CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	209321 (0008)
Drug Name:	Amifampridine (3,4 DAP)
Indication(s):	Lambert Eaton Myasthenic Syndrome
Applicant:	Jacobus
Date(s):	June 15, 2018
Review Priority:	Priority
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Keywords:	Rare Disease

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1 EXECUTIVE SUMMARY

The data from DAPPER study seem to support the efficacy of the drug. Although the sample size is small the p-value is very small ($p<0.0001$) for the primary analysis and this is a rare disease. The results from the single-site parallel group randomized placebo controlled DAP-DUKE study also seem supportive of efficacy.

2 INTRODUCTION

2.1 Overview

IND 054313 is the IND number associated with this drug development.
Amifampridine base (3,4-diaminopyridine, hereafter referred to as 3,4-DAP) is a calcium channel blocker used to treat (b) (4) Lambert-Eaton myasthenia (LEM), previously known as Lambert-Eaton myasthenic syndrome (LEMS). 3,4-DAP free base has been administered for this indication since 1993 through the Jacobus Pharmaceutical Company, Inc. (JPC) compassionate distribution program, to which more than 600 LEM patients have been referred for treatment.
LEM is an ultra-rare, autoimmune, myasthenia-like syndrome caused by antibodies to the voltage-gated calcium channel. These antibodies interfere with the release of acetylcholine (Ach) at the motor nerve terminal.
Progressive proximal muscle weakness is the major clinical presentation with LEM, and the hip girdle is generally more affected than the shoulder girdle [Sanders et al 2014]. As mobility becomes more impaired, the ability to be independent in self-care and basic activities of daily living (ADL) also deteriorates. Patients typically develop increasing difficulty rising from a chair, lifting their feet to walk, and have a characteristic waddling gait [Mahadeva et al 2008]. Many are unable to climb stairs and some become bedridden, and even require mechanical ventilation [Smith and Wald 1996] and tube feeding. Autonomic dysfunction may also be a prominent feature of LEM manifesting most commonly with dry mouth, impotence, difficulty swallowing, and constipation [Waterman 2001].
Occasionally LEM is cured in patients with an underlying cancer treated with antineoplastic therapies. Otherwise, there is no known cure for LEM. Treatment is directed to optimizing function. In LEM patients, 3,4-DAP provides significant improvement in strength, enabling some bedridden individuals to resume normal activities.
At the time of submission there were no effective alternative treatments for LEM patients, although some patients do have incremental benefit from pyridostigmine and immunomodulatory interventions. Treatment with 3,4-DAP is strictly palliative and does not affect the clinical course of the underlying disease. Muscle strength is improved as long as the medication is maintained, but the effect is lost within 24 hours after stopping the medication. Pyridostigmine may improve the duration although generally not the magnitude of the response. The improvement in strength improves overall quality of life, but the underlying disease process remains unchanged.

The clinical development program for 3,4-DAP consists of 1 clinical pharmacology study in healthy subjects and 2 pivotal randomized double-blind placebo-controlled Phase 2 studies in patients with LEM (the DAPPER study and JPC 3,4-DAP DUKE RCT).

•**Study JPC 3,4-DAPPER** (hereafter referred to as the DAPPER study): a JPC-sponsored, Phase 2, pivotal, randomized, double-blind, placebo-controlled withdrawal study to evaluate efficacy and safety in subjects with LEM

•**Study JPC 3,4-DAP DUKE RCT**: a Duke University-sponsored, Phase 2, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effectiveness of 3,4-DAP in subjects with LEM and to determine the acute and long-term side effects of 3,4-DAP

The DAPPER study was a randomized withdrawal design in which subjects whose LEM-related weakness was controlled with 3,4-DAP were gradually tapered off drug over a 3-day period with up to an additional 16 hours with no drug. Patients from 7 centers in the US, Canada, and Argentina participated in DAPPER. The randomized withdrawal design is an example of an enrichment design in which subjects who previously demonstrated a response to treatment are randomly withdrawn or maintained on therapy. Subjects who met entry criteria and were sufficiently responsive to their usual dose of 3,4-DAP during Stage 1 (baseline) of the study were randomized to maintain their dosing regimen or to withdraw from their 3,4-DAP treatment during Stage 2 (withdrawal period of up to 3.5 days). The baseline 3,4-DAP regimen was reinstituted in Stage 3.

Study JPC 3,4-DAP DUKE RCT was a randomized, double-blind, placebo-controlled study to evaluate the effectiveness of 3,4-DAP in subjects with LEM and to determine the acute and long-term side effects of 3,4-DAP. Subjects received 1 capsule of 3,4-DAP 10 to 20 mg or placebo 3 or 4 times a day for 6 to 9 days during the blinded portion of the study, after which subjects received open-label 3,4-DAP. Sanders et al. initially published data from this study [Sanders et al. 2000]. JPC performed a reanalysis of study endpoints using all available efficacy data from the study, for the purposes of validating the published data and providing additional data based on sensitivity analyses.

Table 1 Double Blind Phase 3 Sham Controlled Study Characteristics

Study Name	Phase and Design	Follow-up Period	# of Subjects per Arm	Study Population
DAP-DUKE	2	Variable: 5-9 Days	ITT: 26 total 3,4-DAP 10 to 20 mg TID or QID (n=12) or placebo TID or QID (n=14)	LEM
DAPPER	3 Randomized Withdrawal	3.5 days	ITT: 32 total 14 subjects to 3,4-DAP and 18 to taper to placebo	LEM

2.2 Data Sources

The datasets supporting the DAP-DUKE and DAPPER studies are located in the following directories.

