way crossover TQT study of 56 healthy subjects. The study compared single doses of placebo, 120mg 3,4-DAP, and 400mg moxifloxacin as an active control. Adverse events that occurred in at least 2 subjects are listed in the table below

Table 36: Treatment-emergent Adverse Events in ≥ 2 Subjects in the TQT study

Adverse Reaction	Amifampridine (N=52) n (%)	Placebo (N=49) n (%)
Paresthesia/Dysesthesia*	36 (69)	1 (2)
Abdominal pain	13 (25)	0
Dyspepsia	9 (17)	1 (2)
Muscle Twitching	9 (17)	9 (18)
Dizziness	6 (12)	0
Nausea	5 (10)	1 (2)
Back pain	4 (8)	1 (2)
Hypoesthesia	3 (6)	0
Muscle spasms	3 (6)	1 (2)
Headache	2 (4)	2 (4)

*Includes paresthesia, dysesthesia, and oral dysesthesia.
**Includes abdominal pain and upper abdominal pain.

The table shows similar adverse events to the RPV162 study population, but better demonstrates adverse events that are likely to occur in individuals initially after starting therapy with amifampridine. The applicant also analyzed the safety data by acetylator phenotype and showed that subjects that were slow metabolizers had a greater incidence of adverse events (100%) compared to rapid metabolizers (75%).

8.4.6. Laboratory Findings

Safety laboratory blood tests, for CBC and blood chemistry, were performed during screening and at the start of Stage 3 of the DAPPER study. Shifts from baseline and mean laboratory value time trends in the controlled DAPPER trial database for the following laboratory parameters were reviewed, with comparison between the continuous 3,4-DAP group and the taper-to-placebo group. The ability to extrapolate from these laboratory data to larger populations and treatment durations is limited because of the small sample size, short

Reference ID: 4428593

duration, and small number of adverse events in the DAPPER study.

For the RPV162 database, uniform time points for laboratory test results are not available and there is no placebo group for comparison. The patients in this database had multiple medical comorbidities and concomitant medications that complicate the assessments. Narratives of clinical interest were reviewed and are summarized below.

Although the Sanders et al. (2000) publication reports that "we found no changes in blood test results of renal, hematologic, or endocrine function in any patients in this study", laboratory data from this study were not submitted as part of this NDA.

Hematology:

There were no notable differences in hematological parameters (hemoglobin, hematocrit, total leukocytes, lymphocytes, neutrophils, eosinophils, or platelet count) between continuous 3,4-DAP-treated subjects and taper-to-placebo subjects.

Chemistry:

There were no notable differences in sodium, chloride, potassium, bicarbonate, calcium, total protein, glucose, and albumin between continuous 3,4-DAP-treated subjects and taper-to-placebo subjects. Blood glucose increased to less than two times the upper limit of normal compared to baseline in both treatment groups (in 31% of the continuous 3,4-DAP group and in 50% of the taper-to-placebo group).

Renal Parameters:
There were no notable differences in BUN and creatinine between continuous 3,4-DAP-treated subjects and taper-to-placebo subjects.

In the expanded access RPV162 database, four subjects ([redacted] (b) (6) [redacted]) had adverse events of renal failure.

- Renal failure in subject [redacted] (b) (6) was associated with metastatic renal cell carcinoma and renal vein thrombosis.
- Subject [redacted] (b) (6) was hospitalized with transient "mild renal failure", severe sinusitis, severe pyrexia, and severe asthenia 3 weeks after starting 3,4-DAP. The patient recovered, and 3,4-DAP was continued without further renal events.
- Patient [redacted] (b) (6) developed renal failure related to carboplatin treatment after four doses of 5mg 3,4-DAP. The patient improved following renal dialysis and 3,4-DAP treatment was continued.
- Subject [redacted] (b) (6) had a history of prior renal surgery and developed moderate renal insufficiency an unknown time after starting 3,4-DAP. The subject continued 3,4-DAP

Reference ID: 4428593

until his death from pancreatic cancer.

Liver: Transaminases, Bilirubin, and Alkaline Phosphatase

There were no notable differences in AST, ALT, alkaline phosphatase, and bilirubin between continuous 3,4-DAP-treated subjects and taper-to-placebo subjects. There were no Hy's law cases.

In the expanded access RPV162 database, no Hy's law cases occurred. Adverse events of elevated liver enzymes were reported in 6 patients (3.8%). There were 4 patients (2.5%) with hyperbilirubinemia (1 patient), elevated alkaline phosphatase (2 patients), or jaundice (2 patients). There was one patient (b) (6) with an AE of hepatic failure with elevated transaminases and bilirubin that was associated with metastatic SCLC to the liver that pre-dated treatment with 3,4-DAP.

8.4.7. Vital Signs

This reviewer analyzed the applicant's vital signs data using shift plots and time trends, including heart rate, blood pressure (systolic and diastolic; sitting), pulse oximetry, respiratory rate, weight, and temperature. There were no notable differences in these parameters between the continuous 3,4-DAP-treated subjects and taper-to-placebo subjects.

Vital signs data were not collected for the expanded access programs. Clinically significant changes in vital signs or physical examination findings were reported as AEs, which are reviewed in Section 8.4.5.

8.4.8. Electrocardiograms (ECGs)

There were no significant mean effects on the mean QTcB (corrected QT; Bazett's formula), PR, or QRS intervals in the DAPPER study (see figures in Appendix 13.6). I assessed outliers by examining scatterplots of baseline vs. post-baseline maximum values, and baseline vs. post-baseline nadir values. No important outliers were found. However, interpretation is limited by the small size of the ECG database.

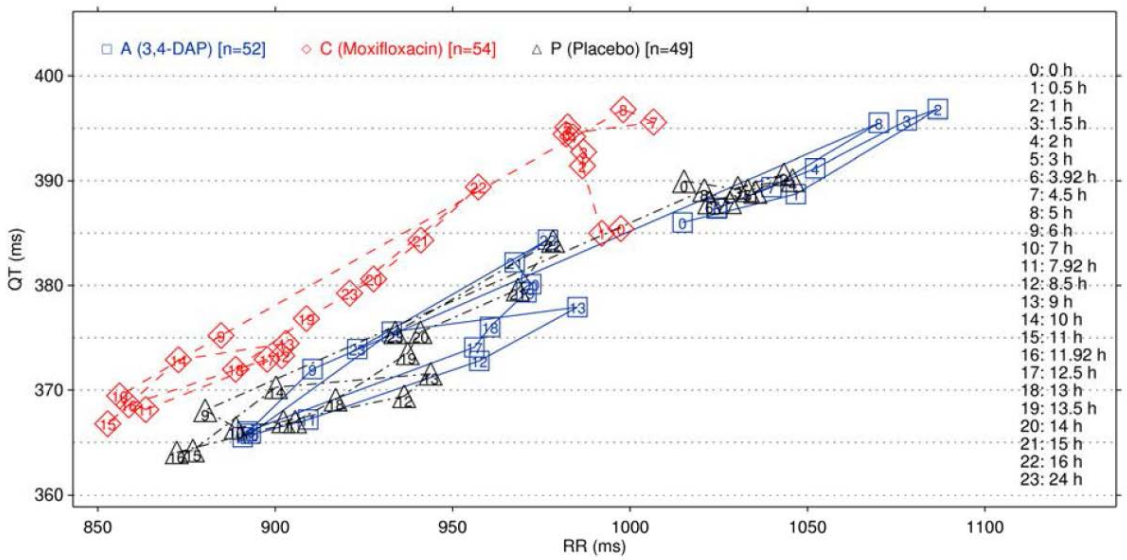
Reference ID: 4428593

8.4.9. **QT**

The applicant performed a thorough QT (TQT) study. The study was reviewed by FDA's QT review team and was found to be adequate. The TQT was a double-blind, double-dummy, placebo- and positive-controlled, 3-way crossover TQT study of 56 healthy subjects. The study compared single doses of placebo, 120mg 3,4-DAP, and 400mg moxifloxacin as an active control. The primary endpoint was the difference between QT corrected according to Fridericia's formula (QTcF) intervals measured post-dose compared with baseline. For the 3,4-DAP treatment, the upper 90% confidence intervals of the placebo-corrected mean changes from baseline were less than 10 ms at all time points studied.