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\\CDSESUB1\evsprod\NDA209321\0000\m5\datasets\dap-
duke\tabulations\sdtm\qs.xpt
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\\CDSESUB1\evsprod\NDA209321\0000\m5\datasets\dapper\tabulations\sdtm\xt.xpt
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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The FDA site inspection identified the following potential data integrity issue.

Each site recorded all laps of the 3TUG Test (the test used to assess the primary endpoint) on video. The site 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 at a later date by a central reviewer who was blinded to the treatment and to the date and time and/or sequence of the actual 3TUG Test. It was the central reviewer's assessment that was primarily used for the primary endpoint. The site's timed assessment was 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. Upon further investigation, he 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 (Edetek, Inc) 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).

The FDA field investigator identified the following two issues.

1. **Use of an excel spreadsheet to record/capture source data:** In general, we do not recommend using excel spreadsheets to capture source data because change control,

including the ability to track changes to a document through the use of audit trails, is not possible. In addition, version control is not possible unless the excel spreadsheet is protected and maintained as a fixed document and the central reviewer did not do this. Since there was no version control and no audit trails for the excel spreadsheet, we cannot verify that the source data was not modified prior to entering in the EDC system by the central reader.

2. **Data discrepancies found between the data listings provided to FDA and the excel spreadsheet that was used to capture the source data**: According to Jacobus, these data discrepancies ranged from 0.01 seconds to 0.17 seconds for approximately 23 records. The central reader, the sponsor, and the stats vendor did not have sufficient policies and procedures in place for transcribing data from the source and performing edit checks on that data. Inaccurate transcribed data was inappropriately used to perform the statistical analysis.

Therefore, the Division recommended that the sponsor have the central reader re-read all the videos for the 3TUG tests and enter the timed assessments directly into the EDC system, with this data then being used to re-analyze the primary efficacy endpoint.

Two blinded readers (Readers #1 and #2) were selected to re-read all of the videos for the 32 subjects who were randomized in the DAPPER trial. All subject videos were randomly assigned to the blinded re-readers. The initial 50 videos used to establish intra-rater reproducibility and inter-reader agreement were re-read in a new EDC environment. As the blinded readers were not presented with the subject IDs, they were not able to determine at which study site the tests were performed. The blinded readers remained blinded to the treatment assignments and completed reading all videos for a given subject before advancing to read videos from the next subject.

The analysis of the re-read 3 TUGS resulted in 13/18 (72.2%) placebo and 0/14 (0%) 3,4 DAP being >30% slower than time-matched baseline at their final double-blind assessment, p=0.0001. Thus, there was no change in results from the original primary analysis based on the single central blinded reader and this lends support to the original primary analysis (as do the original investigator readings, for more details see section 3.2.1.4.2).

3.2 Evaluation of Efficacy

3.2.1 DAPPER Study

Inpatient Double-Blind Placebo-Controlled Withdrawal Study of 3,4-Diaminopyridine Base (3,4-DAP) in Subjects with Known Lambert-Eaton Myasthenic Syndrome (LEMS)

First subject screened: 09-Feb-2012 **Last subject randomized:** 10-Mar-2014
First subject randomized: 15-Apr-2012 **Last subject completed:** 14-Mar-2014

The original protocol was dated 13 Jun 2011 and was amended on 3 October 2011, 1 May 2012, and 16 May 2013. The statistical analysis plan was signed on November 6, 2014. Note that the primary analysis described in the final SAP was the same as described in the protocol.

3.2.1.1 Study Design and Endpoints

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

The study was to examine the impact of withdrawing 3,4 DAP in patients with previously diagnosed LEMS who had been on a steady dose of 3,4-DAP for at least 3 continuous months.

The study was to involve three consecutive inpatient stages. Subjects were to undergo serial daily motor, electrophysiologic and safety assessments throughout the inpatient stages. During Stage I participants will be admitted for 2 ½ days of testing on their stable pre-study treatment regimen to establish each subject's baseline (first half day for acclimation to the testing facility). During Stage II, participants were to be randomized to the withdrawal of 3,4-DAP or continuation of 3,4-DAP. This double-blind withdrawal stage was to last for up to 3/1/2 days with testing. Stage II versus Stage I was to yield the primary and secondary endpoints. During Stage III, all participants were to have their pre-study treatment regimens reinstituted and were to remain for up to one additional day of testing pending improvement or sufficient recovery on TUG to ensure that subjects could be discharged safely. The same dosing schedule the subject used during the 3 months prior to admission was to be utilized throughout the study. It is important to note that there could be more than 3 doses per day. During each study stage TUG testing was to be conducted 15 minutes before and 2 hours after the first dose after 12 am, the first dose after 12 pm, and the first evening dose (first dose after 5 pm).

Subjects randomized to Group B were to be withdrawn from 3,4-DAP by using a steady taper over 3 days. The withdrawal period was to span 5 study days, starting with the last full dose of the baseline, and continuing through 3 days of the gradual taper during Stage II (including 1 full day with no "active" drug) and ending immediately before the first fully "active" dose in Stage III.

Sample size estimates were based on the comparison of 3,4 DAP (Group A) with the placebo treatment group (Group B). The primary efficacy variable is a >30% deterioration in the Timed Up & Go (UG) Test upon withdrawal of medication (Stage II) relative to baseline (Stage I).

It was believed that at most 10% of Group A as compared with 80% of Group B would experience such a deterioration. Using these assumptions and setting α=0.05 and the power at 0.80, a minimum of 10 subjects would be needed in each of the two study groups. To allow for minor departures in these assumptions, a total of 30 subjects, 15 for each treatment group were to be randomized.