As seen in the following figure copied from the submission, there is no notable difference in mean QT versus mean RR between the 3,4-DAP and placebo groups.

Figure 4: Mean QT versus Mean RR Intervals by Treatment and Time Point. Source: QT Study CSR



Note(s): Red diamonds and line: time course of the mean QT versus mean RR intervals for moxifloxacin, black triangles and line: time course of the mean QT versus mean RR intervals for placebo, and blue squares and line: time course of the mean QT versus mean RR intervals for 3,4-DAP

The dose of 3,4-DAP in this study was 120 mg/day split over 4 equal doses every 4 hours. The FDA's QT review team found that this dose/exposure would be adequate to cover high therapeutic exposure, if patients are instructed to take multiple doses at a minimum of 4-hour interval and to avoid prolonged fasting state. The FDA's QT review team concluded that there was no significant QTc prolongation effect of RUZURGI (3,4-diaminopyridine or 3,4-DAP) 120 mg.

Reference ID: 4428593

8.4.10. Immunogenicity

Not applicable. The drug is a small molecule.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Cardiac Disorders

There is no nonclinical evidence of cardiac toxicity associated with 3,4-DAP use. 3,4-DAP belongs to the aminopyridine pharmaceutical class. Based on the drug's mechanism of action of blocking voltage-gated potassium channels, there exists a theoretical potential to lengthen the QT interval and lead to cardiac arrhythmias. The applicant has proposed to advise caution in the label when administering 3,4-DAP in combination with drugs known to prolong the QT interval or in LEMS patients with congenital long QT. As discussed in Sections 8.4.8 and 8.4.9, there was no clinically significant QT prolongation in the TQT study or in the DAPPER placebo-controlled study.

In the DAPPER study, analysis of adverse events found cardiac disorders in 0% of the continuous 3,4-DAP group compared to 17% (3 of 18) of the taper-to-placebo group. There was one AE of QT prolongation in the taper-to-placebo group.

The following are lists of cardiac AEs in the expanded access RPV162 and Special populations datasets. A summary table of these narratives is provided in Appendix 13.3.

RPV162 Dataset: Cardiac disorders 16%; QT prolongation 5%, (8 of 159); arrhythmias 9% (15 of 159); Atrial fibrillation: 3%; cardiac arrest 2.5%; heart rate irregular 2.5%; palpitations 2.5%; SVT 2.5%; tachycardia 2.5%; bradycardia 1.9%; CHF 1.2%; QT prolonged 1.3%; sinus tachycardia 1.3%; atrial tachycardia 0.6%; AV block 0.6%; cardiac failure 0.6%; cardiomegaly 0.6%; heart rate abnormal/increased/decreased 0.6%.

Special populations (pediatric, pregnancy; seizure, cardiac, renal, or hepatic disorders; suicidal): Cardiac arrhythmias: 32% (21 of 66); Atrial fibrillation: 9%; CHF 6%; QT prolonged 6%; palpitations 6%; MI 4.5%; atrial flutter 3%; AV block 3%; ischemic cardiomyopathy 3%;

Reference ID: 4428593

tachycardia 3%; acute MI 1.5%; arrhythmia 1.5%; AV block second degree 1.5%; bundle branch block right 1.5%; cardiac arrest 1.5%; cardiac ventricular thrombosis 1.5%; cardiomyopathy 1.5%; heart rate irregular 1.5%; sinus bradycardia 1.5%; ventricular hypertrophy 1.5%; ventricular tachycardia 1.5%.

The narratives of all patients with cardiac AEs and SAEs were reviewed, including 10 cases in the RPV162 dataset, 9 in the DAPPER study, 1 from the Sanders et al. (2000) study, and 30 in the special populations dataset. These patients generally had multiple comorbidities and risk factors for cardiac events and long intervals between starting 3,4-DAP and the events.

Cardiac-Related Deaths:
There were 13 cardiac-related deaths reported in the application from the RPV162 population, special populations, and in one patient who had previously participated in the DAPPER study. Cardiac-related deaths included congestive heart failure, cardiac arrest in the setting of lung cancer and pneumonia, hypertensive cardiovascular disease, cardiac ablation with transient QT prolongation and atrial fibrillation (subject (b) (6), and coronary artery occlusion with atrioventricular block. A summary table of these narratives is provided in Appendix 13.3. These cases either had confounding risk factors such as lung cancer and metastases or lacked detail to assess the causal relationship to 3,4-DAP.

Cardiac-Related Serious Adverse Events:
In addition to the deaths described above, 30 patients had non-fatal serious cardiac adverse events including heart palpitations, chest pain, bradycardia, ventricular tachycardia, supra-ventricular tachycardia, atrial fibrillation, QTc prolongation, AV block, congestive heart failure, myocardial infarction, syncope, coronary artery disease, cardiomyopathy, and cardiac arrest. Arrhythmias were present in 23 of the 43 (53%) fatal and non-fatal cardiac SAEs. A summary table of these narratives is provided in Appendix 13.3. These cases either had confounding risk factors or lacked detail to assess the causal relationship to 3,4-DAP. The majority of events were not temporally related to the initiation of 3,4 DAP treatment, as most of these events occurred after several years of treatment.

Other:

Two notable cases include one adult congenital myasthenic syndrome patient (b) (6) with possible seizure and QTc prolongation 1 month after starting 3,4-DAP; and one suicide attempt in which a person (b) (6) took 500mg of 3,4-DAP at once, resulting in 15 hours of seizures and QTc prolongation without tachyarrhythmia. There is also a published report (Boerma et al., 1995) of a patient with seizures, paroxysmal supraventricular tachycardia, and cardiac arrest associated with an overdose of 3,4-DAP at 360mg/day for seven days.

The population in the expanded access population was mostly older with multiple

Reference ID: 4428593

comorbidities, such as malignancy. There was also a long duration of exposure in the population with some patients treated up to 27 years. Cardiac events are not unexpected in this population with this long duration of follow-up. Given the patient population and the absence of a control group, it is difficult to attribute causality to amifampridine; however; the contribution of amifampridine phosphate to the events cannot be ruled out. Overall, there is no clear association between 3,4-DAP use and cardiac adverse events, including arrhythmia, at doses up to 100mg per day. These events should be monitored with routine pharmacovigilance.

8.5.2. **Seizures**

Seizures are known to be associated with the drug class aminopyridines, of which 3,4-DAP is a member. Overall, seizures were reported in 26 of 626 (4%) patients in the 3,4-DAP expanded access program, which specified a dose limit of 100mg per day because of the concern for seizures. For comparison, there is approximately a 1% prevalence of epilepsy in the US population.

The narratives of all patients with seizures were reviewed. Patients whose seizures were considered by the investigator to be probably or definitely related to 3,4-DAP use are summarized in Appendix 13.8. These patients generally had multiple comorbidities and risk factors for seizures, such as brain metastases, anoxia, or prior seizure history. Seizures were observed from 1 day up to 12 years after initiating treatment with 3,4-DAP. One pediatric CMS patient, (b) (6) had a seizure after the first dose of 10mg 3,4-DAP. This patient was later able to continue 3,4-DAP treatment at 20mg/day (1mg/kg/day) without further seizures. One adult CMS patient (b) (6) had a possible seizure and QTc prolongation 1 month after starting 3,4-DAP (dose not reported). One patient in the expanded access program discontinued 3,4-DAP because of convulsion. Most patients who experienced a seizure continued 3,4-DAP at a lower dose without recurrence of seizures. No seizures occurred during the DAPPER study.

In nonclinical studies, sustained convulsions occurred in dogs given 3,4-DAP at a dose of 2.1 mg/kg/day. In humans, seizure is a known risk in drugs similar to 3,4-DAP, such as amifampridine phosphate and dalfampridine. The risk of seizure with 3,4-DAP use appears to be dose-dependent, as seen in the cases of deliberate or accidental overdoses. One person who attempted suicide (b) (6) took 500mg of 3,4-DAP at once, resulting in 15 hours of seizures and QTc prolongation without tachyarrhythmia. There is also a published report (Boerma et al., 1995) of a patient with seizures, paroxysmal supraventricular tachycardia, and cardiac arrest associated with an overdose of 3,4-DAP at 360mg/day for seven days. There is additional published literature reporting a dose-dependent seizure risk for 3,4-DAP (Haroldsen et al 2015, Lindquist and Stangel 2011), primarily at high doses of 100 mg/day or higher (Sanders 2003, Strupp et al. 2011, Titulaer et al. 2011, Weimer and Wong 2009). Most of these

Reference ID: 4428593

reports were in patients with additional risk factors for seizures, such as histories of metastatic cancers, prior seizures, or concomitant medications known to lower the seizure threshold.