Compassionate-use 3,4-DAP is available in 10 mg tablets. Enrolled subjects must be on a minimum treatment regimen of 10 mg three times daily. Most patients were expected to be taking concomitant pyridostigmine bromide (PB), which was started prior to or coincident with the initiation of their 3,4-DAP therapy. Subjects who had PB as part of their pre-study treatment regimen were to be continued on their usual dose and brand of PB. Likewise, all other baseline treatments were to continue as usual. Subjects were to be classified into one of the following four strata depending upon their baseline LEMS regimen:

Table 2 DAPPER Randomization Strata

Baseline LEMS treatment regimen			
3,4-DAP	PB	Immunomodulators/ immunosuppressants/ steroids	Approximate population frequency
YES	YES	NO	40%
YES	NO	NO	25%
YES	YES	YES	24%
YES	NO	YES	11%

Within each stratum subjects were to be randomized to either Group A or Group B.

The primary endpoint was to be the categorization of the degree of change in the TUG test (at the theoretical “peak drug effect”, i.e., 2 hours post dose) upon withdrawal of active medication (Stage II). Rescued subjects, advanced subjects, and subjects who withdrew early from the study were to be categorized for analysis of the TUG according to their last observation at theoretical “peak drug effect” during Stage II carried forward. The outcome for the TUG assessment used from Stage II was to be time matched with the corresponding average of the TUG assessments during Stage I.

3.2.1.2 Statistical Methodologies

The primary analysis was to compare the two treatment groups using Fisher's exact tests after determining, for each treatment group, the response rate for outcomes C through G combined (A-B are responders and C-G are non-responders). A supportive analysis, based on the individual 7 categories A through G, was to compare the treatment groups using the Cochran-Mantel-Haenszel test. In addition to summarizing the combined strata Separate summaries for each stratum were to be prepared if sufficient numbers of subjects were enrolled in each baseline LEMS regimen stratum.

Another supportive analysis of TUG was to treat the variables as a continuous response. One analysis would use the last available TUG obtained hours post dose from Stage II, the time point that is the basis for the primary efficacy variable. Another time point was to be the first TUG of the day. Each of these variables was to be analyzed using a one-way analysis of covariance with the reference TUG as the covariate.

The secondary endpoint was to be the W-SAS, the subject self-assessment of LEMS-related weakness, using a categorical scale ranging from Much Much Weaker (-3) to Much Weaker (-2) to Somewhat Weaker (-1) with No Change (0) at the halfway mark. The possibility of improvement is accommodated by the categories Somewhat Stronger (+1), Much Stronger (+2), and Much Much Stronger (+3). The final assessment obtained during Stage II was to be the outcome measure and the treatment groups were to be compared using a t-test.

Categories of 3TUG performance during phase II were:

A >30% faster

B No change ,i.e., between 30%faster and 30% slower

C 30-50% slower

D 50-100% slower

E 100-200% slower

F >200% slower

G cannot perform 3TUG laps of the 3TUG at the end of Stage II

If a subject who was able to complete 3 laps at baseline (Stage I) unable to complete all 3 laps of the 3TUG at the end of Stage II (the subject will be scored as category F.

If a subject was unable to get up from the chair or none of the 3 laps can will be completed the assigned category will be "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 to be scored as category F.

If a subject performed different numbers of laps at a specific time of day during Stage I the average of all available laps from the final 3TUG in Stage II was to be 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)

The 3TUG obtained 2 hours after the last dose during the withdrawal period (i.e., at time of theoretical drug peak) was to be used for the primary analysis. The primary analysis was to use Fisher's exact test to compare the treatment groups after determining for each group the response rate for outcomes C-G.

The individual 7 categories A through G, were to be summarized and compared by treatment groups using Cochran-Mantel-Haenszel test with modified Ridit scores derived from category rankings. Separate summaries for each stratum were to be prepared, if sufficient number of subjects were enrolled in each stratum.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Subject Disposition

Among the 52 subjects screened for this study, 32 subjects were confirmed to be eligible and were randomly assigned to treatment (14 subjects to continuous 3,4-DAP and 18 to taper-to-placebo; Table 3). All 32 subjects completed all 3 study stages and comprise the ITT and Efficacy Populations. One subject in the continuous 3,4-DAP group was excluded from the PP Population.

Seven subjects in the taper-to-placebo group were rescued or advanced early compared to 2 subjects in the 3,4-DAP continuous group (Table 3). The proportion of subjects rescued or advanced early (i.e., 7 versus 2) was not significantly different between groups (p=0.2349; Fisher's exact test).

Table 3 Dapper Study Patient Disposition

Disposition Status	Taper-to-Placebo N=18 n (%)	Continuous 3,4-DAP N=14 n (%)	Total N=32 n (%)
All randomized population	18 (100.0)	14 (100.0)	32 (100.0)
Completed study	18 (100.0)	14 (100.0)	32 (100.0)
Discontinued	0	0	0
Early entry to Stage 3	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 oximetry[a]	1 (5.6)	0	1 (3.1)
Advanced due to			
Inability to rise from a chair[b]	1 (5.6)	0	1 (3.1)
Inability to get out of bed[c]	0	0	0
Subject request for active medication	1 (5.6)	0	1 (3.1)

3,4-DAP = 3,4-diaminopyridine; CSR = clinical study report.
[a] Drop in pulse oximetry 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 at 1 hour apart.
[c] Inability to get out of bed, even with assistance, after 2 efforts at 1 hour apart.

Note: copied from page 29 of the Summary of Clinical Efficacy

The treatment groups were similar with respect to all demographic and baseline disease characteristics in the DAPPER study. The mean age of subjects was 55.5 years, approximately two thirds were female, and the majority were White or Caucasian (
Table 4).

Table 4 DAPPER Baseline Demographics

	Taper-to-Placebo N=18	Continuous 3,4-DAP N=14	Total N=32
Age (years)			
Mean	59.3	50.7	55.5
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 (%)			
White or Caucasian	18 (100)	11 (78.6)	29 (90.6)
Black or African-American	0 (0.0)	3 (21.4)	3 (9.4)

3,4-DAP = 3,4-diaminopyridine; CSR = clinical study report; ITT = intent-to-treat

Baseline LEM characteristics, indicators of disease, or complications due to LEM were similar in both treatment groups (Table 5). The mean duration of LEM diagnosis prior to randomization was 6.7 years. Most subjects had not been hospitalized or intubated previously because of LEM. Most

subjects were taking at least 1 LEM-related concomitant medication during the study for management of LEM (immunosuppressants and/or pyridostigmine).

Table 5 Baseline LEM Characteristics – DAPPER (ITT and Efficacy Populations)

Parameter	Statistic	Taper-to-Placebo N=18	Continuous 3,4-DAP N=14	Total N=32
Age at time of LEM 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 LEM 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 LEM 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 LEM 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 LEM 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 LEM				
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)
LEM-related concomitant medications taken during the study[b]				
Taking at least 1 LEM-related concomitant medication, n (%)		18 (100)	13 (92.9)	31 (96.9)
Immunosuppressants		7 (38.9)	4 (28.6)	11 (34.4)
Mestinon®/Pyridostigmine formulations		15 (83.3)	11 (78.6)	26 (81.3)

3,4-DAP = 3,4-diaminopyridine; c/w = consistent with; CMAP = compound muscle action potential; CSR = clinical study report; ITT = intent-to-treat; LEM = Lambert-Eaton myasthenia; PEG = percutaneous endoscopic gastrostomy.

[a] Definition of positive CMAP c/w LEM at Screening was >100% facilitation on pre-dose CMAP after maximal exercise in at least 1 of 3 muscles tested.

[b] Includes only medications taken during inpatient study and excludes LEM medications taken before admission to inpatient research unit or during follow-up phase of study (ie, 4 subjects, 1 in taper-to-placebo group and 3 in continuous 3,4-DAP group, were on intermittent intravenous immunoglobulin every 3 weeks as a stable component of their LEM-related therapeutic regimen, and treatment was given both before admission and after discharge from the research unit).

The most troubling LEM signs and symptoms were similar in both treatment groups (Table 6).

Table 6 Most Troubling Symptoms in All patients which occurred in ≥ 10% (ITT and Efficacy Pop)

Parameter	Taper-to-Placebo N=18 n (%)	Continuous 3,4-DAP N=14 n (%)	Total N=32 n (%)
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			
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			
Yes	2 (11.1)	2 (14.3)	4 (12.5)
No	16 (88.9)	12 (85.7)	28 (87.5)

3,4-DAP = 3,4-diaminopyridine; CSR = clinical study report; ITT = intent-to-treat; LEM = Lambert-Eaton myasthenia.

Note: copied from page 32 of the sponsor's Clinical summary of Efficacy

The most common troubling LEM signs and symptoms (occurring in at least 50% of subjects overall) were early morning weakness before taking the first 3,4-DAP of the day, heaviness in legs, fatigue, difficulty climbing stairs, and dry mouth (Table 10). In addition, 56.3% of subjects (18/32) had an abnormal gait and 12.5% of subjects (4/32) required an assistive device for walking.

The mean duration of 3,4-DAP treatment prior to study entry was 5.8 years (range, 0.3 to 18.9 years), and the mean duration of the current 3,4-DAP treatment regimen was 3.0 years (range, 0.3 to 12 years; Table 7).

Table 7 3,4-DAP and Other LEM Medication Characteristics at Baseline – DAPPER (ITT and Efficacy Populations)

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 LEM treatment regimen – proportion of subjects, 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)

Note: copied from page 33 of the sponsor's summary of clinical efficacy

The mean total daily dose (TDD) of 3,4-DAP at randomization was 75.5 mg (range, 30 to 100 mg), and the mean number of 3,4-DAP individual daily doses was 4.7 doses per day (range, 3 to 7 doses per day). The most common concomitant medication with 3,4-DAP was pyridostigmine (81.3%). None of the subjects were on prednisone within 3 months of enrolling in the study, although 50% of subjects in both treatment groups had historical exposure to prednisone for LEM.

3.2.1.4 Results and Conclusions

3.2.1.4.1 Sponsor's Results

The 3TUG outcome was only evaluated in the DAPPER study(i.e., not in the earlier DAP-DUKE study). The primary efficacy analysis for DAPPER was based on blinded 3TUG readings. The primary efficacy endpoint evaluated the proportion of subjects with >30% deterioration in final 3TUG test results upon the withdrawal of study drug.
A highly statistically significant difference was observed between treatment groups in favor of the continuous 3,4-DAP group (Table 8). A greater percentage of subjects in the taper-to-placebo group (72.2%) had >30% deterioration in the final 3TUG test upon withdrawal of 3,4-DAP

during Stage 2 compared with no subjects in the continuous 3,4-DAP group (72.2% versus 0.0%, p<0.0001). Results were consistent for the efficacy, ITT, and PP populations.

Table 8 Summary of >30% Deterioration in 3TUG Test Performance Upon Withdrawal of 3,4-DAP - DAPPER (Efficacy, ITT, and PP Populations)

Category of Change in 3TUG[a]	Taper-to-Placebo n (%)	Continuous 3,4-DAP n (%)	P Value[b]
Efficacy Population, n	18	14	
No change or faster (A to B)	5 (27.8)	14 (100.0)	<0.0001
>30% slower (C to G)	13 (72.2)	0 (0.0)	
ITT Population, n	18	14	
No change or faster (A to B)	5 (27.8)	14 (100.0)	<0.0001
>30% slower (C to G)	13 (72.2)	0 (0.0)	
PP Population, n	18	13	
No change or faster (A to B)	5 (27.8)	13 (100.0)	<0.0001
>30% slower (C to G)	13 (72.2)	0 (0.0)	

3,4-DAP = 3,4-diaminopyridine; 3TUG = Triple Timed-Up-and-Go; CSR = clinical study report; ITT = intent-to-treat; N = number of subjects in efficacy population; PP = per-protocol.