The risk of seizures will be described as a Warning in the prescribing information.

8.6. Safety Analyses by Demographic Subgroups

Potential safety signals were analyzed by demographics for the controlled DAPPER study. Treatment emergent adverse events were analyzed by sex and age. There were 11 males and 21 females in the DAPPER study. In the taper-to-placebo group, there were 10 (48%) females with TEAEs compared to 4 (36%) males. In the continuous-3,4-DAP group, there were 5 (24%) females with TEAEs compared to 1 (10%) male.

There were 15 subjects less than or equal to 60 years of age and 17 subjects above age 60. In the taper-to-placebo group, there were 3 (20%) subjects aged <=60 with TEAEs compared to 4 (24%) above age 60. In the continuous-3,4-DAP group, there were 5 (33%) subjects aged <=60 with TEAEs compared to 1 (6%) above age 60.

Given the small number of patients and low number of adverse events in the DAPPER study, it is not possible to make meaningful comparisons of adverse event rates by sex or age.

The following tables show important safety signals by demographics for the open-label RPV162 expanded access dataset.

Table 37: Adverse Events Related to 3,4-DAP Use with Frequency >5% by Sex in RPV162 Dataset

		Sex				
		M		F		
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**	**Total**
Nervous system disorders	Paraesthesia	21	29.6%	18	21.4%	39
	Hypoaesthesia	3	4.2%	4	4.8%	7
	Headache	.	.	1	1.2%	1
Gastrointestinal disorders	Paraesthesia oral	12	16.9%	16	19.0%	29
	Diarrhoea	3	4.2%	1	1.2%	5
	Nausea	2	2.8%	2	2.4%	4
General disorders and administration site conditions	Feeling cold	3	4.2%	6	7.1%	9
Psychiatric disorders	Insomnia	3	4.2%	2	2.4%	5
	Anxiety	1	1.4%	1	1.2%	2
	Depression	1	1.4%	.	.	1
Musculoskeletal and connective tissue disorders	Muscle spasms	3	4.2%	1	1.2%	4
Injury, poisoning and procedural complications	Fall	1	1.4%	.	.	1

	N
Sex	
F	84
M	71

Reference ID: 4428593

There does not appear to be a clinically significant difference in adverse events as a function of sex.

Table 38: Adverse Events Related to 3,4-DAP Use with Frequency >5% by Age in RPV162 Dataset: Age <= 60

Body System or Organ Class	Dictionary-Derived Term	Count	%	Total
Nervous system disorders	Paraesthesia	28	17.6%	28
	Hypoaesthesia	5	3.1%	5
	Headache	1	0.6%	1
Gastrointestinal disorders	Paraesthesia oral	20	12.6%	20
	Diarrhoea	3	1.9%	3
	Nausea	2	1.3%	2
General disorders and administration site conditions	Feeling cold	6	3.8%	6
Musculoskeletal and connective tissue disorders	Muscle spasms	4	2.5%	4
Psychiatric disorders	Insomnia	2	1.3%	2
	Anxiety	1	0.6%	1
	Depression	1	0.6%	1
Injury, poisoning and procedural complications	Fall	1	0.6%	1

Figure 5: Adverse Events Related to 3,4-DAP Use with Frequency >5% by Age in RPV162 Dataset: Age >60

Body System or Organ Class	Dictionary-Derived Term	Count	%	Total
Gastrointestinal disorders	Paraesthesia oral	9	5.7%	9
	Diarrhoea	2	1.3%	2
	Nausea	2	1.3%	2
Nervous system disorders	Paraesthesia	11	6.9%	11
	Hypoaesthesia	2	1.3%	2
Psychiatric disorders	Insomnia	3	1.9%	3
	Anxiety	1	0.6%	1
General disorders and administration site conditions	Feeling cold	3	1.9%	3

Paresthesias were reported more in patients under 60 years of age (~18% under age 60 vs. 7% over 60). There were 111 serious adverse events in patients older than 60 years, compared to 90 SAEs in patients under age 60. These findings may be related to greater disease severity and comorbidity in older patients. The reason for the drop in paresthesias in older patients is unclear, but may be related to declining nerve fiber density with age.

Reference ID: 4428593

As the study population was predemoninantly (>90%) White, comparisons by race are not interpretable.

8.7. Specific Safety Studies/Clinical Trials

No specific clinical safety studies were performed in the 3,4-DAP development program.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

In 40%-60% of patients with LEMS, cancer is present when the weakness begins or is found later. Death usually occurs as a result of the underlying cancer. In the RPV162 pooled safety population, a total of 75 neoplasms were reported before starting 3,4-DAP in 75 patients (46.3%). Cancer was reported as an AE after starting 3,4-DAP in 22% of the 3,4-DAP RPV162 expanded access population. All but 10 of the 47 patients in the RPV162 population who had an AE in the neoplasms system organ class had a prior history of cancer. It therefore appears unlikely that the development of cancer in these patients is related to 3,4-DAP use.

8.8.2. Human Reproduction and Pregnancy

There are no adequate and well-controlled studies of 3,4-DAP in pregnant women. Three female patients with LEMS had a total of 6 pregnancies in the 3,4-DAP expanded access program. No adverse outcomes were reported.

8.8.3. Pediatrics

(b) (4)

Data to support the pediatric safety of 3,4-DAP include its use in seven LEMS pediatric patients in the expanded access program, ranging from ages 9 through 16 years at the start of treatment. Only one patient had serial 3TUG data to objectively document a drug response. Fifteen patients with congenital myasthenic syndrome (CMS), ages 13 months through 7 years at the start of treatment, also received 3,4-DAP through expanded access INDs. These data are summarized in Appendix 13.5. The only adverse events that occurred in more than one pediatric patient were palpitations in two patients and seizures in two patients. One of the patients with seizures developed them after 13 years taking 3,4-DAP following an anoxic brain

Reference ID: 4428593

injury related to respiratory distress in the setting of CMS. The other patient with a seizure (initially thought to be a CMS patient but later diagnosed as centronuclear myopathy) had it after the first 10mg dose of 3,4-DAP but was able to resume treatment with 3,4-DAP later at 20mg (~1mg/kg/day) without further seizures. The dose range reported in the pediatric patients is 5mg to 120mg/day, and 0.48mg/kg/day to 1.1mg/kg/day for patients with reported weights.

These data from 22 pediatric patients treated with 3,4-DAP appear to be adequate to support the safety of 3,4-DAP in this population because they were prospectively assessed over a long duration of time (total exposure of 49.9 patient years; 31.9 of those years were exposure before age 18) with active monitoring of adverse events.

Published literature was reviewed to identify any unique safety signals in the pediatric population; however, the literature was considered supportive and was not relied upon as the primary basis for the determination of safety in the pediatric population. Published reports (Della Marina et al., 2012; Hajjar et al., 2014; Portaro et al., 2014; Schuler et al., 2001; Verbeek et al., 2014) of 3,4-DAP use in pediatric LEMS patients include 5 patients (ages 11-16 years). One 11-year-old patient received 3,4-DAP at 1 mg/kg/day. Two patients received 20mg/day and one patient received 80mg/day. Clinical improvement was noted in all these cases, although there were no objective measures reported. One case (Verbeek et al., 2014) reported resolution of ptosis 1.5 hours after taking an unreported dose of 3,4-DAP. The only adverse events reported were gastrointestinal symptoms in one patient who was also taking prednisone, azathioprine, and pyridostigmine (Verbeek et al., 2014). These published reports are supportive of the safety findings from the pediatric expanded access data.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There was no evidence of a withdrawal syndrome with discontinuation of the 3,4-DAP in the DAPPER study. Adverse events that occurred in greater than 10% of the taper-to-placebo group, and did not occur in the continuous 3,4-DAP group, included nausea, oxygen saturation decreased, abdominal discomfort, dizziness, muscle spasms, and respiratory tract infection. These AEs are generally consistent with the expected re-emergence of LEMS-related weakness following cessation of 3,4-DAP treatment, which may include difficulty in swallowing and shortness of breath.

The applicant conducted human abuse potential studies: two in vitro mechanistic studies, two in vivo abuse potential pre-studies, a drug-discrimination study, a self-administration study, and a physical dependency study. The applicant reported no significant findings from these studies,

Reference ID: 4428593

which have also been evaluated by the Controlled Substance Staff (CSS). CSS has determined that there is no abuse potential.

There is relatively little safety data for 3,4-DAP at doses greater than 100mg/day. The QT Study used single doses of 3,4-DAP at 120mg/day for one day in 56 healthy volunteers. The most frequently reported (>10%) TEAEs during 3,4-DAP treatment in the QT study included dysaesthesia, oral dysaesthesia, upper abdominal pain, dyspepsia, and muscle twitching.

Eleven patients in the expanded access program received more than 100mg 3,4-DAP per day. One patient (b) (6) had unauthorized dosing at 150-200mg/day for 2 months and developed seizures. He had a history of post-surgical seizures as a child.

Two patients, (b) (6), had fatal SAEs at doses of 140mg and 120mg/day, respectively. Review of their narratives found multiple medical comorbidities that prevent making any clear causal association with 3,4-DAP. Patient (b) (6) died at age 85 of cardiac arrest at a dose of 140mg/day for 1 month. One cannot rule out that the drug may have contributed to arrhythmia, although the patient did have a history of cancer, stroke, COPD, coronary artery disease, and aortic aneurysm repair. Three of these 11 patients had no AEs at doses of 120, 120, and 140mg/day.

One subject (b) (6) attempted suicide by ingesting 300mg of 3,4-DAP, leading to agitation, diaphoresis, abdominal pain, and sinus tachycardia without QT prolongation. The patient also developed rhabdomyolysis, which may have been caused by the use of physical restraints in this agitated subject.

The highest reported overdose of 3,4-DAP occurred in a person who attempted suicide (b) (6) by taking 500mg of 3,4-DAP at once, resulting in 15 hours of seizures and 48 hours of QTc prolongation (520 ms) without tachyarrhythmia. Nystagmus lasted for 18 hours. This person required hospitalization but recovered with symptomatic treatment. There is also a published report (Boerma et al., 1995) of a patient with seizures, paroxysmal supraventricular tachycardia, and cardiac arrest associated with an overdose of 3,4-DAP at 360mg/day for seven days. This patient was resuscitated, treated with antiemetics and anticonvulsants, and had resolution of symptoms within 24 hours of stopping 3,4-DAP.

Overall, this limited dataset supports an increased risk of seizure as dose increases and is inconclusive regarding the potential for increased risk of cardiac arrhythmia at higher doses.

Reference ID: 4428593

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable.

8.9.2. Expectations on Safety in the Postmarket Setting

Because of limitations due to the small number of patients exposed and duration of exposure in the clinical trials, it is likely that adverse reactions not identified to date, or of a magnitude not observed to date, will occur in the postmarketing setting.

8.9.3. Additional Safety Issues from Other Disciplines

None.

8.10. Integrated Assessment of Safety

The overall conclusion of this safety review is that the safety profile of 3,4-DAP is acceptable given the evidence of efficacy in the treatment of LEMS and extensive 1189 patient-year history of human exposure.

In the double-blind QT study, RUZURGI was administered at doses greater than the maximum recommended dose (120 mg administered as 4 equal doses of 30 mg at 4-hour intervals) to 52 healthy adult volunteers. Adverse reactions that occurred in at least 5% of subjects during RUZURGI treatment and with incidence at least 2% greater than during placebo treatment included paresthesia/dysesthesia, abdominal pain, dyspepsia, dizziness, nausea, back pain, hypoesthesia, and muscle spasms.

Among patients in the open-label expanded access program, the most common adverse events (>=10%) were infection, paresthesia/hypoesthesia, cancer, diarrhea, abdominal pain, fall, dyspepsia/nausea/vomiting, pneumonia, arrhythmia, and arthralgia.

Reference ID: 4428593

Cancer is commonly associated with LEMS and does not appear to be caused by 3,4-DAP use, given that all but 10 of the 47 patients in the RPV162 population who had an AE in the neoplasms system organ class had a prior history of cancer.

Although there is a theoretical risk of QT prolongation and cardiac arrhythmia based on 3,4-DAP's mechanism of action, there does not appear to be a clinically significant association between 3,4-DAP use and cardiac adverse events, including arrhythmia, at doses up to 100mg per day. Patients in the expanded access program with cardiac adverse events generally had multiple comorbidities and risk factors for cardiac events and long intervals between starting 3,4-DAP and the events. Although the TQT study supported the cardiac safety of 3,4-DAP, case reports of overdoses with prolonged QT interval and cardiac arrest warrant description in the Overdosage section of labeling.

Seizures were reported in 4% of patients in the 3,4-DAP expanded access program. These patients generally had multiple comorbidities and risk factors for seizures and long intervals between starting 3,4-DAP and the events. Seizures also occurred in cases of overdose and should be included as a warning in labeling.

Data from 22 pediatric patients treated with 3,4-DAP were evaluated and appear to be adequate to support the safety of 3,4-DAP in this population because they were prospectively assessed over a long duration of time (total exposure of 49.9 patient years; 31.9 of those years were exposure before age 18) with active monitoring of adverse events. Pediatric adverse events in more than one patient included two patients each with palpitations and seizures. Seizures in one of the patients were caused by anoxic brain injury and were probably unrelated to 3,4-DAP use.

This reviewer concludes that the safety profile of 3,4-DAP is acceptable, but that the label should include under Warnings and Precautions a description of the risks seizure.

9. Advisory Committee Meeting and Other External Consultations

This section is not applicable to this review.

Reference ID: 4428593

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Warnings and precautions should be included in labeling to describe the risk of seizure associated with 3,4-DAP use.

10.2. Nonprescription Drug Labeling

This section is not applicable to this review.

11. Risk Evaluation and Mitigation Strategies (REMS)

None recommended.

12. Postmarketing Requirements and Commitments

None.

13. Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): JPC 3,4-DAP.TQT

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 8		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		

Reference ID: 4428593

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): JPC 3,4-DAPPER

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 35		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

Reference ID: 4428593

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): JPC 3,4-DAP DUKE RCT

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0		

Reference ID: 4428593

Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Reference ID: 4428593

13.3 Cardiac Disorder Narrative Tables

Table 39: Cardiac-Related Deaths in 3,4-DAP Studies

Cardiac-Related Deaths in 3,4-DAP Studies					
List Number	**Study # Patient ID**	**AE/SAE**	**Time on Drug to Event**	**Age at Drug Start**	**Comments/History**
1	(b) (6) [redacted]	CHF	7 months on drug until CHF	64	Death; 40mg/day; no medical history
2	[redacted]	seizure, bradycardia, pacemaker, asystole, cardiac arrest	bradycardia ~1 month after stopped 3,4-DAP. Death ~1 year after last 3,4-DAP.	52	small cell lung cancer 5 months after drug start;
3	[redacted]	Myocardial infarction, cardiac arrest	MI and death ~19 days after starting drug	73	h/o coronary artery disease, hyperlipidemia, hypertension, diabetes; 15mg/day 3,4-DAP
4	[redacted]	CHF, death	13 years	69	h/o small cell lung cancer, hypertension, asthma; 80mg/day
5	[redacted]	heart failure, tachycardia, death	10 days of tachycardia ~10 years after starting 3,4-DAP; cardiac failure ~13 years after starting 3,4-DAP	71	h/o hyperlipidemia, macular degeneration, COPD; 100mg/day