[a] A = >30% faster, B = 30% slower to 30% faster, C = >30% to 50% slower, D = >50% to 100% slower, E = >100% to 200% slower; F = >200% slower, G = cannot perform 3TUG.

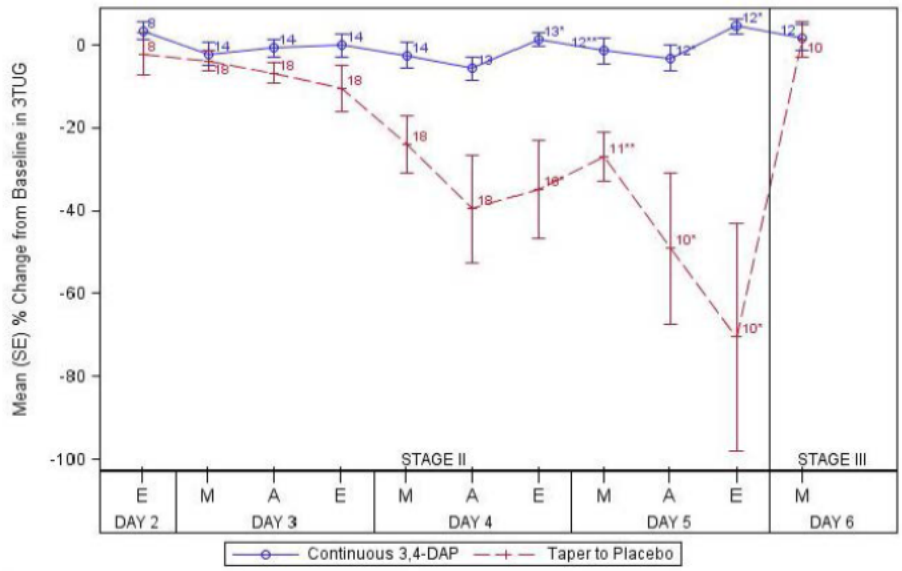
[b] P value was based on Fisher's exact test.

Source: Module 5.3.5.1, Study JPC 3,4-DAPPER CSR, Table 22

Note: This table was copied from page 26 of sponsor's study report

A statistically significant difference between treatment groups was observed for the 2 hour post-dose 3TUG change from baseline beginning with the Day 4 evening dose (p<0.05), and throughout the Day 5 morning (p<0.01), Day 5 afternoon (p<0.05), and Day 5 evening (p<0.001) time points (Figure 1). The post-dose 3TUG test results in the taper-to-placebo group returned to baseline upon reinstitution of 3,4-DAP with the Day 6 morning dose in Stage 3 and were consistent with 3TUG test results in the continuous 3,4-DAP group.

Figure 1 Mean (SE) Percent Change From Baseline in 3TUG at 2 Hours After Dosing Versus Time by Treatment Groups – DAPPER (Efficacy Population)



3,4-DAP = 3,4-diaminopyridine; 3TUG = Triple Timed-Up-and-Go; A = afternoon; ANCOVA = analysis of covariance; CSR = clinical study report; E = evening; M = morning; SE = standard error.
Notes: P value is based on the 1-way ANCOVA model, with the baseline 3TUG tests as the covariate.
* p<0.05, ** p<0.01, *** p<0.001.

Note: The Figure was copied from page 27 of the Sponsor's Clinical Overview

3.2.1.4.2 Reviewer's Results

The baseline treatment randomization strata were as shown in Table 9.

Table 9 Actual Baseline LEMS Treatment Randomization Strata Sizes

Stratum				
STRATUM	Frequency	Percent	Cumulative Frequency	Cumulative Percent
3,4-DAP	1	3.13	1	3.13
3,4-DAP + IM	5	15.63	6	18.75
3,4-DAP + PB	20	62.50	26	81.25
3,4-DAP + PB + IM	6	18.75	32	100.00

Abbreviations: PB= pyridostigmine bromide; IM=immunotherapy/steroids

This reviewer verified the sponsor's primary analysis results. This reviewer also found that a Cochran-Mantel-Haenszel analysis taking the randomization strata into account also supported the primary analysis (p=0.0001). It is not clear why one placebo patient had baseline 3TUGs data according to the investigator but none according to the central rater. The protocol seems unclear on how such a patient should be handled in the analysis. The most reasonable approach may be to impute the central baseline 3TUG with the investigator determined baseline 3TUG but since the protocol was unclear they might also be excluded. However, the p-value is relatively insensitive to the choice of handling this (if the placebo patient has baseline imputed then they are >30% slower with the imputation approach so p=0.00003 or if they are excluded p=0.00009).

This reviewer also found that the p-value was p=0.001 if rescues /early advancers were treated as failures, i.e., were > 30% slower than baseline, (2/14 vs. 14/18 failed).

This reviewer conducted a mixed model for repeated measures (MMRM) sensitivity analysis with an unstructured within patient covariance matrix for the percent change in 3TUG adjusted for matched baseline as well as the Visit Day and Time of Day within Visit Day. The estimated difference (DAP-Placebo) at the Day 5 Evening Assessment was -58.7 with a standard error of 17, p=0.0014.