Reference ID: 4428593

Cardiac-Related Deaths in 3,4-DAP Studies					
List Number	**Study # Patient ID**	**AE/SAE**	**Time on Drug to Event**	**Age at Drug Start**	**Comments/History**
6	(b) (6)	pneumonia, cardiac arrest, death	cardiac arrest 1 year after starting 3,4-DAP	84	h/o COPD, GERD, hypercholesterolemia, tobacco use, stroke, small cell lung cancer, breast CA, lumbar stenosis. 140mg/day
7		atrial fibrillation, cardiac arrest, renal insufficiency, respiratory acidosis, death	3 years to transient afib; cardiac arrest and death 8 years after starting drug	72	h/o COPD, HTN, OSA, respiratory acidosis, colectomy, renal cystic disease; ECG with possible anterior infarct.
8		Ventricular tachycardia	10 years	69	small cell lung cancer, CABG, MI, OA, COPD, abdominal aortic aneurysm surgery; cardiomyopathy, death
9		atrial fibrillation, renal failure, respiratory failure, pneumonia, sepsis, hypotension, oliguria, pleural effusion, chronic pulmonary embolism, multi-organ failure, death	16 years	63	HTN, depression, Sjogren's syndrome, benign neoplasm of thymus,

Reference ID: 4428593

Cardiac-Related Deaths in 3,4-DAP Studies					
List Number	**Study # Patient ID**	**AE/SAE**	**Time on Drug to Event**	**Age at Drug Start**	**Comments/History**
10	(b) (6)	seizure, atrial fibrillation, syncope, myeloid leukemia, diverticulitis, death	1 month to syncope, seizure. 1 year to atrial fibrillation	50	palpitations, tobacco use, breast mass removal, angina pectoris, anemia
11		MI, bladder papilloma, obstructive uropathy, renal failure, death	5 years to ECG showing septal infarct.	73	small cell lung cancer
12		cardiomyopathy, cardiac arrest, renal failure, respiratory failure, pneumonia	20 years to cardiac arrest and death	45	bronchitis, blindness, tobacco use, HTN, obesity, possible left atrial enlargement on baseline ECG.
13		QTc prolongation and anteroseptal infarct on ECG, respiratory depression, death	2.5 months	85	ALS, glaucoma, spinal stenosis

Reference ID: 4428593

Table 40: Cardiac-Related Non-Fatal Serious Adverse Events in 3,4-DAP Studies

Cardiac-Related Non-Fatal Serious Adverse Events in 3,4-DAP Studies					
List Number	**Study # Patient ID**	**AE/SAE**	**Time on Drug to Event**	**Age at Drug Start**	**Comments/History**
1	(b) (6)	palpitations	First dose 6/21/2002; Drug stopped 12/2/2002	55	No ECG; 100mg/day. Unknown time on drug to first palpitation.
2		acute respiratory failure, pneumonia, transient QT prolongation	Off drug for 6 months at time of QT prolongation and pneumonia	67	h/o COPD, hyperlipidemia, HTN, hypothyroidism, peripheral neuropathy, diabetes, myasthenia gravis. 40mg/day. Died of unknown cause while off 3,4-DAP for ~1 month.
3		Transient Atrial fibrillation; Metabolic acidosis	afib 1 day after starting 3,4-DAP 10mg. Drug stopped. Next day had QT prolongation (QTc = 529 ms)	70	h/o small cell lung cancer, metabolic acidosis, hypokalemia, blindness; Died ~3 weeks after last dose of 3,4-DAP.
4		AV block, atrial fibrillation; hypokalemia, pacemaker insertion; orthostatic hypotension; hospitalized for GI problem of unclear origin	AV block & hypokalemia 5 years after starting drug; transient afib 7 years after starting drug	71	h/o colon cancer, breast cancer, SIADH; 80mg/day

Reference ID: 4428593

Cardiac-Related Non-Fatal Serious Adverse Events in 3,4-DAP Studies					
List Number	**Study # Patient ID**	**AE/SAE**	**Time on Drug to Event**	**Age at Drug Start**	**Comments/History**
5	(b) (6)	Supraventricular tachycardia	187 days	48	h/o Supraventricular tachycardia prior to starting 3,4-DAP; underwent curative cardiac ablation therapy; 50mg/day
6		Mild prolonged QTc	5 years	63	h/o Sjogren's syndrome, hyperlipidemia, SLE, chronic renal failure; 60mg/day
7		Episodes of loss of consciousness (seizure or cardiac arrhythmia)	3 years	58	h/o small cell lung cancer; EEG and ECG normal at time of LOC. Later ECG showed inferior infarct. 40mg/day
8		palpitations	2 years	58	h/o pneumonia, osteonecrosis, anemia, C. diff infection, orchiectomy.
9		bradycardia, tachycardia, pacemaker insertion	3.5 years to bradycardia and pacemaker placement; 6 years to SVT and atrial tachycardia	57	h/o myopia, diarrhea, DVT. 60mg/day
10		Transient borderline QTc prolongation	9 years	63	h/o hip surgery for pre-existing avascular necrosis. 80mg/day
11		atrial fibrillation, pneumonia, stroke	19 years to afib and stroke	56	h/o COPD, gunshot wound, alcohol use, substance use; 80mg/day

Reference ID: 4428593

Cardiac-Related Non-Fatal Serious Adverse Events in 3,4-DAP Studies					
List Number	**Study # Patient ID**	**AE/SAE**	**Time on Drug to Event**	**Age at Drug Start**	**Comments/History**
12	(b) (6)	Cardiac (unspecified change in rhythm)	~1 month	32	h/o HTN, diverticulosis, heavy alcohol use, nausea, vomiting. No ECG at time of AE. Later cardiac exam was normal. 80mg/day
13		Heart palpitation; chest pain	3 years	66	tobacco use (prior to 1982), thymectomy (August 2005), hypertension, hypercholesterolemia, hypothyroidism, multiple episodes of C. difficile colitis, hysterectomy, appendectomy, tonsillectomy, deep vein thrombosis (1978), and chronic neck and back pain. Baseline ECG abnormal: R vent conduction delay. 50mg/day. Patient overdosed and took "afternoon dose twice." ECG: left atrial abnormality, QT/QTcB was 388 msec/481 ms; QTcF was 447 msec (normal range).
14		atrial fibrillation with respiratory failure, rapid ventricular response, and hypotension	1 month	62	thymic cancer, HTN, hyperlipidemia, tobacco use, DVT, respiratory failure, hypotension; 90mg/day

Reference ID: 4428593

Cardiac-Related Non-Fatal Serious Adverse Events in 3,4-DAP Studies					
List Number	**Study # Patient ID**	**AE/SAE**	**Time on Drug to Event**	**Age at Drug Start**	**Comments/History**
15	(b) (6) [redacted]	tachycardia (when decreased 3,4-DAP and increased prednisone)	1 month	51	tobacco use, peripheral neuropathy, pneumonia, respiratory failure, COPD, dysphagia, gastrostomy tube, 90mg/day
16	[redacted]	QTc prolongation (from 427 to 446 ms, still in normal range)	2 weeks	54	diverticulitis, GERD, HLD, muscle/TMJ/vulvovaginal pain. Also on nortriptyline. 40mg/day
17	[redacted]	AV block	2 years	57	prior right bundle branch block, left fascicular block; pacemaker placed 7 years after starting 3,4-DAP
18	[redacted]	atrial fibrillation, SVT, palpitations (after switched to Firdapse)	2 years	46	palpitations, syncope, panic attacks, anxiety, substance use, gastric bypass/revision,
19	[redacted]	CHF, MI, QT prolongations	3 months	69	arteriosclerosis, tobacco use, hypothyroidism, pernicious anemia, MI, coronary angioplasty, polyneuropathy, diabetes, benign thyroid neoplasm, pneumonia. Baseline ECG lateral ischemia/PVC/LVH. Echo EF 20%. Bronchial carcinoma
20	[redacted]	tremor, syncope	1 year to syncope	46	muscular dystrophy, bradycardia, abnormal ECG/sinus tachycardia, chest pain. Took albuterol, ephedrine prior to tremor.