Note that the correlation between central and site percent changes from baseline was 0.87. The primary analysis results were very similar for the investigator's version of the 3TUG results. In this case, there were 12/18 (66.7%) placebo > 30% slower as compared to 0/14 (0%)DAP regardless of rescue and 13/18 (72%) vs. 2/14 (14%) when rescues were treated as >30% slower. The mean changes and mean percent changes were also nominally significantly different. Fifteen out of 18 placebo and 13/14 DAP were last assessed at the evening dose (1 placebo and 1 DAP were last assessed in the morning and 2 placebo were last assessed in the afternoon). Seven taper to placebo and 2 DAP were last assessed on Day 4 and 11 taper to placebo and 12 DAP(note: for the blinded assessments one of these DAP was last assessed on Day 2) were last assessed on Day 5 of Stage II. Ten out of 18 (56%; 5 of these were rescued) Placebo and 11/14 (78%; 2 of these were rescued) DAP were last assessed at the Day 5 Evening time. There was no compelling evidence that the results were not consistent across the time of last assessment (Time of Day, as well as Day). If we consider a sensitivity analysis which treats those not assessed at the Day 5 Evening Time as >30% slower irrespective of assigned treatment group then the treatment comparison is still significantly different (83% Placebo vs 21% DAP >30% slower, p=0.001).

Table 10 breaks the primary endpoint down by the Time of Day when last assessed.

Table 10 Time of Day Last Assessed for Primary Analysis

		Time of Day of Last Assessment					All
		Morning		Afternoon	Evening		
		Arm		Arm	Arm		
		Continuous 3,4-DAP	Taper to Placebo	Taper to Placebo	Continuous 3,4-DAP	Taper to Placebo	
Percent Change >30 slower							
Yes	**N**	0	1.0	2.0	0	10.0	13.0
	Pct	0.0	100.0	100.0	0.0	66.7	40.6
No	**N**	1.0	0	0	13.0	5.0	19.0
	Pct	100.0	0.0	0.0	100.0	33.3	59.4
All	**N**	1	1	2	13	15	32

Table 11 breaks the primary endpoint down by Day last assessed since this varied.

Table 11 Day Last Assessed for Primary Analysis

		Day Last Assessed					All
		DAY 2	DAY 4		DAY 5		
		Arm	Arm		Arm		
		Continuous 3,4-DAP	Continuous 3,4-DAP	Taper to Placebo	Continuous 3,4-DAP	Taper to Placebo	
Percent Change >30 slower							
Yes	**N**	0	0	5.0	0	8.0	13.0
	Pct	0.0	0.0	71.4	0.0	72.7	40.6
No	**N**	1.0	2.0	2.0	11.0	3.0	19.0
	Pct	100.0	100.0	28.6	100.0	27.3	59.4
All	**N**	1	2	7	11	11	32

3.2.2 Dap-Duke Study

3.2.2.1 Study Design and Endpoints

Thirty-seven patients with a confirmed diagnosis of LEMS were screened for this study between October 1994 and May 1998. Eleven patients did not meet entry criteria and were not randomly assigned: 7 had QMG scores less than 5.0, 1 had atrial fibrillation, 1 had not completed chemotherapy for small cell lung cancer, 1 had a compression fracture that prevented participation in QMG testing, and 1 was noncompliant. Twenty-six patients who met the inclusion criteria were randomly assigned with intention to treat. All of these completed the study, parallel treatment over 5 days.

3.2.2.2 Statistical Methodologies

After 26 patients the difference in average QMG scores in patients receiving placebo and DAP obtained before and during double blind treatment were to be compared using a 1-sided two-sample t-test. Based on results from preliminary studies it was expected that this would provide 80% power to detect a statistically significant difference at the 5% level.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Thirty-seven subjects with a confirmed diagnosis of LEM were screened for participation in the study. A total of 26 subjects were randomized to receive 3,4-DAP 10 to 20 mg TID or QID (n=12) or placebo TID or QID (n=14) and all completed the study (Table 12).

Table 12 DAP-Duke Patient Disposition

	Placebo	3,4-DAP	Total
Eligible subjects			37
Not randomized[a]			11
Randomized	14	12	26
Completed trial	14	12	26
Entered open-label 3,4-DAP phase			25

3,4-DAP = 3,4-diaminopyridine; QMG = Quantitative Myasthenia Gravis score.
[a] QMG ≤5 (n=7), atrial fibrillation (n=1), compression fracture (n=1), non-compliant (n=1), receiving chemotherapy (n=1).

There was no difference in the age of LEM onset, gender distribution, incidence of SCLC, baseline QMG, or summated CMAP amplitude between the placebo and 3,4-DAP groups (Table 13).

Table 13 Demographic and Baseline Characteristics of Randomized Population – JPC 3,4-DAP

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

3,4-DAP = 3,4-diaminopyridine; CMAP = compound muscle action potential; 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.
[c] One of the 5 subjects in the placebo group had non-small cell cancer.

Note: copied from page 35 of sponsor's clinical summary of efficacy

3.2.2.4 Sponsor's Results

In Study JPC 3,4-DAP DUKE RCT, Jacobus performed a reanalysis of the primary data reported in Sanders et al. 2000. Demographic and baseline characteristics were similar to those presented in Table 12, with no important differences between the treatment groups. Baseline median QMG was not statistically different between treatment groups (12.3 in the placebo group and 8.5 in the 3,4-DAP group; p=0.625). Baseline median CMAP was 1.5 in each treatment group (p=0.817).