Reference ID: 4428593

Cardiac-Related Non-Fatal Serious Adverse Events in 3,4-DAP Studies					
List Number	**Study # Patient ID**	**AE/SAE**	**Time on Drug to Event**	**Age at Drug Start**	**Comments/History**
21	(b) (6)	MI	9 years	55	hyperthyroidism
22		atrial fibrillation, CHF	7 months	65	tobacco use, spinal stenosis, arthralgia, small cell lung cancer, HTN
23		atrial fibrillation, transient QT prolongation, renal insufficiency, cardiac ablation, cardioversion	5 years	59	paraneoplastic cerebellar degeneration, polyneuropathy, arteriosclerosis, atrial fibrillation, cardioversion, thyroidectomy, COPD, hypothyroidism, diabetes, HTN, small cell lung cancer
24		CHF, implanted defibrillator, cardiomyopathy, CAD, coronary angioplasty/stenting	4 months angioplasty, stenting, implanted defibrillator	56	obesity, CHF
25		CHF, atrial flutter, QTC prolonged, cardiomyopathy, pacemaker insertion	8 days to atrial flutter	67	cardiomyopathy, COPD, CHF, diabetes, cardiac pacemaker, prostate cancer, lung mass, abnormal ECG/left anterior fascicular block at baseline
26		fall, hip fracture, possible stroke, MI, coronary arterial stent, Parkinsonian dementia	4 months to fall/stroke/MI	72	CABG, muscular dystrophy, HLD, peripheral neuropathy, ECG: first degree AV block, melanoma

Reference ID: 4428593

Cardiac-Related Non-Fatal Serious Adverse Events in 3,4-DAP Studies					
List Number	**Study # Patient ID**	**AE/SAE**	**Time on Drug to Event**	**Age at Drug Start**	**Comments/History**
27	(b) (6)	suicide attempt by 3,4-DAP overdose of 500mg, QTc prolongation, seizures	single dose	57	mental health disorder. After overdose had 12-15 hours of seizures. QTc prolonged to 520ms for 1-2days. No tachyarrhythmias.
28		atrial fibrillation, possible stroke/MI, seizure, liver and brain metastases	~1 year to afib, stroke, seizure, MI	57	HTN, HLD, atrial fibrillation, cardio-respiratory arrest, tobacco use, small cell lung cancer.
29		pacemaker replacement	2 years to pacemaker replacement	78	atrial flutter, sick sinus syndrome, cardiac pacemaker, aortic valve incompetence, stroke,
30		MI, tachycardia, stroke	3 years to MI	77	med hx not reported

Reference ID: 4428593

13.4 Changes in Translation of Verbatim Terms to Preferred Terms in RPV162

Verbatim Term	Preferred Term	Change
FEVER, CHILLS LIKELY ASSOCIATED WITH FLU	PYREXIA	INFLUENZA
KERATOUVEITIS	EYE DISORDER	KERATOUVEITIS
LIP NUMBNESS	HYPOAESTHESIA ORAL	PARAESTHESIA
NUMBNESS AROUND LIPS	HYPOAESTHESIA ORAL	PARAESTHESIA
DECREASED SENSATIONS AND PINPRICK IN THE DISTAL LOWER EXTREMITIES BILATERALLY	SENSORY DISTURBANCE	PARAESTHESIA
BURNING FINGERS	BURNING SENSATION	PARAESTHESIA
SOME BURNING ON THE SOLES OF FEET	BURNING SENSATION	PARAESTHESIA
CHEST AND BACK BURNING	BURNING SENSATION	PARAESTHESIA
UPPER GUMS, UPPER LIP & TIP OF HER TONGUE HAVE A STRANGE SENSATION	ORAL DISCOMFORT	PARAESTHESIA
BURNING PAIN IN FEET	PAIN IN EXTREMITY	PARAESTHESIA
PERIORAL PARESTHESIAS	PARAESTHESIA ORAL	PARAESTHESIA
TINGLING OR VIBRATING IN THE LIPS AND INSIDE OF HIS CHEEK	PARAESTHESIA ORAL	PARAESTHESIA
TINGLING AROUND MOUTH	PARAESTHESIA ORAL	PARAESTHESIA
TINGLING AND BURNING IN LIPS	PARAESTHESIA ORAL	PARAESTHESIA
TRANSIENT TINGLING AROUND HIS LIPS	PARAESTHESIA ORAL	PARAESTHESIA
PERIORAL TINGLING	PARAESTHESIA ORAL	PARAESTHESIA
PERIORAL NUMBNESS AND PARESTHESIAS	PARAESTHESIA ORAL	PARAESTHESIA
TINGLING AROUND THE MOUTH	PARAESTHESIA ORAL	PARAESTHESIA
PERIORAL TINGLING ABOUT 30 MINUTES	PARAESTHESIA ORAL	PARAESTHESIA
PARESTHESIA LIPS	PARAESTHESIA ORAL	PARAESTHESIA
OCCASIONALLY ORAL PARESTHESIA	PARAESTHESIA ORAL	PARAESTHESIA
TINGLING IN LIPS AND TONGUE	PARAESTHESIA ORAL	PARAESTHESIA
TINGLING IN LIPS	PARAESTHESIA ORAL	PARAESTHESIA
TINGLING MOUTH	PARAESTHESIA ORAL	PARAESTHESIA
TINGLING OF TONGUE WHEN TAKES IT (3,4-DAP) ON AN EMPTY STOMACH	PARAESTHESIA ORAL	PARAESTHESIA
TINGLING OF LIPS	PARAESTHESIA ORAL	PARAESTHESIA

Reference ID: 4428593

Verbatim Term	Preferred Term	Change
NUMBNESS AND TINGLING IN HER LIPS AND MOUTH	PARAESTHESIA ORAL	PARAESTHESIA
PERIORAL PARESTHESIAS (TINGLING)	PARAESTHESIA ORAL	PARAESTHESIA
MOUTH TINGLING	PARAESTHESIA ORAL	PARAESTHESIA
TINGLING IN THROAT AND AROUND LIPS	PARAESTHESIA ORAL	PARAESTHESIA
PARESTHESIAS OF THE MOUTH AND TONGUE	PARAESTHESIA ORAL	PARAESTHESIA
MILD TINGLING IN THE MOUTH	PARAESTHESIA ORAL	PARAESTHESIA
SLIGHT TINGLING IN MOUTH	PARAESTHESIA ORAL	PARAESTHESIA
TINGLING IN TONGUE AND LIPS	PARAESTHESIA ORAL	PARAESTHESIA
CIRCUMORAL PARESTHESIAS	PARAESTHESIA ORAL	PARAESTHESIA
OCCASIONAL PERIORAL PARESTHEISAS	PARAESTHESIA ORAL	PARAESTHESIA
FACIAL AND CHEST NUMBNESS	HYPOAESTHESIA	PARAESTHESIA
VERY MILD LIMB NUMBNESS	HYPOAESTHESIA	PARAESTHESIA
NUMBNESS IN HANDS AND FEET	HYPOAESTHESIA	PARAESTHESIA
DIGITAL NUMBNESS	HYPOAESTHESIA	PARAESTHESIA
FACIAL NUMBNESS	HYPOAESTHESIA	PARAESTHESIA
NUMBNESS IN FINGERS, TOES, NOSE	HYPOAESTHESIA	PARAESTHESIA
BILATERAL NUMBNESS IN FINGERS (CHRONIC)	HYPOAESTHESIA	PARAESTHESIA
HAND NUMBNESS	HYPOAESTHESIA	PARAESTHESIA
NUMBNESS IN ARMS, HANDS, AND LEFT LEG	HYPOAESTHESIA	PARAESTHESIA
NUMBNESS IN MOUTH, LIPS, AND TONGUE	HYPOAESTHESIA	PARAESTHESIA
NUMBNESS OF WHOLE BODY, INCLUDING FACE AND TOES	HYPOAESTHESIA	PARAESTHESIA
BURNING SENSATION AROUND MOUTH	SKIN BURNING SENSATION	PARAESTHESIA
SEIZURES	CONVULSION	SEIZURE
SEIZURE	CONVULSION	SEIZURE
SUSPECTED SEIZURES	CONVULSION	SEIZURE
TRIGEMINAL NEUROPATHY	CRANIAL NERVE DISORDER	TRIGEMINAL NERVE DISORDER