The primary efficacy measure in Study JPC 3,4-DAP DUKE RCT was the change from baseline QMG [Sanders et al. 2000]. Quantitative examination of muscle strength using the QMG was performed at baseline, prior to study drug being introduced, and on the last 2 days of study drug

administration. Duration of study drug administration was variable, and final QMG was measured on the following days:

- Days 5 and 6: 1 subject
- Days 6 and 7: 6 subjects
- Days 7 and 8: 18 subjects
- Days 8 and 9: 1 subject

Subjects who received 3,4-DAP had a statistically significantly greater improvement in QMG than subjects who received placebo (Table 14). The median QMG improved by ≥2 points in 7 of the 12 subjects (58%) who received 3,4-DAP and all reported symptomatic improvement during the blinded portion of the study. Of the 5 subjects who received 3,4-DAP whose QMG improved by <2 points, 4 went on to experience symptomatic improvement during the open-label portion of the study. No subject who received placebo improved more than 1.0 QMG point, and the median QMG improved by only 0.5 points after treatment in these subjects (Table 14). Four subjects in the placebo arm reported symptomatic improvement during the blinded portion of the study.

Table 14 QMG Results From the Double-blind Portion of Study JPC 3,4-DAP DUKE RCT – Per Protocol Population

	Placebo (N=13)	**3,4-DAP (N=12)**	**P Value[a]**
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)[a]	0.220
Change from baseline	-0.5 (-1.0 to 1.0)	-2.0 (-3.0 to 0.0)	0.015

3,4-DAP = 3,4-diaminopyridine; QMG = Quantitative Myasthenia Gravis score.
Values are expressed as median (interquartile range).
[a] Significantly different from baseline value using 2-side 2-sample Wilcoxon's signed rank sum test, Normal Approximation.

Note: This table copied from page 60 of the sponsor's Clinical Overview

Two sensitivity analyses were performed (Table 15).
1) analysis including subjects with a single post-baseline QMG
2) analysis using only the last available post-baseline measures
Overall, the findings of these analyses were consistent with the QMG changes from baseline reported in the Sanders et al. 2000 publication (Placebo arm: 0.25 versus 3,4-DAP arm: -2.0; p=0.01).

Table 15 Sensitivity Analyses of QMG Results From the Double-blind Portion of Study JPC 3,4-DAP DUKE RCT

	Placebo (N=14)	3,4-DAP (N=12)	P Value[a]
Sensitivity analysis 1: Including single post-baseline QMG (Subject (b) (6)			
QMG			
Baseline	12.3 (9.0 to 13.5)	8.5 (7.3 to 17.0)	0.625
Post-baseline	12.8 (9.0 to 13.5)	6.5 (5.0 to 14.3)	0.156
Change from baseline	0.00 (-1.0 to 1.5)	-2.0 (-3.0 to 0.0)	0.009
Sensitivity analysis 2: Using only last available baseline measures			
	(N=14)	(N=12)	
Baseline	12.3 (9.0 to 13.5)	8.5 (7.3 to 17.0)	0. 625
Post-baseline	12.5 (9.0 to 14.0)	6.5 (5.0 to 14.5)	0.140
Change from baseline	-0.3 (-1.0 to 2.0)	-2.0 (-3.3 to 0.0)	0.020

3,4-DAP = 3,4-diaminopyridine; QMG = Quantitative Myasthenia Gravis score.
Values are expressed as median (interquartile range).
[a] P value is derived from a two-side two-sample Wilcoxon's rank sum test, Normal Approximation

Note: this table was copied from age 61 of the sponsor's clinical overview

Reviewer's Comment: This reviewer noted that the number of days treated varied slightly but both groups had a median of 8 days and the distributions of treatment time were similar overall.

In the PP population, subjects treated with 3,4-DAP experienced statistically significant changes from baseline CMAP compared to those who received placebo during the double-blind portion of the study (p = 0.001) (**Table 16**). These results were comparable to those reported in the ITT population in the publication.

Table 16 DAP-DUKE CMAP Results in the Per-Protocol Population

	Placebo (N=13)	3,4-DAP (N=12)	p-Value[a]
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

3,4-DAP = 3,4-diaminopyridine; CMAP = compound muscle action potential.
Values are expressed as median (interquartile range).
[a] p value is derived from a 2-side 2-sample Wilcoxon's rank sum test, Normal Approximation.
Source: JPC 3,4-DAP DUKE RCT, Table 2.2

Note: this table was copied from age 11 of the sponsor's study report

JPC performed 2 sensitivity analyses on the ITT population using CMAP results from the double-blind portion of the study (**Table 17**):
1. analysis including a single post-baseline CMAP (from Subjects (b) (6))
2. analysis using only the last available post-baseline CMAP measures for all subjects
Overall, the findings of these analyses were consistent with those reported in the manuscript by Sanders and colleagues (Sanders et al 2000).

Table 17 Sensitivity Analyses of CMAP Results From the Double-blind Portion of the Study – ITT Population

	Placebo (N=14)	3,4-DAP (N=12)	p-Value[a]
Sensitivity analysis 1: Including a single post-baseline CMAP (from Subjects [redacted] (b) (6))			
CMAP			
Baseline	1.5 (0.8 to 2.2)	1.5 (0.6 to 2.6)	0.817
Post-baseline	1.3 (1.1 to 2.5)	3.1 (1.1 to 5.1)	0.085
Change from baseline	-0.0 (-0.1 to 0.2)	0.8 (0.1 to 2.5)	0.002
Percent change from baseline	-2.8 (-13.1 to 14.2)	41.7 (14.2 to 297.2)	0.002
Sensitivity analysis 2: Using only the last available post-baseline CMAP measures for all subjects			
Baseline	1.5 (0.8 to 2.2)	1.5 (0.6 to 2.6)	0.817
Post-baseline	1.4 (1.1 to 2.4)	3.5 (1.2 to 4.8)	0.105
Change from baseline	-0.1 (-0.1 to 0.3)	1.2 (0.0 to 2.7)	0.011
Percent change from baseline	-6.3 (-15.7 to 14.2)	52.3 (2.5 to 338.6)	0.017

3,4-DAP = 3,4-diaminopyridine; CMAP = compound muscle action potential; ITT = intention-to-treat.
Values are expressed as median (interquartile range).
[a] p value is derived from a 2-side 2-sample Wilcoxon's rank sum test, Normal Approximation.
Source: JPC 3,4-DAP DUKE RCT, Table 2.1 and Table 2.3

Note: this table was copied from age 13 of the sponsor's study report

Four of the 12 subjects (33.3%) randomized to 3,4-DAP (Subjects [redacted] (b) (6) [683%], [redacted] (b) (6) [416%], [redacted] (b) (6) [228%], and [redacted] (b) (6) [366%]) experienced at least a 100% increase in CMAP compared with none of the 14 subjects randomized to placebo.

3.2.2.5 Reviewer's Results

This reviewer verified the sponsor's re-analysis of the DAP-DUKE study data.

3.3 Evaluation of Safety

Safety in general is not addressed in this review. Please see the Clinical safety review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Gender, Race, and Age

In the DAPPER study 21 (66%) were female and 11(34%) were male. Table 18 shows the primary outcome results by Sex groups. The primary outcome results are consistent across Sex groups.

Table 18 DAPPER: Percent Change from Baseline by Sex

	Sex				All
	Female		Male		
	Description of Planned Arm		Description of Planned Arm		
	Continuous 3,4-DAP	Taper to Placebo	Continuous 3,4-DAP	Taper to Placebo	
	N	N	N	N	N
Percent Change from Baseline					
>30 slower	0 (0%)	8(73%)	0 (0%)	5(71%)	13
No change or faster	10(100%)	3 (27%)	4(100%)	2(29%)	19
All	10	11	4	7	32

In the DAPPER study 11 (34%) patients were Age 65 or above and only 3 were non-White (3 African Americans). Among those Age 65 or older, 5/9 Placebo were >30% slower as compared to 0/2 DAP, whereas among those less than age 65, 8/9 placebo were >30%slower as compared to 0/12 DAP. Therefore, there is no compelling evidence that the treatment effect depends on Age.

There were 15 (58%) females and 11 males (42%) in DAP-DUKE. The numbers in the subgroups are small but there is no compelling evidence that the treatment effect varied by sex.

Table 19 DAP-DUKE: QMG Change from Baseline by Sex

		Sex				All
		Female		Male		
		Planned Arm Code		Planned Arm Code		
		DAP	Placebo	DAP	Placebo	
Baseline	**N**	7	8	5	6	26
	Median	7.5	13.3	9.0	11.3	11.3
	Q1	6.5 to 15.5	7.0 to 15.0	8.0 to 18.5	10.5 to 13.0	7.5 to 14.5
	Q3	15.5	15.0	18.5	13.0	14.5
Change	**N**	7	8	5	6	26
	Median	-2.5	-0.8	-2.0	1.3	-1.0
	Q1	-4.5 to 0.5	-1.0 to 0.8	-2.0 to -0.5	-1.0 to 2.0	-2.0 to 0.5
	Q3	0.5	0.8	-0.5	2.0	0.5
All	**N**	7	8	5	6	26

Only 7 patients in DAP-DUKE were over age 65, so an analysis of the Age > 65 subgroup would not be reliable.

There was only 1 non-White subject in DAP-DUKE, so analysis of race differences is not possible.

4.1.2 Geographic Region

4.1.2.1 Individual Sites

For the Dapper study, Table 20 shows the primary outcome results broken down by Site. The UUMC site had the most polar opposite results between groups in terms of Percent Change > 30% slower and the 3rd largest sample size. Duke had the biggest sample size followed by Baylor. Note that no DAP patients had Percent Changes (PCHG) > 30% slower than baseline, (so there is no PCHG > 30% slower =Yes column in the following table).

Table 20 Primary Outcome by Site in DAPPER

	Description of Planned Arm						All
	Continuous 3,4-DAP		Taper to Placebo				
	PCHG>30% slower		PCHG>30% slower				
	No		No		Yes		
	N	Percent	N	Percent	N	Percent	N
Study Site Identifier							
BAYL	2	100.0	2	33.3	4	66.7	8
DUKE	6	100.0	1	33.3	2	66.7	9
INDI	1	100.0	1	100.0	.	.	2
OHSU	0	.	1	33.3	2	66.7	3
UCDA	1	100.0	0	0.0	1	100.0	2
UUMC	2	100.0	0	0.0	3	100.0	5
VAND	2	100.0	0	0.0	1	100.0	3
All	14	100.0	5	27.8	13	72.2	32

The DAP-DUKE study was conducted solely at DUKE, so it is not possible to investigate site or regional differences for the DAP-DUKE study.

4.2 Other Special/Subgroup Populations

No other subgroups were formally analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were some slight differences in last day of assessment and time of day of last assessment but there are no major statistical issues.

5.2 Collective Evidence

Collective evidence is not considered in this review since there was one double-blind, controlled trial with a randomized withdrawal design and one single-site randomized, placebo controlled parallel group design. The two studies also utilized different primary endpoints.

5.3 Conclusions and Recommendations

The data from DAPPER study seem to support the efficacy of the drug. Although the sample size is small the p-value is very small for the primary and several other secondary analyses, this is a rare disease, there is no suggestion of regional or significant site differences and the results appear reasonably consistent over subgroups. The results from the single-site parallel group randomized placebo controlled DAP-DUKE study also seem supportive of efficacy.

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TRISTAN S MASSIE
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KUN JIN
01/28/2019 10:24:00 AM
I concur with the review.

HSIEN MING J HUNG
01/28/2019 11:16:24 AM