Reference ID: 4428593

13.5 Pediatric Safety Data for 3,4-DAP in 22 Patients of the Expanded Access Program: 7 with LEMS, 15 with CMS

Subject	AE/SAE	Time on Drug to Event	Comments/ History	Age at Drug Start (years)	Dose (mg/day)	Sex
(b) (6)	Palpitations	34 months	LEMS, otitis media, Raynaud's phenomenon, pneumonia, scoliosis; Normal ECG and Holter monitor; 85mg/day	11	85mg	F
	None		LEMS, gastrostomy, lobar pneumonia, myopathy	14	95mg	F
	weakness, acute respiratory failure, pneumonia, possible migraine with aura	5 months to respiratory failure	LEMS, Hashimoto's thyroiditis, tibia fracture, sinus tachycardia into the 150-160's, sleep disorder.	9	40mg	F
	None		LEMS, ear tube insertion, tonsillectomy, migraine, meningitis aseptic	13	60mg	F
	anxiety, depression, panic attack, suicidal ideation,	6 years to ectopic couplets/triplets; 15 years to panic attack, major	LEMS; no medical history reported	16	80mg	F

Reference ID: 4428593

Subject	AE/SAE	Time on Drug to Event	Comments/ History	Age at Drug Start (years)	Dose (mg/day)	Sex
	Ventricular ectopic couplets and triplets, palpitations	depression, suicidal ideation				
(b) (6)	None		LEMS; eczema, renal cyst.	16		M
	Possible renal insufficiency, seizures, contracture of knee joint, acute tracheitis, femur fracture, bilateral hip dislocation, chronic osteomyelitis right femur, Enterococcus infection, coagulase negative Staphylococcus infection, patellofemoral disorder, generalized weakness, fever, anoxic brain injury, global encephalopathy, elevated LFTs	9 years to possible renal insufficiency; 13 years to anoxic brain injury and seizures	CMS, respiratory distress, muscle biopsy showed centronuclear myopathy rather than CMS	1 year, 5 months	30mg	M
	bradycardia after overdose	during the 3 days of dosing prior to stopping drug	CMS; chronic respiratory failure, trach/continuous ventilation;	13 months	5mg, 0.48mg/kg/day, exceeded max 0.3mg/kg per dose	M

Reference ID: 4428593

Subject	AE/SAE	Time on Drug to Event	Comments/ History	Age at Drug Start (years)	Dose (mg/day)	Sex
			episodic bradycardia; gastrostomy, hyponatremia, hypokalemia, UTI; ECG: possible rt. Vent. Hypertrophy.			
(b) (6)	Seizure	seizure after first dose	CMS; med hx. Not reported. Resumed 3,4-DAP later without seizure at dose of 20mg, ~1mg/kg/day.	7	10mg	Not reported
	Pneumonia, suicide attempt, pregnancy		CMS; abnormal baseline labs (low Crt, high albumin, slight high LFTs).	7	120mg	F
	Temporary increase of liver function tests. Drug stopped and later restarted. Repeat LFTs have been normal	3 months to transient LFT elevation	CMS	5.9	20mg; 0.8mg/kg	Not reported
			CMS. Tolerating well without side effects.	1	10mg	Not reported
			CMS. Tolerating well without side effects.	1.9	10mg; 0.9mg/kg	Not reported

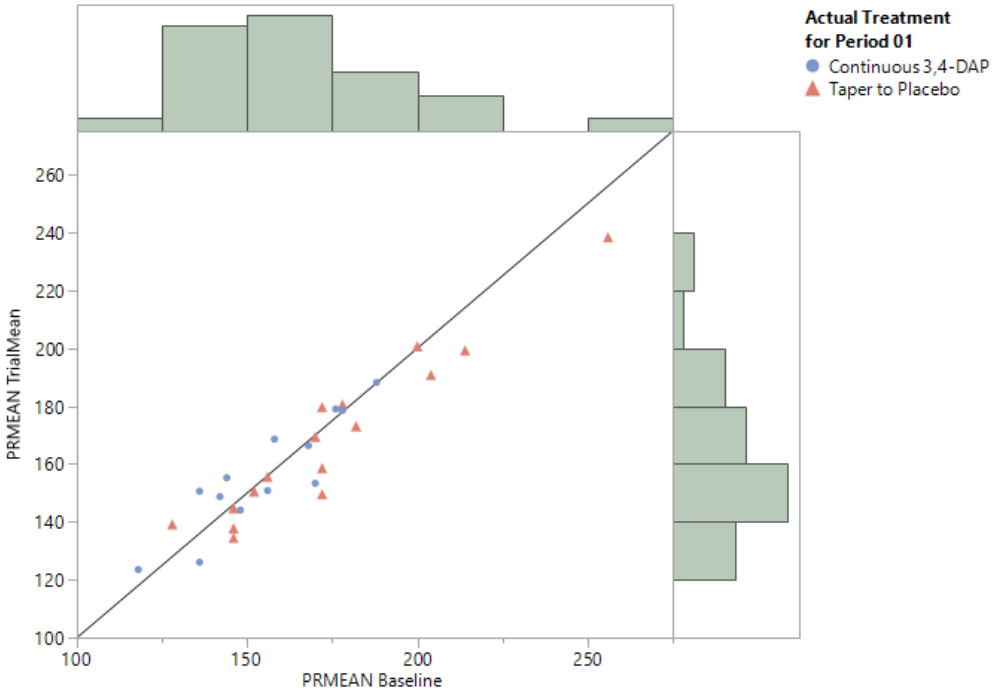
Reference ID: 4428593

Subject	AE/SAE	Time on Drug to Event	Comments/ History	Age at Drug Start (years)	Dose (mg/day)	Sex
(b) (6)			CMS. Tolerating well without side effects.	2.2	10mg; 0.9mg/kg	Not reported
			CMS. Tolerating well without side effects.	1.1	10mg; 1mg/kg	Not reported
			CMS. Tolerating well without side effects.	3.1	12.5mg; 1mg/kg	Not reported
	minor tremor in the hands in the first hour after 3,4-DAP		CMS.	2.6	20mg; 1.1mg/kg	Not reported
			CMS. Tolerating well without side effects.	6	15mg; 0.7mg/kg	Not reported
			CMS. Tolerating well without side effects.	7.6	20mg; 0.9mg/kg	Not reported
			CMS. Tolerating well without side effects.	7.8	40mg; 0.9mg/kg	Not reported
			CMS. Tolerating well without side effects.	14	35mg; 0.6mg/kg	Not reported
			LEMS. Tolerating well without side effects.	15	60mg; 1mg/kg	Not reported

Reference ID: 4428593

13.6 ECG Data Plots for DAPPER Study

Figure 6: Bivariate Fit of Mean Trial PR By Mean Baseline PR Interval Duration (ms)



Reference ID: 4428593

Figure 7: Bivariate Fit of QRS Duration Trial Mean by QRS Duration Baseline (ms)

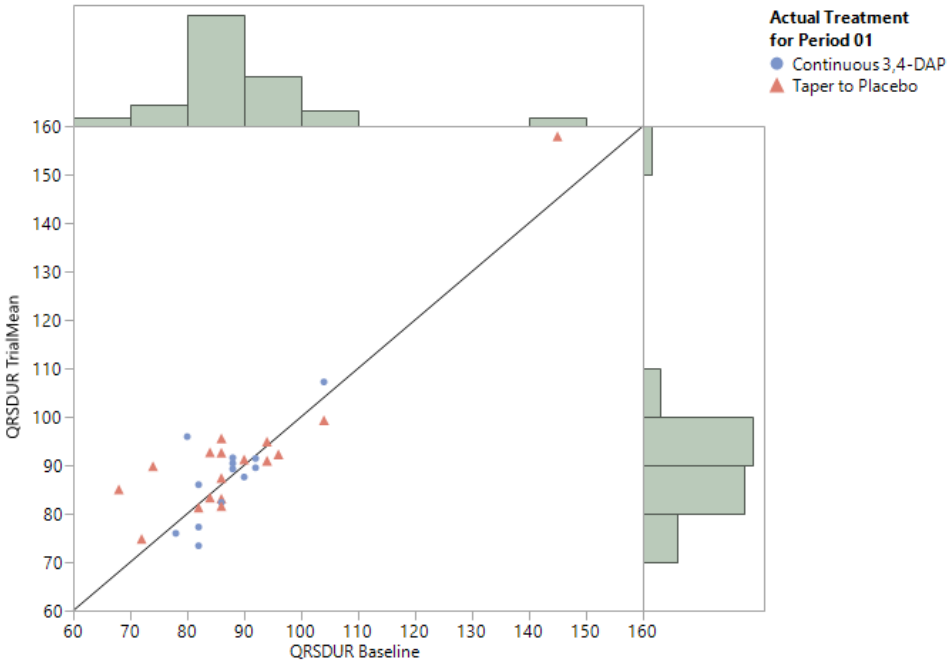
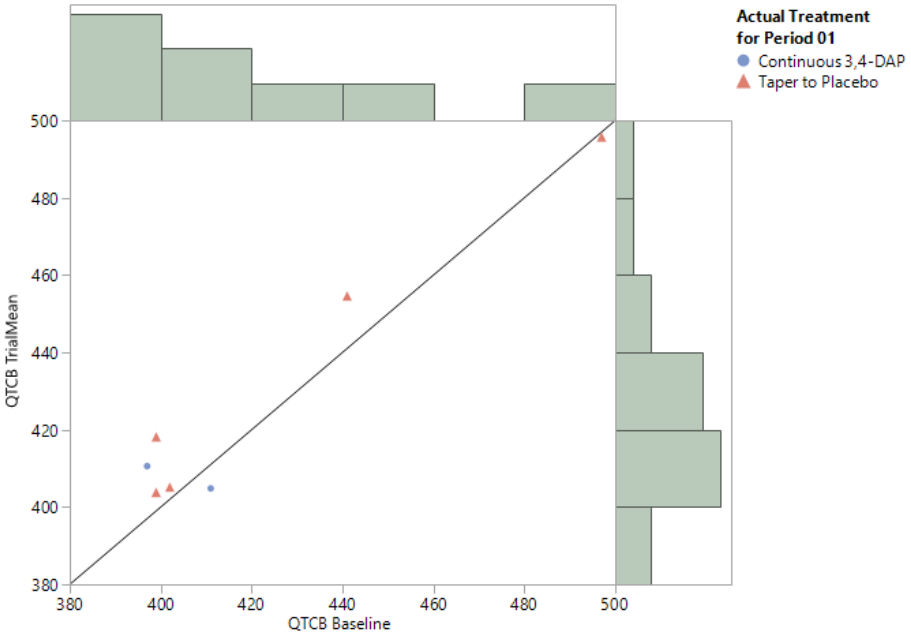


Figure 8: Bivariate Fit of QTCB Trial Mean by QTCB Baseline (ms)



Reference ID: 4428593

13.7 DAPPER Study: Major Protocol Deviations by Subject – All Randomized Subjects. Source: CSR

Subject Number	Treatment Assignment	Protocol Deviation Abbreviated Description
(b) (6)	Continuous 3,4-DAP	Inclusion Criterion #8 not met (Stable Non-LEMS medications for at least 1 month) - Subject received antibiotic for lower UTI since screening
	Continuous 3,4-DAP	Inclusion Criterion #8 not met (Stable Non-LEMS medications for at least 1 month) - Patient reported 10 day course of Septra 7 days prior to admission, 5 days prior to screening, for rose bush thorn-induced abscess which required incision and drainage
		Exclusion Criterion #7 met - Subject did not have at least 30% improvement in TUG scores post dose + at least 75 mg 3,4-DAP per day. Subject's total daily dose was only 60 mg.
	Continuous 3,4-DAP	Inclusion Criterion #7 not met (Stable LEMS medications for at least 3 months) - Subject changed her dosing regimen of PB from 60 mg TID to 30 mg BID on 08 Oct 2013 (to decrease side effects), but noticed no change and therefore increased dosage 1 week prior to admission and was randomized in Nov 2013.
	Taper to Placebo	Exclusion Criterion #4 met - Subject was under active treatment for sleep apnea and met original exclusion criterion #4 which was in effect at the time this subject was randomized
	Taper to Placebo	Inclusion Criterion #7 not met (Stable LEMS medications for at least 3 months) - Subject started Mestinon 25 Oct 2013, screening date was 08 Jan 2014. Ten weeks of Mestinon was not considered materially different from 12 weeks by the sponsor and subject was allowed to randomize.
		Inclusion Criterion #7 not met (Stable LEMS medications for at least 3 months) - Subject's normal dosing regimen was a total of 100 mg 3,4-DAP/day including a dose at 03:00. She takes the 3:00 am dose at home in order to be ready to head off to work promptly. However, taking a dose at 3:00 am would interfere with sleep during the inpatient portion of the study as the patient would be roused 1 to 2 hours pre-dosing for testing around the first dose of the day. The patient was willing to omit the 3:00 am dose and preferred to retain her last night-time dose at 10 mg rather than change it to 15 or 20 mg. Therefore, her total daily dose was decreased to 90 mg/day for the study and she did not meet this inclusion criterion.
(b) (6)	Taper to Placebo	Other - Day 1 TUGs surrounding evening dose were not performed using an assistive device, but for all other TUGs during the study, subject used a cane.
	Taper to Placebo	Exclusion Criterion #7 met - Subject did not have at least 30% improvement in TUG scores post dose + at least 75 mg 3,4-DAP per day; Subject's total daily dose was only 50 mg.

Reference ID: 4428593

13.8 Seizure Narrative Table

Table 41: Seizure Adverse Events from the Expanded Access Program Classified as Probably or Definitely Related to 3,4-DAP Use. Source: Summary of Clinical Safety and Patient Narratives

Patient ID	AE/SAE	Time on Drug to Event	Relationship to 3,4-DAP	3,4-DAP Total Daily Dose	Action Taken with 3,4-DAP	Comments/Medical History
(b) (6)	seizure, atrial fibrillation, syncope, myeloid leukemia, diverticulitis, death	1 month to syncope, seizure. 1 year to atrial fibrillation	Seizure Probably related	100 mg	Dose stopped and restarted at 10mg. Titrated to 80mg later.	palpitations, tobacco use, breast mass removal, angina pectoris, anemia. Loss of consciousness at 100mg/day followed by seizure the next day. Another seizure 2 years later at 15mg.
	seizure, suicide attempt, overdose	12 years	Seizure Probably related	80-120 mg	Dose not changed	depression, cognitive impairment; 87-year-old woman took an overdose (entire daily dose at one time) in possible suicide attempt
	seizure, acute respiratory failure, pneumonia, septic shock	11 years	Seizure Probably related	105 mg	Dose dropped to 75mg.	Microangiopathic multi-infarct disease and atherosclerotic changes of vertebra basilar system. Seizure at a self-administered dose of 105 mg while trying to taper KEPPRA®
	seizure	10 months	Seizure Probably related	100 mg	Dose dropped to 40mg.	Seizure on 3,4-DAP when dose increased from 90 to 100 mg 3,4-DAP and doubling of pyridostigmine in a

Reference ID: 4428593

Patient ID	AE/SAE	Time on Drug to Event	Relationship to 3,4-DAP	3,4-DAP Total Daily Dose	Action Taken with 3,4-DAP	Comments/Medical History
						patient with malignancy
(b) (6)	suicide attempt by 3,4-DAP overdose, QTc prolongation, seizures	single dose	Seizure Probably related	500 mg	No further 3,4-DAP.	Mental health disorder. Took someone else's 3,4-DAP. After overdose had 12-15 hours of seizures. QTc prolonged to 520ms for 1-2days. No tachyarrhythmias.
	hand muscle twitching (normal EEG), death	2 months to twitching	Definitely related	60 mg	Stopped. Later restarted at 20mg.	Ongoing peripheral motor and sensory neuropathy; chemotherapy and whole brain irradiation for SCLC ongoing when started 3,4-DAP
	small cell lung cancer with cerebral mets, visual field defect, seizures	1 year 9months to seizure after cerebral metastases	Seizure Definitely related	60 mg	Stopped.	Seizures persisted after stopping 3,4-DAP.
	respiratory failure, seizure, pneumonia	12 years	Seizure Probably related	80 mg	Dose continued.	tobacco use, small cell lung cancer, cellulitis, anxiety. Two seizures after getting doses 2 hours too early.

Reference ID: 4428593

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